



KMJ

KUWAIT MEDICAL JOURNAL



The Official Journal of The Kuwait Medical Association

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PUBLISHER: The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13013 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw

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Kuwait Medical Journal

Published by the Kuwait Medical Association
Previously known as The Journal of the Kuwait Medical Association (Est. 1967)

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E-mail: kmj@kma.org.kw
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for the financial support accorded to this journal
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Editorial

Money Power

Belle M Hegde

The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*

Manipal University, Manipal, India**

The Middlesex Medical School, University of London, UK†

Northern Colorado University, USA‡

Kuwait Medical Journal 2018; 50 (4): 385-386

The immune system's role in preventing and even treating diseases has been known for centuries in Indian Ayurveda; western medicine started to emphasise this since the 1915 proclamation of the Grimm's law (disease is directly proportionate to the power of the cause, but is inversely related to host resistance- the immune system) by an American physician, Theobald Smith. So there is nothing new about this in 2018 to attract a Nobel Prize. Now that two individuals independently found out how the handshake between the immune cell and the cancer cell takes place, this throws up a potential for the greedy pharma lobby to create a chemical molecule to modify this handshake. Lo and behold, immediately the Nobel committee picked up the old hat on the immune system's role for their award! Similarly, the Nobel Prize to Luc Montagnier nearly a decade ago was motivated by the pharma lobby's monetary interest. Since 1981, Luc's work on the HIV virus as the cause of AIDS was known to be based on very flimsy science of a single case report, in which Luc showed the HIV virus on post-mortem of a young AIDS patient's bone marrow. Luc turned this isolated association in his case report into causality. It was largely forgotten at that time, but the industry made a fortune by selling zidovudine for killing the virus in AIDS patients.

Since then, many papers and even an authoritative book by Peter Duesberg, a great virologist with a longish foreword by Kary Mullis, the father of the PCR test that identifies viruses, strongly refuted the accepted claim that HIV virus causes AIDS syndrome! Fearing a drop in zidovudine sales after

this book "Inventing the Aids Virus" was published; the Nobel committee picked up the 1981 case report of Luc, which was noted above as bad science; and gave him the Nobel Prize in 2008 or so! There was a resurgence of interest in the HIV virus as the cause of AIDS and the drug sales went up, thanks to the Nobel Prize! I can go on and on quoting more such associations from that infamous book "The Prize". When this is the situation, why do we blame greedy politicians for making money through corruption? Motivated by greed and with little regard for ethics, they turn to corruption, knowing full well that money runs this world. How are they any different from greedy science which gains respectability?

The story of the diet-heart connection and the role of fat in heart disease are all based on a pseudo-scientific study by Ancel Benjamin Keys, an American physiologist. The study revealed that the countries where fat consumption was the highest had the most heart disease, supporting the idea that dietary fat caused heart disease. The problem is that he intentionally left out countries where people eat a lot of fat but have little heart disease, such as Holland and Norway. If one cares to see the programme "What the Health" in Netflix, one will get to see many such faux pas in science that I have been highlighting for the last half a century! It is good food for those that swear by the word of science as truth. Truth and science are just not friends. Science is just curiosity. It is the search for truth, just like religion. Science is yet to get at "the truth", although each time it fumbles on "a truth", quickly it also finds that the truth they

Address correspondence to:

Prof. B M Hegde, MD, FRCP, FRCPE, FRCPG, FRCPI, FACC, FAMS, "Manjunath", Pais Hills, Bejai, Mangalore 575004, India. Tel: +91 824 245 0450,

E-mail: hegdebm@gmail.com, website: www.bmhegde.com

*Editor in Chief; ** Cardiologist & Former Vice Chancellor (Retd); †Former Visiting Professor of Cardiology

‡Affiliate Professor of Human Health

found has already changed. Even though Ancel Keys had not done his data manipulations, longer observations would have given him more wisdom. We were being bombarded by this kind of short-cross sectional studies in medical science, which made hapless patients swallow drugs to keep the so-called risk factors at bay; but the bit longer observations in the MRFIT – multiple risk factor interventional trial - showed that none of those risk factors really mattered! There were no risk factors according to MRFIT data. Even if those risk factors were modified by drugs or interventions, the final risk, if any, remained alive!

Now comes the real science! The longest 70-year prospective observation of the Harvard alumni

of the 1930s to date brings us back to the ancient Indian wisdom of Ayurveda: the things that keep people going to old age in good health are good social and family ties and universal compassion. The two deadly enemies of mankind are smoking and alcohol, the two that all governments encourage for tax revenues-money over human health! This is the same that ancient Ayurveda proclaimed to the world. The Diet Heart study in Framingham had earlier shown that the two are not connected. However, Ancel Keys was able to sell his ideas as his study made the crucial money making possibility. Money runs the world in every field. Science needs to be freed from this grant-getting, paper-writing, money-spinning rigmarole.

Review Article

A Review of Literature on the experiences of people with Type 2 Diabetes Mellitus after Bariatric Surgery in Kuwait

Alanoud M I H M Alobaidly, Abdullah Y A M A Hasan, Wendy Abigail, Pauline Hill
College of Nursing and Health Sciences, Flinders University, South Australia

Kuwait Medical Journal 2018; 50 (4): 387 - 398

ABSTRACT

Bariatric surgery (BS) has become a popular intervention for weight loss amongst the obese and morbidly obese population with type 2 diabetes mellitus (T2DM) in Kuwait. Studies conducted in Kuwait have found that BS has positive effects on blood glucose levels of people with T2DM. An integrative review was conducted in five major research databases, where the final 14 articles were analysed thematically. In the western world, patients are provided with professional support to overcome both physiological and psychological concerns. Conversely, Kuwaiti individuals might avoid or neglect psychological supports due to insufficient service support and cultural stigmatisation. Although quantitative research may provide

critical information about the result of BS physically, they neglect the psychological aspects behind undergoing the surgery, and how the lives of patients who have had BS are affected by this intervention. As a trending intervention for the management of T2DM, exploring the psychological effects after BS may provide a better understanding of the daily lives of individuals with T2DM and enable improvements in health care education for the bariatric population. This review provides evidence that there is a need for more qualitative research in Kuwait to address barriers that bariatric patients' might have faced and the importance of providing health care support to maintain long-term physical and psychological well-being.

KEYWORDS: bariatric surgery, culture, obesity, psychological effects, type 2 diabetes mellitus

INTRODUCTION

Kuwait provided a comfortable life for its citizens when the transition from a hard-working lifestyle into a sedentary one occurred after the discovery of oil in 1938^[1]. High-fat low-fibre diets, sedentary lifestyle and high income have contributed to the rise of obesity and comorbidities, such as cardiovascular diseases and type 2 diabetes mellitus (T2DM) in the Kuwaiti population^[2,3]. Additionally, poor eating habits in most Kuwaiti households has aided in the rise of this phenomenon^[4]. Consequently, Kuwait became the eighth highest in the incidence of obesity and the ninth-ranked country for diabetes globally^[5], and the incidence is predicted to double by 2030^[6,7].

Bariatric surgery (BS) has recently gained popularity in managing T2DM and treating obesity in Kuwait^[8,9]. Furthermore, Kuwait has one of the highest prevalence of people undergoing BS in the world^[10]. Positive outcomes in managing blood glucose levels within normal ranges and achieving target weight loss results for the overweight, obese and morbidly obese

population by undergoing BS in Kuwait have been reported^[8,9,11,12]. For example, roux-en-y gastric bypass (RYGB) was found to be the most effective surgical intervention in providing long-term results for weight loss and the management of T2DM^[12]. However, although the effects of BS on the psychological aspects in some obese men were positive, there were also negative consequences of excessive weight loss such as body image disturbance due to multiple skin folds that interfered with their social life, and dietary adjustments to their new digestive systems^[13]. The bariatric population have reported benefits from receiving psychological support in maintaining good health^[14], and that treating this population group psychologically to address underlying issues leading to obesity was essential in maintaining a physically healthy life^[15].

For Kuwaiti individuals however, healthcare support has been limited after BS. This is due to the patient's initial satisfaction from the positive outcomes of the surgery and not requiring support, and

Address correspondence to:

Wendy Abigail, PhD, RN, BN (1st Hons), GdCEd (Higher Ed), GdChH (DM Mgmt & Ed). Senior Lecturer, College of Nursing & Health Sciences, Flinders University, GPO Box 2100, Adelaide 5001, South Australia. Tel: +61 8 82015433; E-mail: wendy.abigail@flinders.edu.au

from stigma associated with seeking psychological support, particularly due to cultural factors such as family reputation and gossip^[16]. The lack of support, potentially, acts as a barrier between the healthcare team and the bariatric population. However, the lack of support might not be an issue in cultures known to have extended families who value their relationships with close friends and families, thus replacing the need for experts^[17,18].

In order to establish the effectiveness of the role of family support for bariatric patients in Kuwait and for understanding the importance of the effects of BS on the psychological aspects of this population group, this integrative review has been conducted. The purpose of this review is to provide an understanding of the role of healthcare support for people with T2DM after BS in Kuwait and to answer the research question. To our knowledge, no other reviews have been conducted on this topic, hence, this review aims to (1) synthesise existing quantitative and qualitative research to determine the outcomes of BS in people with T2DM, (2) contribute information for developing bariatric programs in Kuwait, and (3) improve health care policy and procedures for the bariatric population.

METHODS

The methodology in this review followed Whittemore and Knaff's definition of integrative reviews^[19], which was guided by the primary research question: 'What are the experiences of people with T2DM after BS in Kuwait?'

Search strategy

A comprehensive electronic database search of the literature used the following key concepts: bariatric surgery, weight loss surgery, metabolic surgery, diabetes surgery, laparoscopic adjustable gastric band, sleeve gastrectomy, RYGB, biliopancreatic diversion with duodenal switch, type 2 diabetes, patients experience and behaviour (Table 1). These keywords were used as sub-topics and MeSH terms in the following major research databases: Cumulative Index to Nursing and Applied Health Literature (CINAHL), Medical Literature Analysis and Retrieval System Online (MEDLINE), SCOPUS and Google Scholar. A hand-search on the reference lists of relevant articles was also conducted. The limits included identified human subjects only and peer-reviewed articles from 2013 to 31st July 2017. The chosen timeline was to include most recent surgical intervention in people with T2DM in Kuwait after a 3-month suspension period of performing bariatric surgery in 2013 by the Kuwaiti Minister of Health Dr Mohammed Al-Haifi to update policy, medical protocols and procedure^[6].

Table 1: Search strategy

S.No	Key terms	Results
1	Diabetes type 2	28,207
2	T2DM	1,512
3	Diabetes II	28,207
4	1 or 2 or 3	28,573
5	Obese*	37,022
6	Morbid obese*	37,001
7	Overweight	35,036
8	5 or 6 or 7	37,022
9	BS	3046
10	Weight loss	3046
11	Roux-en-Y gastric bypass	3040
12	Metabolic surgery	300
13	BPDDS	3046
14	Sleeve gastrectomy	154
15	Gastric band	54
16	9 or 10 or 11 or 12 or 13 or 14 or 15	3151
17	Experience	102,431
18	Attitude	100,021
19	Behavior*	25,600
20	Perception	18,698
21	Lifestyle	100,024
22	Culture	157,856
23	17 or 18 or 19 or 20 or 21	117,879
24	4 and 8 and 16 and 22 and 23	162
25	Limit 23 to English language and yr="2013-current"	70

T2DM: type 2 diabetes mellitus; BS: bariatric surgery; BPDDS: biliopancreatic diversion with a duodenal switch

The inclusion and exclusion criteria were established, which applied the Population, Intervention, Comparison, Outcome, Time (PICO/T) method^[20]. The inclusion criteria were: adults (18 years old and above) who had one of the following BS - laparoscopic adjustable gastric band (LAGB), sleeve gastrectomy (SG), RYGB or biliopancreatic diversion with duodenal switch (BPD-DS) surgery; who had a diagnosis of T2DM with outcomes reporting changes in glycosylated haemoglobin (HbA1c) or blood glucose levels (BGLs); and reported patients' experiences six months after BS. Excluded articles were on adolescence; weight-loss interventions for T2DM other than BS such as medical T2DM therapy, weight loss pills and diets; and comorbidities other than T2DM.

Using the PRISMA flow diagram (Figure 1), the generated publications were screened, and irrelevant articles were excluded after applying inclusion and exclusion criteria. Both quantitative and qualitative articles were included.

Synthesis and analysis of the results

Details from each article were extracted, which included documenting the author(s) names, year of publication, the name of the journal in which the articles were published, the title of the article, the country, research aim, method used, sample

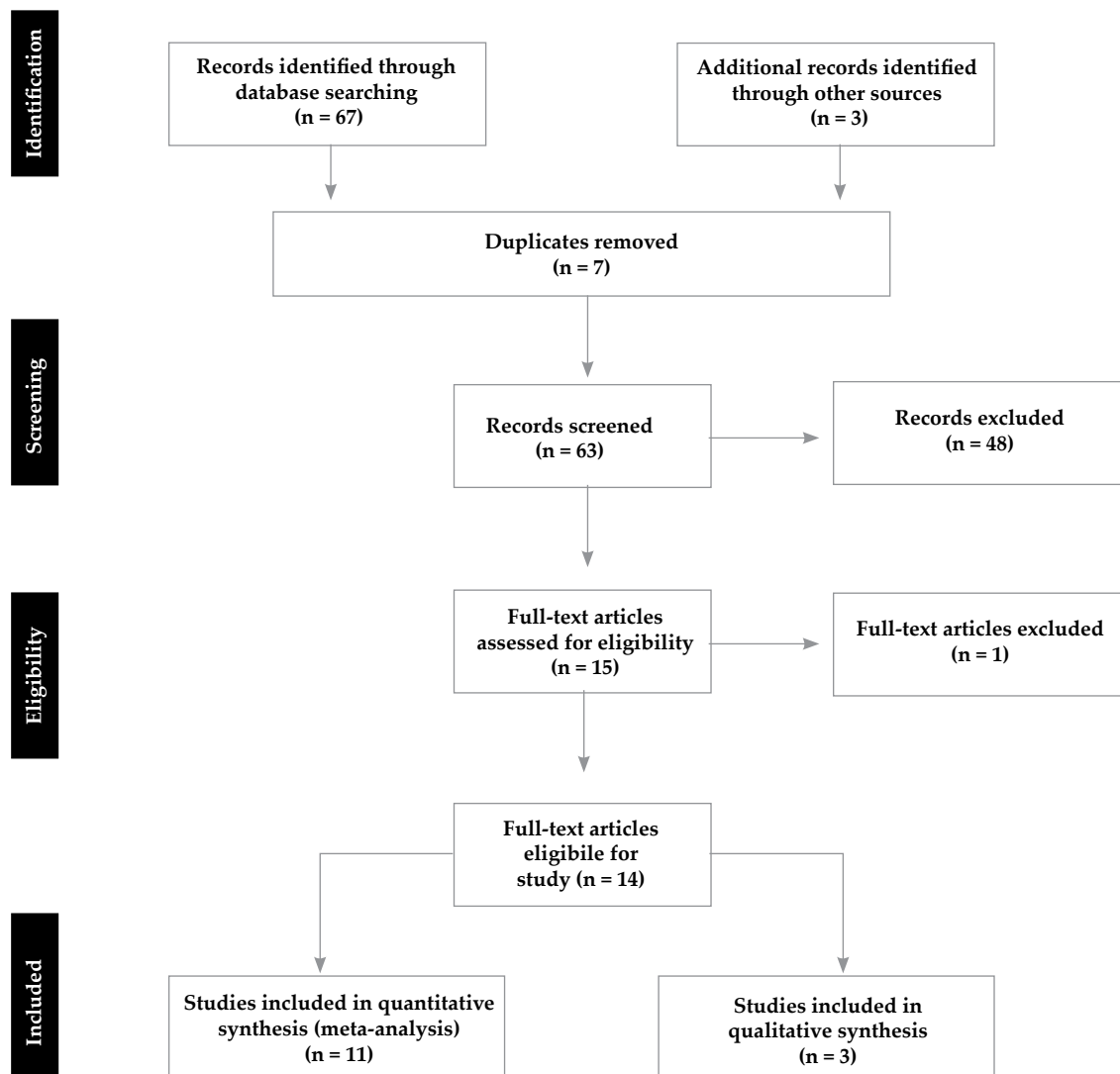


Fig 1: Flow chart of study selection process

population and findings. The primary researcher (AA) extracted the data from the articles and documented the findings. Another researcher (AH) extracted the data independently, and then the two researchers compared their findings with the original articles. The final step involved a review by the other two researchers (WA, PH) for completeness and precision.

To check the quality of the articles, the Critical Appraisal Skill Program (CASP) tool was utilised to critique the articles that included randomised control trials (RCTs), qualitative and cohort studies. The Joanna Briggs Institute (JBI) appraisal tool was utilised for articles on cross-sectional studies and literature reviews^[21]. Both tools were helpful in understanding the weaknesses and strengths of the articles. A table was constructed to present the year of publication

and location of the included articles (Table 2), details of each of the articles (Table 3), and limitations and significance of the articles to the research question (Table 4). A narrative review was also conducted to report the findings of the articles.

The databases generated 70 articles; seven were duplicates, 63 screened and then 49 excluded after reviewing the title and abstract, resulting in 15 articles. After conducting a full-text analysis to examine the relevance of the articles, one was excluded. A total number of 14 articles were included in this review; two publications were RCTs that investigated the physiological effects of patients undergoing different types of weight loss surgeries^[22,23], four articles were cohorts studies, two were retrospective^[24,25] and two were prospective studies^[26,27]. There were two

Table 2: Included articles

Authors	Date of Publication	Journal / Title	Country
Almarri <i>et al</i>	2017	Obesity Surgery/ A call for more research from the Arabian Gulf	Arabian Gulf
Courcoulas <i>et al</i>	2014	JAMA Surgery/ Surgical vs. medical treatment for type 2 diabetes mellitus: A randomised clinical trial	USA
Edward <i>et al</i>	2016	American Journal of Men's Health/ Personal descriptions of life before and after BS from overweight or obese men	Australia
Gautier <i>et al</i>	2012	Obesity Surgery/ Indications and mid-term results of conversion from sleeve gastrectomy to Roux-en-Y gastric bypass	France
Himpens <i>et al</i>	2012	Obesity Surgery/ Long-term results of laparoscopic Roux-en-Y gastric bypass: Evolution after 9 years	Unclear
Ikramuddin <i>et al</i>	2013	JCOM Journal/ Should we bypass meds in favour of surgery? BS for the moderately obese diabetic patient	USA and Taiwan
Jamal and Aminian	2015	Kuwait Medical Journal/ Bariatric surgery: is it a safe treatment modality?	Unclear
Julia <i>et al</i>	2013	Diabetes & Metabolism/ Quality of life after Roux-en-Y gastric bypass and changes in body mass index and obesity-related comorbidities	France
Jumbe, Hamlet and Meyrick	2017	Current Obesity Report/ Psychological aspects of BS as a treatment for obesity	Unclear
Lier <i>et al</i>	2015	Journal of Clinical Nursing/ Patients' daily experiences five years after gastric bypass surgery - A qualitative study	Norway
Mayer and Dwyer	2016	Nutrition Today/ BS or conventional medical therapy? which is best for severely obese adults with type 2 diabetes?	Unclear
Neff <i>et al</i>	2013	Obesity Surgery/ Beyond weight loss: Evaluating the multiple benefits of BS after Roux -en-Y gastric bypass and adjustable gastric band	UK
Ritter, Vetter and Sarwer	2012	Postgraduate Medicine/ Lifestyle modifications and surgical options in the treatment of patients with obesity and type 2 diabetes	USA
Yan, Cohen and Aminian	2017	Surgery for Obesity and Related Diseases/ Re-operative bariatric surgery for treatment of T2DM	Unclear

qualitative research studies: one was a descriptive-exploratory study that examined the psychological effect of BS on six male patients^[13], and the other a phenomenological study that conducted in-depth interviews to understand how excessive weight loss had changed participants' lives^[28]. The included studies were conducted in the United States of America (USA), Taiwan, France, Norway, Australia, and the Arabian Gulf. There were six literature reviews included: five focused on the effect of BS on BGLs in people with diabetes^[8,12,29-31] in which two reviews included the Kuwaiti population^[8,12], and one was a qualitative review that presented the importance of addressing factors that lead to obesity^[15].

LITERATURE REVIEW

The articles revealed two main categories namely, physiological effects and psychological effects of BS. Each category generated sub-categories that represented the outcomes for people with T2DM who had BS.

Physiological effects

Surgical alteration to various parts of the digestive system affected the body in several ways. These changes caused individuals to lose excess weight and reduced levels of comorbidities (e.g. glycaemic levels, low-density lipoprotein (LDL)

levels, systolic blood pressure (SBP) and nutrients). This review focuses on two identified physiological effects: weight loss and BGLs.

Weight loss

The main goal of BS was for obese and morbidly obese people to reduce weight to a level that made it easier for them to achieve good health and reduce complications. Patients who had undergone RYGB after unsuccessful weight loss from LAGB achieved the same outcomes after conversion to RYGB as patients who had primary RYGB surgery^[24,31]. RYGB is considered the most successful method for weight loss with minimal side-effects reporting that participants lost significant weight one year after surgery^[23,24]. The highest percentage of weight loss was in the three months after BS^[26]. However, studies reported that patients regained weight between five to nine years after LAGB, RYGB and SG^[15,25].

Blood glucose levels (BGLs)

Three RCTs reported a change in BGLs of people with T2DM as a primary outcome of BS and found that 25% of their sample had T2DM remission at the end of 12 months post-BS^[22,23,27]. However, studies by Courcoulas *et al* and Gautier *et al* found that participants with T2DM had relapsed and needed oral hypoglycaemic medication to manage their hyperglycaemia^[22,24].

Table 3: Characteristics of included articles

S.No.	Authors	Study Design	Research Aim / Statement	Method	Sample	Outcomes / Findings
1	Almarri F, Alsabah S, Alhaddad E, Vaz, J.D.	Literature review	To examine all studies published on BS in the Arabian Gulf and evaluate quality, quantity and impact	unclear	Original papers, systematic reviews and case report was done in: Kuwait, KSA, Qatar, UAE vs. USA and Australia	<ul style="list-style-type: none"> No publications before 2000, sharp increase of publication 2012 onwards Majority of publication in clinical outcomes of weight loss procedures (47%), studies on anaesthesia during bariatric procedure (14%) Retrospective (54.4%, majority @ Alammiri hospital by Dr Salman Alsabah), 31% on sleeve gastrectomy (popular at that time), 75% in Obesity Surgery Journal Articles from Kuwait (44), Bahrain and Qatar (6), UAE and KSA (19). Studies on pre-op surgery, effects of surgery on obesity-related comorbidities, long-term survival benefits of surgical weight loss Only 3% from Arabian Gulf vs. 30% worldwide are RCT Kuwaiti adolescent population has the highest prevalence of obesity (male 34.8%, female 20.6%) RYGB showed most significant weight loss and HbA1c at the end of 12 months, then LAGB. No significance in LWLI group. T2DM remission observed in 27-50% in RYGB, 23-25% in LAGB. Reduction in antidiabetic meds in all groups, especially in RYGB and LAGB. Anti-hypertensive meds were reduced in all groups Only three severe side effects reported (RYGB - 1 Ulcer, LAGB - 2 dehydration.) Telephone interviews may contribute to willingness of participants and the authentic of their experiences fully Improved medium and long-term outcomes for men who require BS Need more information targeted for men who are deciding to undergo BS Readily accessible information of life experiences of other men who had BS may be preferred by men Internet-based healthcare information may offer a private first step for males considering weight loss surgery Improvements significant after conversion to RYGB and had similar outcomes as primary RYGB patients
2	Courcoulas A, Goodpaster B, Eagleton J, Belle S, Kalarchian M, Lang W, Toledo F, Jakicic J, Edward KL, Hii MW, Giandinoto JA, Hennessy J, Thompson L.	Quantitative, RCT	Feasibility of RCT and compare outcomes of BS (RYGB and LAGB) and structured weight loss program	12 months, three arm RCT at a single centre	69 (adults 25-55 years) with BMI 30-40 kg/m ²	
3	Gautier T, Sarcher T, Contival N, Roux Y, Alves A.	Qualitative, descriptive exploratory	<ul style="list-style-type: none"> Explore descriptions from male bariatric patients before and after surgery - adaptation to a new lifestyle, boundaries post-surgery • Illuminate potential barriers to seeking consultation for BS 	<ul style="list-style-type: none"> In-depth semi-structured interviews • Data collected and analysed between May and October 2016 • Recruited via advertisement flyer 	<ul style="list-style-type: none"> Morbidly obese or obese male who had undergone BS • Ages 27-69 years 	
4	Himpens J, Verburghe A, Cadere CB, Everaerts W, Greve JW.	Quantitative, cohort, retrospective data	To evaluate long-term results of LRYGB	Conversion from SG to RYGB (October 2006 to July 2011)	18 patients (BMI > 50 kg/m ²) with one or more comorbidities	
5		Quantitative, cohort, retrospective data		measured reflux, sleep apnoea, BMI, SBP and diabetes	Participants aged 24-55 years old	
				Retrospective data from (2001 - 2002) and analysed in 2011	77 patients (including 18 with the previous BS)	
					No post-op mortality	<ul style="list-style-type: none"> BMI lost (52±29%) • 27% developed new onset diabetes • 4 hospitalised due to hypoglycaemia • 2 underwent reversal of BS due to metabolism problems • QoL was fair in all

- 6 Ikrumuddin S, Komer J, Lee W, Block J, Jay M, Hwang U, Vijayaraghavan M, Lewis K, Hung W
- Quantitative, RCT
- To determine if RYGB is better than medical management to improve diabetes, dyslipidaemia and hypertension in patients with BMI 30-39.9 kg/m²
- RCT - 2008-2011 - 3 centres in USA and one centre in Taiwan
 - RYGB vs. medical therapy
 - RYGB-discontinue meds after surgery
 - Medical therapy group - meds titrated to have HbA1c < 7%, LDL < 100mg/dL, SBP < 130 mmHg
 - Both groups received intensive lifestyle modification intervention (counselling and meetings included)
 - At least 325 minutes of physical activity per week.
- Review of the current literature concerning BS and its complications and safety
- 7 Jamal M, Aminian A.
- Literature review
- Discuss the types of bariatric surgeries and their safety and complications
- 120 participants randomised (block randomisation)
 - 60 RYGB and 60 medical therapy
 - T2DM with HbA1c > 8.0% (at least 6 months)
 - BMI 30-39.9 kg/m²
 - Free from psych disease, cardiovascular disease, malignant disease and no prior gastrointestinal surgeries.
- Papers on bariatric surgeries in Kuwait
- LAGB is the safest and least invasive bariatric procedure, non-threatening complications
 - LSG relatively simple and safe with reasonably low complication rates in very high-risk patients
 - LQP is after LSG with even lesser complications due to no gastric resection involved, post 24 months average of 3.7% reoperate. Absence of durability of weight loss from LQP
 - RYGP most common, beneficial effects on weight and co-morbidities especially T2DM and GERD
 - BPD high incidence of marginal ulcers at gastro-ileal anastomosis and gallstone
 - BPD-DS is the modified version of BPD at the gastric portion of operation that shows excellent and durable weight loss but technically difficult, higher perioperative and late complications and nutritional deficits
 - In BPD-DS, lifetime follow up and supplements are essential to maintaining good health.
 - Most significant data were measured at three months post-surgery.
 - Remission of DM in 41%, dyslipidaemia in 85%, hypertension in 52% and sleep apnoea in 78%
 - PSC significantly higher in female over time?!
 - PSC independent of change in BMI
 - MSC not significant
- 8 Julia C, Ciangura C, Capuron L, Bouillot J, Basdevant A, Poitou C, Oppert J
- Quantitative, cohort, prospective data
- To investigate early and midterm changes in QoL after RYGB and their relationship to BMI, DM, HTN and increased LDL
- QoL questionnaires (French version) with two dimensions: physical and mental QoL, taken at 3, 6, and 12-month post-op.
 - Hospital admissions for RYGB (March 2007- October 2009) excluded patients with previous BS
 - 80% women with mean age 42.1 ± 11.2
 - 124 (53 excluded - incomplete data), (57 of 71 included are female)
- Dropouts (3 in each group lost in follow-up), 1 had RYGB, 2 refused surgical intervention, no deaths
- No significant changes between groups in LDL and SBP
- RYGB achieved better HbA1c and BMI results (diabetes remission)
- RYGB have nutritional deficiencies (iron and vit B)
- 22 RYGB advert reactions, 15 in medical therapy
- Cost to have RYGB is high

- | | | | | | | |
|----|---------------------------------------|-------------------|---|--|---|--|
| 9 | Jumbe S,
Hamlet C,
Meyrick J. | Literature review | <ul style="list-style-type: none"> • Discuss the literature behind the psychological impact of BS • Explore whether the procedure addresses the underlying condition that can lead to morbid obesity • Effect on eating behaviour post-op. | unclear | unclear | <ul style="list-style-type: none"> • Psychological problems linked to disordered relationship with food • Need to identify risk group among BS patient who might need additional support • Lack of post-BS psychological follow-up despite the undisputed leading intervention in weight loss • Psychological problems linked to physiological changes (body image, mood, concerns, stress, substance use and weight regain) |
| 10 | Lier HØ,
Aastrom S,
Rørtveit K. | Qualitative | <ul style="list-style-type: none"> • Qualitative method using content analysis • Guided semi-structured in-depth interview audio-taped (60-90 minutes) • Asked via telephone to participate | <ul style="list-style-type: none"> • 11 patients, 10 accepted to participant (3 men, four women) • Ages 39-57 years old • Participants had LGBP (gastric bypass) in 2008 and 2009 | <ul style="list-style-type: none"> • Body image has an impact on patients' emotional well-being after excessive weight loss that can be challenging in close relationships • Hanging skin is problematic, effects everything from sexual attractiveness to everyday wardrobe dilemmas, clothing becomes a focal that protects dignity, hides embarrassing bodily issue • Long-lasting difficulties in eating habits (dumping - food doesn't stay in body) • Improved self-esteem, weight closer to societal norm convinces other that one has self-control • Fear of regaining weight • Feeling attractive changes from look good dressed to looking bad naked • Patients are mainly satisfied with their lives • Study can serve as basis or knowledge for patients (patient education) and awareness for people wanting to have BS (both helps in increasing quality of treatment and care) | |
| 11 | Mayer J,
Dwyer J. | Literature review | <ul style="list-style-type: none"> • Explores the risks and benefits of conventional therapies and Roux-en-y gastric bypass in morbidly obese adults. | unclear | <ul style="list-style-type: none"> • Morbid obese T2DM treated conventionally (diet, meds and lifestyle) vs. BS (Sleeve Gastrectomy vs. gastric bypass) • RYGB most effective for T2DM and maintaining weight loss and least malabsorption and side effect. • RYGB effective in T2DM remission due to alteration in anatomy • SG causes oesophageal reflux and weight regain • RYGB vs. SG = RYGB 80% recovery from DM and if DM gain only single drug or diet needed, weight is maintained, lipoprotein levels and systolic blood pressure and albuminuria reached normal within one year vs. conventional • RYGB unclear on diabetic neuropathy (mild vs. severe) • Long life supplement needed for RYGB vs. conventional treatment (costly) • Dumping syndrome reduced at 15-18 months post op in RYGB • QoL in RYGB is better than in conventional treatment • BS expensive as treatment pre-and post op, body contouring costs in the future | |

12	Neff K, Chuah L, Aashiem E, Jackson S, Dubb S, Radhakrishnan S, Sood A, Olbers T, Godsland I, Miras A, Roux C.	Quantitative, cohort, prospective data	<ul style="list-style-type: none"> To evaluate the outcomes after RYGB and LAGB using modified King's Obesity Staging System before and 12 months after surgery. To assess the impact of treatment on multiple patient outcomes after RYGB and LAGB To evaluate the effects on respiratory functions after RYGB and LAGB To emphasise a modified King's obesity staging system with high clinical utility <p>Review on current practices in the treatment of obesity as it specifically pertains to the management of T2DM</p>	<ul style="list-style-type: none"> Assessing obesity-related comorbidities via modified King's Obesity Staging system including BMI and glycaemic markers assessed by clinicians pre-op. and 12 months postop. Chi-square test McNemar-Bowker test Statistics via PASW and STATA 8.0 	<ul style="list-style-type: none"> 217 consecutive patients (RYGB 148, LAGB 69) - non-randomised Majority is female LAGB younger and healthier than RYGB 	<ul style="list-style-type: none"> RYGB is more effective than LAGB in DM remission and BMI RYGB and LAGB are equally effective in most domains LAGB was not significant in gonadal, economic and image domains Recommendations for further studies to include more domains like hypertension, neurological disease, kidney disease, medication and gastro-oesophageal reflux. Need for further research with a bigger sample was implied.
13	Ritter S, Vetter M, Sarwer D.	Literature review	<ul style="list-style-type: none"> To summarise the evidence and determine whether revisional surgery can have a positive impact on metabolic diseases that were not reversed by initial BS 	unclear	unclear	<ul style="list-style-type: none"> BS is an option for obese people with uncontrolled T2DM DM remission also relies on lifestyle modification after surgery.
14	Yan J, Cohen R, Aminian A.	Literature review	<ul style="list-style-type: none"> To summarise the evidence and determine whether revisional surgery can have a positive impact on metabolic diseases that were not reversed by initial BS 	unclear	30 studies	<ul style="list-style-type: none"> Revisions induced 20–80% additional excess weight loss, or further decrease of body mass index by 10–30% Conversion to Roux-en-Y gastric bypass (RYGB) yielded improvement of diabetes in 79%, 72%, and 62% of patients who previously had VBG, AGB or SG, respectively Converting AGB to SG improved diabetes in 65% of patients, and SG to duodenal switch improved diabetes in 79% of patients Revision of the gastric pouch or stoma in RYGB yielded improvement of diabetes in 79% of patients

BS: bariatric surgery; RCT: randomised control trials; RYGB: roux-en-y gastric bypass; LAGB: laparoscopic adjustable gastric band; BMI: body mass index; HbA1C: glycosylated haemoglobin; T2DM: type 2 diabetes mellitus; SG: sleeve gastrectomy; SBP: systolic blood pressure; HTN: hypertension; LDL: low-density lipoprotein; LSG: laparoscopic gastric plication; GERD: gastroesophageal reflux; BPD: biliopancreatic diversion; LGBP: laparoscopic gastric bypass; VBG: vertical banded gastroplasty; AGB: adjustable gastric banding

Table 4: Limitations of included articles

Authors	Limitations
Almarri <i>et al</i> (2017)	<ul style="list-style-type: none"> • High quality studies less cited than other due to a factor of time. • Failure to reveal contribution in development of BS and metabolic surgery over the past 60 years • Bahrain was not included in search strategy, although it is one of the GCC • Lack of quantitative studies included
Courcoulas <i>et al</i> (2014)	<ul style="list-style-type: none"> • Small sample size, single centre • Drop-outs due to randomizations? • Long-term effects need to be studied • Longer, and bigger sample size need to be studied to have generalised findings
Edward <i>et al</i> (2015)	<ul style="list-style-type: none"> • Culture of the men interviewed, all white, homogeneous sample • Types of BS and the severity (How long before going back to almost normal) • Keywords like 'Life' and 'information' were not included in the search strategy • Time of interview after surgery was not mentioned
Gautier <i>et al</i> (2012)	<ul style="list-style-type: none"> • No limitations mentioned. • Unclear in diabetes parameter and improvement measurements • Period of data collection after surgery was not clear • Type of analysis was not stated • No implications or recommendations made
Himpens <i>et al</i> (2012)	<ul style="list-style-type: none"> • Subjective data with telephone interviews regarding weight and diabetes [majority of patients] • Location of cohort, country not mentioned or sample population
Ikramuddin <i>et al.</i> (2013)	<ul style="list-style-type: none"> • BMI >40 was not included • LDL and SBP were close to normal at the beginning of intervention for both groups • Small sample can't be generalised • Results in physical activity was not found in the outcome.
Jamal and Aminian (2015)	<ul style="list-style-type: none"> • Safety of RTGB not mentioned • LGP durability in weight loss (not mentioned) • No research to compare data with from bariatric surgeries in Kuwait (lack of data -complications, mortality) • Sample size of 44 only in bariatric surgeries that the author yielded data from (unpublished study or not referenced) • Mortality has decreased significantly in comparison to BS 20 years ago • Databases reported 4% complication rate • Possible overestimation of medical approach benefit and surgical approach risk
Julia <i>et al</i> (2013)	<ul style="list-style-type: none"> • Authors reported significant (higher) change in female PSC (due to 80% women participants) - not accurate • Remission of T2DM - Study follow-up period might not be enough to diagnose remission. • Male population data was not mentioned (considered as insignificant)
Jumbe, Hamlet and Meyrick, J. (2017)	<ul style="list-style-type: none"> • Psychological research relies heavily on self-report quantitative data
Lier, Aastrom and Rørtveit (2016)	<ul style="list-style-type: none"> • Possible loss of meaning in translation (from Norwegian to English) • Sample had similar background/culture
Mayer and Dwyer (2016)	<ul style="list-style-type: none"> • The review did not include the timeframe of papers collected • The review did not clearly state the inclusion criteria of their papers
Neff <i>et al</i> (2013)	<ul style="list-style-type: none"> • Age group not specified • Inclusion criteria not clearly stated. • LAGB were healthier than RYGB pre-op. • Not equal number between genders in the groups • Location of the cohort was not mentioned • No reports of dropouts in the whole period. • No reports of complications post-op.
Ritter, Vetter and Sarwer (2012)	<ul style="list-style-type: none"> • Time frame was not mentioned • Number of articles included was not clear.
Yan, Cohen and Aminian (2017)	<ul style="list-style-type: none"> • Time frame was not clear • Inclusion criteria of articles was between 1 and 5 years after BS, which presented several variables.

Long term effects of BS included reoccurrence of T2DM being diagnosed nine years after BS^[25], and that T2DM remission relied on lifestyle changes after BS^[30]. A qualitative study reported that patients still found challenges adjusting to their new diet five years after BS and suggested providing patient education before BS to help deal with the undesired outcomes that may arise after surgery^[28]. Literature reviews from the Middle-Eastern and Western countries supported weight loss surgery as a new treatment for T2DM^[8,12,15,29]. However, lifestyle modification and bariatric education were reported as being essential to maintaining positive outcomes^[13,28,30]. Apart from diabetes, improvements in SBP, LDL, sleep apnoea, gastroesophageal reflux and dumping syndrome were reduced 15 - 18 months post surgery. Conversely, absorption was affected adversely, which lead to micronutrient deficiency (e.g. iron and vitamin B)^[23,24,26,29].

Psychological effects

As a consequence of rapid weight loss, psychological aspects such as level of confidence and stigma on patients may have been affected. Studies found boosts in the confidence of bariatric individuals as well as the removal of stigmatisation linked with their obesity^[13,15]. These impacts affected the bariatric population's daily routine and gave them new experiences, such as participating in outdoor activities and socializing^[15,28]. This review focused on two psychological effects of BS on individuals with T2DM: quality of life (QoL) and psychological support.

Quality of Life (QoL)

Positive changes in the patients' quality of life were mentioned among people who had BS; this included increased physical activities, removal of stigmatisation and boosts in confidence levels^[13,15,29]. In contrast, some individuals who had BS found it hard to adjust to their new eating habits and changes in their digestion^[28].

Psychological Support

The importance of having support both professionally and personally was reported in two studies^[15,28]. The significance of counselling and addressing the reasons behind bariatric people's obesity may be an essential factor in preventing obesity and maintaining weight loss for a longer period in people after BS^[15].

The articles in this review focused on BS carried out in countries that were reported to have a high prevalence of obesity, which included Kuwait. The significance and limitations in these articles were examined; for example, AlMarri *et al* failed to mention whether qualitative studies were included in their

literature search^[8]. Similarly, a review conducted by Jamal and Aminian on published BS articles in Kuwait also failed to mention the timeframe of the collected data and the lack of reporting the inclusion of qualitative studies or mixed methods^[12]. Despite these limitations, a clear description of the safety and effectiveness between the different types of bariatric surgery and their findings would be considered as justification for the preferable BS in Kuwait^[8,12]. The recommendations from two studies that included Kuwait suggest a regional guideline in BS to provide standard care in the Arabian gulf countries^[8,32]. Conducting qualitative research is essential to gain deep understanding of the experiences that people with T2DM in Kuwait have gone through after BS.

A couple of RCT in the bariatric field was conducted, both significant despite the sample size due to the difficulty of accessing participants for this type of surgery^[22,23]. A cohort study by Courcoulas *et al* reported findings from 69 participants, which is considered a small sample size for this type of study, but due to the absence of sample drop-outs, the generalisability and transferability of this study may be a limitation^[22]. Another RCT by Ikramuddin *et al* recruited 120 participants from three different centres (two in USA and one in Taiwan) where the intervention group and control group had close to normal levels of blood glucose at the beginning of the study, so changes in them were not substantial, therefore, not reflective of the bariatric population in Arabian Gulf countries^[23].

Two quantitative literature review articles were included in this paper^[27,29]. A literature review on BS versus conventional medical therapy for T2DM showed significant findings including T2DM remission due to the surgical changes in anatomy and not weight loss^[29]. Mayer and Dwyer found that people who had BS achieved healthy reductions in comorbidities within one year of surgery compared to the unachieved levels in the conventional therapy group^[29]. People who choose RYGB instead of LAGB had favourable levels in weight loss, diabetes, hypertension, gonadal, economic and body image, but the inclusion criteria and settings were unclear, and no dropouts were mentioned in the study^[27].

Three qualitative articles were examined in this review^[13,15,28]. Edward *et al* conducted a qualitative study by collecting data via telephone, which provided participants with more freedom to express their feelings and describe their experiences^[13]. Nevertheless, the sample was homogeneous (privileged male) and the timeframe was not mentioned, which could affect the experiences that the participants were going through at the time^[13]. The study findings by Lier, Aastrom, and Rørtveit's corresponds with Jumbe, Hamlet and Meyrick findings that highlighted the importance

of conducting further research in the qualitative paradigm to understand the outcomes of BS on individuals physically and mentally^[15,28]. However, a limitation was identified by Jumble, Hamlet and Meyrick in obtaining data that relied on patients' self-reported quantitative data^[15].

Significant outcomes were found in the included articles such as: patient education is needed for BS people, highlighting that T2DM remission can only be achieved if changes in daily living habits are made^[30]. The only long-term study that was found in the selection process was a nine-year study that followed 77 patients, which revealed that reoccurring T2DM in 27% of the sample population, and two individuals reversed their BS due to metabolism complications^[25]. However, it also stated a possible limitation was that participants could have provided incorrect weight and glycaemic levels^[25]. A study by O'Brien *et al* supports these findings in their 15-year follow up study that showed maintained weight-loss until the time of follow up^[33], which contradicts the findings of Himpens *et al* that reported weight gain within eight years of undergoing BS^[25]. Approximately 25 - 50% of T2DM remission was reported after five years in other studies^[24,25,29,30,33,34]. A review by Yan, Cohen and Aminian revealed that although RYGB was successful in improving glycaemic levels in people with T2DM, 20 - 30% of people with T2DM that have undergone BS surgery have reported poor glycaemic management^[31].

Although bariatric surgery appears to have promising results on weight and comorbidities leading to increased quality of life, the literature suggests that living a long and healthy life after BS is possible through lifestyle change and patient education. To accomplish this would require clinicians to be aware of the physiological and psychological impact of BS on individuals, as well as involving policy-makers to improve the care needed by the bariatric population.

The evidence behind BS as an alternative intervention for the treatment of T2DM has been explored in this review. The strengths of this review lie in the synthesis of both qualitative and quantitative data. Notable gaps in knowledge have been highlighted, particularly in qualitative research in Kuwait. However, limitations were evident in each article, such as timeframe of data collected or small sample size. Although this review included several literature reviews on BS and T2DM, the literature combined identified a gap in knowledge when dealing with the bariatric population in the Arabian Gulf countries.

CONCLUSION

Bariatric surgery has been shown to have promising results on body mass index and co-

morbidities especially in regard to type 2 diabetes mellitus, hence, leading to increased quality of life. Lifestyle modification and patient education are necessary to maintain a healthy life for people who have undergone BS. Furthermore, it is essential to address the psychological well-being of people who have had BS in Kuwait. However, professional psychological support has been avoided by Kuwaiti individuals due to the effect of cultural stigmatisation, thereby acting as a barrier between the healthcare team and the bariatric population. The lack of knowledge on the effects of BS on the psychological aspects of people in Kuwait needs to be explored further, particularly from a qualitative research perspective. Having a greater understanding of individual patient experiences could improve the overall quality of life for all patients who undergo bariatric surgery, as well as contribute to higher quality care provision.

ACKNOWLEDGMENTS

The authors would like to thank Sara Ellias and SDU Team at JAAFH for helping with the distribution of information sheet at the Surgical and Bariatric Clinics. This work was supported by the Civil Services Commission in Kuwait via RHD at Flinders University.

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Original Article

A 45 bp Insertion/Deletion Polymorphism of the Human Uncoupling Protein 2 Gene is associated with Central Obesity in a population from Turkey

Mehmet Ali Sozen¹, Dilek Bayrak², Selman Yaman², Burcu Sarikulak², Abdurrahim Kavaklılar², Betül Gurbuz²

¹Department of Medical Biology, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar, Turkey

²School of Medicine, Afyon Kocatepe University, Afyonkarahisar, 03200, Turkey

Kuwait Medical Journal 2018; 50 (4): 399 - 405

ABSTRACT

Objective: To investigate whether there is an association between the 45bp insertion/deletion polymorphism in the uncoupling protein 2 (UCP2) gene, and obesity and/or obesity-related phenotypes

Design: A prospective analytical case control survey

Setting: Afyon Kocatepe University Medical Faculty and Afyonkarahisar State Hospital, Turkey

Subjects: A total of 138 obese cases and 75 non-obese controls from Western population of Turkey were included in this study.

Interventions: Anthropometric data were obtained by measurements of weight, height and circumferences of waist; and hip and body mass index and waist-hip ratio (WHR) were calculated. DNA was isolated from peripheral blood and statistical analysis was conducted using the SPSS programme (version 17.0). The genotypes for the UCP 45 bp ins/del

polymorphism were identified by polymerase chain reaction.

Main outcome measures: The relationship between the 45bp insertion/deletion polymorphism in the UCP2 gene and obesity and/or obesity related phenotypes

Results: No significant difference was detected between obese cases and non-obese controls regarding genotype distribution and allele frequencies. However, the WHRs from phenotypes among obese cases having Del/Del and Ins/Del genotypes were found to be respectively higher (0.87 +/- 0.09 and 0.90 +/- 0.10) than in the ones having Ins/Ins genotypes (0.81 +/- 0.13) ($p < 0.05$).

Conclusions: This is the first study supporting the role of the 45 bp insertion/deletion polymorphism in obesity in Turkey. Further studies with larger sample sizes may confirm these findings.

KEY WORDS: Association study, gene variant, genetic analysis, metabolic disease, waist-to-hip ratio

INTRODUCTION

Obesity, an important public health issue with its increasing prevalence, is a risk factor for many disorders including cardiovascular diseases and type 2 diabetes^[1]. Besides some rare monogenic forms, obesity is usually inherited in the polygenic, multifactorial mode of inheritance and characterized by a positive energy balance, and an increase in the ratio of body fat. It is generally measured by body mass index (BMI)^[2].

So far, many candidate genes involved in the genetics of obesity have been studied in different

populations^[2]. One of them is the uncoupling protein 2 (UCP2) gene, whose product is a member of the transmembrane carrier protein family and is involved in energy homeostasis, thermogenesis and body weight regulation^[3]. UCP2 gene is localized on chromosome 11 (7q13) and the 45-bp ins/del polymorphism studied is located in the 8th exon at 3' untranslated region. Its association with obesity and relevant phenotypes have been shown, although some controversial results were observed in different reports.

Among them, a study carried out in Pima Indians

Address correspondence to:

Dr. Mehmet Ali Sozen, Department of Medical Biology, Faculty of Medicine, Afyon Kocatepe University, Ali Çetinkaya Kampusu, Afyonkarahisar, 03200, Turkey. Tel: +90 272 246 3301; Fax: +90 272 246 3300; E-mail: masozen@hotmail.com

showed an association between UCP2 variants and metabolic rate during sleep^[4]. In another study in the Pima Indian population, the UCP2 gene polymorphisms were reported to be associated with 24-hour energy expenditure^[5]. Yanovski *et al*^[6] reported that the UCP2 gene exon eight 45 bp ins/del polymorphism, particularly the insertion allele, was found to be associated with childhood-onset obesity; in particular, some obesity phenotypes such as BMI, body circumferences and skinfold thicknesses. One of two studies carried out in a Spanish population showed a higher risk of developing obesity in individuals carrying the exon-8 insertion allele in the UCP2 gene, independent of sex, age, physical activity, and sedentary lifestyle^[7]; and in another report, a haplotype including UCP2 del45bp allele was found to be associated with obesity and insulin resistance^[8]. In a report from Japan, a positive correlation was found between the UCP2 gene exon eight 45 bp ins/del polymorphism and BMI changes^[9]. Additionally, in a study in a Korean population, the 45-bp ins/del polymorphism was not found to be associated with risk of metabolic syndrome (MeS), but was observed to be associated with BMI and waist circumference^[10-11]. In addition, a report from Denmark showed the minor allele (del allele) of the same UCP2 45bp ins/del polymorphism (rs1800795) was found to be associated with increased BMI, increased abdominal obesity, and increased hip circumference, as well as UCP2 -866G>A (rs6593669) being associated with borderline increased fat BMI^[12]. Similarly, the same 45-bp ins/del variant in the UCP2 gene was found to be associated with MeS in the Iranian population^[13], while it was observed to be associated with overall adiposity, particularly in women, from Malaysia^[14]. The only study carried out in Turkey also showed an association between this polymorphism and childhood obesity and related metabolic disorders^[15]. However, no associations were reported between the 45-bp ins/del variant in the UCP2 gene and obesity in some other populations from Denmark, Italy, Greece and China respectively^[16-19].

The prevalence of obesity in adults in Turkey has substantially increased over the past 20 years. The overall prevalence of obesity in adults was 18.6% in the year 1990. Ten years later in 2000, the prevalence was 21.9%, and it increased to 36% in 2010 (44% among women and 27% among men). In addition, according to the WHO report, the overall prevalence rate of obesity calculated on the basis of the BMI value in adults was 41.6%^[20-22].

The aim of this study was to investigate further involvement of the human UCP2 gene 45-bp ins/del polymorphism in obesity and obesity related phenotypes in an adult population of Turkey. For this case control study, a polymerase chain reaction (PCR)

and gel electrophoresis analysis was carried out for the 45-bp ins/del polymorphism of the UCP2 gene in order to determine whether or not the variant of the UCP2 gene participates in the development of obesity in a population of Turkey.

SUBJECTS AND METHODS

Subjects

A total of 138 patients (68 women and 70 men) whose BMI values are 30 and above (obese group) and 75 controls (28 women and 47 men) whose BMI values are between 18 and 25 were included in this study from a population of Western Turkey. All anthropometric measurements were carried out in the Physiology lab in the Faculty of Medicine at Afyon Kocatepe University. The subjects having type 2 diabetes, Cushing syndrome, hypo and hyperthyroidism, and pregnant women were excluded from the study.

Anthropometric measurements

Body composition parameters were determined by the bioelectrical impedance analysis (BIA) system (Bodystat 1500, Bodystat Ltd., Douglas, Isle of Man, UK). The basic premise of the BIA procedure is that the volume of fat-free tissue in the body will be proportional to the electrical conductivity of the body^[23]. Some precautions were taken before the measurements. The participants were instructed to avoid eating or drinking within 4 hours, using diuretics within 7 days, participating in strenuous exercise for 24 hours, and consuming alcohol for 48 hours prior to the test procedure^[23]. The data were analyzed using the manufacturer's software, and body fat percentage, total body fat, lean body mass, body water percentage, total body water and dry lean weight were determined for each subject. BMI was calculated as body weight divided by the square of the height (kg/m²).

Circumference measurements were taken with a 7 mm wide tape measure while subjects were standing in a straight but relaxed position. The tape measure was held parallel to the ground and completely surrounded the part of the body but did not compress the subcutaneous fat tissue. Duplicate measurements were taken at each site, and retests were made if the duplicate measurements were not within 7 mm^[23]. The waist and hip sites were used for circumference measurements. The waist/hip ratio (WHR), which reflects central obesity, was also calculated.

Genotyping

For PCR amplification, genomic DNA's were used as a template, extracted using the NucleoSpin (Macherey-Nagel) genomic DNA isolation kit. The primers for PCR were as follows: F: 5'- CAGTGAGGGAAGTGGGAGG - 3' and R: 5'- GGGGCAGGACGAAGATTC - 3'^[15]. The

Table 1: The UCP2 gene 45-bp ins/del polymorphism genotype distribution and allele frequencies in obese cases versus population-matched non-obese controls in a population from Turkey

Groups	n	Genotype*			χ^2	p-value	Allele*		p-value
		DD (Del/Del)	ID (Ins/Del)	II (Ins/Ins)			D (Del)	I (Ins)	
Controls	75	43 (0.573)	26 (0.346)	6 (0.08)			110 (0.743)	38 (0.256)	
Obese cases	138	86 (0.623)	45 (0.326)	7 (0.05)	0.944	0.64**	217 (0.786)	59 (0.213)	0.34***

*Genotype and allele data are presented as counts and frequency

**Genotype p-values were calculated by χ^2 (2 df)

Allele frequency p-values were calculated by Fisher's exact test, 2-tailed. P-values <0.05 were accepted as significantly higher than controls.

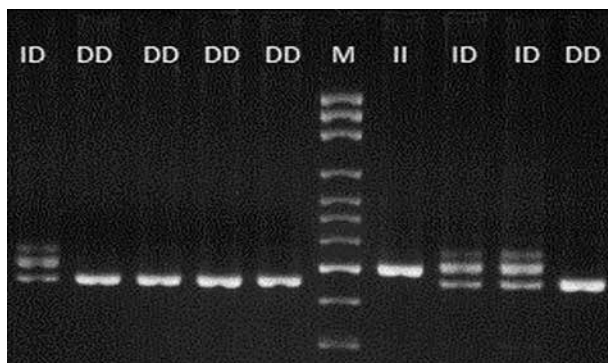


Fig 1: PCR detection of the UCP2 gene 45-bp ins/del polymorphism by an agarose gel electrophoresis (2%) followed by ethidium bromide staining and UV transillumination was performed to visualize and genotype the PCR products together with 100 base pair (bp) DNA marker (Axygen Biosciences). The expected product sizes are: homozygotes (D/D or I/I) having either 457 or 502 bp bands respectively; heterozygotes (D/I) having both 457 bp and 502 bp bands. DD: Deletion/Deletion genotype (lanes 2, 3, 4, 5, 10), II: Insertion/Insertion genotype (lane 7), ID: Insertion/Deletion genotype (lanes 1, 8, 9), D: Deletion allele, I: Insertion allele, M: Marker or DNA Ladder (lane 6).

PCR products amplified were then electrophoresed in 2% agarose gel, followed by visualization under UV light and genotyped. As can be seen in Fig 1, the ones

having only one band of 457 bp were genotyped as DD (del/del) and 502 bp II (ins/ins), and the ones that have both 457 bp and 502 bp bands were genotyped as DI (del/ins). Afterwards, genotype distributions and allele frequencies were calculated for both obese and non-obese subjects.

Statistical analysis

The obtained results were analyzed statistically using χ^2 and Fisher's exact tests for genotype distributions and allele frequencies respectively, as well as Kruskal Wallis test for average anthropometric measurements such as WHR values to see if there is any significance between the cases and controls. Logistic regression analysis was performed to evaluate if the polymorphism could predict the risk of obesity. Also, a regression analysis for WHR as a quantitative model was carried out to determine the effects of independent variables (gender, age and genotypes) on WHR risk.

Ethics

The study protocol was approved by the Local Ethics Committee at Afyon Kocatepe University

Table 2: Demographic and phenotypic data (anthropometric measurements) of control group according to genotype

Variable	Genotype			p-value**
	Del/Del (n = 43)	Ins/Del (n = 26)	Ins/Ins (n = 6)	
Age	29.857 ± 10.855*	28.115 ± 10.992	31 ± 11.387	0.577
Height	166.619 ± 9.249	167.23 ± 9.114	172 ± 7.979	0.326
Weight	64.19 ± 11.327	63.711 ± 9.589	64.857 ± 7.603	0.812
BMI	23.062 ± 2.457	22.753 ± 2.221	21.885 ± 1.925	0.387
Waist (cm)	75.65 ± 9.1	75.084 ± 7.167	77.357 ± 4.668	0.772
Hip (cm)	93.776 ± 5.354	93.142 ± 5.21	78.5 ± 34.726	0.575
WHR	0.80* ± 0.095	0.8 ± 0.075	0.71 ± 0.317	0.741
Body fat (%)	23.997 ± 7.42	21.573 ± 7.313	22.52 ± 8.907	0.483
Body fat (kg)	15.24 ± 4.872	13.538 ± 4.677	13.72 ± 4.530	0.342
Lean body mass	49.188 ± 10.827	50.057 ± 9.854	48.68 ± 10.054	0.905
Total mass	64.428 ± 10.925	63.596 ± 9.649	62.4 ± 7.469	0.832
Dry lean mass	14.502 ± 4.315	14.607 ± 4.313	15.42 ± 3.518	0.854
Water (%)	53.852 ± 5.472	55.823 ± 6	52.98 ± 7.494	0.401
Water (kg)	36.019 ± 10.669	35.45 ± 6.332	33.26 ± 7.22	0.794

BMI: body mass index; WHR: waist-to-hip ratio

*Phenotypic data are presented as means ± standard deviation

**P-values were calculated using Kruskal-Wallis test and p-values <0.05 between compared groups were regarded as significant statistically.

Table 3: Demographic and phenotypic data (anthropometric measurements) of obese group according to genotype

Variable	Genotype			p-value**
	Del/Del (n = 86)	Ins/Del (n = 45)	Ins/Ins (n = 7)	
Age	42.326 ± 10.491*	41.864 ± 9.816	41.864 ± 9.679	0.933
Height	163.395 ± 9.123	164.400 ± 9.785	158.856 ± 5.113	0.356
Weight	96.151 ± 10.491	96.333 ± 18.916	89.142 ± 10.589	0.483
BMI	36.074 ± 5.344	35.660 ± 6.417	35.314 ± 3.601	0.557
Waist (cm)	100.105 ± 11.323	103.447 ± 14.044	92.657 ± 13.064	0.199
Hip (cm)	113.696 ± 17.121	114.140 ± 13.174	114.214 ± 12.805	0.767
WHR	0.87 ± 0.092	0.90 ± 0.106	0.81 ± 0.131	0.046
Body fat (%)	39.848 ± 9.716	40.375 ± 9.882	38.600 ± 7.327	0.944
Body fat (kg)	38.900 ± 11.759	38.471 ± 12.667	33.450 ± 6.766	0.494
Lean body mass	57.052 ± 13.777	56.314 ± 12.936	53.716 ± 10.568	0.635
Total mass	96.288 ± 13.534	94.785 ± 16.977	87.166 ± 10.088	0.261
Dry lean mass	15.909 ± 4.987	15.907 ± 4.987	15.600 ± 7.077	0.883
Water (%)	43.593 ± 5.900	42.857 ± 6.106	45.350 ± 4.884	0.697
Water (kg)	41.948 ± 7.955	40.389 ± 8.225	40.283 ± 5.915	0.590

BMI: body mass index, WHR: waist-to-hip ratio

*Phenotypic data are presented as means ± standard deviation

**P-values were calculated using Kruskal-Wallis test and p-values <0.05 between compared groups were regarded as significant statistically.

Medical Faculty, in accordance with the Helsinki Declaration. All subjects gave their informed consent.

RESULTS

In order to conduct an association analysis between 45-bp ins/del polymorphism in the UCP2 gene and obesity and obesity related phenotypes, a total of 138 obese and 75 non-obese controls were included in this study. To carry out a case-control survey, we first compared the genotype and allele frequencies for the 45-bp ins/del polymorphism of the UCP2 gene in obese cases versus non-obese controls. The distributions of the 45-bp ins/del genotype for these two groups ($\chi^2 = 0.12$, $p = 0.73$ for obese group and $\chi^2 = 0.52$, $p = 0.47$ for control group) were in Hardy-Weinberg equilibrium. For UCP2 45-bp ins/del polymorphism (Table 1), there was no significant difference in the genotype distribution between obese cases and non-obese controls ($p = 0.64$). Likewise, the allele frequencies were not different among obese cases when compared with controls ($p = 0.34$). However, when some obesity related phenotypes (BMI, waist circumference, hip circumference, percentage fat, etc.) were analyzed in groups in regard to the genotypes (DD, DI and II) the individuals carry, there was no significant difference

in terms of all anthropometric measurements in the non-obese group (Table 2). In addition, it was similar in the obese group for many phenotypic parameters. Interestingly, in the obese group, only mean WHR values were found to be significantly lower in cases with II genotypes who carry only Ins allele (0.81 ± 0.13) than the ones with DD and DI genotypes (0.87 ± 0.09 and 0.90 ± 0.10) who carry Del allele ($p = 0.046$), showing an association between obesity (WHR in particular) and UCP2 45-bp ins/del polymorphism, particularly with Del allele and central obesity in the studied population (Table 3). In addition, Table 4 shows that females were 2.242 times more likely to be obese; and this risk seems 1.136 times more likely to increase as the subjects get older. Also, II genotype-based analysis showed that DD genotype was 2.123, and DI genotype 2.044 times more likely to be obese. When WHR was also used as a quantitative model, and the age, gender and genotype were taken into account as independent variables, it was found that the gender effect on WHR was more prominent than the age, whereas the genotypes had no effect (Table 5). Analysis of variance test was used to validate if the model is working. R square was found as 0.429, showing that gender, age and genotypes altogether accounted for 43% of WHR risk (Table 6).

Table 4: Logistic regression analysis for obesity to assess relative risk

Variable	B	S.E.	Wald	Df	Sig.**	Odds Ratio (95% CI)
Gender*	- 0.807	0.352	5.26	1	0.022	0.446 (0.224, 0.899)
Age	- 0.128	0.019	43.381	1	0.000	0.880 (0.847, 0.914)
DD genotype***	- 0.754	0.689	1.197	1	0.274	0.471 (0.122, 1.816)
ID genotype	- 0.716	0.715	1.004	1	0.316	0.489 (0.120, 1.983)
Constant	4.952	0.984	25.34	1	0.000	141.496

*The male-based analysis was carried out and the relative risk were calculated for females.

**P-values <0.05 between compared groups were regarded as significant statistically.

***The II genotype-based analysis was carried out and the relative risks were calculated for genotypes of DD and II.

Table 5: Regression analysis for WHR as a quantitative model

Variable*	B (Unstandardized)	S.E.	B (standardized)	T	Sig.**	95% CI for B (lower and upper bound)
Constant	0.559	0.031		18.212	0.000	0.498, 0.619
Gender	0.128	0.012	0.553	10.515	0.000	0.104, 0.152
Age	0.003	0.001	0.324	6.150	0.000	0.002, 0.004
Genotype	-0.014	0.010	-0.076	-1.443	0.151	-0.033, 0.005

*Dependent variable: WHR (waist-to-hip ratio)

**P-values <0.05 between compared groups were regarded as statistically significant.

Table 6: ANOVA* table to test the validity of the regression model

Variable	Sum of Squares	df	Mean Square	F	Sig.***
Regression*	1.199	3	0.400	51.913	0.000
Residual	1.593	207	0.008		
Total	2.792	210			

*Dependent variable: WHR

**Predictors: (Constant), Age, Gender, Genotype

***P-values <0.05 between compared groups were regarded as statistically significant.

DISCUSSION

The association of the UCP2 gene 45-bp ins/del polymorphism with obesity has been studied in many populations and conflicting results were obtained. Several studies found no association with obesity^[16-19], while several others found association but with different aspects of obesity. For instance, in a study carried out in the USA, the variant has been associated with the metabolic rate^[4], energy expenditure^[5] in adults, while it was found to be associated with BMI, body circumference measurements and skin folds as well as body fat mass by Yanovski *et al*^[6]. In addition, the variant was found to be associated with BMI changes in Japan^[9], the BMI and waist circumference in Korea and Germany^[10-11], obesity risk in Spain^[7,8], increased BMI, increased abdominal obesity and increased hip circumference^[12], MeS in Iran^[13], as well as overall adiposity but not central obesity (WHR) status in Malaysian women^[14]. Moreover, a report from Turkey found this polymorphism as a risk for childhood obesity and metabolic diseases, while observing an association between central obesity with another UCP2 variant (rs6593669)^[15]. However, in some populations, no association was observed between the UCP2 gene 45-bp ins/del polymorphism and obesity or related phenotypes^[16-19].

A main finding in the current study was the mean WHR values, an indicator of central obesity, in obese cases were found to be lower in individuals having ins/ins genotype than the individuals having DD and ID genotypes ($p = 0.046$). In contrast, in a report from Denmark, the UCP2 Ins45bp allele (minor allele) of the same gene variant (rs1800795) was also associated with increased BMI, increased abdominal obesity, and increased hip circumference as well as another variant of the UCP2, -866G>A (rs6593669),

being associated with borderline increased fat and BMI^[12]. In another two reports from USA, del/ins genotype of the same polymorphism was associated with higher body fat mass in children^[6], while the same genotype (del/ins) and Ins allele was found to be associated with overall adiposity only in women from Malaysia^[14]. In addition, the genotype (Ins/Ins) and Ins allele was also found to be associated with risk of obesity and metabolic syndrome in children from Turkey^[15]. Altogether, this polymorphism is clearly associated with different obesity measures in different populations. Therefore, all these studies confirm that this polymorphism plays a role in obesity in the majority of the populations, although the associated phenotypes are still controversial. This is also true for the relations of the phenotypes with the variants per se. For example, several obesity phenotypes such as waist circumference, central adiposity as well as BMI have been reported to be associated with distinct genotypes of the different UCP2 gene polymorphisms (rs660339 and rs659366)^[15,24-25]. A study even found that a haplotype including rs659366-G in the UCP3 gene was associated with higher WHR^[26], since it is localized to the human genetic locus 11q13 which contains both UCP2 and UCP3 genes, and has been linked to several factors that are believed to be relevant for the regulation of body weight^[27-30]. Therefore, the current report is in agreement with the ones that support the role of UCP2 45bp del/ins polymorphism on overall obesity risk, in particular, the ones that support the role of this polymorphism on central obesity^[6,12,15,24,26]. However, the only difference is that the associations of some obesity phenotypes found in them were either due to different alleles or related to different UCP2 gene variants (rs660339 and rs659366)^[6,12,15,24,26], while in the current study, the WHR phenotype was associated

with the other UCP2 gene variant (rs1800795). This is similar to the report by Kring *et al*^[12], in which the same UCP2 gene variant was also associated with it, despite the allelic difference. They found that the minor allele for UCP2 Ins45bp was associated with increased hip circumference and abdominal obesity as well as increased BMI, although our results showed that the major allele for UCP2 Ins45bp was associated with lower WHR and central obesity. These discrepancies in the studies may be attributed to the differences in the study design, population, sample size, age, race, and the degree of obesity. Nonetheless, while these similar findings support the role of the UCP2 gene in obesity, the details of the exact causative variant and allele with their mechanisms remain to be clarified.

It has been established that WHR is an indication of central obesity (≥ 0.85 in women and ≥ 0.95 in men), and also constituting a risk for many disorders such as cardiovascular system diseases and diabetes. Therefore, these results suggest that the UCP2 gene 45-bp I/D polymorphism, Del allele in particular, might be a risk factor for central obesity in obese cases in the studied population. It also suggests that "Ins/Ins" genotype might be associated with decreased risk of abdominal obesity.

One of the limitations of this study is the relatively small sample size. We recommend further studies with larger sample sizes in order to have a better understanding on the effect of this single nucleotide polymorphism in obesity, as well as identifying the specific contributions of the uncoupling proteins and their DNA sequence variations in the complex response to chronic positive energy balance and recovery processes.

CONCLUSION

This study presents evidence that supports the role of the UCP2 gene 45-bp ins/del polymorphism in obesity. Thus, it is the first report showing its allelic frequency and association with obesity in an adult population of Turkey. These results are very interesting and they can contribute to a substantial improvement for elucidating the genetic factors involving the development of obesity in Turkish population. However, it must be kept in mind that the sample size for this study was small. Therefore, one must be careful to point out that this study will have to be repeated in other centers with larger numbers before the results are accepted as conclusive, and it needs to be confirmed further to reveal its exact role in obesity.

ACKNOWLEDGMENT

This work was supported by Afyon Kocatepe University Scientific Research Projects Commission

grant 11.TIP.09 to M.A.S. We are also thankful to Dr. Ismet Doğan for his contribution to the statistical analyses for this study.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Original Article

Predictors of Prostate Cancer Diagnosis at repeat Prostate Biopsy in patients initially diagnosed with Atypical Small Acinar Proliferation

Cem Yucel, Ozgur Cakmak, Okan Nabi Yalbuздag, Orcun Celik, Mehmet Zeynel Keskin, Zafer Kozacioglu
Department of Urology, Tepecik Training and Research Hospital, Izmir, Turkey

Kuwait Medical Journal 2018; 50 (4): 406 - 409

ABSTRACT

Objective: To determine the predictors of prostate cancer at repeat biopsy in patients initially diagnosed with atypical small acinar proliferation (ASAP)

Design: Retrospective study

Setting: Tepecik Training and Research Hospital, Turkey

Subjects: Among 1240 patients, only 54 patients diagnosed with ASAP on initial biopsy underwent repeat biopsy.

Intervention: Patients were classified into cancer, benign and ASAP groups according to their final pathological results after repeat biopsy.

Main outcome measure: The final pathological results of repeat biopsy were compared according to the clinico-

biological features.

Results: At the repeat 24 core prostate biopsy, the diagnoses were benign prostate, prostate cancer and ASAP in 26/54 (48.2%), 20/54 (37.03%) and 8/54 (14.8%) patients, respectively. In the cancer, ASAP and benign groups, the mean age was 67.2 ± 5.4 , 56.3 ± 6.7 and 61.8 ± 8.5 years, respectively. The cancer detection rate was 37.03%. Except for patient age, we found no clinical or pathological features predicting prostate cancer in patients with ASAP at repeat biopsy.

Conclusion: Only the age of the patients is a predictive factor of prostate cancer at repeat biopsy in patients diagnosed with ASAP.

KEY WORDS: acinar proliferation, biopsy, prostate

INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men worldwide^[1]. PCa is usually suspected on the basis of an abnormal digital rectal examination (DRE) and/or elevated prostate specific antigen (PSA) levels. The definitive diagnosis of prostate cancer depends on the histopathological confirmation of adenocarcinoma in prostate biopsy^[2]. In some biopsy specimens, there are foci of small acinar structures that are highly suggestive of malignancy, but insufficient histological atypia required for the accurate diagnosis of adenocarcinoma, and hence, these structures are defined as atypical small acinar proliferation (ASAP)^[3]. ASAP is observed in approximately 5% of prostate biopsies^[4,5]. Patients with ASAP have a 40% risk of developing PCa in subsequent biopsies^[6]. The literature recommends that all patients with an initial diagnosis of ASAP should undergo a repeat biopsy within 3–6 months^[7]. Many researchers claim that ASAP is a condition in

which the pathologist has insufficient tissue for the definitive diagnosis of PCa^[8]. If inadequate tissue sampling were a prohibitive factor for the definitive diagnosis of PCa, an extended or saturation biopsy scheme should be used for repeat biopsy. The incidence of PCa is 30 - 43% in saturation prostate biopsy^[9]. The cancer detection rate of saturation prostate biopsy may depend on the number of cores sampled during biopsy; therefore, obtaining more prostate tissue can increase the cancer detection rate^[10]. After the diagnosis of ASAP, determining the predictors of prostate cancer is controversial in repeat biopsy^[11]. We examined repeat biopsy results of patients with ASAP. The aim of the present study was to determine the predictors of prostate cancer on repeat biopsy in these patients.

MATERIALS AND METHODS

The medical records of 1240 patients who had undergone initial transrectal ultrasound (TRUS)-

Address correspondence to:

Cem Yucel, MD, Tepecik Training and Research Hospital, Yenisehir Mah, Gaziler Cad. No: 468, Konak, Izmir, Turkey. Tel: 05376676983 ; E-mail: meclecuy@hotmail.com

guided 12 core prostate biopsies in our institution between June 2013 and August 2016 were reviewed retrospectively. This study was conducted in accordance with the declaration of Helsinki, and approval was obtained from the institutional ethics committee. After obtaining informed consent from the patients, all biopsies were performed transrectally with ultrasonography guidance using a 25 cm 18-gauge, side-notch cutting (Tru-cut) needle. The biopsies were performed with the patient in the lateral decubitus position with periprostatic nerve blockage. The initial biopsy results of patients were classified into four categories: prostate cancer (adenocarcinoma), normal prostates or benign prostatic hyperplasia, high grade prostatic intraepithelial neoplasia (HGPIN) and ASAP.

In this study, we included 54 patients diagnosed with ASAP at the initial biopsy. These patients underwent TRUS-guided 24-core saturation biopsy for repeat biopsy. The clinico-biological features of the patients were recorded. The patients were excluded if they had a prior diagnosis of PCa or HGPIN. We also excluded patients who had undergone core prostate biopsy of under 24 for repeat biopsy.

The patients were classified into cancer, benign and ASAP groups according to the final pathological diagnosis after repeat biopsy. These groups were compared according to age, initial total PSA, total PSA, DRE findings, prostate volume, TRUS findings, and total and mean core length of biopsy. We also identified the Gleason scores of the cancer group. Patients with one or more hypoechoic lesions at TRUS were accepted as having an abnormal TRUS.

Statistical analysis

The conformity of the variables to the normal distribution was assessed with the Shapiro-Wilk test. The Student's t-test and the chi-squared test were used for inter-group analyses of continuous variables. Independent averages of more than two were compared with the analysis of variance and the Kruskal-Wallis tests. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Illinois, USA) version 24.0 and a p-value <0.05 was considered significant.

RESULTS

The incidence of ASAP was 4.35% (54/1240). Of the 54 patients diagnosed with ASAP on initial biopsy and who underwent repeat biopsy, the mean age was 63 years (range: 48 - 76 years), the mean initial PSA was 8.6 ng/mL (range: 2.3 - 17.6 ng/mL), the mean total PSA was 9.5 (range: 3.2 - 28.1 ng/mL), the mean prostate volume was 52.5 ml (range: 26 - 121 mL), and the total and mean core lengths of biopsies were 26.8 cm (range: 21.4 - 32.4 cm) and 1.1 cm (range: 0.89 - 1.35 cm), respectively. The clinicopathological features of the

patients have been summarized in Table 1. The mean interval between the first and the second prostate biopsies was 5.4 ± 1.3 months.

Table 1: Clinico-biological characteristics of patients undergoing saturation biopsy

Variables	Mean (SD)
Age (years)	63 ± 7.9
Initial PSA (ng/ml) ^a	8.6 ± 6.8
PSA (ng/ml)	9.5 ± 6
Prostate volume (ml)	52.5 ± 39.8
Total core length (cm)	26.8 ± 3.6
Mean core length (cm)	1.1 ± 0.2
DRE (n(%))	
Normal	42 (77.8)
Abnormal	12 (22.2)
TRUS finding (n(%))	
Normal ^b	14 (25.9)
Abnormal ^c	40 (74.1)
Gleason (n(%))	
6	10 (50)
7	10 (50)

PSA: prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal prostatic ultrasound

^a: for only 54 patients; ^b: have no hypoechoic lesions in TRUS; ^c: have hypoechoic lesions in TRUS

At repeat 24 core prostate biopsy, the diagnoses were benign prostate, prostate cancer and ASAP in 26/54 (48.2%), 20/54 (37.03%) and 8/54 (14.8%) patients, respectively. The cancer detection rate was 37.03% (20/54). The Gleason score was determined to be 6 in 10 patients (50%), and 7 in 10 patients (50%) who had been diagnosed with PCa after repeat biopsy. In the cancer, ASAP and benign groups, the mean age was 67.2 ± 5.4 , 56.3 ± 6.7 and 61.8 ± 8.5 years, respectively. The difference was determined to be statistically significant ($p = 0.032$). When these groups were compared with each other, there was no statistical difference in the initial total PSA, total PSA, DRE findings, prostate volume, TRUS findings, and the total and mean core lengths (Table 2).

DISCUSSION

In this study, we found only the age of patients to be a predictive factor for prostate cancer at repeat biopsy in patients diagnosed with ASAP. The cancer detection rate in patients with ASAP on repeat biopsy is approximately 40%, and the urologist should obtain additional biopsy from the zones of the prostate in which ASAP was detected in the initial biopsy^[12]. Iczkowski *et al* reviewed the medical data of 6026 patients who had undergone prostate biopsy and determined the incidence of ASAP as 3.3%^[13]. The incidence of ASAP varies from 0.7 - 23.4% in many studies. The average incidence of ASAP is 5% in the literature^[14]. Consistent with the literature, our incidence was 4.35% and the cancer detection rate on repeat biopsy was 37.03%.

Table 2: Characteristics of patients undergoing saturation biopsy according to pathological results

Variables	Benign (n = 26)	ASAP (n = 8)	Cancer (n = 20)	p-value
Age (years)	61.8 ± 8.5	56.3 ± 6.7	67.2 ± 5.4	0.032
Initial PSA (ng/ml) ^a	9.9 ± 8.9	5.8 ± 3.6	8.1 ± 3.9	0.394
PSA (ng/ml)	10.9 ± 7.8	7.1 ± 2.5	8.6 ± 3.8	0.463
Prostate volume (ml)	61 ± 50.5	37.1 ± 14.1	47.7 ± 29.7	0.558
Total core length (cm)	26.2 ± 3.2	29.8 ± 3.9	26.3 ± 3.6	0.167
Mean core length (cm)	1.09 ± 0.1	1.24 ± 0.1	1.09 ± 0.1	0.236
DRE (n(%))				0.249
Normal	22 (84.6)	8 (100)	12 (60)	
Abnormal	4 (15.4)	0 (0)	8 (40)	
TRUS finding (n(%))				0.845
Normal ^b	8 (30.8)	2 (25)	4 (20)	
Abnormal ^c	18 (69.2)	6 (75)	16 (80)	

PSA: prostate-specific antigen; DRE: digital rectal examination; TRUS: transrectal prostatic ultrasound; ASAP: Atypical small acinar proliferation

^a: for only 54 patients; ^b: have no hypoechoic lesions in TRUS; ^c: have hypoechoic lesions in TRUS

After the diagnosis of ASAP, determining the predictors of prostate cancer is controversial in subsequent biopsy. Iczkowski *et al* found no predictor factor for detecting PCa in patients with ASAP after the initial biopsy^[13]. Epstein *et al* reported that there was no association between PCa and the clinicopathological features of patients with ASAP^[15]. Park *et al* reported that age and DRE were predictors of PCa in patients with ASAP^[16]. Similar to this study, we found that age was an independent predictor of cancer, but DRE was not a significant cancer detection variable in patients with ASAP at repeat biopsy. Mearini *et al* reviewed the data of 1274 patients who had undergone prostate biopsy^[17]. They determined the incidence of ASAP to be 5.9% and observed that the total PSA was a predictor of PCa at subsequent biopsy. Contrary to this study, we found that the initial total PSA and total PSA levels were not significantly increased in patients with ASAP at repeat biopsy. Similar to our study, many investigators recommend a repeat biopsy within 3 - 6 months, irrespective of follow-up of the PSA values^[14,18].

Levine *et al* observed that the PCa detection rate decreased with increasing prostate volume^[19]. They reported that the cancer detection rates were 43%, 27% and 24% in patients with prostate volumes of lower than 30 cc, between 30 cc and 50 cc, and greater than 50 cc, respectively. Scattoni *et al* reported that 12 core biopsy may not have been sufficient for correct sampling of the prostate glands larger than 50 ml in which ASAP is present^[20]. In our study, we used the 24 core saturation biopsy scheme for repeat biopsy and observed that the cancer group prostate volume was smaller than that of the benign group, but the difference was not statistically significant.

In spite of the presence of many studies on the core number and location of cores, there is a limited number of studies on the biopsy core length, which is

one of the most important parameters in determining the quality of the biopsy^[21,22]. Although there are studies suggesting that a greater core length increases the rates of PCa diagnosis, there have also been studies suggesting that the diagnosis of PCa is not affected by core length^[19,20,23]. In our study, the total and mean core lengths were not significant variables predicting the cancer detection rate in patients with ASAP.

Warlick *et al* reported that 17.3% of patients with ASAP had high-grade (Gleason >7) PCa on repeat biopsy^[24]. In another study, Raskolnikov *et al* determined that 5% of patients with ASAP had high grade PCa on subsequent prostate biopsy^[18]. In this study, we observed that 18.5% of patients with ASAP were subsequently found to have high-grade (Gleason >7) PCa.

While there are studies advocating the benefit of magnetic resonance imaging (MRI) prior to repeat biopsy in determining hidden cancers that have escaped the eye, despite previously negative prostate biopsies in patients in whom the suspicion of cancer persists, there are also studies that contradict this^[25]. Due to the MRI being a costly procedure, it has not been used prior to re-biopsy.

There are several limitations in our study. The first limitation of our study is its retrospective nature. The second limitation of this study is that the biopsy cores were not examined by the same pathologist. The other limitation of this study is the small number of patients with ASAP included in the study, and this limitation has affected the interpretation of the results. A larger pool of patients will provide a more accurate picture.

CONCLUSION

ASAP is associated with an approximate rate of 40% of PCa at repeat biopsy. All patients diagnosed with ASAP need repeat biopsy within 3 - 6 months. We observed that only the age of patients was a predictive

factor of prostate cancer at repeat biopsy in patients with ASAP. Large-scale, multi-center, prospective studies will provide a more accurate picture for the clinical significance of the predictors of prostate cancer at repeat biopsy in patients with ASAP.

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Original Article

Prevalence and Patterns of Psychiatric Co-morbidity among Adult Medical Inpatients: A Cross-sectional Study

Abdulrahman A Al-Atram

Department of Psychiatry, College of Medicine, Majmaah University, Kingdom of Saudi Arabia

Kuwait Medical Journal 2018; 50 (4): 410 - 416

ABSTRACT

Objective: Psychiatric and medical conditions tend to co-occur, with each potentially complicating the course and treatment outcome of the other. However, the data regarding psychiatric co-morbidity among medical patients in Saudi Arabia is scarce. This study was designed to assess the prevalence and patterns of psychiatric co-morbidity in adult medical inpatients and to look at the rates of various psychiatric disorders by type of medical illness.

Design: Cross-sectional observational study

Settings: The King Khalid Hospital Majmaah and the Zulfi General Hospital from November 2016 to February 2017

Subjects: This study was conducted among 400 medical inpatients that were selected by convenience sampling

Interventions: The General Health Questionnaire was administered as a screening tool to identify "cases". All other

participants were considered "non-cases". The identified cases then had the Mini International Neuropsychiatric Interview Plus and the Hospital Anxiety and Depression Scale questionnaires administered.

Main outcome measure(s): The prevalence of psychiatric disorders in the sample was analyzed using Statistical Package for Social Sciences version 23 software.

Results: Psychiatric disorders were present in 28% of the included medical inpatients. In general, chronic diseases were associated with higher psychiatric co-morbidity.

Conclusions: Psychiatric disorders are prevalent among medical inpatients. Identifying psychiatric disorders among in-patients is important because appropriate treatment can improve treatment outcomes for the co-morbid medical illness.

KEY WORDS: adjustment disorder, anxiety, depressive disorder, psychiatric disorders

INTRODUCTION

Psychiatric co-morbidity refers to the co-occurrence of psychiatric and physical disorders in the same person, regardless of the chronological order in which they occurred or the causal pathway linking them. The mind was once seen as the domain of religion, with the body seen as the concern of physicians, and this distinction led to the separation between psychiatric and physical health. However, research now shows that psychological stress can affect the body at the cellular and molecular level, and thereby diminish a person's physical health and quality of life^[1,2]. This is particularly important when one considers that psychiatric co-morbidity is prevalent in medical patients^[3]. Moreover, the negative implications of this untreated co-morbidity have been documented

in relation to the prognosis of the medical condition, the patient's quality of life, and the costs of medical treatment^[4]. It is, therefore, essential that we understand the nature and prevalence of psychiatric disorders among physically ill patients.

People with physical illness have at least twice the rate of psychiatric illness than the general population. The most common co-morbidities are depressive and anxiety disorders, which are present in approximately one-third of medical patients. In addition to the personal suffering of the patient, psychiatric co-morbidity is strongly associated with increase in disability, healthcare costs, and mortality risk^[5].

Psychiatric co-morbidity can also affect treatment adherence. Obviously, diagnosing psychiatric disorders is insufficient to improve outcomes if used in

Address correspondence to:

Dr. Abdulrahman A Al- Atram, Associate professor, Department of Psychiatry, College of Medicine, Majmaah University, Kingdom of Saudi Arabia. Tel: +966505214617; E mail: a.atram@mu.edu.sa

isolation, but if the recognition of a psychiatric disorder is closely linked to the initiation of adequate treatment, patient outcomes may improve significantly. Despite this clinical significance, only 30 - 50% of patients with psychiatric co-morbidity are identified by medical doctors^[6]. Few hospitals have any formal services to meet the psychological needs of their patients, instead relying on a mixture of informal provision in some areas and neglect in others.

To date, very few studies have investigated the true prevalence of psychiatric disorders among hospitalized patients in the Kingdom of Saudi Arabia and neighboring countries^[7,8]. Hence, in the present study, the aim was to expand our knowledge of psychiatric co-morbidity in medical patients. Such research may expand efforts to recognize and treat psychiatric co-morbidity.

SUBJECTS AND METHODS

This was a cross-sectional, questionnaire-based study of in-patients at The King Khalid Hospital, Majmaah, and in the Zulfi General Hospital from November 2016 to February 2017. Convenience sampling was used to obtain a sample of 400 participants. The study was approved by the ethical committee of Majmaah University, and written informed consent was a requirement of inclusion.

For inclusion, individuals were required to be admitted to medical and specialty wards, aged between 18 and 65 years, able to read and write Arabic, and willing to participate in the study. Patients were excluded if they were critically ill or were unwilling to participate in the study.

A general proforma was prepared to collect the socio-demographic details and clinical characteristics of each subject. The General Health Questionnaire (GHQ) was used to screen patients, and those who had a score of five and above were considered "cases." These patients were then interviewed using the Mini International Neuropsychiatric Interview (MINI Plus) and the Hospital Anxiety Depression Scale (HADS). The MINI Plus is a brief, structured interview used to identify major Axis I psychiatric disorders, as defined by the DSM-IV and the ICD-10. It is a more detailed version of the MINI and can be administered in a shorter period. MINI Plus assesses the presence of DSM-IV mood disorders, anxiety disorders, somatoform disorders, substance abuse disorders, psychotic disorders, eating disorders, conduct disorder, and adjustment disorder. Psychometric examination of the MINI-Plus shows acceptable test-retest and inter-rater reliability. The MINI-Plus was selected over other screening instruments because of its ease of administration, the relatively brief training needed for its use, its broad coverage, and its reported

quick administration time. The mean duration of the interview was 21 minutes. A validated translated version of MINI plus was used in this study^[9].

The HADS scale was administered to all subjects who were diagnosed as having psychiatric disorders using MINI Plus. For patients with more than one medical diagnosis, the reason for the current admission was taken as the main diagnosis. Acute medical illness was defined as that less than one month, while chronic medical illness was defined as that more than one month.

A previously validated Arabic copy of the HADS-anxiety (HADS-A) was used in this study^[10]. The HADS is a 14-item questionnaire that consists of seven items for HADS-A and seven items for depression (HADS-D). Anxiety and depression items are loaded as separate factors. The anxiety and depression sub-scales shared 54% of the explained variance. These were then scored and the data were entered for analysis.

Data were analyzed using IBM SPSS, Version 23 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe the sample characteristics. Percentages and frequencies are used to describe the distribution of psychiatric disorders across various medical illnesses, socio-demographic variables, and clinical characteristics. For group comparisons, Pearson's chi-square tests or Fischer's exact tests were used for categorical variables and independent t-tests were used for continuous variables. The level of statistical significance was set at $p < 0.05$.

RESULTS

Table 1 shows the distribution of the sample by socio-demographic variables. Participants were aged 39.24 years (range: 18 - 65 years) and most were males (68%). Overall, the highest percentages of psychiatric disorders were seen in those aged 18 - 30 years (41.4%), women (40%, compared to 29% in men), single patients (43.4%), and the unemployed (60%). There were equivalent numbers with acute (51%) and chronic (49%) medical illness, but the rate of psychiatric disorders in the chronic group (38.8%) was more than double that in the acute group (17.6%).

The test results by illness duration were compared by the Pearson chi-square test or Fisher's exact test and are summarized in Table 2. The GHQ score ($t = 3.57$, $p = 0.001$), HADS-D score ($t = 2.09$, $p = 0.045$), and MINI diagnoses ($p = 0.042$) were all significantly higher in patients with chronic illness compared to those with acute illness. Anxiety, depression, adjustment disorder, and mixed anxiety and depression were all significantly higher in patients with chronic illness, and psychiatric disorders were more common in those with a family history of psychiatric illness (30%) than in those who did not (27.6%).

Table 1: Distribution of sociodemographic variables across the sample

Medical inpatients (%) (n = 400)	Non-cases n = 268, Mean(SD) / n(%)	Cases n = 132, Mean(SD) / n(%)	t/ χ^2	p-value
Age (years)				
18-30	68 (58.6)	48 (41.4)	14.84	0.001
Mean(SD)=39.21(13.21) Range: 18 – 65				
31-50	160 (78.4)	44 (21.6)		
51-65	60 (75)	20 (25)		
Sex			4.95	0.026
Male	192 (70.8)	80 (29.2)		
Female	76 (59.4)	52 (40.6)		
Education			4.777	0.091
Primary	56 (20.9)	40 (30.3)		
Secondary	120 (44.8)	48 (36.4)		
College	92 (34.3)	44 (33.3)		
Marital status			Fisher's exact p = 0.015	
Single	52 (19.4)	40 (30.3)		
Married	200 (74.6)	80 (60.6)		
Widow/widower/ divorced	16 (6)	12 (9.1)		
Residence			0.626	0.428
Urban	48 (17.9)	28 (21.2)		
Rural	220 (82.1)	104 (78.8)		
Socioeconomic status			Fisher's exact p = 0.027	
LSES	112 (41.8)	72 (54.5)		
MSES	152 (56.7)	60 (45.5)		
USES	4 (1.5)	0 (0)		
Occupation			Fisher's exact p = 0.031	
Self employed	200 (74.6)	92 (69.7)		
Unemployed	8 (3)	12 (9.1)		
Employed	60 (22.4)	28 (21.2)		
Duration of current medical illness			0.001	
Less than a month	168 (82.4)	36 (17.6)		
More than a month	120 (61.2)	76 (38.8)		
Family history of psychiatric illness			P = 0.55 $\chi^2 = 0.340$	
Absent	204 (72.9)	76 (27.1)		
Present	84 (70)	36 (30)		

The General Health Questionnaire was used to screen patients, and those who had a score of five and above were considered cases.

The distribution of medical illness by psychiatric diagnosis is shown in Table 3. Infections (53%) were the most common reason for admission, but gastrointestinal (12%), respiratory (8%), cardiovascular (7%), neurological (7%), endocrine (6%), and renal (4%) disorders were other prominent reasons. By contrast,

only 1% were admitted because of cancer and only 2% were admitted because of attempted suicide. The prevalence of each major psychiatric illness identified by the MINI Plus is also shown in Table 3 (overall prevalence, 28%). Of these, most had either a depressive disorder (14%) or an anxiety disorder (9%). Adjustment

Table 2: Comparison of test results by illness duration

Duration	GHQ	HADS-A	HADS-D	MINI diagnosis			
				Anxiety Disorder	Depressive Disorder	Adjustment Disorder	Mixed Anxiety Depression
Short duration n=196 Mean (SD)/n(%)	2.86 (3.09)	6.92 (2.78)	6.58 (2.06)	16 (7.8)	12 (5.9)	4 (2)	4 (2)
Long duration n=204 Mean (SD)/n(%)	5.82 (5.03)	7.10 (2.32)	9.33 (4.26)	20 (10.2)	44 (22.4)	12 (6.1)	0 (0)
t/ χ^2	3.57	1.98	2.09	-	-	-	-
p	0.001**	0.844	0.045*	Fisher's exact p = 0.042*			

*p < 0.05, **p < 0.01 (2-tailed)

GHQ: General Health Questionnaire; HADS-A: Hospital Anxiety Depression Scale-Anxiety; HADS-D: Hospital Anxiety Depression Scale-Depression; MINI: Mini International Neuropsychiatric Interview

Acute medical illness was defined as that less than one month, while chronic medical illness was defined as that more than one month.

Table 3: Distribution of psychiatric disorders by medical illness

Medical diagnosis categories	No MINI Plus diagnosis F (%) (n = 288)	MINI Plus Diagnosis F (%) (n = 112)	f (% within Medical Diagnosis Categories) (n = 112)			
			Depressive disorder	Anxiety Disorder	Adjustment Disorder	Mixed Anxiety Depression
Cardiovascular	24 (85.7)	4 (14.3)	4 (14.3)	0 (0)	0 (0)	0 (0)
Respiratory	24 (75)	8 (25)	4 (12.5)	4 (12.5)	0 (0)	0 (0)
Endocrine	20 (83.3)	4 (16.7)	0 (0)	4 (16.7)	0 (0)	0 (0)
Infection	152 (71.7)	60 (28.3)	20 (9.4)	24 (11.3)	12 (5.6)	4 (1.9)
Neurological	16 (57.1)	12 (42.9)	8 (28.6)	4 (14.3)	0 (0)	0 (0)
Gastrointestinal	36 (75)	12 (25)	8 (16.7)	4 (8.3)	0 (0)	0 (0)
Renal	4 (25)	12 (75)	8 (50)	0 (0)	4 (25)	0 (0)
Cancer	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Others	8 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

MINI: Mini International Neuropsychiatric Interview

Psychiatric disorders were diagnosed based on the MINI Plus

disorder and mixed anxiety and depression were present in 4% and 1% of the sample, respectively.

Psychiatric disorders were present at the following rates by type of medical illnesses: 75% (12/16) of patients with renal disorders, 42.9% (12/28) with neurological disorders, 39.5% (60/212) with infections, 25% (8/32) with respiratory disorders, 25% (12/48) with gastrointestinal disorders, 16.7% (4/24) with endocrine disorders, and 14.8% (4/28) with cardiovascular disorders. Four patients with psychiatric illness had cancer. Table 3 also shows that 20% (12/60) of patients suffering from infections had an adjustment disorder. It may also be significant to note that 50% (8/16) of patients suffering from a renal disorder had a comorbid depressive disorder and that 25% (4/16) had an adjustment disorder. Anxiety disorders were also more prevalent than other psychiatric illnesses in patients with endocrine disorders (16.7%; 4/24) and infections (11.32%; 24/212), whereas depression and anxiety disorders were present at equivalent rates among patients with respiratory disorders (12.5%). Only four patients suffering from infection had mixed anxiety and depression.

Table 4 depicts the HADS depression and anxiety scores for cases. As shown, the HADS depression score only indicated that "less than mild" depressive features

were present for most cases (45.5%). By contrast, mild features were seen in 27.3%, moderate features in 24.2%, and severe features in 3%. Similarly, most patients only had anxiety features considered less than mild (57.6%), with mild and moderate anxiety features present in 33.3% and 9.1% of the sample, respectively.

Table 4 shows the results when HADS-A and HADS-D scores were cross-tabulated with psychiatric disorders (Table 4). The HADS-A score for depressive disorders was either less than mild (85.7%) or mild (14.3%); for anxiety disorders, it was mild (66.7%) or moderate (33.3%). Concerning adjustment disorders, 50% each had less than mild and mild scores. The HADS-D score for depressive disorders was either mild (50%), moderate (42.9%), or severe (7.1%); however, all cases of anxiety had depression scores in the less than mild category. Concerning adjustment disorders, most had moderate scores (50%), but 25% each had less than mild or mild scores. Mild HADS-A and HADS-D scores were seen for patients with mixed anxiety and depression.

DISCUSSION

The key finding of this study was that 28% of medical inpatients had a psychiatric disorder, as diagnosed by using the MINI Plus questionnaire. However, in a

Table 4: HADS Depression and Anxiety Scores for subjects who scored >5 on the GHQ

HADS/A HADS/D	Degree of severity	Medical inpatients f (%) (n = 132)	HADS Depression Score f (%) (n = 112)			
			Depressive disorder	Anxiety Disorder	Adjustment Disorder	Mixed Anxiety Depression
HADS Depression Score	Less than mild	60 (45.5)	0 (0)	36 (100)	4 (25)	0 (0)
	Mild	36 (27.3)	28 (50)	0 (0)	4 (25)	4 (100)
	Moderate	32 (24.2)	24 (42.9)	0 (0)	8 (50)	0 (0)
	Severe	4 (3)	4 (7.1)	0 (0)	0 (0)	0 (0)
HADS Anxiety Score	Less than mild	76 (57.6)	48 (85.7)	0 (0)	8 (50)	0 (0)
	Mild	44 (33.3)	8 (14.3)	24 (66.7)	8 (50)	4 (100)
	Moderate	12 (9.1)	0 (0)	12 (33.3)	0 (0)	0 (0)

study conducted in Denmark, a considerably higher prevalence of psychiatric disorders was reported in medical inpatients (38.7%)^[11]. Whereas, our findings are similar to the prevalence of psychiatric disorders reported in medical inpatients in Nigeria (30.6%)^[12]. Another study conducted in Kenya had a higher prevalence rate (42.6%), possibly because they considered patients from all medical settings (not only inpatients)^[13]. In general though, research consistently indicates that psychiatric conditions are more common in medical settings, with up to 40% of medical and surgical inpatients possibly requiring treatment.

The common psychiatric disorders in the present study were depression, anxiety, and adjustment disorder, similar to the finding in other studies^[14]. In the present sample, depressive disorder was the most prevalent of the psychiatric disorders (14%), which is consistent with the results of studies indicating that depression is common in medical wards and that anxiety is common in emergency wards^[15].

Infections (*e.g.*, varicella, brucellosis, influenza) were the most common reasons for admission (53%) in the present sample, with other illnesses accounting for fewer than 15% each. Nevertheless, gastrointestinal disorders (13%) (acid-peptic disease, cirrhosis, pancreatitis) and respiratory disorders (8%) (bronchial asthma, chronic obstructive pulmonary disease) were also common. This is at variance with other studies regarding the distribution of medical illnesses, because these show that cardiovascular diseases are usually the reason for most admissions^[16]. However, observed variance could be dependent on the sampling method, catchment area of the hospital, available healthcare facilities, type of center (primary, secondary, or tertiary), treatment-seeking behavior, and economic or other related factors^[17].

The duration of medical illness was clearly associated with the presence of psychiatric disorders in our study. Patients who had chronic medical illness had a significantly higher rate of psychiatric co-morbidity (38.8%), with significantly higher GHQ ($p = 0.001$) and HADS ($p = 0.045$) scores in this group. This result is consistent with many studies showing that as a physical illness becomes more chronic, the likelihood of developing a co-morbid psychiatric illness increases. This may reflect the association of chronic medical disorders with increasing emotional and financial burdens on the patient and their family^[18,19].

Patients with renal disorders accounted for most medical cases with co-morbid psychiatric disorders. This may reflect the fact that renal disorders are usually chronic, requiring multiple admissions. Indeed, most of the patients with renal disorders in the present sample had illness durations more than one month, which could have affected the presence

or absence of psychiatric disorders (75%). It was also shown that neurological disorders were associated with high psychiatric co-morbidity in the present study (42.9%), which is consistent with studies indicating co-morbidity rates of 75% and 39.6%^[19,20]. In addition, although four patients with cancer did not have any psychiatric illness in this study, and although other research has shown that co-morbidity rates are usually high for cancer^[21,22], the very small sample of patients with cancer in this study precludes any meaningful conclusions. Adjustment disorders were the most commonly seen co-morbidity in patients with infections, and were mainly of the depressive type (50%). A similar study showed an association between depressive symptoms and human immunodeficiency virus/acquired immunodeficiency syndrome^[23]. Regarding respiratory disease, 25% had co-morbid psychiatric illness in this study, which is similar to results from India where there was 28% psychiatric co-morbidity in patients with chronic obstructive pulmonary disease^[24].

Major depression is a frequent psychiatric presentation of patients with endocrine disorders^[25,26], which is in contradiction to the high co-morbidity rate for anxiety disorders (16.7%) in this study. The small sample size, geographic variation and social cultural factors of the participants in this study could be the influential factors for this variation. Consistent with other studies, a co-morbidity of 30.8% was shown for gastrointestinal disorders, with anxiety and depression present in 23.1% and 7.7%, respectively^[27]. Diseases of the cardiovascular system (*e.g.*, hypertension, cardiomyopathies) have been associated with psychological dysfunction, such as anxiety states, and this research showed that cardiovascular diseases were often associated with co-morbid anxiety (14.3%)^[28].

Medical inpatients in this sample tended to have mild psychiatric disorders, which is consistent with the results of a Kenyan study, indicating that most co-morbid psychiatric disorders may only be mild^[29]. Despite this mild nature, psychiatric disorders should still be considered an important factor when assessing prognosis and treatment outcomes. This study also highlighted the fact that specific medical conditions and chronic conditions have higher rates of psychiatric co-morbidity, indicating that such groups should be identified for regular psychiatric evaluation.

However, it should be noted that this study employs a cross-sectional design with convenience sampling method, which has its own limitations. The sample size was relatively small and was taken from a general hospital setting, in which most admissions were to general medical wards rather than specialty wards. Therefore, psychiatric co-morbidity was not adequately documented among patients suffering

from malignancies and similar conditions, and this should be addressed in future research. Equally, such research should include emergency wards so that the prevalence of co-morbid psychiatric conditions can be assessed in acute conditions.

CONCLUSION

Based on this observational cross-sectional study, it can be concluded that psychiatric illness was prevalent enough among medical inpatients to warrant clinical attention. Therefore, consultation-liaison psychiatry should be encouraged, specific training should be given to help medical doctors identify psychiatric conditions, and psychiatric care should be administered at the same time as medical treatment when psychiatric comorbidity is identified. In particular, groups at high risk should be screened periodically, and a holistic approach of treating mind and body should be emphasized. Future research is needed to confirm the findings of this study in a broader range of inpatient settings and hospitals.

ACKNOWLEDGMENT

Conflict of interest: None

Financial support: None

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Original Article

Considerations for Redirection of Care in Muslim Neonates: Issues and Recommendations

Vivek V Shukla¹, Amal K Ayed², Mariam K Ayed³¹The Hospital for Sick Children, Division of Neonatology, 555 University Avenue, Toronto, ON M5G 1X8, Canada²Department of Obstetrics, Division of Fetomaternal medicine, Farwaniya Hospital, Subah An Nasser, Kuwait³Neonatal department, Subah An Nasser, Farwaniya Hospital, Kuwait.

Kuwait Medical Journal 2018; 50 (4): 417 - 421

ABSTRACT

Objectives: To identify and formulate recommendations regarding challenges faced while considering redirection of care (ROC) for Muslim neonates based on experiences of neonatologists frequently encountering such situation

Design: Cross-sectional survey

Setting: Anonymous web-based questionnaire was distributed between August and September 2015

Subjects: Neonatologists practicing in select countries with predominantly Muslim population (Kuwait, Oman, Saudi-Arabia and Egypt)

Intervention: Anonymous web-based questionnaire

Main outcome measure: Challenges toward ROC

Results: A total of 120 neonatologists were requested for the survey, out of which 98 (82%) responded by completing the survey. A total of 36 (36.7%) respondents were against ROC because of the uncertainty of the prognosis (100%), the uncertainty of the religious edicts (Fatwa)(80%), belief that ROC was against Islamic

ideals (50%) and fear of legal repercussions (10%). On the other hand, 63.2% (n = 62) were of the opinion that ROC should be offered to neonates with unfavorable prognosis related to extreme prematurity and its related complications (61%), severe asphyxia (74%), multiple congenital anomalies (80.5%), and genetic syndromes (92%). Training background was significantly associated with neonatologists who considered ROC after adjusting for possible confounders (odds ratio = 3.1; 95% confidence interval: 1.1 to 8.8; P = 0.03). The major religious barriers identified with respect to ROC were the lack of clarity and fear of breaching Islamic ideals. All respondents felt that ethical codes conforming to Islamic and legal standards were urgently required.

Conclusion: ROC consideration for Muslim neonates has many socio-cultural and religious barriers. Comprehensive ethical codes conforming to Islamic and legal standards are required to aid decision-making.

KEYWORDS: Islam, neonatology, social and ethical issues

INTRODUCTION

Advances in perinatal-neonatal medicine in the last few decades have improved the survival of neonates who were previously considered unviable^[1,2]. However, the causes for mortality and morbidity have more or less been constant^[1,3,4]. Neonatal deaths remain a major contributor to overall pediatric mortality, and they are frequently encountered in neonatal intensive care settings^[5]. Neonatal care providers routinely face infants with life-limiting conditions with poor prognosis where they have to make decisions for redirection of care (ROC), *i.e.* either withdrawal or withholding life prolonging treatments^[6,7].

Decisions regarding neonatal ROC are overwhelming and irrevocable, often involving significant anxiety and distress for the families and care providers^[8]. Recent research has shown that neonatal ROC can have long term psychological implications for the family^[9]. These stresses are compounded by cultural and religious differences between the family and care providers. With the increase in international migration and globalization, neonatologists are frequently faced with such issues^[10]. Cultural and religious differences in ROC related issues should be respected and addressed in an empathetic manner to avoid potential misunderstandings and grievances^[11].

Address correspondence to:

Mariam Khader Ayed MD, FAAP, FRCPC, Neonatal department, Farwaniya Hospital, Subah An Nasser, Kuwait city, Postal code 81400, Kuwait. Tel: 965-98880553; Email- mariam.ayed@hsc.edu.kw

Islamic theology is centred in Allah's message, revealed by Prophet Muhammad and noted in Quran; it serves as the basis of religious beliefs, attitudes, morals and guidelines for human interaction^[12-14]. ROC discussion with Muslim patients therefore necessitates a more considerate approach due to their distinct religious convictions that "Life is an exam and perseverance in face of challenges (including disease and death) would result in salvation (Quran 2:155-57)" and "Any act which leads to human death is a grave sin (Quran 5:32)"^[15]. Novel questions posed by medical advances, such as those related to neonatal ROC, require a degree of interpretation and application of Quran by authoritative teachers (Imams). This has led to diverse inferences and continues to be an extremely challenging topic needing awareness and knowledge on the side of neonatal care providers^[14].

We sought to assess the challenges faced when considering ROC for Muslim neonates and to formulate recommendations based on the experiences of neonatologists frequently encountering such situations.

SUBJECTS AND METHODS

An anonymous, web-based questionnaire with open-ended questions and descriptive responses was developed covering the following components: demographic variables, knowledge, attitude and practices regarding ROC decision-making, factors impacting ROC decisions and opinions on how ROC decisions should be best approached. ROC was defined as the process of moving from curative to palliative care^[16]. Related published studies were also used to identify challenges and recommendations. The investigators individually prepared the questionnaires. The final questionnaire was prepared by incorporating suggestions from all authors. Any differences were debated and all investigators mutually agreed on the final questionnaire. The questionnaire was designed to reach the neonatologists practicing in select countries with a predominantly Muslim population (Kuwait, Oman, Saudi-Arabia and Egypt). These countries are representative of different Islamic sects, hence were carefully selected for generalizable conclusions. The questionnaire was distributed via email between July and September 2015 to the medical directors of neonatal intensive care units in the selected countries. Two email reminders were distributed after the first month of conducting the survey. Informed consent was implied by the submission of a completed survey. Responders were divided into two groups; Group A – those respondents who were against any consideration for ROC, and Group B- those respondents who were open to consider ROC in specific circumstances. The Ministry of Health of Kuwait Clinical Research Ethic Board approved the study.

Analysis was done by Stata 14 statistical software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Descriptive statistics (number and percent) were reported for demographic characteristics and survey responses. Fisher's exact test was used for statistical differences between responses. Logistic regression models were used to assess the variables influencing physician's attitudes. Odds ratios (OR) with 95% confidence intervals (CI) were calculated and p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 120 neonatologists were invited, out of whom 98 (82%) responded by completing the survey. Of the total 98, 33 (33.7%) respondents were from Oman, 24 (24.5%) from Egypt, 23 (23.5%) from Saudi-Arabia and 18 (18.4%) from Kuwait. Sixty of the respondents (61.2%) were male and 38 (38.8%) were female. A majority of the respondents (n = 56, 57%) were between 35 - 44 years old. Sixty-four of the respondents (65.3%) received their neonatal training in Middle East Asia and the remaining 34 (34.7%) respondents were trained in North America.

On views regarding neonatal ROC, 36 (36.7%) respondents were against any consideration for ROC (Group A) and 62 (63.2%) respondents were open to consider ROC in specific circumstances (Group B). The reasons for opposition to ROC in Group A were related to the uncertainty of prognosis (100%), uncertainty of the religious edicts (Fatwa) (80%), a belief that ROC was against Islamic ideals (50%) and fear of legal repercussions (10%). Respondents in Group B were of the view that allowed ROC for neonates with an unfavourable prognosis related to extreme prematurity and its related complications (61%), severe asphyxia (74%), multiple congenital anomalies (80.5%) and genetic syndromes (92%). The method of choice for ROC was "do not resuscitate", withdrawal of life support and withholding of fluid/nutrition for 90.5%, 8% and 1.5% of respondents from group B respectively.

Comparative analysis between the two groups showed that North American training was associated significantly with ROC consideration (Group B), 43.5% in group B vs. 20% in group A (p = 0.013) (Table 1). On multivariable logistic regression analysis, North American training was significantly associated with neonatologists who considered ROC after adjusting for possible confounders (years of experience and self-rated religious background) (OR = 3.1; 95% CI: 1.1 to 8.8; p = 0.03). There were a higher percentage of respondents against ROC from Oman (42.4%) and Saudi Arabia (39.1%) than Egypt (33%) and Kuwait (27.8%), although this trend

Table 1: Baseline characteristics

Characteristics	Disagree with ROC n = 36 (Group A)	Agree with ROC n = 62 (Group B)	p-value
Age (n(%))			0.930
25 - 34	9 (25)	17 (27.4)	
35 - 44	22 (61)	34 (54.8)	
45 - 55	4 (11)	9 (14.5)	
> 55	1 (28)	2 (3.2)	
Gender (n(%))			0.407
Male	21 (58.3)	39 (63)	
Female	15 (41.7)	23 (37)	
Years of experience			0.217
< 5	2 (5.5)	11 (17.7)	
5-10	22 (61)	31 (50)	
> 15	12 (33.5)	20 (32.3)	
Children			0.323
Yes	29 (80)	46 (74)	
No	7 (20)	16 (26)	
Country of residency			0.743
Kuwait	5 (14)	13 (21)	
Oman	14 (39)	19 (30)	
Saudi-Arabia	9 (25)	14 (23)	
Egypt	8 (22)	16 (26)	
Country of neonatal training			0.013
Middle East	29 (80)	35 (56.5)	
North America	7 (20)	27 (43.5)	
Religion is important in medical practice?			0.369
Agree	33 (92)	54 (87)	
Disagree	3 (8)	8 (13)	
Self rated religious background			0.165
Very religious	13 (36)	20 (32)	
Somewhat religious	20 (56)	26 (42)	
Not very religious	1 (2)	3 (5)	
Not religious	2 (6)	13 (21)	
Confidence in leading discussion with families of critically ill infants about their religious or spiritual beliefs?			0.456
Not at all	2 (6)	10 (16)	
Somewhat well	16 (44)	21 (34)	
Reasonably well	14 (39)	23 (37)	
Very well	4 (11)	8 (13)	

was not statistically significant ($p = 0.743$). Other variables including age, gender, experience, number of children, religious background, and self-reported confidence in ROC-related discussion were not found to be statistically different between the two groups (Table 1).

The majority of respondents from both groups reported themselves to be religious (92% and 74% from groups A and B respectively). Respondents from both groups believed that ROC discussion and decision-making should involve family members and an authoritative teacher (Imam) (95 and 80% in groups A and B respectively). The major barriers identified with respect to ROC discussion and decision making were the lack of clarity and a fear of breaching Islamic ideals. All respondents felt the need for ethical codes conforming with Islamic and legal standards was urgent.

DISCUSSION

We aimed to identify and formulate recommendations regarding the challenges faced by neonatologists while considering ROC for Muslim neonates. As neonatology has developed rapidly during the last few decades, an increasing number of critically ill neonates receive life support treatment^[1-4]. This has led to improved survival, however, fairly large numbers of neonates encounter complications impacting short and long term survival and morbidity^[1-4]. ROC has assumed an increasingly important application in neonatology for decreasing pain and suffering for neonates and their families with poor prognosis^[6,7,17-19]. Redirection and end of life of care requires comprehensive and compassionate support for optimal coping by the family^[20]. The belief, attitudes, knowledge and communication skills of neonatal care providers can greatly influence family

experiences and coping, secondary to redirection and end of life of care^[20,21]. Redirection and end of life care needs specialized training for neonatal care providers for comprehensive care and for increasing awareness towards potential errors and omission^[22]. Our results confirm that training background has an impact on practice and attitude towards neonatal ROC. We found that North American training was associated significantly with ROC consideration on bivariate ((Group B), 43.5% in group B vs. 20% in group A ($p = 0.013$) (Table 1)) and multivariate logistic regression analysis (OR = 3.1; 95% CI: 1.1 to 8.8; $p = 0.03$). This could be attributed to differential exposure and training, and hence is indicative that ROC and end of life care should be incorporated in formal training for better care provision and experiences.

People from Muslim background firmly believe in following Allah's directives as noted in Quran^[12-15]. Novel questions posed by medical advances such as those related to neonatal ROC require interpretation and application of Quran by authoritative teachers (Imams), this has led to varied inferences and confusion^[14]. In our survey, we found that the majority of respondents from both groups reported themselves to be religious (92% and 74% from Group A and B respectively) and a large number of them (36.7%) were against any consideration for ROC. A significant proportion of those who were open to consideration would consider ROC only for specific diseases. The reasons for reservations against ROC were mainly religious (uncertainty of the religious edicts (80%) and the belief that ROC was against Islamic ideals (50%)). This represents a significant challenge regarding ROC consideration. This finding is in agreement with previous research suggesting that religious and cultural background of the patient and the care-providers impacts ROC decision-making^[23-28]. As physicians are considered as having authoritative and decision-making role in Islamic culture, the responsibility of physicians to consider and discuss options for treatment is further pronounced^[29]. The major barriers identified with respect to ROC discussion and decision making were lack of clarity and fear of breeching Islamic ideals. All respondents felt that ethical codes confirming with Islamic and legal standards for neonatal ROC were urgently required.

There have been recommendations from previous studies suggesting improved family comfort and better emotional outcomes in neonatal ROC when religious clergy and family members were involved in ROC decision making^[21,29-31]. Our study reiterates similar findings: respondents from both groups felt that ROC discussion and decision-making involving family members and authoritative teacher (Imam)

was better (95 and 80% in group A and B respectively). Additionally, the presence of Imam may help decrease the feeling of guilt accompanying ROC decision for the family as well as neonatal care providers involved in the decision-making.

Research focusing on issues, challenges and considerations for ROC in Muslim neonates is scant. Our questionnaire-based interview of neonatologists serving in middle-east Asia, who frequently face terminally ill Muslim neonates qualifying for ROC, is precisely targeted to address this issue. Our research highlights key recommendations for ROC in Muslim neonates and would prove helpful to neonatal care practitioners around the world when in such a scenario. The results of this study will help in increasing awareness of the neonatal care providers to better understand and manage the specific issues related to ROC for Muslim neonates. This study is based on interviews from neonatologists from four Islamic countries with adequate number of respondents, increasing the applicability and generalizability of the findings.

Limitations

As with any interview based research, there is a possibility of response bias. Although we asked open-ended questions and sought descriptive answers to minimize the bias, impact of response bias cannot be ascertained or ruled out.

CONCLUSION

ROC consideration for Muslim neonates has many socio-cultural and religious barriers. Neonatal care providers should be sensitive to the unique socio-religious context to better manage the specific issues related to ROC for Muslim neonates. Comprehensive ethical codes conforming Islamic and legal standards are urgently required to aid decision-making.

ACKNOWLEDGMENTS

Competing interests: The authors declare that they have no competing interests.

Authors' contributions

VS, AA and MA conceptualized & planned the study, drafted the manuscript, did the data collection, revised the manuscript and consented to the final manuscript as submitted.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Future directions: Development and application of neonatal ROC and end of life protocols specific

for Muslim families should be researched in further detail.

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Original Article

The Awareness and Attitudes of Medical and Dental Students in Health Science Center (HSC) toward Cardiopulmonary Resuscitation (CPR)

Abdulaziz HGhA Malik¹, Bushra AMA Ahmad², Sarah HEAA Alkanderi², Mohammad Abdulwahab³

¹Division of Internal Medicine, Al-Adan Hospital, Ministry of Health, Kuwait

²Dental Division, Ministry of Health, Kuwait

³Department of Surgical Sciences, Faculty of Dentistry, Kuwait University, Kuwait

Kuwait Medical Journal 2018; 50 (4): 422 - 424

ABSTRACT

Objectives: This study assessed: i) the level of cardiopulmonary resuscitation (CPR) education and training; and ii) the readiness among the students in case they are presented during an emergency outside of work.

Design: A cross-sectional study

Setting: Health Science Centre, Kuwait University (HSC-KU)

Subjects: Medical and dental students in their clinical years

Intervention: A self-administered, anonymous questionnaire composed of three sections and proposed different hypothetical situations was distributed in the HSC-KU.

Main outcome measures: Whether students had adequate knowledge about CPR, and their confidence in performing CPR.

Results: Of 331 invited participants, 208 (62.8%) agreed

and completed the questionnaire. Of 208 participants, 53.4% participants were not confident to perform CPR. The correct answers to 9 of 11 questions set as an adequate knowledge score was achieved only by 23.6% of the respondents. We found that the attitude of the rescuers changes with the situation faced.

Conclusion: Our findings show that even though students have received training in CPR, they are uncertain about applying their skills. This information may provide the guidelines to improve the current training program. Additionally, we suggest that clinically simulated scenarios may increase the confidence of students to perform in emergencies outside the hospital.

KEYWORDS: health education, medical education, resuscitation

INTRODUCTION

Cardiac arrest is the sudden cessation of cardiac rhythm. It is a devastating event as it is usually sudden and life threatening. Therefore, any intervention that can help in reducing the mortality of this event is important. One intervention is cardiopulmonary resuscitation (CPR)^[1]. Sudden cardiac arrests lead to an estimated 295,000 deaths per year in the United States of America and the chance of survival falls by 7 – 10% per minute that passes without intervention^[2]. As survival rate goes down with each minute, early initiation of bystander CPR has demonstrated improved survival as well as better quality of life for those who survive cardiac arrest^[3]. In addition, skill retention was found to decline as early as 2 weeks after the initial training and often reaches the pre-training

levels after 1 or 2 years^[4]. Therefore, CPR training is emphasized during medical training and evaluated; however, the level of confidence about their CPR skills and their readiness to actually perform it, in case they face any such situation. This study assessed the level of CPR training, education and their attitude towards managing cardiac arrest among medical and dental students at Health Science Center (clinical years) of Kuwait University.

SUBJECTS AND METHODS

We used a questionnaire that assessed the general knowledge and attitude among medical and dental students in the clinical years towards CPR. There were 3 sections in the questionnaire regarding questions about i) demographics such as age, gender and level of

Address correspondence to:

Abdulaziz H Gh A Malik, Al Qusour, Block 7, Street 3, House No 23, Mubarak Al Kabeer, State of Kuwait. Tel: +965-66060083; Email: drahmalik@gmail.com

Table 1: Level of CPR training and education among medical and dental students in Health Sciences Center

Question	Yes (%)	No (%)	Not Sure (%)
Do you feel confident in your CPR skills?	46	22	31
Will your decision to perform CPR be affected by appearance?	6	81	11
Will you attempt CPR in public?	48	8	42
Will you attempt CPR surrounded by family members indoors?	62	5.8	31

education; ii) the second section had questions about the participants' last CPR training; and iii) section comprised questions about participants' general knowledge about CPR and cardiac arrest management.

This questionnaire was reviewed by a professional with expert knowledge in CPR to critically evaluate the pertinence and accuracy of questions for our objective. Participants were informed that all data would be collected anonymously and that this data would be used in statistical analysis.

Descriptive statistics including percentage and frequency distribution of responses were computed using IBM SPSS statistics version 21.

RESULTS

In this study, 331 students were invited to participate, but 208 (62.8%) agreed and filled in the questionnaire. The remaining participants are medical students. Most of the participants were female (168, 81.6%) compared to males (38, 18.4%). The largest group of participants were enrolled in their fifth year (81, 39.4%), as opposed to sixth year students (73, 35.4%), and seventh year (52, 25.2%). Students aged 22 - 24 years constituted most participants (187, 91.7%). Twelve of those who participated were above 25 years old (5.9%) and five were under 22 (2.5%). It was estimated that most of the students received the official American Heart Association (AHA) training within the last 12 months (109, 53.2%).

We found that only 81 (39.3%) of the participants identified themselves as qualified to perform CPR in an emergency, 40 (19.4%) felt they were not qualified, and 110 (53.4%) participants were not confident that they had enough skill to provide adequate CPR (Table 1). Most participants prefer to have another rescuer assisting (187, 92.1%). As to their ability to perform appropriate resuscitation, 96 (46.6%) felt that they have enough skill, while 46 (22.3%) felt otherwise. A large percentage of the participants also feared a bad outcome (71, 35.5%). Only 49 (23.6%) of the respondents answered 9 or more out of 11 questions correctly, which was set as the adequate knowledge score. On the other hand, 158 (76%) did not meet the adequate knowledge score.

Regarding the attitude of the rescuers, we found that it changes based on the scenario they are facing. Furthermore, concerning a scenario where a family member needed CPR, the majority said they would

provide it (150, 73.9%), while a minority (26.1%) said they would not because they don't know how to resuscitate well. For a case in which the victim is a spouse, 146 (72.3%) said they would do CPR, compared to 27.7% who would not due to their anxiety about a bad outcome. When asked about their intent to perform CPR on a child, 130 (64%) answered yes, while 36% answered no, mainly because they felt that they don't know how to resuscitate. A similar result was obtained in case the patient was old, with numbers showing that 122 (60.1%) would perform CPR as opposed to 81 (39.9%) who would not do; whereas for scenarios in which the victim is a stranger or there is bleeding, the number of people who were not sure whether to perform CPR or not were 100 (49.5%) and 96 (47.3%), respectively. Gender was not a barrier to performing CPR as only 21 (10.3%) were not willing to perform CPR on a stranger of the opposite gender, however, 81 (39.9%) were hesitant. One hundred and ninety-two (94.1%) of those surveyed said that appearance is not an issue, while 12 (5.9%) said that the appearance of the victim may change their minds (Table 1). A majority (131, 64.5%) of the participants said they were ready to perform CPR in case the person is of another nationality, whereas 14 (6.9%) and 58 (28.6%) felt that they would not or were hesitant, respectively.

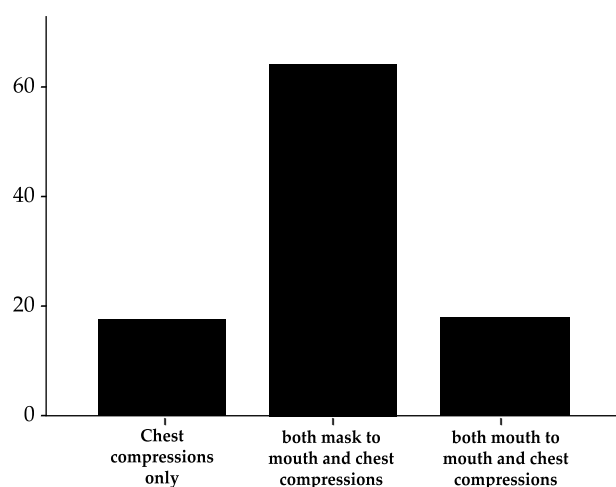


Fig. 1: Frequency of responses to question: if a stranger collapses in front of you, you are able to perform

Fig. 1: Frequency of responses to question: if a stranger collapses in front of you, will you be able to perform; i) chest compressions only, ii) mask to mouth and chest compression, iii) both mouth to mouth and chest compressions

Personal conflict with the victim was not a deterrent to performing CPR as the majority (135, 66.8%) said they would attempt to do CPR in such a case.

When the participants were asked about their attempt to perform CPR based on the place of emergency, about half of them (101, 49.5%) are willing to perform CPR in public, and 128 (62.7%) are willing to perform CPR indoors (Table 1)

A majority of the participants (129, 64.2%) are willing to perform both mask to mouth and chest compressions, in case the victim is a stranger. However, 36 (17.9%) of them prefer chest compressions only or both mouth to mouth and chest compressions (Fig 1).

DISCUSSION

Effective and fast action is paramount to increase the chance of survival in a cardiac arrest case. In our study, we found that the majority of students have received the required training, but only half of them have the will to perform CPR in a hypothetical situation. Reasons given include fear of a bad outcome. Forty-nine (23.6%) of those in the survey had good knowledge about CPR. This can explain why only half the students have the confidence to do CPR in an imagined setting. It has been shown that the knowledge and skill of CPR degrade with time^[5-6]. Furthermore, the number and intensity of the CPR sessions may not have been sufficient for all students^[5-6].

There were two main hypothetical situations where students were more likely to be reluctant to perform CPR. The first was in case of trauma or bleeding. The other situation was in case victim was of the opposite gender. This can be explained by the culture in our society and as it may be perceived as inappropriate behavior. However, we noted that mask usage increases the will to provide CPR. A reason as to why some students may prefer that is fear of disease transmission^[7]. However, this cannot be provided readily outside the hospital as pocket masks are rare.

We provided several reasons as to why some students might provide CPR. The fact that respondents were more likely to perform CPR indoors may highlight the stress associated with a public performance of CPR. Also, respondents prefer performing CPR indoors to in public which creates more stressful situation. Low self-confidence and fear of a bad outcome were factors in deciding to not offer CPR. All the above mentioned factors were a possible explanation that contribute to

the unwillingness among many of the medical and dental students to perform CPR, even with the training they received.

This study has few limitations; first, as it was done only on HSC students, there was no control group from another medical school for comparison. Furthermore, only students were tested. A study on doctors would add practical information about this issue. Finally, as the data collection method was a questionnaire, no testing was done to compare the student's confidence with his or her actual CPR skill.

CONCLUSION

Our findings showed that even though students have received training in CPR, they were hesitant to apply their skills. This information warrants the need to improve the students' knowledge, skills and confidence to provide CPR if situation demands so. Clinically simulated scenarios may increase the confidence of students to perform in emergencies outside the hospital.

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Original Article

Uterine Smooth Muscle Tumors of Undetermined Malignant Potential (STUMP): A clinicopathological study with a focus on outcome

Nisreen Abu Shahin¹, Ali- Alkhader¹, Ahmad Aqel¹, Kamel Fram²

¹Department of Pathology, Faculty of Medicine, University of Jordan, Amman, Jordan

²Department of Obstetrics & Gynecology, Faculty of Medicine, University of Jordan, Amman, Jordan

Kuwait Medical Journal 2018; 50 (4): 425 - 431

ABSTRACT

Objectives: To study the clinicopathological features, management and outcomes of uterine smooth muscle tumors of uncertain malignant potential (STUMPs), which is a rare group of smooth muscle tumors difficult to categorize as benign or malignant

Design: Retrospective study

Setting: Jordan University Hospital, Amman, Jordan

Subjects and Methods: Women who underwent surgical removal of uterine smooth muscle tumors and were diagnosed as STUMP by histopathology during the last ten years; following approval by Faculty of Medicine's Ethics Committee.

Interventions: Clinical data were collected from patients' medical records, including age, medical and family history, treatment modalities, and follow up data. Representative H&E microscopic slides of all cases were reviewed for recording histologic features.

Main outcome measures: Twenty one patients were studied

according to clinical, radiological, surgical, histopathological and postoperative characteristics.

Results: Two patients (9.5%) experienced disease recurrence (as STUMP and leiomyosarcoma). The rest of the patients remained recurrence-free (mean follow-up of 40 months) including those treated with myomectomy alone. The disease-free survival was 100%, even in cases with recurrences (post recurrence follow-up average 35 months). One patient had successful pregnancy following myomectomy. None of the histological features had a significant impact on outcome.

Conclusion: Current cases had low recurrence rate and high rate of disease-free survival. Limited surgical management followed by close clinical and radiological follow-up maybe safe measures, especially in patients with fertility desire. Hysterectomy is best in postmenopausal women. Larger studies are needed to set parameters to identify patients at risk of recurrence who may benefit from more resolute surgical approach.

KEYWORDS: leiomyoma, leiomyosarcoma, smooth muscle tumors of undetermined malignant potential

INTRODUCTION

Smooth muscle tumors of uncertain malignant potential (STUMPs) designate rare uterine smooth muscle tumors that cannot be categorized definitely as benign or malignant, as based on histopathological criteria set by Kempson *et al*^[1] (Stanford criteria) for malignant behavior of uterine smooth muscle tumors. Those are a set of histopathological features that include: diffuse moderate-to-severe nuclear atypia; mitotic figures (MF) $\geq 10/10$ high power fields (HPF); and tumor coagulative necrosis (TCN). At least two criteria are required for a diagnosis of uterine leiomyosarcoma (ULMS). Among those criteria, many

gynecologist pathologists believe that TCN is the strongest predictor of dreadful behavior^[1].

Review of the literature had shown that the term STUMP was first used by Kempson *et al* in 1973^[2], and later adopted by the WHO^[3], as a label of a group of borderline tumors, that fall intermediate between uterine leiomyoma (ULM) and ULMS. Although STUMP does not have definite diagnostic criteria of its own, it is said that a diagnosis of STUMP is made histologically and given to tumors that display any unusual combination of Stanford criteria that does not qualify as ULMS^[4]. Therefore, any of the following histopathological scenarios are diagnostic of STUMP:

Address correspondence to:

Nisreen Abu Shahin, M.D., Assistant Professor of Pathology, Department of Pathology, Faculty of Medicine, University of Jordan, Queen Rania Street, Aljubaiha 11942, Amman, Jordan. Tel: 962 798504920; E-mail: nisreenshahin@yahoo.com

1. no/mild atypia + TCN+ MF \leq 10 /10 HPF
2. moderate/severe focal atypia + no TCN + MF > 10 /10HPF
3. moderate/severe focal atypia + no TCN + MF < 10/10HPF; while some researchers prefer to call this category as atypical leiomyoma-low risk of recurrence; others insist that it should be included under STUMP^[5,6].

Pre-operative diagnostic imaging techniques such as computed tomography or magnetic resonance imaging, are not competent to distinguish between ULM and STUMP in many cases^[7]. A sonographic-guided fine needle biopsy as a diagnostic tool had been described in literature^[8], however, STUMP were hardly distinguishable from ULMS and ULM. Intra-operative frozen section examination is similarly of limited diagnostic value for STUMP, as the features used to diagnose malignancy in smooth muscle tumors are very difficult to ascertain due to freezing artifact^[9]. Thus, the most reliable method of distinction so far is post-operative histopathological examination. Immuno histochemical stains (IHCs) as a potential diagnostic tool of STUMP were recently tried^[10,11]; however, current available reports display controversial results, and up to date there are no reliable diagnostic IHC markers for STUMP.

Future immunophenotypic and molecular studies on larger sample sizes are needed to set new tumor markers that may be helpful in diagnosis and prognosis applications.

Scarcity of STUMP studies had lead to poor understanding of pathogenesis and molecular background, and to controversy about the appropriate management of patients. Whether STUMP will turn out to be a mere exaggeration of a ULM, or a low grade ULMS is the subject of future investigations at the molecular level^[12,13]. Distinction is significant since while ULMs are considered the most common female benign tumors, with nil risk of malignant transformation, ULMS are aggressive neoplasms with high rates of recurrence and fatal outcome.

The available data so far, however, indicates a low level of aggressive behavior, low rate of recurrences, and prolonged survival rate of STUMP when compared to leiomyosarcoma, however, recurrence is a recognized feature of STUMP^[1], with literature review figures ranging from 8 - 11%^[6], usually as LMS or STUMP.

Until now, no standard protocols for STUMP management have been approved, but the mainstay is still surgical excision by either myomectomy or hysterectomy, although there are no studies so far to compare any difference in patient outcome. Moreover, solid guidelines for patient management remains controversial, especially in women with fertility desire.

In this case series, we represent our experience with

STUMP over 10 years at a tertiary care center, aiming to correlate histopathological features with patient outcome, and try to set appropriate management guidelines, especially for the purpose of fertility preservation.

SUBJECTS AND METHODS

Following Institutional Ethics Committee and Review Board approval, the histopathological records at our institution were reviewed covering the period from 2007 to 2016, with a search for histopathological diagnosis of uterine STUMP, and a total of 21 cases were found. For those, the patient's medical records were retrieved for clinical data including age, parity, comorbidities, other gynecological or breast conditions, smoking, family history of cancers or similar conditions, initial treatment, additional treatments received, clinical follow up (FU) data regarding symptoms resolution, imaging studies, residual or recurrent disease, follow up period (FUP) and final outcome for each case. Histopathological features were collected from pathology reports; and H&E microscopic slides reviewed by a gynecological pathologist.

RESULTS

Prevalence of STUMP

During the period covered by this study, a total of 1812 uterine leiomyomas were diagnosed in our institution (including 28 cellular leiomyomas, 9 symplastic, 5 lipoleiomyomas, and one myxoid leiomyoma). Thus, the prevalence of STUMP among presumed uterine fibroids is estimated as 1.2%.

Clinical features

STUMP patient ages ranged from 32 - 48 years (mean: 41.3 years). The FUP ranged from 6 - 100 months (mean: 39.3 months). Four patients had co-morbidities (three had diabetes mellitus, hypertension, with one of them having dyslipidemia; the 4th patient had multiple sclerosis). Five patients were active smokers. One patient gave a positive family history of breast cancer and one of colon cancer, four had other gynecologic or breast-related conditions (20%), including bilateral ovarian cysts (two), endometriosis (one), genital warts/positive human papillomavirus tests (two), and breast fibroadenoma (one).

The most common clinical presentation was menorrhagia (13/21; 61.9%), followed by abdominal pain (8/21; 38%). Six patients gave a history of a previous miscarriage. Out of 13 fertility-seeking patients, six had fertility issues (6/13; 46.2%), including primary (four) and secondary (two) infertility. In parous patients, the parity ranged from one to 15 (mean: 5.3). Hormonal therapy was given to six patients (28.5%) for different purposes, including menorrhagia/ irregular cycles

Table 1: Clinical features of STUMP cases

No	Age	FUP ^e	Primary therapy	Conc ^c fibroids	Recurrence (site/mo)	Follow up outcome	Addition Therapy	Follow up by imaging
1	41	9	Myo ^h	0	-	AWND ^a	-	no
2	38	7	TAH ⁱ	3	-	AWND	-	yes
3	36	45	myo	0	-	AWND	-	yes
4	48	25	TAH	0	-	AWND	-	yes
5	47	41	myo	7	-	AWND	-	no
6	48	59	myo	6	-	AWND	-	yes
7	39	18	Lap ^g myo	0	-	AWND	TAH & BSO Hor ^f Rx	no
8	44	85	TAH & BSO ^b	7	-	No data	No data	No data
9	42	100	myo	29	-	No data	No data	No data
10	42	5	TAH	4	-	AWND	-	no
11	46	50	TAH	0	-	No data	No data	No data
12	44	15	myo	1	-	AWND	-	yes
13	32	34	myo	1	-	AWND	-	yes
14 ^t	35	33	myo+ bil. Ov ⁱ cyst	0	Uterus / 24 mo	AWND (11mo)	TAH & BSO	yes
15	41	32	myo	0	-	AWND	-	yes
16	48	21	TAH	0	-	AWND	-	yes
17	33	79	myo	0	-	AWND	-	yes
18 ^c	33	65	myo	0	-	AWND	-	no
19	44	63	myo	0	-	AWND	-	no
20	44	21	TAH & BSO	0	-	AWND	-	no
21 ^t	46	65	TAH	10	Perineum / 6mo	AWND (59mo)	exc ^d	yes

†: cases with recurrence; ^c: case with post operative successful pregnancy; ^a: alive with no disease; ^b: bilateral salpingo-oophorectomy; ^c: concurrent; ^d: excision; ^e: follow up period; ^f: hormonal therapy; ^g: laparoscopic; ^h: myomectomy; ⁱ: ovarian; ^j: total abdominal hysterectomy

(four), infertility treatment (one), and treatment of ovarian cysts (one).

The primary management was myomectomy (myo.) in 13 cases (61.9%), followed in frequency by total abdominal hysterectomy (TAH) in seven (33.3%), in one patient myo. was performed followed by TAH. FU information was available in 18 cases. FU imaging studies were performed in 14 patients (66.7%) with clinical improvement in 12 cases and persistent/recurrent abnormalities in two. Clinical notes taken during FU showed that overall improvement of symptoms was reached in 14/18 patients (77.8%), while two still complained of symptoms, and two mentioned worsening symptoms (each representing 11.1%). Additional managements were set to two patients (one had hormonal therapy; two had TAH and bilateral salpingo-oophorectomy (BSO)).

Interestingly, one patient aged 33 years (case 18) treated conservatively with myo. had a successful pregnancy 1 year post myo. Two other patients had unsuccessful pregnancy trials, with one missed abortion, and one failed IVF.

By the time of writing this manuscript (mean FUP of 40 months), two patients (case 14 and case 21) (9.5% of all, 11% of cases with FU) developed a recurrence, one after six months, and one at two years' post surgery evidenced by imaging studies and subsequent histopathological examination. Following second surgery, both patients were alive without disease with a FUP of 11 months and 59 months respectively (average secondary FUP:35 months). Clinical features of STUMP cases are summarized in Table 1.

Histopathological features

Tumor sizes ranged from 1.5 - 28 cm (mean: 7.6 cm); and presented as a solitary uterine lesion in 11 cases, while it was associated with concurrent ULMs in 10 cases (47.6%), synchronous fibroids when present ranged from 10- 29. TCN was evident in 18 cases (85.7%). MF/10HPF were ≤ 5 in 14 cases, and >5 in seven cases (33.3%). Actual MF/10HPF ranged from 1 - 22 (mean: 4.6). Nuclear atypia was mild in 16 cases (76%), moderate in 4 (19%), and severe in one case (4.8%). Significant atypia was focal in four and diffuse in two cases. Histopathological features of STUMP cases are summarized in Table 2.

STUMP cases with recurrence

Rec.1: A para2, 46-year-old woman (Case 21) presented to the clinic with a one year history of menorrhagia and cyclic pain. Her medical history was unremarkable except for having antiphospholipid syndrome. She did not have a significant family cancer history or gynecological conditions. She denied receiving any hormonal therapy, intrauterine device use or smoking. She underwent ultrasound evaluation, which showed bulky uterus with multiple fibroids. She underwent TAH, revealing ten intramural masses, the largest being 12 cm in diameter. The other masses ranged from 1 - 5 cm.

Histopathological examination of the smaller masses confirmed multiple leiomyomata uteri exhibiting hyaline degeneration, with average MF 3 /10HPF. Meticulous examination of the largest mass had demonstrated microscopic foci of TCN, mild

Table 2: Histopathological features of STUMP cases

No.	Size (cm)	TCN ^d	Atypia	MF ^e	MF (< 5 or ≥5)	Atypia ^a grade	Complete exc. ^b
1	8	no	focal	22	≥5	2	yes
2	8	+	-	0	<5	1	yes
3	5	+	-	4	<5	1	yes
4	4	+	-	3	<5	1	yes
5	2.5	+	-	6	≥5	1	yes
6	13	+	-	4	<5	1	yes
7	7	+	-	3	<5	1	no
8	11	no	diffuse	9	≥5	3	yes
9	3.5	+	-	2	<5	1	yes
10	1.5	+	-	2	<5	1	yes
11	4	+	-	5	≥5	1	yes
12	13.5	+	-	1	<5	1	yes
13	6	+	-	6	≥5	1	yes
14 [†]	6	no	diffuse	8	≥5	2	no
15	5	+	-	7	≥5	1	yes
16	6	+	focal	4	<5	2	yes
17	5.5	+	-	2	<5	1	yes
18 ^ε	7.5	+	focal	2	<5	1	yes
19	4	+	-	1	<5	1	yes
20	28	+	-	1	<5	1	no
21 [†]	12	+	focal	5	<5	2	yes

[†]:cases with recurrences; ^ε: case with post operative successful pregnancy; ^a: atypia was graded as 1=mild; 2= moderate; and 3= severe; ^b: complete excision was diagnosed if lesion was excised intact, without fragmentation, and show free surgical margins; ^c: mitotic figure/10 HPF; ^d: tumor coagulative necrosis.

atypia, and a maximum MF 5/ 10HPF. A diagnosis of STUMP was given. Following her TAH, the patient underwent BSO revealing bilateral ovarian hemorrhagic corpus luteal cysts with no evidence of malignancy.

Six months later, the patient complained of perineal mass for which she underwent excision. The resection consisted of fragments of tissue with whorled cut surface, measuring 10x8x3.5cm with foci of pinpoint hemorrhages. Microscopy revealed a tumor of hypo and hypercellular areas. The tumor cells were whorled slender cells showing hyperchromatic nuclei arranged in variable-sized fascicles. Hypocellular areas contained myxoid extracellular material highlighted by Hale's colloidal special stain (Fig 1). The highest MF is 7/10HPF in hypercellular areas. Taking into consideration the patient's previous diagnosis, a panel of immunohistochemical markers was performed, and proved to be positive for smooth muscle actin (SMA), H-caldesmon, and estrogen receptors; while negative for EMA, S-100, CD117, and neurofilament. The perineal mass was diagnosed as leiomyosarcoma with focal myxoid features. During the second FUP of 59 months, with close clinical and radiological monitoring, no evidence of another recurrence was detected.

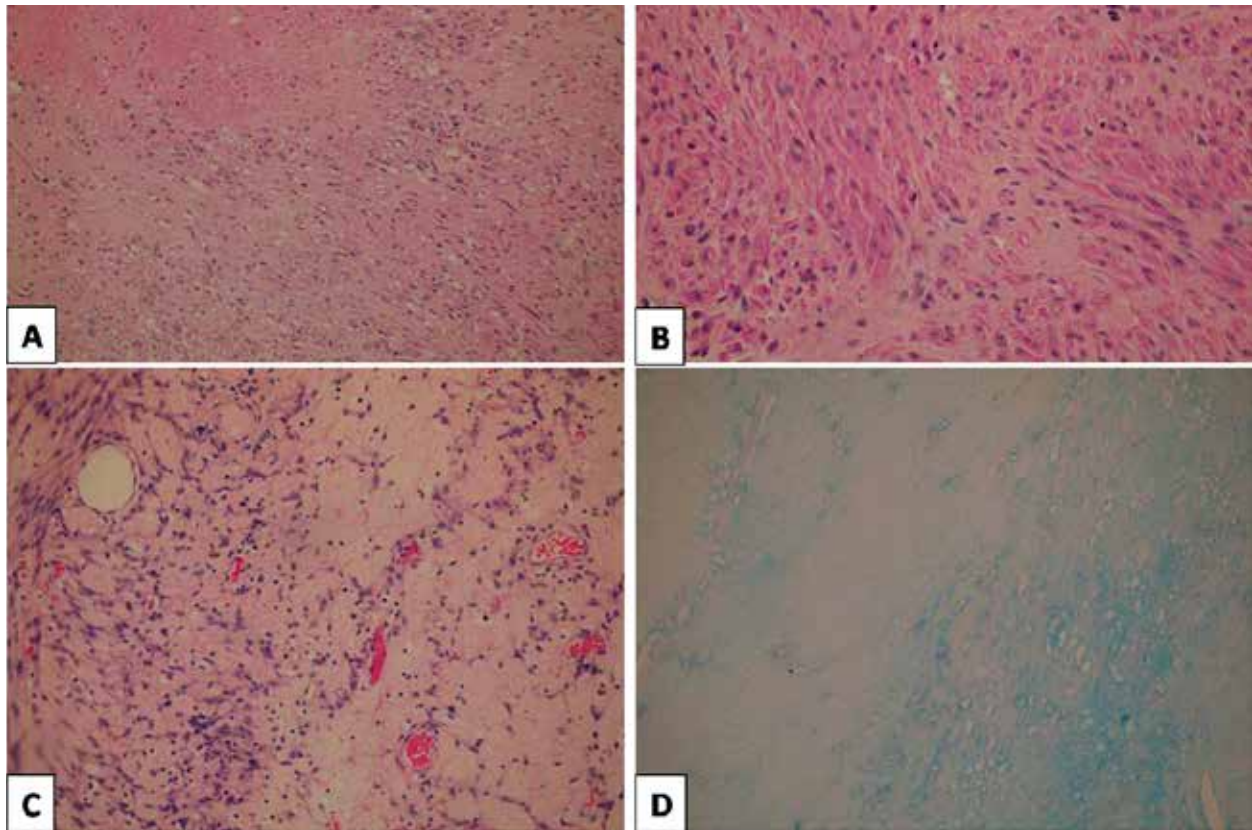


Fig 1: STUMP case with recurrence (**Rec. 1**). Uterine STUMP showing areas of coagulative tumor necrosis (A), and mitotic activity (B). Recurrence as perineal myxoid leiomyosarcoma, myxoid changes as seen on H&E (C), and using Hale's colloidal iron special stain for acidic mucin (D). (Original magnifications 200, 400x)

Rec.2 : A 36-year-old, nulliparous woman (Case 14) was visiting the clinic for primary infertility. Her gynecologic history was also significant for vulval warts and irregular cycles. Abdominal ultrasound examination revealed single subserosal fibroid and bilateral adnexal cysts. She underwent laparotomy myomectomy and bilateral ovarian cysts excision. Histopathology showed a 5 cm uterine mass with whorled cut surface and central blackish area. The ovarian cystic lesions were endometriotic cyst and a luteal cyst. The uterine mass was composed of spindle and epithelioid cells arranged in fascicles with focal moderate atypia and irregular nuclear contour. MF was 8/10 HPF. Central hemorrhage was seen, however, no TCN was identified. Safe surgical margins were not seen as the tumor reached the inked surgical margins. STUMP was diagnosed. Eighteen months later, the patient described unresolved abdominal pain and irregular cycles and went to a different hospital where she had radiological studies suspicious for "recurrent disease in uterus", thus she underwent TAH 24 months following her initial diagnosis that confirmed residual STUMP. Since then, the patient had no evidence of recurrence with a FUP of 11 months.

DISCUSSION

The current STUMP case series displayed a low recurrence rate (9.5%), no mortalities, and a high rate of disease-free survival during a relatively long follow up period (mean FUP of 40 months), which is compatible with previous studies. The rest of the patients remained recurrence-free; including those treated with myomectomy alone. The disease-free survival was 100%, even in the two cases with recurrences that were treated surgically (post recurrence average FUP: 35 months). Moreover, one of our patients had a successful pregnancy following conservative surgery (myomectomy) and is recurrence-free till the writing of this manuscript.

Clinical presentation of our STUMP cases was undistinguishable for fibroids, and typically included menorrhagia (13/21; 61.9%), and abdominal/pelvic pain^[4]. A significant number of married patients also had infertility issues (6/13; 46.2%). STUMP also affects women at comparable age to that of ULM and ULMS, our patients' ages ranged from 32 - 48 years (mean: 41.3 years), similar to most patients presenting with symptomatic fibroids.

In fact, many of the previous case series described concurrent existence of ULM and STUMP in the uterus^[6]. Ten of our cases (48%) had concurrent benign fibroids.

As stated earlier in the introduction, pre-operative imaging studies, and intra-operative frozen section had very limited diagnostic yield in uterine smooth muscle tumors^[7-9]. Thus, our diagnosis of STUMP cases

was mainly dependent on Stanford histopathological criteria performed on formalin-fixed tissue from resection specimens. Our aim was to investigate the significance of those criteria and to determine if possible, which one is more predictive of worse prognosis and risk of recurrence.

IHCs as a potential diagnostic tool of STUMP were recently tried, with controversial results.

The differential diagnosis of STUMP should include other uterine smooth muscle tumors (LM and LMS) as well as other mesenchymal tumors like endometrial stromal sarcoma and perivascular cell tumors. As smooth muscle tumors, STUMP share in common with LM and LMS the immuno-expression of smooth muscle markers such as desmin, H-caldesmon, and SMA. They are usually distinct from other types of uterine mesenchymal tumors such as endometrial stromal sarcomas and epithelioid perivascular neoplasms by being negative for CD10 and HMB-45, respectively^[4].

Some researchers described increased expression of proliferation markers such as Ki-67, and over expression of p53 and p16 in STUMP in comparison to ULM^[6,10]. Progesterone receptor (PR) expression had been detected in more than 80% of STUMP in some studies, with a significant difference compared to LMS that tend to be negative for PR^[10], although the difference is not significant between LM and STUMP. Whether PR may be a potential therapeutic strategy needs future examination.

Despite the controversial results of those studies, they somehow suggested an intermediate position of STUMP between LM and LMS in that regard^[10].

A potential role of those markers in recognizing STUMP with higher risk of recurrence was described in literature^[11]. However, up to date there are no reliable diagnostic IHC markers for STUMP.

STUMP is not equivalent to the term atypical leiomyoma (ALM) that shows only marked nuclear atypia without TCN or high MF. ALM is thus a variant of benign ULMs. Another type of tumors that need to be distinguished from STUMP is the mitotically active ULM (defined as MF ranging from 5 to 19/10 HPF, without TCN or diffuse atypia), as this tumor also shows benign behavior with no risk of recurrence or metastasis^[5]. Moreover, the practicing pathologist should be cautious when evaluating TCN, which should be strictly defined as abrupt transition between viable tumor cells and necrotic areas, avoiding mixing it up with innocuous hyalinization, superficial ulceration of sub mucosal ULM, or hemorrhage within ULM.

The available case studies to date are generally indicating a low level of aggressive behavior and prolonged survival rate when compared to ULMS. However, recurrence is a recognized feature of

STUMP. In a comprehensive review, Ip *et al* estimated recurrences of 8 - 11%, including 67% recurring as leiomyosarcoma, and delayed-recurrences (ranged from 15 months - 9 years)^[4]. Other reports documented recurrence as STUMP^[13,14]. Site of recurrences was frequently in abdomen/pelvis. Extra-abdominal sites^[4,15], however, were also detected such as lymph node, bone^[1], as well as lung metastasis^[16].

So far, prediction of recurrence in STUMPs is problematic^[1], as previous data failed to show significant association with ethnicity, cigarette smoking, and even serum tumor markers like CA125^[17]. Some previous papers observed that patients with recurrence were younger than those with uneventful course^[6]. One of our cases with documented recurrence was a 36-year-old, but the other was a 46-year-old, thus we assume that generalization should be avoided in this regard.

Correspondingly, even Stanford Criteria don't attain conformity regarding association with recurrence risk, specifically TCN which is believed to be the highest predictor of malignant behavior in ULMS^[1]. The reason is that many STUMPs contain TCN but only a few display a recurrence. Similarly, our results showed that none of the histological features had a significant impact on outcome. Of the current cases, 86% showed TCN while only one of the cases with recurrence had TCN. Recently, a potential role of some molecular markers of cell cycle in predicting recurrence had been presumed, including BCL-2^[18]; demonstrated by marked amplification of the BCL2 in STUMP cells as well as in their recurrences.

The relative infrequency of STUMP has led to limited clinical, histopathological and molecular studies. Thus, appropriate patient management of this entity remains controversial, especially in women with fertility desire.

Until now, no standard protocols for STUMP management have been approved. The first logical approach is surgical with either myomectomy with free margins or TAH. The limited available case series show excellent overall survival and disease-free survival with both approaches^[12]. There is no documented use of chemotherapy, hormonal, or radiotherapy as first line management^[1]. In reported STUMP cases with recurrence, the mainstay was also surgical excision followed by adjuvant therapy when needed, such as pelvic irradiation, chemotherapy (doxorubicin and cisplatin), and hormonal therapy *e.g.* medroxyprogesterone^[11] and gonadotropin-releasing hormone analogue^[14]. Regardless of the used regimens, most cases with recurrences had good overall prognosis^[19] with exceptional deaths due to disease^[1].

STUMP represents borderline tumors in comparison

to ULM and ULMS; with a reported 5 year-overall survival of 92%^[13,20]. Even cases with documented recurrent disease show good overall prognosis and long term survival. Conservative surgical management is relatively followed by good results, and as previously reported^[21], successful pregnancy in fertility desiring patients is possible and one of our patients had an uneventful pregnancy 12 months post STUMP-excision. Our case series had an overall 5 year survival of 100% even in cases with recurrent disease. Cases with recurrences were alive with no disease for an average of 35 months post- recurrence.

CONCLUSION

Based on literature review and our current findings, we believe that in case of STUMP, young patients with fertility desire should be offered conservative surgical treatment with safe margins followed by close radiological follow up. TAH with strict radiological follow up may be the best practice in older and postmenopausal patients.

ACKNOWLEDGMENTS

None

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

Funding/Support Statement: None

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Original Article

Do we use too much Propofol for Sedation in Colonoscopy? An Observational Study with Sedline Monitor

Duygu Kara¹, Asli Demir¹, Alev Saylan¹, Umit Karadeniz¹, Tahsin Dalgic², Busra Tezcan¹

¹Department of Anesthesiology and Reanimation, Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey

²Department of Gastrointestinal Surgery, Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey

Kuwait Medical Journal 2018; 50 (4): 432 - 436

ABSTRACT

Objectives: Propofol and midazolam are popular sedatives in colonoscopy. Our aim was to measure depth of sedation with propofol-fentanyl and midazolam-fentanyl in patients undergoing colonoscopy using a blinded electroencephalogram (EEG)-based SEDLine monitor.

Design: Non-randomized, prospective, observational

Setting: Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey

Subjects: One hundred and eight adult volunteers with American Society of Anesthesiologist (ASA) class I-II-III, aged 18 – 80 years, and undergoing colonoscopy with propofol-fentanyl (Group P) or midazolam-fentanyl (Group M)-based sedation

Interventions: Demographic variables, depth of sedation and recovery times were recorded.

Main outcome measures: Depth of sedation was measured and recorded with an EEG-based SEDLine monitor. Patient State Index (PSI) values at colonoscopy

insertion, removal, and at return of verbal responsiveness after colonoscopy withdrawal were documented.

Results: Patients in group P were younger ($p < 0.0001$) and had lower ASA scores ($p = 0.02$) than group M patients. Group P patients experienced significantly deeper degrees of sedation at all times and longer sedation and recovery times ($p < 0.0001$ and $p = 0.01$). Group P patients were more deeply sedated and had lower PSI values at the 5th minute ($p < 0.0001$) and lower PSI scores after recovery ($p < 0.0001$). Group M had more comorbidity but more stable PSI values. Their sedation levels were also closer to normal.

Conclusion: Clinical signs for sedation showed that propofol was over-used. The titration of propofol using a processed-EEG monitor, such as SEDLine, can improve sedation procedures by reducing time spent in states of deep sedation/general anesthesia while maintaining the clinical advantages of propofol.

KEY WORDS: depth of sedation, electroencephalography (EEG)-based monitor, midazolam, propofol

INTRODUCTION

Colonoscopy is a diagnostic and therapeutic procedure that causes discomfort and pain. Maintenance of amnesia with sedation is advised during the procedure in order to minimize these complaints, as well as patient anxiety, especially in cancer patients who require multiple procedures^[1]. Sedoanalgesia is also performed in order to increase tolerance on the part of the patients who require close attention and careful monitoring in order to avoid the risk of complications^[2]. Sedative agents may affect patient satisfaction, safety and ease of procedure,

and thus also endoscopist satisfaction. Propofol is a well-known drug frequently used during induction and maintenance of anesthesia in adult and pediatric patients and with no analgesic properties. It is preferred during colonoscopy for the maintenance of conscious sedation. In subhypnotic doses, it results in sedation and amnesia^[3,4]. Studies have evaluated the effects and efficacy of many drugs, including propofol. Wide use of propofol sedation has been crucial in improving patient tolerance. Patient compliance has also improved, thus permitting extensive screening. The efficiency of endoscopy units has also increased due to early

Address correspondence to:

Duygu Kara, MD, Department of Anesthesiology and Reanimation, Turkey Yuksek Ihtisas Training and Research Hospital, Kizilay Street, Number 4, Siihiye, 06230, Ankara, Turkey. Tel: +90 506 928 8141, +90 312 306 1000; Fax: +9 0312 306 0000; E-mail: drduygukara@yahoo.com

and lucid recovery, in turn making early discharge possible. While similar studies have investigated depth of sedation using other monitors, few have investigated depth of sedation in patients undergoing colonoscopy using a SEDLine monitor (SedlineInc., San Diego, CA, USA)^[5,6]. The purpose of this study was to calculate depth of sedation in an objective manner by means of an electroencephalography (EEG)-based SEDLine monitor.

SUBJECTS AND METHODS

Local ethical committee approval was granted for the enrollment of patients undergoing outpatient colonoscopy over a 6-month period. This non-randomized prospective study was performed in the colonoscopy unit in Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey. Patients undergoing colonoscopy and receiving either propofol-fentanyl based sedation (Group P) or midazolam-fentanyl sedation (Group M) were included. The recruitment period lasted approximately 6 months (2014 – 2015), and 108 adults (58 males, 50 females) were finally enrolled. An approved signed informed consent form was received from all patients prior to the start of the operation. Patients aged 18 – 80 years, American Society of Anesthesiologists (ASA) scale I to III, and undergoing colonoscopy for various reasons and receiving sedation during the operation were included. No acute intoxication or chronic alcoholism was present in any patient, and all patients were referred from outpatient clinics. Depth of sedation was monitored using a SEDLine EEG (Masimo Corp., Irvine, CA, USA)-based monitor, a device that measures and displays the patient state index (PSI), a recognized and validated indicator of depth of sedation. PSI scores of 0 – 25 indicate deep general anesthesia, 25 – 50 indicates general anesthesia/deep sedation, and 50 – 100 indicate mild to moderate sedation^[7,8]. Patients were not allocated to groups P or M on a random basis. We prefer to use midazolam-based sedation for comorbid patients, and propofol for others in our routine clinical approach. The use of sedatives is based on various factors, including age (propofol-based sedation is recommended for younger patients) and comorbidity. In this study, the anesthesiologist added fentanyl to sedatives for analgesia, and sedative drugs were administered by an experienced anesthesiologist. The level of sedation was examined using the Richmond Agitation-Sedation Scale. It was attempted to keep all the patients at the same level. No other sedatives or analgesic medications were administered. All patients received supplemental oxygen via nasal cannulae. Intravenous propofol, typically at 0.5-2 mg kg⁻¹, and fentanyl at 1 µg kg⁻¹ were started simultaneously in group P. Further propofol boluses were administered

in the light of the patient's reaction to the ongoing stimulation. In group M, midazolam was administered at 0.03 - 0.1 mg kg⁻¹ and fentanyl at 1 µg kg⁻¹. Following routine procedure under normal conditions, the anesthesiologist administers any extra doses of the sedative drugs required according to the patient's needs. Meanwhile, it is desirable that the patient's spontaneous breathing should be maintained, so respiratory rate and pulse oximetry are monitored. The sedation administrator was blinded to the depth of sedation indicators, and the SEDLine monitor was concealed for the anesthesiologist. PSI scores were recorded at the 5th minute after drug administration, with colonoscope insertion, and when the patient started to respond to instructions after colonoscope removal. The numbers of patients at different depths of sedation (PSI scores of 0–25, 25–50 and 50–100) were accessed from the computer database.

Statistical Analysis

Descriptive statistics were used to analyze demographic data. Central tendencies were expressed by the use of mean (parametric data) and median values (non-parametric data). Normality of distribution was analyzed using the Kolmogorov-Smirnov test. Parametric data (mean SEDLine score) were analyzed using Student's unpaired t-test. Frequency data (gender distribution in groups) were compared using Pearson's Chi-square test. Intergroup comparison of non-parametric data (patient ASA status distribution) was performed using the Mann-Whitney U test.

RESULTS

One hundred and eight patients were enrolled in this study, 49 receiving propofol-fentanyl (Group P) and 59 patients receiving midazolam-fentanyl (Group M). There were meaningful statistically significant differences between the two groups in terms of demographic variables (mean age and ASA score). ASA scores of Group P patients were lower than those of Group M patients ($p = 0.02$) (Table 1), while mean baseline and recovery PSI values differed (60.8 ± 9.9 and 77 ± 10.2) ($p < 0.0001$). PSI scores at time of scope insertion (5th min) were significantly lower in Group P in comparison to Group M (53.9 ± 9.7 vs 69.5 ± 9.8 respectively) ($p < 0.0001$). Similarly, PSI scores at the end of the procedure, when patients were once again responsive to verbal commands, were significantly lower in Group P in comparison to Group M (60.8 ± 9.9 vs 77 ± 10.2 respectively) ($p < 0.0001$). PSI values associated with general anesthesia/deep sedation were significantly prolonged in Group P (PSI scores of 0 – 50) in comparison to Group M ($p < 0.0001$) (Table 2). Similarly, analysis showed a significant difference in the number of patients with PSI values below 25, an

Table 1: Comparison of demographic and clinical variables in terms of sedation protocols during colonoscopy under SEDline monitoring

Variables	Group P (n = 49)	Group M (n = 59)	p-value
Age (years) (mean±SD)	44.1 ± 8.9	66.7 ± 7	<0.0001*
Gender (male/female)	25/24	33/26	0.3
Weight (kg) (mean±SD)	75.7 ± 15.1	73.4 ± 12.2	0.3
Height (cm) (mean±SD)	167 ± 9	164 ± 7	0.1
Body mass index (kg/m ²) (mean±SD)	26.8 ± 4	26.9 ± 4.1	0.9
ASA scores (I/II/III)	36/12/1/0	23/33/3/0	0.02*
Comorbidities	13 (26.5%)	32 (54.2%)	0.004*
Sedation time (min) (mean±SD)	17.2 ± 4.6	13 ± 6.1	<0.0001*
Recovery time (min) (mean±SD)	13.8 ± 14.6	8.4 ± 5.3	0.01*

Group P: patients who received the propofol-fentanyl protocol; Group M: patients who received the midazolam-fentanyl protocol; *: statistically significant; SD: standard deviation; ASA: American Society of Anesthesiologist

indicator of deep general anesthesia [2 patients in Group P vs 0 patients in Group M (p <0.0001)] (Table 2). Patients in Group M who had more comorbidity had more stable PSI values. Their sedation levels were also closer to normal values. Patients were transferred to the recovery room once hemodynamic stability and verbal responsiveness had been confirmed.

Table 2: Comparison of depth of sedation using SEDline monitoring between the groups in terms of sedation protocols

PSI level	Group P (n = 49)	Group M (n = 59)	p-value
5 th min PSI n (%)			<0.0001*
0-25	2 (4.1)	0 (0)	
25-50	16 (32.7)	3 (5.1)	
50-75	29 (59.2)	26 (44.1)	
75-100	2 (4.1)	30 (50.8)	
5 th min PSI (mean±SD)	53.9 ± 9.7	69.5 ± 9.8	<0.0001*
Post recovery PSI (mean±SD)	60.8 ± 9.9	77 ± 10.2	<0.0001*

Group P: patients who received the propofol-fentanyl protocol; Group M: patients who received the midazolam-fentanyl protocol; *: statistically significant; SD: standard deviation; PSI: patient state index

DISCUSSION

The aim of this study was to monitor depth of sedation with a blinded anesthetist during a procedure that we perform many times every day. Following routine procedure under normal conditions, the anesthesiologist administers any extra doses of sedative drugs required according to the patient's needs. Meanwhile, it is desirable that the patient's spontaneous breathing should be maintained, so respiratory rate and pulse oximetry are monitored. In our study, patients were sedated and monitored in a routine manner, and by applying this approach we recorded the degree of sedation depth. Our findings showed that propofol was used more than clinically required.

The anesthetist should aim to limit unnecessary deep anesthesia while still preserving suitable conditions. One recent large study demonstrated a significant increase in the risk of pulmonary aspiration with propofol-based sedation in patients undergoing colonoscopy^[4]. When we used the clinical signs for sedation in this study, it emerged that propofol was used considerably more than necessary. The use of propofol also enhances both patient's satisfaction and compliance. However, one of the difficulties involved in propofol sedation concerns titration for the appropriate sedation depth. The majority of anesthetists employ end points including loss of verbal contact or eyelash reflex to assist with administration. However, these are not entirely reliable, and also entail a risk of over-sedation and even, on rare occasions, cardiorespiratory arrest^[9]. Additionally, even experienced administrators may not have a full understanding of the pharmacokinetic and pharmacodynamic variations deriving from individual patient variability^[10,11]. The use of a validated EEG-based monitor to guide sedation will facilitate titration. New, appropriately powered clinical trials are now needed to investigate this. Cerebral function monitors are safer and more efficient in general anesthesia, and are also used for guiding conscious sedation for various procedures^[12]. Bispectral Index (BIS) values exhibit good correlation with sedation levels, and previous studies have validated the role of BIS as an objective technique for monitoring sedation^[13,14]. BIS monitoring is commonly employed in a range of surgical and endoscopic procedures. Research has confirmed that propofol dosages can be lowered and recovery accelerated with the use of BIS in endoscopic retrograde cholangio-pancreatography (ERCP)^[15]. Previous researches have also described the benefits of BIS monitoring in submucosal dissection or ERCP, and a significant difference in propofol doses or levels of satisfaction on the part of both endoscopists and patients have also been reported^[15,16]. Studies performed using BIS monitors^[17,18] have also reported that the PSI can be used to assist the administration of intravenous and inhaled anesthetics to optimize drug delivery to meet the needs of the individual patient, thus facilitating an earlier recovery from anesthesia. Pierce *et al*^[19] suggested that using the PSI for propofol administration significantly lowered maintenance dosage requirements and resulted in earlier recovery times, with no increase in side-effects. The PSI monitor displayed PSI values during the operation of the electrocautery unit better than the BIS monitor. Baseline PSI values in this study were significantly lower in group P compared to group M. Propofol provides a wide range of sedation, from conscious to deep and to general anesthesia, but

is also difficult to regulate. However, midazolam has a limited capacity to induce deep sedation at recommended dosages. These sedatives also exhibit pharmacokinetic differences, resulting in a shorter wake-up time using propofol despite deeper degrees of sedation. Recovery times were also measured. Only 5.1% of the total time was spent in a state of general anesthesia/deep sedation in group M, compared to 32.7% with propofol sedation. Based on the current dosing strategies, while propofol can provide greater patient satisfaction, there is nevertheless a genuine and not uncommon risk of over-sedation^[20,21]. Unfortunately, in clinical practice, greater doses than necessary may be administered to provide adequate depth of sedation, due to pharmacokinetic and pharmacodynamic variations deriving from individual subject variability. This in turn results in consequences such as an increased risk of aspiration pneumonia^[2]. A higher incidence of aspiration has been observed in patients undergoing colonoscopy with propofol-based sedation^[3]. One suggested mechanism involved is the greater probability of passive regurgitation and aspiration in patients sedated with propofol. The risk of aspiration and the total level of propofol consumed can be reduced by titrating propofol administration to a lighter depth of sedation. An additional outcome is that patients may probably wake up earlier and be discharged sooner. This may also help in reduction of cost. Another highly significant factor is that deeper levels of sedation will also result in a greater risk of hypotension. Patients frequently become hypovolemic following bowel preparation, with an attendant increase in the risk of intraprocedural hypotension^[22].

Propofol-based sedation produces significantly deeper sedation in subjects undergoing colonoscopy compared to other forms of intravenous conscious sedation. Our study findings explicitly reveal this using objective measurements. The doses of midazolam and fentanyl employed in group M produced mild sedation, while the amount of propofol employed in group P elicited a level of sedation compatible with general anesthesia. Cohen *et al* performed all procedures using a lower dose of propofol and reported a high degree of patient satisfaction^[23]. Anesthetists generally administer higher doses of propofol, leading to a deeper degree of sedation. However, this can exacerbate the risks of aspiration and hypotension, in turn resulting in a lower level of patient satisfaction. An increased depth of sedation may also cause complications such as colonic perforation^[24]. As detailed in the results, the propofol dose in this study was within the range of general anesthesia. Better titration may therefore be possible with the use of a cerebral function monitor.

Dissatisfaction reported by gastroenterologists represents another limitation^[11]. However, the use of a validated EEG-based monitor may be of assistance to anesthetists in administering appropriate depths of sedation.

There are some limitations to this study. First, the propofol and midazolam groups were not randomized. We also did not collect data regarding patient satisfaction in order to compare the clinical applicability of the two materials investigated. However, this was not one of the aims of the study.

CONCLUSION

The use of clinical signs for sedation in this study showed that propofol was used considerably in excess of requirements. In the literature, midazolam has been associated with delayed discharge and decreased patient satisfaction. Propofol provides better patient satisfaction, although overdose is more common. Propofol titration with a processed-EEG monitor, such as the SEDLine device, can improve sedation procedures by reducing length of deep sedation/general anesthesia while preserving the known clinical advantages posed by propofol. EEG-based monitoring can result in more objective, uncomplicated and tolerable sedation. Lighter titrations of sedative drugs may also result in improved patient care, such as reducing the risks of aspiration and hypotension, and lower levels of delayed discharge.

ACKNOWLEDGMENT

No conflict of interest was declared by the authors.

The authors declare that this study has received no financial support.

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Original Article

Retrospective Evaluation of Neutrophil to Lymphocyte Ratio in patients with Metastatic Testicular Cancer

Yigit Akin^{1,2}, Sacit Nuri Gorgel¹, Osman Kose¹, Eser Ordek², Ercan Yeni², Yuksel Yilmaz¹

¹Department of Urology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey

²Department of Urology, Harran University School of Medicine, Sanliurfa, Turkey

Kuwait Medical Journal 2018; 50 (4): 437 - 441

ABSTRACT

Objectives: Our aim was to evaluate the impact of neutrophil to lymphocyte ratio (NLR) in patients with metastatic testicular cancer (tCa).

Design: Retrospective view of prospective recorded data

Setting: Clinical study was conducted at multicentre between May 2010 and September 2016

Subjects: Patients with tCa who underwent radical orchiectomy were enrolled. Similar surgical methods, laboratory analyses, and radiologic examinations were performed and all patients were divided into 2 groups. Group 1 (n = 108) consisted of patients with non-metastatic testicular cancer; Group 2 (n = 38) consisted of patients with metastatic (solid organ-lymph node metastasis) tCa.

Intervention: Radical orchiectomy, blood sample

Main outcome measures: Demographic, preoperative, and postoperative data were noted. Postoperative complications were interpreted according to modified Clavien classifications. Statistical significant p was $p \leq 0.05$. Receiver

operating curves (ROC) were obtained for determining cut-off value NLR in terms of tCa metastases.

Results: Mean follow-up was 36.4 (4 - 72) months. Mean age was 39 years (19 - 71 years). There were significant differences between groups in preoperative NLR, tCa markers and diameter of tumour ($p = 0.03$, $p < 0.001$, $p = 0.01$, respectively). Besides, invasion to lymphovascular, rete testis, cord, epididymis, and surgical margin positivity, postoperative tCa markers were significantly higher in group 2 than group 1. Area under ROC curve was 0.69, ($p < 0.001$) and cut-off value for NLR was 3.11 in terms of any metastasis. There was no serious complication after operation. Five patients experienced wound infections (Clavien 1).

Conclusions: Preoperative NLR could help us to predict lymph node and solid organ metastasis in patients with tCa. If the NLR is over 3.1, clinicians should be aware of metastasis.

KEY WORDS: inflammation, metastasis, testicular neoplasms

INTRODUCTION

Testicular cancer (tCa) is seen in 1% of all male cancers^[1]. Besides, 3/100,000 new cases are consisted per year worldwide^[1,2]. Incidence of tCa has also been increasing in developed countries^[3,4].

Germ cell tumours are the most common type of tCa (90 - 95%) and bilateral ones are rare^[1]. The peak incidence is observed in the 3rd decade of life for non-seminoma, and in the 4th decade for pure seminoma. The tCa has excellent response to chemotherapy, specifically to cisplatin^[5]. It is very important to make accurate staging at time of diagnosis. Thus, adequate and early treatments can be performed. In the course of diagnosis, clinicians usually use traditional tCa markers and radiologic examinations such as abdominal and thorax computed tomography (CT). The lower stage of

tCa can be treated surgically by radical orchiectomy in peripheral hospitals^[6]. However, the metastases of tCa can be misdiagnosed and relapses in metastatic sites can be annoying^[7]. The advanced diagnostic modalities such as positron emission tomography (PET/CT) can show metastasis of tCa. However, the peripheral hospital might not have CT and PET/CT devices. Besides, the frequency of post-chemotherapy residual tumour resection has been associated with perioperative mortality and overall survival^[8,9]. In view of these lines, accurate diagnosis of metastases should be performed.

On the other hand, involvement of systemic inflammation and progression was reported in tCa during the cancer development^[10]. Increases in neutrophils with decrease of lymphocytes were

Address correspondence to:

Yigit Akin, M.D., Department of Urology, Izmir Katip Celebi University School of Medicine, 35620, Izmir, Turkey. Tel: +90-232- 3293535; Fax: +90-232-3860808; E-mail: yigitakin@yahoo.com

Table 1: Comparison of mean data in groups

Parameters	Group 1 (n = 108)	Group 2 (n = 38)	p-value
Age	39.3 (19 - 71)	36.9 (20 - 55)	0.9
Preoperative AFP	483.3 (0.7 - 8802)	6650 (1.3 - 54260)	0.001*
Preoperative bHCG	2597.8 (0 - 181999)	132592.5 (1.35 - 1164157)	0.001*
Preoperative LDH	322.5 (114 - 2779)	890.5 (188 - 2782)	0.001*
Preoperative NLR	3.3 (1.04 - 21.9)	4.9 (1.5 - 14.5)	0.003*
Tumour size	4.4 (0.3 - 17)	6.1 (0.9 - 13)	0.25
Lymphovascular invasion	0.3 (0 - 1)	0.5 (0 - 1)	0.13
Rate of invasion to rete testicle	0.06 (0 - 1)	0.3 (0 - 1)	0.001*
Rate of invasion to cord	0.06 (0 - 1)	0.2 (0 - 1)	0.001*
Rate of invasion to epididymis	0.05 (0 - 1)	0.2-0.4 (0 - 1)	0.001*
Rate of surgical margin positivity	0.009 (0 - 1)	0.1 (0 - 1)	0.001*
Rate of lymphadenopathy in retroperitoneum	0.2 (0 - 1)	0.9 (0 - 1)	0.001*
Postoperative AFP	3.1 (0 - 25)	11.9 (0 - 107)	0.001*
Postoperative bHCG	1.9 (0 - 2.8)	7600 (0 - 145276)	0.001*
Postoperative LDH	170.8 (0 - 276)	379.6 (0 - 1635)	0.001*
Rate of receiving chemotherapy	0.6 (0 - 1)	0.7 (0 - 1)	0.28
Rate of receiving radiotherapy	0.2 (0 - 1)	0.2 (0 - 1)	0.72
Rate of RPLND	0.07 (0 - 1)	0.5 (0 - 1)	0.43
Alive	0.9 (0 - 1)	0.4 (0 - 1)	0.001*
Living in months	45.5 (3 - 124)	25.2 (1 - 84)	0.27

AFP: alpha-fetoprotein; bHCG: beta human chorionic gonadotropin; LDH: lactate dehydrogenase; NLR: neutrophil to lymphocyte ratio; RPLND: retroperitoneal lymphnode dissection

*Statistical significant p-value.

One-way ANOVA test was used.

shown in literature that was related with systemic inflammatory response development against the tumour. The neutrophil to lymphocyte ratio (NLR) has been used as an indicator of systemic inflammatory response^[11]. The mechanism includes the increased supply of factors that promote carcinogenesis and tumour progression by cells of the innate immune systems and decreased anti-tumour response by immune cells of the adaptive system^[12].

The NLR, which can easily be calculated from routine complete blood count (CBC) with differentials, is an emerging marker of host inflammation^[13]. This was also shown to be an independent prognostic factor for a variety of solid malignancies^[14,15]. There are some emerging studies on impact of NLR in usage of secondary marker of tCa^[16]. However, there has not been a published study on comparison of NLR between metastatic and non-metastatic tCa in literature.

We here investigated the impact of NLR in metastasis of tCa to lymph nodes and solid organs. We also determined cut-off value of NLR in terms of metastasis to these tissues. Our hypothesis was NLR could increase more in tCa patients than in non-metastatic ones.

SUBJECTS AND METHODS

Patient data

This is a multicentre study including retrospective view of prospective collected data. Additionally, the present study is an on-going study. Institutional

review board and ethical committee approved the study. Signed consent forms were obtained from all patients. Between May 2010 and September 2016, all patients with tCa who underwent surgery (radical orchiectomy)^[17], enrolled in the study. Exclusion criteria were metastasis to brain and irregular follow-up.

All patients were divided into 2 groups as group 1 (n = 108) consisting of non-metastatic tCa and group 2 (n = 38) consisting of metastatic (solid organ and lymph node metastasis) tCa.

Data collection

Demographic, preoperative, and postoperative data of patients were collected. The collected data was noted on Microsoft Excel Data Sheet. Laboratory analyses included alpha-fetoprotein (AFP), beta human chorionic gonadotropin (HCG), lactate dehydrogenase (LDH), CBC, scrotal ultrasound (USG), abdominal USG (when needed), abdomen-pelvic CT and thorax CT. The NLR was calculated from CBC. Similar surgical technique was performed in all cases for radical orchiectomy^[17].

Metastatic sites were decided according to pathology reports, CT, and PET/CT slides. Additionally, if the patient had neurologic symptoms, cranial enhanced CT was performed for detecting brain metastasis of tCa. Besides, some of the metastatic tissues occurred in the follow-up.

Postoperative complications were classified according to modified Clavien classification^[18].

Statistical analyses

Statistical Package for the Social Sciences (SPSS, V16.0, Chicago, IL) was used for statistical analyses. One-way ANOVA tests were used for comparing mean values in groups. The receiver operating curves (ROC) were drawn and cut-off value for NLR was determined in terms of tCa metastasis. The significant p-value was $p \leq 0.05$.

RESULTS

The mean follow-up was 36.4 months (range: 4 - 43). The mean age was 39 years old (range: 19-71). There were statistically significant higher elevations in group 2 than group 1 in terms of preoperative beta HCG, LDH, NLR ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.003$, respectively). Mean age, tumour size and the rate of lymphovascular invasion were similar in both groups.

Besides, statistically significant elevated ratio of invasion to rete testis-cord-epididymis, surgical margin, and lymph node in retroperitoneum were obtained in group 2 than group 1 (for all parameters; $p < 0.001$).

The mean values of postoperative AFP, beta HCG, and LDH were higher in group 2 than group 1 in follow-up (for all parameters; $p < 0.001$). The rate of used chemotherapy and radiotherapy were comparable in both groups. Patients with stage 1 seminoma and/or non-seminoma tCa were rarely administered chemotherapy. All these were summarized in Table 1.

Table 2 shows the comparable changing pathologic diagnosis of tCa in both groups. Group 1 consisted of stage 1 patients. Besides, there were 27 stage 2 and 11 stage 3 patients in group 2.

Table 2: Pathology data of patients in groups

Parameters	Group 1 (n = 108) n (%)	Group 2 (n = 38) n (%)	p-value
Seminoma	43 (39.8)	10 (26.3)	0.7
Germ cell tumour	4 (3.7)	11 (28.9)	
Mixt type	47 (43.5)	10 (26.3)	
Embryonal cell carcinoma	6 (5.5)	2 (5.2)	
Teratocarcinoma	4 (3.7)	1 (2.6)	
Teratoma	2 (1.8)	3 (7.8)	
Lymphoma	2 (1.8)	1 (2.6)	

We drew the ROC curve for determining cut-off value of NLR in terms of tCa metastases. The area under ROC curve was 0.69 ($p < 0.001$). The cut-off value for NLR was 3.11 (Fig. 1).

The most common complication was wound infection (Clavien 1) that was treated with medication. We additionally performed wound dressing regularly during follow-up. There were no Clavien 3b, 4, and 5 complications.

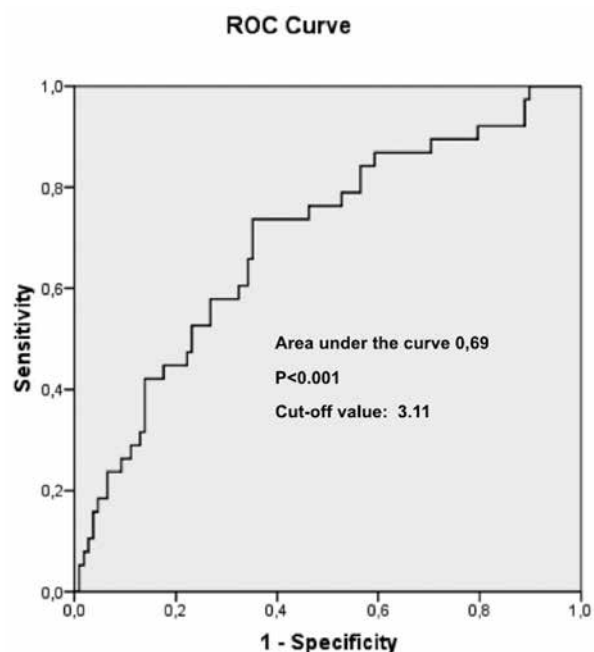


Fig. 1: Receiver operating curves was used to determine cut-off value of neutrophil to lymphocyte ratio in terms of metastasis.

DISCUSSION

In the present study, we found significantly higher NLR in patients with metastatic tCa than non-metastatic ones. The blood tests and radiological evaluations are performed for diagnosing tCa. We determined the cut-off NLR for predicting tCa metastases by using simple laboratory tests. Thus, our hypotheses were proved with these findings. If the tCa patient's NLR is over 3.11, clinicians should be aware of metastases.

One of the common points of tCa and NLR is the inflammation that can easily be put forward^[16]. Our hypothesis was based on these. We traditionally use tCa laboratory tests and radiological examinations as AFP, beta HCG, LDH and thorax, abdomen, and pelvic CT, respectively. Additionally, PET/CT can be used in suspicious cases for detecting metastases of tCa. However, PET/CT could mostly determine tCa metastases to retroperitoneal lymph nodes easily. Since these radiological diagnostic tools may not be available in peripheral hospitals, metastases can be misdiagnosed. At this point, NLR value may warn clinicians. Besides, it is very easy to access CBC for detecting NLR. To our best knowledge, this is the first study in which impact of NLR was presented in patients with metastatic tCa. Additionally, the cut-off NLR value for tCa metastasis was determined.

We found significantly higher preoperative NLR in group 2. Additionally, preoperative AFP, beta HCG, and LDH were significantly higher in group 2. Yuksel *et al* reported that higher NLR in tCa can be used as a secondary marker for tCa^[16]. In their study, there were

36 tCa patients with mean NLR at 2.58^[16]. Higher mean preoperative NLR was determined in the present study than study of Yuksel *et al.* Besides, we determined the cut off value for NLR in ROC curves as 3.11, for metastatic tCa. These may relate to higher numbers in groups, in our study. We determined metastases according to pathology in retroperitoneal lymph node dissections and CT, PET/CT slides. Zhao *et al* reported use of PET in determining tCa metastasis^[19]. Höltl *et al* reported spread of tCa by vessels^[20]. In view of these lines, we accepted lymph node involvement as metastasis. In the light of the above data, it is clear that metastases of tCa increase inflammation. Therefore, all those caused to increase NLR. Besides, if the NLR is higher than 3.11, in patients with tCa, clinicians should be aware of metastasis.

Postoperative pathology results supported higher clinical stages of tCa in our study. The invasion to rete testis-cord-epididymis, surgical margin, and lymph nodes in retroperitoneum were significantly higher in group 2. Additionally, these were parallel to postoperative mean serum tCa markers such as significantly higher postoperative AFP, beta HCG, and LDH in group 2. All these are similar to published literature on tCa and its metastases^[21]. Wu and Zhou showed molecular pathways that linked inflammation in the way of tumour metastasis^[22]. Rajput and Wilber published similar findings with them^[23]. Porta *et al* also concluded that inflammation showed progression of the tumour^[24]. However, we did not perform any molecular based analyses. Our findings in terms of higher NLR in metastatic tCa could support those literatures above. It is inevitable that molecular basis of higher inflammation in metastatic tCa should be investigated in detail with molecular studies.

On the other hand, Takashi *et al* reported that increased preoperative NLR was strongly associated with poor prognosis in patients with upper urinary tract urothelial carcinoma^[25]. We showed significantly higher survival rates in group 1 than group 2. This is also similar to published literature on this topic.

We have some limitations in this study. There was unequal distribution of patients in the 2 groups and low number of participants in the groups. Additionally, we retrospectively evaluated patient files and follow-up database. We also used CT and PET/CT slides for determining metastases, knowing this examination could easily detect retroperitoneal lymph nodes. We did not have the opportunity to perform biopsy for tissue diagnosis in most cases. However, we focused on higher NLR in metastatic tCa.

To the best of our knowledge, this is the first study that showed higher NLR was obtained in metastatic NLR than non-metastatic ones. Thus, higher

preoperative NLR (>3.11) may not be an independent marker for metastasis of tCa, but it could show poor prognosis in tCa patients. The molecular evidence of these findings should be investigated in detail in future studies.

CONCLUSION

The preoperative NLR can be higher in metastatic tCa than non-metastatic ones. The NLR can be easily calculated from CBC and could be a pathfinder for clinicians in tCa patients. If the NLR is higher than 3.11, clinicians should be aware of metastases of tCa. Thus, misdiagnosis could be overcome in metastasis of tCa. More molecular based studies are needed on this topic for showing details of inflammation modalities for tCa metastasis.

ACKNOWLEDGMENT

Conflicts of interest: The authors declare no conflicts of interest.

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Original Article

Association between Fibromyalgia and Autoimmune Thyroid Disease

Shafieh Movassaghi¹, Hoda Karmostaji¹, Nooshin Shirzad^{2,3}, Fatemeh Esfahanian³, Mahboobeh Hemmatabadi², Mostafa Qorbani^{4,5}

¹Rheumatology Research Center, Valiasr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

²Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

³Endocrine Research Center, Valiasr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

⁴Department of Community Medicine, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

⁵Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Kuwait Medical Journal 2018; 50 (4): 442 - 446

ABSTRACT

Objective: To investigate the prevalence of fibromyalgia (FM) among patients with Hashimoto's thyroiditis (HT) and association of thyroid antibodies with FM severity among affected individuals.

Design: Cross-sectional

Setting: Two endocrinology outpatient clinics

Subjects: Euthyroid patients with HT were recruited

Intervention: Assessment for detection of fibromyalgia

Main outcome measure(s): Prevalence of fibromyalgia and association with Hashimoto's thyroiditis. Diagnosis of FM was made using the 2010 American College of Rheumatology criteria. Serum concentrations of thyroid stimulating hormone (TSH) and anti-thyroid peroxidase (anti-TPO) antibodies were determined.

Results: Average age of the patients was 38.5 years and

93.1% were female. Among the 102 patients, diagnosis of FM was made in five patients (prevalence rate, 95% CI: 4.9%, 0.7 - 9.1). Age, sex, level of education, marital status, menopause status, duration of thyroid disease, TSH, and anti-TPO concentrations were comparable between patients with and without FM ($p > 0.05$ in all tests). Among patients with FM, the indices of FM severity (widespread pain index, and symptom severity) were not significantly correlated with TSH or anti-TPO concentrations.

Conclusion: Despite previous reports suggesting an increased risk of FM in HT, among Iranian patients with HT, the prevalence of FM seems to be comparable with the prevalence reported in the female general population. A possible link between HT and FM needs further investigation in large population-based studies.

KEYWORDS: hashimoto disease/diagnosis, rheumatic diseases/diagnosis, thyroid disorders

INTRODUCTION

Hashimoto's thyroiditis (HT), the most common cause of hypothyroidism, is a disorder of autoimmune origin characterized by the activation of auto-reactive, thyroid-specific antigen T cells and subsequent aberrant production of anti-thyroid antibodies by B cells^[1]. While elevated concentrations of thyroid antibodies might be present in as many as 10% of the general population^[2], the evident dysfunction of the thyroid gland – often manifesting as hypothyroidism – is found in around 0.1 - 2% of adults^[3]. A female preponderance, similar to several other autoimmune

disorders, is noted^[3]. The prevalence of HT increases with age, peaking between 45 - 65 years^[3].

Rheumatologic manifestations of HT have long been recognized^[4]. Musculoskeletal complaints seem to be present even in the absence of frank thyroid hormone abnormalities^[5]. In the past few years, a number of clinical studies have suggested that the prevalence of fibromyalgia (FM) – a common diagnosis in rheumatology practice – is increased among patients with HT and the two disease entities might somehow be interrelated. Initial reports have suggested FM comorbidity among patients with HT is

Address correspondence to:

Nooshin Shirzad, MD, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Shariati Hospital, North Kargar Avenue, 1411413137, Tehran, Iran. Tel: +982188220037-8; Fax: +982188220052; E-mail: nshirzad@tums.ac.ir

a common occurrence and can be identified in 31 - 59% of the subjects^[4,6]. Additionally, a high prevalence of thyroid autoimmunity among FM patients have also been documented^[7]. No study to date has investigated the possible association among Iranian patients. In the present study, we aimed to determine the prevalence of FM in a sample of Iranian euthyroid patients with HT. From an epidemiological perspective, we hypothesized that if there is a link between FM and HT, the prevalence of FM is expected to be greater than the general population. Further, assuming such an association, we postulated that serum concentrations of thyroid antibodies among patients with comorbid HT and FM would positively correlate with FM disease severity.

SUBJECTS AND METHODS

Patients

In this cross-sectional study, between March 2009 and July 2013, consecutive patients with a confirmed diagnosis of HT who visited the endocrinology and metabolism clinics of two teaching hospitals (Arash and Vali-Asr), affiliated with Tehran University of Medical Sciences (Tehran, Iran), were assessed for eligibility. Inclusion criteria were as follows: 1) confirmed diagnosis of HT; 2) age equal or greater than 18 years; 3) being euthyroid for at least the past three months; and 4) having complaints of non-specific musculoskeletal and/or somatic symptoms. Patients were not included if they had previous diagnoses of comorbid autoimmune or connective tissue diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, spondyloarthropathy, polymyalgia rheumatica, and Sjögren's syndrome), degenerative joint diseases, bursitis, tendinitis, myofascial pain syndrome, comorbid infections with hepatitis C or human immunodeficiency virus or malignancy. Patients with a previous diagnosis of neuropsychiatric disorders including multiple sclerosis, schizophrenia, bipolar mood disorder, and major depression were also excluded. Patients with peripheral neuropathies were excluded as well.

Diagnosis of HT was made on the basis of clinical history, physical examination, ultrasonography assessment, measurement of serum concentrations of anti-thyroid peroxidase antibodies (anti-TPO). Serum concentrations of thyroid stimulating hormone (TSH) were measured using the chemiluminescence immunoassay method and the range 0.5 - 4.3 mIU/L was deemed normal according to the manufacturer's instructions. Serum concentrations of anti-TPO were measured using the enzyme-linked immunosorbent assay method and values > 35 IU/ml were considered higher than normal. All procedures dealing with human subjects in the present study were conducted

in accordance with the ethical guidelines laid down in the latest revision of Helsinki declaration. Ethics committee of the Tehran University of Medical Sciences also approved the study protocol. Written informed consent was obtained from all participants prior to enrollment.

Assessment and diagnosis of fibromyalgia

Eligible patients were referred to the Rheumatology clinic of the hospital and underwent assessment for diagnosis of FM using history and physical examination. A thorough medical history along with the information obtained from patient's file was recorded in pre-designed standard questionnaires. In physical examination, patients complaining of bodily pains were carefully examined and if a competing diagnosis that could explain the symptom pattern was suspected (e.g. osteoarthritis, inflammatory arthritis, discopathies), the patient was excluded. Additionally, in more ambiguous cases, serum concentrations of rheumatoid factor, and anti-nuclear antibodies were ordered, and patients with positive results on either of the tests were excluded as well.

The 2010 American College of Rheumatology (ACR) criteria was used to diagnose FM^[8]. Using the 2010 updated criteria, an FM diagnosis can be made if the following three conditions are satisfied: 1) presence of symptoms for at least three months; 2) absence of disorders that could otherwise explain the pain; and 3) a widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 . If WPI < 7, then a diagnosis can be made only if WPI is between 3 - 6 and SS ≥ 9 . The evaluation for FM diagnosis was done by two independent assessors (S. M.) and (H. K.). The independent assessors then compared their evaluations and disagreements were resolved by consensus. The kappa measure of inter-rater agreement was 0.884, indicating an excellent level of agreement.

Statistical Analysis

Statistical analyses were conducted using the Software Package for Social Sciences (SPSS) version 17 for Windows (SPSS Inc., Chicago, IL). Continuous variables with normal distributions are presented as mean \pm standard deviation and categorical variables as proportions. Given the non-normal distribution of thyroid disease duration, it is presented as median (interquartile range). Independent t-test (or Mann-Whitney U test where appropriate) was used to compare continuous variables between patients with and without FM. To compare the distribution of proportions between the two groups, Chi square test (or Fisher's exact test where appropriate) was used. In the subset of patients with FM, the correlations between continuous variables and WPI/SS were assessed using

Table 1: Baseline characteristics of euthyroid Hashimoto thyroiditis patients

Variable	Value
Age, years (mean± SD)	38.5 ± 11.9
Sex (female) n (%)	95 (93.1)
Education (years) (mean± SD)	11.5 ± 4.2
Marital status (married, n) (%)	90, (88.2)
Menopause status ^b (menopause, n) (%)	18, (18.9)
Duration of thyroid disease ^a (months)	36 (14-99)
Anti-TPO (IU/ml) (mean± SD)	364.1 ± 37.7
TSH (mIU/l) (mean± SD)	2.53 ± 1.37

TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone

^a presented as median (interquartile range)

^b the denominator is the total number of females (n=95)

Pearson's product moment correlation coefficient. In all tests, a two-sided p-value <0.05 was considered necessary to reject the null hypothesis.

RESULTS

Initially, 131 patients met the inclusion criteria and underwent detailed assessment for diagnosis of FM. However, among these, 29 patients did not agree to participate, had an exclusion criteria unraveled only after the second assessment, or the diagnosis of HT could not be confirmed. Therefore, the final statistical analyses were conducted on the remaining 102 patients. Baseline characteristics of the patients with HT are summarized in Table 1. Females comprised the majority of the sample (93.1%). The average age of the patients was 38.5 years and ranged from 20 to 65 years. The median duration of thyroid disease was 36 months and ranged from 1 to 444 months. Among the 102 patients, five fulfilled the ACR criteria set for FM, giving rise to a prevalence rate of 4.9% (95% CI: 0.7 - 9.1). A case-by-case description of HT patients with FM is presented in Table 2. All diagnosed cases

were female and the sex distribution between FM positive and negative groups was not significantly different ($p = 1.000$). The average age of cases was 46.8 ± 9.3 years. Compared with patients without FM, cases were on average 8.7 years older, yet the inter group difference did not reach statistical significance (46.8 vs. 38.1 , $p = 0.111$). Level of education, marital status, and menopause status were also comparable between FM positive and negative patients ($p = 0.961$, 1.000 , and 0.371 , respectively). The median duration of thyroid disease in FM patients was 143 months and was higher than the rest of the sample (median: 36 months), yet the difference did not reach statistical significance ($p = 0.413$). The mean serum concentrations of anti-TPO and TSH among FM patients were 270 ± 51 IU/ml and 2.53 ± 0.37 mIU/L, respectively and were similar to the rest of the sample ($p = 0.554$ and 1.000 , respectively). The association between FM severity (WPI and SS) and serum concentrations of anti-TPO and TSH was evaluated in the subgroup of FM patients using correlation analysis. Neither WPI nor SS were significantly correlated with anti-TPO or TSH ($p > 0.05$ for all tests).

Among the 97 patients without FM, complaints of fatigue, waking unrefreshed, and cognitive symptoms were frequent and were collectively seen in 69 patients (71.1%). However, in all cases, the somatic symptoms were not accompanied by the wide-spread pain syndrome characteristic of FM or the severity of symptoms were not high enough to warrant the diagnosis of FM.

DISCUSSION

In the present cross-sectional study, we aimed to elucidate the frequency of FM among patients with HT and to also investigate whether thyroid antibody concentrations correlate with FM severity among

Table 2: Case by case description of patients with fibromyalgia

Age (years)	Sex	Duration of thyroid disease (months)	Anti-TPO (IU/ml)	TSH (mIU/l)	WPI ^a	Somatic symptoms ^b		Cognitive symptoms	Somatic symptoms	SS score
						Fatigue	Waking unrefreshed			
1	36	F	5	169	2.23	8	2	1	1	5
2	38	F	120	297	2.84	6	3	2	2	9
3	51	F	12	148	2.20	13	3	2	1	7
4	52	F	120	310	1.60	7	1	2	1	5
5	57	F	444	425	3.80	7	1	1	2	6

TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone; WPI: wide-spread pain index; SS: symptoms severity

^a describes the number of painful areas in the past week. Nineteen areas (from jaw to lower leg) are reviewed and hence WPI can range between 0 and 19.

^b each of the three somatic symptoms is scored from 0 (no problem) to 3 (severe, life-disturbing problems) which describes the severity of each complaint over the past week. A fourth indicator (somatic symptoms) is then scored from 0 (no symptoms) to 3 (a great deal of symptoms) to present a semi-quantitative index of the number of somatic symptoms. The four indicators are then summed to calculate a single score (SS) which is indicative of the extent of the somatic symptoms a patient is having and can range between 0 and 12. A diagnosis of fibromyalgia can be made if $WPI \geq 7$ and $SS \geq 5$ or $WPI = 3-6$ and $SS \geq 9$

these patients. Based on our findings, among 102 patients with HT, a concomitant diagnosis of FM was warranted in only five, giving rise to a prevalence rate of 4.9% (95% CI: 0.7 - 9.1). This rate is comparable to the prevalence rate of the disease among a nationally-representative community-based sample of urban females in Iran. Recently, Sandoughi *et al* using the Community Oriented Program for the Control of Rheumatic Disease survey method investigated the prevalence of musculoskeletal disorders in a large sample of urban residents comprising of 1179 females aged 15 and above^[9]. Based on this report, the prevalence of FM among the general population is believed to be around 3.66 (2.59 - 4.73)^[9]. Therefore, given the level of confidence limits, the rate observed among HT patients herein falls in the same range as to that of the general population. In concert with our findings, Hezarkhani *et al* also demonstrated that the prevalence of FM among patients with thyroid autoimmunity is relatively low^[10]. In their assessment of 65 Iranian patients with either HT or Graves' disease, while 86.2% of the patients had musculoskeletal symptoms, clinical diagnosis of FM was made in only three patients (5.3%), which is again comparable to 4.9% prevalence rate observed herein^[10]. Similar observations have also been made in Turkey. In a 2003 study of patients with a range of thyroid diseases (euthyroid, toxic, or partially thyroidectomy goiter, HT, and Graves' disease), Cakir *et al* reported prevalence rates ranging from 4.3% in patients with subclinical thyrotoxicosis to 8.7% in hypothyroid patients^[11].

Our findings are in stark contrast to a number of previous studies that have reported FM to be highly prevalent among HT patients. In a sample of 46 patients with HT from a referral rheumatology practice in New York by Tagoe *et al*, a diagnosis of FM was made in 27 (59%) of the cases^[5]. The prevalence of FM in the general female population of the United States appears to be significantly lower and around 3.4%^[12]. In another study of Italian HT patients, with or without subclinical hypothyroidism, FM comorbidity was found in 31% of the subjects^[6]. Further, they observed that duration of thyroid disease was higher among patients with comorbid FM^[6]. Similar finding was replicated here, yet the inter group difference failed to reach statistical significance. Among FM patients identified within our sample, the serum concentrations of thyroid antibodies did not correlate with FM disease severity, further questioning a possible association between the two entities, albeit indirectly. In a case-control study of FM versus healthy subjects, Suk *et al* demonstrated that FM patients are significantly more likely to have positive anti-TPO antibodies (19% versus 7%). However, as shown here, anti-TPO concentrations were not associated with the severity of

FM defined using a pain visual analogue scale and also a continuous scale for degree of disability caused by the musculoskeletal disease^[13].

The precise reasons for significant discrepancies between the aforementioned studies remain to be determined. However, two points in this regard should be borne in mind. First, the criteria used for the diagnosis of FM among different studies differ; whereas previous studies have based their assessment on the original ACR criteria or clinical judgement, in the present study, the modified ACR criteria published in 2010 was employed. This is particularly relevant since previous research has suggested that the prevalence of FM varies according to the classification scheme used^[14], and a moderate discordance between different criteria sets is ineluctable^[15]. Therefore, a direct comparison between rates reported by different research groups may not be feasible. Second, an important caveat inherent to all studies investigating the prevalence of FM in patients with thyroid autoimmunity, the present study included, is that a relatively small number of patients have been recruited from outpatient clinics often limited to a single or few clinical centers. We believe that this introduces an important source of selection bias and might result in notable overestimation, or less likely underestimation of the FM prevalence among the recruited sample. Consequently, the conduct of large and multi-center studies involving HT patients are clearly needed to determine the prevalence of FM devoid of selection bias. Such a study should preferably include a sample of age- and sex- matched control subjects to provide a comparative perspective.

Two plausible scenarios can explicate the link between thyroid autoimmunity and FM. First, patients with autoimmune thyroid disease are at an increased risk for other diseases of autoimmune aberration. A large population-based study of Caucasian subjects with autoimmune thyroid disease indicated that another autoimmune disease can be detected in 14.3% of the patients diagnosed with HT^[16]. HT significantly increased the risk of celiac disease, pernicious anemia, vitiligo, Addison's disease and systemic lupus erythematosus by more than tenfold^[16]. Indeed, if FM is considered an autoimmune entity, a genetic predisposition toward FM could be expected in patients with HT. Fragmentary evidence suggest a role for autoimmunity in the pathogenesis of FM^[17]. For instance, elevated levels of an anti-nuclear antibody to a 68/48 KDa protein have been reported in patients with primary FM but not in healthy individuals or patients with other connective tissue diseases^[18]. Further, increased concentrations of several inflammatory cytokines such as interleukins 8 and 10, and tumor necrosis factor alpha have been found in

plasma of patients with FM and correlated with clinical manifestations of the disease^[19]. These findings suggest that a heightened immune-inflammatory response might be involved in the hyperalgesia phenomenon observed in FM. In an alternative scenario however, the widespread pain syndrome observed in the context of FM could be viewed as a systemic manifestation of thyroid disease, and not a separate but overlapping entity. Once considered an organ-specific condition confined to the thyroid gland, autoimmune thyroid disease is now being widely described as a systemic disease with its ramifications extending well beyond merely endocrine dysfunction.

CONCLUSION

Implications of the hypothetical association between thyroid autoimmunity and FM for patient management are far-reaching. Yet, we could not establish a firm relationship between HT and FM in our study as suggested by other research groups. In our study, the frequency of FM among HT patients was comparable to the prevalence reported in the female general population. Further, among HT patients, levels of thyroid antibodies did not correlate with indices of FM severity. From an epidemiological stand point, further case-control studies which recruit large numbers of patients from several clinical settings are paramount to establish or refute a possible link between the two disease entities.

ACKNOWLEDGMENT

Conflict of Interest: The authors declare they have no conflicts of interest.

Funding disclosure: None

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Original Article

Thymol enhances Antioxidant defense and inhibits Lipid Peroxidation in 1, 2-dimethylhydrazine-induced Colon cancer

Karthikkumar Venkatachalam^{1,2}, Subashini Vnayakam², Keshavardini Sahathevan², Nurulfiza Mat Isa³

¹Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Annamalaiagar – 608002, Tamilnadu, India

²Department of Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, UPM - 43400, Selangor, Malaysia

³Department of Cell and Molecular Biology, Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, UPM - 43400, Selangor, Malaysia

Kuwait Medical Journal 2018; 50 (4): 447 - 454

ABSTRACT

Objective: The aim of our study was to evaluate the anticarcinogenic properties of thymol against 1,2-dimethylhydrazine (DMH) induced colon cancer in rats.

Design: Experimental study

Settings: Annamalai University, Tamilnadu, India.

Subjects: Animals randomly assorted into four groups and fed with high fat diet. Group 1 served as (control), groups 2 and 4 received daily treatment of thymol (5 mg/kg b.w.) for a duration of 30 weeks, and groups 3 and 4 received subcutaneous injections of DMH (20 mg/kg b.w.) in the groin for the first 15 weeks. The animals were sacrificed after the experimental duration.

Intervention: Subcutaneous injections of DMH

Main outcome measures: The levels of lipid peroxidation were measured by estimating the formation of thiobarbituric

acid reactive substances (TBARS), and the antioxidant status was measured by activities of enzymic and non-enzymic antioxidants.

Results: All animals received DMH developed tumors, which was significantly reduced by thymol treatment. DMH also caused a significant increase in lipid peroxidation (plasma, lysate TBARS), which was associated with a significant decrease in the tissue level of antioxidant status (superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferase, glutathione reductase, glutathione) compared to control rats. These changes were significantly ($p < 0.05$) reversed by thymol co-administration along with DMH.

Conclusion: From these findings, we presumed that thymol exhibits marked anticarcinogenic and antioxidant effects in experimental colon cancer rats.

KEY WORDS: colon cancer, DMH, SOD, tumor incidence

INTRODUCTION

Colon cancers arise due to a series of pathological alterations from the adenoma to carcinoma sequence, which includes activations, deletions and other mutations in oncogenes and tumor suppressor genes^[1]. Epidemiological studies revealed that there exists a link between the development of colon cancer and high fat consumption, which may be due to the increased levels of bile acids being passed into the colon^[2].

1,2-dimethylhydrazine (DMH), a colon specific carcinogen, is readily metabolized by the liver^[3], which produces a highly electrophilic carbonium ion through several processes, and produces oxidative stress. Carbonium ion methylates DNA, induces point mutations, micronuclei and sister chromatid

exchanges leads to the colon specific carcinogenesis^[4]. DMH at the dosage of 20 mg/kg b.w. has produced a number of tumors in the colonic lumen, which was evidenced by several reports^[5-7]. Generally, colon cancers need a latent period to fully grow, once it's initiated with carcinogen it may take another few weeks for the promotion and progression stages. The first 15 weeks are needed for carcinogen induction and the next 15 week interval is needed for the promotion and progression stages^[8].

Several experimental studies involved in DMH-induced colon carcinogenesis revealed that morphological changes such as proliferative activity and dysplasia in colonic mucosal epithelium were started during the early stages of carcinogenesis^[9]. It

Address correspondence to:

Dr. Karthikkumar Venkatachalam, Department of Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, UPM - 43400, Selangor, Malaysia. Tel : +60 1126219171; E-mail: karthiklalisa@gmail.com

suggests that oxygen and free radical intermediates are strongly involved in the various stages of carcinogenesis^[10].

Exposure to UV light, cigarette smoke, environmental pollutants and gamma radiation may enhance the generation of reactive oxygen species (ROS) including superoxide anions, hydrogen peroxide, hydroxyl radicals and nitric oxide. These free radicals are highly unstable molecules that interact rapidly and aggressively with nucleic acids, polyunsaturated fatty acids and proteins^[11].

However, ROS are almost harmless under normal cellular conditions, but when there is an imbalance between free radicals and antioxidant defense, the metabolite becomes toxic and leads to the initial step of carcinogenesis^[12].

A diet that is rich in fruits and vegetables may protect against colon cancer, due to the presence of fiber and other micronutrients^[13].

A number of micronutrients have been reported to reduce the risk of colon cancer, which are associated with fruits and vegetables^[14]. Chemoprevention is an active primary prevention against cancer development, attracting researchers to identify possible chemopreventive agents^[15], especially those that are naturally found in foods. Terpenoids, non-nutritive constituents from fruits and vegetables, may contribute to a decreased incidence of cancer. It deserves special attention because of its presence in dietary vegetables, fruits and roots^[16]. Plant derived secondary metabolites could be considered as good candidates for chemopreventive or therapeutic agents against ROS-associated diseases^[17].

Thymol, a monoterpene compound, is present in the essential oil of *Thymus vulgaris* (Lamiaceae), *Carum copticum* (Apiaceae) and known for several beneficial biological effects such as antioxidant, antibacterial, anti-inflammatory and antispasmodic effects^[18-21].

Thymol has been used in herbal medicine. It is an antioxidant that can protect various human cells against oxyradicals generated in situ. It exhibits various biological actions, such as antioxidant, anti-inflammatory, antimicrobial, and free radical scavenging properties, to varying degrees^[22-25]. The biological action of thymol could be regulated by different kinds of intra cellular mechanism^[26]. These findings led us to investigate the possible modulatory effects of thymol against DMH-induced rat colon carcinogenesis using circulatory lipid peroxidation and antioxidant status as biomarkers.

MATERIALS AND METHODS

Animals and animal husbandry

Male Wistar rats with a body weight of 120 - 140 g were obtained from the Central Animal house, Rajah Muthiah Medical College, Annamalai University,

Annamalainagar, and were acclimatized to the normal diet for around one week. Rats were maintained as per the principles and guidelines of the Ethics Committee of Animal Care of Annamalai University in accordance with the Indian National Law on animal care and use (Reg. No. 160/1999/ CPCSEA/423). The animals were housed in a hygienic bed of husk in a specific-pathogen free animal room under controlled conditions of a 12 h light/dark cycle, and relative humidity of $50 \pm 10\%$ at a temperature of $24 \pm 2^\circ\text{C}$ till the end of the experimental period. Normal standard pellet diet (Hindustan Lever Ltd, Mumbai, India) was powdered and mixed with peanut oil (15.8%), making a total of 20% fat in the modified diet. Animals were allowed free access to modified pellet diet and tap water *ad libitum* until the end of the experimental period of 30 weeks.

Chemicals

DMH and thymol were purchased from Sigma Chemical Company, St Louis, MO, USA. All other chemicals used were of analytical grade and obtained from Hi-Media Laboratories, Mumbai.

DMH administration

The carcinogen DMH was dissolved in 1 mM EDTA, pH adjusted to 6.5 with 1 mM NaOH and used immediately for subcutaneous injections. The animals in groups 3 and 4 received DMH (20 mg/kg body weight) injections once every week for the first 15 weeks^[27].

Thymol treatment

Thymol (5 mg/kg body weight) was dissolved in drinking water and given orally everyday using an intragastric tube. The dose was adjusted according to the animal weight to ensure a constant dose.

Experimental design

The animals were randomly assigned to four experimental groups (6 animals per group). Group 1 served as control, and groups 2 and 4 received 5 mg/kg b.w. thymol orally everyday for 30 weeks. Groups 3 and 4 received the subcutaneous injection of DMH (20 mg/kg b.w.) for the first fifteen weeks. Initial body weight of all the animals in this study protocol were ensured to be between 120 - 140 g. Food consumption and animal body weight were monitored weekly throughout the experimental period of 30 weeks.

Tissue sample preparation

The experiment was terminated at the end of 30 weeks. Animals were sacrificed under anesthesia (i.p. administration of ketamine hydrochloride, 30 mg/kg body weight), by decapitation between 7.30 am to 9.30 am after an overnight fast. The colon was split open longitudinally and gross tumors were counted.

Preparation of plasma and hemolysate

Blood samples were collected in heparinized tubes and plasma was separated by centrifugation at 2000×g (REMI, India) for 10 minutes. After the separation of plasma, the buffy coat was removed and packed cells. The red blood cells (RBCs) were washed thrice with cold physiological saline. To determine the activity of RBC antioxidant enzymes, RBC lysate was prepared by lysing a known volume of RBC with hypotonic phosphate buffer (pH 7.4), centrifuging at 3000g for 10 min at 2 °C and the hemolysate separated^[28].

Biochemical estimations

Assay of lipid peroxidative byproducts

Lipid peroxidation was estimated by measuring the levels of the tissue lipid peroxidation byproducts, such as thiobarbituric acid reactive substances (TBARS), conjugated dienes and lipid hydroperoxides by the method of Yagi K^[29], Jiang Z-Y *et al*^[30] and Recknagel *et al*^[31] respectively.

Superoxide dismutase and catalase activities

Superoxide dismutase (SOD) was based on 50% inhibition of the formation of NADH-phenazine methosulphate nitroblue tetrazolium (NBT) formazan at 520 nm^[32]. Enzyme unit was defined as the amount of enzyme required for 50% inhibition of NBT reduction per minute per mg protein. The activity of catalase (CAT) was determined as described earlier, and was expressed as moles of H₂O₂ utilized per minute per mg protein^[33].

Assay of glutathione dependent enzymes

Glutathione peroxidase (GPx) activity was assayed by the method of Rotruck *et al*^[34] and the values are expressed as mol of glutathione (GSH) utilized per minute per mg protein. Glutathione reductase (GR) activity was assayed using the method of Carlberg *et al*^[35] and the values are expressed as mol of NADPH oxidized per minute per mg protein. Reduced GSH was determined by the method of Ellman GL^[36] and the values are expressed as mmol/mg tissue.

Levels of Vitamin C and E

Vitamin C was measured according to the method of

Baker *et al*^[37] and the amount of vitamin C was expressed as mg/dL plasma or mmoles/mg tissue. Vitamin E was determined by the method of Roe *et al*^[38] and the values are expressed as mg/dL for plasma or mg/100g for tissues.

Histopathological examinations

The colon segments were excised from the experimental groups, fixed in 10% formalin immediately and parafin embedded. Thin sections (2 - 3 μm) were selected using a microtome, stained with hematoxylin and eosin dyes, and viewed under a light microscope.

Statistical analysis

The data are presented as means ± SD of 10 rats in each group, and were analysed using one-way analysis of variance (ANOVA) and the group means were compared by Duncan's multiple range test (DMRT). The results were considered statistically significant at p <0.05. All statistical analyses were made using SPSS 11.0 software package (SPSS, Tokyo, Japan).

RESULTS

Effect of Thymol

Tumors are found in the colon of the DMH treated group only (Table 1). There were no tumors formed in the colon of the rats from the control group (group 1) and rats treated with only thymol (group 2). Macroscopically visible tumors are found in the large intestine (Table 2). Apart from the large intestine, there were no neoplasms found in any of the other organs examined from groups 3 and 4. Tumors from groups 3 and 4 were sessile or pedunculated and histologically classified as adenocarcinomas.

The occurrence of colon adenocarcinomas in the rats treated with DMH alone (group 3) was 81%, which was significantly higher than that of the rats treated with DMH and supplemented with thymol (group 4). We found a significant reduction in the size and total number of tumors in the group 4 rats.

Effects of Thymol on DMH-induced serum lipid peroxidation

Lysate and plasma TBARS were found to be increased significantly in the rats treated with DMH alone (group 3) (Table 3), when compared to the group

Table 1: Colon tumor and tumor load

Groups	No. of rats	No. of tumor bearing rats	Tumor incidence*(%)	Total tumor number	No. of tumors/tumor-bearing rats
Control	6	0	0	Nil	Nil
Control+Thymol	6	0	0	Nil	Nil
DMH	6	13 ^a	81 ^a	17 ^a	1.30 ^a
DMH+ Thymol	6	6 ^b	37 ^b	7 ^b	1.16 ^b

Values are expressed as means ± SD (n = 6), values not sharing common superscript (a-b) are significant with each other at p <0.05 (ANOVA followed by DMRT)

*(Number of tumor-bearing rats/total number of rats in each group) × 100

Table 2: Effect of DMH and thymol on circulatory TBARS of control and experimental rats

Parameters	Control	Control+Thymol	DMH	DMH+Thymol
Lysate TBARS (pmoles/mg Hb)	1.84 ± 0.16 ^a	1.87 ± 0.18 ^a	4.76 ± 0.47 ^c	2.83 ± 0.28 ^b
Plasma TBARS (nmoles/mL)	1.85 ± 0.17 ^a	1.89 ± 0.18 ^a	4.72 ± 0.43 ^c	2.56 ± 0.21 ^b

Values are expressed as means ± SD (n = 6), values not sharing common superscript (a-c) are significant with each other at p < 0.05 (ANOVA followed by DMRT)

DMH : 1,2-dimethylhydrazine; TBARS: thiobarbituric acid reactive substances

Table 3: Effect of DMH and thymol on erythrocyte lysate enzymic and non-enzymic antioxidants of control and experimental rats

Parameters	Control	Control+Thymol	DMH	DMH+Thymol
SOD [†]	3.87 ± 0.38 ^a	3.94 ± 0.39 ^a	2.12 ± 0.21 ^c	3.15 ± 0.27 ^b
CAT [‡]	2.81 ± 0.20 ^a	2.76 ± 0.27 ^a	1.84 ± 0.16 ^c	2.24 ± 0.17 ^b
GPx [§]	29.50 ± 2.74 ^a	29.80 ± 2.98 ^a	16.29 ± 1.51 ^c	22.51 ± 2.24 ^b
GR [¶]	50.79 ± 4.92 ^a	51.65 ± 5.11 ^a	32.48 ± 3.23 ^c	41.60 ± 4.15 ^b
GSH(mg/dL) [¶]	35.41 ± 3.54 ^a	35.24 ± 3.52 ^a	20.81 ± 2.08 ^c	27.47 ± 2.74 ^b

Values are expressed as means ± SD (n = 6), values not sharing common superscript (a-c) are significant with each other at p < 0.05 (ANOVA followed by DMRT)

[†]Superoxide dismutase; Enzyme required for 50% inhibition of NBT reduction/min/mg hemoglobin

[‡]Catalase; µmoles of H₂O₂ utilized/min/mg hemoglobin

[¶]Glutathione µmoles of CDNB-GSH conjugate formed/min/mg hemoglobin

[§]Glutathione peroxidase; µmoles of GSH utilized/min/mg hemoglobin

[¶]Glutathione reductase; µmoles of NADPH oxidized/min/mg hemoglobin

1 control rats at the end of the experimental period of 30 weeks (Table 3). Oral administration of thymol to DMH-treated rats (group 4) during the entire period of study significantly reduced the lysate and plasma levels of TBARS, when compared to the group 3 rats exposed to the carcinogen (DMH) alone (Table 3).

Effects of Thymol and DMH-induced on the circulatory levels of enzymic and non-enzymic antioxidants

The enzymic (SOD, CAT, GPx, glutathione S-transferase (GST) and GR) and the non-enzymic antioxidant levels (GSH) were significantly decreased in the rats treated with DMH alone (group 3) in comparison to the control rats (group 1). Co-

administration of thymol (group 4) significantly replenished the activities of erythrolysate SOD, CAT, GPx, GST, GR and the levels of GSH in comparison to the rats treated with DMH alone (group 3).

Effect of Thymol and DMH on tissue levels of enzymic and non-enzymic antioxidants

The activities of SOD and CAT were significantly decreased in the rats exposed to carcinogen alone (group 3) as compared to the control rats in group 1 (Table 4).

Oral administration of thymol to the DMH-treated rats (group 3) significantly increased the activities of SOD and CAT in the liver and colon, which is significantly comparable to the group 3 rats that were exposed to the

Table 4: Effect of DMH and thymol on the activities of tissue enzymic antioxidants

Parameters	Groups	Control	Control + Thymol	DMH	DMH + Thymol (Entire Period)
SOD [†]	Liver	18.83 ± 1.7 ^a	17.13 ± 1.6 ^b	8.18 ± 0.5 ^c	15.23 ± 1.3 ^b
	Colon	12.59 ± 1.1 ^a	11.52 ± 0.9 ^a	3.86 ± 0.3 ^c	10.96 ± 0.9 ^{ab}
CAT [‡]	Liver	82.56 ± 8.2 ^a	79.85 ± 7.3 ^a	48.76 ± 4.6 ^c	75.60 ± 7.0 ^a
	Colon	69.67 ± 6.7 ^a	66.50 ± 7.0 ^a	21.10 ± 2.2 ^c	60.80 ± 6.7 ^a
GPx [§]	Liver	6.51 ± 0.6 ^a	6.78 ± 0.6 ^a	2.34 ± 0.2 ^c	5.79 ± 0.5 ^a
	Colon	21.03 ± 2.1 ^a	20.12 ± 2.2 ^a	8.05 ± 0.9 ^c	19.84 ± 2.1 ^a
GR [¶]	Liver	18.93 ± 1.8 ^{ab}	19.45 ± 1.9 ^a	8.26 ± 0.8 ^d	27.03 ± 2.6 ^{bc}
	Colon	10.25 ± 1.0 ^a	10.07 ± 1.0 ^a	2.39 ± 0.2 ^c	7.96 ± 0.7 ^b

Values are expressed as means ± SD (n = 6), values not sharing common superscript (a-d) are significant with each other at P < 0.05 (ANOVA followed by DMRT)

[†]Superoxide dismutase; Enzyme required for 50% inhibition of NBT reduction/min/mg hemoglobin

[‡]catalase; µmoles of H₂O₂ utilized/min/mg hemoglobin

[§]glutathione peroxidase; µmoles of GSH utilized/min/mg hemoglobin

[¶]glutathione reductase; µmoles of NADPH oxidized/min/mg hemoglobin

Table 5: Effect of DMH and thymol on tissue non enzymic antioxidants

Parameters	Groups	Control	Control + Thymol	DMH	DMH + Thymol (Entire Period)
GSH	Liver	32.75 ± 3.4 ^a	34.32 ± 3.1 ^a	19.58 ± 1.9 ^c	24.48 ± 2.3 ^b
	Colon	37.82 ± 3.6 ^a	36.25 ± 3.5 ^a	17.85 ± 1.6 ^c	32.98 ± 3.1 ^a
Vitamin C	Liver	4.14 ± 0.4 ^a	4.12 ± 0.4 ^{ab}	1.25 ± 0.1 ^c	3.76 ± 0.2 ^b
	Colon	5.36 ± 0.4 ^a	5.22 ± 0.5 ^a	8.41 ± 0.4 ^c	6.76 ± 0.2 ^a
Vitamin E	Liver	2.38 ± 0.2 ^a	2.90 ± 0.2 ^a	0.98 ± 0.1 ^c	2.08 ± 0.2 ^a
	Colon	3.19 ± 0.2 ^a	3.09 ± 0.3 ^a	5.91 ± 0.5 ^c	4.07 ± 0.4 ^b

Values are expressed as means ± SD (n=6), Values not sharing common superscript (a-c) are significant with each other at p < 0.05 (ANOVA followed by DMRT).

GSH: glutathione peroxidase

carcinogen alone (Table 5). Supplementation of thymol to control group 2 rats did not show any alterations in the activities of antioxidants (Table 5).

A significant decrease was observed in the levels of GSH, vitamin C and E in group 3 rats exposed to DMH alone as compared to the group 1 control rats (Table 4). Supplementation with thymol significantly enhanced the levels of GSH, vitamin C and E in the liver and colon as compared to group 3 rats exposed to carcinogen alone (Table 4).

Histopathology

Rats from the control group and rats administered

with thymol alone showing normal colonic architecture and mucosa, submucosa and serosa within normal limits in the groups 1 and 2 animals (Fig 1). Rats from group 3 that were exposed to the carcinogen alone showed lake of mucin in which tumor cells float (Fig 2). Thymol-supplemented, DMH-treated rats showed mucosa with aberrant crypt foci.

DISCUSSION

The incidence of colon cancer was formerly low in India, but has currently shown to be an increasing trend with an increased migration of people from rural to urban parts of the country and changes in their dietary

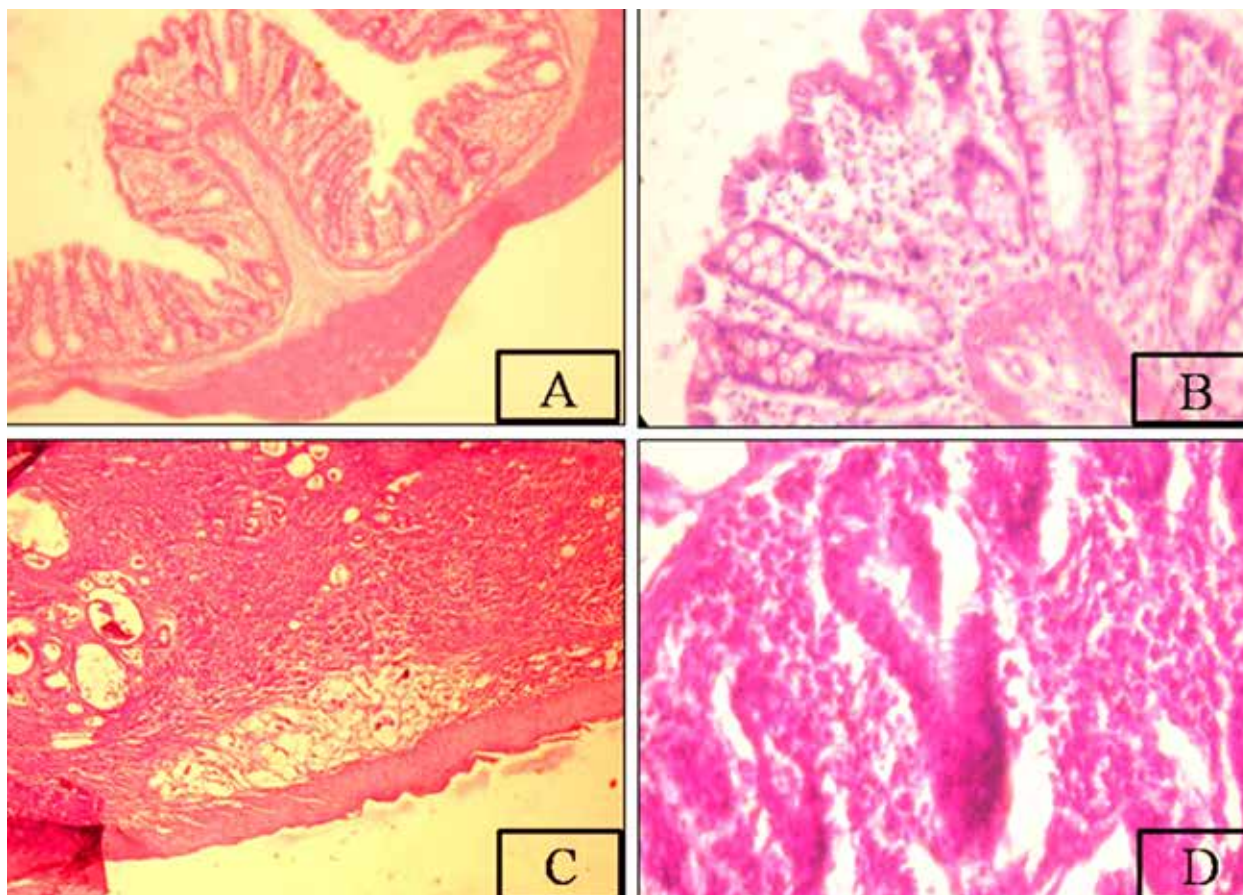


Fig 1: A and B colonic sections showing mucosa, submucosa and serosa within normal limits. C, Lake of mucin in which tumor cells float. D, Mucosa showing aberrant crypt foci

habits. Low intake of fruits, vegetables and fiber and high intake of fat are the major cause for the increased incidence of colon cancer. The increased consumption of dietary fat may extend the bowel transit time and increases the exposure time for fecal bile acids in the colon. These bile acids, such as cholic and deoxycholic acid, have the ability to act as potential carcinogens on the colonic mucosa and can cause colonic cancer^[39]. In general, numerous radicals are synthesized in the body during normal metabolism, human antioxidant defense system has the capability to prevent the oxidative damages. However, in cancers, there is a high level of oxidants which damages tissues and biomolecules. There is growing interest about the dietary supplements which can act as antioxidants and protect the body from the oxidative insult. Blood can reflect the culpability of the entire body to oxidative circumstances and it is one of the prime targets for oxygen radical attack^[40]. Free radicals released into circulation eventually cause haemolysis^[41]. When an imbalance between the prooxidants and antioxidants occurs, it leads to an increase in the free radical production, inactivation of antioxidant enzymes, and consumption of antioxidants leading to oxidative damage^[42], and an induction of the carcinogenesis. In our study, we used procarcinogen (DMH) to induce colonic tumors. DMH is slowly released to the blood and once it reaches the liver, its metabolic activation converts this from procarcinogen to an active carcinogen^[43].

Spices and condiments are the most important products used for flavouring foods around the worldwide. They are well known for pharmacological properties and also extensively used in perfumery and cosmetics. Spices are used as appetizers and help to cool the body by increasing the rate of perspiration^[44,45]. In addition, they possess several other properties like antioxidant and anti-inflammatory properties^[46].

In the present study, thymol displayed a remarkable inhibitory activity against colon carcinogen DMH-induced tumor formation, when thymol was administered to experimental rats at a dose of 5 mg/kg body weight. Tumor formation and their multiplicity were increased in rats from groups 3 and 4 show the carcinogenic ability of DMH. However, the colonic tumor prevalence were reduced in the DMH+thymol treated rats as compared to the rats treated with carcinogen alone. Thus, the macroscopic results clearly revealed that thymol has a potent chemopreventive effect against the known procarcinogen 1,2-dimethylhydrazine induced colon tumorigenesis.

The circulatory lipid peroxidation (plasma and lysate TBARs) levels were significantly elevated in rats treated with carcinogen alone (group 3). The DMH-induced lipid peroxidation is a free radical

mediated chain reaction, which involves oxidation of unsaturated lipids and tissue damages, ultimately causing degradation of lipid membrane. In addition, carcinogen exposure may result in the decrease of circulatory antioxidants due to the presence of abundant free radicals.

The rise of lipid peroxides and reduction of protective antioxidants may produce epoxides, which covalently bind to the DNA, RNA and proteins by a spontaneous reaction^[44]. These kinds of reactions may enable cytotoxicity, mutagenicity and/or carcinogenicity^[45]. In general, there is an inverse connection between the levels of lipid peroxidation and the amount of cell proliferation, as high levels of lipid peroxidation in the tissue reduces the rate of cell division^[46]. Thymol supplementation throughout the experimental period showed remarkable reduction in circulatory lipid peroxidation (plasma & lysate TBARs), with the values being near to normal with a simultaneous induction of antioxidant enzymes. This may be due to the anti-proliferative activity and the induced repair mechanism by thymol^[47]. This repair mechanism may be responsible for the inhibition of carcinogenesis.

The major antioxidant enzymic systems are SOD, CAT and GPx^[48]. SOD represents the front line defense mechanism against free radicals, indeed it is the only enzyme capable of dismutate highly toxic superoxide anion in the cells^[49]. This detoxification process involves two main steps, the first one carried out by SOD, which dismutates $O_2^{\bullet-}$ to H_2O_2 and oxygen. The second reaction involves the action of GPx and catalase, which converts the H_2O_2 to H_2O ^[50]. SOD and CAT activity in the circulation showed a significant decrease on DMH treatment, it may be due to the tumor cells that exhibit decreased expression of Mn-SOD and Cu-Zn-SOD. Fall of these enzymes may further promote the oxidative process, which causes the elevated levels of ROS and subsequent increase of oxidized DNA bases asset for mutagenesis and carcinogenesis^[51]. Thymol administration to the DMH-exposed animals increased the circulatory antioxidants such as SOD and CAT, which may be due to the ability of thymol to inhibit oxidative process, inhibit cell proliferation, and induce DNA repair mechanisms; thereby leading to a reduced risk of mutagenesis and carcinogenesis.

The tripeptide GSH directly scavenges free radicals by neutralizing HO^\bullet radicals, bring back the damaged molecules by donating a hydrogen, lowers peroxides and protects protein thiols in the reduced state^[52]. Erythrocytes are the major place for GSH and glutathione disulfide (GSSG). The reduction in the circulatory GSH may be due to the non availability of substrate for GSH synthesis^[53]. Reduced levels of GSH may pave the way for an abundant production of free radicals and lipid peroxides. These molecules

can damage cell membrane and cellular components (DNA, RNA) leading to neoplasia^[54]. Our study reveals that thymol treatment could normalize the depleted GSH levels in DMH exposed rats. The elevated levels of GSH are known to maintain cellular proteins against oxidative damage through glutathione redox cycle, and also directly neutralizes reactive oxygen species and/or neutralize reactive intermediate species. In addition, it also controls the tumor cell proliferation. This may be one of the mechanisms by which thymol inhibits proliferation of tumor cells.

The selenium-containing enzyme GPx destroys peroxides before they can damage cell membranes^[55]. GPx involved in the detoxification of H₂O₂ in low concentrations, when the GPx pathway reaches saturation with substrate, then catalase comes and play with H₂O₂^[56]. The current study results also demonstrate decreased GPx in the rats treated with DMH alone. Low levels of GPx activity increases the free radical damages in the cell membrane. Thymol supplementation to the DMH exposed rats enhances the GPx activity which may possibly help to improve the detoxification reaction of the cell organelles, and thus thymol may be a potent blocking agent against chemically induced colon carcinogenesis.

GR utilizes NADPH to reduce the oxidized glutathione to reduced glutathione and it regulates the GSH-GSSG cycle in the cell. In the present study, the circulatory GR levels were lowered in rats exposed with DMH alone (group 3) as compared to control rats. The inhibition of GR activity is likely to be deleterious to cells because it efficiently maintains the basal levels of cellular GSH. Thymol supplementation to the DMH exposed rats enhances the GR levels which may be predictable to biological importance of eliminating reactive free radicals that may otherwise affect the normal cell functioning.

CONCLUSION

To conclude, our overall key findings emphasize the anticancer efficacy of thymol by virtue of its ability to (a) inhibit the formation of neoplastic lesions, (b) modulate the tissue and circulatory lipid peroxidation levels, (c) prevent oxidative damage (d) enhances the circulatory and tissue enzymic and non enzymic antioxidants. Thymol appears to be markedly effective, less toxic and quite safe to be used for prolonged time periods, and thus it may be one of the promising candidates for future studies.

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Original Article

Urinary Albumin-to-Creatinine Ratio as a useful Risk Marker in patients with Cerebral Infarction

Sen-Lin Mao¹, Sha Luo², Ben-Ping Zhang¹, Feng Li¹, Jin Fu¹

¹Department of Neurology, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, People's Republic of China, 150086

²Heilongjiang Province Forestry General Hospital, Harbin, Heilongjiang Province, China, 150086

Kuwait Medical Journal 2018; 50 (4): 455 - 460

ABSTRACT

Objective: To evaluate the urinary albumin-to-creatinine ratio (UACR) as a risk factor for the incidence, severity of neurological deficits, and cerebral arterial stenosis in cerebral infarction.

Design: Case control study, cross-sectional study

Setting: The Second Affiliated Hospital of Harbin Medical University, Heilongjiang, China

Subjects: This study included 111 patients with acute ischemic stroke, consisting of 81 patients with atherothrombotic cerebral infarction (ATCI) and 30 patients with lacunar infarction (LI) between September 2015 and August 2016. A total of 57 subjects with risk factors for cerebral infarction who did not have acute stroke were included as controls.

Intervention: None

Main outcome measures: UACR, stroke scale score, the rate of cerebral arterial stenosis

Results: There were no significant differences between the two groups on their baseline clinical characteristics. The positive rate of microalbuminuria was significantly higher in patients with acute ischemic stroke compared to controls. ATCI patients had a higher rate of microalbuminuria than LI patients. In ATCI patients, those with microalbuminuria exhibited a higher severity of neurologic deficits and a higher rate of cerebral arterial stenosis compared to those without microalbuminuria.

Conclusions: UACR was a risk factor for cerebral infarction. It was closely correlated with the incidence, severity of neurological deficits, and cerebral arterial stenosis in ATCI patients.

KEYWORDS: cerebrovascular disorders, microalbuminuria, risk factors

INTRODUCTION

There are many risk factors of cerebral infarction, with the majority attributed to hypertension, diabetes, dyslipidaemia, and smoking. Although interventions such as smoking cessation, regulation of cholesterol, hypertension and diabetes, and the use of antiplatelet drugs have been done, the incidence of cerebral infarction remains high. In recent years, extensive research on the identification of untraditional risk factors, including microalbuminuria (MA), has been conducted^[1]. MA refers to a urinary albumin concentration that is greater than normal but not detectable with routine protein testing. Small amounts of albumin in the urine can be detected by radioimmunoassay. MA is typically defined as a urinary albumin excretion between 30 mg and 300 mg per 24 hours^[2]. Urinary creatinine excretion is

relatively stable and could correct the influence caused by the difference of urinary volume on urinary albumin excretion. A morning single-spot urinary albumin-to-creatinine ratio (UACR) has been widely used in lieu of a 24-hour urinary albumin excretion^[3]. Studies have shown that a high UACR is not only a sensitive marker for early diabetic nephropathy, but is also a risk factor for cardiovascular disease (CVD)^[4]. This study aims to investigate the association between UACR and cerebral infarction, particularly in patients with atherothrombotic cerebral infarction (ATCI).

SUBJECTS AND METHODS

Subject selection

We included stroke patients who were consecutively admitted to the Second Affiliated Hospital of Harbin Medical University between September 2015 and

Address correspondence to:

Jin Fu, Department of Neurology, The Second Affiliated Hospital of Harbin Medical University, No.157 Baojian Road, Nangang District, Harbin 150086, PR China. Tel.: +86-451-8629-6488; E-mail: maosenlin001@hotmail.com

August 2016. The inclusion criteria were as follows: (1) patients with acute ischemic stroke (ATCI, lacunar infarction (LI)) according to the fourth China cerebrovascular disease conference using the "various types of cerebrovascular disease diagnosis points"^[5]; and (2) patients who presented within 72 hours of symptom onset. Exclusion criteria included the following: (1) patients with medical conditions that influenced their urinary albumin excretion, such as chronic renal failure, obstructive uropathy, urinary tract infections or other chronic infections, long term usage of nephrotoxic drugs (*e. g.*, NSAIDs, aminoglycosides), malignancy, fever, and menstruating patients who may provide false positive results; (2) patients who were lost to follow up within the second week of symptom onset. Finally, 111 cases (81 ATCI patients, 30 LI patients) were included in the study based on the inclusion and exclusion criteria. For controls, we recruited patients at random who did not have acute ischemic stroke but had traditional risk factors for cerebral infarction, such as hypertension, diabetes, dyslipidaemia, elevated homocysteine, smoking habits, and prior ischemic stroke. These control patients were recruited from the outpatient department of our hospital. The controls were matched to the cases based on age, sex, and other traditional risk factors to minimize confounding factors on the results of our study. A total of 57 patients were included in the study. This study was approved by the Regional Ethics Committee of the Second Affiliated Hospital of Harbin Medical University.

Data collection

The following information was recorded for each subject: (1) demographic factors (age and gender); (2) risk factors for cerebral infarction including hypertension, serum lipid levels, diabetes mellitus, homocysteinemia, smoking habits, and a history of ischemic stroke or ischemic heart disease. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic pressure ≥ 90 mmHg, or the use of antihypertensive medications. Diabetes was defined as the use of diabetic therapies, a fasting plasma glucose greater than 7 mmol/l, or a non-fasting plasma glucose greater than 11.1 mmol/l. Smoking habits (including their history) were also recorded. Prior ischemic stroke was defined as a previous diagnosis of ischemic stroke with treatment. Prior ischemic heart disease was defined as a previous diagnosis of myocardial infarction and/or angina with treatment. Venous blood in all patients was obtained the morning after admission in the fasting state; (3) the assessment of UACR was made on the morning after admission by a spot urine collection in patients while they were fasting. Urinary albumin was measured with

the immunoturbidimetry method. Urinary creatinine was measured using the Jaffe method. The urinary albumin excretion was estimated as the UACR in mg/g in accordance with American Diabetes Association (UACR < 30 mg/g creatinine (normal albuminuria), $30 \leq$ UACR < 300 mg/g creatinine (microalbuminuria))^[6].

Each case underwent a brain computed tomography scan and a diffusion-weighted MRI. Neurologists evaluated the neurologic signs and symptoms in the cases during hospitalization. Past medical history and risk factors were obtained from the patients or their families. The neurological status was assessed using the National Institute of Health Stroke Scale (NIHSS) and the Barthel Index (BI) score upon admission and on the 14th day of hospitalization. The intracranial arteries were examined with magnetic resonance angiography (MRA) in ATCI patients within 7 days of admission. MRA scans were performed using a 3.0T Siemens superconducting scanner. We evaluated the following intracranial arterial segments: petrous internal carotid artery (ICA), cavernous ICA, supraclinoid ICA, M1 of middle cerebral artery, A1 of anterior cerebral artery, P1 of posterior cerebral artery, basilar artery, and distal vertebral artery. The formula used to calculate the degree of cerebral artery stenosis is as follows^[7]: stenosis percentage = $[1 - (\text{lumen diameter of the maximally stenotic region} / \text{lumen diameter of a nearby normal segment of the vessel})] * 100\%$.

A standardized five-grade system was employed: normal (0% - 30% diameter stenosis, grade 1), mild stenosis (31% - 49%, grade 2), moderate stenosis (50% - 79%, grade 3), severe stenosis (80%-99%, grade 4), and occlusion (no flow detected, grade 5). An artery with stenosis of 50% or greater was considered to be significantly diseased (grade 3 - 5)^[8].

Statistical analysis

All statistical analyses were performed with SPSS software package (version 17.0). Continuous variables were presented as the mean \pm SD or median (interquartile range) according to whether the data was normally distributed or not, respectively. The categorical variables were expressed as frequencies. The Chi-square test and the Fisher's exact test were used to compare categorical variables or proportions. The Student t-test was used to compare normally distributed continuous variables between two groups. P-values < 0.05 were considered to be statistically significant.

RESULTS

Over a period of 12 months, 334 acute ischemic stroke patients were admitted to our stroke unit. Of these, 111 patients met the inclusion criteria and were

Table 1: Clinical characteristics of the cases and the controls

Items	Cases	Controls	p-value
Age (years)	63.21 ± 7.46	61.9 ± 8.6	0.31
Male gender (%)	58.52	60.31	0.23
Diabetes (%)	38.90	36.81	0.54
Hypertension (%)	77.73	76.12	0.80
TC (mmol/l)	5.27 ± 1.32	5.12 ± 0.82	0.06
TG (mmol/l)	1.62 ± 1.3	1.72 ± 0.87	0.47
LDL-C (mmol/l)	2.96 ± 0.84	3.07 ± 0.79	0.53
HDL-C (mmol/l)	1.06 ± 0.75	1.18 ± 0.31	0.73
Hcy (mmol/l)	12.56 ± 1.93	14.33 ± 1.68	0.55
FBG (mmol/l)	7.37 ± 1.27	7.11 ± 2.36	0.17
Smoking (%)	36.27	38.64	0.19
Ischemic heart disease (%)	37.86	41.63	0.54
Prior stroke (%)	31.41	30.12	0.26

TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; Hcy: homocysteine; FBG: fasting blood glucose

studied as cases (mean age = 63 ± 7 years, 59% male). A total of 57 subjects were recruited from the outpatient department as controls (mean age = 62 ± 9 years, 60% male). The baseline characteristics of the two groups are shown in Table 1. There were no significant differences in the mean age, gender distribution, serum lipid levels, smoking status, the prevalence of hypertension, diabetes mellitus, homocysteinemia, and prior stroke or ischemic heart disease between the cases and controls.

Table 2: The positive rates of MA between cases and controls

Group	MA(+)	MA(-)	Total	Positive rate
Cases	55	56	111	49.5%
Controls	14	43	57	24.6%
Total	69	97	168	41.1%

MA(+): microalbuminuria (30 ≤ UACR < 300 mg/g creatinine); MA (-): normal albuminuria (UACR < 30 mg/g creatinine)

As shown in Table 2, the prevalence of microalbuminuria was present in 49.5% of the cases and 24.6% of controls. The frequency of microalbuminuria was significantly higher in the cases than in controls ($\chi^2 = 9.716$, $p = 0.002$). Table 3 shows that microalbuminuria was found in 56.8% of ATCI patients and in 30% of LI patients. The ATCI patients had a significantly higher frequency of microalbuminuria than in LI patients ($\chi^2 = 6.285$, $p = 0.012$).

Table 3: The positive rates of MA between ATCI and LI patients

Group rate	MA(+)	MA(-)	Total	Positive
ATCI patients	46	35	81	56.8%
LI patients	9	21	30	30.0%
Total	55	56	111	49.5%

ATCI: atherothrombotic cerebral infarction; LI: lacunar infarct; UACR: urinary albumin-to-creatinine ratio; MA(+): microalbuminuria; MA (-): normal albuminuria

Stroke scale scores were performed on all ATCI subjects upon admission and on the 14th day of hospitalization. The ATCI subjects were divided into 46 patients with microalbuminuria and 35 patients without microalbuminuria. The NIHSS score was significantly higher in patients with microalbuminuria compared to those without microalbuminuria on the 1st and 14th days, respectively ($p < 0.05$, Table 4). In contrast, the BI in patients with microalbuminuria was significantly lower ($p < 0.05$, Table 4).

Table 4: Comparison of the NIHSS score and the Barthel index in ATCI patients

Stroke Scale score	MA(+)	MA(-)
NIHSS 1d	10.77 ± 3.21*	6.21 ± 2.46
NIHSS 14d	7.64 ± 2.57*	5.42 ± 1.08
Barthel index 1d	27.12 ± 4.16*	38.3 ± 5.41
Barthel index 14d	34.08 ± 6.32*	44.29 ± 8.65

* Compared with UACR-negative groups, $p < 0.05$

NIHSS: National Institutes of Health Stroke Scale; MA (+): patients with microalbuminuria; MA (-): patients with normal albuminuria

The rate of intracranial arterial stenosis (50% or greater) was 65.2% in ATCI patients with microalbuminuria, compared to 37.1% in ATCI patients without microalbuminuria (Table 5). The differences were statistically significant ($\chi^2 = 6.290$, $p = 0.012$).

Table 5: Comparison of the rates of intracranial stenosis in ATCI patients

Group	Intracranial stenosis (grade 3-5)	Intracranial stenosis (grade 1-2)	Total	Rate of stenosis (grade 3-5)
MA (+) patients	30	16	46	65.2%
MA (-) patients	13	22	35	37.1%

MA(+): microalbuminuria; MA (-): normal albuminuria; grade 3-5: An artery with stenosis of 50% or greater

DISCUSSION

MA was initially proposed and used in clinical trials in 1970s. Albumin is a medium-sized, negative charge protein with a relative molecular weight of 690,000. Under normal circumstances, due to the interaction with the negative charge and a relatively smaller endothelial gap on the filtration membrane surface, only a small amount of albumin could be filtered by the glomerulus. The majority of albumin is reabsorbed by the renal tubules. Any causes of glomerular arteriosclerosis and high perfusion could result in damage to the filtration barrier. This phenomenon leads to an increase in the rate of urinary albumin excretion. A quantitative measurement of 24-hour urinary albumin has been the gold standard method for the diagnosis of MA. Unfortunately, the difficulty in collecting a 24-hour urine sample and the

addition of preservatives make this method unfeasible. Patients exhibited lower compliance, and a random urine sample could be erroneous due to urinary concentration or dilution. The urinary creatinine excretion rate is relatively stable and is independent of urinary dilution in the human body. Using a single-spot UACR in lieu of the 24-hour urinary albumin excretion has become a widely accepted method. The American Diabetes Association recommends that the UACR for people with diabetes should be tested yearly. JNC 8 guidelines indicate that UACR is one of the indicators of risk stratification in patients with hypertension. Chinese hypertension prevention and treatment guidelines state that an increased UACR is an indicator of end-organ damage. The clinical application value of UACR has received extensive attention.

MA was originally introduced to clinical practice as a useful marker of incipient diabetes or hypertensive nephropathy. Pontremoli R *et al* stated that the pathological structure in the kidneys changed in the presence of MA, and MA reflected renal damage in patients with hypertension in the early stages^[9]. In the last few years, many studies have reported an association of MA with cardiovascular events and its risk factors. The MONICA study, the PREVEND study, and the HUNT study all showed that MA could predict cardiovascular events^[10-12]. Increased UACR was a prognostic marker that was associated with increased RV and LV remodelling, and was also associated with longitudinal systolic dysfunction^[13]. The pathogenesis of CVD is similar to cerebrovascular disease; however, few studies have focused on the association between MA and cerebrovascular disease. In the present study, we found that 49.5% of the case group exhibited MA, while 24.6% of the control group had MA. Additionally, 56.8% of the ATCI subgroup exhibited MA, while 30% of the LI subgroup had MA. These data suggested that UACR could be used as a marker to monitor the risk of acute ischemic stroke.

An increased urinary albumin excretion rate is closely related to ischemic cerebrovascular events. However, the exact pathophysiological mechanism that links MA to cerebrovascular disease remains unclear. One plausible explanation is that MA is a marker of generalized systemic vasculopathy^[14-15] that is independent of diabetes and hypertension^[16-17]. MA may reflect several physiologic derangements, including endothelial dysfunction, which plays an important role in atherosclerosis, inflammation, and elevated central aortic pressure^[18]. The presence of MA suggests that the glomerular capillary endothelium is injured, resulting in the leakage of albumin from the glomerulus. MA is also a sign of systemic vascular endothelial damage. Since various harmful factors can cause glomerular capillary endothelial damage,

the intracranial vascular endothelial cells in the same internal environment will be damaged as well. Vascular endothelial cells have important physiological functions. The integrity of these cells is important in thrombosis prevention. Arterial vascular endothelial dysfunction is the first step that results in abnormal vascular function^[19]. The damaged endothelia can promote the penetration of atherogenic lipoprotein particles and plasma molecules into the arterial wall. It also releases tissue plasminogen activator, extravascular coagulation, and high levels of inflammatory cytokines that promotes and augments atherosclerotic development and oxidative stress^[20-22]. The injured arterial endothelium plays an important role in the initiation and progression of atherosclerosis^[23]. In our study, we focused on the association between UACR and atherothrombotic cerebral infarction in patients. ATCI is the most common subtype of ischemic stroke. Its primary pathology is atherosclerosis, which occurs in vessels with larger lumens (*e.g.*, carotid, middle cerebral, basilar arteries and the main-branch vessels of these arteries). With the progression of atherosclerosis, the lumen of intracranial artery becomes narrowed or occluded, eventually leading to the formation of a thrombus. The severity of intracranial atherosclerosis was evaluated by MRA at 3.0T. The results showed that patients with MA had a higher degree of cerebral arterial stenosis than those without MA in the ATCI subjects. This finding suggested that increased UACR could serve as a marker of cerebral arterial stenosis.

A recent study found that albuminuria could predict early neurological deterioration in patients with acute ischemic stroke within 7 days of admission^[24]. In the present study, we evaluated the correlation between UACR and the severity of neurological deficits. The NIHSS score and the BI score were performed in all ATCI patients on admission and the 14th day of hospitalization. We found that the NIHSS score of patients with MA was higher than those without MA on the first day and the 14th day after admission. The BI in patients with MA was lower than those without MA. This result showed that the neurological deficits of patients with MA was more severe. An increased UACR could be used to reflect the severity of the neurological deficits in patients with acute ischemic stroke.

High UACR is caused by injuries to the glomerular capillary endothelium or by glomerular sclerosis. This is a sign of renal microvascular lesions. It is also an early marker of vascular lesions in other parts of the body. Murtaugh *et al* found that MA was a marker of heart, brain, kidneys, and other end-organ damage^[25]. In recent years, many studies have found that UACR has an important application value in the occurrence and development of ischemic cerebrovascular disease. Prior to patients suffering from cardiovascular and

cerebrovascular events, paying attention to the warning signs and taking measures to treat them will greatly reduce the occurrence of catastrophic health events. A high UACR suggests that the patients have a risk of ischemic cerebrovascular disorders. Other risk factors should be actively sought and controlled. Interventions should be carried out for patients with MA, including smoking cessation, weight loss, regulation of blood lipid levels, diabetes intervention, use of ACEi/ARBs, and prescribing antiplatelet drugs in order to reduce the incidence of ischemic cerebrovascular events.

A comprehensive understanding of UACR is very important. UACR is not only an early indicator of glomerular damage but is also a sensitive marker of systemic vascular endothelial damage and is an important risk factor for cerebral infarction. With increasing research and multiple large-scale clinical trials, the correlation between UACR and cerebral infarction and their pathophysiology will become clearer, and the clinical value of UACR will be further confirmed. UACR will have better clinical applications in future.

Limitations

Several limitations should be considered when interpreting our study. First, our study was a single centre study with a relatively small number of samples. These results require further verification in a larger, prospective, multi-centred, cohort study that would include patients with normal albuminuria and those with microalbuminuria to measure end-point events (occurrence and recurrence of ischemic stroke). Second, UACR was only measured in a spot morning urine sample on admission. Although the early morning spot-test is equivalent to a 24-hour urine albumin excretion, future studies should evaluate multiple time-points to validate the role of UACR. Third, the potential confounders of UACR cannot be completely ruled out. For example, albuminuria can sometimes occur during the course of acute stress, dehydration, or infection. Thus, a detailed evaluation would be necessary to reduce the influence of the pathophysiological state of the body on UACR. Lastly, no treatment group was involved in our study to demonstrate whether reducing albuminuria can improve the prognosis of stroke.

CONCLUSION

In our study, MA was considered a risk factor for acute ischemic stroke. MA was frequently found in patients with acute ischemic stroke. The results showed that nearly half of the patients with acute ischemic stroke and an even higher percentage of ATCI patients had detectible levels of MA. The prevalence of microalbuminuria in ATCI patients was higher than in LI patients. The presence of microalbuminuria

could be a useful risk marker that predicts a worse clinical course in ATCI patients. High UACR could imply severe neurologic deficits and a poor functional outcome in ATCI patients. Our study provides a noteworthy contribution to the link between UACR and arteriostenosis of the cerebral arteries in ATCI patients. The presence of microalbuminuria may indicate a worse degree of cerebral arteriostenosis. Evaluation of UACR could be an easy, cost effective, non-invasive detection method with high clinical utility. A comprehensive understanding of UACR is important for the prevention and treatment of ischemic stroke.

ACKNOWLEDGMENT

Disclosures: None

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Original Article

Association of Obesity with Pelvic Floor Disorders and its effect on the Quality of Life in women awaiting Bariatric Surgery

Ghadeer K Al-Shaikh¹, Leena Ibrahim², Hazem Al-Mandeel¹, Reem AlShaikh³, Sadiqa B Syed⁴

¹Department of Obstetrics & Gynaecology, College of Medicine, King Saud University, PO box 2454, Riyadh, Saudi Arabia

²King Faisal Specialist Hospital and Research center, Zahrawi Street, Al Maather, Riyadh 12713, Saudi Arabia

³College of Medicine, Al-Faisal University, Al Zahrawi Street, Al Maather, Al Takhassusi Rd, Riyadh 11533, Saudi Arabia

⁴College of Medicine, Princes Nourah bint Abdulrahman University, Al Imam Abdullah Ibn Saud Ibn Abdul Aziz Road, King Khalid International Airport, Riyadh, Saudi Arabia

Kuwait Medical Journal 2018; 50 (4): 461 - 466

ABSTRACT

Objectives: To assess the association of obesity with frequency of pelvic floor disorders (PFDs) and their effects on quality of life (QoL) in obese women

Design: A case-matched study

Setting: University hospital in Saudi Arabia between October 2014 and October 2015

Subjects: Seventy-five obese (BMI >30 kg/m²) women awaiting bariatric surgery and 91 age and parity-matched, non-obese controls were selected.

Intervention: Three validated disease-specific and QoL questionnaires about PFD (PFDI-20, PFIQ-7 and International Consultation on Incontinence Questionnaire-Urinary Incontinence (ICIQ-UI)) were administered to all participants.

Main outcome measures: The frequency of PFD and the effect on QoL. Data were analyzed by chi-square and t-test.

Results: Overall, PFDs were frequently present in 47 (62.7%) women in the obese group compared to 30 (32.9%) in the non-obese group (odds ratio = 3.41, 95% confidence interval: 1.79 - 6.48, p <0.001). Obese women were found to experience symptoms of pelvic organ prolapse (POP) (p <0.001), stress urinary incontinence (p = 0.003) and fecal incontinence (p = 0.011) as compared to non-obese women. Regarding the different QoL questionnaires, total mean scores of PFDI and ICIQ were statistically higher in the obese group compared with non-obese women.

Conclusion: The frequency of POP, urinary incontinence, and fecal incontinence was increased in obese women awaiting bariatric surgery. Low self-esteem and limited religious activities were the most negative impacts of these symptoms on QoL.

KEYWORDS: fecal incontinence, pelvic organ prolapse, urinary incontinence

INTRODUCTION

Obesity is a growing problem all over the world affecting approximately 500 million individuals. It is defined as excessive fat accumulation that is measured by body mass index (BMI), derived from a person's weight (in kilograms) divided by the square of height (in meters). An adult with a BMI >30 is considered to be obese, and is further categorized as class I (BMI ≥30-35), class II (BMI ≥35-40), and class III (BMI ≥40)^[1]. According to the National Center for Health Statistics, an estimated 68% of USA adults are either overweight or obese, the majority being female^[2]. The prevalence

of obesity in Saudi women was reported as 20.3%, while 25.2% were overweight^[3]. Moreover, according to a WHO report, obesity is estimated to become 78% in Saudi women by the year 2022^[4].

The effect of weight gain on female health has been linked to development of several co-morbidities such as hypertension, type II diabetes, cardio-respiratory diseases, strokes, arthritis, depression, some types of cancers as well as pelvic floor disorders (PFDs)^[4,5]. PFD is a term for a broad spectrum of clinical conditions such as pelvic organ prolapse (POP), urinary incontinence (UI), fecal incontinence (FI) and sexual dysfunction.

Address correspondence to:

Ghadeer Al-Shaikh MBBS, FRCS, Associate Professor, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia. Mob: +96653044090; Tel: +966-1469-9339; Fax: +966-1467-9557; Email: ghadeer-alshaikh@hotmail.com

Symptoms of PFDs include pelvic pain, pressure, urinary or anal incontinence, incomplete emptying of bladder and bowel, dyspareunia and pelvic organ protrusion through the vagina^[6,7], that create significant medical, social, emotional and economic issues for many women^[8]. Regarding PFDs in Saudi women, the prevalence of UI has been reported by local studies as 29 to 41%^[9,10], while that of POP and anal incontinence as 47.7% and 8.5% respectively^[11,12].

Obesity along with age, race, parity, size of infant and vaginal delivery have been identified as independent risk factors for PFDs^[13,14]. Although previous studies have demonstrated convincingly the significance of age and vaginal delivery as the dominant contributory factor^[15-17], higher body weight has emerged lately as a potential causative factor for the development of all categories of PFDs^[18,19].

A study in the USA documented the greater prevalence of PFDs, including stress urinary incontinence (SUI), urge urinary incontinence (UUI), and all forms of anal incontinence in obese women, associated with an increased severity of symptoms^[8]. As such, obese women are more likely to develop these symptoms with significant negative effects on their quality of life^[20,21]. The mechanism by which obesity disrupts vaginal and bladder function is not well understood. However, a hypothesis describes a disruption of endopelvic fascia leading to lack of support to the pelvic structures as a causative mechanism^[22,23]. As the population is aging in most countries and obesity is on the rise, the rates of UI and POP are rising beyond expectations^[21].

To our knowledge, there are no studies available on the association of PFDs with obesity and their effects on quality of life (QoL) in Saudi women (in this part of the world) to-date. Since the prevalence of obesity is increasing alarmingly in Saudi society, it is of utmost importance to evaluate these associations. The objectives of this study were to assess the frequency of pelvic floor disorders, including POP, urinary disorders and bowel disorders in obese women compared to non-obese women and to determine the severity and quality of life impact of PFDs in these women.

SUBJECTS AND METHODS

This was a case-matched study conducted in a university hospital in Saudi Arabia. The study was approved by the Institutional Review Board. The study included obese women awaiting bariatric surgery between October 2014 and October 2015. Age and parity-matched group of non-obese women was used for comparison. Patients with obstetric trauma, paraplegia, pelvic floor surgery and who refused to complete the questionnaire were excluded.

Sample size calculation was done based on the prevalence of PFDs in obese women, which was reported to be as low as 44%, and this was two-fold higher than the non-obese population. Based on 22% expected prevalence in non-obese women and by setting type 1 error at 0.05 and 80% power with 95% confidence interval (CI), we will need a minimum of 71 subjects for obese group and 90 subjects for non-obese group.

Ninety women on the waiting list for bariatric surgery (BMI ≥ 30 kg/m²) in the hospital were approached and 75 (84%) agreed to participate. For control group, age-matched cases of new referrals to the general gynecology clinics were selected. One hundred and fifteen non-obese females (BMI <30 kg/m²) were approached and 91 (79%) age and parity-matched women agreed to participate.

All participants were briefed about the study and their informed consents taken prior to participation. Both groups were interviewed and the following data were recorded: demographic information (age, weight, height); pertinent obstetric history (parity, mode of delivery, complications associated with delivery); past medical history of comorbidities (diabetes, chronic cough); relevant surgical history (such as hysterectomy); and drug history (use of hormone replacement therapy, laxatives or bulking agents). Both groups were asked to complete three Arabic validated questionnaires of PFDs namely Pelvic Floor Distress Inventory (PFDI), Pelvic Floor Impact Questionnaire (PFIQ) and International Consultation on Incontinence Questionnaire-Urinary Incontinence (ICIQ-UI)^[24,25]. The PFDI-20 is a condition-specific questionnaire with 20 items that is used to assess frequency of symptoms and the degree of bother in three main domains, *i.e.* pelvic organ prolapse distress/impact (POPDI), colorectal-anal distress/impact (CRADI) and urogenital distress/urinary incontinence impact (UDI). The frequency was evaluated according to presence of symptoms (yes or no) and further elaboration to degree of bother (mild, moderate and severe) by asking six questions related to urinary incontinence (UDI-6), eight questions related to colorectal anal distress (CRADI-8) and six questions regarding POPDI (POPDI-6). The range of total mean score varied from 1 to 100, with higher scores representing more severe symptoms.

The original PFIQ-7 questionnaire includes seven questions related to the effects of bladder, bowel or vaginal symptoms each and degree of bother on daily activities like household chores, relationships and feelings such as social obligations and mood disturbances over the last three months duration. Each question starts in a yes or no basis and further elaborates to degree of bother (mild, moderate and severe). The modified validated PFIQ measure includes

Table 1: Demographic data, medical and obstetrical history of participants

Characteristics	Non-obese BMI <30 kg/m ² n = 91	Obese BMI >30 kg/m ² n = 75	p-value
Age (mean ± SD)	36 ± 10.9	35.9 ± 11.5	0.934
Nulliparity (n (%))	39 (42.8%)	34 (44.7%)	0.749
Median parity	2	3	0.414
Number of vaginal delivery (n (%))	47 (51.6%)	34 (45.3%)	0.417
Postmenopausal (n (%))	9 (9.9%)	5 (6.6%)	0.459
Chronic cough (n (%))	0	1 (1.3%)	0.271
Diabetes mellitus (n (%))	7 (7.7%)	4 (5.3%)	0.542
Hysterectomy (n (%))	1 (1.1%)	2 (2.7%)	0.453

BMI: body mass index; SD: standard deviation

an additional question related to effect of UI (IIQ-8), and colorectal symptoms (CRAIQ-8) on prayers; the responses ranged from 0 to 3 describing no effect at all to stoppage of praying. The mean score was obtained in the range of 0 to 100.

The ICIQ-UI questionnaire includes four items and provides a brief, quick and strong measure to assess the impact of symptoms of UI alone on quality of life with regards to frequency, amount of leakage, and daily life degree of bother score. Mean score was obtained by summing up scores of first three questions. IIQ and ICIQ measure different factors associated with QoL.

The questions referring to loss of urine at times of exertion such as laughing, sneezing, coughing, lifting weights define stress incontinence while questions referring to urine loss preceded by an urge to void or uncontrollable voiding with little or no warning define urge incontinence. Self-reported symptoms of stress or urge incontinence had an accuracy of 69% in predicting an urodynamic diagnosis^[26]. The symptom of prolapse was considered to be present if there was a positive response to any of the prolapse items. The data was obtained from all sampled women including obese and non-obese subjects.

Statistical analysis

Data were collected and encoded in MS Excel 2007, and imported to Statistical Package for Social

Table 2: Overall frequency of symptoms of PFDs in obese and non-obese women

Variable	Non-obese BMI <30 kg/m ² n = 91(%)	Obese BMI >30 kg/m ² n = 75 (%)	p-value
PFD	30 (32.9)	47 (62.7)	<0.001*
POP	5 (5.5)	23 (30.6)	<0.001*
SUI	24 (26.4)	36 (48)	0.003*
UUI	23 (25.3)	28 (37.3)	0.093
FI	7 (7.7)	16 (21.3)	0.011*

BMI: body mass index; PFD: pelvic floor dysfunction; POP: pelvic organ prolapsed; SUI: stress urinary incontinence; UUI: urge urinary incontinence; FI: fecal incontinence

Sciences (SPSS) version 20 (SPSS Inc., IBM, Chicago, Illinois, USA) for analysis. Categorical variables were presented as percentage and continuous variables as mean and standard deviation. Independent t-test was used to determine the significant difference between two means, and Chi-square test was done to determine difference between two groups using categorical variables. P-values less than 0.05 were considered statistically significant.

RESULTS

The mean BMI in the obese group was 41.7 ± 8.6 kg/m², whereas in the non-obese group it was 24.9 ± 2.9 kg/m². The main characteristics between the two groups are described in Table 1. There were no statistically significant differences among these variables between the obese and non-obese groups.

Overall PFDs were frequently present in 47 (62.7%) women in the obese group compared to 30 (32.9%) in the non-obese group (odds ratio (OR) = 3.41, 95% CI 1.79 - 6.48, P <0.001). Frequency of PFDs in obese group remained significantly higher than women in non-obese group, even after adjusting for baseline demographics and obstetric differences between the two groups (Table 2).

Table 3: Comparison of mean scores of different symptoms of pelvic floor dysfunctions among obese and non-obese women as measured by PFDI-20

Characteristics	Non-obese BMI (<30)	Obese BMI (>=30)	p-value
PFDI-20	46.3	58.6	0.134
UDI-6	15.4	18.5	0.327
Frequency	3.5	3.3	0.794
UUI	2.3	4.9	0.004*
SUI	2.1	5.2	<0.001*
Drops	0.7	0.9	0.537
Difficulty	1.9	1.0	0.093
Pain	3.0	4.8	0.037
CRADI-8	17.3	23.5	0.050*
Constipation	3.4	4.6	0.088
Incomplete evacuation	2.0	3.1	0.055
Lose well-formed stools	0.3	0.3	0.818
Lose not well formed stools	2.1	2.5	0.539
Lose gases	1.9	3.1	0.031*
Painful defecation	1.9	1.9	0.964
Urgency	1.7	2.8	0.078
Rectal prolapse	2.2	3.9	0.008*
POPDI-6	10.4	19.4	0.002*
Pressure, lower abdomen	2.3	5.2	0.008*
Heaviness, vagina	2.5	4.4	0.022*
Something protruding	0.9	2.4	0.023*
Splint to defecate	1.8	3.4	0.036*
Incomplete bladder evacuation	2.3	3.7	0.054
Splint to void	0	0.2	0.137

BMI: body mass index; PFDI: pelvic floor distress inventory; UDI: urinary distress inventory; SUI: stress urinary incontinence; UUI: urge urinary incontinence; CRADI: Colo-rectal-anal Distress Inventory; POPDI: Pelvic Organ Prolapse Distress Inventory

Table 4: Comparison of frequency and total mean scores of pelvic floor disorders among obese and non-obese women

Variable	Non-obese n= 91		Obese n= 75		p-value Frequency	p-value Mean score
	Frequency (%)	Mean score	Frequency (%)	Mean score		
PFDI-20						
POPDI-6	37 (40.6)	8.7	68 (90.7)	23.7	0.113	<0.001*
CRADI-8	52 (57.1)	14.4	72 (96.0)	28.8	0.550	<0.001*
UDI-6	40 (43.9)	15.4	62 (82.7)	18.5	0.115	<0.001*
PFIQ-7						
IIQ-8	23 (25.3)	4.8	24 (32.0)	5.4	0.337	0.768
CRAIQ-8	29 (31.8)	7.1	38 (50.7)	8.8	0.689	0.143
POPIQ-7	10 (10.9)	4.1	24 (32.0)	8.5	0.038	0.028*
ICIQ-UI	34 (37.4)	10.9	40 (53.3)	20.4	0.076	0.006*

PFDI: pelvic floor distress inventory; POPDI: pelvic organ prolapse distress inventory ; CRADI: colo-rectal-anal distress inventory; UDI: urinary distress inventory; PFIQ: pelvic floor impact questionnaire; IIQ: incontinence impact questionnaire; CRAIQ: colo-rectal-anal impact questionnaire; POPIQ: pelvic organ prolapse impact questionnaire; ICIQ-UI: international consultation on incontinence questionnaire-urinary incontinence

Regarding the scores of degree of bother, the total mean score of PFDI-20 was higher in obese as compared to non-obese women with highly significant difference in mean score of POPDI (0.002) and CRADI (0.050) as compared to UDI (0.327) (Table 3). The symptoms of prolapse including pressure in lower abdomen, heaviness in vagina, something protruding, splint to defecate were statistically significant in obese women. Among the colorectal symptoms, flatus incontinence was significantly higher in obese group.

When frequency and mean scores of PFDI-20 and PFIQ-7 were compared in two groups, significantly higher values were noted in all items of PFDI-20, with statistically highest difference observed in scores of POP; likewise in PFIQ scores, significant difference was found in frequency of prolapse and its effects on daily activities, social and emotional aspects in obese women ($p = 0.028$). Moreover, religious activities were highly affected by UI in both groups. The frequency and mean scores of ICIQ were also higher in obese women (20.4 vs. 10.9), indicating greater risk of UI in them as compared to non-obese women (Table 4).

DISCUSSION

This study evaluated the association of obesity with frequency of PFDs along with degree of bother and distress on the quality of life in morbidly obese women awaiting bariatric surgery as compared to non-obese women. Despite relatively young age of obese and non-obese women in our study, PFD's were found to be present in both groups, though significantly higher in obese as compared to non-obese women (62.7% vs 32.9%).

Our results revealed significantly higher frequency with moderate to severe symptoms of prolapse in obese women, which is consistent with several studies, indicating that increased BMI plays a major role in the development of prolapse^[2,27,28]. The two most common

symptoms of prolapse included lower abdominal pressure and vaginal heaviness, believed to result from weakening of pelvic floor caused by increased intra-abdominal pressure^[29]; 40% of symptomatic patients in obese group complained of constipation showing an additional effect of stretching of levator ani muscle and lack of support to pelvic viscera while straining during defecation.

Current studies and theories do not adequately explain the development of prolapse or UI in women with zero gravidity, suggesting the primary importance of modifiable risk factors like obesity or existence of some genetic predisposition.

Our finding of increased frequency and bother from SUI and UUI with higher degree of obesity as measured by PFDI-20, PFIQ-7 and ICIQ questionnaires, confirmed the association between increasing BMI and severity of UI as reported by many studies^[6,30,31]. Female UI is prevalent in Saudi Arabia as documented by two local studies; however, they reported the symptoms in normal-weight females only^[10,11].

ICIQ was used to measure impact of UI on everyday life as it is more specific about number of incontinence episodes, whereas IIQ specifically assessed the amount of UI and its impact on various activities, roles and emotional aspects. Using either measure, younger women with higher BMI reported increased frequency of stress and urge incontinence and worse UI-specific QoL ($p = 0.004$ and $p = 0.001$) as compared to non-obese women. Obese women were also disproportionately affected by colorectal symptoms related to PFD including flatus incontinence ($p = 0.031$) compared with their normal weight peers. The mechanism may be related to excessive weight, which in addition to having chronic pressure on pelvic floor may alter autonomic nervous system, pudendal nerve conduction or sphincter mechanism^[6,9].

In our study, QoL measures encompassing physical,

social and emotional aspects were most significantly affected by symptoms of PFD including POP, FI and UI. Effects of anal disturbances were more bothersome in obese group as compared to non-obese group. There was a general reduction in activities such as social visits, entertainment and travelling, in addition to problems faced during prayers. In Muslim women, urinary or fecal incontinence strongly interferes with their ritual purity recommended for prayers as an incontinent woman has to wash every time before a prayer and this is a constant source of frustration and low self-esteem^[32]. Our results revealed that religious activities were highly affected in both groups as compared to household or social activities. Similar consequences have been reported in other studies such as limitations of daily activities, social isolation, stigmatization, depression and end of independent living for some women^[33].

Furthermore, studies have demonstrated that weight loss by surgical and non-surgical methods can improve the symptoms of PFD including UI, FI, and symptoms of POP^[34,35]. Subak *et al* reported a 50% reduction in incontinence frequency after only a 5% decrease in weight^[36].

Limitations of study include further categorization of BMI in the obese group, according to the classification of obesity, was not done. In addition, the study was a questionnaire based assessment and no physical examination or other objective assessments were performed. However, the study was a good addition to the literature as it used multiple validated PFD questionnaires and it was conducted on Saudi women with scarcity of related studies. Large scale research in such a population should focus on identifying all modifiable risk factors such as obesity.

CONCLUSION

The frequency of pelvic organ prolapse, urinary incontinence, and fecal incontinence was increased in obese women awaiting bariatric surgery. Low self-esteem and limited religious activities were the most negative impacts of these symptoms on quality of life as compared to other personal and social activities. Studies on the effect of weight reduction on the prevalence and impact of pelvic floor disorders on obese women are warranted.

ACKNOWLEDGMENT

The authors would like to thank the Deanship of Scientific Research at King Saud University for the support and funding this project through Research Group Project # RGB-241". Also, we would like to extend our appreciation to Ms. Bella Rowena Magnaye for all the technical support and administrative help that she has given us.

Declaration of interest: The authors report no declaration of interest

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Case Report

Hypercalcemia and Hypertensive Pulmonary Edema associated with Vitamin D Toxicity: A case report

Huseyin Yildiz, Behiye Deniz Kosovali, Mustafa Volkan Demir

Department of Internal Medicine, Malatya State Hospital, Turgut Ozal Boulevard Number:4 44330, Malatya, Turkey

Kuwait Medical Journal 2018; 50 (4): 467 - 469

ABSTRACT

Vitamin D deficiency is frequently seen all over the world and recognised as pandemic. This leads to widespread use of vitamin D supplements. Its indiscriminate use potentially may lead to enhance the incidence of vitamin D intoxication, which is considered a rare disorder. We present

a case of an 82-year-old female patient diagnosed with rheumatoid arthritis, chronic renal failure, osteoporosis and hypertension controlled by single drug therapy-developed hypercalcemia and hypertensive pulmonary edema due to vitamin D overuse.

KEY WORDS: hypercalcemia, vitamin D intoxication

INTRODUCTION

Vitamin D is an important prohormone that plays a vital role in calcium homeostasis, bone mineralisation, cell differentiation and immunomodulation^[1]. The etiology of autoimmune diseases is still unknown but it is believed that vitamin D, through its immunomodulatory role, might be a key component in the treatment of these diseases due to the correlation between the reduced intake of Vit D and the prevalence of autoimmune diseases^[2]. Recently, vitamin D usage is increasing but vitamin D toxicity is extremely rare because of its wide therapeutic index. In vitamin D toxicity, patients may be presented with hypercalcemia, acute renal failure, hyperphosphatemia, polyuria, polydipsia and hypertension^[3]. We present a case of an 82-year-old female patient diagnosed with rheumatoid arthritis (RA), chronic renal failure (CRF), osteoporosis and hypertension (HT) who developed hypercalcemia and hypertensive pulmonary edema due to vitamin D overuse.

CASE REPORT

An 82-year-old woman diagnosed with osteoporosis for 4 years, RA for 50 years, HT for 20 years and non-dialysis CRF for 1 year presented to the emergency department with complaints of

nausea, vomiting, dispnea and fatigue. She was taking vitamin D 300.000 IU intramuscular (i.m) irregularly without council or consent from her treating physician, leflunomide 20 mg once a day, methothrexate 2.5 mg tablet per oral (p.o) once a week, gabapentin 600 mg p.o once a day, calcium + vitamin D p.o three times a week, folic acid 5 mg p.o once a week and amlodipine 10 mg p.o once a day. On initial physical examination, the patient was oriented to time and place and her consciousness was clear. Pupils were normal size and reactive to the light. Her body temperature was: 36.2 °C, blood pressure 210/86 mm-Hg, heart rate 118/min and respiratory rate 20/min. In laboratory tests; white blood cell count: 11,800/mm³ (normal range: 4500 – 10,000/mm³), hemoglobin: 13.6 g/dl (normal range: 12 – 16 g/dl), urea: 88 mg/dl (normal range: 7 - 45mg/dl), creatinine: 2.25 mg/dl (normal range: 0.5 - 1.1 mg/dl), sodium: 135 mmol/L (normal range: 135 – 145 mmol/L), chlorine: 106 mmol/L (normal range: 98 – 109 mmol/L), albumin: 2.1 (normal range: 3.5 - 5 g/dl), calcium: 10.9 mg/dl- corrected calcium level due to hypoalbuminemia: 12.4 (normal range: 8.4 - 10.2 mg/dl), C-reactive protein (CRP): 6.24 mg/dl (normal range: 0 - 0.5). Other laboratory results and blood gases were within normal range. On

Address correspondence to:

Mustafa Volkan Demir, Department of Internal Medicine, Malatya Education and Research Hospital, Turgut Ozal Boulevard Number:4 44330, Malatya, Turkey. Tel: +905303406422; E-mail: mvolkandemir@gmail.com

her chest X-ray, infiltration was detected on both lungs and cardiothoracic ratio was greater than $\frac{1}{2}$. Tachycardia and left heart hypertrophy were seen on electrocardiography. On echocardiography, ejection fraction was found to be 60% and no ventricular dysfunction was observed. She was admitted to internal medicine intensive care unit with the suspicion of pneumonia and hypertensive crisis. Nitrogliserine infusion and furosemid were started. Due to high CRP level and infiltration on chest x-ray, ceftriaxon was started intravenously. In the following days, hypoxemia, tachypnea and acidosis in blood gas were seen and infiltration on chest x-ray progressed, then patient was connected to the non-invasive mechanic ventilation (NIMV). On the third day of NIMV application, significant improvement in blood gases and general status of patient were observed. There was no need of NIMV anymore and NIMV application was ended. Meanwhile, furosemid and saline infusion were started as hypercalcemia treatment. She was tested for serum vitamin D levels and findings showed levels of 70 ng/ml (normal: 10-44 ng/ml), parathormone level was: 14.4 pg/ml (normal: 15-65 pg/ml) and urine calcium level was normal. Vitamin D toxicity was found to be the reason of hypercalcemia. Control serum calcemia level was 13 mg/dl and methylpredisolon 80 mg/day daily was started. Serum calcium level promptly returned to normal after rehydration, furosemid and steroid treatment. The patient was asked to discontinue administration of vitamin D and calcium supplements and advised to repeat vitamin D and calcium after 3 months.

DISCUSSION

The use of vitamin D supplementation has recently been increasing because of its effect on reducing the risk of diseases such as rickets and osteoporosis^[1]. Additionally, in several recent studies, the association between vitamin D deficiency and autoimmune diseases such as RA, multiple sclerosis, systemic lupus erythematosus has been shown, and it probably contributed to a rise in vitamin D usage^[2,4]. Vitamin D toxicity usually results from overuse of supplementation. Unfortunately, the upper limit of daily vitamin D intake is still unknown. It is believed that the toxic effects of vitamin D occur when exceeding the level of 150 ng/mL^[5].

The patient described in this case report had osteoporosis, RA, HT, CRF and was diagnosed with hypercalcemia, pneumonia and pulmonary edema while taking oral and i.m vitamin D and calcium supplements. Symptomatic hypercalcemia is usually related with underlying malignant neoplasm or hyperparathyroidism, but these diagnoses were

unlikely given our patient's low serum PTH and normal 24-hour-urine calcium level. Hypervitaminosis D leads to a rise in intestinal calcium consumption^[6]. As a result, hypercalcemia occurs, which in turn may cause cardiac arrhythmia and hypertension. Due to hypercalcemia resulting from vitamin D toxicity, she developed hypertensive crisis leading to pulmonary edema^[7,8]. The mechanism of pulmonary edema is usually related with left ventricular dysfunction^[8]. However, in our case, her left heart function was normal. In a study, it is found that diastolic dysfunction may also be an important contributor to acute hypertensive pulmonary edema in patients with baseline systolic dysfunction^[9]. However, ischemia and hypoxemia may contribute to diastolic dysfunction without causing a measurable reduction in the ejection fraction or in the extent of regional wall motion^[10].

Initial management of patients who experience pulmonary edema should focus on the "ABCs" of resuscitation and then pharmacologic therapy and ventilatory support to provide improvements in preload, afterload and cardiac output^[11]. As in the case described above, the patient responded well to the medical treatment and NIMV.

CONCLUSION

This study emphasizes the careful dosing of vitamin D in clinical use and also assumes importance of the fact that physicians need to be wary of prescribing vitamin D in high doses without monitoring and consider the potential toxic effects of it. Biochemical testing can be periodically done in clinical follow-up for prompt recognition. Additionally, long-term randomized studies are needed to detect the dose of vitamin D providing optimal immunomodulatory effect for RA without leading to hypercalcemia, which can cause severe clinical problems.

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Case Report

A healthy baby born under the treatment of Eculizumab in a PNH patient after two fetal losses: Turkish Eculizumab baby

Fergun Yilmaz, Fusun Gediz, Demet Kiper

Izmir Katip Celebi University, Ataturk Education and Research Hospital, Izmir, Turkey

Kuwait Medical Journal 2018; 50 (4): 470 - 472

ABSTRACT

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder affecting all systems and organs. It may present with many different scenarios to all specialists. Therefore, the diagnosis is difficult if it is not suspected. Eculizumab is an effective and safe treatment in PNH patients, but there is lack of evidence for its use during pregnancy. A 32-year-old female was referred us due to anemia. The laboratory results revealed non-immune hemolytic anemia. The past medical history was remarkable with two fetal losses due to thrombosis of the placental veins. PNH was suspected due to hemolytic anemia with habitual fetal loss and fluorescently-labeled aerolysin reagent test confirmed the diagnosis. The

eculizumab treatment was initiated. At the 13th week of treatment, she became pregnant. Eculizumab was continued. At the 35th week of gestation, a healthy male baby was delivered. No major adverse event was observed during gestation and the postpartum period. All the physicians should be aware of PNH, because affected patients may present to all specialists rather than hematologists with different clinical scenarios. With eculizumab treatment, the signs and symptoms of PNH will dramatically diminish and wellbeing of the patients increases. As a result, women with PNH may have healthy babies with effective eculizumab treatment.

KEY WORDS: eculizumab, pregnancy, paroxysmal nocturnal hemoglobinuria

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder caused by somatic mutations that result in the absence of glycosylphosphatidylinositol (GPI) anchor protein and GPI linked proteins such as CD 55 and 59. In the absence of these proteins, complement mediated hemolysis occurs and the risk of thromboembolism (TE) increases dramatically^[1]. TE is associated with high mortality and morbidity rates in patients with PNH^[2]. TE and ongoing non-immune hemolysis are the hallmarks of the disease^[1].

PNH has a slight female predominance in their 30s^[1]. Especially after an increase in awareness, the number of female patients at childbearing ages being diagnosed as PNH have increased. However, the rate of complications has increased during pregnancy and the postpartum period. Maternal and fetal mortality rates are as high as 8 - 10% and 4 - 8%, respectively^[3,4]. In the light of these data, pregnancy is considered as a relative contraindication in patients with PNH. After introducing eculizumab, a monoclonal antibody

that inhibits formation of C5b and membrane attack complex, incidence of complications in patients with PNH decreases and eculizumab improves quality of life, survival rates and wellbeing in women at childbearing ages^[5]. Therefore, the number of PNH women who desire to become pregnant increases. Although the data regarding eculizumab during pregnancy is scarce, its safety and efficacy has been reported in the literature^[6].

In this case, we reported a patient diagnosed as PNH after two fetal losses, who had a healthy baby under the treatment of eculizumab.

CASE REPORT

A 32-year-old female was admitted to the hematology outpatient clinic due to anemia. Her medical history revealed two fetal losses: a premature labor at 27th week of gestation and a still birth at 33rd week of gestation. The pathologic examination of the placenta revealed thrombus of the placental veins. In the laboratory tests, hemoglobin (Hb)

Address correspondence to:

Fergun Yilmaz, MD, Izmir Katip Celebi University, Ataturk Education and Research Hospital, Izmir, Turkey. Tel: +90 232 244 44 44 (2703); E-mail: fergunaydin@hotmail.com

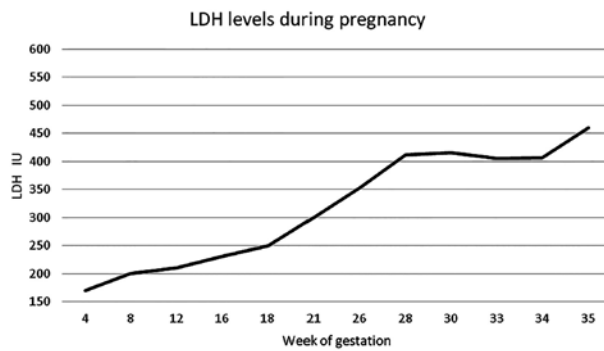


Fig 1: LDH levels during pregnancy

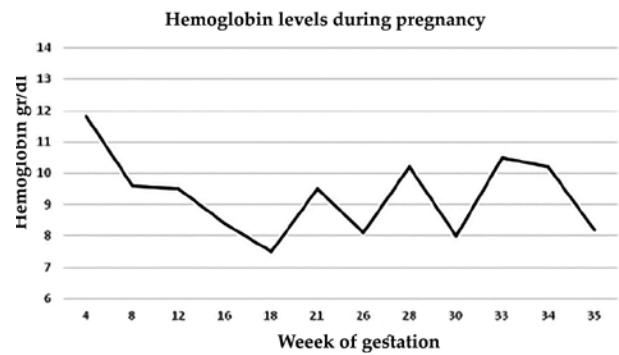


Fig 2: Hemoglobin levels during pregnancy

and mean corpuscular volume was 10.5 gr/dl and 101 fl, respectively. Macrocytosis, anisocytosis and polychromasia were observed in peripheral blood smear. A high lactate dehydrogenase (LDH) (656 U/l, normal range: 125 - 220 U/l) and reticulocyte levels were remarkable. Direct coombs test was negative and vitamin B12 and folic acid levels were within normal range. These findings indicated a non-immune hemolytic anemia. Other possible conditions causing thrombophilia were also investigated. Protein C, S and antithrombin 3 levels were normal. Anti-cardiolipin antibodies and lupus anticoagulants were negative. She was heterozygote positive for methylenetetrahydrofolate reductase gene mutation.

Fluorescently-labeled aerolysin reagent test for PNH was performed due to association of non-immune hemolytic anemia with habitual fetal loss. The type II and type III erythrocytes were 0.6% and 12.4% respectively. The PNH clone was 70.4% in monocytes. The bone marrow aspiration was normocellular with prominent erythroid hyperplasia. Eculizumab treatment was initiated in November 2015 (600 mg every week for four weeks, followed by 900 mg every two weeks)^[1]. At the 9th week of treatment, the hemolysis was under control with normal LDH, Hb and reticulocyte levels. At the 13th week of treatment, she became pregnant. The patient's informed consent was received and treatment with 900 mg every two weeks was continued with close monitoring. Enoxaparin and acetylsalicylic acid (ASA) were initiated (levels of anti X_A was 0.9 and 0.7%).

The Hb decreased, especially after 8th week of gestation, below 10 gr/dl. At the 18th week of gestation, 2 units of red blood cells (RBC) were transfused due to symptomatic anemia (Hb: 7.5 gr/dl). The indication of transfusion was accepted as symptomatic anemia and fetal distress. During the pregnancy period, she received a total of 8 units of RBCs to maintain Hb levels at 8 gr /dl and to keep the mother asymptomatic. The Hb and LDH levels

were demonstrated in Figure 1 and 2. At the 35th week of gestation, caesarean section was performed due to fetal distress. A 3130 gr healthy male baby was delivered. At the 40th day postpartum, the Hb level increased to 11.3 gr /dl with normal LDH and reticulocyte. There was no adverse event including thrombosis during pregnancy and the postpartum period. Low molecular weight heparin (LMWH) was discontinued 6 weeks after delivery. She is still followed up at the hematology department.

DISCUSSION

PNH mainly affects females at their reproductive ages^[1]. With effective eculizumab treatment, more female patients desire to become pregnant. In this case, we report a healthy Turkish baby who was born under eculizumab treatment without any adverse (including TE) effects, except a slight increase in hemolysis and transfusion requirement in the mother.

There are many risks in pregnant women with PNH. First, pregnancy itself is a hypercoagulable state, which increases the risk of TE in pregnant patients with PNH. Second, increased risk of TE was associated with high mortality and morbidity^[4]. Third, transfusion requirement, which also adds additional risk,^[3] is increased during pregnancy. Fourth, the efficacy and safety of eculizumab is not well documented during pregnancy. The largest study evaluating eculizumab in PNH patients consisted of 75 pregnancies^[6]. In that study, the patients experienced an increased need for transfusion and bleeding episodes under the treatment of eculizumab. We also observed an increased transfusion need in our patient that is compatible with the study by Kelly *et al.* The authors reported the rate of thrombosis as 3% among 75 pregnancies^[6]. One of the thrombotic attacks occurred after plasma infusion and high complement levels in plasma were blamed for increasing the risk of thrombosis in that patient. Therefore, it was recommended to avoid plasma infusions in this

group of patients^[6]. Their study revealed that the rates of thrombosis in pregnant patients with PNH decreased after introducing eculizumab treatment (3% versus 16%)^[4,6]. Our patient did not experience any bleeding or thrombotic episodes.

Although it is recommended to use anticoagulant therapy in especially high risk patients such as those with a previous history of TE, recurrent fetal losses, large PNH clones and patients in the postpartum period^[7], the efficacy and safety of anticoagulation is not systematically evaluated. The alternatives for anticoagulation in this population included LMWH, unfractionated heparin or fundaparinox^[6,7]. LMWH may be a good alternative for several reasons. First, it does not cross the placenta. Second, different dose alternatives are available and third, it has a short half-life. It is also easy to administer and its use is suitable in outpatient clinic. Similarly, the efficacy of ASA is also controversial. We treated our case with LMWH and ASA during pregnancy and continued for 6 weeks post-partum without any complications.

Besides the risks to the mother, PNH is also associated with high mortality rates of the fetus^[3] mostly due to premature delivery, still births and late miscarries especially beginning eculizumab treatment. Compatible with these data, two fetal losses were reported in our patient before the diagnosis.

In the literature, case reports and case series reported healthy babies born to women with PNH under eculizumab treatment^[6-9]. In a study of 7 pregnant patients exposed to eculizumab, all patients except one who preferred elective termination, had healthy babies^[9].

Although the eculizumab may be detected in cord blood at very low levels, this level may not affect the complement system activity of the baby^[6,10]. While these data increase the safety profile of the drug during pregnancy, it should be confirmed in large clinical trials.

CONCLUSION

The patients with PNH may present to different specialists with different scenarios because it may affect all systems and organs. The awareness of PNH should be increased among specialists other than hematologists. Under the treatment with eculizumab, healthy babies may be delivered even in patients with habitual fetal losses due to PNH. One should keep in mind that suspicion is the hallmark for early diagnosis of PNH.

ACKNOWLEDGMENTS

We thank Prof. Dr. Teksin Cirpan, Ege University Hospital, Department of Obstetrics and Gynecology for successful follow up during gestation and Assoc. Prof. Dr. Bahriye Payzin, Izmir Katip Celebi University, Ataturk Education and Research Hospital for treatment and her kind support.

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Case Report

Wandering Spleen containing Mesothelial Cyst: A case report and review of literature

Khalid H Al-Hammad, Adel Al-Fudari, Mohammed Ibrahim
Kuwaiti Board of Surgery
Department of Surgery, Mubarak Al-Kabir Hospital, Kuwait

Kuwait Medical Journal 2018; 50 (4): 473 - 477

ABSTRACT

Wandering spleen, defined as a spleen without peritoneal attachment, is very rare and the presence of a cyst in it makes it even rarer. We report a case of a wandering spleen

containing a mesothelial cyst. The case presented with recurrent lower abdominal pain. A CT scan was diagnostic, and laparoscopic assisted splenectomy was performed.

KEY WORDS: cyst, splenectomy, wandering spleen

INTRODUCTION

The spleen develops from the mesoderm in the dorsal mesogastrum. It lies in the left hypochondrium behind the stomach, and is approximately 12 cm long and 7 cm wide^[1]. The spleen is fixed by five ligaments or peritoneal reflections, which are embryological condensations^[2]. Wandering spleen, defined as a spleen without peritoneal attachment, is a rare entity with an incidence of less than 0.5%^[3]. Splenic cysts are classified as parasitic and non-parasitic cysts, the non-parasitic are further categorized as primary (epithelial-true) and secondary (pseudo-false) cysts based on the lining of the cyst^[4]. We report a case of a wandering spleen containing a mesothelial cyst, discussing the possible ways of management.

CASE REPORT

A 17-year-old female was referred to our surgical outpatient clinic with a few days history of occasional dull aching left and lower abdominal pain with no associated symptoms. On examination, a painless and partially mobile pelvi-abdominal mass was felt, occupying mainly the suprapubic region. An ultrasonography of the abdomen was performed and showed a pelvi-abdominal mass containing a unilocular cystic mass measuring 10 x 9 x 9.8 cm with

turbid internal echoes. The impression was most likely pelvic spleen with a cyst within it (Fig 1). The patient was admitted to the hospital for further workup. Her laboratory tests were within normal limits. A CT scan of the abdomen with contrast enhancement showed a wandering spleen measuring 19.3 x 14.6 cm with a large splenic cyst in the centre measuring 9.7 cm with a very thin wall (Fig 2). The case was discussed with the patient and her family and they agreed for splenectomy. After receiving anti-pneumococcal, Hemophilus influenza and meningococcal vaccines, the patient underwent laparoscopic assisted splenectomy via 3 ports. A 10 mm supra-umbilical port was used beside a 10 mm port in the right mid-clavicular line just above the level of the umbilicus and a 5 mm port at the McBurney's point. The spleen was found in the pelvis with fine ligament attachments. Splenic pedicle was dissected and separated by staplers, the freely mobile spleen was fitted into an endo-bag and extracted through the supra-umbilical port site after enlargement of the incision (Fig 3). The patient tolerated the procedure well and was discharged two days later. The histopathological examination revealed a mesothelial type of splenic cyst (Fig 4). After more than three months follow-up, the patient is free of abdominal pain.

Address correspondence to:

Dr. Khalid Hamad Al-Hammad, Department of Surgery, Mubarak Al-Kabir Hospital, Al-Jabriya, P.O.Box 43787, Code: 32052 Kuwait. Tel: (+965)99100191; E-mail: duke_alhammad@hotmail.com



Fig 1: Ultrasonography display of the abdomen and pelvis showing the wandering pelvic spleen and a large splenic cyst.

DISCUSSION

The first description of a wandering spleen is attributed to Von Horne in 1667, as an autopsy finding on an adult^[5]. Wandering or ectopic spleen

has two possible aetiologies: congenital and acquired. The congenital form occurs due to failure of the dorsal mesogastrium to develop when the lesser sac is formed. The acquired form occurs mostly in multiparous female, as the ligament, which holding the spleen in position become lax^[6]. The male to female ratio is about 1:7 in adults and most females are in the child-bearing age group of 20 to 40 years^[3]. Wandering (ectopic or floating) spleen as an entity is very rare and the presence of a cyst in it makes it even rarer^[7]. The splenic cysts are classified as parasitic and non-parasitic cyst. Parasitic cysts are generally seen in endemic areas and are usually caused by *Echinococcus granulosus* infestations. The true or primary non-parasitic cysts maybe congenital or neoplastic in origin and are lined by mesothelial, squamous or transitional epithelium. Secondary or pseudo non-parasitic cysts are usually post-traumatic, due to failure of organization of sub-capsular or parenchymal hematomas^[8]. Non-parasitic cysts of the spleen are rare and are incidentally discovered, derived from the mesothelial cell lining of the splenic capsule^[9]. Embryonic inclusion of epithelial cells from adjacent structure, epithelial cell metaplasia from adjacent structures or vascular endothelium from peritoneal inclusions are some of the theories to explain the genesis of these congenital cysts^[9]. Also, capsular surface mesothelial invagination results in subsequent cyst formation^[4]. Primary true cysts of the spleen account for about 10% of all non-parasitic cysts of the spleen^[10]. Mesothelial cysts have a characteristic gross and microscopic appearance^[9]. Grossly, they are usually unilocular and vary in size, with whitish or greyish-white cut surface^[11]. Microscopically, the lining cells stain positive for calretinin, a mesothelial marker,

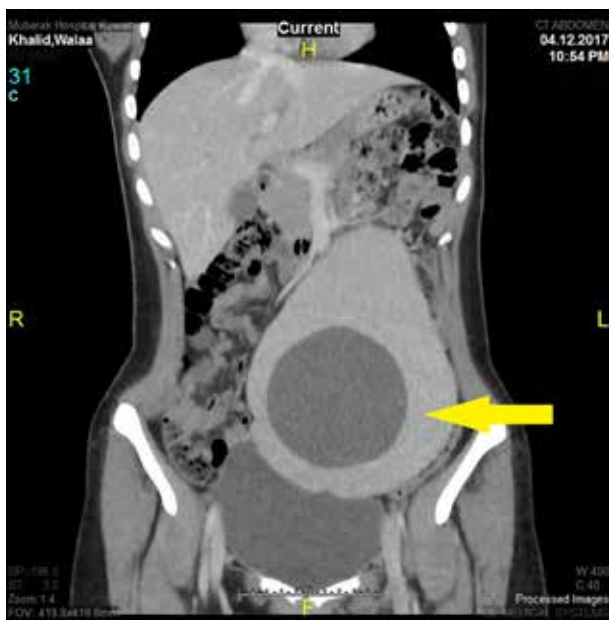


Fig 2 (A&B): Computed tomography scan abdomen (A) coronal (B) sagittal view, showing a large cyst in a wandering pelvic spleen.

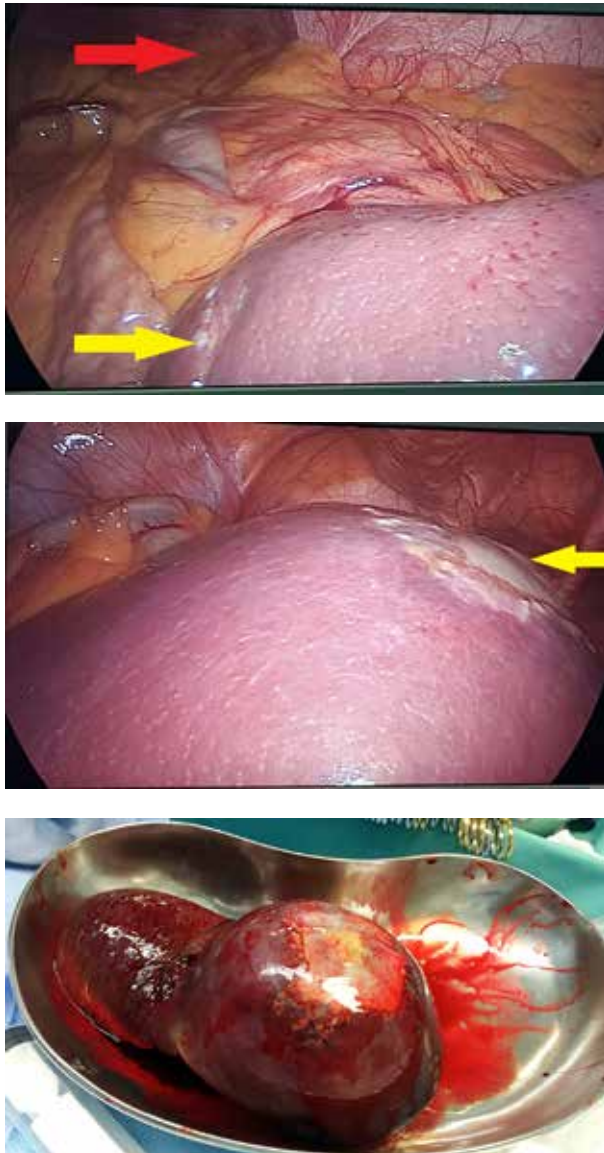


Fig 3 (A,B&C): Intra-operative picture (A) laparoscopic view with the yellow arrow pointing to the pelvic spleen and the red arrow pointing to normal anatomical site (B) the pelvic spleen with the cyst (C) the extracted spleen.

and secrete CA 19-9 which can be used as a screening tool in the management of these lesions^[12]. Studies have indicated a rise in CA 19-9 in association with primary mesothelial cyst and the reduction of its level after cyst removal, offering a screening test to indicate recurrence in case of spleen preserving surgeries^[11]. Clinical presentation of these cases (wandering spleen with or without a cyst) usually present with an asymptomatic abdominal mass or a mass associated with recurrent pain, also may present as an acute abdomen if it becomes complicated by torsion^[13]. Wandering spleen also can predispose to other life-threatening complications such as splenic infarction, portal hypertension or gastrointestinal bleeding^[14].

Imaging studies such as a colour ultrasonography, visceral arteriography, splenic radionucleotide scan and contrast enhanced spiral CT are very useful in reaching a definitive diagnosis of a wandering spleen^[15]. Regarding mesothelial cyst, the preoperative diagnosis is rare, but they can be suspected in case of unilocular cysts with no previous history of trauma, infection, or exposure to hydatid infection. Imaging may be useful in the investigation, such as ultrasound of the abdomen, which shows whether the cysts are

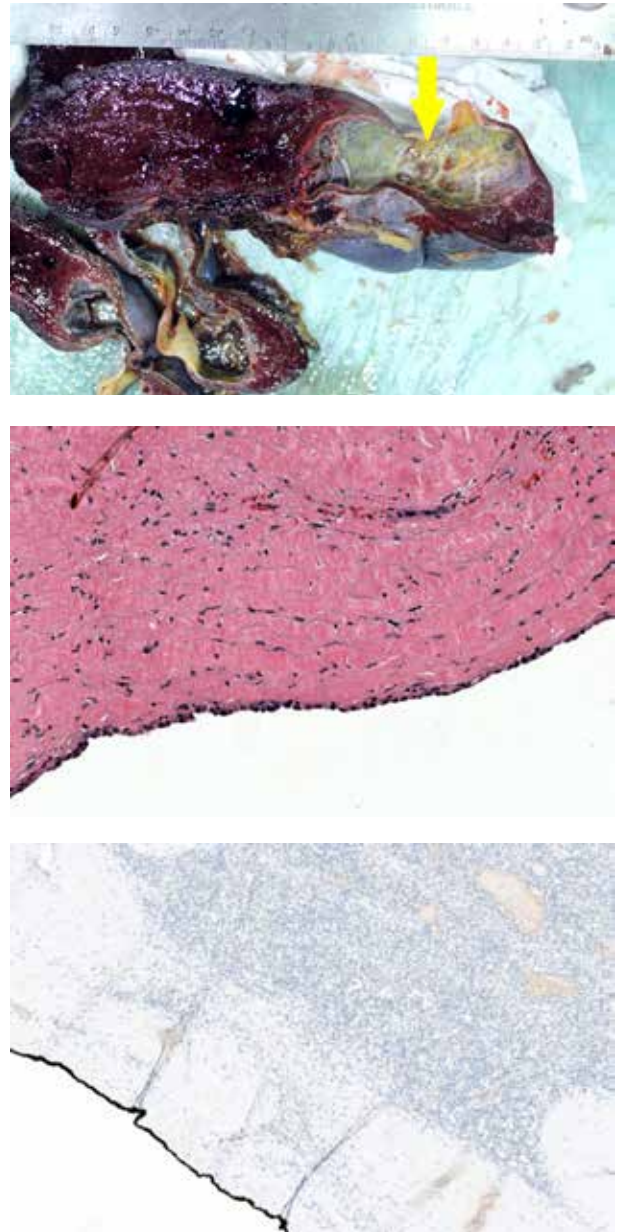


Fig 4 (A,B&C): Histopathological examination of the splenic cyst (A) cut section showing a single large fibrous trabeculated cyst (B) microscopy showing the cyst wall lined by cuboidal mesothelium (H & E x100) (C) cyst epithelial lining showing positivity for calretinin (immunohistochemistry x200).

anechoic or hypoechoic, in addition to showing wall thickness. Computed tomography scans (CTs) and magnetic resonance imaging, can provide additional information regarding the morphology of the cyst, the composition of the cyst fluid, the precise location of the cyst in the spleen, and its anatomical relationship with the surrounding abdominal organs. The diagnosis is confirmed histopathologically^[16]. Splenectomy has traditionally been used for wandering spleen, splenopexy is increasingly used in the pediatric population to anchor the spleen and preserve splenic function. Concerns over overwhelming post-splenectomy sepsis make splenopexy the first line of treatment if there was no evidence of infection or any other complicating pathology^[17]. However, a multicentric study reported complications after salvage with splenopexy in 60% of cases resulting in post splenopexy splenic ischemia^[18]. Regarding splenic cyst, conservative treatments with regular scans may be an option for cysts that are up to 5 cm in diameter, completely asymptomatic, and which exhibit the most typical characteristic of non-parasitic splenic cysts. In cases with surgical indication and due to the growing population of spleen preservation to preserve immune function, many alternative treatment options have been suggested^[10,19]. Also, surgery is the gold standard treatment for symptomatic and large (>5 cm) splenic cysts and the surgical procedure is tailored depending on the patient's age and the size, nature and location of the cyst. The various surgical procedures described are open complete splenectomy, partial splenectomy, cystectomy, marsupialization and cyst decapsulation^[20]. Laparoscopic management of splenic cysts offers the advantage of minimally invasive surgery, faster recovery, shorter hospital stay, and reduced morbidity. Anterior surface splenic cysts are more amenable to laparoscopic fenestration than the posterior surface cysts as greater splenic mobility is needed in the latter. Open partial or complete splenectomy is advocated for centrally located splenic cysts^[21]. Anti-pneumococcal, hemophilus influenza, and meningococcal vaccines are indicated before elective splenectomy and shortly after non-elective splenectomy^[22]. In our case, the wandering spleen was diagnosed by ultrasonography and confirmed by a CT scan. The aetiology of the spleen was most likely congenital, but it could be acquired due to the lax and fine ligament attachments found intra-operatively as a result of the large cyst. The splenic cyst was diagnosed as a primary cyst due to the age of the patient, the negative history of any previous infectious or exposure to hydatid infection, and the finding of unilocular cysts in both the ultrasonography and the CT scan. After receiving the vaccinations, a laparoscopic assisted total splenectomy was performed. We preferred total

splenectomy as it is indicated in case of wandering spleen and due to the presence of a large central cyst.

CONCLUSION

Wandering spleen as an entity is very rare and the presence of a cyst within it makes it even rarer. A laparoscopic approach for splenectomy in such cases is an option, but laparoscopic assisted approach is much safer, especially in case of a large splenic cyst. We would like to draw attention to this rare entity in the differential diagnosis of an abdominal mass with minimal symptoms.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2018; 50 (4) : 478 - 481

Total Gastric Necrosis Due to Mucormycosis: A Rare Case of Gastric Perforation

Salah Termos,¹ Feras Othman,¹ Mohammad Alali,¹ Bader M.S. Al Bader,¹ Talal Alkhadher,¹ Wael Fathi Hassanaiah,¹ Ali Taqi,¹ and Abhijit Sapkal²

¹Department of Surgery, Al-Amiri Hospital, Kuwait City, Kuwait

²Department of Pathology, Al-Amiri Hospital, Kuwait City, Kuwait

Am J Case Rep. 2018; 19: 527–533. doi: 10.12659/AJCR.908952

Patient: Female, 52

Final Diagnosis: Gastric mucormycosis

Symptoms: Sepsis • surgical abdomen

Medication: Liposomal amphotericine b

Clinical Procedure: Total gastrectomy

Specialty: Surgery

OBJECTIVE

Rare disease

BACKGROUND

Spontaneous gastric perforation is usually a complication of peptic ulcer disease, or a postoperative complication resulting from gastric torsion. Mucormycosis (or zygomycosis) is an uncommon opportunistic fungal infection that is usually seen in immunocompromised patients and is associated with significant morbidity and mortality. This report is of a rare case of spontaneous gastric perforation due to mucormycosis infection.

CASE REPORT

A 52-year-old woman, with a past medical history of heroin abuse, diabetes mellitus, hypertension, and chronic kidney disease treated by dialysis, presented to the emergency department with cellulitis of the arms. Following hospital admission, her medical condition deteriorated, and she developed septic shock and multiorgan failure, requiring transfer to the intensive care unit (ICU), where she was diagnosed with a perforated hollow viscus as the cause. Surgical exploration showed that the mucosa of the stomach was necrotic and perforated, but the remaining bowel appeared normal. Total gastrectomy was performed, and a jejunostomy feeding tube was inserted. Histopathology of the gastric tissue confirmed infection with mucormycosis. The patient was treated with adjunctive liposomal amphotericin B, her condition improved, and she was extubated on postoperative day 2. However, the patient died on postoperative day 21 due to sepsis and multiorgan failure.

CONCLUSIONS

Mucormycosis is an opportunistic angioinvasive fungal infection, and gastric perforation is a rare clinical presentation. However, knowledge of the association between gastric necrosis and perforation and mucormycosis infection might lead to early diagnosis and treatment and reduce patient morbidity and mortality.

Normal reference ranges for aortic diameters in preterm infants

Abushaban L^{1,2}, Mariappa TV¹, Rathinasamy J¹, Sharma PN³

¹Chest Diseases Hospital, Ministry of Health, Kuwait City, Kuwait

²Department of Paediatrics, Kuwait University, Kuwait City, Kuwait

³Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait City, Kuwait

J Saudi Heart Assoc. 2018 Apr;30(2):86-94. doi: 10.1016/j.jsha.2017.09.003. Epub 2017 Oct 1

OBJECTIVE

To establish normal reference ranges and Z-scores for aortic diameters in preterm infants according to the body surface area and assess their correlation with body weight, body surface area, and gestational age.

PATIENTS AND METHODS

In a prospective study, 268 preterm infants who fulfilled the criteria for inclusion were examined. Echocardiograms were performed to measure the ascending aorta, transverse aorta, and aortic isthmus diameters on 0 days to 6 days of life and at weekly intervals until the babies reached 36 weeks. Body surface area was divided into 13 groups from 0.07 m² to 0.19 m².

RESULTS

The mean gestational age was 29.8 [\pm 2.38 standard deviation (SD)] weeks, ranging from 24 weeks to 35 weeks. The mean body weight was 1479 (\pm 413 SD) g, ranging from 588 g to 3380 g, and the mean body surface area was 0.13 m², ranging from 0.07 m² to 0.19 m². All the aortic diameters correlated well with both body weight and body surface area. Reference ranges with the mean \pm SD, range, and Z-scores were calculated for aortic diameters according to the body surface area. A significant gradual increase was observed in ascending aorta, transverse aorta, and aortic isthmus diameters with increasing body surface area. Overall, a progressive and significant increase in ascending aorta, transverse aorta, and aortic isthmus diameters was observed during the first 9 weeks of life.

CONCLUSION

The ascending aorta, transverse aorta, and aortic isthmus diameters exhibited a significant correlation with the body surface area and body weight. This study provides reference data with Z-scores that can be used as a normal reference tool for the ascending aorta, transverse aorta, and aortic isthmus diameters for preterm infants based on the body surface area.

Human papillomaviruses other than 16, 18 and 45 are the major high risk HPV genotypes amongst women with abnormal cervical smear cytology residing in Kuwait: Implications for future vaccination strategies

Mallik MK¹, Alramadhan B¹, Dashti H¹, Al-Shaheen A¹, Al Juwaiser A¹, Das DK^{1,2}, George SS², Kapila K^{1,2}.

¹Cytopathology Unit, Mubarak Al Kabeer Hospital, Kuwait.

²Department of Pathology, Faculty of Medicine, Kuwait University, Kuwait.

Diagn Cytopathol. 2018 Oct 24. doi: 10.1002/dc.24035. [Epub ahead of print]

OBJECTIVES

The study was undertaken to determine the prevalence of different high risk HPV (HR-HPV) genotypes amongst women residing in Kuwait with epithelial abnormalities in cervical smears and to detect any difference in the distribution of these genotypes between Kuwaiti and Non-Kuwaiti women or between the cytological diagnosis groups.

MATERIALS AND METHODS

Thinprep specimens from women with epithelial abnormalities on cervical smears were subjected to Aptima HR-HPV assay and those found to be HR-HPV positive were genotyped using the Aptima HPV genotyping assay into three groups (i) HPV 16, (ii) HPV 18/45 and (iii) others.

RESULTS

HR-HPV was found in 229 (30.57%) of the 749 cases with epithelial abnormalities. Of the 116 cases subjected to further genotyping, the non-16, 18, 45 genotype accounted for the most prevalent group accounting for 62.93% of the cases, followed by HR-HPV 16 (31.04%) cases and HPV 18/45 (6.03%) of cases. There was no significant difference between Kuwaiti and non-Kuwaiti women nor was any difference noted between the various cytological diagnosis group.

CONCLUSION

Most HR-HPV infections amongst women residing in Kuwait with epithelial abnormalities are due to HPV types other than the 16, 18 and 45. As HPVs 16 and 18 are considered to be the most prevalent HR-HPV genotypes worldwide, causing invasive cancer, the findings of this study is significant from an epidemiological standpoint. It should also be taken into account before undertaking any HPV vaccination program since the available HPV vaccines protect against HR-HPVs 16 and 18 only.

Risk of avascular necrosis of the femoral head in children with sickle cell disease on hydroxyurea: MRI evaluation

Adekile AD^{1,2}, Gupta R^{3,4}, Al-Khayat A³, Mohammed A⁵, Atyani S³, Thomas D¹.

¹Department of Pediatrics, Faculty of Medicine, Kuwait University, Safat, Kuwait

²Pediatric Hematology Unit, Mubarak Al-Kabeer Hospital, Safat, Kuwait

³Department of Radiology, Faculty of Medicine, Kuwait University, Safat, Kuwait

⁴Department of Radiology, Mubarak Al-Kabeer Hospital, Safat, Kuwait

⁵Center for Medical Education, Faculty of Medicine, Kuwait University, Safat, Kuwait

Pediatr Blood Cancer. 2018 Oct 21:e27503. doi: 10.1002/pbc.27503. [Epub ahead of print]

BACKGROUND

There are conflicting reports on the role of hydroxyurea (HU) in the pathogenesis of avascular necrosis of the femoral head (AVNFH) in patients with sickle cell disease (SCD).

PROCEDURE

The present study is a prospective cohort study of Kuwaiti children with SCD who were treated with HU. They had magnetic resonance imaging of the hips before starting HU and at regular intervals during a follow-up period, ranging from 1 to 15 years.

RESULTS

There were 40 patients (18 SS, 19 S β 0-thalassemia, and three SD genotypes), aged 6-20 years. Pre-HU, 11 (27.5%) had varying grades of AVNFH, while post HU, the prevalence was 32.5%. Two patients developed new lesions during the study, while five (45.5%) that had lesions pre-HU remained static, another five (45.5%) progressed, and one (9%) improved radiologically. The older patients who had been on HU the longest were more likely to deteriorate. The only hematological parameter that was consistently associated with AVNFH was the reticulocyte count.

CONCLUSIONS

The frequency and rate of progression of AVNFH in this study is much less than that previously reported for our patients not treated with HU. There is no evidence that HU therapy is a risk factor for AVNFH. It may, in fact, prevent new lesions and deter the progression of existing AVNFH.

Treatment of iron deficiency and iron deficiency anemia with intravenous ferric carboxymaltose in pregnancy.

Abdelazim IA^{1,2}, Nusair B³, Svetlana S⁴, Zhurabekova G⁵.

¹Department of Obstetrics and Gynecology, Ahmadi Hospital, Kuwait Oil Company (KOC), P.O. Box: 9758, 61008, Al Ahmadi, Kuwait. dr.ibrahimanwar@gmail.com.

²Department of Obstetrics and Gynecology, Ain Shams University, Cairo, Egypt dr.ibrahimanwar@gmail.com.

³Department of Obstetrics and Gynecology, King Hussein Medical Center (KHMC), Amman, Jordan

⁴Department of Obstetrics and Gynecology, Marat Ospanov, West Kazakhstan State Medical University (WKSMU), Aktobe, Kazakhstan

⁵Department of Normal and Topographical Anatomy, Marat Ospanov, West Kazakhstan State Medical University (WKSMU), Aktobe, Kazakhstan

Arch Gynecol Obstet. 2018 Oct 22. doi: 10.1007/s00404-018-4943-x. [Epub ahead of print]

BACKGROUND

Iron deficiency (ID) and iron deficiency anemia (IDA) in pregnancy are global health issues, affecting around 30% of women in high-resourced countries, and increasing to over 50% of women in low-resourced countries.

OBJECTIVES

Froessler et al. study published in Archives of Gynecology and Obstetrics (2018) 298: 75. <https://doi.org/10.1007/s00404-018-4782-9>, raised many queries and we would like to know the answers of those queries from the authors if possible.

RESULTS

Diagnosis of IDA should be based on hemoglobin concentration (gm/dl), serum ferritin (ug/l), mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), and the efficacy of the treatment of IDA evaluated by comparing pre-treatment values of hemoglobin, serum ferritin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) by the post-treatment values. Parenteral iron dose for correction of IDA calculated according to the formula; total iron needed in mg = $2.4 \times$ pre-pregnancy weight in kg \times (target hemoglobin concentration - actual hemoglobin concentration) gm/dl + 500 mg.

CONCLUSION

The efficacy of the treatment of IDA evaluated by comparing pre-treatment values of hemoglobin, serum ferritin, MCV, and MCH by the post-treatment values. Parenteral iron dose for correction of IDA calculated according to the formula; total iron needed in mg = $2.4 +$ pre-pregnancy weight in kg + (target hemoglobin concentration - actual hemoglobin concentration) gm/dl + 500 mg.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2018; 50 (4): 482 - 488

18th International Congress of **Endocrinology** / 53rd
Annual Society for Endocrinology, Metabolism &
Diabetes of South Africa Congress
Dec 1 - 4, 2018
South Africa / Cape Town
Contact: Event Management, Scatterlings Conference
& Events
Phone: 011 - 27 - 21 - 422 - 2402
Fax: 011 - 27 - 11 - 463 - 3265

21st International Symposium on **Endoscopic
Ultrasonography** (EUS 2018)
Dec 1 - 2, 2018
Thailand / Bangkok
Contact: Warapa Saipow, Kenes Group Thailand
Phone: +66 - 2 - 748 - 7881
Email: wsaipow@kenes.com

2018 National **Osteoporosis** Society (NOS)
Conference
Dec 2 - 4, 2018
United Kingdom / Birmingham
Contact: NOS
Phone: 011 - 44 - 80 - 8800 - 0035

Topics in **Emergency Medicine**
Dec 2 - 7, 2018
Aruba / Palm Beach (Aruba)
Contact: Northwest Seminars
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Email: info@northwestseminars.com

Introduction to Adult **Echocardiography**
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United States / Florida / St. Petersburg
Contact: Casey Green, Business Development
Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811
Email: learn@gcus.com

Current Topics in **Anesthesia**
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United States / Georgia / Savannah
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8th Annual Congress on Clinical **Microbiology** and
Infectious Diseases
Dec 5 - 6, 2018
Canada / **Vancouver**
Email: carolesmith2018@protonmail.com

9th International Conference on Global Warming,
Climate Change and Pollution Control
Dec 5 - 6, 2018
Canada / Vancouver
Email: pollution@toxicologyconferences.org

9th International Conference on **Recycling**: Reduce,
Reuse and Recycle
Dec 5 - 6, 2018
Canada / **Vancouver, British Columbia**
Email: recycle@annualamericacongress.org

13th World Congress on **Virology**, Infections and
Outbreaks
Dec 5 - 6, 2018
Canada / **Vancouver**
Email: viraldiseases@annualamericacongress.org

28th International Conference on Chemistry & **Drug
Designing** 2018
Dec 5 - 6, 2018
Canada / **Vancouver, British Columbia**
Email: worldchemistry@annualamericacongress.com

31e Congres Francais De **Rhumatologie**
Dec 9 - 11, 2018
France / Paris
Contact: Societe Française De Rhumatologie
Phone: +33 - 1 - 4250 - 0018
Email: sfr@rhumatologie.asso.fr

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Current Topics in Emergency Medicine

Dec 13 - 16, 2018

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Email: info@northwestseminars.com

10th Annual Conference on Emergencies & Challenges in Pediatrics

Dec 14 - 15, 2018

United States / New York / New York

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

22nd Annual Conference on Emergencies & Challenges in Primary Care

Dec 14 - 15, 2018

United States / New York / New York

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

24th Annual Conference on Challenges in Gynecology

Dec 14 - 15, 2018

United States / New York / New York

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Current Topics in Anesthesia

Dec 17 - 20, 2018

United States / Florida / Miami

Contact: Northwest Seminars

Phone: 800 - 222 - 6927

Fax: 509 - 547 - 1265

Email: info@northwestseminars.Com

Society of Nuclear Medicine & Molecular Imaging 2019 Mid - Winter Meeting

Jan 17 - 20, 2019

United States / California / Palm Springs

Contact: Society of Nuclear Medicine & Molecular Imaging

Phone: 703 - 708 - 9000; Fax: 703 - 708 - 9015

2019 Tropical Medicine Excursion to Uganda

Jan 27 - Feb 8, 2019

Uganda / Entebbe

Contact: Kay Schaefer, MD, Tropical Medicine Excursions

Phone: +49 - 152 - 5569 - 8101

2019 Semi - Annual NRG Oncology Meeting

Feb 7 - 9, 2019

United States / Arizona / Phoenix

Contact: NRG Oncology

Email: meeting - reg@nrgoncology.org

Next Gen Nursing

Feb 20 - 21, 2019

United States / San Francisco

Email: nursingcongresscanada@gmail.com

World Kidney Meeting

Feb 20 - 21, 2019

United States / Dallas

Email: kidneycongress@annualamericacongress.org

3rd International Conference on Renewable Energy and Resources

Feb 22 - 23, 2019

United States / San Francisco

Email: renewableenergy@americameetings.com

13th World Drug Delivery Summit

Feb 22 - 23, 2019

United States / San Francisco

Email: drugdelivery@pharmaceuticalconferences.org

14th International Conference on Biofuels, Energy & Economy

Feb 22 - 23, 2019

United States / Dallas

Email: biofuelsconference@gmail.com

20th Chemistry Education on Analytical & Medicinal Drug Discovery

Feb 22 - 23, 2019

United States / San Francisco, CA

Email: analytica2018@americameetings.com

International Conference on Dental Research & Dental Treatments

Feb 22 - 23, 2019

United States / Dallas

Email: dentalhealth@annualamericacongress.com

World Congress on Immunity and Immuno Therapies

Feb 22 - 23, 2019

United States / Dallas, Texas

Email: immunologyresearch@immunologyconferences.org

World Pediatric Allergy and Immunology Summit

Feb 22 - 23, 2019

United States / San Francisco, California

Email: worldpediatric@annualamericacongress.org

2nd International Summit on Conventional and Sustainable Energies

Mar 18 - 19, 2019

United States / Chicago

Email: sustainableenergy@americameetings.com

3rd International Conference on **Ecology, Ecosystem and Conservation Biology**
Mar 18 - 19, 2019
United States / Chicago, Illinois
Email: ecologyecosystems@annualamericacongress.org

3rd International Conference on **Microbial Ecology & Eco Systems**
Mar 18 - 19, 2019
United States / Chicago
Email: microbialecolology@americameetings.com

3rd World Congress on **Embryology and In Vitro Fertilization**
Mar 18 - 19, 2019
United States / New York
Email: ivf@americameetings.net

4th Annual World Congress on **Pediatric Nutrition, Gastroenterology and Child Development**
Mar 18 - 19, 2019
United States / Chicago
Email: pediatricgastroenterology@americameetings.net

7th International Conference on **HIV/AIDS, STDs and STIs**
Mar 18 - 19, 2019
United States / New York
Email: std@americameetings.net

14th International Conference on **Metabolomics and Enzymology**
Mar 18 - 19, 2019
United States / New York
Email: metabolomics@americameetings.net

19th International Conference on **Healthcare, Nutrition & Fitness Expo**
Mar 18 - 19, 2019
United States / New York
Email: johnsonscott8457@gmail.com

20th Annual World Congress on **Pediatrics**
Mar 18 - 19, 2019
United States / Chicago
Email: pediatrics@pediatricsconferences.com

30th World Summit on **Positive Psychology, Mindfulness, Psychotherapy and Philosophy**
Mar 18 - 19, 2019
United States / Chicago, Illinois
Email: positivepsychologymeetings@gmail.com

31st American **Psychiatry, Psychology and Nursing Congress**
Mar 18 - 19, 2019
United States / Chicago, Illinois
Email: globalpsychiatry1@gmail.com

33rd Annual **Vaccines & Vaccination Congress**
Mar 18 - 19, 2019
United States / New York
Email: vaccinescongress@americameetings.net

International Conference on **Obesity, Diet Management & Nutrition** Conference
Mar 18 - 19, 2019
United States / New York
Email: obesityconference8457@gmail.com

2nd International Conference and Exhibition on **Pharmaceutical Nanotechnology and Nanomedicine**
Mar 20 - 21, 2019
United States / New York
Email: nanopharma@annualamericacongress.org

4th International Conference on **Food Microbiology and Food Market**
Mar 20 - 21, 2019
United States / New York
Email: foodmicrobiology2019@aol.com

6th World Congress on **Mental Health, Psychiatry and Wellbeing**
Mar 20 - 21, 2019
United States / New York
Email: mentalhealth@americameetings.com

19th Global **Chemistry** Conference
Mar 20 - 21, 2019
United States / New York
Email: globalchemistry@americanevent.org

19th World Conference on **Chromatography & Spectrometry**
Mar 20 - 21, 2019
United States / New York
Email: spectrochrome@americanevent.org

2019 **Tropical Medicine** Excursion to Ghana
Mar 20 - 30, 2019
Ghana / Accra
Contact: Kay Schaefer, MD, Tropical Medicine Excursions
Phone: +49 - 152 - 5569 - 8101

St. Gallen International **Breast Cancer** Conference:
Primary Therapy of Early Breast Cancer - Evidence,
Controversies, Consensus

Mar 20 - 23, 2019

Austria / Vienna

Contact: St. Gallen Oncology Conferences

Phone: +41 - 71 - 243 - 0032

Email: info@oncoconferences.ch

5th International Conference on **Antibiotics**

Mar 22 - 23, 2019

United States / Florida / Orlando

Email: antibioticssummit@annualamericacongress.org

29th Annual American **Dentistry** Congress

Mar 22 - 23, 2019

United States / New York

Email: americandentistry@dentistryconferences.com

4th International Conference on **Holistic Medicine
and Nursing Care**

Mar 25 - 26, 2019

United States / Florida / Orlando

Email: alternativemedicine@americameetings.net

11th World Congress and Expo on Cell & **Stem Cell
Research**

Mar 25 - 26, 2019

United States / Florida / Orlando

Email: cellandstemcell@usaconference.org

21st Global **Nursing** Education Conference

Mar 25 - 26, 2019

United States / Florida / Orlando

Email: globalnursingeducation@americanevent.org

World Congress on **Pharmaceutical Biotechnology &
Bioengineering**

Mar 25 - 26, 2019

United States / Florida / Orlando

Email: biotech@pharmaceuticalconferences.org

2nd World Congress on **Oculoplastic Surgery and
Clinical Ophthalmology**

Mar 27 - 28, 2019

Hong Kong

Email: oculoplasty@conferencesworld.org

5th International Conference on **Clinical Pharmacy
and Health Care**

Mar 27 - 28, 2019

United States / Texas / San Antonio

Email: clinicalpharmacy@annualamericacongress.com

4th International Conference on **Prosthodontics &
Restorative Dentistry**

Apr 8 - 9, 2019

Canada / Toronto, Ontario

Email: prostho2019@gmail.com

7th International Conference and Expo on

Acupuncture and Alternative Medicine

Apr 8 - 9, 2019

Canada / Toronto

Email: acupuncture@conferenceseries.net

7th International Conference on **Smart Materials and
Sustainable Technologies**

Apr 8 - 9, 2019

Canada / Toronto

Email: rosalinamario92@gmail.com

33rd Annual World **Dentistry** Summit

Apr 8 - 9, 2019

Canada / Toronto

Email: danieljonesusa73@gmail.com

International Conference on **Advanced Materials and
Physical Metallurgy**

Apr 8 - 9, 2019

Canada / Toronto

Email: sydneywilson554@gmail.com

3rd International Conference on **Influenza** and
Emerging **Infectious Diseases**

Apr 10 - 11, 2019

Canada / Toronto

Email: influenzaresearch@annualamericacongress.org

4th World Congress on **Nursing Practice & Research**

Apr 10 - 11, 2019

Canada / Toronto

Email: nursepractice@conferencescanada.com

4th World Congress on **Nursing Education & Research**

Apr 12 - 13, 2019

Canada / Toronto

Email: nursingeducationcongress@conferencescanada.org

23rd International Conference on **Food Fraud & Safety**

Apr 12 - 13, 2019

Canada / Toronto

Email: foodfraud@annualamericacongress.org

25th International Conference on **Organic & Inorganic
Chemistry**

Apr 12 - 13, 2019

Canada / Toronto, Ontario

Email: organicchemistry@americanevent.org

Annual Congress on **Child Care: Mental Health, Psychology and Nursing**
Apr 12 - 13, 2019
Canada / Toronto
Email: childcare@annualamericacongress.org

Medical CBT: 10 - Minute Techniques For Real Doctors (**Cognitive Behavior Therapy**)
Apr 13 - 27, 2019
Tahiti / Papeete
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877 - 466 - 8228
Email: registrar@cbt.ca

4th International Conference on **Sexual & Reproductive Health and Family Planning**
Apr 17 - 18, 2019
United States / New York
Email: reproductive@annualamericacongress.com

11th World Congress on **Pharmacology & Therapeutics**
Apr 17 - 18, 2019
Canada / Montreal
Email: christopher@pharmaceuticalconferences.org

28th International Conference on **Clinical & Experimental Cardiology Research**
Apr 17 - 18, 2019
Canada / Montreal
Email: cardiology@americameetings.net

Annual **Neurochemistry and Neuropharmacology** Congress
Apr 17 - 18, 2019
Canada / Montreal
Email: neuropharma@conferencesamerica.org

International Conference on **Food Quality, Testing & Supply Chain Management**
Apr 17 - 18, 2019
Canada / Toronto
Email: foodsupplychain@americaconferences.org

World Congress on **Cardiac Surgery & Medical Devices 2019**
Apr 17 - 18, 2019
Canada / Montreal, Quebec
Email: cardiacsurgery@americameetings.net

World **Heart and Brain** Congress
Apr 19 - 20, 2019
United States / Chicago
Email: heartbraincongress@gmail.com

6th World Congress on **Climate Change and Global Warming**
Apr 24 - 25, 2019
Canada / Vancouver
Email: climatechange@annualamericacongress.org

13th International Conference on **Bio Banking and Tissue Preservation**
Apr 24 - 25, 2019
Canada / Vancouver
Email: cordblood2019@protonmail.com

14th International Conference on **Tissue Science, Engineering & Regenerative Medicine**
Apr 24 - 25, 2019
Canada / Vancouver
Email: tissueengineeringusa@gmail.com

22nd International Conference on Past and Present Research Systems on **Green Chemistry**
Apr 24 - 25, 2019
Canada / Vancouver, British Columbia
Email: greenchemistry@americanevent.org

International Conference on **Digital Health**
Apr 24 - 25, 2019
United States / Houston
Email: digitalhealth@americanevent.org

7th International Conference and Exhibition on **Bacteriology & Antibiotics**
Apr 26 - 27, 2019
Canada / Vancouver
Email: bacteriology@annualamericacongress.org

International Pan Pacific Conference of **ART & Perinatology**
Apr 29 - 30, 2019
United States / Chicago, IL
Email: amelia.smth5308@gmail.com

2nd Annual Industrial **Biotechnology and Bioprocessing** Congress
May 10 - 11, 2019
Canada / Montreal
Email: bioamerica@americameetings.net

4th Global **Food Security, Food Safety & Sustainability** Conference
May 10 - 11, 2019
Canada / Montreal
Email: oliviacarisella999@yahoo.com

7th International Conference on Breast Pathology and Cancer Diagnosis

May 10 - 11, 2019

Canada / Montreal

Email: cancerdiagnosis@americanevent.org

4th International Conference on Infectious Diseases: Control and Prevention

May 17 - 18, 2019

United States / Philadelphia, Pennsylvania

Email: preventioncontrol@infectiousconferences.com

4th International Conference on Nursing & Midwifery

May 17 - 18, 2019

United States / Philadelphia

Email: nursingmidwifery@annualamericacongress.com

2nd International Conference on Pharmaceutical Research & Innovations in Pharma Industry

May 30 - 31, 2019

United States / Florida / Orlando

Email: pharmaresearch@annualamericacongress.org

5th International Conference on Antibiotics & Antibiotic Resistance

May 30 - 31, 2019

United States / Florida / Orlando

Email: antibioticssummit@annualamericacongress.org

21st International Conference on Radiooncology & Combinatorial Cancer Therapies

May 30 - 31, 2019

United States / Florida / Orlando

Email: tarajacqueline94@gmail.com

6th International Conference and Exhibition on Polymer Chemistry

Jun 12 - 13, 2019

Canada / Montreal

Email: polymerchemistry@americanevent.org

22nd Canada Meetings on Radiology & Novel Cancer Therapies

Jun 12 - 13, 2019

Canada / Montreal, Quebec

Email: sophianora089@gmail.com

31st International Conference on Materials Chemistry and Science

Jun 12 - 13, 2019

Canada / Montreal, Quebec

Email: materialschemistry@americanevent.org

Canada Meetings on Vascular and Interventional Radiology

Jun 12 - 13, 2019

Canada / Montreal

Email: interventionalradiology2019@outlook.com

4th Annual Meeting on Pedodontics and Geriatric Dentistry

Jun 14 - 15, 2019

Canada / Montreal

Email: pedodontics@annualamericacongress.com

18th Annual World Congress on Neonatology

Jun 14 - 15, 2019

Canada / Montreal, Quebec

Email: neonatal@pediatricsconferences.com

25th American Dental Research & Future Dentistry

Jun 14 - 15, 2019

Canada / Montreal, Quebec

Email: futuredentistry@annualamericacongress.com

2nd International Combined Meeting of Orthopaedic Research Societies (ICORS)

Jun 19 - 22, 2019

Canada / Quebec, Montreal

Contact: 2019 ICORS Secretariat, Canadian Orthopaedic Research Society

Phone: 514 - 874 - 9003

Email: meetings@canorth.org

8th International Conference on Current Trends in Mass Spectrometry and Chromatography

Jul 5 - Jul 6, 2019

United States / Columbus, Ohio

Email: massspectrometry2018@aol.com

39th International Conference on Nursing & Healthcare

Jul 5 - 6, 2019

United States / Columbus, Ohio

Email: nursingcongressottawa@gmail.com

World Congress on Insulin Resistance Diabetes, Endocrinology Metabolism and Nursing

Jul 5 - 6, 2019

United States / Columbus

Email: diabetesmedicare@annualamericacongress.com

Women Oncology Conference 2019

Jul 17 - 18, 2019

United States / Atlanta

Email: womenoncology2019@zoho.eu

2nd International Conference on Pediatric Pathology and Nursing Care

Jul 19 - 20, 2019

United States / Atlanta

Email: pediatricpharma@annualamericacongress.org

8th International Conference on Clinical Trials

Jul 19 - 20, 2019

United States / Atlanta

Email: christopher@pharmaceuticalconferences.org

5th International Conference on Palliative care, Medicine and Hospice Nursing

Jul 24 - 25, 2019

Canada / Vancouver

Email: palliativecare@americanevent.org

11th World Congress and Expo on Immunology

Jul 24 - 25, 2019

Canada / Vancouver

Email: immunology@conferenceseries.net

4th International Conference on Food Chemistry & Nutrition

Jul 26 - 27, 2019

Canada / Vancouver

Email: foodchemistry@foodtechconferences.com

5th International Conference on Cytopathology and Histopathology

Jul 26 - 27, 2019

Canada / Vancouver

Email: cytology@americameetings.net

22nd Global Summit on Food Processing, Safety and Technology

Jul 26 - 27, 2019

Canada / Vancouver, British Columbia

Email: foodprocessingconference@gmail.com

6th International Conference on Glycobiology, Lipids & Metabolic Disorders

Jul 29 - 30, 2019

United States / Chicago, Illinois

Email: glycobiology@americameetings.net

12th International Conference on Diabetes & Metabolism

Jul 29 - 30, 2019

United States / Chicago, Illinois

Email: Diabetes Metabolism 2019

31st International Conference & Exhibition on Dental Medicine & Dental Implants

Jul 29 - 30, 2019

United States / Chicago, Illinois

Email: dentalmedicine_usa@yahoo.com

32nd International Conference on Dental Science & Advanced Dentistry

Jul 29 - 30, 2019

United States / Chicago

Email: advanceddentistry@annualamericacongress.com

2nd Annual Biotechnology Congress

Jul 31 - Aug 1, 2019

United States / Chicago

Email: biotechnologysummit@gmail.com

27th International Congress on Cardiology and Medical Interventions

Jul 31 - Aug 1, 2019

United States / Chicago, Illinois

Email: cardiac@americameetings.net

WHO-Facts Sheet

1. Echinococcosis
2. Legionellosis
3. Substandard and falsified medical products
4. Typhoid
5. West Nile virus

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2018; 50 (4): 489 - 499

1. ECHINOCOCCOSIS

Key facts

- Human echinococcosis is a parasitic disease caused by tapeworms of the genus *Echinococcus*.
- The two most important forms of the disease in humans are cystic echinococcosis (hydatidosis) and alveolar echinococcosis.
- Humans are infected through ingestion of parasite eggs in contaminated food, water or soil, or through direct contact with animal hosts.
- Echinococcosis is often expensive and complicated to treat, and may require extensive surgery and/or prolonged drug therapy.
- Prevention programmes focus on deworming of dogs and sheep, which are the definitive hosts. In the case of cystic echinococcosis, control measures also include improved food inspection, slaughterhouse hygiene, and public education campaigns. Vaccination of lambs is currently being evaluated as an additional intervention.
- More than 1 million people are affected with echinococcosis at any one time.
- WHO is working towards the validation of effective cystic echinococcosis control strategies by 2020.

Human echinococcosis is a zoonotic disease (a disease that is transmitted to humans from animals) that is caused by parasites, namely tapeworms of the genus *Echinococcus*. Echinococcosis occurs in 4 forms:

- cystic echinococcosis, also known as hydatid disease or hydatidosis, caused by infection with *Echinococcus granulosus*;
- alveolar echinococcosis, caused by infection with *E. multilocularis*;

- polycystic echinococcosis, caused by infection with *E. vogeli*; and
- unicystic echinococcosis, caused by infection with *E. oligarthrus*.

The two most important forms, which are of medical and public health relevance in humans, are cystic echinococcosis (CE) and alveolar echinococcosis (AE).

Transmission

A number of herbivorous and omnivorous animals act as intermediate hosts of *Echinococcus*. They become infected by ingesting the parasite eggs in contaminated food and water, and the parasite then develops into larval stages in the viscera.

Carnivores act as definitive hosts for the parasite, and host the mature tapeworm in their intestine. They are infected through the consumption of viscera of intermediate hosts that harbour the parasite.

Humans act as so-called accidental intermediate hosts in the sense that they acquire infection in the same way as other intermediate hosts, but are not involved in transmitting the infection to the definitive host.

Several distinct genotypes of *E. granulosus* are recognised, some having distinct intermediate host preferences. Some genotypes are considered species distinct from *E. granulosus*. Not all genotypes cause infections in humans. The genotype causing the great majority of cystic echinococcosis infections in humans is principally maintained in a dog–sheep–dog cycle, yet several other domestic animals may also be involved, including goats, swine, cattle, camels and yaks.

Address correspondence to:

Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: <http://www.who.int/>

Alveolar echinococcosis usually occurs in a wildlife cycle between foxes, other carnivores and small mammals (mostly rodents). Domesticated dogs and cats can also be infected.

Signs and symptoms

Cystic echinococcosis / hydatid disease

Human infection with *E. granulosus* leads to the development of one or more hydatid cysts located most often in the liver and lungs, and less frequently in the bones, kidneys, spleen, muscles, central nervous system and eyes.

The asymptomatic incubation period of the disease can last many years until hydatid cysts grow to an extent that triggers clinical signs, however approximately half of all patients that receive medical treatment for infection do so within a few years of their initial infection with the parasite.

Abdominal pain, nausea and vomiting are commonly seen when hydatids occur in the liver. If the lung is affected, clinical signs include chronic cough, chest pain and shortness of breath. Other signs depend on the location of the hydatid cysts and the pressure exerted on the surrounding tissues. Non-specific signs include anorexia, weight loss and weakness.

Alveolar echinococcosis

Alveolar echinococcosis is characterized by an asymptomatic incubation period of 5–15 years and the slow development of a primary tumour-like lesion which is usually located in the liver. Clinical signs include weight loss, abdominal pain, general malaise and signs of hepatic failure.

Larval metastases may spread either to organs adjacent to the liver (for example, the spleen) or distant locations (such as the lungs, or the brain) following dissemination of the parasite via the blood and lymphatic system. If left untreated, alveolar echinococcosis is progressive and fatal.

Distribution

Cystic echinococcosis is globally distributed and found in every continent except Antarctica. Alveolar echinococcosis is confined to the northern hemisphere, in particular to regions of China, the Russian Federation and countries in continental Europe and North America.

In endemic regions, human incidence rates for cystic echinococcosis can reach more than 50 per 100 000 person-years, and prevalence levels as high as 5%–10% may occur in parts of Argentina, Peru, East Africa, Central Asia and China. In livestock, the prevalence of cystic echinococcosis found in slaughterhouses in hyperendemic areas of South America varies from 20%–95% of slaughtered animals.

The highest prevalence is found in rural areas where older animals are slaughtered. Depending on the infected species involved, livestock production losses attributable to cystic echinococcosis result from liver condemnation and may also involve reduction in carcass weight, decrease in hide value, decrease of milk production, and reduced fertility.

Diagnosis

Ultrasonography imaging is the technique of choice for the diagnosis of both cystic echinococcosis and alveolar echinococcosis in humans. This technique is usually complemented or validated by computed tomography (CT) and/or magnetic resonance imaging (MRI) scans.

Cysts can be incidentally discovered by radiography. Specific antibodies are detected by different serological tests and can support the diagnosis. Biopsies and ultrasound-guided punctures may also be performed for differential diagnosis of cysts from tumours and abscesses.

Treatment

Both cystic echinococcosis and alveolar echinococcosis are often expensive and complicated to treat, sometimes requiring extensive surgery and/or prolonged drug therapy. There are 4 options for the treatment of cystic echinococcosis:

- percutaneous treatment of the hydatid cysts with the PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique;
- surgery
- anti-infective drug treatment
- “watch and wait”.

The choice must primarily be based on the ultrasound images of the cyst, following a stage-specific approach, and also on the medical infrastructure and human resources available.

For alveolar echinococcosis, early diagnosis and radical (tumour-like) surgery followed by anti-infective prophylaxis with albendazole remain the key elements. If the lesion is confined, radical surgery can be curative. Unfortunately in many patients the disease is diagnosed at an advanced stage. As a result, if palliative surgery is carried out without complete and effective anti-infective treatment, frequent relapses will occur.

Early detection of *E. granulosus* and *E. multilocularis* infections, especially in low-resource settings, is still needed in addition to the evaluation of clinical treatment options. Further assessment and potential commercialization of a vaccine for *E. granulosus* recombinant oncosphere antigen (EG95) is on trial in sheep to impede *E. granulosus* infection of lambs. This could supplement control measures such as the treatment of dogs and culling of older sheep.

Health and economic burden

Both cystic echinococcosis and alveolar echinococcosis represent a substantial disease burden. Worldwide, there may be in excess of 1 million people living with these diseases at any one time. Many of these people will be experiencing severe clinical syndromes which are life-threatening if left untreated. Even with treatment, people often face reduced quality of life.

For cystic echinococcosis, there is an average of 2.2% post-operative death rate for surgical patients and about 6.5% of cases relapse after an intervention, thereby requiring prolonged recovery time.

The 2015 WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) estimated echinococcosis to be the cause of 19 300 deaths and around 871 000 disability-adjusted life-years (DALYs) (1) globally each year.

Annual costs associated with cystic echinococcosis are estimated to be US\$ 3 billion for treating cases and losses to the livestock industry.

Surveillance, prevention and control

Robust surveillance data is fundamental in order to show burden of disease and to evaluate progress and success of control programmes. However, as for other neglected diseases which are focused in underserved populations and remote areas, data is especially scarce and will need more attention if control programmes are to be implemented and measured.

Cystic echinococcosis / hydatid disease

Surveillance for cystic echinococcosis in animals is difficult because the infection is asymptomatic in livestock and dogs. Surveillance is also not recognized or prioritized by communities or local veterinary services.

Cystic echinococcosis is a preventable disease as it involves domestic animal species as definitive and intermediate hosts. Periodic deworming of dogs, improved hygiene in the slaughtering of livestock (including the proper destruction of infected offal), and public education campaigns have been found to lower and, in high-income countries, prevent transmission and alleviate the burden of human disease.

Vaccination of sheep with an *E. granulosus* recombinant antigen (EG95) offers encouraging prospects for prevention and control. Small-scale EG95 vaccine trials in sheep indicate high efficacy and safety with vaccinated lambs not becoming infected with *E. granulosus*.

A programme combining vaccination of lambs, deworming of dogs and culling of older sheep could lead to elimination of cystic echinococcosis disease in humans in less than 10 years.

Alveolar echinococcosis

Prevention and control of alveolar echinococcosis more complex as the cycle involves wild animal species as both definitive and intermediate hosts. Regular deworming of domestic carnivores that have access to wild rodents should help to reduce the risk of infection in humans.

Deworming of wild and stray definitive hosts with anthelmintic baits resulted in significant reductions in alveolar echinococcosis prevalence in European and Japanese studies. Culling of foxes and unowned free-roaming dogs appears to be highly inefficient. The sustainability and cost-benefit effectiveness of such campaigns are controversial.

WHO and country response

WHO assists countries to develop and implement pilot projects leading to the validation of effective cystic echinococcosis control strategies by 2020. Working with the veterinary and food safety authorities as well as with other sectors is essential to attain the long-term outcomes of reducing the burden of disease and safeguarding the food value chain. WHO supports capacity building through training courses targeting medical and paramedical personnel, focused on the clinical management of cystic echinococcosis in rural areas of affected countries.

The WHO Informal Working Group on Echinococcosis (WHO-IWGE) continues to identify priorities to develop guidance on detection and clinical management of cystic echinococcosis through improved case detection and management. The group is also working to promote the collection and mapping of epidemiological data.

Morocco finished a project aimed at decentralizing diagnostic and therapeutic techniques and promoting the PAIR (puncture, aspiration, injection, re-aspiration) strategy in rural and hyperendemic areas. As a complement, the emphasis needs to be put on prevention in the animal and food safety sector.

Mongolia has recognized the importance of echinococcosis as a public-health problem and, at the request of the Ministry of Health, WHO in 2013 conducted an initial situation analysis. The analysis focused on implementing early diagnosis and building a basic surveillance system covering humans and animals to understand the actual burden of the disease. No significant investment for echinococcosis has been made, and therefore programmatic progress has stalled.

China is integrating echinococcosis prevention, control and treatment in their economic and development plans to raise attention to the vast problem in the country, especially the Tibetan plateau, as well as in the Central Asian Republics.

(1) One DALY (disability-adjusted life year) can be thought of as one lost year of “healthy” life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age free of disease and disability.

2. LEGIONELLOSIS

Key facts

- The bacterium *L. pneumophila* was first identified in 1977, as the cause of an outbreak of severe pneumonia in a convention centre in the USA in 1976.
- The most common form of transmission of *Legionella* is inhalation of contaminated aerosols produced in conjunction with water sprays, jets or mists. Infection can also occur by aspiration of contaminated water or ice, particularly in susceptible hospital patients.
- Legionnaires’ disease has an incubation period of 2 to 10 days (but up to 16 days has been recorded in some outbreaks).
- Death occurs through progressive pneumonia with respiratory failure and/or shock and multi-organ failure.
- Untreated Legionnaires’ disease usually worsens during the first week.
- Of the reported cases 75–80% are over 50 years and 60–70% are male.

Legionellosis varies in severity from a mild febrile illness to a serious and sometimes fatal form of pneumonia and is caused by exposure to *Legionella* species found in water, and potting mixes.

It is often categorized as being community, travel or hospital acquired based on the type of exposure.

Worldwide, waterborne *Legionella pneumophila* is the most common cause of cases including outbreaks. *Legionella pneumophila* and related species are commonly found in lakes, rivers, creeks, hot springs and other bodies of water. Other species including *L. longbeachae* can be found in potting mixes.

The bacterium *L. pneumophila* was first identified in 1977, as the cause of an outbreak of severe pneumonia in a convention centre in the USA in 1976. It has since been associated with outbreaks linked to poorly maintained artificial water systems, particularly cooling towers or evaporative condensers associated with air conditioning and industrial cooling, hot and cold water systems in public and private buildings, and whirlpool spas.

The infective dose is unknown, but can be assumed to be low for susceptible people, as illnesses have occurred after short exposures and 3 or more km from the source of outbreaks. The likelihood of illness depends on the concentrations of *Legionella* in the water source, the production and dissemination of aerosols, host factors such as age and pre-existing health conditions and the virulence of the particular strain of *Legionella*. Most infections do not cause illness.

The cause

The causative agents are *Legionella* from water or potting mix. The most common cause of illness is the freshwater species *L. pneumophila* which is found in natural aquatic environments worldwide. However, artificial water systems which provide environments conducive to the growth and dissemination of *Legionella* represent the most likely sources of disease.

The bacteria live and grow in water systems at temperatures of 20 to 50 degrees Celsius (optimal 35 degrees Celsius). *Legionella* can survive and grow as parasites within free-living protozoa and within biofilms which develop in water systems. They can cause infections by infecting human cells using a similar mechanism to that used to infect protozoa.

Transmission

The most common form of transmission of *Legionella* is inhalation of contaminated aerosols. Sources of aerosols that have been linked with transmission of *Legionella* include air conditioning cooling towers, hot and cold water systems, humidifiers and whirlpool spas. Infection can also occur by aspiration of contaminated water or ice, particularly in susceptible hospital patients, and by exposure of babies during water births. There is no direct human-to-human transmission.

Distribution

Legionnaires’ disease is believed to occur worldwide.

Extent of the disease

The identified incidence of Legionnaires’ disease varies widely according to the level of surveillance and reporting. Since many countries lack appropriate methods of diagnosing the infection or sufficient surveillance systems, the rate of occurrence is unknown. In Europe, Australia and the USA there are about 10–15 cases detected per million population per year.

Of the reported cases 75–80% are over 50 years and 60–70% are male. Other risk factors for community-

acquired and travel-associated legionellosis include: smoking, a history of heavy drinking, pulmonary-related illness, immuno-suppression, and chronic respiratory or renal illnesses.

Risk factors for hospital-acquired pneumonia are: recent surgery, intubation, which is the process of placing a tube in the trachea, mechanical ventilation, aspiration, presence of nasogastric tubes, and the use of respiratory therapy equipment. The most susceptible hosts are immuno-compromised patients, including organ transplant recipients and cancer patients and those receiving corticosteroid treatment.

Delay in diagnosis and administration of appropriate antibiotic treatment, increasing age and presence of co-existing diseases are predictors of death from Legionnaires' disease.

Symptoms

Legionellosis is a generic term describing the pneumonic and non-pneumonic forms of infection with Legionella.

The non-pneumonic form (Pontiac disease) is an acute, self-limiting influenza-like illness usually lasting 2–5 days. The incubation period is from a few and up to 48 hours. The main symptoms are fever, chills, headache, malaise and muscle pain (myalgia). No deaths are associated with this type of infection.

Legionnaires' disease, the pneumonic form, has an incubation period of 2 to 10 days (but up to 16 days has been recorded in some outbreaks). Initially, symptoms are fever, loss of appetite, headache, malaise and lethargy. Some patients may also have muscle pain, diarrhoea and confusion. There is also usually an initial mild cough, but as many as 50% of patients can present phlegm. Blood-streaked phlegm or hemoptysis occurs in about one-third of the patients. The severity of disease ranges from a mild cough to a rapidly fatal pneumonia. Death occurs through progressive pneumonia with respiratory failure and/or shock and multi-organ failure.

Untreated Legionnaires' disease usually worsens during the first week. In common with other risk factors causing severe pneumonia, the most frequent complications of legionellosis are respiratory failure, shock and acute kidney and multi-organ failure. Recovery always requires antibiotic treatment, and is usually complete, after several weeks or months. In rare occasions, severe progressive pneumonia or ineffective treatment for pneumonia can result in brain sequelae.

The death rate as a result of Legionnaires' disease depends on: the severity of the disease, the appropriateness of initial anti-microbial treatment, the setting where legionella was acquired, and host factors

(for example, the disease is usually more serious in patients with immuno-suppression). The death rate may be as high as 40–80% in untreated immuno-suppressed patients and can be reduced to 5–30% through appropriate case management and depending on the severity of the clinical signs and symptoms. Overall the death rate is usually within the range of 5–10%.

Response

There is no vaccine currently available for Legionnaires' disease.

The nonpneumonic form of infection is self-limiting and does not require medical interventions, including antibiotic treatment. Patients with Legionnaires' disease always require antibiotic treatment following diagnosis.

The public health threat posed by legionellosis can be addressed by implementing water safety plans by authorities responsible for building safety or water system safety. These plans must be specific to the building or water system, and should result in the introduction and regular monitoring of control measures against identified risks including Legionella. Although it is not always possible to eradicate the source of infection, it is possible to reduce the risks substantially.

Prevention of Legionnaires' disease depends on applying control measures to minimize the growth of Legionella and dissemination of aerosols. These measures include good maintenance of devices, including regular cleaning and disinfection and applying other physical (temperature) or chemical measures (biocide) to minimize growth. Some examples are:

- the regular maintenance, cleaning and disinfection of cooling towers together with frequent or continuous addition of biocides;
- installation of drift eliminators to reduce dissemination of aerosols from cooling towers;
- maintaining an adequate level of a biocide such as chlorine in a spa pool along with a complete drain and clean of the whole system at least weekly;
- keeping hot and cold water systems clean and either keeping the hot water above 50 °C (which requires water leaving the heating unit to be at or above 60 °C) and the cold below 25 °C and ideally below 20 °C or alternatively treating them with a suitable biocide to limit growth, particularly in hospitals and other health care settings, and aged-care facilities;
- reducing stagnation by flushing unused taps in buildings on a weekly basis.

Applying such controls will greatly reduce the

risk of *Legionella* contamination and prevent the occurrence of sporadic cases and outbreaks. Extra precautions may be required for water and ice provided to highly susceptible patients in hospitals including those at risk of aspiration (for example, ice machines can be a source of *Legionella* and should not be used by highly susceptible patients).

Control and prevention measures must be accompanied by proper vigilance on the part of general practitioners and community health services for the detection of cases.

WHO makes available technical resources to support the management and control of *Legionella* and advises Member States when specific queries are raised.

3. SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS

Key facts

- Substandard and falsified medical products may cause harm to patients and fail to treat the diseases for which they were intended.
- They lead to loss of confidence in medicines, healthcare providers and health systems.
- They affect every region of the world.
- Substandard and falsified medical products from all main therapeutic categories have been reported to WHO including medicines, vaccines and in vitro diagnostics.
- Anti-malarials and antibiotics are amongst the most commonly reported substandard and falsified medical products.
- Both generic and innovator medicines can be falsified, ranging from very expensive products for cancer to very inexpensive products for treatment of pain.
- They can be found in illegal street markets, via unregulated websites through to pharmacies, clinics and hospitals.
- An estimated 1 in 10 medical products in low- and middle-income countries is substandard or falsified.
- Substandard and falsified medical products contribute to antimicrobial resistance and drug-resistant infections.

Falsified medical products may contain no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient.

They are also found to commonly contain corn starch, potato starch or chalk.

Some substandard and falsified medical products have been toxic in nature with either fatal levels of the wrong active ingredient or other toxic chemicals.

Substandard and falsified medical products are often produced in very poor and unhygienic conditions by unqualified personnel, and contain unknown impurities and are sometimes contaminated with bacteria.

Substandard and falsified medical products are by their very nature difficult to detect. They are often designed to appear identical to the genuine product and may not cause an obvious adverse reaction, however they often will fail to properly treat the disease or condition for which they were intended, and can lead to serious health consequences including death.

Definitions

Substandard also called “out of specification”, these are authorized medical products that fail to meet either their quality standards or specifications, or both.

Unregistered/unlicensed medical products that have not undergone evaluation and/or approval by the National or Regional Regulatory Authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

Falsified medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Identifying a substandard or falsified medical product

Some falsified medical products are almost visually identical to the genuine product and very difficult to detect. However, many can be identified by:

- examining the packaging for condition, spelling mistakes or grammatical errors;
- checking the manufacture and expiry dates and ensuring any details on the outer packaging match the dates shown on the inner packaging;
- ensuring the medicine looks correct, is not discoloured, degraded or has an unusual smell;
- discussing with your pharmacist, doctor or other healthcare professional as soon as possible if you suspect the product is not working properly or you have suffered an adverse reaction; and
- reporting suspicious medical products to your National Medicines Regulatory Authority.

Substandard and falsified medical products and the Internet

Unregulated websites, social media platforms, and smartphone applications can also be direct conduits of substandard and falsified medical products. Risks to consumers are significantly increased when obtaining medical products from unlicensed and unregulated sources.

Consumers should be cautious of the following:

- spam email advertising medicines
- lack of authenticity; no verification logo or certificate
- spelling mistakes and poor grammar on the packaging
- websites that do not display a physical address or landline
- websites offering prescription only medicines without a prescription
- suspiciously low-priced products.

Checklist for medicines purchased online

- Is it exactly the medicine ordered?
- Is it the correct dosage?
- Is the packaging in good condition, clean, with a patient information leaflet and in the language in which it was advertised?
- Does the medicine look, feel and smell as it should?
- Are security seals intact with no signs of tampering?
- Does any customs declaration or postal label declare the contents as medicines?
- Does the batch number and expiry date on the primary internal packaging match the batch number and expiry date on the secondary (external) packaging?
- Have you noticed any unusual activity on your credit card since the purchase?

Who is at risk?

Falsified medical products are manufactured in many different countries and in all regions. Many countries and the media frequently report successful operations against manufacturers of substandard and falsified medical products. Some reports refer to large-scale manufacturing and others to small back street operations. With the availability of tableting machines, ovens, specialist equipment, ingredients and packaging materials, clandestine manufacturing facilities are quick and easy to assemble.

No countries remain untouched by this issue – from North America and Europe through to sub-Saharan Africa, South East Asia, and Latin America. What was once considered a problem limited to developing and low-income countries has now become an issue for all. With the exponential increase in internet connectivity those engaged in the manufacture, distribution and supply of substandard and falsified medical products have gained access to a global market place. This extends both to consumers and business forums. A culture of self-diagnosis and self-prescribing has led to the emergence of thousands of unregulated websites providing unsupervised access to substandard and falsified medical products. However, it is in low- and middle-income countries and those in areas of conflict, or civil unrest, where health systems are weak or non-

existent that bear the greatest burden of substandard and falsified medical products.

Substandard and falsified medical products are most likely to reach patients in situations where there is constrained access to quality and safe medical products, poor governance and weak technical capacity.

An estimated 1 in 10 medical products in low- and middle-income countries is substandard or falsified.

WHO response

WHO Member State Mechanism

The Member State Mechanism is the global platform where countries can convene, coordinate, decide and organize actions to address substandard and falsified medical products.

It was established in order to protect public health and promote access to affordable, safe, efficacious and quality medical products, through effective collaboration between Member States and WHO to prevent and control substandard and falsified medical products and associated activities.

WHO Surveillance and Monitoring System

In 2013, WHO launched the Global Surveillance and Monitoring System to encourage countries to report incidents of substandard and falsified medical products in a structured and systematic format, to help develop a more accurate and validated assessment of the problem. The system:

- provides technical support in emergencies, links incidents between countries and regions, and issues WHO medical product alerts; and
- gathers a validated body of evidence to more accurately demonstrate the scope, scale and harm caused by substandard and falsified medical products and identify the vulnerabilities, weaknesses and trends.

As of November 2017, WHO had issued 20 global medical product alerts and numerous regional warnings, and has provided technical support in over 100 cases.

WHO has trained a global network of over 550 regulatory staff in 141 Member States to report substandard and falsified medical products to the WHO Global Surveillance and Monitoring System. WHO also works with 18 of the largest international procurement agencies.

The structured reporting system allows for a fast response to emergencies and the issue of alerts in the most serious cases. It also facilitates in-depth analyses of the medical products most at risk, the vulnerabilities and weaknesses in health systems, the harm caused to public health and the need for investment, training and stronger regulations and standards.

4. TYPHOID

Key facts

- Typhoid fever is a life-threatening infection caused by the bacterium *Salmonella Typhi*. It is usually spread through contaminated food or water.
- An estimated 11–20 million people get sick from typhoid and between 128 000 and 161 000 people die from it every year.
- Symptoms include prolonged fever, fatigue, headache, nausea, abdominal pain, and constipation or diarrhoea. Some patients may have a rash. Severe cases may lead to serious complications or even death.
- Typhoid fever can be treated with antibiotics although increasing resistance to different types of antibiotics is making treatment more complicated.
- Two vaccines have been used for many years to prevent typhoid. A new typhoid conjugate vaccine with longer lasting immunity was prequalified by WHO in December 2017.

Typhoid fever is a life-threatening infection caused by the bacterium *Salmonella Typhi*. It is usually spread through contaminated food or water. Once *Salmonella Typhi* bacteria are eaten or drunk, they multiply and spread into the bloodstream.

Urbanization and climate change have the potential to increase the global burden of typhoid. In addition, increasing resistance to antibiotic treatment is making it easier for typhoid to spread through overcrowded populations in cities and inadequate and/or flooded water and sanitation systems.

Symptoms

Salmonella Typhi lives only in humans. Persons with typhoid fever carry the bacteria in their bloodstream and intestinal tract. Symptoms include prolonged high fever, fatigue, headache, nausea, abdominal pain, and constipation or diarrhoea. Some patients may have a rash. Severe cases may lead to serious complications or even death. Typhoid fever can be confirmed through blood testing.

Epidemiology, risk factors, and disease burden

Improved living conditions and the introduction of antibiotics resulted in a drastic reduction of typhoid fever morbidity and mortality in industrialized countries. In developing areas of Africa, the Americas, South-East Asia and the Western Pacific regions, however, the disease continues to be a public health problem.

WHO estimates the global typhoid fever disease burden at 11–20 million cases annually, resulting in about 128 000–161 000 deaths per year.

Typhoid risk is higher in populations that lack access to safe water and adequate sanitation. Poor communities and vulnerable groups including children are at highest risk.

Treatment

Typhoid fever can be treated with antibiotics. As resistance to antibiotics has emerged including to fluoroquinolones, newer antibiotics such as cephalosporins and azithromycin are used in the affected regions. Resistance to azithromycin has been reported sporadically but it is not common as of yet.

Even when the symptoms go away, people may still be carrying typhoid bacteria, meaning they can spread it to others through their faeces.

It is important for people being treated for typhoid fever to do the following:

- Take prescribed antibiotics for as long as the doctor has prescribed.
- Wash their hands with soap and water after using the bathroom, and do not prepare or serve food for other people. This will lower the chance of passing the infection on to someone else.
- Have their doctor test to ensure that no *Salmonella Typhi* bacteria remain in their body.

Prevention

Typhoid fever is common in places with poor sanitation and a lack of safe drinking water. Access to safe water and adequate sanitation, hygiene among food handlers and typhoid vaccination are all effective in preventing typhoid fever.

Two vaccines have been used for many years to protect people from typhoid fever:

- an injectable vaccine based on the purified antigen for people aged over 2 years
- a live attenuated oral vaccine in capsule formulation for people aged over 5 years

These vaccines do not provide long-lasting immunity and are not approved for children younger than 2 years old.

A new typhoid conjugate vaccine, with longer lasting immunity, was prequalified by WHO in December 2017 for use in children from the age of 6 months.

All travelers to endemic areas are at potential risk of typhoid fever, although the risk is generally low in tourist and business centres where standards of accommodation, sanitation and food hygiene are high. Typhoid fever vaccination should be offered to travelers to destinations where the risk of typhoid fever is high.

The following recommendations will help ensure safety while travelling:

- Ensure food is properly cooked and still hot when served.
- Avoid raw milk and products made from raw milk. Drink only pasteurized or boiled milk.
- Avoid ice unless it is made from safe water.
- When the safety of drinking water is questionable, boil it or if this is not possible, disinfect it with a reliable, slow-release disinfectant agent (usually available at pharmacies).
- Wash hands thoroughly and frequently using soap, in particular after contact with pets or farm animals, or after having been to the toilet.
- Wash fruits and vegetables carefully, particularly if they are eaten raw. If possible, vegetables and fruits should be peeled.

WHO response

In December 2017, WHO prequalified the first conjugate vaccine for typhoid. This new vaccine has longer-lasting immunity than older vaccines, requires fewer doses and can be given to children from the age of 6 months.

This vaccine will be prioritized for countries with the highest burden of typhoid disease. This will help reduce the frequent use of antibiotics for typhoid treatment, which will slow the increase in antibiotic resistance in *Salmonella Typhi*.

In October 2017, the Strategic Advisory Group of Experts (SAGE) on immunization, which advises WHO, recommended typhoid conjugate vaccines for routine use in children over 6 months of age in typhoid endemic countries. SAGE also called for the introduction of typhoid conjugate vaccines to be prioritized for countries with the highest burden of typhoid disease or of antibiotic resistance to *Salmonella Typhi*.

Shortly after SAGE's recommendation, the Gavi Board approved US\$ 85 million in funding for typhoid conjugate vaccines starting in 2019.

5. WEST NILE VIRUS

Key facts

- West Nile virus can cause a fatal neurological disease in humans.
- However, approximately 80% of people who are infected will not show any symptoms.
- West Nile virus is mainly transmitted to people through the bites of infected mosquitoes.
- The virus can cause severe disease and death in horses.
- Vaccines are available for use in horses but not yet available for people.
- Birds are the natural hosts of West Nile virus.

West Nile Virus (WNV) can cause neurological disease

and death in people. WNV is commonly found in Africa, Europe, the Middle East, North America and West Asia. WNV is maintained in nature in a cycle involving transmission between birds and mosquitoes. Humans, horses and other mammals can be infected.

West Nile Virus (WNV) is a member of the flavivirus genus and belongs to the Japanese encephalitis antigenic complex of the family Flaviviridae.

Outbreaks

West Nile Virus (WNV) was first isolated in a woman in the West Nile district of Uganda in 1937. It was identified in birds (crows and columbiformes) in Nile delta region in 1953. Before 1997 WNV was not considered pathogenic for birds, but at that time in Israel a more virulent strain caused the death of different bird species presenting signs of encephalitis and paralysis. Human infections attributable to WNV have been reported in many countries in the World for over 50 years.

In 1999 a WNV circulating in Israel and Tunisia was imported in New York producing a large and dramatic outbreak that spread throughout the continental United States of America (USA) in the following years. The WNV outbreak in USA (1999-2010) highlighted that importation and establishment of vector-borne pathogens outside their current habitat represent a serious danger to the world.

The largest outbreaks occurred in Greece, Israel, Romania, Russia and USA. Outbreak sites are on major birds migratory routes. In its original range, WNV was prevalent throughout Africa, parts of Europe, Middle East, West Asia, and Australia. Since its introduction in 1999 into USA, the virus has spread and is now widely established from Canada to Venezuela.

Transmission

Human infection is most often the result of bites from infected mosquitoes. Mosquitoes become infected when they feed on infected birds, which circulate the virus in their blood for a few days. The virus eventually gets into the mosquito's salivary glands. During later blood meals (when mosquitoes bite), the virus may be injected into humans and animals, where it can multiply and possibly cause illness.

The virus may also be transmitted through contact with other infected animals, their blood, or other tissues.

A very small proportion of human infections have occurred through organ transplant, blood transfusions and breast milk. There is one reported case of transplacental (mother-to-child) WNV transmission.

To date, no human-to-human transmission of WNV

through casual contact has been documented, and no transmission of WNV to health care workers has been reported when standard infection control precautions have been put in place.

Transmission of WNV to laboratory workers has been reported.

Signs and symptoms

Infection with WNV is either asymptomatic (no symptoms) in around 80% of infected people, or can lead to West Nile fever or severe West Nile disease.

About 20% of people who become infected with WNV will develop West Nile fever. Symptoms include fever, headache, tiredness, and body aches, nausea, vomiting, occasionally with a skin rash (on the trunk of the body) and swollen lymph glands.

The symptoms of severe disease (also called neuroinvasive disease, such as West Nile encephalitis or meningitis or West Nile poliomyelitis) include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, and paralysis. It is estimated that approximately 1 in 150 persons infected with the West Nile virus will develop a more severe form of disease. Serious illness can occur in people of any age, however people over the age of 50 and some immunocompromised persons (for example, transplant patients) are at the highest risk for getting severely ill when infected with WNV.

The incubation period is usually 3 to 14 days.

Diagnosis

West Nile virus can be diagnosed by a number of different tests:

- IgG antibody sero-conversion (or significant increase in antibody titers) in two serial specimen collected at a one week interval by enzyme-linked immunosorbent assay (ELISA);
- IgM antibody capture enzyme-linked immunosorbent assay (ELISA);
- neutralisation assays;
- viral detection by reverse transcription polymerase chain reaction (RT-PCR) assay, and
- virus isolation by cell culture.

IgM can be detected in nearly all cerebrospinal fluid (CSF) and serum specimens received from WNV infected patients at the time of their clinical presentation. Serum IgM antibody may persist for more than a year.

Treatment and vaccine

Treatment is supportive for patients with neuro-invasive West Nile virus, often involving hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections. No vaccine is available for humans.

Vector and animal hosts

WN virus is maintained in nature in a mosquito-bird-mosquito transmission cycle. Mosquitoes of the genus *Culex* are generally considered the principal vectors of WNV, in particular *Cx. pipiens*. WNV is maintained in mosquito populations through vertical transmission (adults to eggs).

Birds are the reservoir hosts of WNV. In Europe, Africa, Middle East and Asia, mortality in birds associated with WNV infection is rare. In striking contrast, the virus is highly pathogenic for birds in the Americas. Members of the crow family (*Corvidae*) are particularly susceptible, but virus has been detected in dead and dying birds of more than 250 species. Birds can be infected by a variety of routes other than mosquito bites, and different species may have different potential for maintaining the transmission cycle.

Horses, just like humans, are “dead-end” hosts, meaning that while they become infected, they do not spread the infection. Symptomatic infections in horses are also rare and generally mild, but can cause neurologic disease, including fatal encephalomyelitis.

Prevention

Preventing transmission in horses

Since WNV outbreaks in animals precede human cases, the establishment of an active animal health surveillance system to detect new cases in birds and horses is essential in providing early warning for veterinary and human public health authorities. In the Americas, it is important to help the community by reporting dead birds to local authorities.

Vaccines have been developed for horses. Treatment is supportive and consistent with standard veterinary practices for animals infected with a viral agent.

Reducing the risk of infection in people

In the absence of a vaccine, the only way to reduce infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the virus.

Public health educational messages should focus on the following:

- Reducing the risk of mosquito transmission. Efforts to prevent transmission should first focus on personal and community protection against mosquito bites through the use of mosquito nets, personal insect repellent, by wearing light coloured clothing (long-sleeved shirts and trousers) and by avoiding outdoor activity at peak biting times. In addition community programmes should encourage communities to destroy mosquito breeding sites in residential areas.

- Reducing the risk of animal-to-human transmission. Gloves and other protective clothing should be worn while handling sick animals or their tissues, and during slaughtering and culling procedures.
- Reducing the risk of transmission through blood transfusion and organ transplant. Blood and organ donation restrictions and laboratory testing should be considered at the time of the outbreak in the affected areas after assessing the local/regional epidemiological situation.

Vector Control

Effective prevention of human WNV infections depends on the development of comprehensive, integrated mosquito surveillance and control programmes in areas where the virus occurs. Studies should identify local mosquito species that play a role in WNV transmission, including those that might serve as a "bridge" from birds to human beings. Emphasis should be on integrated control measures including

source reduction (with community participation), water management, chemicals, and biological control methods.

Preventing infection in health-care settings

Health-care workers caring for patients with suspected or confirmed WNV infection, or handling specimens from them, should implement standard infection control precautions. Samples taken from people and animals with suspected WNV infection should be handled by trained staff working in suitably equipped laboratories.

WHO response

The WHO regional office for Europe and WHO region of the Americas are intensively supporting WNV surveillance and outbreak response activities respectively in Europe and in North America, Latin America and the Caribbean, together with country offices and international partners.

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Kuwait Medical Journal

2018; Volume 50

Kuwait Medical Journal 2018, 50 (4) : 500 - 502

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