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Review Article

Radiological findings from patients with COVID-19: A meta-analysis of clinical studies

Tareef Sahal Daqqaq
Department of Radiology, College of Medicine, Taibah University, Madinah, Saudi Arabia

Kuwait Medical Journal 2021; 53 (2): 117 - 123

ABSTRACT

Objectives: To present quantitative assessment using a meta-analysis of published clinical studies on radiological findings of COVID-19 and to quantify the role of imaging and radiography in definitive analysis of COVID-19 cases
Design: To present a meta-analysis on radiological findings for patients with COVID-19 using clinical studies
Setting: This study includes all clinical trials, such as observational studies, covering radiological findings to perform meta-analysis.
Subjects: A total of nine studies were found eligible from three different databases: PubMed, Web of Science and SCOPUS.
Interventions: A random-effects model meta-analysis was performed to calculate the pooled prevalence and the 95% confidence interval.
Main outcome measure(s): The study reports the I2 index, measures of heterogeneity and Cochran's Q statistic.
Result(s): In total, 71 articles were retrieved, of which 25 were selected for full-text evaluation after screening but nine were included for quantitative assessment. Of 669 patients, 47.94% presented with bilateral pneumonia, 21.68% with unilateral pneumonia and 30.32% with ground-glass opacity. Predominant distribution was presented in 61.58% of patients (heterogeneity=4.24, χ^2=39.36, I2=80%, *P*=.002).
Conclusion(s): Patients with typical imaging findings must be isolated and reverse transcription-polymerase chain reaction (rRT-PCR) should be repeated to prevent misdiagnosis, given that the results of rRT-PCR might be false-negative.

KEY WORDS: chest CT, clinical trials, COVID-19, epidemic, radiological findings

INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to the development of coronavirus disease-19 (COVID-19) as the first pandemic infectious disease[1-3]. The same group of RNA-viruses develops its genome, causing Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome[4-6]. Varied clinical outcomes can be a result of this infection, from asymptomatic to extreme life-threatening course. Cough and high temperature are classified as dominant clinical presentation[7,8]. It is significant that the role of radiology and imaging becomes important in the evaluation of extremeness and disease advancement in COVID-19 infection[9]. The awareness of radiologists in this situation is important, related to the imaging manifestations of the COVID-19 infection[10]. Currently, the foundation of the diagnostic strategy is based on clinical features, real-time polymerase chain reaction (RT-PCR) assay and history of exposure from specimens acquired by tracheal aspirate, oropharyngeal or nasopharyngeal swab or bronchoalveolar lavage[11]. These specimens are followed by imaging modalities such as computed tomography (CT), ultrasound, and chest X-ray[8].

Recently, radiologists have used chest CT for

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Fig 1: Search strategy keywords

COVID-19 diagnosis. The unavailability and high false negative rate of RT-PCR assays in the preliminary phase of the outbreak restricted rapid diagnosis of infected patients, even though it remains the gold standard for making a conclusive identification of COVID-19 infection[12,13]. Radiological examinations play a vital role in combating this infectious disease, specifically thin-slice chest CT[14]. Preliminary lung infection can be identified through chest CT and, in turn, expedite response and public health surveillance systems[15-17]. At present, clinical diagnoses are mainly confirmed through chest CT findings.

Therefore, timely and comprehensive review of radiological findings remains mandatory and urgent. Considering its pivotal role, this study aims to present a meta-analysis on radiological findings from patients with COVID-19 undertaking clinical trials. After the beginning of the COVID-19 pandemic, case reports and studies had already been published in international medical and scientific journals. The focus of these studies was entirely on the response to clinical questions such as progression and outcomes, possible risk factors and laboratory, imaging and clinical findings. However, a quantitative assessment of radiological findings related to COVID-19, to consolidate what has been learned from each study, is still lacking. In this context, the main study objectives are as follows:

- To present quantitative assessment using a meta-analysis of published clinical studies on radiological findings of COVID-19.
- To quantify the role of imaging and radiography in definitive analysis of COVID-19 cases.

METHODS

The referred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in this study[18]. A meta-analysis was conducted through Web of Science, Medline/PubMed and Scopus using the following search terms: "COVID-19", "Novel Coronavirus 2019", "SARS-CoV-2", "Radiological Findings", "Clinical Studies", "2019 nCoV" and "Novel Coronavirus". Other search terms used for relevant databases are illustrated in Figure 1.

Only English publications from January 1, 2020 were included. The search was concluded on April 20, 2020. Two researchers independently assessed the search results. The following criteria were proposed to fulfill the eligibility of included studies: published peer-reviewed articles confirming reported cases for radiological findings as well as imaging diagnostics of RT-PCR-confirmed infection. This meta-analysis was followed by only cohort and case-control study designs.

Initially, title and abstract were screened for the results of the search strategy. As shown in Figure 2, the full texts of appropriate articles were examined for inclusion and exclusion criteria. We excluded studies reporting cases without imaging diagnosis and with incomplete information. We also excluded reviews and letters to the editors that did not report cases associated to radiological findings related to SARS-CoV-2. The information of duplicate articles was combined to obtain complete data, but both articles were counted as a single entry.

Data extraction forms include information on the publication type, the publishing institution, country, date and year of publication, reported cases, age, gender and radiological findings. A third researcher checked the article list as well as data extraction to exclude duplicate information or articles of the same subject and further resolved issues related to study inclusion.

The Quality Appraisal of Case Series Studies Checklist of the Institute of Health Economics was used to assess the quality of included studies[19]. A funnel plot was used to evaluate the publication bias. The pooled prevalence and 95% confidence interval were calculated through a random-effects model, considering variable degrees of data heterogeneity. All

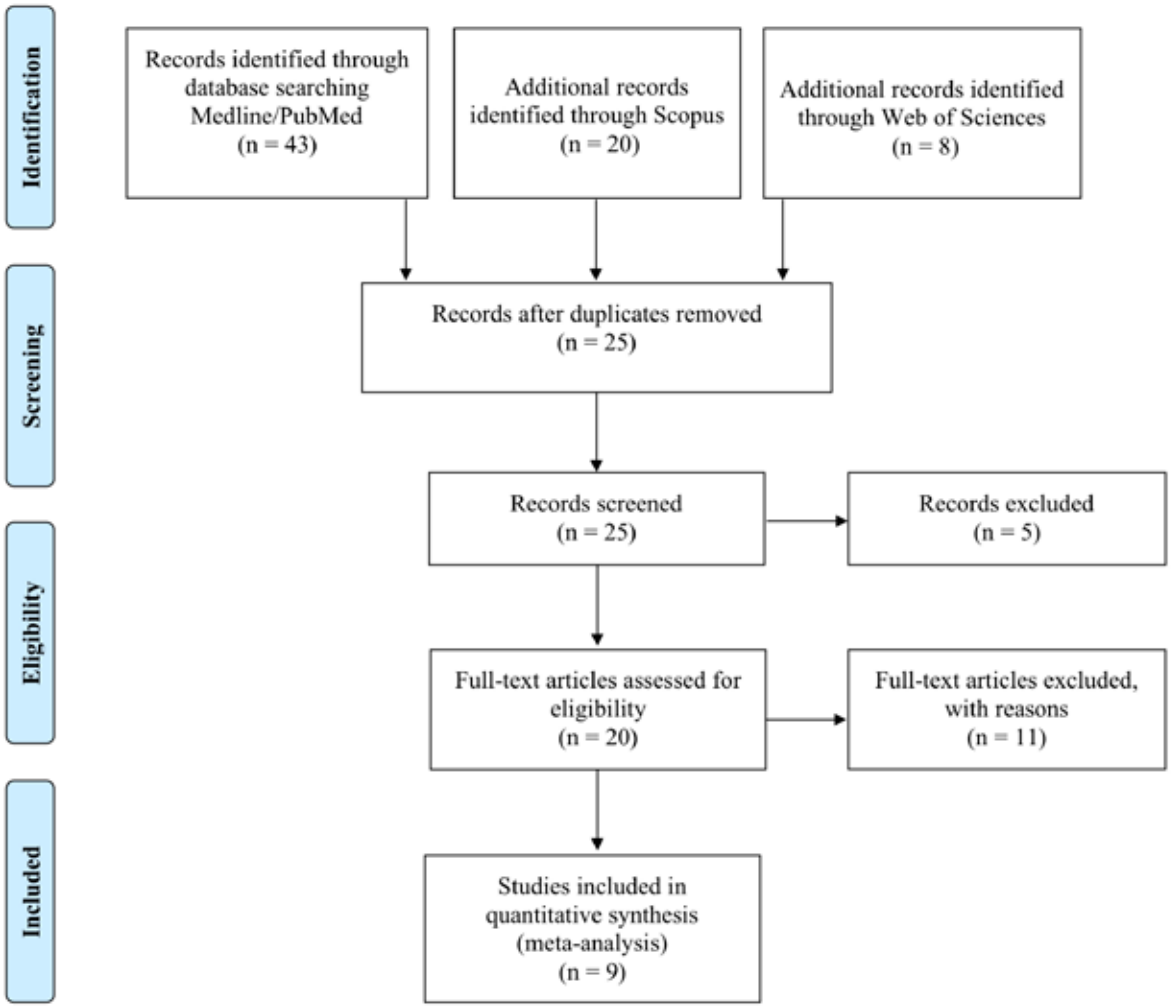

Fig 2: PRISMA flow diagram

units were converted to a standard measurement of each variable to resolve the unit discordance for variables. Means ± standard deviations and percentages were computed for explaining the distributions of continuous and categorical variables, respectively. Weighted means and standard deviations were reported as individual patient information was not available for all patients. The RevMan version 5.3 was used to analyze the baseline data. The study uses reported and estimated measures of heterogeneity, the I2 index, the tau-squared test and Cochran's Q statistic.

RESULTS

Study selection and characteristics

In total, 71 articles were retrieved using the search strategy. Of these, 25 articles were selected for full assessment after screening by abstract and title, but five articles were excluded due to lack of details. Out of the remaining 20 articles, 11 were excluded based on various reasons and nine were finally included for final quantitative assessment (meta-analysis) (Fig. 2). No qualitative synthesis was performed; however, demographical characteristics were reviewed. Table 1 shows the main characteristics of the included studies.

The review included nine studies from January 1, 2020 to April 20, 2020. The majority of them were from China (n=6)[16-28], Italy (n=1)[21], USA (n=1)[24] and Hong Kong (n=1)[25]. A total of 669 patients were included, ranging from a pathological study[23] to a cross-sectional study of 204 subjects[22]. Almost all studies were cross-sectional studies (Table 1). In total, six variables were analyzed for the meta-analysis. A funnel plot was used to assess the publication bias for the standard error by logit event, with no evidence of bias (Fig. 3).

Demographical characteristics

Mean patient age in the studies included was 52 years; out of 669 patients, 230 were male (34.37%) (Table 2).

Table 1: Characteristics of the included studies on radiological findings on COVID-19

Author	Journal	Date	Country	Study type	N	Quality score	Reference
Yuan	PLOS ONE	19th March	China	Cross-sectional	27	7	20
Lomoro	European Journal of Radiology Open	1st April	Italy	Cross-sectional	58	6	21
Long	European Journal of Radiology	11th March	China	Cross-sectional	204	8	22
Tian	Modern pathology	23rd March	China	Cross-sectional	4	6	23
Bernheim	Radiology	6th April	USA	Cross-sectional	121	8	24
Wong	Radiology	27th March	Hong Kong	Cross-sectional	64	7	25
Xu	International Journal of Infectious Diseases	7th March	China	Cross-sectional	51	6	26
Shi	Lancet Infect Dis	24th February	China	Cross-sectional	81	8	27
Liu	Journal of Infection	21st March	China	Cross-sectional	59	7	28

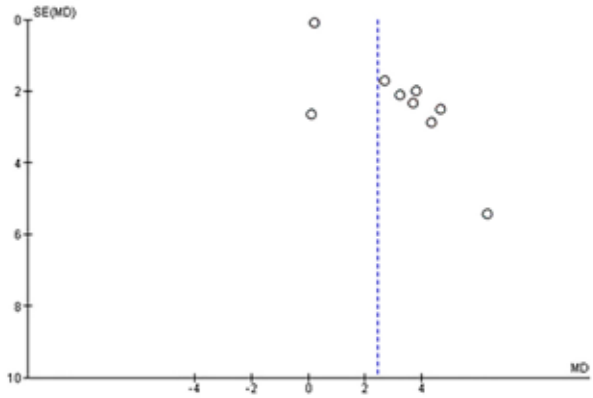

Fig 3: Funnel plot for publication bias

Radiological findings

The radiological findings were based on six variables including pleural effusions, anatomic sides involved, predominant distribution, involved zone, signs and appearance of lesions (Figs. 4-6). Table 3 presents the summary of the radiological findings.

LITERATURE REVIEW

In this meta-analysis, chest CT fundamental findings were unilateral or bilateral pleural effusions, predominant distribution with ground-glass opacity (GGO) with or without consolidations, and crazy-paving appearances comprised by GGO with interlobular or reticular septal thickening. Surprisingly, the corresponding presence of these trends in some instances recommends an advancement of pulmonary involvement. Regarding lesion distribution, there was a consistency in the presence of multifocal and bilateral lung involvement with data of previous studies. Pleural effusion and lymphadenopathy were the common findings based on recent available literature[29,30].

Table 2: Demographical characteristics

Author	N	Mean age (years old)	Age range	Sex (male)
Yuan	27	60	47-69	12
Lomoro	58	66.3	18-98	36
Long	204	44.8	-	20
Tian	4	73	59-78	3
Bernheim	121	45.3	18-80	61
Wong	64	56	-	26
Xu	51	41.6	24-65	25
Shi	81	49.5	25-81	42
Liu	59	31.5	22-58	5

Table 3: Summary of radiological findings

Images	N	Percentage
Bilateral pneumonia	250	47.94
Unilateral pneumonia	113	21.68
Ground-glass opacity at chest CT scan	158	30.32
Pneumonia compromise		
Unilateral	136	20.32
Bilateral	246	36.77
Predominant distribution	412	61.58

CT: computed tomography

In addition, a peculiar CT manifestation of COVID-19 was represented through perilesional vascular thickening, which has previously been reported[31-33]. Furthermore, expression of temporal changes and an acute inflammatory response were correlated with perilesional vascular thickening. In particular, disease advancement has been associated with different CT manifestations on the basis of acute lung injury physiopathology persuaded by viral pneumonia. In this regard, Jin *et al*[7] identified five temporal phases, characterized as dissipation, rapid progression, consolidation, early and ultra-early phases. The CT elements might be single or multiple focal GGO in the ultra-early stage, enclosed by air-bronchogram signs, GGO and patchy consolidations. In addition, the preliminary stage is classified by a combination of interlobular septal thickening of increased interlobular interstitial edema, exudate fluid in the alveolar sac, patchy consolidations, alveolar capillary congestion and multiple GGO[34].

There is a reduction of the inflammatory damage linked with CT characteristics including contextual air bronchograms and large consolidative opacities throughout the quick progression. These findings may progressively worsen in density and size throughout

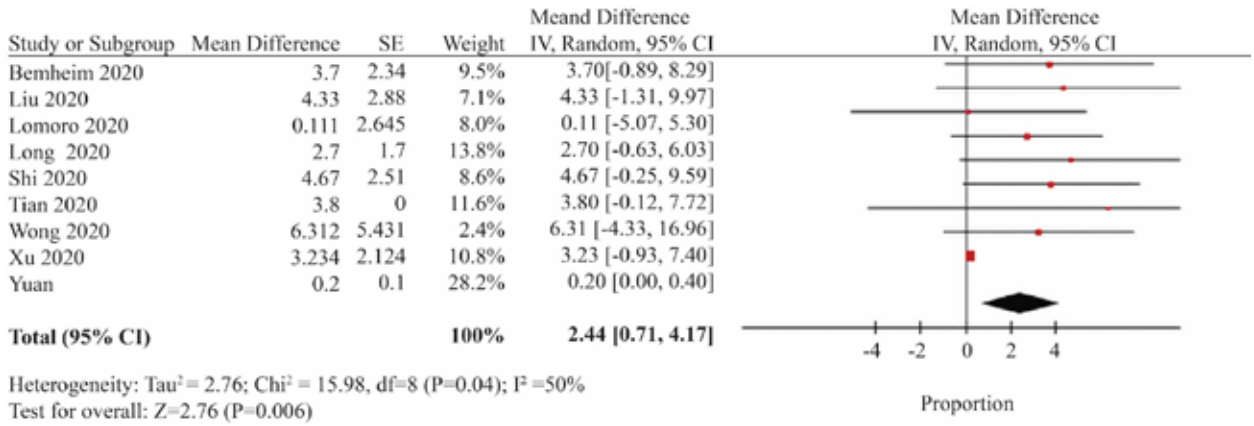

Fig 4: Mean difference for pleural effusions

the consolidation phase. Lastly, lesions might be worsening regarding extension and number with reticular opacities and interlobular septal thickening, as well as small ill-defined consolidative opacities[34]. Other viral pneumonia can overlap with the proteiform spectrum of CT imaging aspects throughout the similar Coronaviridae family due to the same pathogenesis, leading to alveolar damage and diffuse interstitial damage[35]. Nonetheless, this study shows the representation of bilateral and multilobar lung involvement of SARS-CoV-2 and distinguishes it from unifocal lung disease of patients with Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome[36].

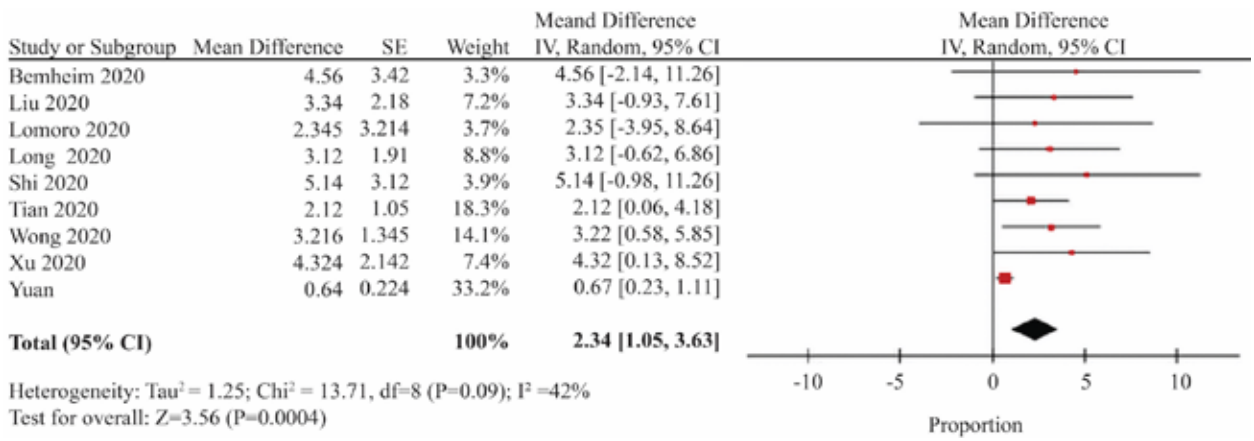

Fig 5: Mean difference for anatomic sides

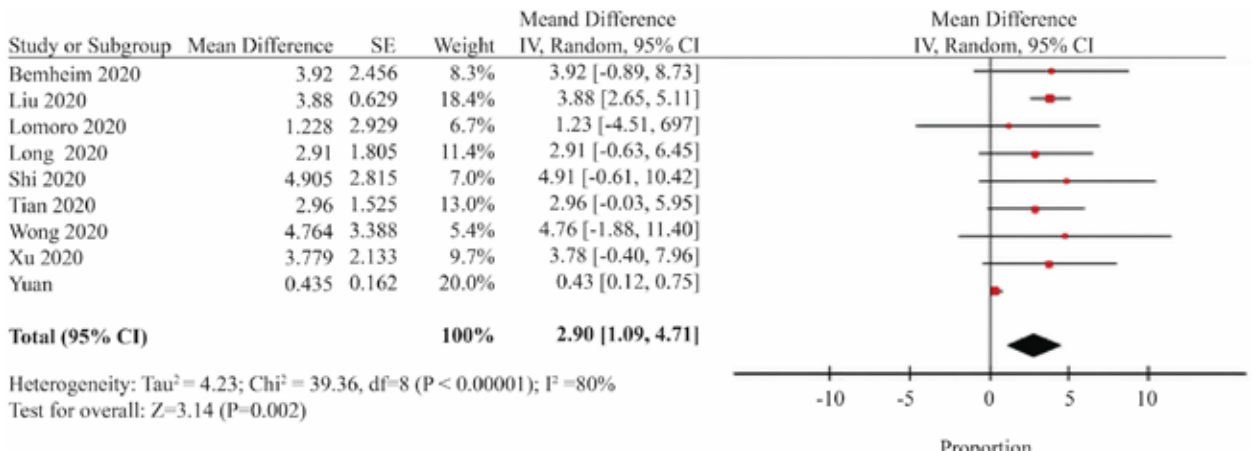

Fig 6: Mean differences for predominant distribution

In addition, Lomoro *et al*[21] have identified pulmonary nodules and reversed halo-sign among the related COVID-19 pneumonia signs, which is in agreement with previous studies[24,32]. Moreover, other processes of organizing pneumonia and influenza pneumonia were identified through chest CT appearance of COVID-19 pneumonia of bilateral peripheral GGO[37]. Long *et al*[22] have shown a 97.2% sensitivity of initial CT and an 83.3% sensitivity for rRT-PCR. This might be associated with sample selection, as nasal sampling and pharyngeal oral sampling are the easiest collection methods. On the contrary, lower respiratory tract sampling are comparatively complicated to perform, with medical staff vulnerable for infections. False negatives can also participate in the sensitivity of the rRT-PCR kit[38]. Chung *et al*[39] have indicated normal CT findings with patients diagnosed with COVID-19 pneumonia.

The current pandemic COVID-19 pneumonia explains a comparatively high infection. Moreover, there are no particular vaccines and drugs available for COVID-19. Therefore, it is important to diagnose patients with COVID-19 in the early stage along with the healthy population. At present, patients should be distinguished for treatment to control the epidemic. Chest CT is superior to RT-PCR in sensitivity for the preliminary diagnosis of COVID-19, but this meta-analysis included only one study with such findings[22].

Limitations

This meta-analysis has several limitations. First, very few studies related to radiological findings are available for inclusion. The majority of the studies were from China, which restricts this meta-analysis in terms of a comprehensive cross-country analysis to understand the outbreak of COVID-19 and the use of chest CT as a radiological modality. Second, randomized controlled trials were unavailable in most studies at the time of analyses due to the lack of detailed patient information, specifically regarding clinical findings. However, this meta-analysis covers mostly clinical studies with radiological findings, but there is a need to present detailed image characterization.

CONCLUSION

COVID-19 is a new clinical contagious pandemic which causes significant compromise, specifically in patients with comorbidities such as sore cough and fever. Almost one-fifth of them require the intensive care unit, sometimes with incurable consequences. In conclusion, CT findings emerge as sensitive for virus detection, while false-negative outcomes might be produced by rRT-PCR. This meta-analysis emphasizes the need to publish clinical studies for increasing the possibility to depend on these findings in the absence of blood tests, such as immunological tests and PCR, to diagnose COVID-19 and to further determine the severity of the disease.

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Original Article

Evaluation of Speed-oligo Mycobacteria assay for rapid differentiation and identification of *Mycobacterium tuberculosis* and nontuberculous mycobacteria in MGIT 960 system cultures from human clinical samples

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ABSTRACT

Objectives: Rapid species-specific identification is of clinical relevance since treatment varies according to the *Mycobacterium* species causing infection. The aim of this study was to evaluate the ability of Speed-oligo Mycobacteria (SpO-M) assay to correctly identify most frequently isolated *Mycobacterium* spp. cultured from clinical samples.
Design: Comparative study
Setting: Mycobacteriology Reference Laboratory, Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait
Subjects: *Mycobacterium* species isolates (n=82) grown from human clinical samples in mycobacteria growth indicator tube (MGIT) 960 system and previously identified by molecular methods were tested.
Interventions: DNA from liquid cultures was extracted, amplified by polymerase chain reaction (PCR), amplified products were detected by using the dipstick and results were interpreted according to SpO-M kit instructions. PCR-sequencing of 16S-23S internal transcribed spacer region of rDNA was used to confirm and validate SpO-M results.
Main outcome measures: Concordance between SpO-M and original identification
Results: The SpO-M correctly identified species/species complex for all *Mycobacterium tuberculosis* (n=34), and 45 of 48 nontuberculous mycobacteria. *Mycobacterium lentiflavum* was detected only as *Mycobacterium* species. One *M. kansasii* isolate was potentially misidentified as *M. tuberculosis* but a careful examination of SpO-M data resolved the discrepancy. Only one isolate, *Mycobacterium parascrofulaceum*, was misidentified as *M. tuberculosis*.
Conclusions: Our data show that SpO-M is a rapid and reliable oligochromatographic test for detection and identification of most frequently isolated *Mycobacterium* species from clinical specimens in MGIT 960 system cultures for proper management of mycobacterial infections.

KEY WORDS: *Mycobacterium tuberculosis*, nontuberculous mycobacteria, PCR-sequencing of 16S-23S rDNA, Speed-oligo Mycobacteria

INTRODUCTION

Although the genus *Mycobacterium* comprises more than 140 species, most human infections are caused by *Mycobacterium tuberculosis* or other members of *M. tuberculosis* complex and few major nontuberculous mycobacteria (NTM) which are environmental opportunistic pathogens[1-3]. Although tuberculosis (TB) is the most common mycobacterial infection in developing countries, the incidence of NTM infections is increasing and these infections are now more common than TB in developed countries[1,3]. The increasing trend in NTM infections is mainly due to an increase in the population of susceptible hosts such as elderly subjects with one or more debilitating conditions and individuals with defects in the cellular immune system due to disease or immunosuppressive treatment[3,4].

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Similar to TB, NTM infections also mostly involve the lungs and some NTMs such as *Mycobacterium kansasii* and *Mycobacterium abscessus* can also cause pulmonary infections in immunocompetent individuals[1,5-8]. Furthermore, NTM infections often resemble TB, both clinically and radiographically, however, treatment strategies and the prognosis of NTM disease are quite different[9-13]. Thus, rapid species-specific identification of *M. tuberculosis* and NTM is crucial for appropriate treatment of mycobacterial infections.

About 95% of nearly 800 mycobacterial infections in Kuwait are caused by *M. tuberculosis*, while the remaining ~5% are caused by NTM every year[14-16]. Infections by other members of *M. tuberculosis* complex (e.g. *M. bovis*) are extremely rare. Furthermore, nearly 80% of all TB cases and nearly 90% of drug-resistant TB cases in Kuwait occur in expatriate individuals mainly originating from TB endemic countries of South/South-East Asia, while NTM infections are more common among Kuwaiti nationals[14,16-20]. Also, most NTM infections in Kuwait are caused by only seven NTM species/species complex isolates[14]. This study evaluated the ability of a novel DNA strip assay (Speed-oligo Mycobacteria, SpO-M), based on multiplex polymerase chain reaction (PCR) and double-reverse hybridization on a dipstick using probes bound to colloidal gold and to the membrane, to correctly identify mycobacterial strains isolated from clinical samples in Kuwait. A multiplex PCR assay that can differentiate *M. tuberculosis* from NTM was also used. PCR-sequencing of 16S-23S internal transcribed spacer (ITS) region of rDNA was used as gold standard to confirm the results of SpO-M.

MATERIALS AND METHODS

Mycobacterium species isolates

A total of 82 clinical mycobacterial isolates belonging to *M. tuberculosis* and 10 different NTM species most frequently encountered in clinical specimens[3-9] were obtained from Kuwait National TB Reference Laboratory. The isolates were grown from 66 pulmonary (sputum, n=58; bronchoalveolar lavage, n=6 and endotracheal aspirate, n=2) and 16 extra-pulmonary (fine needle aspirate/pus, n=12; urine, n=2; lymph node, n=1 and tissue biopsy, n=1) specimens collected from 82 patients as part of routine patient care and diagnostic work-up and data are reported in this paper anonymously. Non-sterile clinical specimens were processed by the standard *N*-acetyl-L-cysteine and sodium hydroxide method while sterile samples were processed directly for culture in automated mycobacteria growth indicator tube (MGIT) 960 system (Beckton-Dickinson, Sparks, MD, USA) according to the manufacturer's instructions and as described previously[16,21]. The isolates were identified to the species-level previously by a commercial line probe assay and/or by PCR-sequencing of 16S-23S ITS region of rDNA, as described earlier[14]. The study was approved by the Ethics Committee of the Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait (Approval no. VDR/EC/2 dated 9-2-2015).

Template DNA preparation and multiplex PCR assay

Genomic DNA was prepared from MGIT 960 system cultures of *Mycobacterium* species isolates by incorporating the removal of PCR inhibitors with Chelex-100 (Sigma-Aldrich Co. St. Louis, MO, USA) as described previously[22]. The isolates were also tested by a multiplex PCR assay designed to differentiate *M. tuberculosis* from NTM species[23]. The multiplex PCR assay with six primers (IGRF, 5′-AGCGTCTGGTCGCGTAGGCAGTG-3′; IGRR, 5′-GGTGAAGTAGTCGCCGGGCTGCT-3′; MTCF, 5′-TACGGTCGGCGAGCTGATCCAAA-3′; MTCR, 5′-ACAGTCGGCGCTTGTGGGTCAAC-3′; NTMF, 5′-GGAGCGGATGACCACCCAGGACGTC-3′ and NTMR, 5′-CAGCGGGTTGTTCTGGTCCATGAAC-3′) was performed as described previously[23]. This assay yields two amplicons of 473 bp and 235 bp from *M. tuberculosis* isolates but only a single amplicon of 136 bp from NTM members[23].

Speed-Oligo Mycobacteria assay

The SpO-M assay kit (Vircell, Granada, Spain) identifies the bacterial isolates belonging to *Mycobacterium* genus. The test also simultaneously detects *M. tuberculosis* complex (*M. tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti* and *Mycobacterium caprae*) members and several different NTM species/ species complex comprising *Mycobacterium abscessus/M. chelonae* complex, *Mycobacterium gordonae, Mycobacterium kansasii*, *Mycobacterium avium/M. intracellulare/M. scrofulaceum* complex and *Mycobacterium fortuitum*. The SpO-M kit was used according to the kit instructions. Briefly, the DNA (5 µl) from each isolate was amplified by using 15 µl of ready-to-use reconstituted PCR mix, the PCR products were denatured by heating at 95 °C for one min and then cooled on ice immediately. A 10 µl portion of the denatured PCR product was then added to 35 µl of hybridization solution (provided with the kit) preheated to 55 °C in a 1.5 ml microcentrifuge tube, the test strip (provided with the kit) was inserted into the tube and the results were interpreted after ten minutes of incubation at 55 °C according to kit instructions. The test strip has seven (TL1 to TL7) probes in addition to product control and PCR control. Probe TL1 reacts with *M. abscessus/M. chelonae* complex, TL2 reacts with *M. gordonae*, TL3 reacts with *M. kansasii*, TL4 (in addition to weak reaction with TL3) reacts with *M. tuberculosis* (and other *M. tuberculosis* complex)

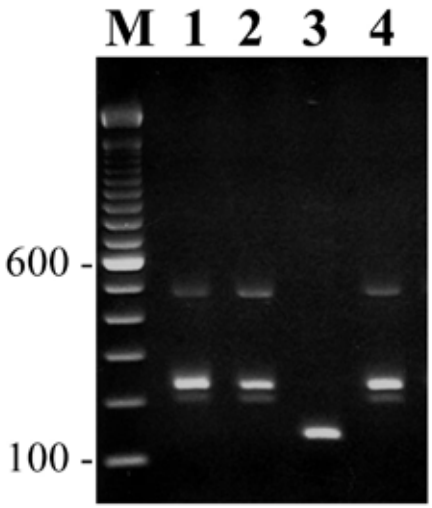

Fig 1: Representative agarose gel of multiplex PCR products using genomic DNA extracted from mycobacterial growth indicator tube (MGIT) 960 system cultures of four selected *Mycobacterium* species isolates and showing MTB-specific pattern with 473 bp and 235 bp products (lanes 1, 2 and 4) or NTM-specific pattern with 136 bp product (lane 3). Lane M is 100 bp DNA ladder and the position of migration of 100 bp and 600 bp fragments are marked.

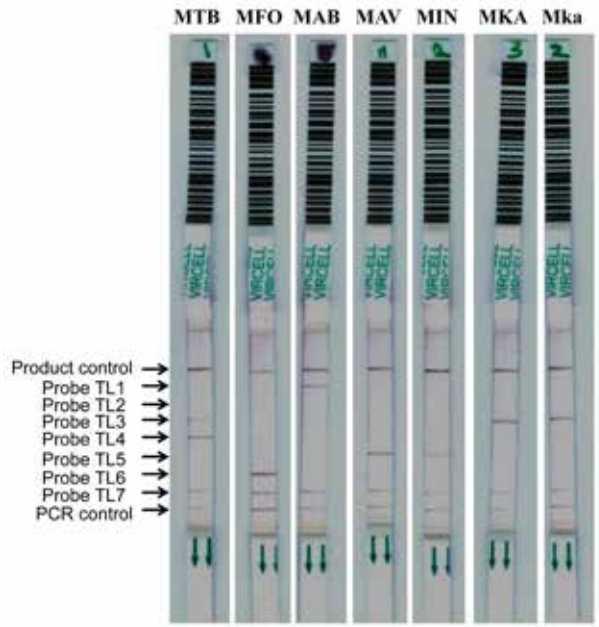

Fig 2: Representative hybridization results of Speed-Oligo Mycobacteria (SpO-M) test strips with DNA from *M. tuberculosis* (a member of *M. tuberculosis* complex) (lane MTB), *M. fortuitum* (lane MFO), *M. abscessus* (a member of *M. abscessus/M. chelonae* complex) (lane MAB), *M. avium* (a member of *M. avium/M. intracellulare/M. scrofulaceum* complex) (lane MAV), *M. intracellulare* (a member of *M. avium/M. intracellulare/M. scrofulaceum* complex) (lane MIN), *M. kansasii* (lane MKA) and *M. kansasii* isolate showing additional weak reactivity with TL4 (in addition to TL3 and TL7) that is potentially misidentified as *M. tuberculosis* (lane Mka). The arrows mark the positions of species/complex-specific probes TL1 to TL7. The band positions for product control and PCR control are also marked.

isolates, TL5 reacts with *M. avium/M. intracellulare/M. scrofulaceum* complex, TL6 reacts with *M. fortuitum* and TL7 reacts with all *Mycobacterium* species isolates. The visual interpretation of test results was based on the presence or absence of different bands appearing on the test strip according to the reference band patterns provided with the kit instructions. The *M. tuberculosis* $H_{37}Rv$ DNA was used as positive control while water instead of DNA was used as negative control.

Resolution of discrepant results

Discrepant results between SpO-M assay and the original identification were resolved by PCR-sequencing of 16S-23S ITS region of rDNA.

PCR-sequencing of 16S-23S ITS region of rDNA

The results of SpO-M assay for selected isolates were confirmed by PCR-sequencing of 16S-23S ITS region of rDNA. The ITS region of rDNA was amplified by using forward (SAKW135; 5′-GATTGGGACGAAGTCGTAACAAG-3′) and reverse (SAKW136, 5′-AGCCTCCCACGTCCTTCATCGGCT-3′) primers and the touchdown PCR amplification and cycling conditions described previously[22]. The amplicons were purified by using PCR product purification kit (Qiagen, Hilden, Germany) which was used according to kit instructions. Both strands of purified amplicons were sequenced by using the same amplification primers as well as two internal (ITSIF, 5′-TGGATAGTGGTTGCGAGCAT-3′ and ITSIR, 5′-GATGCTCGCAACCACTATCCA-3′) primers as sequencing primers and ABI BigDye terminator (version 3.1) cycle sequencing kit (Life Technologies Corp., Austin, TX, USA). Sequencing reactions were performed and processed as described previously[24]. Basic local alignment search tool searches (http://www.ncbi.nlm.nih.gov/BLAST/Blast.cgi) of DNA sequence data were performed with data from GenBank and sequence identity of >99% with reference strains or well-characterized clinical isolates of various *Mycobacterium* species was used for species identification.

RESULTS

A total of 82 mycobacterial isolates cultured in MGIT 960 system from 66 pulmonary and 16 extra-pulmonary clinical specimens obtained from 82 patients were tested by SpO-M assay. The isolates were previously identified by molecular methods and included 34 *M. tuberculosis* and 48 NTM. When multiplex PCR assay that differentiates *M. tuberculosis*

Table 1: Differentiation of MGIT 960 system cultures as MTB or NTM by multiplex (m)PCR and species-specific identification of isolates by Speed-Oligo Mycobacteria (SpO-M) assay and PCR-sequencing of 16S-23S ITS region of rDNA

No. of isolates	*Mycobacterium* species identified by*		
	mPCR	Probe pattern in SpO-M assay and interpretation	DNA Sequencing of rDNA
10	MTB	TL3, TL4, TL7: *M. tuberculosis*	*M. tuberculosis*
24	MTB	TL3, TL4, TL7: *M. tuberculosis*	Not done
6	NTM	TL6, TL7: *M. fortuitum*	*M. fortuitum*
5	NTM	TL6, TL7: *M. fortuitum*	Not done
8	NTM	TL5, TL7: *M. avium/M. intracellulare/M. scrofulaceum complex*	*M. avium complex*
7	NTM	TL5, TL7: *M. avium/M. intracellulare/M. scrofulaceum complex*	*M. intracellulare complex*
1	NTM	**TL3, TL4, TL7: *M. tuberculosis***	***M. parascrofulaceum***
8	NTM	TL3, TL7: *M. kansasii*	*M. kansasii*
1	NTM	TL3, TL4 (weak), TL7: *M. kansasii*	*M. kansasii*
7	NTM	TL1, TL7: *M. abscessus/M. chelonae complex*	*M. abscessus*
2	NTM	TL1, TL7: *M. abscessus/M. chelonae complex*	*M. chelonae*
1	NTM	TL1, TL7: *M. abscessus/M. chelonae complex*	*M. immunogenum*
1	NTM	TL2, TL7: *M. gordonae*	*M. gordonae*
1	NTM	TL7: *Mycobacterium* species	*M. lentiflavum*

*Discordant results by Speed-Oligo Mycobacteria and PCR-sequencing of rDNA are indicated in bold

from NTM was performed (data from four selected isolates are shown in Fig. 1), 34 isolates yielded *M. tuberculosis*-specific pattern of two amplicons of 473 bp and 235 bp while 48 isolates yielded a single amplicon of 136 bp which is characteristic of NTM species.

The SpO-M assay yielded interpretable results (data from seven selected isolates are shown in Fig. 2) for all 82 isolates. The SpO-M assay correctly identified all 34 *M. tuberculosis* isolates (Table 1) as they showed strong reaction with probe TL7 and TL4 in addition to weak reaction with probe TL3 (Fig. 2, lane MTB). The SpO-M assay also correctly identified all 11 *M. fortuitum* isolates as they showed reaction with probes TL7 and TL6 (Fig. 2, lane MFO) and one *M. gordonae* isolate as it reacted with probes TL7 and TL2 (Table 1). Seven isolates of *M. abscessus* (Fig. 2, lane MAB), two isolates of *M. chelonae* and one isolate of *M. immunogenum* were also correctly identified as *M. abscessus/M. chelonae* complex isolates (Table 1) as they reacted with probes TL7 and TL1. Similarly, eight isolates of *M. avium* (Fig. 2, lane MAV) and seven isolates of *M. intracellulare* (Fig. 2, lane MIN) were identified as *M. avium/M. intracellulare/M. scrofulaceum* complex isolates as they reacted with probes TL7 and TL5. However, one *M. parascrofulaceum* isolate was misidentified as *M. tuberculosis* (Table 1) as it reacted with probes TL7 and TL4 in addition to weak reaction with TL3. Of nine *M. kansasii* isolates, eight isolates were correctly identified as they reacted with probes TL7 and TL3 only (Fig. 2, lane MKA); however, one isolate was potentially misidentified as *M. tuberculosis* (Table 1) since probe TL4 also reacted, albeit weakly, in addition to probes TL7 and TL3 (Fig. 2, lane Mka). One *M. lentiflavum* isolate was identified to the genus level as it reacted with probe TL7 only. The *M. kansasii* isolate showing additional weak reaction with probe TL4 was confirmed as *M. kansasii* by PCR-sequencing of ITS region of rDNA. The *M. parascrofulaceum* identified as *M. tuberculosis* by SpO-M assay was confirmed as *M. parascrofulaceum* by PCR-sequencing of ITS region of rDNA (Table 1).

DISCUSSION

Although TB, particularly pulmonary TB, is the major mycobacterial disease in most of the developing countries, the incidence of NTM infections has surpassed TB in resource-rich developed countries[1-3]. The NTM infections are usually acquired through contact with contaminated environment[2,25]. Lung disease is the most common manifestation of NTM infection, while extra-pulmonary infections usually include lymphadenitis and cutaneous or disseminated disease but may also involve lymph nodes, soft tissue, bone and joints[2,4-8,26,27]. Patients with NTM infections often mimic disease presentation indistinguishable from TB both clinically and radiographically and are older with predisposing pulmonary abnormalities[4-7,10,11,26]. A definitive diagnosis of NTM lung disease also requires differentiation from colonization or contamination due to their abundance in the environment[25]. Successful treatment of TB is dependent on rapid diagnosis but also requires accurate drug susceptibility of *M. tuberculosis* isolates to anti-TB drugs due to increasing reports of multidrug-resistant TB (infection with *M. tuberculosis* strains resistant at least to rifampicin and isoniazid, the two most active anti-TB drugs) in many countries[28]. The virulence of NTM varies considerably and the susceptibility of NTM to anti-TB drugs and other antibiotics also varies markedly among members belonging to different species/species complex, which necessitates different treatment strategies for different NTM infections[5-9,12,27]. Furthermore, *in*

vitro susceptibility does not always correlate with effective *in vivo* response to antibiotics[4,8,9,27]. Thus, rapid differentiation of MTB from NTM and accurate identification of NTM species is crucial for proper treatment and appropriate patient management.

Kuwait is a low (23 cases per 100,000 population) TB incidence country[15,16,29]. Nearly 800 mycobacterial infections are diagnosed every year, with 95% of these infections occurring due to *M. tuberculosis* while 5% of infections are caused by NTM[14-16,26]. Furthermore, 80% of TB cases and ~90% of drug-resistant TB cases occur in expatriate patients, while NTM infections are more common in Kuwaiti subjects[14,16-18,26,29]. Most NTM infections in Kuwait are caused by only few species which mainly include *M. fortuitum, M. kansasii, M. abscessus* complex, *M. avium* complex and *M. intracellulare* complex members[14]. In this study, we evaluated SpO-M assay that has been developed for rapid differentiation of mycobacterial strains in MGIT 960 system cultures. This dipstick test directly detects denatured PCR amplicons from *M. tuberculosis* and most common NTM species in only two pipetting steps. The procedure requires a total time of nearly three hours and a hands-on time of only 30 minutes[30]. Our data on 82 mycobacterial strains showed that all *M. tuberculosis* (n=34), all *M. fortuitum* (n=11), all *M. abscessus*/*M. chelonae* complex members isolates (n=9) (including seven *M. abscessus* and two *M. chelonae* isolates), all *M. avium* (n=8), all *M. intracellulare* (n=7) and one *M. gordonae* isolate were correctly identified. The probe for *M. abscessus*/*M. chelonae* complex also reacted with *M. immunogenum*, a species closely related to *M. abscessus* and *M. chelonae*[31]. One *M. lentiflavum* isolate was identified to the genus level as it reacted with probe TL7 only since no specific probe is included in the SpO-M kit for this rare *Mycobacterium* species. Although eight *M. kansasii* isolates were correctly identified, one isolate was potentially misidentified as *M. tuberculosis* and one *M. parascrofulaceum* isolate was misidentified as *M. tuberculosis*.

Thus, application of SpO-M on MGIT 960 system cultures of mycobacterial strains in Kuwait showed concordant results for 79 of 82 (96%) isolates. Other investigators have also reported similar results. Quezel-Guerraz *et al*[32] reported a concordance of 97.2% for 182 mycobacterial isolates collected from various Spanish mycobacteriology laboratories with only 13 of 157 NTM isolates identified at genus level while the remaining 144 NTM isolates were identified to the correct species/species complex level. Significant discordance was noted only for two *Mycobacterium marinum* isolates which were identified as *M. kansasii*[32]. Similar results were also reported for another isolate from Czech Republic[33]. O'Donnell *et al*[34] also reported a concordance of 98% between SpO-M and AccuProbe assay for the identification of mycobacterial strains. On the contrary, Ramis *et al*[35] using an updated version reported a concordance of only 93.5% with one *M. chelonae* isolate failing to react with any probe, one *M. kansasii* isolate misidentified as *M. tuberculosis* and one *M. peregrinum* isolate misidentified as *M. abscessus*. These misidentifications are significant due to differences in antimicrobial susceptibility profiles of these NTM, which could influence treatment decisions and outcome[2,5,7-9]. Similar to the findings of Ramis *et al*[35], one *M. kansasii* isolate in our study was also potentially misidentified as *M. tuberculosis*. However, a closer look at our data showed that this isolate exhibited stronger reaction with probe TL3 and much weaker reaction with probe TL4, while *M. tuberculosis* isolates exhibit stronger reaction with probe TL4 and weaker reaction with probe TL3. Thus, careful examination of SpO-M data identified the isolate correctly as *M. kansasii*. Similar to our study, *M. lentiflavum* was also not specifically identified in other studies using SpO-M assay as there is no specific probe for its identification[32,33]. One *M. parascrofulaceum* isolate in our study was misidentified as *M. tuberculosis*. It is not known at present if *M. parascrofulaceum* isolates are routinely misidentified as *M. tuberculosis* by this test since other studies using SpO-M assay have not used *M. parascrofulaceum* isolates[30,32-35].

Other tests such as matrix assisted laser desorption ionization-time of flight mass spectrometry has also been used for rapid detection of *Mycobacterium* species. However, the method requires expensive equipment and also needs cultures on solid media, which is time consuming, while the performance in rapid liquid cultures is only around 90%[36-38].

A limitation of our study is that many mycobacterial isolates (such as those belonging to *M. abscessus* and *M. chelonae* or *M. avium* and *M. intracellulare*) were only identified to the species complex level rather than specifically to the individual species due to inclusion of only few probes on test strips. Although an updated version of SpO-M assay has been developed recently that can specifically identify *M. tuberculosis* complex members (*M. tuberculosis, M. bovis* etc.) and 13 NTM species (including *M. abscessus, M. avium, M. chelonae, M. fortuitum, M. gordonae, M. interjectum, M. intracellulare, M. kansasii, M. malmoense, M. marinum*/*M. ulcerans, M. peregrinum, M. scrofulaceum* and *M. xenopi*), many other NTM species such as *M. lentiflavum, M. mucogenicum, M. porcinum* and several other rarely occurring NTM species (e.g. *M. canariasense*) still cannot be specifically identified[39].

CONCLUSION

Our data on 82 mycobacterial isolates showed that all 34 *M. tuberculosis* isolates were accurately identified

and 45 of 48 NTM isolates were accurately identified to the species/species-complex level. Careful examination of SpO-M data also correctly identified one *M. kansasii* isolate that showed additional weak reaction with probe TL4 while one isolate (*M. lentiflavum*) was identified only at the genus level. Only one isolate (*M. parascrofulaceum*) yielded inaccurate identification. Our data show that Speed-Oligo Mycobacteria is a reliable test for routine diagnostics of *Mycobacterium* species isolates in MGIT 960 system cultures.

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

Suhail Ahmad and Eiman Mokaddas designed the study. Noura M Al-Mutairi performed the experiments and analyzed the data. Suhail Ahmad and Eiman Mokaddas wrote the manuscript. All authors read and approved the final version of the manuscript.

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Original Article

Do all Familial Mediterranean Fever (FMF) patients with recurrent chest pain have cardiac problems?

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ABSTRACT

Objectives: Familial Mediterranean Fever (FMF) is a hereditary autosomal recessive autoinflammatory genetic disorder. One of the important complications of FMF is cardiac disorder. We aimed to research the evaluation of cardiological parameters in FMF cases who had chest pain and *MEFV* gene variant.
Design: Experimental study
Setting: This study was conducted at Department of Cardiology and Medical Genetics of Duzce University, Turkey.
Subject: Totally, thirty-four individuals with recurrent sharp retrosternal chest pain that exacerbate with deep inspiration and clinically diagnosed as FMF and at least one variant on *MEFV* gene were included in the study.
Interventions: Physical and cardiological evaluation were performed and *MEFV* gene sequenced for each case.
Main outcome measures: To determine if the chest pain is caused by cardiac problems or derived from other problems such as tendonitis, myalgia, etc. in cases with FMF
Result: Seven cases (20.5%) had previous history of pericarditis. Two of these cases had small pericardial effusion and one had pericardial thickness. All three were adults. Also, one case (2.9%) had aortic regurgitation, eight cases (23.5%) had mitral regurgitation, thirteen cases (38.2%) had tricuspid regurgitation and one case (2.9%) had pulmonary regurgitation. Valvular disease is seen in over half of the cases.
Conclusions: We concluded that cases with FMF who had chest pain and at least one *MEFV* gene variant have increased risk for cardiac problems. These cases should be routinely followed up life long for cardiac problems.

KEY WORDS: cardiac, cardiac problem, familial mediterranean fever, MEFV gene, recurrent chest pain

INTRODUCTION

Familial Mediterranean Fever (FMF) is a hereditary autosomal recessive autoinflammatory genetic disorder characterized by short and self-resolving recurrent attacks of inflammation of serosal membranes. In this manner, FMF results in acute fever, abdominal pain, joint pain, chest pain, synovitis, myalgia and erythema[1]. *MEFV* gene mutations are responsible for the disease. *MEFV* genes are located on chromosome 16p13.3 and encodes pyrin including 10 exons. The disease is genarally seen in eastern Mediterranean populations including Armenians, non-Ashkenazi Jews, Turks and Arabs[2].

FMF affects different organs and systems such as the musculoskeletal, renal, gastrointestinal systems, etc. Although the relation between FMF and cardiovascular risk is rarely reported, the cardiac complications increase morbidities and/or mortality in FMF[3].

The most significant complication of FMF that may cause cardiac disease is secondary systemic AA amyloidosis[4]. Cardiac deposition of amyloid, which causes increased morbidity and mortality in FMF patients, may lead to cardiovascular mortality[5]. Cardiac manifestations related to FMF may genarally be associated with secondary AA amyloidosis. The most commonly reported cardiac manifestations in FMF are pericarditis, idiopathic recurrent pericarditis,

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cardiac tamponade and abnormal cardiovascular reactivity[6].

One of the most important symptoms of FMF is chest pain. While the chest pain may be caused by cardiac problems, it may be also caused by non-cardiac reasons such as tendonitis, myalgia, etc. To the best of our knowledge, there is no study about the evaluation of cardiological parameters in FMF cases with different variants of *MEFV* gene who had chest pain in the literature. It was not clear whether the chest pain resulted from any cardiac problem or was derived from other problems such as tendonitis, myalgia, etc. in cases with FMF. For this reason, we performed the current study.

Aim of the our study:

1. To evaluate cardiological parameters in FMF cases with different variants of *MEFV* gene who had recurrent chest pain
2. To assess whether the chest pain in FMF is caused by any cardiac problem or if it is derived from other problems such as muscle pain, etc.

SUBJECTS AND METHODS

Genetic and routine biochemical analysis

Thirty-four individuals who had recurrent sharp retrosternal chest pain that exacerbated with deep inspiration and diagnosed clinically as FMF and at least one variant on *MEFV* gene (20 male and 14 female; age ranged between 6-47 years old) were included in the current study. Physical examinations were performed and demographical features were obtained. For *MEFV* gene mutation analaysis, 2 cc peripheral blood samples were collected in tubes containing ethylenediaminetetraacetic acid for DNA isolation from the cases. Genomic DNA was isolated. All exons of *MEFV* gene (1-10) were amplified using polymerase chain reaction technique and whole exome sequencing analysis of the gene was performed. Duzce University Human Research Ethics Committee approved the study. Written informed consent was obtained from participants. Also, routine serum and urine biochemical analysis were carried out for each case. All patients clinically diagnosed as FMF with at least one variant on *MEFV* gene underwent detailed cardiac examination.

Cardiological examination

Electrocardiogram (ECG)

Twelve-lead ECG (NIHON KOHDEN Cardiofax ECG 1250K model) was done for each case at rest. Routine evaluations were done.

Echocardiography

All of the patients in the study were evaluated with transthoracic echocardiography (Siemens Acuson SC 2000). Transthoracic two dimensional, M mode and color Doppler echocardiogram were performed with suitable probes according to age. Cardiac anatomy, ventricular function and valve competence were assessed using standard projections and measurements according to the recommendations of the American Society of Echocardiography[7].

Table 1: Demographical and biochemical features of the cases with children and adults

Case features	Cases <18 years old (n)	Cases ≥18 years old (n)
Sex		
Male	8(47.1%)	12(70.6%)
Female	9 (52.9%)	5 (29.4%)
Age (mean±SD)	12.824±3.644	38.118±8.710
BMI (mean±SD)	19.457±4.407	24.604±2.525
Cases with family history	13 (76.5%)	11 (64.7%)
Cases without family history	4 (23.5%)	6 (35.3%)
Age onset of symptom	5.103±3.517	21.544±12.149
Recurrancy of attacks		
More than once a month	9(52.9%)	6(35.3%)
Once in a month	3(17.6%)	4(23.5%)
Once in three months	5(29.4%)	6(35.3%)
Once in six months		1(5.9%)
ESR (mmHg)	12.177±9.174	10.412±9.612
Creatinin (mg/dl)	0.514±0.167	0.699±0.155
HB (g/dl)	13.277±1.736	14.235±2.019
WBC	7205.882±2947.556	7500±1390.593
Platelet (103/uL)	307.471±59.835	268.118±30.864
C-Reactive Protein (mg/dL)	0.236±0.178	0.418±0.350

SD: standard deviation; BMI: body mass index; ESR: erythrocyte sedimentation rate; HB: hemoglobin; WBC: white blood cell

Statistical analysis

All analyses were performed using the Statistical Package for Social Sciences (SPSS version 15.0). The descriptional statistics were done for all data. The data are given as mean ± SD or frequency values. The relation between the mutation and clinical parameters

Table 2: Clinical features of the cases

Clinical features	Cases <18 years old n (%)	Cases ≥18 years old n (%)
Cases with chest pain	17 (100)	17 (100)
Cases with abdominal pain	16 (94.1)	14 (82.4)
Cases with arthritis	11 (64.7)	12 (70.6)
Cases with fever	11 (64.7)	7 (41.2)
Cases with pericarditis	1 (5.8)	6 (35.3)
Cases with amyloidosis	0 (0)	2 (11.8)
Cases with appendicectomy	0(0)	2 (11.8)
Cases with erythema	3 (17.6)	6 (35.3)
Dsypnea	5 (29.4)	5 (29.4)
Palpitation	1 (5.9)	6 (35.3)
Oedema	0 (0)	0 (0)
Syncop	0 (0)	0 (0)

Table 3: Variant type of the cases

Variant type	Cases <18 years old n (%)	Cases ≥18 years old n (%)
Heterozygous R202Q	6 (35.3)	6 (35.3)
Homozygous R202Q	1 (5.9)	0 (0)
Heterozygous M694V	1 (5.9)	2 (11.8)
Heterozygous E148Q	2 (11.8)	1 (5.9)
Compound heterozygous R202Q/M694V	2 (11.8)	3 (17.6)
Compound heterozygous R202Q/M694V/ M680I	1 (5.9)	0 (0)
Homozygous R202Q/M694V	1 (5.9)	2 (11.8)
Heterozygous V726A	3 (17.6)	2 (11.8)
Heterozygous P369S	0 (0)	1 (5.9)

was evaluated with Pearson's χ^2 test depending on the type of variables.

RESULTS

A total of 34 individuals (20 male and 14 female; age ranged between 6-47 years old) were divided into two groups: <18 years old (n=17) and ≥18 years old (n=17). The demographical features of cases are given in Table 1 and clinical features of the cases are given in Table 2. According to mutation analysis results of cases, 12 cases had heterozygous R202Q (35.3%), one case had homozygous R202Q (2.9%), three cases had heterozygous M694V (8.8%), three cases had heterozygous E148Q (8.8%), five cases had compound heterozygous R202Q/M694V (14.7%), one case had complex genotype R202Q/M694V/M680I (2.9%), three cases had homozygous R202Q/M694V (8.8%), five cases had heterozygous V726A (14.7%) and one case had heterozygous P369S mutation (2.9%) (Table 3).

Cardiac assessment of FMF patients

All patients had chest pain. The systolic and diastolic blood pressures were within normal range. 12-lead ECG was done and no anomaly was detected in any case. Echocardiographic testing revealed pericardial thickening in one patient and mild pericardial effusions in two patients. These three cases had recurrent pericarditis history. None of the cases had cardiac tamponade. One case had aortic regurgitation, which was grade I. Eight had mitral regurgitation; six of them had grade I and two of them had grade II. Thirteen cases had tricuspid regurgitation grade I. One case had pulmonary regurgitation, which was grade I. Left ventricular functions of all patients were normal (Table 4). Also, serum and biochemical analaysis results of all cases are within normal range (Table 1).

Table 4: Echocardiographical findings of the cases

Cardiac findings	Cases <18 years old n (%)	Cases ≥18 years old n (%)
Aortic	0 (0)	1 (5.9)
Mitral	4 (23.5)	4 (23.5)
Tricuspit	5 (29.4)	8 (52.9)
Pulmonary	0 (0)	1 (5.9)
Pericardial effusion	0 (0)	2 (11.8)
Pericardial thickness	0 (0)	1 (5.9)

The cardiac findings according to the mutation type are given in Table 5 and Figure 1.

DISCUSSION

FMF is an autoinflammatory disease caused by inflammatory attacks of peritonitis, pleuritis and pericarditis accompanied by fever and arthritis. Increased proinflammatory cytokines and acute phase reactants are seen throughout inflammatory attacks of FMF. Chronic inflammation may also be associated with the cardiovascular risk in cases with FMF[8].

The variability of abnormal heart rate with AA amyloidosis was reported in FMF cases[9]. Morphological analysis of cardiac tissues from the patients who died of congestive heart failure revealed amyloid deposits in the endocardium, stroma of the myocardium as well as the vascular walls. It was reported that the backlog of amyloid was less obvious in lung and liver than spleen, kidneys, endocrine and digestive organs of cases with FMF. Morphological analysis of cardiac tissues from the cases who died due to congestive heart failure revealed amyloid

Table 5: Cardiac findings according to variant type

Variant type	Aortic	Mitral	Tricuspit	Pulmonary	Pericarditis	Pericardial effusion	Pericardial thickness
Heterozygous R202Q	-	-	5	-	2	-	-
Homozygous R202Q	-	3	-	-	-	-	-
Heterozygous M694V	-	-	1	-	1	-	-
Heterozygous E148Q	-	1	1	-	2	1	-
Compound heterozygous R202Q/M694V	-	2	2	-	1	-	1
Compound heterozygous R202Q/M694V/M680I	-	-	-	-	-	-	-
Homozygous R202Q/M694V	-	-	1	1	1	-	-
Heterozygous V726A	-	2	2	-	-	1	-
Heterozygous P369S	1	-	1	-	-		-

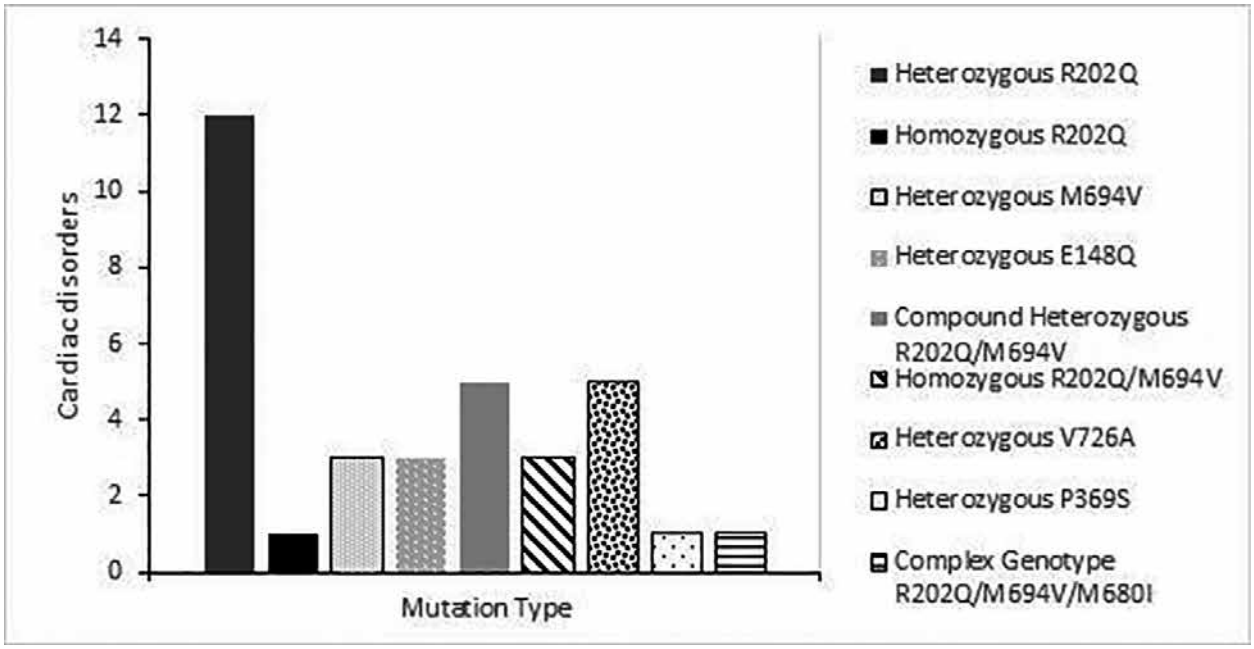

Fig 1: Cardiac disorders according to variant type

accumulation in the vascular walls, endocardium and stroma of the myocardium[10]. It was reported that cardiac amyloidosis can lead to heart failure and death in FMF even before renal failure and uremia. Heart failure can occur by amyloid deposits in heart valves and myocardium. Amyloid angiopathies and coronary vasculitis are important risk factors for myocardial infarction in cases with FMF[10]. According to our results, two cases had amyloidosis. One of them with M694V variant had tricuspid regurgitation.

Many studies showed higher incidence of pericarditis in FMF patients than the general population. The prevalence of pericarditis was 0.7-1.4% in some research studies[11,2]. It was reported that acute pericarditis, constrictive pericarditis and pericardial tamponade may even be the initial symptoms of FMF[12,13]. Turkish FMF study group reported that 60 (2.4%) FMF cases among 2468 had at least one episode of pericarditis during the course of their disease[2]. According to our results, seven cases (20.5%) (one case <18 years old and six cases ≥18 years old) had previous pericarditis history. The high rate of pericarditis in our study is due to inclusion of all cases with recurrent chest pain in the study. Also, two of these cases had small pericardial effusion and one case had pericardial thickness. All three of those case were adults. Therefore it may be said that when the age increased, the cases with FMF had increased risk for pericardial diseases. Thus, the cases with FMF, especially those with chest pain, should be routinely followed up for the cardiac problem.

In a research study, different degrees of tricuspid regurgitation were reported[14]. Also, in another study, it was shown that valves are affected in around half of the cases, rates vary as 21.8% for aortic valve, 16% for mitral valve, and 11% for the pulmonary valve[15]. In our study, one case (2.9%) had aortic regurgitation, which was grade I. Eight cases (23.5%) had mitral regurgitation; six of them had grade I and two of them had grade II. Thirteen cases (38.2%) had tricuspid regurgitation, which was grade I. One case (2.9%) had pulmonary regurgitation, which was grade I (Table 4). According to our findings, valvular disease affects over half of the cases.

FMF is an autosomal recessive autoinflammatory disease. Heterogeneous genetic basis is seen in this syndrome. More than 314 mutations and polymorphisms have been reported to date[16]. According to our results, 22 cases (64.7%) had R202Q carrier, 12 cases (35.3%) had M694V carrier, five cases (14.7%) had V726A carrier, three cases had (8.8%) E148Q carrier and one case (2.9%) had P369S carrier (Table 3). When the cardiac findings are taken into consideration with mutation type of cases, the number of the cardiac disorders are 19 in cases with R202Q carrier, 11 in cases with M694V carrier, five in cases with E148Q carrier, five in cases with V726A carrier and 1 in cases with P369S carrier (Table 5). So it may be said that cases with FMF variant (especially R202Q and M694V etc.) who had recurrent chest pain, have increasing risk for cardiac problems. Thus, these cases should be routinely followed up life long for cardiac problems.

CONCLUSION

We conclude that patients with FMF and recurrent

chest pain have increasing risk for cardiac problems. Therefore, those cases should be routinely followed up life long for cardiac problems.

ACKNOWLEDGMENT

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Duzce University Human Research Ethics Committee approved the study. Written informed consent was obtained from participants.

Conflict of interest : The authors declare that there is no conflict of interest.

Disclosure: The authors have no financial or competing interests in relation to this work.

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Original Article

Can we detect index tumor using transrectal ultrasound-guided prostate biopsy?

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ABSTRACT

Objective: To examine the rate of detecting index tumor using transrectal ultrasonography-guided prostate biopsy (TRUS Bx) in patients who underwent radical prostatectomy
Design: Retrospective study
Setting: Urology Clinic of Tepecik Health Research and Application Center (SUAM) of the University of Health Science
Subjects: The study included 418 patients who had TRUS Bx and were diagnosed with prostate cancer and underwent radical prostatectomy between 2007- 2014.
Intervention: Patients' data such as age, prostate volume before TRUS Bx, positive cores in TRUS Bx, the highest percentage of cancer in one core, index tumor volume in the specimen and D'Amico risk class were recorded, as well as the detectability of index tumor by TRUS Bx.
Main outcome measures: The rate of detecting index tumor with TRUS Bx was examined.
Results: Mean age of the included 418 patients was 63.25±6.10 years, prostate volume was 48.50±23.27 cc and preoperative prostate specific antigen value was 11.08±8.27. Index tumor was detected in 260 (62.2%) patients by biopsy but could not be detected in 158 (37.8%) patients.
Conclusion: It was thought that biopsy method could be used in detection of index tumor, especially in patients with low risk or large tumor volume.

KEY WORDS: index tumor, radical prostatectomy, transrectal ultrasonography-guided prostate biopsy

INTRODUCTION

Prostate cancer is the most common non-skin cancer in men over 70 years of age in Europe. It is considered to be one of the most important health problems affecting particularly elderly men in developed countries. The incidence is highest in North and West Europe (>200 in 100,000)[1].

The diagnosis of prostate cancer (PCa) is based on the clinical suspicion aroused in digital rectal examination and/or with the prostate-specific antigen (PSA) value, which is then confirmed by a prostate tissue analysis[2]. The diagnosis and treatment of localized PCa showed a significant improvement along with the widespread use of transrectal ultrasonography guided prostate biopsies (TRUS Bx) and serum PSA level measurements in clinical practice[3].

Cross-sectional analysis of PCa specimens remains to be the standard approach to characterize PCa. About 67-87% of the clinically localized PCa cases are heterogeneous and multifocal[4-6]. In multifocal cases, the index tumor (IT) is identified as the tumor with the highest Gleason score (GS), and in case of having more than one tumor with the same GS, it is the tumor with the largest volume. It is remarked that IT has an important place in the prognosis of the disease, so that exact detection of IT can influence treatment decision[7].

The aim of this study was to examine the rate of detecting index tumor using TRUS Bx in patients who underwent radical prostatectomy (RP).

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SUBJECTS AND METHODS

Ethics Committee approval

Patient data were retrospectively analyzed from the patient files, pathology reports, follow-up files and the operating system of the hospital for the patients who underwent RP in the Urology Clinic of Tepecik Health Research and Application Center of the University of Health Science. The study was approved by the institutional review board of Health Sciences University Tepecik Education and Research Hospital. Patients who underwent TRUS Bx and were diagnosed with prostate adenocarcinoma and then treated with RP duly, with a pathological confirmation for prostate adenocarcinoma, were included in the study. Patients who refused to undergo RP, or whose RP biopsy result yielded no prostate adenocarcinoma, or who were treated with neoadjuvant chemotherapy, and those with missing data were excluded from the study.

A total of 418 patients who underwent RP in our hospital between 2007 and 2014 and met these criteria were included in our study.

A detailed physical examination, digital rectal examination and PSA measurement were performed for each patient before the operation, and those with elevated PSA level or abnormal digital rectal examination findings underwent TRUS Bx.

Patients' data such as age, prostate volume before TRUS Bx, positive cores in TRUS Bx, the highest percentage of cancer in one core, IT volume in the specimen and D'Amico risk class were recorded, as well as the detectability of IT by TRUS Bx.

IT was accepted as the tumor present in the extracapsular area, giving priority to location and irrespective of its extent in the RP specimen; but if not present there, IT was accepted to be the tumor with the highest GS. However, in case of presence of more than one tumor with the same GS, it is accepted as the tumor with the largest volume among them.

Statistical method

SPSS 22.0 (IBM Corparation, Armonk, New York, United States) program was used to analyze the variables. Shapiro-Wilk test was used to evaluate the concordance of the data to normal distribution. The Mann-Whitney U test was used in conjunction with Monte Carlo test results in comparing two independent groups in terms of quantitative data. In these comparisons, the Pearson Chi-Square results test was assessed with the Monte Carlo simulation technique. Quantitative variables were shown as mean±SD (standard deviation) and median range (maximum-minimum), and categorical variables as n (%). Variables were examined at 95% confidence level and $P<.05$ was accepted as significant.

Table 1: Demographic data of the patients

Demographic data	N	Average±SD	Median (max/min)
Age	418	63.25±6.10	64 (78/46)
Prostate volume	418	48.50±23.27	43 (250/21)
Preoperative PSA	418	11.08±8.27	8 (69/3)
TRUS Bx core number	418	12.13±2.54	12 (24/4)
TRUS Bx positive core number	418	4.22±2.80	4 (14/1)
TRUS Bx highest cancer percentage of positive cores	418	50.11±28.16	50 (100/5)
IT volume (cc)	418	1.61±1.05	1.3 (6.2/0.2)

PSA: prostate specific antigen; TRUS Bx: transrectal ultrasonography-guided prostate biopsy; IT: index tumor

RESULTS

Mean age of the 418 patients included in the study was determined as 63.25±6.10 years, prostate volume as 48.50±23.27 cc and preoperative PSA value as 11.08±8.27 ng/mL. Mean number of biopsy cores obtained in TRUS-Bx was 12.13±2.54 cores, mean number of positive cores was 4.22±2.80 cores and mean highest percentage of cancer was 50.11±28.16%. Mean volume of IT detected in RP specimen was 1.61±1.05 cc (Table 1).

Table 2: Index tumor detection rates according to D'amico risk grouping

D'Amico risk classification	IT in TRUS Bx		*P*-value
	Positive (%)	Negative (%)	
Low	64 (37.2%)	108 (62.8%)	.995
Moderate	63 (38.2%)	102 (61.8%)	
High	31(38.3%)	50 (61.7%)	
Total	158 (37.8%)	260 (62.2%)	

TRUS Bx: transrectal ultrasonography-guided prostate biopsy; IT: index tumor

As we have a look at IT detection rate by TRUS Bx, we see that IT was detected in 260 cases (62.2%) while it was not found in 158 cases (37.8%). When we classify the patients according to D'amico risk group, IT was detected in 108 (62.8%) of the 172 low-risk patients, 102 (61.8%) of the 165 moderate-risk patients and 50 (61.7%) of the 81 high-risk patients (Table 2). Regarding the association between IT detection and IT volume,

Table 3: Index tumor detection rates according to index tumor volume

IT in TRUS Bx	IT volume (cc) Median (max/min)*	*P*-value
Negative (n=158)	0.9 (2.9/0.2)	<.001
Positive (n=260)	1.7 (6.2/0.3)	

*Mann Whitney U test (Monte Carlo)
TRUS Bx: transrectal ultrasonography-guided prostate biopsy; IT: index tumor

the mean tumor volume was 1.7 cc in detected cases whereas 0.9 cc in non-detected cases (P<.001) (Table 3).

DISCUSSION

It is pointed out in previous studies that PCa is a heterogeneous and multifocal disease[8]. Detection of IT in multifocal cases provides us with significant information regarding the progression of the disease and treatment decision[7].

Magnetic resonance imaging (MRI)-targeted biopsies are one of the new methods becoming available in recent years to increase the detection rate of PCa and they are applied clinically in three ways: MRI based cognitive fusion biopsy (the lesion is detected by MP-MRI then correlated with TRUS to obtain biopsy), direct MRI-guided biopsy and MRI TRUS fusion biopsy[9].

In a meta-analysis evaluating the results of direct MRI-guided biopsies and standard biopsies, no difference was determined between MRI-targeted biopsies and TRUS Bx in PCa detection. In detection of low-risk PCa however, higher rates of PCa was detected with TRUS Bx with respect to MRI-targeted biopsies[10].

In a study by Siddiqui *et al* in 2013, MRI TRUS fusion biopsy was compared with standard 12-core TRUS biopsy on 582 patients. The rate of cancer detection was 43.8% with standard biopsy and 43.5% with MRI TRUS fusion biopsy[11]. Kuru *et al* examined 347 patients and reported cancer detection rate as 50.4% with TRUS Bx and 50.6% with MRI TRUS fusion biopsy[12]. In the literature review, MRI-targeted biopsies were found to be successful in detecting moderate- and high-risk PCa, especially with less number of cores, while TRUS Bx was successful in detecting low-risk cancers.

In the literature, the rate of patients whose biopsy GS <7 changed to GS ≥7 after RP was between 20% and 36%. In the study by Lattouf *et al*, GS ≥7 was determined in the prostate specimens among 24.1% of 311 patients with biopsy GS <7[13]. In a similar study, Fine *et al* reported that 23.1% of 1057 patients with biopsy GS <7 had prostate specimen GS ≥7[14]. In another study evaluating the Johns Hopkins series, this ratio was shown to be 36%[15]. In our study however, the rate of determining IT in low-risk patients was 62.8% and the results were consistent with the literature. TRUS Bx was considered safe in low-risk patients and the patients under active follow-up.

In a study by Baco *et al*, IT detection rate was 95% with MRI fusion biopsy. In the evaluation of the patients whose IT could not be detected, tumor volume in RP specimen was found to be <0.4 cc[16]. In another study, the rate of IT detection with MRI fusion biopsy was found to be 92%. In this study, the rate of MRI detection for all tumors was determined as 70%, but this value was calculated to be 86% when the tumors smaller than 0.5 cc were excluded[17]. In our study, we found the IT detection rate of TRUS Bx as 62.2%. There was no significant difference between the groups when we classified patients according to risk groups. As for the relation between IT detection rate and the detected IT volume, the mean tumor volume was 1.7 cc in IT detected patients and 0.9 cc in IT non-detected patients. Although TRUS Bx was not as efficient as MRI in IT detection, it was concluded to be a convenient method to be used in cases with larger tumor volume. It was concluded that TRUS Bx can be performed safely and effectively in patients with a high IT detection rate.

Retrospective design of the study can be seen as a limitation of the study. In addition, TRUS Bx was performed by different physicians, which may be another parameter that can possibly affect the results. Specimens obtained by biopsy and at operation were examined by different pathologists, which is another drawback that may eventually affect the results.

CONCLUSION

In conclusion, TRUS Bx was acknowledged as a method that can be used in the detection of IT, especially in low risk patients or when the tumor volume is high.

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Conflicts of Interest: The authors declare that they have no competing interest.

Authors' contributions: Mustafa Karabicak and Hakan Turk contributed with the conception and design of the study and drafted the manuscript; Mustafa Karabicak and Batuhan Ergani collected data; and Zafer Kozacioglu, Gokhan Koc and Yusuf Ozlem Ilbey have contributed on the critical revision of this manuscript. All authors read and approved the final manuscript.

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Original Article

Effect of BMI on outcome in peritoneal dialysis patients: a single Saudi center review

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ABSTRACT

Objective: To evaluate the effect of obesity on peritoneal dialysis (PD) including technique survival, incidence of complications and mortality
Design: Retrospective cohort analysis
Settings: Nephrology unit at King Saud University in Riyadh, Saudi Arabia between January 1st, 2005 and December 31st, 2014
Subjects: Ninety-eight patients treated in the PD unit. Out of these, 36 had healthy weight and 28 were overweight, while 34 patients were obese.
Intervention: As a retrospective study, no intervention in patient medication or dialysis was performed.
Main outcome measure: The main outcome measure was patient mortality or cessation of PD (transplant or transfer to hemodialysis (HD)). Other measures included infection and complications.
Results: The mean age was 52.14 years (range: 16-77 years) for obese patients compared with 49.83 years (range: 16-84 years) in overweight and 47.53 years (range: 19-86 years) in normal weight patients. Peritonitis rate was 0.38 per patient years in normal weight, 0.22 in overweight and 0.35 in obese patients. The mortality rate was 0.09 per patient years in normal, 0.07 in overweight and 0.06 in obese patients. Six (15%) patients in the normal weight group shifted to HD, compared to 7 (25%) overweight and 14 (32.5%) obese patients (*P*=.045). Six (15%) patients in normal weight group underwent renal transplant, compared to 2 (7.1%) overweight and 4 (9.3%) obese patients (*P*=.020).
Conclusion: Our results revealed no significant differences in terms of infections, complications and patient mortality. However, obese patients had higher transfer to HD and lower renal transplant.

KEY WORDS: dialysis, end stage renal disease, obesity

INTRODUCTION

Peritoneal dialysis (PD) as a mode of renal replacement therapy has witnessed a rapid evolution in the last decade[1]. However, in most countries, only a small percentage of end stage renal disease (ESRD) patients are using PD[2] compared to hemodialysis (HD), even as the outcomes for PD patients continue to improve and are comparable to HD[3,4]. Obesity has been recognized as a worldwide problem affecting all populations, including ESRD patients. Studies have shown that obesity, as measured by an increasing body mass index (BMI), is linked to a number of adverse metabolic effects, as well as increasing the risk of coronary heart disease, ischemic stroke and type 2 diabetes mellitus in the general population[5-7]. It has also been postulated to have an effect on kidneys, leading to chronic kidney disease, either directly or through the increased presence of hypertension and diabetes in people with a higher BMI[8,9].

Obesity and dialysis patients

A number of studies of patients undergoing HD have demonstrated that increasing BMI is correlated with decreased mortality risk[10-12]. However, similar studies have shown varied and often opposing results among patients treated with PD[13-16]. The population of ESRD patients in Saudi Arabia has enlarged exponentially in the preceding decades, largely due to rise in the incidence of diabetes mellitus and metabolic syndrome[17,18]. PD has been used increasingly in the

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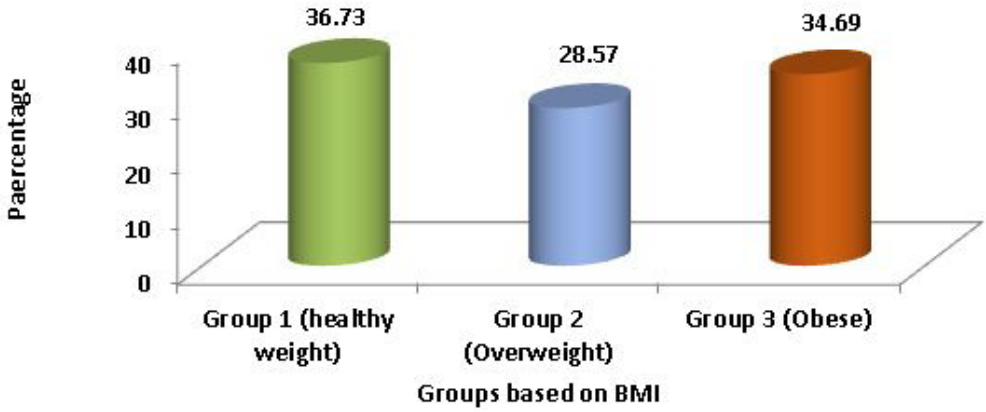

Fig 1: Distribution of groups

Middle East as an effective renal replacement therapy with good results[19]. In Saudi Arabia, PD was started in King Saud University and has shown to have outcomes and complications comparable to international guidelines[20]. However, the number of patients on PD is still a small fraction of the ESRD population, as shown by Saudi Center for Organ Transplant reports[21]. There have been very few studies on the effect of obesity in HD patients from Middle East[9] and almost none relating to PD patients.

SUBJECTS AND METHODS

This study was conducted on behalf of the Nephrology unit at King Saud University in Riyadh, Saudi Arabia with full support and no objection from the unit or the Department of Medicine.

This is a single center, retrospective cohort analysis comparing groups of patients on the basis of BMI. A total of 98 patients treated in the PD unit between January 1st, 2005 and December 31st, 2014 were included in the study. All patients had used regular PD for at least six months. All patients who were less than 16 years of age, had significant growth retardation due to renal or other metabolic disease, or had discontinued PD before completing the initial six months of dialysis were excluded from the study.

The BMI was calculated at the start of PD therapy. Body weight was assessed without PD fluid in the

Table 1: Patient demographics in different BMI group

Demographics	Group 1 Healthy weight	Group 2 Overweight	Group 3 Obese
No. of patients	36	28	34
Male to female ratio (M:F)	20:16	13:15	14:20
Age (years)	47.53 (19-86)	49.83 (16–84)	52.14 (16-77)
Time on PD (patient years)	103.78	100.14	122.97
Mode of dialysis			
CAPD	20	7	6
APD	16	21	28
Primary Renal Disease (%)			
Diabetes mellitus	11 (30.56%)	15 (53.57%)	11 (32.35%)
Glomerulonephritis	10 (27.78%)	5 (17.86 %)	8 (23.53%)
Hypertension	9 (25 %)	4 (14.28%)	8 (23.53%)
Nephrolithiasis	0	0	4 (11.76%)
Solitary kidney	1 (2.78%)	1 (3.57%)	0
Sickle cell disease	2 (5.56%)	0	0
APCKD	0	0	1 (2.94%)
Chronic pyelonephritis	0	1(3.57%)	1 (2.94%)
Reflux nephropathy	0	1(3.57%)	0
Multiple myeloma	1 (2.78%)	0	0
Unknown	2 (5.56%)	1(3.57%)	1 (2.94%)
Mean BMI (kg/m^2)	22.16	27	33.2
Mean albumin (g/L)	29.3	30.61	30.27
Mean Kt/V	2.23	2.34	1.98

PD: peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; APD: automated peritoneal dialysis; APCKD: adult polycystic kidney disease; BMI: body mass index; Kt/V: weekly urea clearance

Table 2: Frequency of patients' complications and outcomes in different BMI groups

Variables	Healthy weight	Overweight	Obese	*P*
Pertonitis (no. of episodes)	40	28	43	.76
ESI (no. of episodes)	18	11	16	.417
Catheter migration (no. of episodes)	7	7	2	.496
Catheter leak (no. of episodes)	1	1	1	.991
Catheter replacement (no. of episodes)	4	2	5	.341
Deaths (no of patients died)	9	7	8	.822
Outcome- renal transplant	6 (15%)	2 (7.1%)	4 (9.3%)	.020
Outcome- shifted to HD	6 (15%)	7 (25%)	14 (32.5%)	.045

ESI: exit site infections; HD: hemodialysis

abdominal cavity. Patients were divided into three groups (Fig 1) on the basis of BMI (calculated as weight in kilograms divided by the square of height in meters (kg/m^2)) and categorized according to the World Health Organization classification[20] as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (>30.0 kg/m^2).

The patients were followed up at regular appointments in the PD clinic. Any episode of peritonitis or exit site infection (ESI) was managed according to International Society for Peritoneal Dialysis guidelines and recommendations. Different variables were compared between the groups including time on PD, episodes of peritonitis, ESI and PD catheter related complications. In this study, the primary patient outcome was death and the secondary outcomes included transfer to HD, renal transplant, peritonitis, ESI and catheter complication. Twenty-five patients were continuing PD till end of study period. The mortality and infection rates were calculated in accordance with the international recommendations by calculating the total time on dialysis as patient months.

RESULTS

The mean age of obese patients was higher (52.14 years; range: 16-77 years) compared with overweight (49.83 years, range: 16-84years) and normal weight patients (47.53 years, range: 19-86 years).

The frequency of diabetes mellitus as primary renal disease was higher (53.57%) in overweight patients compared with other groups. On the other hand, hypertension was more frequent in normal weight patients (25%) compared with other groups. The patient demographics are summarized in Table 1.

Table 2 shows the results of the complications and outcomes among patients in different groups. The results revealed that there was no significant difference between different groups on the basis of peritonitis rates (calculated according to International Society for Peritoneal Dialysis guidelines) as the overall peritonitis rate was 0.38 episodes per patient years in normal weight patients, 0.22 per patient years among overweight patients and 0.35 per patient years among obese patients. For ESI, the overall rate was 0.17 episodes per patient years in normal weight patients, 0.11 per patient years among overweight patients and 0.13 per patient years among obese patients.

The results also showed that there was no significant different between groups in ESI rates. The ESI rate was 0.17 episodes per patient years among normal weight patients, 0.11 per patient years among overweight patients and 0.13 per patient years among obese patients (Table 2).

DISCUSSION

Obesity is recognized as an increasingly common health issue worldwide, and it affects morbidity and mortality in all age groups[6]. Furthermore, in ESRD patients, presence of uremia and uremic complications including fluid retention, protein-energy wasting, inflammation and oxidative stress further contribute to a metabolic syndrome-like picture in these patients[8,14]. Especially susceptible are the PD patients exposed to glucose-based PD fluids, which further enhance the risk of developing metabolic complications[8]. A number of studies of patients undergoing hemodialysis have demonstrated that increasing BMI is correlated with decreased mortality risk[10-12]. Obesity was previously considered a relative contraindication to PD due to increased risk of metabolic and mechanical complications (including catheter migration, hernia), hypertriglyceridemia, poor solute clearance and infections. However, PD has increasingly been used in patients with a higher BMI in current years[14].

The current study focuses on the local Arab population in Saudi Arabia, which has seen an exponential increase in patients with ESRD during the preceding decades, attributed largely to increasing incidence of diabetes mellitus and metabolic syndrome[18,19].

In PD patients, studies based on BMI have not shown a clear relation between BMI and patient outcome and survival, unlike HD population. We compared our results to a 2014 study in India by Prasad *et al*[15] including 328 incident patients on PD. Their results showed that death-censored technique survival

was statistically similar in all BMI categories. In comparison with the reference category, peritonitis occurrence was 1.8 (95%CI: 0.9-3.4; *P*=.086) for underweight patients; 1.7 (95%CI: 0.9-3.2; *P*=.091) for overweight patients and 3.4 (95%CI: 1.8-6.4; *P* <.001) for obese patients. We did not find any statistically significant difference in peritonitis and ESI between patient groups, but as seen in the aforementioned study, our analysis did not reveal any significant difference in patient mortality. Additionally, the results from our study are somewhat similar to a 2009 study in the Netherlands by de Mutsert *et al*[14] which included 688 patients with ESRD starting with PD. The researchers concluded that PD patients who are obese at the start of dialysis do not have a worse survival compared with PD patients with a normal BMI. However, PD patients with a low BMI during dialysis have a twofold increased mortality risk. Our study did not include patients with a low BMI, as very few of our patients had a BMI less than 18.5.

On the other hand, other authors have found worse outcomes in obese patients using PD[16]. A 2003 study by McDonald *et al* studied 9679 new adult patients using data from the Australia and New Zealand Dialysis and Transplant Registry between April 1, 1991 and March 31, 2002. They found that obesity was independently associated with death during PD treatment (*P* <.05) and technique failure (*P* <.01).

The results of our study showed no statistically significant differences between the three groups in terms of mortality and infection rates (Table 2). Diabetes mellitus was the most common primary disease in the overweight group (53%), whereas about one-third of the obese and normal weight patients were diabetic. Adequacy studies showed a slightly higher Kt/V in normal and overweight patients compared to obese patients, but that can be due to higher body surface as well as differences in the residual renal function. Still, the average adequacy rates were above 1.7 in all groups.

Obesity is often considered to be a risk factor for catheter related complications including migration of catheter. However, there were no statistically significant differences found among the groups, with obese patients having the lowest number of episodes of catheter migration.

The patients in the obese category had a higher likelihood of PD technique failure and transfer to HD as compared to the other two groups (*P* = .02) and fewer renal transplants (*P* = .045). This can be due to relatively older age and presence of comorbidities.

CONCLUSION

We can conclude that obesity should not be treated as a contraindication to PD therapy and such patients can be started on PD, provided that no absolute contraindications are present. Moreover, the chances of developing infectious as well as catheter related complications are similar to patients with a lower BMI.

However, the results cannot be considered absolute as this was a retrospective study with a small number of patients in a single center. Larger multicenter trials are needed to fully understand the effect of obesity and increased BMI in ESRD patients, especially the PD population where weight control is considerably difficult because of universal use of glucose based fluids.

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Original Article

Is Gleason score in transrectal ultrasound guided prostate biopsy consistent with Gleason score in radical prostatectomy?

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ABSTRACT

Objective: To search for the consistency of Gleason scores (GS) between patients with radical prostatectomy (RP) and with transrectal ultrasonography-guided prostate biopsy (TRUS-Bx)
Design: Retrospective study
Setting: Urology Clinic of Tepecik Health Research and Application Center of the University of Health Science
Subjects: A total of 418 patients diagnosed with prostate cancer following TRUS-Bx and who underwent subsequent RP between 2007 and 2014 were included in the study.
Intervention: All patients' ages, prostate specific antigen values before TRUS-Bx, prostate volumes, biopsy GS, number of positive cores in TRUS-Bx, highest percentage of cancer in a biopsy core, RP specimen GS and risk class by D'Amico risk classification were recorded.
Main outcome measures: The compatibility of GS was investigated using prostatectomy and biopsy specimens.
Results: GS of biopsy and RP specimens were compatible in 282 (67.5%) patients but incompatible in 136 (32.5%) patients. Of the 136 patients having discordant values of GS, higher GS were determined in 97 (23.2%) whereas lower GS were detected in 39 (9.3%) patients at the end of RP. The sensitivity rates for having low, moderate and high risk after TRUS-Bx were 93.7%, 72.3% and 74.1%, respectively, which was statistically significant in the low risk group (P <.001)
Conclusion: In two-thirds of patients, biopsy GS was consistent with RP specimen GS.

KEY WORDS: Gleason score, radical prostatectomy, transrectal ultrasonography guided prostate biopsy

INTRODUCTION

Prostate cancer (PCa) is the most common non-skin cancer in men over 70 years of age in Europe, with the highest incidence in North and West Europe (>200 in 100,000)[1]. Patient's age, co-morbidities, expectations, tumor prevalence in prostate biopsy material and Gleason score (GS) play important roles in determining treatment method in PCa[2,3].

Gleason grading system is the most commonly used method in PCa grading. GS obtained from radical prostatectomy (RP) material was proven to be reliable for the prognosis of the disease. The biopsy GS obtained from transrectal ultrasonography-guided prostate biopsies (TRUS-Bx) however, is an important data in the evaluation of treatment options. Nevertheless, studies revealed GS differences between TRUS-Bx specimens and RP specimens. This leads to delays in the curative treatment in some patients, while some may receive additional treatment as a result of incompatible evaluation of GS[4,5].

In this study, we investigated the reliability of TRUS-Bx in the diagnosis of PCa. For this purpose, we compared the concordance between GS determined in patients with RP and with TRUS-Bx.

MATERIALS AND METHODS

Patient data were retrospectively analyzed from the patient files, pathology reports, follow-up files and

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the operating system of the hospital for the patients who underwent RP in the Urology Clinic of Tepecik Health Research and Application Center of the University of Health Science. The study was approved by the Institutional Review Board of Health Sciences University Tepecik Education and Research Hospital. Patients included in the study were the ones having abnormalities in digital rectal examination and/or elevated prostate specific antigen level, underwent TRUS-Bx and diagnosed with prostate adenocarcinoma and then duly treated with RP, with a pathological confirmation for prostate adenocarcinoma. Patients who underwent TRUS-Bx but did not accept RP, who received neoadjuvant chemotherapy and those with missing data were excluded from the study.

Table 1: Demographic data of patients

Demographic data	N	Average ± SD	Median (max / min)
Age	418	63.25±6.10	64 (78/46)
Prostate volume	418	48.50±23.27	43 (250/21)
Preoperative PSA	418	11.08±8.27	8 (69/3)
TRUS-Bx core number	418	12.13±2.54	12 (24/4)
TRUS-Bx positive core number	418	4.22±2.80	4 (14/1)
TRUS-Bx highest cancer percentage of positive cores	418	50.11±28.16	50 (100/5)

SD: standard deviation; PSA: prostate specific antigen; TRUS-Bx: transrectal ultrasonography-guided prostate biopsy

In the end, 418 patients who underwent RP in our hospital between 2007 and 2014 and meeting these criteria were included in our study.

All patients' ages, prostate specific antigen values before TRUS-Bx, prostate volumes, biopsy GS, number of positive cores in TRUS-Bx, highest percentage of cancer in a biopsy core, RP specimen GS and risk class by D'Amico risk classification were recorded. We compared the concordance of GS results between TRUS-Bx and RP specimens.

Statistical method

SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. Shapiro-Wilk test was used to assess if data were compatible with a normal distribution. Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups with respect to quantitative results. Cohen's Kappa Test was used for the compatibility and consistency of categorical variables. Quantitative variables were shown in tables as mean ± standard deviation and median range (maximum-minimum) while categorical variables were shown as n(%). Variables were examined at 95% confidence level and P <.05 was accepted as significant.

Table 2: TRUS-Bx GS and RP GS distribution of the patients

Gleason score	Number	Percentage
TRUS-Bx GS		
6	244	58.4
7a	80	19.1
7b	56	13.4
8	31	7.4
9	6	1.4
10	1	0.2
RP GS		
6	199	47.6
7a	110	26.3
7b	57	13.6
8	24	5.7
9	26	6.2
10	2	0.5

TRUS-Bx: transrectal ultrasonography-guided prostate biopsy; RP: radical prostatectomy; GS: Gleason score

RESULTS

Demographic data of patients and TRUS-Bx core information are shown in Table 1. TRUS-Bx GS distribution, RP GS distribution, overall GS concordance of the patients and their distribution by the risk groups according to the results of TRUS-Bx and RP are presented in Tables 2 and 3.

In this study including 418 cases, GS was concordant in TRUS-Bx and RP specimens in 282 (67.5%) patients while discordant in 136 (32.5%) patients. TRUS-Bx GS sensitivities are shown in Table 4. Of the 136 patients having discordant values of GS, higher GS were determined in 97 (23.2%) whereas lower GS in 39 (9.3%) patients at the end of RP (Table 4).

The concordance of TRUS-Bx GS and RP GS among low, intermediate and high-risk are shown in Table 5.

As for the relation between GS concordance and the number of positive cores in TRUS-Bx, there was GS concordance for positive cores ≤3 in number and there

Table 3: Gleason score concordance rates

Concordance rate	Number	Percentage
Gleason score concordance	136	32.5
Discordant	282	67.5
Concordant		
D'Amico risk classification for TRUS-Bx		
Low	172	41.1
Moderate	165	39.5
High	81	19.4
RP risk groups		
Low	142	34.0
Moderate	195	46.7
High	81	19.4
Concordance status according to risk		
Discordant	84	20.1
Concordant	334	79.9

TRUS-Bx: transrectal ultrasonography-guided prostate biopsy; RP: radical prostatectomy

Table 4: Consistency of TRUS-Bx GS and RP GS

TRUS-Bx GS	RP GS						Total	*P*-value
	≤6 n (%)	7a n (%)	7b n (%)	8 n (%)	9 n (%)	10 n (%)		
≤6	184 (92.5)	37 (33.6)	16 (28.1)	5 (20.8)	2 (7.7)	0 (0)	244	<.001
7a	8 (4.0)	59 (53.6)	6 (10.5)	4 (16.7)	3 (11.5)	0 (0)	80	
7b	6 (3.0)	9 (8.2)	26 (45.6)	6 (25.0)	9 (34.6)	0 (0)	56	
8	1 (0.5)	5 (4.5)	9 (15.8)	8 (33.3)	8 (30.8)	0 (0)	31	
9	0 (0)	0 (0)	0 (0)	1 (4.2)	4 (15.4)	1 (50.0)	6	
10	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.0)	1	
Total	199 (100)	110 (100)	57 (100)	24 (100)	26 (100)	2 (100)	418	concordant= 67.5%

TRUS-Bx: transrectal ultrasonography-guided prostate biopsy; RP: radical prostatectomy; GS: Gleason score

was GS discrepancy for positive cores ≥4 (*P* <.001). With respect to the relation between GS concordance and the highest percentage of positive cores in TRUS-Bx, higher concordance rate was determined for cases with ≤40% whereas lower rates were seen for cases with ≥60% (*P* <.001) (Table 6).

DISCUSSION

Today, Gleason grading is the most commonly used method for PCa grading[6,7]. The GS of RP specimens was proved to be a reliable indicator of survival[7,8]. The accuracy of GS of the specimens obtained with TRUS-Bx is particularly important because GS in patients with PCa is an important factor in determining the prognosis and evaluating treatment options[9-12]. However, some authors argued that there may be differences between the GS of the specimens taken with TRUS-Bx and taken after RP[13-15]. These differences were thought to originate from the heterogeneity and multicentric character of PCa. In the literature, concordance between TRUS-Bx GS and RP GS varied between 28% and 68%[16].

In our study, GS showed a concordance of 67.5% in TRUS-Bx specimens of the patients who underwent RP and their RP specimens, which was consistent with the literature. In their series of 1363 cases, Rajinikanth *et al* found GS was 59% compatible in TRUS-Bx and RP specimens, where grading in TRUS-Bx specimens was low in 32% whereas high in 9% of the patients[17]. In a meta-analysis involving 14,839 patients, the concordance between TRUS-Bx and RP GS was found to be 63%. In TRUS-Bx specimens, 30% of patients had a low grading while 7% had a high grading[18].

In our study however, TRUS-Bx GS and RP GS were found to be compatible in 67.5% of the patients. In TRUS-Bx specimens, 23.2% of the patients had a low grading while 9.3% had a high grading.

In a study conducted with more than 1000 patients in 2006, RP and TRUS-Bx GS were compared and the concordance rate was found to be 81% for GS <7, 68% for GS=7 and 70% for GS=8-10[19] . In our study however, TRUS-Bx sensitivities for GS ≤6, 7a, 7b, 8, 9 and 10 were 92.5%, 53.6%, 45.6%, 33.3%, 15.4% and 50%, respectively. GS 6 sensitivity is higher than other GS. The number of patients included in the study is low. Therefore, the results may not show the actual population.

In a meta-analysis, patients were classified as having low, moderate and high risk in PCa and compared for GS. In that study, the sensitivity of TRUS-Bx was found to be 90%, 40% and 33% for patients having low, moderate and high risk respectively[18]. In our study, the sensitivity of TRUS-Bx was found to be 93.7%, 72.3% and 74.1% in low-, moderate- and high-risk patients respectively. In a study, those patients who identified as low-risk group on TRUS-Bx GS were shown to be actually moderate-risk group in 20.3% and high-risk group in 2.5% of the

Table 5: Comparison of TRUS-Bx GS and RP GS according to the D'Amico risk group

TRUS-Bx	RP			Total n (%)	*P*-value
	Low n (%)	Moderate n (%)	High n (%)		
Low	133 (93.7)	35 (17.9)	4 (4.9)	172	<.001
Moderate	7 (4.9)	141 (72.3)	17 (21.0)	165	
High	2 (1.4)	19 (9.7)	60 (74.1)	81	Concordant
Total	142 (100)	195 (100)	81 (100)	418	= 79.9%

TRUS-Bx: transrectal ultrasonography-guided prostate biopsy; RP: radical prostatectomy; GS: Gleason score

Table 6: Relation of GS concordance with the number of positive cores and the highest percentage of positive cores

TRUS-Bx	GS concordance rates		*P*-value
	Discordant* (n=136)	Concordant* (n=282)	
TRUS-Bx positive core number	4 (14 / 1)	3 (13 / 1)	.001
TRUS-Bx highest cancer percentage of positive cores	60 (100 / 5)	40 (100 / 5)	.001
TRUS-Bx core number	12 (24 / 4)	12 (24 / 8)	.778

Mann Whitney U test (Monte Carlo); * Median (max/ min)
TRUS-Bx: transrectal ultrasonography-guided prostate biopsy; GS: Gleason score

patients[20]. In our study, the patients graded as low-risk on TRUS-Bx were upgraded to moderate-risk in 20.3% and high-risk in 2.4% after RP.

Over-grading the patients on TRUS-Bx may lead to the implementation of unnecessary or redundant treatments in some patients. On the other side, under-grading is more common in biopsies, which may cause patients to miss the opportunity of a curative treatment such as RP. However, it is known that other active treatments such as external radiotherapy and brachytherapy are increasingly preferred by the patients in recent years, which are of choice in localized PCa treatment[17]. Since a real GS cannot be obtained with these treatments as it is obtained on RP, it is a matter of fact that GS on biopsy is one of the most important and valuable criteria for deciding these treatments. Active follow-up is a preferred approach in patients with low-risk PCa. The identification of patients with low-risk PCa to be followed up actively is also based on biopsy GS. In our study, 20.3% of the patients identified as low-risk on TRUS-Bx were determined to have moderate-risk and 2.4% high-risk due to RP GS. Hence, it should be kept in mind that some of the low-risk PCa patients who are actually moderate- and high-risk may be treated inadequately due to agreed active follow-up in their initial treatment.

In a study, tumor involvement ≥10% in each core or tumor involvement in more than one core in TRUS-Bx was associated with GS discordance[21]. In our study, GS discordance increased in cases with tumor involvement ≥60% in each core and with ≥4 positive cores.

There are many reasons of under-grading on TRUS-Bx specimens. The first of these is the nonconformity between pathologists as well as inexperienced pathologists with inadequate expertise on this subject. One of the ways to improve conformity is to provide an uropathologist for specimen assessment, if possible, and request for consultation from experienced centers in dubious cases[22]. In our study, biopsy specimens and RP specimens were evaluated by different pathologists. Another reason is that PCa is a heterogeneous and multifocal disease where the biopsy specimen cannot represent the entire prostate[23].

Over-grading TRUS-Bx specimens is rare. In our study, approximately 25% of the high-risk patients on TRUS-Bx GS were changed to moderate- and low-risk on RP GS. Tertiary Gleason pattern is another reason to obtain under-graded or over-graded TRUS-Bx GS[24]. In our study, we did not evaluate tertiary Gleason pattern results.

Retrospective design can be a limitation of the study. Also, handling of TRUS-Bx by different physicians and examination of biopsy and operative specimens by different pathologists are possible reasons that may affect the results. Finally, this study focused on the GS and D'Amico risk stratification after TRUS-Bx and RP, and the patients were not evaluated with regard to their treatment regimen and prognosis.

CONCLUSION

In conclusion, the Gleason scoring system is an important parameter in determining the treatment and prognosis in PCa. In the end, TRUS-Bx GS and RP GS were found to be concordant in two-thirds of patients. Nevertheless, efforts to improve the concordance between TRUS-Bx and RP specimens will have positive contributions on the treatment and follow-up of the disease.

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Conflicts of Interest: The authors declare that they have no competing interest.

Authors' contributions: Mustafa Karabicak and Hakan Turk contributed with the conception and design of the study and drafted the manuscript; Mustafa Karabicak and Batuhan Ergani collected data; Zafer Kozacioglu, Gokhan Koc and Yusuf Ozlem Ilbey have contributed on the critical revision of this manuscript. All authors read and approved the final manuscript.

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Original Article

Comparison of equal doses of bupivacaine and levobupivacaine in terms of efficiency in lateral approach to popliteal sciatic nerve blocks: a randomized controlled trial

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ABSTRACT

Objective: We aimed to compare equal doses of bupivacaine and levobupivacaine in terms of efficiency, block quality and side effects on lateral approach to popliteal block in patients who would undergo foot/ankle surgery.
Design: Prospective study
Setting: Goztepe Training and Research Hospital
Subjects: Thirty patients who were planned for foot/ankle surgery
Intervention: After the block was performed, mean blood pressure, heart rate and peripheral oxygen saturation values were recorded at the 1st,15th, 30th and 45th minute and at the end of the operation. Sensory block formation time was tested with pin-prick test in five minute intervals after completion of block. Time to motor and sensory block durations and time for the first analgesic utilization were recorded.
Main outcome measure: Time to complete sensory blockade/ time to complete block duration and administration time of the first analgesic of patients
Results: There were no differences in mean time to complete sensory blockade/time to complete block duration and first analgesic administration times of patients. Total fentanyl doses used in Group L and Group B were 40±38.73 μg and 43.33±37.16 μg, respectively. Sensory block quality formed in dermatome area of sciatic nerve was similar in both groups. Group B was found to be superior in both plantar flexion and dorsal flexion evaluations.
Conclusion: It was concluded that adequate, qualified and safe block could be achieved with bupivacaine and levobupivacaine in lateral popliteal blocks. These two drugs provided pain control after the operation and they had no significant difference with regard to side effects.

KEY WORDS: block, bupivacaine, levobupivacaine, nerve

INTRODUCTION

Foot and ankle operations cause severe and prolonged postoperative pain and they require high doses of parenteral opioid frequently. Sciatic nerve block with popliteal approach is an effective method in providing efficient anesthesia and analgesia in foot and ankle surgeries[1-5].

For sciatic nerve block, anterior and lateral approaches have been proposed with the goal of avoiding positioning problems that are common in obese, pregnant or trauma patients[2]. Distal sciatic nerve block (popliteal fossa block) is a relatively simple technique that results in reliable surgical anesthesia of the calf, tibia, fibula, ankle and foot[5]. The sciatic nerve is blocked near the bifurcation of the common peroneal and posterior tibial nerves[6]. The advantage of the lateral approach to popliteal block is that the patient does not need to be positioned in the prone position as with all posterior approaches[5]. The lateral approach to the block of the sciatic nerve provides analgesia

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comparable to that obtained with the posterior approach, with a faster onset and longer postoperative duration[7]. Besides the local anesthetic, various factors markedly affect the onset time of peripheral nerve blocks such as the type of evoked motor response[2]. The long acting local anaesthetic agents provide prolonged postoperative analgesia[8], and so we used levobupivacaine (the levorotatory S-enantiomer of racemic bupivacaine) and bupivacaine. Whereas both the R– and S– enantiomers of bupivacaine have anesthetic activity, previous preclinical studies in animals and volunteers have suggested that levobupivacaine has less cardiovascular system (CVS) and central nervous system (CNS) toxicity than bupivacaine[9-12].

In this study, the primary outcome was to compare the efficacy of equal doses of levobupivacaine and bupivacaine in patients to whom lateral approach to popliteal block was performed with the help of peripheral nerve stimulator in foot and ankle surgery.

SUBJECTS AND METHODS

This study was conducted at the Goztepe Training and Research Hospital after approval by the Goztepe Training and Research Hospital Local Ethics Committee (Approval Number: 57/A3).

Forty patients with American Society of Anesthesiologist physical status classification (ASA) I-II who were between 18 and 70 years of age and were planned to undergo foot and ankle surgery in the orthopedics clinics with their informed consent, were included to the study. Patients with neurological or neuromuscular diseases, body mass index >30, with acquired or congenital coagulopathy, who were allergic to local anesthesia, who were treated for chronic analgesia and with skin infection in block area (n=7) were excluded from the study. This study is a prospective double blind randomised controlled trial where patients were randomly divided into two groups. Thirty-three patients who recieved peripheral nerve blocks for foot and ankle surgery were included respectively to Group L and Group B. Thirty mL 0.5% levobupivacaine was administered to Group L and 30 mL 0.5% bupivacaine was administered to group B.

Demographic characteristics (age, sex, weight, height) of the patients were recorded. Premedication was performed with intravenous midazolam 0.03mg kg^{-1}. Initial non invasive systolic and diastolic blood pressure, mean blood pressure (MBP) and heart rate (HR) were monitored with electrocardiogram and peripheral oxygen saturation (SpO_2) was monitored with Petaş PM 150. Nerve block points of application of the patients were determined with the method described by Vloka JD *et al*[13] at supine position. Stimulator (Stimuplex®-HNS11, B.Braun Co., Germany) and 21Ga.x100mm (Stimuplex®-A100, 4 inch) block needle were used in the study. Electrode of peripheral nerve stimulator was attached to the foot where block would be performed, stimulator starting current was set to 1.5mA, 0.1ms, 2Hz. After antisepsis is achieved in the region where nerve block would be applied, 100 mm stimuplex needle was inserted with an angle of 45° at the needle access point and 1-2 mL of local anesthesia was administered to subcutaneous area. Then, the nerve was attempted to be localized by accessing it with block needle. The twitching response of sciatic nerve common peroneal (dorsal flexion) or tibial branch was evaluated as a successful localization.

After the current was reduced to 0.3 mA and stopped motor response, 5 mL injection was performed at the beginning and 30 mL 0.5% levobupivacaine (Group L) or 0.5% bupivacaine (Group B) was administered while aspiration tests were performed after every 5 mL. MBP, HR and SpO_2 values were recorded at the 1st, 15th, 30th and 45th minutes after the block was performed and at the end of operation.

After injection, the sensory spread of the block was evaluated by pinprick testing with a hypodermic needle in the sensory territories of tibial and common peroneal nerves in the foot. The end of injection was considered time zero and sensory assessment was conducted at five minute intervals for 25 minutes. The localization of the nerve was considered successful when either tibial nerve response or common peroneal response was obtained. A successful block was defined as a complete sensory block affecting both divisions of the sciatic popliteal nerve within 30 minutes and absence of pain on surgical instrumentation. Surgery proceeded once sensory anesthesia in the surgical field was documented by pinching the skin by the surgeon using a hemostat clamp. When the block was solid, the surgery was started.

Sensory blockade was determined by pinprick and graded in accordance with the scale proposed by Hollmèn: 0: normal sensation of pinprick; 1: pinprick felt as sharp-pointed but weaker compared with the same area in the other upper extremity; 2: pinprick recognized as touch with a blunt object; 3: no perception of touch. The gradation of motor blockade was 0: normal muscular function; 1: slight depression in muscular function compared with preanesthetic strength; 2: very weak action persisting in muscles; and 3: complete block[14].

Additional amounts of fentanyl and midazolam used were recorded. Surgeon satisfaction was evaluated using a 4 point scale at the end of the operation (1: perfect; 2: good; 3: medium; 4: not acceptable). Patient satisfaction was evaluated with 5 point scale at the end of the operation and at postoperative 24th hour (1: very satisfied; 2: satisfied; 3: a little satisfied; 4: not satisfied;

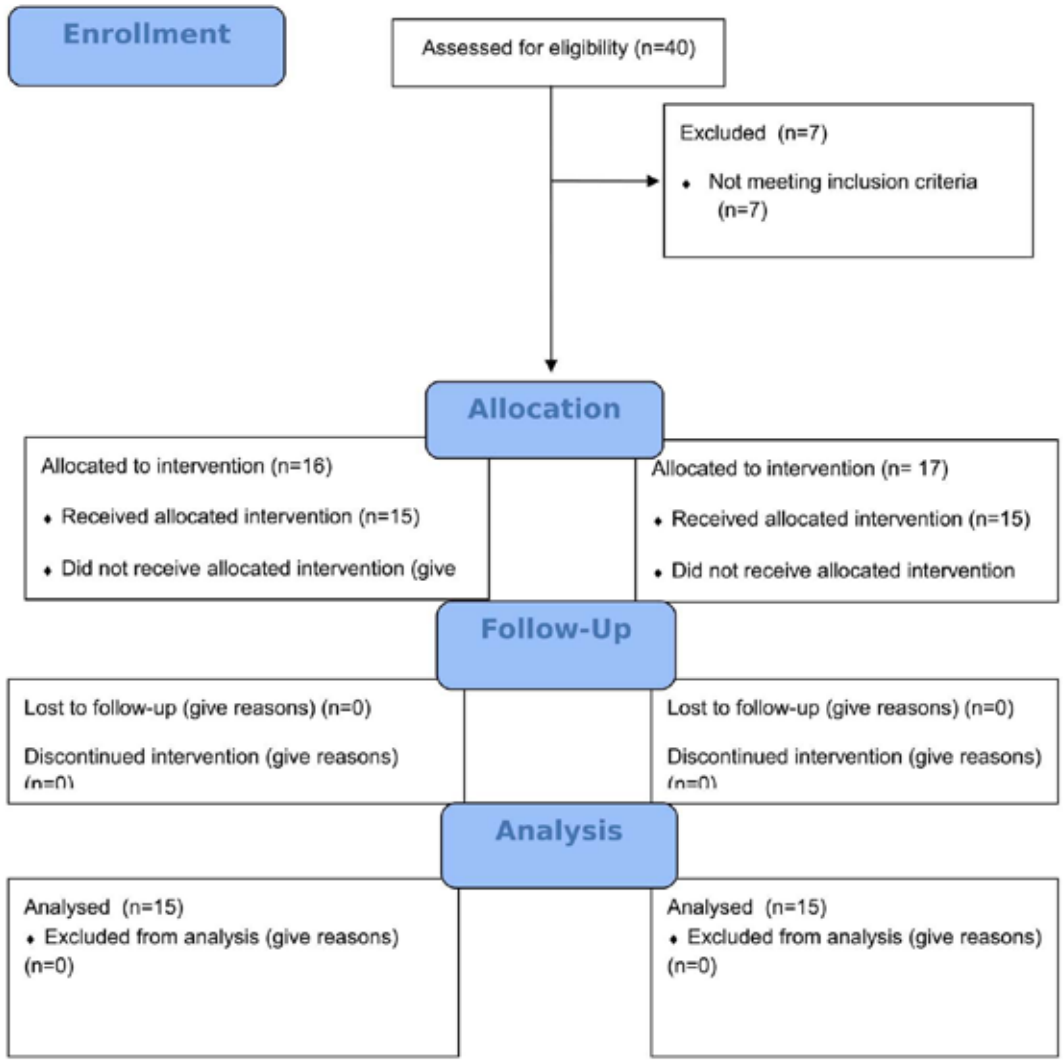

Fig 1: CONSORT flow diagram

5: not at all satisfied). Postoperative motor and sensory block durations and first analgesic administration time was recorded. Complications, hypotension, bradycardia, desaturation, hypoesthesia, neuropathy and prolonged motor block were followed up.

Statistical analysis

NCSS 2007 package program was used in statistical evaluation. Results were evaluated in $P < .05$ significance level.

RESULTS

We started the study with 40 patients but seven patients were excluded from the study. As general anesthesia was applied to two patients in levobupivacaine group and one patient in bupivacaine group due to failed block, these three patients were also excluded from the study analysis. The remaining 30 patients, 15 in Group B and 15 in Group L, were included in the study analysis (Figure 1).

Table 1: Time to complete sensory blockade/time to complete block duration and administration time of first analgesic of patients.

Time	Group L	Group B	Mann Whitney	*P*
Time to sensory blockade (minute)	21.66±5.23	21.80±6.74	106.5	.799
Time to block duration (hour)	9.87±1.73	10.07±3.26	101.0	.629
Administration time of first analgesic (hour)	11.80±2.7	10.57±2.06	75.5	.194

Data are presented as mean ± SD

Table 2: The gradation of sensory blockade of total patients

Sensory blockade	Group L		Group B		*P*
	n	Percentage	n	Percentage	
Lateral sural cutaneous					χ^2:4.8
Felt as sharp-pointed but weaker	1	6.7	4	26.7	*P*=.091
Recognized as touch with a blunt object	11	73.3	11	73.3	
No perception of touch	3	20.0	0	0.0	
Sural					χ^2:5.18
Felt as sharp-pointed but weaker	1	6.7	3	20.0	*P*=.075
Recognized as touch with a blunt object	10	66.7	12	80.0	
No perception of touch	4	26.7	0	0.0	
Superficial peroneal					χ^2:3.94
Felt as sharp-pointed but weaker	0	0.0	3	20.0	*P*=.139
Recognized as touch with a blunt object	12	80.0	8	53.3	
No perception of touch	3	20.0	4	26.7	
Deep peroneal					χ^2:2.83
Felt as sharp-pointed but weaker	1	6.7	4	26.7	*P*=.243
Recognized as touch with a blunt object	11	73.3	7	46.7	
No perception of touch	3	20.0	4	26.7	

Data are presented as number and percentage of total patients.

Demographic characteristics of 30 patients in the study were similar (age (years): 41.25±7.98 (Group L), 40.87±8.64 (Group B); sex (M/F): 7/8 (Group L), 5/10 (Group B); weight (kg): 70.8±10.5 (Group L), 74.07±9.27 (Group B); height (cm):166.53±7.58 (Group L), 167.6±5.45 (Group B)). No significant statistical difference according to ASA classifications was detected between two groups (ASA I/II: 11/4 (Group L), 10/5 (Group B)).

Time to complete sensory blockade/time to complete block duration and administration time of the first analgesic of patients are shown in Table 1. The end of injection was considered time zero and sensory assessment was conducted at five minute intervals for 25 minutes. We defined a successful block as one that allowed the surgery to proceed within 30 minutes after injection. Sensory block quality of patients is shown in Table 2. When plantar flexion (n.tibialis) and dorsal flexion (n.peronealis) motor block quality were evaluated, the number of patients with reduced muscle function and full motor block developed was found higher in bupivacaine group (Table 3). Patient and surgeon satisfaction levels are shown in Table 4. MBP, HR and SpO_2 measurements are shown in Table 5.

Total fentanyl doses used in levobupivacaine group (to four patients) and bupivacaine group (to three patients) were 40±38.73 μg and 43.33±37.16 μg, respectively. Total midazolam doses used in levobupivacaine group and bupivacaine group were 0.93±0.46 mg and 0.87±0.64 mg respectively. No significant difference was detected between groups with regards to total fentanyl or midazolam dose used. In conformity with-additional analgesic application time, patient and surgeon satisfaction after the operation were high and there was no difference between groups. While nausea was encountered in one patient in both groups, hypotension and hypoesthesia was seen in one patient in bupivacaine group. No significant difference was detected between groups with regard to incidence of side effects.

Table 3: The gradation of motor blockade of total patients

Motor blockade	Group L		Group B		*P*
	n	Percentage	n	Percentage	
Plantar flexion					χ'':12.2
Normal muscular function	1	6.7	0	0.0	*P*=.007
Slight depression in muscular function	10	66.7	2	13.3	
Very weak action persisting in muscles	4	26.7	9	60.0	
Complete block	0	0.0	4	26.7	
Dorsal flexion					χ'':10.6
Normal muscular function	1	6.7	0	0.0	*P*=.014
Slight depression in muscular function	9	60.0	2	13.3	
Very weak action persisting in muscles	5	33.3	9	60.0	
Complete block	0	0.0	4	26.7	

Data are presented as number and percentage of total patients.

Table 4: Patient and surgeon satisfaction levels

Satisfaction levels	Group L		Group B		*P*
	n	Percentage	n	Percentage	
Postoperative patient satisfaction					χ″:2.2
Very satisfied	11	73.3	10	66.7	*P*=.534
Satisfied	3	20.0	4	26.7	
A little satisfied	1	6.7	0	0.0	
Not satisfied	0	0.0	1	6.7	
Patient satisfaction postoperative 24th hour					χ″:0.37
Very satisfied	14	93.3	13	86.6	*P*=.500
Satisfied	1	6.7	2	13.4	
Postoperative surgeon satisfaction					χ″:0.18
Perfect	12	80.0	11	63.6	*P*=.500
Good	3	20.0	4	36.4	

Data are presented as number and percentage of total patients.

DISCUSSION

The increase observed in the number of outpatient surgeries and the number of comorbid patients and the increase in complication risk related to central neuroaxial blocks in patients using anticoagulants maximize the importance of peripheral nerve blocks gradually in lower extremity surgery[1-3,8,15]. Among the different peripheral nerve block techniques used for forefoot surgery, sciatic nerve block at popliteal fossa provides safe and effective analgesia, reducing the doses of local anesthetic, opioids and minimizing the risk of complications[16]. Distal sciatic nerve (popliteal) block is more advantageous than proximal sciatic nerve blocks and it is easier to perform because this technique allows the protection of knee functions of the patients and enables them to move with supports[6]. In our study, popliteal block was performed with lateral approach to thirty patients that would undergo foot and ankle surgery. Lateral approach to popliteal block was preferred because it presented various advantages when compared with posterior approach[7].

The block can be formed in the area belonging to two branches by administering the drug with a single needle after detecting one of the peroneal or tibial nerves[17]. In our study, one of the branches of sciatic nerves was detected with peripheral nerve stimulator and block process was performed by administering all of the local anesthetic at a time. In all the block performed cases, sensory and motor block in various levels were obtained in areas appropriate to both

Table 5: Changes in MBP, HR and SpO_2 at various specified timings in two groups

Vital parameters	Time	Group L	Group B	Mann Whitney	*P*
MBP	Start	91.87±10.72	94.40±10.91	95.5	.480
	Block	91.00±9.76	96.67±12.09	80.5	.182
	1st min	88.87±12.05	94.80±12.41	82.5	.212
	15th min	94.13±11.90	93.47±15.21	109.0	.884
	30th min	94.13±10.55	93.67±15.24	109.0	.884
	45th min	92.47±8.18	92.27±9.09	106.5	.803
	End of surgery	93.40±9.69	92.00±9.53	103.0	.692
	Friedman p	0.004	0.006		
HR	Start	73.47±8.33	79.53±8.70	67.5	.061
	Block	74.27±8.20	77.73±8.89	80.0	.176
	1st min	70.87±7.82	74.73±5.02	79.5	.170
	15th min	71.67±7.35	76.20±9.96	80.0	.176
	30th min	75.07±6.70	75.20±8.50	111.5	.967
	45th min	74.67±8.07	75.13±8.22	99.0	.575
	End of surgery	75.00±8.82	75.67±7.08	102.0	.663
	Friedman p	0.339	0.463		
SpO_2	Start	98.07±0.96	97.93±0.59*	91.0	.310
	Block	98.13±1.06	98.33±0.62	107.5	.818
	1st min	98.20±0.68	98.53±0.64	81.5	.155
	15th min	98.20±0.77	98.33±0.72	102.0	.637
	30th min	98.33±0.62	98.33±0.72	110.0	.909
	45th min	98.60±0.63	98.60±0.63	112.5	.999
	End of surgery	98.67±0.62	98.87±0.35*	96.5	.340
	Friedman p	0.004	0.000*		

Data are presented as mean ± SD; MBP: mean blood pressure; HR: heart rate; SpO_2: peripheral oxygen saturation

branches of sciatic nerves (lateral cutaneus sural, sural, superficial peroneal and deep peroneal).

In the study conducted by Urbanek *et al*[11], when 20 mL doses of 0.5% bupivacaine, 0.5% levobupivacaine and 0.25% levobupivacaine were compared in femoral block applications, it was reported that time to sensory blockade/total block times of bupivacaine and levobupivacaine (27min/1053min, 24min/1001min) were similar and time to sensory blockade of 0.25% levobupivacaine (30min/707min) was higher and total block time was shorter. In our study, time to complete sensory blockade/time to complete block duration for levobupivacaine and bupivacaine were detected respectively as 21.66min/9.87hours and 21.8min/10.07hours, which were compatible with the studies in the literature.

While in the study performed by Liisanantti *et al*[18] on axillary block, motor total block formation percentages for ropivacaine, bupivacaine and levobupicaine were reported respectively as 67%, 47%, 30%, in the study conducted by Connolly *et al*[8] on distal sciatic nerve block with posterior approach, this percentage for 7.5mg mL^{-1} ropivacaine and 5mg mL^{-1} bupivacaine was reported respectively as 75% and 58%. In the study conducted by de Leeuw *et al*[19] on psoas compartment and sciatic block, no significant difference was reported with regards to sensory block quality between bupivacaine, levobupivacaine and ropivacaine groups. However, in our study, while no significant difference was detected between bupivacaine and levobupivacaine with regards to sensory block quality, the incidence of reduced muscle function and full motor block in bupivacaine group was significantly higher than the incidence in levobupivacaine group.

In femoral nerve block performed by Urbanek *et al*[11], no difference was reported between levobupivacaine and bupivacaine in the terms of analgesic efficiency and it was stated that these two drugs provided effective pain control. In the study performed by de Leeuw *et al*[19] on psoas compartment and sciatic nerve block, it was reported that levobupivacaine, bupivacaine and ropivacaine provided an efficient postoperative analgesic effect and there was no significant difference between these drugs with regards to analgesic effect.

In the study performed by McLeod *et al*[20] with 20 mL 0.5% bupivacaine, postoperative first analgesic requirement was reported as 18 hours on average in lateral popliteal block performed patients. In another study on distal sciatic block, postoperative first analgesic requirement time for 0.5% levobupivacaine, 0.75% levobupivacaine and 0.75% ropivacaine was reported respectively as 16 hours, 18 hours and 13 hours respectively[21]. In our study, postoperative first analgesic requirement time was detected as 11.8 hours for levobupivacaine group and 10.57 hours for bupivacaine group and no significant difference was found between the groups. In literature, in different studies, it is detected that there are differences between postoperative first analgesic requirement periods[18,20,21]. It is considered that this difference may depend on local anesthetic doses used, whether the local anesthetics are diluted, type of surgical intervention applied and variability of pain sensitivity of the patients.

In the study performed by McLeod *et al*[20] on the lateral popliteal block using 20 mL 0.5% bupivacaine, it was reported that a high level of patient satisfaction was reached and 95% of the patients was satisfied with this method. In our study, very satisfied and satisfied patient percentages in levobupivacaine and bupivacaine groups were 93.3% and 93.4% respectively.

Hadzic *et al*[22] classified the potential complications for lower extremity peripheral nerve blocks as local anesthetic systemic toxicity, hemorrhagic, infectious and neurological. There is convincing evidence that the probability of an adverse event related to the CNS and CVS toxicity of local anesthetics can be reduced when levobupivacaine is used instead of bupivacaine[23]. This arises primarily from the higher toxicity of the R(+)-stereoisomer of bupivacaine[11,23]. Hence, levobupivacaine is presented as a suitable alternative for bupivacaine[11]. Systemic toxicity related to local anesthetics was not detected in any group. Peripheral nerve blocks are associated with minimal haemodynamic disturbance[24]. In the study conducted by Urbanek *et al*[11], HR, noninvasive blood pressure and SpO_2 showed no statistically significant inter- or intragroup differences during the entire study period. Also in that clinical trial, no signs of CVS or CNS toxicity were observed. In our study, no significant changes in MBP, HR and SpO_2 were encountered in any of the groups. Also, no toxic effect on CVS or CNS was detected.

The limitation of this study was that the efficacy of levobupivacaine and bupivacaine was compared only in lateral approach to popliteal sciatic nerve blocks. Besides, if this study was performed with ultrasonography, doses used and complication risk could decrease.

CONCLUSION

In line with similar studies in literature and with the findings of our study, it was determined that both 0.5% concentrated 30 mL bupivacaine and 0.5% concentrated 30 mL levobupivacaine used in lateral popliteal nerve block for foot and ankle surgery were sufficient to perform the block and provided sufficient anesthesia quality. Although bupivacaine group was statistically more efficient in terms of motor block

quality, there were no differences between the two drugs with regard to sensory block quality and side effect. Patient and surgeon satisfaction was found to be high and no difference was found between the two drugs. Levobupivacaine or bupivacaine can be used in lateral approach to popliteal block for foot and ankle surgery because of both of these agent's similar anesthesia quality, patient/surgeon satisfaction and side effects.

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The authors declare that they have no conflict of interest.

Author contribution:

Ozkan Orhan: study design, literature review, article writing; Melek Gura: study control, study design; Ali Nadir Ozcekic: surgical examination and literature review; Namik Kemal Ozkan: surgical examination and literature review; Sevgi Kesici: literature review and article writing.

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Original Article

Functional independence level of Wagner grade 3 diabetic foot ulcer patients using diabetic foot ulcer scale

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ABSTRACT

Objective: To determine the functional independence level (FIL) of patients with Wagner Grade 3 diabetes foot ulcer with a diabetic foot ulcer scale (DFUS)
Design: Prospective descriptive study
Setting: Department of General Surgery and Physiotherapy, Saveetha Medical College and Hospital, India
Subjects: Three hundred and twenty subjects with Wagner grade 3 diabetic foot ulcers (DFU) based on the inclusion and exclusion criteria were assessed and included in the study. These include subjects above the age of 35, ulcer without infections and grade 3 ulcers based on Wagner grading.
Intervention: Demographic data were documented in the data collection form and the patients were administered with the DFUS questionnaire. Majority of the patients were male (67.4%). The average age of the study population was 63.34±13.04 years. The average DFUS score was 66.47±13.07. Majority of the diabetic patients had the DFUS score between 70 and 50. Patients without much problem had a better DFUS score.
Main outcome measures: The FIL of Wagner grade 3 diabetes foot ulcer patients were measured with DFUS. There was a statistically significant correlation with various parameters such as age, duration of diabetes history, HbA1c, number of complications and type of complication verses DFUS of diabetic patients ($P<.05$)
Result: Proper wound management and strict glycemic control is important to prevent progression and occurrence of complications to maintain a better FIL in DFU patients.
Conclusion: Overall, patients with Wagner grade 3 DFU have a negative impact on their FIL with or without complications.

KEY WORDS: diabetes complications, diabetic foot ulcer, diabetes mellitus questionnaires, functional independence level, prevention and control

INTRODUCTION

Diabetes mellitus is the most common disease outbreak in India in the twenty-first century with an incidence of 69.2 million (8.7%) among the total population in the year 2015[1]. However, it was estimated to be 62 million in the year 2014[2]. It seems to be an increase of epidemic proportion, with the number of people affected between 2014-15[3,4]. Diabetes mellitus is caused due to impaired glucose tolerance by the body. One of the major complications of diabetic patients is diabetic foot syndrome, otherwise known as diabetic foot ulcer (DFU), which is often the main cause for non-traumatic foot amputation[5]. This is the most common health issue faced by an enormous number of people worldwide. The quality of life, in general, is decreased in diabetic patients regardless of gender[6]. The patients with complications of diabetes mellitus suffer from a variety of lifestyle problems[7-9].

Diabetes mellitus is a condition which increases the blood glucose level due to reduced insulin production by the pancreas, or it can also be due to reduced absorption of insulin by the body, which leads to damage to the endothelial cells. These cells are responsible for various inflammatory actions of the cell[10]. If these cells are damaged, the process of wound healing stops in the inflammatory phase and cell proliferation does not take place, which leads to worsening of the wound and also causes delayed

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wound healing, leading to non-healing chronic ulcers[11].

These ulcers are the main cause of morbidity and expense. There have been several surgical and conservational procedures followed to treat these ulcers. Even so, healing of ulcers seems to be difficult. Medical management includes cleaning of the wound, wound debridement, skin grafting, antibiotics, vasodilators, bandaging and pain management[12-14]. In light of these complications, we aimed to find the functional independence level (FIL) of diabetic ulcer patients in this study.

SUBJECTS AND METHODS

A prospective descriptive study was conducted in Saveetha Medical College and Hospital after obtaining approval from the Saveetha University Human Ethics Committee. The study lasted for a total duration of seven months. It is a non-interventional survey.

Patients were recruited based on the following inclusion criteria: subjects with type II diabetes, above 35 years of age, ulcer without infections and grade 3 ulcers based on Wagner grading. Subjects were excluded if they had ischemia, infection and ulcers on body parts other than the foot.

During the study period, a total of 320 participants had 80% power to detect the quality of life accounting for a 15% non-compliance and 15% drop-out rate. The significance was set at $P \leq .05$. A sample size of 320 also had 80% power for outcome measures.

The intervention

The data was collected at Saveetha Medical College and Hospital during the period of June 2017 to November 2017. Eligible participants were type 2 diabetes patients with DFU who randomly visited the hospital and who consented to participate in the study. Patients with severe comorbidity which could affect FIL were excluded. Patients were asked to answer the diabetic foot ulcer scale (DFUS) questionnaire along with socio-demographic and other diabetes-specific questions. Completion time was approximately 20 minutes and 320 out of 336 patients visiting the hospital during the study period agreed to participate (89% response rate). These were done after obtaining their consent. All data were collected by the doctor in-charge in the ward and outpatient department, who were blinded. The DFUS questionnaire is a specific tool made to assess foot ulcers and their treatment on quality of life in people with diabetes. DFUS consists of 58 items grouped into 11 domains: leisure (five items), physical health (six items), daily activities (six items), emotions (seventeen items), non-compliance (two items), family (five items), friends (five items), positive attitude (four items), treatment (one item), satisfaction (five items) and financial (two items) (Table 1, 2). Domain scores are based on the sum of all items associated with that individual domain.

Table 1: DFUS domains and item numbers

Item Numbers	Domains	Number of items in each domain
1	Leisure	5
2	Physical health	6
3	Daily activities	6
4	Emotions	17
5	Non-compliance	2
6	Family	5
7	Friends	5
8	Positive attitude	4
9	Treatment	1
10	Satisfaction	5
11	Financial	2

Diabetic foot ulcer scale (DFUS) and its individual domains with their subcategories for each domain in numbers (Total domain is 11 and total items are 58)

Table 2: Response category and scores of diabetic foot ulcer scale

Domain Number	Response category in each domain (Scoring)
1,6,7,10	1→5
2,3	1→6
4	1→17
5,11	1→2
8	1→4
9	1→1

In diabetic foot ulcer scale, each domain varies with their response category. For example, domain number 1 (Leisure) has 5 subcategories (questions) and patients will be validated from 1-5. Likewise, each domain has individual subcategories for scoring.

Various demographic parameters such as gender, age group, duration of diabetic history, the number of diabetic drugs prescribed, the prescription pattern of diabetic drugs and laboratory tests on admission were collected along with DFUS. Those patients with a DFUS score of more than 4 had a poor FIL, those with a DFUS score of less than 4 had a moderate FIL, and those with less than 2 had a good FIL in relation to individual domain.

Statistical analysis

Unpaired t-test was applied for comparing the mean of two groups and the one way ANOVA test was applied for comparing the means of three or more groups. *P*-value <.05 was considered significant.

RESULTS

As per the study, the 320 diabetic patients admitted were included and the majority of them were male members as shown in Table 3. Among the 320 patients, 10 (6.4%) patients were <40 years of age, 130 (56.6%) patients were in the age group of 40-65 years and 80 (35.1%) patients were >65 years of age. The mean age

Table 3: Demographics of diabetes patient

S.No	Variables	Number of patients (%)
1	Gender (N=320)	
	Male	210 (67.4)
	Female	110 (33)
2	Fasting blood sugar (mg/dl)	
	< 110	155 (25.4)
	110-126	98 (5.6)
	> 126	67 (69)
3	HbA1c (%) (n=160)	
	4-7	32 (22.6)
	7-8	22 (14.3)
	More than 8	106 (63.1)
4	BMI (kg/m^2) (n=109)	
	≤18.4	5 (6.9)
	18.5-22.9	30 (24.6)
	23-24.9	12 (13.8)
	≥25	62 (54.6)
5	Comorbidity	
	Hypertension	112 (49.6)
	Kidney disease	32 (18.4)
	Liver disease	10 (4.8)
6	DM with and without complication	
	DM without complication	153 (65.2)
	DM+1 complication	55 (26)
	DM+2 complication	23 (5.2)
	DM+3 complication	6 (2.8)
	DM+4 complication	1 (0.8)
7	Types of diabetic complication	
	Retinopathy	20 (25.3)
	Nephropathy	14 (27.6)
	Neuropathy	12 (16.1)
	Diabetic foot	12 (19.5)
	IHD	29 (44.8)
	Ketoacidosis	3 (5.7)
8	Number of diabetic drugs prescribed (N=320)	
	One	243 (53.6)
	Two	50(24.4)
	Three	25(15.2)
	Four	2 (1.2)

Mean percentage of patients for various categories who were selected for the study
HbA1c: glycated haemoglobin; BMI: body mass index; DM: diabetes mellitus; IHD: ischemic heart disease

of patients was found to be 50.33±12.03 years. We observed that out of 320 patients, 37 (14.2%) had a history of diabetes for less than 1 year, 30 (15.8%) had diabetes for 1-5 years, 67 (30%) for 6-10 years and 86 (40%) for more than 10 years.

Out of 320 patients, 102 (46.4%) had health insurance and 118 (53.6%) did not have any health insurance. Patients were prescribed with 1 to 4 medications for diabetes treatment; the majority of the patients were on monotherapy (Table 3). On analysis of DFUS questionnaire, the average quality of life score was 64.47±15.07. The number of patients under a different range of DFUS score is represented in Table 4.

The FIL of Wagner grade 3 diabetic ulcer patients were assessed with respect to diabetes-related complaints using DFUS with the domains leisure, physical health, daily activities, emotions, non-compliance, family, friends, positive attitude, treatment, satisfaction and financial with a statistically significant effect on FIL. The detailed summary of the result is given in Table 5.

Table 4: Assessment of diabetic foot ulcer scale of diabetic patients

DFUS Score	No. of patients (%) (N=320)
Less than 5	205 (41.2)
3-4	75 (42.4)
> 5	40 (16)

Table 5: Assessment of diabetic foot ulcer scale based on the domain

S.no	Domain	(Mean ± S.D)	*P*-values
1	Leisure	60.47±13.70 75.80±10.14	<.0001
2	Physical health	51.42±12.90 58.20±14.29	<.0001
3	Daily activities	50.69±13.51 60.82±12.89	<.0001
4	Emotions	51.53±13.40 65.38±10.91	<.0001
5	Non-compliance	50.26±14.25 59.35±12.72	<.0001
6	Family	50.24±13.88 60.982±12.38	<.0001
7	Friends	53.23±13.87 56.88±14.08	.059
8	Positive attitude	56.31±16.47 57.82±12.39	<.0001
9	Treatment	50.71±13.07 65.20±11.71	<.0001
10	Satisfaction	51.34±13.77 57.65±13.80	.001
11	Financial	50.81±13.87 61.22±12.5	<.0001

Values are expressed as mean ± SD or numbers (%); for various components, P <.05, was considered statistically significant.

DISCUSSION

The present study aimed at assessing the FIL in diabetic patients where 320 patients were admitted. We found that patients with diabetes generally had a negative impact on the quality of life (64.47±15.07). The majority of the study subjects were males (164, 64.4%) and this was similar to the observation from the study carried out by Papadopoulos *et al*[15], in which the majority of the patients were males. In our study, the majority of diabetic patients had a history of more than 8-10 years and their FIL score was poor compared to those with a history of fewer than 8-10 years. We included patients with grade 3 DFU as per Wagner grading since it is deep compared to grades 0-2. Grade 3 DFU is more difficult for patients regarding healing time. Previous studies in relation

to DFU were conducted in general which includes all grades; none of the studies were isolated towards the depth of the ulcer and quality of life. If the ulcer is deep, the healing time will be longer, which increases the patient's hospital stay and in turn, affects the patient's functional activities much more. Malepati *et al* reported in their study that ulcers of Wagner's grade 3 were predominant in the 346 cases which were enrolled; Armstrong DG and Shea JD reported that 48% of ulcers were grade 3 in their studies. We find that all these recent studies reported that Wagner grade 3 DFU is predominant in patients with DFU. Hence, we isolated and included only grade 3 DFU in terms of Wagner grading in our study[16-21].

The FIL scores for patients on combination therapy with insulin and oral hypoglycaemic agents were better than the patients on monotherapy with only insulin or oral hypoglycaemic agents[19-21]. These may be attributed to the fact that using combination therapy of insulin and oral hypoglycaemic agents gives better glycemic control[22-24]. The subjects with health insurance had a better FIL than those without insurance. This can be attributed to regular checkups and the cost of medication being covered by the insurance company.

The patients with a body mass index of <18.4 kg/m^2 had a better FIL than the patients with a body mass index >25 kg/m^2, but there is no statistically significant difference in the quality of life scores. Previous studies independently looking at the association between obesity and FIL have clearly indicated that obesity impairs the FIL[25-27].

The limitations we encountered were a failure to obtain an equal number of patients with different complications, patients without diabetic complications for better comparison of the outcome and the short duration of the study period. Future studies should overcome all these limitations.

CONCLUSION

Overall, patients with type II diabetes having Wagner grade 3 DFU have a negative impact on their FIL with or without complications. It also shows that diabetic foot ulcer affects various domains such as leisure, physical health, daily activities, emotions, non-compliance, family, friends, positive attitude, treatment, satisfaction and financial in a patient's life, thereby affecting the FIL.

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Competing interests: The authors have no conflict of interest to declare.

Author contributions: Kamalakannan M and Chitra S were involved in the conceptualization and design of the study. Kamalakannan M, Chitra S and Shruthikamal V were involved in conducting of the research, data analysis and interpretation of the data. Kamalakannan M drafted the manuscript. All authors read and approved the final submitted version.

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Original Article

Effects of 5α-reductase inhibitor therapy with dutasteride on bone metabolism in patients with benign prostatic hyperplasia

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ABSTRACT

Objectives: The aim of this study was to investigate the effect of dutasteride on bone metabolism in patients with benign prostate hyperplasia (BPH).
Design: Prospective study
Setting: Sakarya University Sakarya Training and Research Hospital
Subjects: Fifty patients were administered 0.5 mg dutasteride daily for treatment of BPH.
Interventions: All patients were evaluated prior and six months after the treatment for bone metabolism.
Main outcome measure: Standard parameters of bone metabolism and serum osteoprotogerin (OPG) levels, which is an important regulator for bone metabolism, were evaluated.
Results: Seven of the 50 patients were lost to follow up and the remaining 43 patients were included in the study. Mean age of patients was 60.3±5.5 (range: 48-74) years. Dutasteride significantly increased serum testosterone and estradiol levels compared to pretreatment values. Mean OPG level increased from 198.3±40.5 pg/ml to 240±90.1 pg/ml (P=.019). Except T score of femur neck, there was an increase of T-Z scores in the lumbar spine and in the femur neck (P >.05). There was an increase in bone mineral density levels of the body, but only the increase in L4 vertebral value was statistically significant (P <.008). The treatment with dutasteride also caused significant decrease in prostate specific antigen levels and prostate volume as expected.
Conclusions: It seems that, in addition to the benefits on prostatism symptoms, the short-term results of 5ARI on bone metabolism are promising.

KEY WORDS: Osteoclasts, osteopenia, osteoprotogerin

INTRODUCTION

More than 90% of testosterone is converted to dihydrotestosterone (DHT), the most potent androgen in prostate, irreversibly. 5α-reductase converts testosterone to DHT, which starts during intrauterine development, leading to differentiating of prostate. There are 2 isozymes of 5α-reductase in humans. Type 1 enzyme is mainly seen in the skin, adult scalp and liver, but detected with lesser degrees in the prostate. Type 2 isozyme, which is the dominant isoform, is seen in the prostate[1,2].

Dutasteride is a 5α-reductase inhibitor and inhibits both isozymes of 5α-reductase (types 1 and 2). Continuous administration of dutasteride decreases the serum DHT concentration to approximately 95% and prostate DHT concentration to 85-90%[3]. Blocking conversion of the testosterone results in an increase in testosterone level[4]. It is also well known that the increase of testosterone may cause an increase of the serum estradiol (E2) level, due to effect of an aromatase enzyme which converts testosterone to E2[5]. Low serum androgen level is related with an increased risk

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of osteoporosis and also fracture. It was demonstrated in the literature that the levels of bioavailable and free fractions of testosterone and E2 were positively associated with calcaneal quantitative ultrasound parameters, and that testosterone increases the bone mineral density (BMD)[6,7].

5 ARIs have been used in men for the treatment of benign prostatic hyperplasia (BPH) for a long time. Since BPH is a disease of the elderly men in population who are also prone to osteoporosis, we believe that it is also important to demonstrate whether dutasteride has any effect on bone metabolism in addition to BPH symptoms. In the present study, we aimed to investigate the effect of dutasteride, a 5 ARI, on bone metabolism in elderly men with BPH.

SUBJECTS AND METHODS

After having obtained approval of the Institutional Ethics Committee, we performed a prospective analysis of 50 patients administered with 0.5 mg dutasteride daily for treatment of BPH. All patients were evaluated prior and six months after the treatment for bone metabolism and also for bladder outlet obstruction symptoms.

Table 1: Effect of dutasteride on serum hormones

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Total testosterone (ng/ml)	5.4±1.9	7.0±2.7	<.001*
Estradiol (pg/ml)	30±10.1	35±14	.011*
LH (mmol/ml)	4.6±1.9	5.3±2.9	.060#
FSH (mmol/ml)	6.1±3.1	6.4±3.5	.230*
SHBG (mmol/l)	45±25	48.4±26.9	.744*
OPG (mmol/ml)	198.3±40.5	240±90.1	.019*
fTest (pg/ml)	7.05±3.2	6.41±2.44	.068*

OPG: osteoprotogerin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; SHBG: sex hormone-binding globulin; *Wilcoxon Signed Ranks Test; #Paired T test.

Patients with bone metabolism disorders like multiple myeloma, endocrinological disease that could affect the results of blood samples, or who were administered any drugs which could affect the results such as androgen replacement therapy were excluded from the study.

After having a signed informed consent, patient's body mass index, prostate size measurements and uroflowmetric evaluation were recorded prior and six months after the treatment. BMD at the lumbar spine (L1-L4) and femur neck were measured in all patients, and TZ scores were measured by using whole-body dual-energy X-ray absorptiometry. Blood samples were analyzed for hemogram and biochemistry parameters with testosterone, E2, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, dehydroepiandrosterone sulfate, vitamin D, parathormone, bone alkaline phosphatase and osteoprotegerin (OPG) prior and six months after the treatment. Serum lipid profile including total cholesterol, triglycerides, high density lipoprotein and low-density lipoprotein were also analyzed. Hormone measurements were all analysed on the same assay to reduce variability.

Table 2: Effect of dutasteride on lumbar and femur T and Z scores.

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Lumbar T score	-0.944±1.33	-0.862±1.43	.269#
Lumbar Z score	-0.262±1.30	-0.227±1.50	.724#
Femur T score	-0.607±1.10	-0.748±0.83	.431*
Femur Z score	0.355±1.07	-0.241±0.76	.308*

*Wilcoxon Signed Ranks Test; #Paired T test

All statistical analyses were performed on SPSS (Statistical Package for the Social Science, Chicago, USA) version 20. Data were expressed as mean ± SD. The normal distribution of variables was determined by the Shapiro-Wilk test. A paired t-test is used to compare pre- and post-treatment observations on the same subjects when the differences of mean were normally distributed. Wilcoxon signed ranks test was used when the population cannot be assumed to be normally distributed. For all comparisons, P <.05 was considered significant.

RESULTS

Seven of the 50 patients were lost to follow up and the remaining 43 patients were included in the study. Mean age of patients was 60.3±5.5 (range: 48-74) years. Dutasteride significantly increased serum testosterone and E2 levels compared to pretreatment values. Total testosterone and E2 values increased from 5.4±1.9 ng/ml to 7.0±2.7 ng/ml (P <.001) and from 30±10.1 pg/ml to 35±14pg/ml (P=.011), respectively. However, there was no effect of the treatment on serum levels of luteinizing hormone, follicle-stimulating hormone or sex hormone-binding globulin. We also found that the dutasteride treatment increased OPG levels, which results in osteoblastic activity. Mean OPG level

Table 3: Effect of dutasteride on lumbar vertebral BMD scores

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
BMD L1	0.877±0.154	0.895±0.155	.228#
BMD L2	0.956±0.156	0.977±0.172	.209#
BMD L3	0.996±0.183	1.012±0.163	.148#
BMD L4	1.018±0.182	1.057±0.189	.008#
BMD total	0.978±0.151	0.992±0.160	.065#

BMD: bone mineral density; #Paired T test

increased from 198.3±40.5 pg/ml to 240±90.1 pg/ml, which was statistically significant (*P* = .019) (Table 1). Except T score of femur neck, we demonstrated that there was an increase of T-Z scores in the lumbar spine and in the femur neck, but the change between baseline and month 6 of treatment was not statistically significant (*P* >.05) (Table 2). In addition, we detected an increase in BMD levels of the body, but only the increase in L4 vertebral value was statistically significant (*P* <.008) (Table 3).

Table 4: Effect of dutasteride on lipid profile and body image

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Total cholesterol (mg/dl)	188±30.4	202±37	<.001*
LDL cholesterol (mg/dl)	114±23	129±32	<.001*
HDL cholesterol (mg/dl)	40.9±10.3	44.1±9.5	<.001*
Triglyceride (mg/dl)	138.9±84.6	140.6±71.8	.836‡
Weight (kg)	83.44±5.5	85.58±13	<.001*
BMI (kg/m^2)	28.05±3.7	29.1±3.9	<.001*
Waist circumference (cm)	105.6±10.7	111±9.2	<.001*

LDL: low density lipoprotein; HDL: high density lipoprotein; BMI: body mass index; *Wilcoxon Signed Ranks Test; ‡Paired T test

At the end of 6-month administration of the treatment, a statistically significant increase of total cholesterol, low-density lipoprotein cholesterol and also high-density lipoprotein cholesterol was detected (*P* <.001). However, the increase in triglyceride was not statistically significant (*P* = .836). In addition, an increase of body mass index, weight and waist circumference was also detected (*P* <.001) (Table 4).

Table 5: Effects of dutasteride on urologic parameters

Variable	Before treatment (Average ± SD)	After treatment (Average ± SD)	*P*-value
Prostate volume (cc)	53±20.6	35±17.2	<.001‡
Uroflowmetry data			
Qmax (ml/sn)	11±2.9	16.1±4.7	<.001‡
Average flow rate (ml/sn)	5.7±2.0	7.5±1.7	< 001‡
Voiding volume (ml)	265±82.7	256±106	.508‡
Post voiding residue (ml)	107±37.3	38±29.7	<.001‡
Sum of IPSS	17.4±5.1	8.8±5.1	<.001‡

IPSS: International Prostate Symptom Score; ‡Paired T test

The treatment with dutasteride also caused 50% decrease in prostate specific antigen levels at the end of the six months. Mean prostate volume decreased from 53±20.6 gr to 35±17.2 gr (*P* <.001). International prostate symptom score and uroflowmetric parameters including Qmax, Qaverage and post voiding residual volume were significantly improved with the treatment of dutasteride (*P* <.001) (Table 5).

DISCUSSION

The effect of androgens on bone metabolism has been investigated in several studies in the literature. While E2 is positively associated with bone maturation and BMD, testosterone is associated with bone size in adolescents[8]. However, in men over the age of 40 years, testosterone level drops with an average decrease of 1-2% per year. Low serum testosterone is associated with osteopenia in elderly men and there is an increased incidence of osteoporosis, as well as increased falls and fractures, resulting in increased mortality[7,9-11]. The results of androgen suppression therapies in men with prostate cancer have also reported how important testosterone is for bone metabolism. According to Chernichenko *et al*'s study, the drop of testosterone to castration level due to androgen suppression therapies was strongly associated with the decrease in BMD. They found out a decrease in BMD in 78.6% of the patients administered with androgen suppression therapies[12]. It has been shown in several studies that the administration of testosterone results in an increase in the level of BMD by suppressing bone resorption[6,7]. In addition to the direct effect of testosterone, the conversion to E2 by the aromatase enzyme also has an important effect on bone metabolism. The protective effect of E2 from osteopenia is as important as testosterones[9,10].

The E2 receptors are detected more on osteoblasts than on osteoclasts. Here, E2 regulates and increases the amount of growth hormone, insulin growth factor binding protein-4 in osteoblastic cells. It also increases the transforming growth factor-β, which inhibits osteoclastic bone activity[13]. In addition, it has been reported that E2 has an effect on bone metabolism by inhibiting osteoclast formation and resorption, just like testosterone[13,14].

5alpha-reductase inhibitor increases the testosterone and E2 levels by blocking the conversion of testosterone to DHT. When we analyzed the literature, the first study about the effects of 5alpha-reductase inhibitor on bone metabolism was published by Amory *et al* in 2008[2]. They found out that dutasteride and finasteride did not have a significant impact on BMD and markers of bone metabolism after one year of treatment. In 2014, Mačukat *et al* evaluated dutasteride and finasteride by comparing with a control group[15]. They found out that total testosterone and E2 levels were higher in the dutasteride group and that dutasteride group had significantly higher BMD and mean T and Z scores at femoral neck than control group. Recently, Wada *et al* investigated the effect of dutasteride on bone metabolism[16] by evaluating the BMD in the lumbar and femur neck. Although they did not find a significant increase in testosterone level, they detected

an increase of BMD in lumbar and femur neck in patients with increased testosterone. They evaluated only 17 patients, and it seems that the low number of the patients was the main limitation of their study. In these previous studies, none of the authors evaluated the OPG, which is an important regulator for bone. OPG was used for evaluating bone metabolism in our study for the first time.

In the present study, testosterone and E2 levels were significantly increased after treatment with dutasteride for a six-month period. The increase in the androgen levels resulted in an improvement of the bone metabolism markers. Mean OPG level, which is an important bone metabolism regulator, was significantly increased after the dutasteride administration. OPG protein, which is one of the members of tumor necrosis factor receptor families, and which is produced by osteoblastic cells, inhibits the osteoclastic activity by binding and inhibiting the receptor activator of nuclear factor kappa-B ligand[13]. It has been well known that E2 and testosterone both enhance the OPG levels so that they can be called as protective factors for bone[13,17,18]. We believe that the increase in testosterone and E2 after dutasteride is an important factor that increased OPG level in the early period of the treatment.

An increased BMD level was detected in all measurements and in total, but only the increase in L4 vertebral value was statistically significant. Except for the T score of femur neck, there was an increase of T-Z scores in the lumbar spine and in the femur neck, but the change between baseline and month 6 of treatment was not statistically significant. It may be that long-term results of the therapy would be necessary to evaluate BMD due to slow turnover of bone tissue.

In addition to bone metabolism, dutasteride improved the prostatism symptoms and uroflowmetric parameters significantly, as expected. Post voiding residual volume amount, prostate volume and prostate specific antigen levels decreased significantly six months after the treatment, as reported in the literature[19].

The present study shows that increased androgens with six-month administration of dutasteride has significantly improved bone regulation by increasing OPG. In addition, due to slow turn-over of the bone tissue, it would be better to evaluate BMD after long term treatment. Although there is no cut-off value for evaluating the most suitable treatment period for drug studies, six months can be considered a short time to evaluate bone metabolism. This may be considered as a limitation of the study. Another limitation of the present study is that a control group was not used, although this is a prospective study. Despite the limitations, we believe that the results of this study are important since there are limited numbers of studies on this topic.

CONCLUSION

Treatment with dutasteride resulted in significant improvement of BMD and T-Z scores in the lumbar spine and in the femur neck. This is due to increased levels of testosterone, E2, as well as OPG which inhibits the osteoclastic activity. It seems that, in addition to benefits on prostatism symptoms, the short-term results of 5ARI on bone metabolism are promising.

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Original Article

Validity of Paprosky and Saleh acetabular bone loss classifications for CLS expansion cup revision surgery

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ABSTRACT

Objectives: To determine the validity of Paprosky and Saleh classifications in predicting bone loss at revision of CementLess Spotorno expansion cups
Design: Prospective
Setting: Istanbul Training and Research Hospital, Orthopaedics and Traumatology Clinic
Subjects: Twenty-one patients who required revision of expansion cup between January 2014 and December 2015 were prospectively evaluated for periacetabular bone loss.
Interventions: Preoperative radiographs were analyzed and bone defects were assessed according to Paprosky and Saleh classification systems. Estimated bone stock loss was compared to the actual deficiency. Cases which required second revision during the follow-up period were considered as failure, whereas arthroplasties that survived this period were deemed successful.
Main outcome measures: Level of agreement between preoperative and intraoperative assessment was calculated using kappa statistics. The relation between the failed implants, the reconstruction method proposed by the classification scheme and the intervention preferred by the surgeon was evaluated.
Results: Paprosky and Saleh classifications showed moderate (Kappa=0.939, *P*<.001) and very good to excellent (Kappa=0.588, *P*<.001) agreement respectively. Acetabular defect was underestimated in seven cases using Paprosky classification. The reconstruction deemed necessary by the senior surgeon was 95% consistent with the treatment proposed according to Saleh classification. With Paprosky classification, there was 29% disagreement between the proposed method of reconstruction for the identified bone defect and the reconstruction performed by the surgeon.
Conclusion: Acetabular bone loss classification systems based on radiographs remain valuable for predicting bone loss. Saleh classification is more advantageous over Paprosky system at predicting the bone loss in revision arthroplasty of expansive cup failures.

KEYWORDS: acetabular osteolysis, hip revision, Paprosky, Saleh, validity

INTRODUCTION

Total hip arthroplasty is described as one of the most successful operations. Approximately 400,000 total hip arthroplasties are performed each year in the USA and this number is increasing[1]. It is estimated that about 0.83% of the total U.S. population has been using hip replacement components by the year 2010[2]. New prosthesis designs are constantly introduced, some of which will stand the test of time while some will fall short of clinical expectations. As life expectancy and number of young patients undergoing total hip arthroplasty increases, more people will outlive their implants[3]. It is no surprise that demand for revision surgeries is also on the rise[4].

A major and perhaps the most important factor for a successful acetabular revision is the management of periacetabular bone loss. There are several classifications to define the severity of periacetabular osteolysis. Paprosky classification is the most widely used one, which focuses on degree and location of bone

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loss and identifies the structures that are deficient[5]. There are 4 anatomical structures that Paprosky system puts emphasis on for classification; anterior column, posterior column, superior dome and medial wall. It relies on integrity of these supporting structures, rather than extent of volumetric bone loss. Paprosky *et al* defined the main theme of their classification as "the presence or absence of an intact acetabular rim and its ability to provide a rigid support for an implanted acetabular component"[5,6]. Despite its common and longtime use, the reproducibility and the ability of this classification system to predict actual bone loss are questioned by several authors[7].

A more recent classification was described by Saleh *et al*, which had promising initial reliability and validity[8]. Both classifications propose the augments and constructs that are likely to be needed during revision surgery based on bone loss severity. Even though initially described to delineate the status of pelvic bone encountered at the surgery, their use is largely confined to predicting bone loss preoperatively using two-dimensional imaging. This guides the surgeon to estimate the complexity of the revision procedure, which may range from a simple cup exchange to pelvic reconstruction in severe cases[9].

In our clinic, CementLess Spotorno expansion shell was extensively used for primary hip arthroplasty during late 1990s and early 2000s. Due to its expansive design, these components have several wide slits devoid of metal back originating from base of the cup reaching to the outer rim[10]. This provides a relatively large passage for the wear particles to reach acetabular bone. Our clinical experience with expansion cups has been that these implants remained well fixed despite extensive periacetabular osteolysis and patients could remain asymptomatic even with shells with broken wings. By the time patients got symptomatic, substantial acetabular defect had already occurred. As we performed numerous revisions of this cup design, we noted that preoperative radiographs underestimated the extent of osteolysis in several cases.

The aim of this study is to assess the validity of two acetabular bone deficiency classifications, Paprosky and Saleh, in predicting bone loss at revision of CementLess Spotorno expansion cups. Our second objective was to evaluate which type of defects could be managed with cementless cups and morselized autograft alone and which types would require more complex reconstruction procedures.

SUBJECTS AND METHODS

Following approval from Institutional Ethics Committee of Istanbul Training and Research Hospital (Registration no: 356), 21 patients who required revision of expansion cup between January 2014 and December 2015 were prospectively evaluated for functional outcome and loss of bone stock during a two year period. Sixteen patients were female and 5 patients were male. The average time from index operation was 15.1 years (13-24 years). Mean age at the time of revision surgery was 64.1 years (47-78 years). Patient radiographs were evaluated preoperatively by one surgeon blinded to patient names. Acetabular bone loss was classified according to Paprosky *et al* and Saleh *et al* using antero-posterior and lateral radiographs. Results were compared to actual bone defect noted intraoperatively.

Table 1: Levels of agreement according to two different criteria using Kappa statistics

Landis and Koch		Svanholm *et al*	
Kappa	**Level of agreement**	**Kappa**	**Level of agreement**
0-0.20	Poor	0-0.50	Poor
0.21-0.40	Fair	0.51-0.75	Moderate
0.41-0.60	Moderate	0.76-1.00	Excellent
0.61-0.80	Good		
0.81-1.00	Very good		

All the revision surgeries were done by the same senior surgeon. Actual bone loss was defined by visualization and palpation once metal back and fibrous tissue were removed[11]. Intraoperative findings and used implants and grafts were noted. Validity measured by percentage agreement for classification subgroups was calculated. Cumulative agreement was assessed using the weighted Kappa statistics in order to eliminate the agreement that would occur by chance. A Kappa score of 1 represents perfect agreement; whereas a score of 0 indicates agreement that would be expected by pure chance. Levels of agreement were evaluated using the criteria of both Landis and Koch and Svanholm *et al*, as outlined on Table 1. Of these two Kappa statistics interpretation models, Landis and Koch is the widely used one whereas Svanholm *et al*'s is more stringent[7].

Table 2: Percentage agreement of subgroups between the preoperative radiographs and intraoperative findings using the Paprosky classification

Preop Classification	Actual Defect					Agreement in percentages
	2A	2B	2C	3A	3B	
2A	2	1	1			50
2B		4	1	4		44
2C			1			100
3A				6		100
3B					1	100
Total						67

RESULTS

Mean follow-up after revision surgery was 20.4 months (12-31 months). Mean Harris score at the time of last follow-up was 71.8 (60-90). Reason for revision surgery was acetabular component breakage in three cases, repeating prosthesis dislocations in two cases and symptomatic acetabular loosening in 16 cases. Of these 18 cases with preoperative radiographs with intact acetabular component, metal shell was found to be broken during surgery in six cases. Revision arthroplasty was performed with cementless cup in 16 cases and cemented cups and cages in five cases. Three patients required additional revision surgeries because of acetabular cup protrusion. A mean volume of 75 cc (range 20-150 cc) morselized allograft was used in 17 cases.

Table 3: Percentage agreement of subgroups between the preoperative radiographs and intraoperative findings using the Saleh classification

Preop Classification	Actual Defect				Agreement in percentages
	2	3	4	5	
2	4				100
3		11	1		92
4			4		100
5				1	100
Total					95

Using the Paprosky classification, actual bone loss could be predicted successfully in 15 cases using the preoperative radiographs. The bone defects were underestimated in the remaining six cases. Hundred percent of Type 3A defects classified preoperatively were able to accurately reflect intraoperative findings, whereas group 2A and 2B showed the least accurate estimations (50%) (Table 2). Using the Saleh classification, actual bone loss was successfully predicted in 20 cases. Only one actual Type 4 defect was underestimated as Type 3 during preoperative evaluation of pelvis radiographs (Table 3). Paprosky classification showed moderate agreement (Kappa=0.588, *P*<.001) between the predicted and actual bone loss according to both criteria, whereas Saleh classification yielded very good and excellent agreement (Kappa = 0.939, *P*<.001) (Table 4).

Table 4: Levels of agreement

Classification	Kappa	*P*	Landis and Koch	Svanholm *et al*
Paprosky	0.59	<.001	Moderate	Moderate
Saleh	0.94	<.001	Very Good	Excellent

All the acetabular defects which were classified preoperatively as Paprosky Type 2 (A, B, or C) (14 cases) were managed with morselized allograft and cementless cups. Two of these cases were complicated with acetabular protrusion in the early period and required second revision with cage construct. Five of the seven cases which were classified preoperatively as Paprosky Type 3 required cage construct and cemented cups, whereas remaining two were managed with allograft and cementless cups. One of these two cases was complicated with acetabular protrusion in the early period and required a second revision with cage construct (Figure 1).

Fifteen out of 16 acetabular defects which were classified preoperatively as Saleh type 2 or 3 were

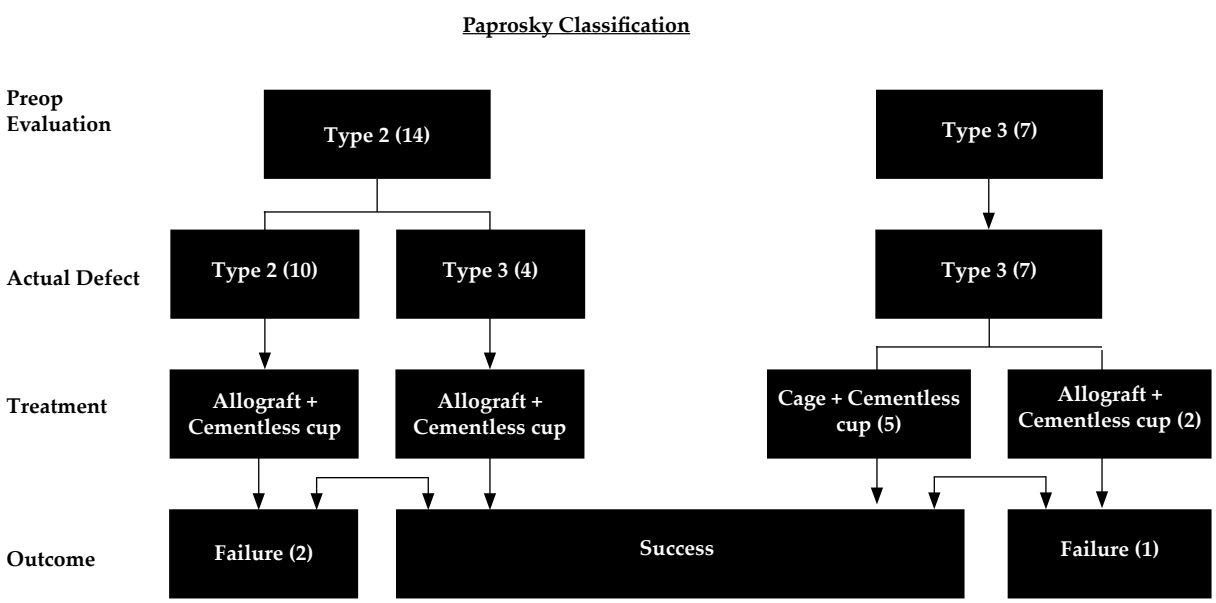

Fig 1: Flow-chart diagram of revision procedures with acetabular defect described according to Paprosky classification.

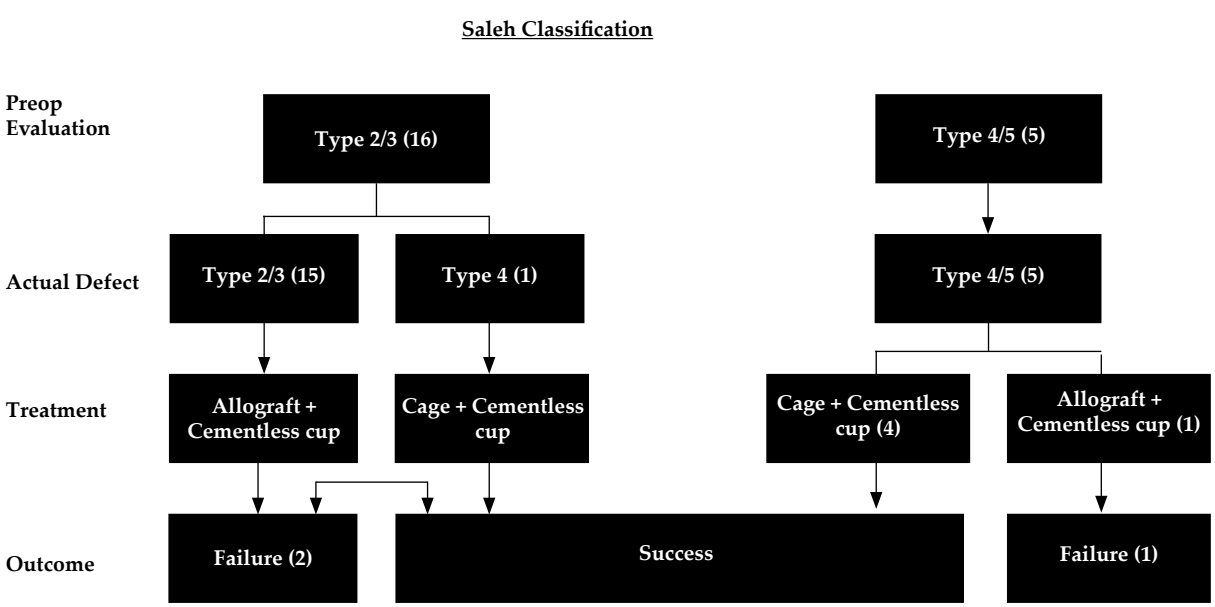

Fig 2: Flow-chart diagram of revision procedures with acetabular defect described according to Saleh classification.

managed with morselized allograft and cementless cups. Two of these 15 cases were complicated with acetabular protrusion in the early period and required second revision with cage construct. One patient who was thought to have type 3 defect turned out to be type 4 intra-operatively and cage-cemented cup construct was used. Four of the 5 cases which were classified preoperatively as Saleh type 4 or 5 required cage construct and cemented cups, whereas the remaining one was managed with allograft and cementless cup. This case was complicated with acetabular protrusion in the early period and required a second revision with cage construct (Figure 2).

Based on the actual bone loss encountered in the operating theater, all the Paprosky type 2 defects and Saleh type 2 and 3 defects could be initially treated with allograft and cementless cups. Of these, two cases did not survive during the follow-up period and developed early protrusion, requiring second revision with cage construct. Five of the 11 cases with Paprosky type 3 (A or B) defect required cage augmentation, and one of the remaining 6 cases which were managed with allograft alone developed acetabular protrusion during follow-ups and underwent second revision. Five of the six cases with Saleh type 4 or 5 defect required cage augmentation, and the remaining case which was managed with allograft alone developed acetabular protrusion during follow-ups and underwent second revision. Details of cases which required second revision are outlined in Table 5.

DISCUSSION

Revision hip arthroplasty has several technical difficulties, among which periacetabular bone stock loss is one which requires meticulous preoperative evaluation and preparation[3,12]. Periacetabular bone loss may lie anywhere from small osteolytic lesions around the acetabular rim to pelvic discontinuity. Several authors have proposed different classifications to define either the degree or location of the acetabular bone loss to assist the surgeon during preoperative planning[6,12,13].

While plain radiography still remains the most practical and important method for assessing periacetabular bone loss, many defects in the complex architecture of the acetabulum are obscured by the radiopaque components[14]. This creates a tendency for preoperative radiographs to underestimate the extent of actual bone loss[15,16]. This was also evident in our study, where acetabular defect was underestimated in seven cases using Paprosky classification. No defect was overestimated. The validity study by Gozzard

Table 5: Cases that required second revision

Cases	Preop Paprosky	Perop Paprosky	Preop Saleh	Perop Saleh	1st revision
1	2A	2A	2	2	20 cc Allograft + cementless cup
2	2B	2B	3	3	60 cc Allograft + cementless cup
3	3A	3A	4	4	120cc allograft + cementless cup

et al stands out as an exception, in which 20% of the cases were overestimated as opposed to 4% of underestimation using the Paprosky classification[3].

While interobserver and intraobserver reliability studies of classification systems are numerous, studies focusing on the ability to depict the actual bone loss noted during the operation are relatively rare. Among the two classification systems we have evaluated, the one proposed by Paprosky *et al* is used more frequently. Validity and interobserver and intraobserver reliability studies of this classification have reported generally moderate agreement, although results are dispersed in a spectrum ranging from poor to good agreement. In their study where they compared the validity of American Academy of Orthopaedic Surgeons and Paprosky classification systems, Gozzard *et al*[3] reported good agreement using Paprosky classification (k=0.65). We have noted moderate agreement (Kappa=0.588, $P<.001$) between the predicted and actual bone loss according to both criteria. Even though our results were inferior to the ones reported by Gozzard *et al*, kappa values were relatively close. Saleh classification is a relatively new system, and the only validity study to date is performed by its developers, where they reported good to excellent agreement with weighted and unweighted kappa values ranging from 0.73 to 0.9[13]. Similarly, in our study, we achieved very good and excellent agreement (Kappa = 0.939, $P<0.001$) using Saleh classification.

These classification systems guide the surgeon on the extent of reconstruction necessary for the defined bone defect. Typically, Paprosky type 3 and Saleh type 4 defects are advised to be managed with cage constructs or augmentation with structural graft and/or plate-screws by the developers of the classification systems[13]. In our study, the reconstruction deemed necessary by the senior surgeon was 95% consistent with the bone loss identified according to Saleh classification and the proposed treatment. With Paprosky classification, there was 29% disagreement between the proposed method of reconstruction for the identified bone defect and the reconstruction performed by the surgeon. The superiority of Saleh classification may be expected, since groups are divided according to the ability of the remaining bone stock to host acetabular component firmly. On the other hand, Paprosky system focuses on integrity of certain anatomical landmarks.

Overall, all cases which required second revision were the ones who were treated with morselized allograft and cementless cup. These 3 cases were classified as Paprosky type 2A/Saleh type 2, Paprosky type 2B/Saleh type 3, and Paprosky type 3A/Saleh type 4, with complete preoperative and intraoperative agreement. None of the cases with cage-cement construct failed during the follow-up. It is expected that the defects that required more extensive reconstruction would be more prone to failure. Our results indicate the opposite, with failed components occurring in group of patients with milder bone defect. One possible explanation is that cage-cement reconstruction provides superior initial mechanical stability than cementless cups and allograft which require incorporation of the graft and biological fixation of the cup for optimum stability. Another possibility is that the senior surgeon who performed the operations failed to accurately identify the bone defects and performed a less extensive reconstruction than was necessary.

CONCLUSION

Acetabular bone loss classification systems based on radiographs remain valuable for predicting bone loss. Categorizing the morphology of bone defect helps the surgeon to perform the appropriate reconstruction procedure. Saleh classification is more advantageous over Paprosky system at predicting the bone loss in revision arthroplasty of expansive cup failures.

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Author Contributions

Specific contributions made by each author are listed below.

Cenk Ermutlu: Design of the work, drafting the work, approval of the version to be published, agreement to be accountable for all aspects of the work

Tolga Tuzuner: Conception of the work, revising it critically for important intellectual content, approval of the version to be published, agreement to be accountable for all aspects of the work

Emrah Kovalak: Interpretation of data for the work, revising the work critically for important intellectual content, approval of the version to be published, agreement to be accountable for all aspects of the work

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Original Article

Effects of sevoflurane and desflurane on microcirculation during non-cardiac surgery

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ABSTRACT

Objectives: Assessment of microcirculation is thought to be a surrogate of tissue perfusion and anesthetic drugs are known to alter the microcirculation in cardiac surgery patients, but their effects in less complicated non-cardiac surgery remain unknown. Our aim is to investigate the effects of sevoflurane and desflurane on the microcirculation parameters during non-cardiac surgery.
Design: Prospective cohort study
Setting: Hacettepe University Medical Faculty and Hospital
Subjects: Patients with American Society of Anesthesiologists (ASA) score of I-II who underwent ≥2 hours of non-cardiac surgery were randomly divided into two groups: sevoflurane (n=20) and desflurane (n=19).
Intervention: Sevoflurane or desflurane
Main outcome measures: Demographic, hemodynamic (heart rate, mean arterial pressure) and laboratory parameters (hematocrit, hemoglobin, urea and creatinine) were measured. Microcirculation imaging was performed by using side stream dark field imaging.
Results: There were no statistical differences in demographic, hemodynamic and laboratory parameters between groups. In the sevoflurane group, the proportion of perfused vessel (PPV) was slightly increased at the second hour intraoperatively compared to the post-induction period in small vessels (94.7% vs 93%, *P*=.036), but other parameters (microvascular flow index, total vascular density and perfused vascular density) were comparable in both measurement periods. In the desflurane group, all microcirculation parameters were comparable between post-induction period and second hour intraoperatively.
Conclusions: Sevoflurane anesthesia slightly increases the PPV in small vessels, whereas desflurane has no effect on microcirculation parameters in ASA I-II non-cardiac surgery patients. Neither sevoflurane nor desflurane have major effects on microcirculation in this patient population.

KEY WORDS: anesthesia, desflurane, microcirculation, non-cardiac surgery, sevoflurane

INTRODUCTION

Microcirculation is a blood vessels network consisting of <100 μm diameter arterioles, capillaries and venules. Microcirculation is essential for adequate tissue oxygenation and important for organ function. Alterations in microcirculation can cause inadequate tissue oxygenation and may lead to organ failure[1].

Microcircular oxygen delivery cannot be predicted from global hemodynamic measurements and thus, microcirculation provides a novel way of assessing tissue perfusion. Sidestream dark field (SDF) is a new microcirculation imaging technique that allows bedside in vivo microcirculation imaging[2,3]. It is one of the most commonly used devices for assessing tissue perfusion and decreases in any of the measured parameters (proportion of perfused vessels (PPV), microvascular flow index (MFI), total vascular density (TVD), perfused vascular density (PVD)) reflect tissue hypoperfusion[4].

Previous animal studies showed that various injectable and inhalation anesthetic agents can cause microcirculatory alterations[5,6] and there are various reports about microcirculatory alterations in humans with sepsis, shock and cardiac failure. However, it is

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unknown whether anesthetics have a direct effect on microcirculation or their effects become evident in the presence of severe hemodynamic changes in these serious conditions. To our knowledge, there are no reports about microcirculatory alterations in humans during non-severe conditions or minor surgery.

Sevoflurane and desflurane are among the most commonly used inhalation anesthetics. Volatile anesthetics may cause global hemodynamic changes including hypotension and tachycardia through their effects on the myocardium and by decreasing systemic vascular resistance[7], and this hypotension may be associated with acute kidney injury and myocardial injury in patients undergoing non-cardiac surgery[8]. The effects of general anesthetics on microcirculation during coronary artery bypass graft surgery by using orthogonal polarization spectral imaging were investigated and the authors concluded that sevoflurane, but not desflurane, had a negative effect on microcirculation during cardiac surgery[9]. It has also been shown that cardiopulmonary bypass caused significant microvascular alterations during cardiac surgery[10], which was thought to be due to increased prevalance of hypothermia, surgical trauma, hemodilution and inflammatory reaction in this patient population. We hypothesized that inhalation anesthetics might have a direct effect on microcirculation and aimed to investigate microcirculatory alterations in non-cardiac surgery patients in whom the confounding effects of hemodynamic alterations are minimal, and also investigate whether a differential effect between sevoflurane and desflurane exists in this low-risk patient population.

SUBJECTS AND METHODS

Patients and procedures

The Institutional Ethical Committee approved the study protocol (approval number: 04-116-12) and informed consent was obtained from each patient. This prospective study was performed in a tertiary university hospital. All patients were evaluated preoperatively by the study team and patients who have end-stage organ failure, obstructive/restrictive respiratory disease, sepsis, shock and multi organ failure were excluded. A total of 39 patients with American Society of Anesthesiologists (ASA) score of I-II who underwent elective non-cardiac surgery (general surgery, urology, plastic surgery, gynecology, orthopedics and non-cardiac vascular surgery) were included. Patients were randomly divided into two groups and groups were named according to the inhalation agents used: sevoflurane (n=20) and desflurane (n=19).

In the operating room, patients were routinely monitored with electrocardiogram, pulse oximetry, non-invasive blood pressure and capnography. Anesthesia induction was performed using intravenous propofol (2 mg/kg), fentanyl (1 mcg/kg) and rocuronium (0.6 mg/kg). For anesthesia maintenance, inhalation agents were given at 1 MAC (sevoflurane 2% and desflurane 6%) in 50%-50% oxygen-air mixture. Inhalation agents were used in these patients during the entire surgery period. All patients were ventilated with synchronized intermittent mandatory ventilation mode. The ventilation parameters were tidal volume 6-8 ml/kg, ventilator frequency 10-12/min and all these parameters were adjusted to maintain an end-tidal CO_2 level between 35-45 mmHg.

The patients' demographic and clinical characteristics (age, sex, body weight, duration of anesthesia, comorbidities, drugs, fluid infusion) were recorded. The heart rate and blood pressure were also recorded after induction and at the 2nd hour of surgery. Laboratory parameters (hematocrit, hemoglobin, creatinine, blood urea nitrogen) were measured in the preoperative period.

Microcirculation analysis

Sublingual microcirculation was imaged using SDF method and recorded after induction and at the 2nd hour of surgery. A hand-held microscope was held steadily and perpendicular to the tissue surface without pressure to record the images from a mix of large and small vessels[11]. The video clips were taken for longer than 5 seconds from 5 different sublingual sites in each patient. The imaging output is red blood cell flowing as dark globules against a white/grayish background[12]. The analysis was performed as previously described by an investigator blinded to the inhalation agent used[9]. The SDF (MicroVision Medical, Amsterdam, the Netherlands) probe, covered by a sterile cap, was placed on a sublingual tissue surface to avoid pressure according to consensus report[13]. Image analysis was performed blindly in the recorded video clips by using the computer software (AVA 3.1; MicroVision Medical BV, Amsterdam, the Netherlands)[14]. The vessels were automatically detected by the program and then corrected by hand with a computer mouse. After the vessels were identified through analysis, the flow of every vessel was determined as absent (0), intermittent (1), sluggish (2) or continuous (3). The software provided the results of MFI score, TVD, PVD and PPV results of small, medium and all vessels with a report. MFI is the average of the flow in four quadrants. The PPV (%) is calculated with 100 * (total number of vessels – (no flow + intermittent flow))/ total number of vessels. PVD, an estimate of functional capillary density, is

Table 1: Patient characteristics and operative values (mean ± standard deviation)

Patient characteristics	Sevoflurane (n=20)	Desflurane (n=19)	Total (n=39)
Age (year)	47.9 ± 15.7	49.6 ± 14.5	48.7 ± 14.9
Female / Male (n/n)	11 / 9	10 / 9	21 / 18
Weight (kg)	71.6 ± 13.9	68.9 ± 18.2	70.3 ± 16
Anesthesia duration (min)	138.5 ± 57.4	152.1 ± 81.7	145.1 ± 69.7
Crystalloid fluid (ml)	1550 ± 705.2	1765.7 ± 858.3	1655.1 ± 780.7
Colloid fluid (ml)	282.5 ± 375.3	352.6 ± 367.2	316.6 ± 368.2
Blood transfusion (number of units)	1	2	3

calculated by multiplying vessel density by the proportion of perfused vessels[13].

Statistical analysis

Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL). All values are expressed as mean±standard deviation. The variables were analyzed using Kolmogorov-Smirnov/Shapiro-Wilks test to determine whether they were distributed normally. Statistical significance was tested using one-way ANOVA for parametric variables and Mann-Whitney U test for nonparametric variables. P <.05 was accepted as statistically significant

Table 2: Preoperative laboratory values (mean ± standard deviation)

Lab values	Sevoflurane (n=20)	Desflurane (n=19)	*P*-value
Hematocrit (%)	40 ± 5.2	39.7 ±3.3	0.870
Hemoglobin (g/dl)	13.5 ± 1.9	13.5 ± 1.1	0.884
Creatinine (mg/dl)	0.79 ± 0.15	0.92 ± 0.47	0.252
Blood urea nitrogen (mg/dl)	13.4 ± 4.5	17.8 ± 19.5	0.331

RESULTS

Patient characteristics, laboratory and hemodynamic parameters

There were no significant differences in the patients' characteristics and operative parameters between the groups (Table 1). During surgery, none of the patients received any vasodilator and/or vasoconstrictor drugs. Preoperative hematocrit, hemoglobin, creatinine and blood urea nitrogen values were similar among groups (Table 2). At the 2nd hour of surgery, heart rate significantly decreased in both groups compared to after induction values (P <.05). Mean arterial pressure and heart rate were similar in both groups during all time points (Table 3).

Table 3: Heart rate (beats/min) and mean arterial pressure (mmHg) in groups (mean ± standard deviation)

Hemodynamics	Sevoflurane	Desflurane	*P*-values#
Heart rate			
After induction	82.45 ± 13.56	83.16 ± 12.58	0.867
2nd hour	76.90 ±11.83*	70.26 ± 11.83*	0.065
At the end of surgery	77.90 ± 15.65	76.00 ± 12.21	0.676
Mean arterial pressure			
After induction	89.25 ± 19.91	85.02 ±10.81	0.418
2nd hour	87.37 ± 13.25	83.05 ± 10.18	0.263
At the end of surgery	86.85 ± 12.89	87.09 ± 11.58	0.952

* P <.05; compared to after induction; # P-values among sevoflurane and desflurane groups

SDF parameters of small, medium-large and all vessels

In the sevoflurane group at the second hour, MFI, TVD or PVD remained unchanged compared to post-induction period in small vessels (P >.05, Table 4). PPV of small vessels increased slightly (93% to 94.7%) at the second hour compared to post-induction period and this increase was statistically significant (P=.036). When medium-large vessels are analyzed, there were no changes in MFI, TVD, PVD or PPV in sevoflurane group at the second hour compared to post-induction period. When all vessels are analyzed together there was a slight but statistically significant increase in PPV at the second hour compared to post-induction period (P=.037), and the changes in MFI, TVD or PVD were not significant (P >.05).

In the desflurane group, there were no significant changes in MFI, TVD, PVD and PPV at second hour of anesthesia compared to post-induction period when

Table 4: SDF values in small, medium-large sized and all vessels in sevoflurane and desflurane groups (mean ± standard deviation)

Vessel type and measurement time	MFI (AU)		TVD (mm/mm²)		PVD (mm/mm²)		PPV (%)	
	Sevoflurane	Desflurane	Sevoflurane	Desflurane	Sevoflurane	Desflurane	Sevoflurane	Desflurane
Small vessels								
After induction	2.63 ± 0.2	2.69 ± 0.3	16.01 ± 1.9	16.51 ± 1.7	14.90 ± 1.9	15.59 ± 1.9	93.05 ± 4.2	94.24 ± 3.8
2nd hour	2.75 ± 0.3	2.73 ± 0.3	15.18 ± 2.0	16.17 ± 2.1	14.38 ± 2.1	15.16 ± 2.2	94.73 ± 3.7*	93.50 ± 5.2
Medium-large								
After induction	2.78 ± 0.3	2.88 ± 0.2	0.65 ± 0.4	0.56 ± 0.2	0.49 ± 0.4	0.46 ± 0.2	99.41 ± 2.6	97.96 ± 6.0
2nd hour	2.82 ± 0.3	2.86 ± 0.2	0.69 ± 0.3	0.50 ± 0.4	0.51 ± 0.4	0.39 ± 0.4	100.0 ± 0.0	97.71 ± 9.3
All vessels								
After induction	2.71 ± 0.3	2.79 ± 0.2	16.50 ± 1.8	16.97 ± 1.7	15.39 ± 1.8	16.04 ± 1.9	93.23 ± 4.2	94.39 ± 3.7
2nd hour	2.79 ± 0.2	2.81 ± 0.2	15.69 ± 2.0	16.57 ± 2.2	14.90 ± 2.2	15.55 ± 2.2	94.87 ± 3.6*	93.65 ± 5.1

*P<.05 compared to after induction, P >.05 for all other comparison, SDF: sidestream dark field; MFI: microvascular flow index; TVD: total vessel density; PVD: perfused vessel density; PPV: proportion of perfused vessels.

small and medium-large vessels are analyzed separately or together (P >.05, Table 4).

There were no significant differences between sevoflurane and desflurane groups for MFI, TVD, PVD and PPV at any time points studied (Table 4).

DISCUSSION

Microcirculation is essential for adequate tissue perfusion and oxygenation. Imaging of microcirculation provides information about a novel aspect of circulation evaluation for patients. Previous studies investigated the role of microcirculation in serious medical conditions such as sepsis, shock and cardiac surgery[9,10,15,16] and showed sevoflurane, but not desflurane, had a negative effect on microcirculation during cardiac surgery. Those patients have major hemodynamic alterations such as hypothermia, hypotension, surgical trauma and inflammatory reaction, which are known to directly affect microcirculation. In this study, we investigated microcirculation alterations in ASA I-II patients undergoing non-cardiac surgery in order to investigate the direct effects of anesthetic drugs in microcirculation, as this low-risk population has minimal hemodynamic alterations. Our results showed that sevoflurane and desflurane do not have substantial effects on microcirculatory parameters and that the agent of choice does not have any significant effects on these parameters in ASA I-II non-cardiac surgery patients.

The microcirculatory alterations during cardiac surgery have been well investigated. Cardiac surgery can alter microcirculation, especially during cardiopulmonary bypass (CPB) period, which causes significant changes in temperature, hematocrit, systemic blood pressure and arterial perfusion pressure that can affect systemic oxygen requirement[9]. Bauer *et al* showed that functional capillary density is decreased during cardiac surgery[17]. Uil *et al* compared sublingual microcirculation in CPB patients with sevoflurane anesthesia before and after surgery. They concluded that microvascular blood flow of medium and large vessels are decreased during CPB, and this decrease was not associated with hemodynamic parameters[18]. De Backer *et al* compared microcirculation in off-pump and on-pump cardiac surgery patients. They showed that PPV is dramatically decreased during CPB and on admission to the recovery room, PPV is still decreased in both off-pump and CPB patients, but the decrease in the latter is slightly more severe (60% vs. 64% in off-pump group). They also showed that in their control group (thyroidectomy patients), use of similar anesthetic procedure (propofol + remifentanil) also impairs PPV during surgery, but it is normalized in the recovery room in these patients. Therefore, they concluded that cardiac surgery alters microcirculation independent from CPB usage and the effects of anesthesia on microcirculation are transient[10]. Ozarslan *et al* investigated the effects of sevoflurane, isoflurane and desflurane on microcirculation in coronary artery bypass graft surgery. They showed that microcirculation is greatly altered during CPB period and sevoflurane use is associated with further decrease in TVD (14.7%), PVD (22%) and PPV (5.97%), whereas desflurane use was associated with a slight but statistically significant decrease in PPV (1.4%) and no significant changes in TVD or PVD[9]. In our study, sevoflurane slightly increased the PPV of small vessels (~2%) while desflurane had no effect on microcirculation in non-cardiac surgery in ASA I-II patients.

The effects of injectable anesthetics on microcirculation have been widely studied using other techniques. Landsverk *et al* used laser doppler to measure skin microcirculation and showed that propofol infusion impairs microcirculation in healthy subjects[19]. Koch *et al* investigated the effect of propofol on microcirculation in ASA I patients by using SDF and they concluded that propofol decreased microcirculation transiently[20]. Blasi *et al* investigated effects of sevoflurane + remifentanil and propofol + remifentanil combination on microcirculation in healthy patients during maxillofacial surgery by using near infrared spectroscopy[21]. In both groups, microcirculation parameters increased during surgery. In our study, we used a more advanced and new technique, SDF, to quantify microcirculation and demonstrated that sevoflurane and desflurane do not induce substantial changes in microcirculatory parameters.

It is known that microcirculation is impaired in sepsis. De Backer *et al* compared sublingual microcirculation in 10 healthy volunteers, 16 patients who will undergo cardiac surgery, 10 acutely ill patients without sepsis and 50 patients with severe sepsis by using orthogonal polarization spectral. They showed that microvascular blood flow alterations are common in sepsis patients and there is no correlation between arterial blood pressure and microcirculation[15]. Sakr *et al* showed that impairment in microcirculation is associated with mortality in septic shock patients, and that survivors have improvement in small vessel perfusion, whereas those that did not survive had no improvement[16]. Another study showed that severity of microcirculation impairment is correlated with organ dysfunction and mortality[22]. In addition, De Backer *et al* showed that microcirculatory alterations are frequent in acute severe cardiac failure patients[23].

The main limitation of our study is the small patient population who underwent different types of short-duration minor surgeries and due to limited number

of patients, separate analysis by surgery type could not be done, which can potentially affect microcirculation. Whether microcirculation is affected by the type of minor surgery requires further investigation. Also, none of our patients had post-surgical organ failure. As a result, we could not investigate whether there is a correlation between microcirculation and post-surgical organ failure development in this low-risk patient population. Future studies investigating effects of sevoflurane and desflurane in development of post-surgical organ failure in a larger group of patients or higher risk patients are warranted.

CONCLUSION

We showed that neither sevoflurane nor desflurane alter microcirculation substantially during non-cardiac surgery in ASA I-II patients. Our results suggest that anesthetic of choice is not of critical importance in this patient population in terms of tissue perfusion.

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Original Article

Vitamin D deficient diet and autism

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ABSTRACT

Objectives: To study the role of vitamin D deficient diet in development of autism spectrum disorders in Saudi children aged 3-10 years in Northern region (Arar) and Eastern region (Dammam) in the Kingdom of Saudi Arabia
Design: Case-control study
Setting: Al Amal Mental health complex, Arar; Shumua Al Amal Centre for Special Education and Rehabilitation, Shamah Autism Centre and Prince Sultan Rehabilitation Complex, Dammam, Saudi Arabia
Subjects: Data on 100 Saudi autistic children aged 3-10 years and 100 normal children were collected via a questionnaire. The questionnaire inquired about sociodemographic characteristics, family history, ante-natal history and developmental history of the children.
Intervention: Non-interventional
Main outcome measure: To find out the association between vitamin D rich diet and development of autism in children
Results: There was a significant association between vitamin D deficient diet and autism**.** Increased maternal age was observed in autistic children when compared to normal children.
Conclusion: Children were found to have a deficiency in consumption of food rich in vitamin D. The vitamin D deficient diet of the child along with increased maternal age during pregnancy may contribute to development and severity of autism.

KEY WORDS: autism, diet, vitamin D

INTRODUCTION

Autism spectrum disorders (ASD) are developmental disorders which affect communication and behavior. The prevalence is about 1% in the general population[1]. Standardized interviews of parents of children with autism and child observation help in differentiating children with ASD from children with other developmental disabilities[2-4]. Other than bone development anomalies, vitamin D (25(OH)D) deficiency has been considered as a potential environmental factor which can trigger autoimmune disorders including ASD[5-6].

Some researchers found low levels of maternal vitamin D and lack of exposure to sunlight as risk factors for ASD[7-12]. In Chinese autistic children, serum 25(OH)D levels were significantly lower when compared with normal children. The researchers were of the opinion that the lower 25(OH)D levels may be independently associated with severity of ASD among Chinese children[13].

There were also contradictory reports with regard to role of vitamin D deficiency in the development of autism. Animal studies in mice concluded that prenatal deficiency in vitamin D has had no correlation with autism relevant behavior[14]. A recent review on vitamin D and autism concluded that there was no significant difference in vitamin D levels between normal children and autistic children, though they commented that further studies on this aspect of autism were necessary[15].

Since vitamin D level is a risk factor that can be corrected, understanding the role of vitamin D deficiency on brain development can help in the treatment and prevention of autism. Some researchers

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support the hypothesis that maternal vitamin D supplements during pregnancy and vitamin D supplementation to infants and toddlers might reduce the incidence of autism[16].

In a clinical review of vitamin D and autism, the researchers concluded that vitamin D deficiency during pregnancy or early childhood can act as an environmental trigger for ASD in individuals who are genetically predisposed for the broad phenotype of autism and that there was a need for further research in the field[17]. The present study was therefore undertaken to find the association of vitamin D deficient diet of children and autism.

SUBJECTS AND METHODS

After confirming the diagnosis of autism using DSM-V criteria, data were collected by parent interviews of 100 Saudi autistic children aged 3-10 years who attended the child psychiatry clinic of Al Amal Mental health complex, Arar; Shumua Al Amal Centre for Special Education and Rehabilitation; Shamah Autism Centre and Prince Sultan Rehabilitation Complex, Dammam, Saudi Arabia. The subjects were selected by convenient sampling. Informed consent was taken from the parents before interviewing them. Ethical committee approval was given by Local Committee of Bioethics of Northern Border University, Arar, Saudi Arabia and Ministry of Heath, Arar, Saudi Arabia (IRB number: 11/38/H).

A specially designed questionnaire which included family characteristics of the child, family income, nutritional status of the mother during pregnancy, birth weight of the child, dietary intake of the child (especially diet rich in vitamin D), was used in the study for data collection. The questionnaires were administered to the mothers individually to enable investigators to assist them. The 100 autistic children were compared to 100 normal children from the same age group who attended the Department of Paediatrics, Arar Maternity and Child Health Centre, Arar, Saudi Arabia and Baraam AlSharqiyah School, Dammam, Saudi Arabia. Autistic children who had congenital malformations, metabolic disorders or deafness were excluded from the study. The Childhood Autism Rating Scale was used to assess the severity of autism. It is a 15-item behaviour-rating scale which helps to detect the symptoms of autism.

Statistical analysis was done using Stata 15 Statistical Software and *P*-value <.05 was considered significant. A composite measure for vitamin D rich diet was formed and used as a proxy by summing the possible responses of milk intake, fish, fruit and vegetables, and regular meal consumption and categorising into either sufficient or deficient vitamin D consumption. Univariate analyses were expressed as counts and percentages for categorical data and means ± standard deviations for continuous data. Bivariate analyses were performed followed by multi-nominal logistic regression since the proportional odds assumption did not hold. Regression was performed with age and sex to test for factors associated with the severity of autism with reference to the normal category. Model fit diagnostics including residual analyses were done to check for the best model fit, the model that minimised both the Akaike's Information Criteria and the Bayesian Information Criteria was chosen.

RESULTS

Table 1 shows descriptive statistics per level of severity of autism. Majority of children were males below 5 years of age. Age difference between siblings of autistic children was found to be higher in the mild to moderate category of autism and the mean age

Table 1: Child and family characteristics of the 200 Saudi children

Child and family characteristics	Normal n(%) (n=100)	Mild to moderate n(%) (n=69)	Severe n (%) (n=31)
Child's age			
Above 5 years old	36 (36)	11 (15.94)	02 (06.45)
Below 5 years old	64 (64)	58 (84.06)	29 (93.55)
Sex			
Male	53 (53)	57 (82.61)	19 (61.29)
Female	47 (47)	12 (17.39)	12 (38.71)
Age difference between siblings	2.51 (01.49)	2.82 (01.36)	2.12 (00.98)
Mother's occupation			
Administrative job	10 (10)	02.00 (02.90)	0
Teaching	18 (18)	12 (17.39)	05 (16.13)
Housewife	46 (46)	51 (73.91)	24 (77.42)
Health sector	18 (18)	04 (05.80)	02 (06.45)
Other	08 (08)	0	0
Father's occupation			
Administrative job	23 (23)	14 (20.29)	04 (12.90)
Engineer	14 (14)	06 (08.70)	0
Health	08 (08)	01 (01.45)	01 (03.23)
Police and military	26 (26)	22 (31.88)	13 (41.94)
Teaching	15 (15)	11 (15.94)	05 (16.13)
Other	09 (09)	08 (11.59)	01 (03.23)
Unemployed	05 (05)	07 (10.14)	07 (22.53)
Adequate income			
No	13 (13)	23 (33.33)	07 (22.58)
Yes	87 (87)	46 (66.67)	24 (77.50)
Dietary supplements of mother			
No	07 (07)	15 (21.74)	04 (12.90)
Yes	93 (93)	54 (78.26)	27 (87.10)
Age of mother when child was born	26.68 (4.95)	28.92 (6.01)	31 (4.93)
Birth weight			
Normal	92 (92)	60 (86.96)	30 (96.77)
Low weight	07 (07)	07 (10.14)	01 (03.23)
Overweight	01 (01)	02 (02.90)	0

Table 2: Vitamin D rich food diet intake between different categories of autism severity

Food intake of children	Normal n(%) (n=100)	Mild to moderate n(%) (n=69)	Severe n (%) (n=31)
Regular meals			
No	14 (14)	17 (24.64)	14 (45.16)
Yes	86 (86)	52 (75.36)	17 (54.84)
Milk intake			
No	17 (17)	25 (36.23)	21 (67.74)
Yes	82 (82)	44 (63.77)	10 (32.26)
Fish and eggs intake			
No	10 (10)	20 (28.99)	15 (48.39)
Yes	90 (90)	49 (71.01)	16 (51.61)
Fruits			
No	15 (15)	28 (40.58)	18 (58.06)
Yes	85 (85)	41 (59.42)	13 (41.94)
Vitamin D rich diet			
No	34 (34)	42 (60.87)	23 (74.19)
Yes	66 (66)	27 (39.13)	08 (25.81)

difference was 2.82 years (± 01.36 SD). An increase in the mean age of the mother at the time of childbirth was found to increase with the severity of autism. The mean age of mothers of normal children was 26.68 years (±4.95 SD) while the mean age of mothers of children with mild to moderate autism was 28.92 years (± 6.01 SD) and with severe autism was 31 years (± 4.93 SD).

Table 2 describes the food intake of the children. Of the children with a severe degree of autism, 45.16% were not taking regular meals when compared to 24.64% in the mild to moderate group and 14% in the normal children category. Regarding vitamin D rich diet intake, 74.19% of severely autistic children were deficient, compared to 60.87% in the mild to moderate and 34% in the normal children category.

The multinominal logistic regression after adjusting for both age and sex showed that factors like family income and vitamin D rich diet in children with mild to moderate degree of autism had a negative association (OR=0.32, 95% CI=0.13-0.81 and OR=0.27, 95% CI=0.12-0.57 respectively) while the age of the mother when the child was born had a positive association (OR=1.10, 95% CI=1.02-1.18) (Table 3).

Severity of autism was found to be lower in females when compared to males, although not statistically significant (OR=0.60, 95% CI=0.22-1.63), as well as with increasing age difference between siblings (OR=0.56, 95% CI=0.37-0.84) and a very high and significant protective effect for vitamin D rich diet consumption (OR=0.13, 95% CI=0.04-0.37). There was a highly positive association between age of the mother when the child was born and autism where OR was 1.23 (95% CI=1.11-1.36).

DISCUSSION

It has been reported that vitamin D influences brain function, neuronal differentiation and axonal connectivity[18]. Several studies have shown that maternal vitamin D deficiency is a risk factor for development of autism in children. It has been suggested that low birth weight could be related to maternal vitamin D deficiency[19].

Some researchers were of the opinion that oral vitamin D supplementation can improve signs and symptoms of ASD[20]. A study done on 100 autistic children showed dramatic improvements in 25% of children who were treated with high doses of vitamin D[21].

It has been reported that the pathogenesis of autism may begin in fetal life and special attention has to be given to metabolic disorders during pregnancy as it can increase the risk of ASD in children[22]. Even though it has been established that mother's dietary deficiency during pregnancy can contribute to the development of autism in children, there is a paucity of literature regarding the role of nutritional status of children during early childhood in the development of autism.

According to the Dietitians of Canada report[23] and the USDA National Database for Nutrient Reference[24], milk, yoghurt, fish and egg yolk are rich sources of vitamin D. In the present study, only 75.36% of the

Table 3: Multinominal logistic regression of child and family characteristics for severity of autism

Child and family characteristics	Mild to moderate*			Severe*		
	RRR	95% CI	*P*-value	RRR	95% CI	*P*-value
Age	3.57	1.49-8.54	0.004	14.17	2.72-73.79	0.002
Sex						
Female	0.21	0.09-0.46	0.000	0.60	0.22-1.63	0.322
Age difference	1.02	0.78-1.33	0.855	0.56	0.37-0.84	0.006
Income						
Yes	0.32	0.13-0.81	0.017	0.68	0.19-2.34	0.543
Age of mother when child was born	1.10	1.02-1.18	0.006	1.23	1.11-1.36	0.000
Vitamin-D rich diet						
Yes	0.27	0.12-0.57	0.001	0.133	0.04-0.37	0.000

*Normal children were used as reference group
RRR: relative risk ratio

children with mild to moderate degree of autism and 54.84% of children with severe degree of autism were taking regular meals when compared to 86% of children who were in the normal category.

63.77% of children with mild to moderate degree of autism and 32.26% of children with severe degree of autism were consuming milk regularly while 82% of normal children consumed milk regularly.

In the current study, 90% of normal children had a daily consumption of egg and fish while it was 71.01% in children with mild to moderate degree of autism and 51.61% in children who had severe autism.

Overall consumption of vitamin D rich diet was found in 8% in children with severe degree of autism and 39.13% in children with mild to moderate degree of autism when compared to 66% of children in the normal category.

CONCLUSION

Vitamin D deficient diet can be a risk factor for autism. Severity of autism can also be associated with severity of vitamin D deficiency. More studies should be done with larger sample to establish the effect of vitamin D deficiency on autism.

Limitations of the study: Small sample size of 100 autistic children included in our study could have caused a degree of sampling error. Bigger sample size is needed to establish the association of vitamin D deficiency with autism.

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Conflict of interest: The authors declare no potential conflicts of interests.

Author's contribution: Reem AlOmar did the statistical analysis and manuscript writing; Anitha Oommen collected data from Arar and contributed to writing the manuscript; Halah Aljofi collected data from Dammam and wrote the discussion.

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Original Article

Intubating conditions with articulating vs. intubating stylet during video laryngoscope intubation in anticipated difficult airway patients

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ABSTRACT

Objective: To evaluate the intubation conditions and length of intubation duration of a conventional stylet and an articulating stylet during video laryngoscopy in anticipated difficult intubations
Design: A prospective randomized comparative study
Setting: University of Health Sciences Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey
Subjects: Forty-nine patients aged 18-65 years assigned for elective surgery with anticipated difficult intubation were randomized to intubation with either an articulating stylet (Group AS, n=25) or intubating stylet (Group IS, n=24) during videolaryngoscopy.
Interventions: Standard anesthesia induction was performed and muscle relaxation was facilitated with rocuronuim 0.6 mg/kg after assessment of mask ventilation. In all patients, the same video laryngoscope and angulated blade was used. Anticipated difficult airway scores, thyromental distances (cm), maximum mouth opening, existence of buckteeth, cervical spine range of motion, Mallampati scores, time to intubation (TTI) and number of attempts were recorded. Mean arterial pressure, heart rate and oxygen saturation were recorded before anesthesia induction (T0), one minute after induction (T1), before attempt of intubation (T2) and one minute after intubation (T3).
Main outcome measures: Success rate and duration of intubation during videolaryngoscopy
Results: The mean TTI was significantly shorter in the AS group than in the IS group (51.8±26.2 s vs 112.8±84.7 s) (*P*=.001). Successful intubation performance (percent) in the first attempt was 60% in AS group and 16% in IS group (*P*=.032).
Conclusion: During intubation with highly angulated videolaryngoscopes in patients with anticipated difficult intubation, the use of articulating stylets which provide this angulation simultaneously might facililate intubation.

KEY WORDS: articulating stylet, difficult airway, tracheal intubation, videolaryngoscope

INTRODUCTION

Video laryngoscopes (VLs) provide a better view of laryngeal structures when compared with conventional direct laryngoscopy. However, although they provide a better view, tracheal intubation can still be difficult because the pharyngo-laryngo-tracheal axis might not be in alignment.

The use of blades with a greater vertical angle might provide a better glottic view, but their use can also make intubation more difficult; having a good view of the glottis does not ensure an easy intubation[1,2]. To direct the endotracheal tube (ETT) to the target, many anesthesiologists prefer to use stylets. Without stylets, intubation often takes longer, requires repeated attempts, and in some cases, can be unsuccessful all together[3]. As such, the use of preformed vertically angled stylets with a suitable blade angle has been suggested[4].

Articulating stylets are loaded in the tracheal tube before intubation and enable angling during intubation. This study investigates the success rate and duration of intubation when using a conventional stylet versus that of an articulating stylet during videolaryngoscopy in anticipated difficult intubations.

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SUBJECTS AND METHODS

This prospective, randomized, single-blind study was conducted after ethics committee approval was obtained from the ethical committee of the Ministry of Health Diskapi Yildirim Beyazit Training and Research Hospital (Ethical Committee 27/28; approved on 22/03/2016) and written informed consent was obtained from patients. This trial was registered at www.clinicaltrials.gov (NCT02805569).

Included in this study were eligible patients between the ages of 18 and 65 who had American Society of Anesthesiologists scores of 1 or 2 and who were assigned for elective surgery with anticipated difficult intubation due to anticipated difficult airway scores greater than 6[5] (Table 1). Patients who had undergone oropharyngeal surgery before, had an immobilized cervical spine, required rapid sequence induction, required emergency surgery, had a tendency to bleed, required awake fiberoptic intubation or were pregnant were excluded from the study. Patients were randomly assigned to either the articulating stylet (AS) group or to the intubating stylet (IS) group using computer-generated random numbers.

Table 1: Anticipated Difficult Airway (ADA) Score*

Airway Factors	0	1	2
Mallampati classification	Class I	Class 2	Class III-IV
Tyromental distance (cm)	>6.5	6-6.5	<6
Head and neck movement (degrees)	>90	90	<90
Body mass index (kg/m^2)	<25	≥25	NA
Buck teeth	No	Mild	Severe
Inter-incisor gap(cm)	>5	4-5	<4

*Easy airway strata: ADA score ≤ 6; difficult airway strata >6; NA not applicable[5]

In the preoperative assessment, each patient's anticipated difficult airway score, thyromental distance (cm), maximum mouth opening (cm), existence of buckteeth, cervical spine range of motion and Mallampati score were recorded[6]. Patients did not receive any premedication and they were monitored using an electrocardiogram, pulse oximetry (SpO_2) and a non-invasive blood pressure monitor in the operating room. All patients received 100% oxygen at a rate of 5L/min with a closed breathing circuit until their end-tidal oxygen reached over 90.

Anesthesia induction was managed using 1 mcg/kg fentanyl and 2 mg/kg propofol, and muscle relaxation was facilitated using 0.6 mg/kg rocuronium after assessing mask ventilation. For all patients, the same type of VL and blade (C-Mac Storz D-Blade®, Karl Storz Endoscopy, Tuttlingen, Germany) were used. Male patients received 7.5 to 8 cuffed ETTs, while female patients received 6.5 to 7.

After lubrication, the stylet (Truphatec® International Ltd., Netanya, Israel) was loaded with the suitable ETT for the patients in the AS group (Figure 1). When glottis view was achieved, the ETT loaded with an AS shaped in the appropriate manner advanced through the glottis. While the AS was being removed after the intubation, the AS was returned to its neutral position in order to facilitate the withdrawal of the ETT. For the patients in the IS group, the stylet (Work® Lotus Global Co. Ltd., London, UK) was loaded with the adequate ETT and given the same angle as the blade (*i.e.*, the ETT was shaped according to the curvature of the VL blade).

The anesthesiologist performing the videolaryngoscopy advanced the stylet loaded with the ETT only if the laryngeal inlet view of glottic opening score percentage was above 40%. The intubations completed in this study were performed by three anesthesiologists, each of whom had more than 10 years of experience and completed at least 50 successful intubations using a VL.

Primary outcome monitored in this study was the time to intubation (TTI), which is defined as the time from inserting the blade between the patient's incisors to viewing the first end-tidal carbon dioxide tracing on the capnograph. The stopwatch was stopped if the intubation was unsuccessful during the first attempt. In other attempts, the stopwatch was started again from the same point. Only successful tracheal intubation times were counted in the analysis. An attempt was still counted if the VL or ETT needed to be removed for reoxygenation or for the reshaping of the stylet. During each intubation attempt, another experienced anesthesiologist, as well as difficult airway equipment, was kept at the ready in case of "can't intubate, can't oxygenate" situations, according to Difficult Airway Society guidelines[7].

When intubation duration exceeded 2 minutes or peripheral SpO_2 decreased below 95%, the attempt was accepted as a failed attempt and mask ventilation was used instead. A maximum of three attempts was allowed for intubation, with anesthesia being discontinued if a fourth attempt using a different intubation method also failed.

The intubation performance of the stylets was classified as "easy", "medium" or "difficult". Blood on the VL blade was reported as indicating oropharyngeal bleeding, and mucosal bleeding after intubation was recorded as "none", "trace", "moderate" or "severe".

Mean arterial pressure, heart rate and SpO_2 were recorded before anesthesia induction (T0), one minute after induction (T1), before intubation attempt (T2) and one minute after intubation (T3).

Patients were extubated after the reversal of the neuromuscular block and after having ensured

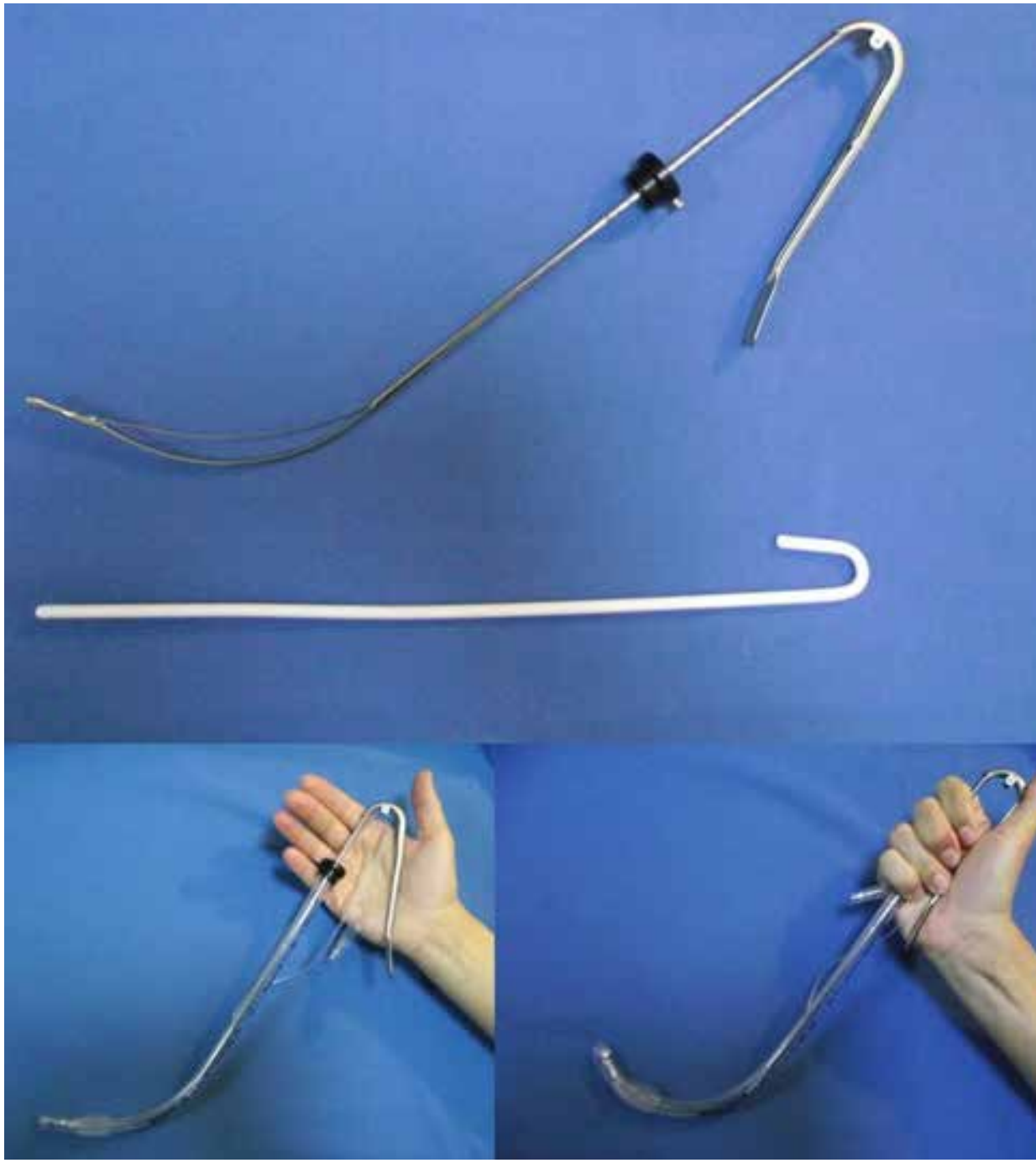

Fig 1: Truflex® articulating stylet and the Work® intubating stylet

a sufficient tidal volume and that the patient is responsive to verbal stimuli, by administering 4 mg/kg sugammadex intravenously, taking precautions for difficult reintubation (*e.g.*, changing catheters). Complications such as bleeding, laryngospasm, bronchospasm and desaturation were recorded.

Group size was calculated according to the results of a pilot study (AS group: n=4, 50.88±28 s; IS group: n=4, 105.27±85 s TTI), on the basis of detecting a 50% decrease in the TTI in the AS group when compared with the IS group. A minimum of 24 patients was required in each group (α=0.05, power 80%). In this study, 26 patients were included in each group because of dropout.

Statistical analysis was performed using SPSS 15.0 software (SPSS Inc., Chicago, Illinois, USA). Data

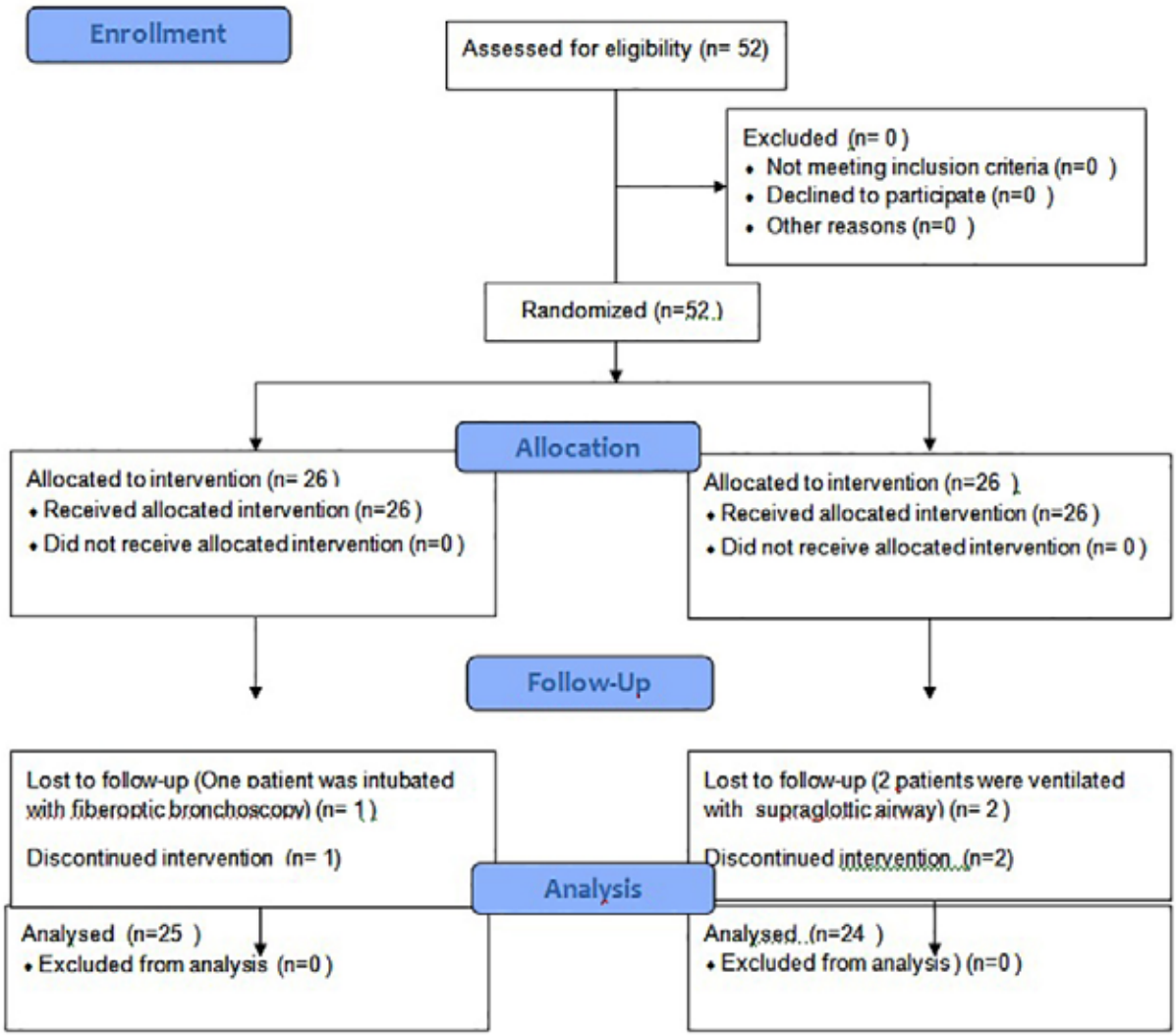

Fig 2: Consort diagram (AS, Articulating Stylet; IS, Intubation Stylet)

are presented as mean±SD, percentages, medians or ranges. All data were tested for normal distribution using the Kolmogorov–Smirnov test. Statistical analysis was performed using the t-test for continuous variables, the Mann–Whitney U test for nonparametric variables and the x^2 or Fisher's Exact test for categorical variables. A *P*-value <.05 was considered statistically significant. A repeated measure analysis of variance test was performed for the analyses of hemodynamic variables.

RESULTS

Of the 52 patients considered in this study, 49 patients participated (Figure 2). One patient from the AS group was intubated using fiberoptic bronchoscopy and two patients from the IS group were ventilated

Table 2: Demographic details of the patients

Demographic details	Group AS (n=25)	Group IS (n=24)	*P*
Age (years) (mean±SD)	46.8±10.3	49.0±13.1	.627
Sex (Female/Male)(n)	12/13	8/16	.296
BMI (kg/m^2)	26.5±4.5	28.4±4.45	.139
Mallampati score (1/2/3/4) (n)	0/3/17/5	0/0/19/5	.213
Head and neck movement degrees (>90/90/<90) (n)	17/6/2	9/10/5	.09
Tyromental distance (cm)	6.1±0.63	6.2±0.69	.551
Inter-incisor gap (cm)	4.7±0.6	4.9±0.7	.455
Buck teeth (No/Mild/Severe) (n)	19/6/0	19/5/0	.791
ADA score (7/8/9/10) (n)	4/10/10/1	4/9/10/1	.998

ADA: anticipated difficult airway
Data are presented as mean ± SD or number.*P <.05 significant differences between the groups.

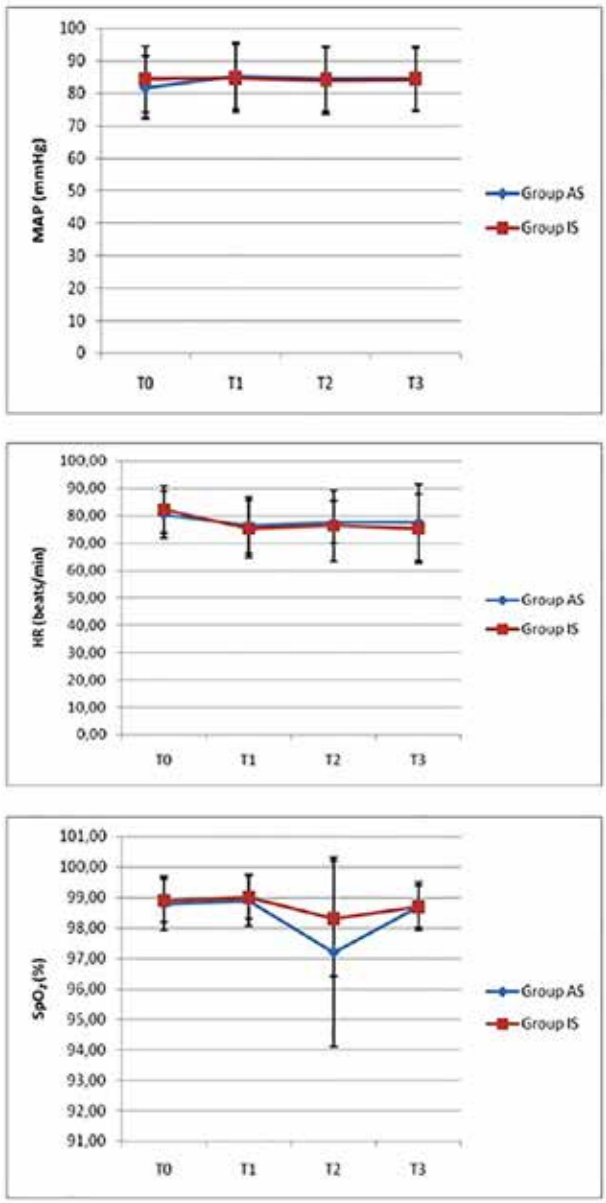

Fig 3: Hemodynamic and SpO_2 changes during anesthesia induction. **P* <.05 compared between the Group AS and Group IS. Data are expressed as mean±SD.

using supraglottic airway devices; as such, these three patients were excluded from the study.

The demographic details of the patients were similar (*P* >.05, Table 2). The two groups in the analysis were homogeneous, with no significant differences among the participants. The mean arterial pressure, heart rate and SpO_2 values of the patients were similar at all assessment periods (*P* >.05, Figure 3).

The mean TTI was significantly shorter in the AS group than it was in the IS group (51.8±26.2 s vs. 112.8±84.7 s, *P*=.001, Table 3). The number of attempts for successful intubation was also significantly lower in AS group than it was in the IS group, with the successful intubation rate upon first attempt in the AS group being 60% and in the IS group 16% (*P*=.032, Table 3). The percentage of glottic opening, bleeding and ease of intubation scores were similar in both groups (*P* >.05, Table 3).

Table 3: Intubation profiles

Intubation profiles	Group AS (n=25)	Group IS (n=24)	*P*
POGO (%)(mean±SD)	61.4±10.3	51.8±26.2	.185
TTI (s) (mean±SD)	51.8±26.2	112.8±84.7	.001*
Number of attempt (1/2/3)(n)	15/9/1	4/14/6	.032*
Bleeding (none/trace/moderate/severe)	16/9/0/0	17/7/0/0	.610
Ease of intubation (easy/moderate/difficult)	11/6/8	5/11/8	.224

POGO: percentage of glottic opening; TTI: time to intubation
Data are presented as mean ± SD or number.**P* <.05 significant differences between the groups.

There were no complications related to intubation or extubation such as laryngospasm or bronchospasm in the perioperative period.

DISCUSSION

The results of this study indicate the rates of intubation success of ASs and ISs are comparable; however, ASs lead to 50% faster intubation and fewer intubation attempts during intubation with VLs.

Guidelines have been created for performing difficult intubations and the use of VLs features in these guidelines[8]. The C-Mac D-Blade is a significantly angled blade that was specially designed for difficult laryngoscopy[9]. This blade, with its increased slope, was designed for performing difficult indirect laryngoscopy in patients with a Cormack–Lehane grade of 3 or 4. However, even with the aid of the C-Mac D-Blade and even when the glottis is clearly in view, it can still be difficult to direct the ETT to the trachea[10].

An AS is a stylet for which the 3 cm distal part can be curved to an angle of 30 to 60 degrees with the aid of an operator. In other words, the AS permits the dynamic shaping of the curvature of the distal end of the premounted ETT based on the angle required during videolaryngoscopy[5]. Hence, in addition to facilitating intubation, it can increase the operator's comfort, as this study determined that comfort of the anesthesiologist was better in the AS group than it was in the IS group.

In a mannequin study, Mc Elwain *et al* pointed out that it is not necessary to use a stylet in cases of easy laryngoscopy but that, in cases of difficult laryngoscopy, the angulation of the distal part of the ETT can optimize intubation[11]. It was also reported

that, in a study that used five different stylets—including the C-Mac D-Blade—on mannequins simulating difficult laryngoscopy, stylet use was necessary, but there was a little difference among the stylets in terms of intubation duration.

Some previous studies have recommended using ASs with specially angled blades before intubation, such as C-Mac D-Blades[12]. However, anterior commissure produces resistance, which impedes the advance of the ETT to the trachea[13]. Therefore, shaping the stylet according to the blade during the intubation attempt and reshaping it during the advance to the trachea may facilitate intubation.

The intubation time was found to be shorter in the AS group in this study (51.8±26.2 s vs. 112.8±84.7 s). This result may be due to angulation of the preloaded ETT as well as the anesthesiologist's ability to manipulate this angle when needed. In a mannequin study conducted by Batuwitage, which compared TTI in difficult settings using a tube that was distally loaded at the tip and a proximally loaded bougie tube with intubating stylets, the TTIs were 16.5 seconds (14-21 seconds) and 16.5 seconds (15-20.5 seconds), respectively[14]. In a study by Lee, however, routine videolaryngoscopy was used for intubation and TTI was 29.3±6.4 s versus 32.5±9.4 s, with a 60°-angled IS versus a 90°-angled IS, respectively[13]. In the latter study, the mean TTI was longer than it was in the current study, which might be because all patients in the current study were candidates for difficult intubation.

The primary finding of this study is that the number of intubation attempts was lower in the AS group than it was in the IS group. This might be due to the need to withdraw the ETT to reshape the style in the IS group.

There are a few limitations in this study. First, as the patients were assessed as candidates for difficult intubation and videolaryngoscopic intubations are handled by a senior anesthesiologist, the intubation attempts might have been fewer and the intubation duration might have been shorter because of the high level of experience of those performing the intubation. Hence, another study could be conducted to examine the performance of these stylets in less experienced hands. Second, there may be reporting bias in this study, as it was not a double-blind study.

CONCLUSION

This study demonstrated that during intubation with highly angulated VLs in patients with anticipated difficult intubation, stylets must be set to an angle that is similar to that of the blade used. The use of ASs, which allow for this angulation to be performed, can therefore facilitate intubation.

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Author contribution

Derya Ozkan: design analysis and/or interpretation, manuscript writing; Burak Nalbant: data collection and/or processing; Ilkay Baran: data collection and/or processing, supervision; Murat Sayin: materials and literature search; Julide Ergil: resources; Asli Donmez: resources.

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Case Report

Primary mucinous adenocarcinoma of the renal pelvis with signet ring cell formation

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ABSTRACT

Primary mucinous adenocarcinoma is exceedingly rare in renal pelvis neoplasms, and a signet ring cell formation in this kind of tumor is even more uncommon. Our report presents a unique case of this tumor with a concise review of the literature. From this case, we can conclude that primary mucinous adenocarcinoma with a signet ring cell formation may be a sign of poor prognosis.

KEY WORDS: metastasis, mucinous adenocarcinoma, pathological diagnosis, renal pelvis, signet ring cell

INTRODUCTION

Primary mucinous adenocarcinoma of the renal pelvis (MARP) is an exceptionally rare tumor with a poor prognosis, while MARP with a signet ring cell formation is even more uncommon[1,2]. Our report presents a case of MARP with signet ring cell changes diagnosed by pathological examination. We conclude that MARP with signet ring cell differentiation is a predictor of poor prognosis.

CASE REPORT

A 30-year-old woman was admitted to our hospital because of abdominal pain and discomfort. She denied having hematuria or a fever. Physical examination revealed an abdominal mass. After an abdominal ultrasound evaluation, a large cystic tumor was found in her left retroperitoneal area. Tests of routine blood, blood coagulation function, and liver and kidney function were unremarkable. Elevated serum levels of CA199 and CEA were 56.7 U/ml (normal value: less than 27U/ml) and 236.3 ng/ml (normal value: less than 5ng/ml) respectively. Computed tomography and magnetic resonance imaging were performed and showed a 11.0 cm solid-cystic calcified tumor located in the left kidney (Figure 1). Local enlarged lymph nodes and multiple lesions in the liver and lung were discovered. A clinical diagnosis of primary renal cancer and distant metastasis was considered. The patient consented to a laparoscopic radical nephrectomy via the intraperitoneal route without lymph node dissection. Gross examination of the specimen showed a cyst-solid mixed tumor containing a significant amount of thick, jelly-like mucus (Figure 1). Hematoxylin-eosin (Figure 2) staining showed an abundant mucin pool. Neoplastic cells with hyperchromatic pleomorphic nuclei infiltrated the renal pelvis and some floated in the mucin pool. However, the tumor did not invade the adjacent adrenal gland and renal parenchyma. Some neoplastic cells had signet ring cell features. The mucous membrane of the renal pelvis was completely eroded by tumor cells. The patient followed up for three months and did not have surgical complications or disease progression. She continued therapy on Chinese medicine only.

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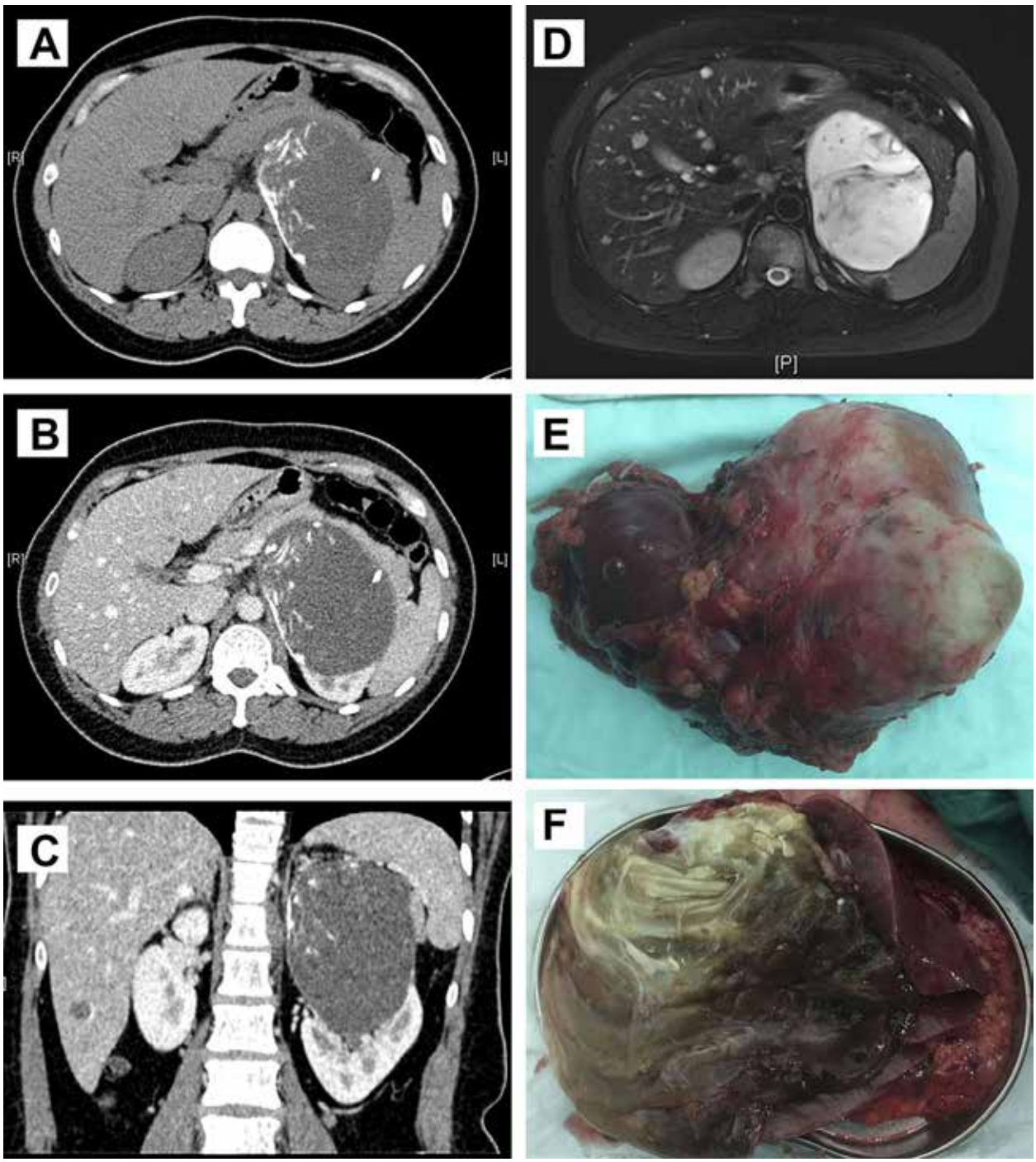

Fig 1: Axial computed tomography (CT) (A, non-enhanced; B, contrast-enhanced) and coronal CT (C) images show a giant cyst-solid mixed tumor located in the left kidney. Multiple lesions in the liver were also discovered (B, C, and D, magnetic resonance images). Gross investigation showed a cyst-solid mixed tumor containing an abundant thick, jelly-like and taupe mucus (E and F).

DISCUSSION

The rarity of primary MARP makes a preoperative diagnosis difficult to achieve, as patients with MARP usually present with nonspecific symptoms or may even be asymptomatic. Some patients complain of hematuria. Our case presented with abdominal pain only, which is considered a sign of late-stage MARP[1].

The pathogenesis of MARP is still unknown. According to previous clinical reports, it may be associated with chronic inflammation and long-term irritation by stones[2]. Our case also had stones or calcified plaques in the tumor; however, it is uncertain

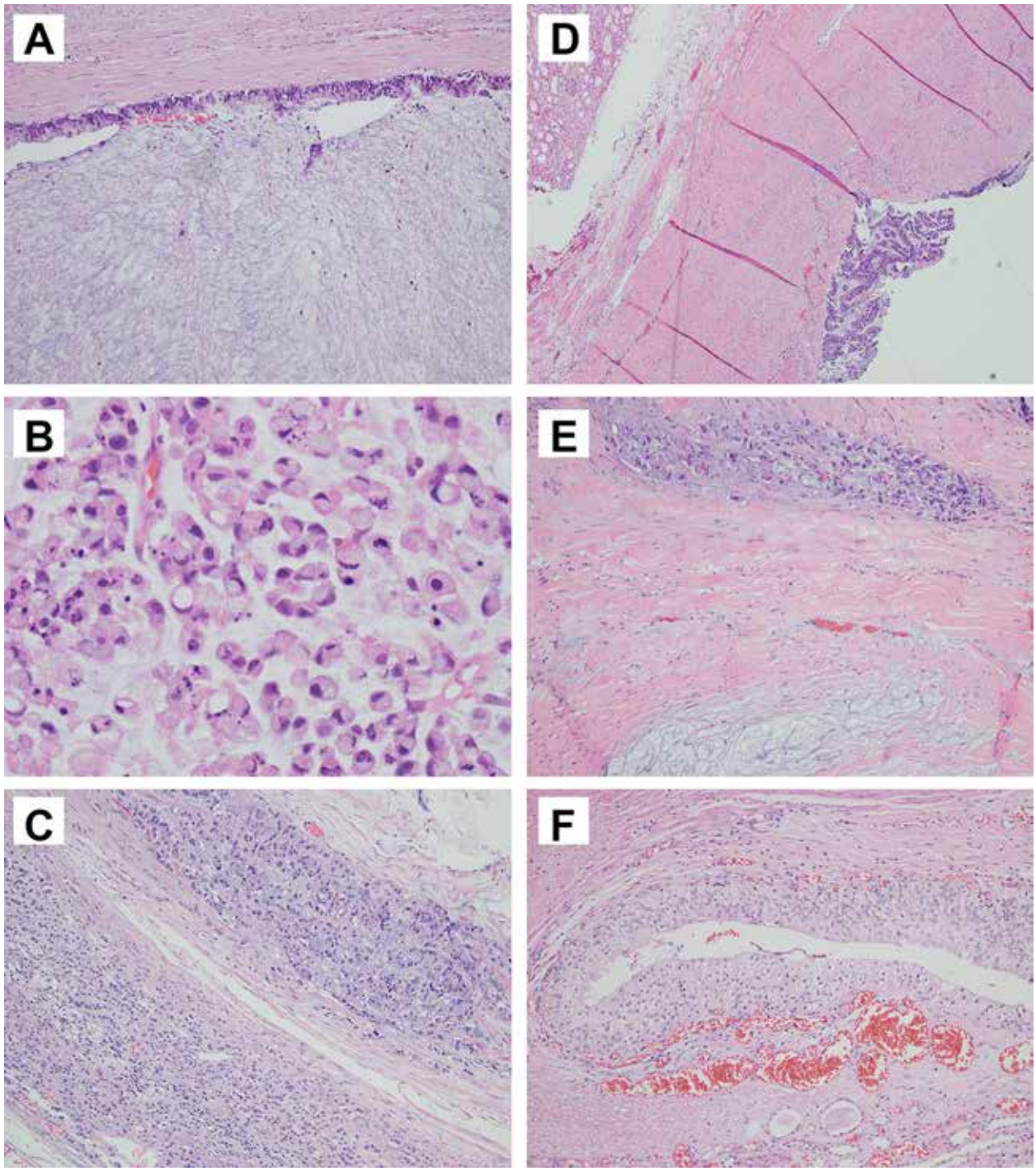

Fig 2: Hematoxylin-eosin (HE) staining presented an abundant mucin pool and neoplastic cells with hyperchromatic pleomorphic nuclei infiltrating the renal pelvis and floating in the mucin pool (A, 100×). Some of the neoplastic cells had signet ring cell features (B, 200×). The adjacent adrenal gland (C, 100×) and renal parenchyma (D, 100×) were not invaded by the tumor. The neoplastic cells infiltrated into the renal pelvis resulting in mucosal and mesenchymal destruction (E, 100×), while no neoplastic cells were observed in other parts of the renal pelvis (F, 100×).

whether they preceded the tumor or were secondary to it. We assume the latter, as multiple calcified lesions were observed in the pool of mucus. Elevated CEA and CA19-9 were considered predictors of MARP prognosis[3,4]. The same results were also discovered in the presented case. Previous data indicated that MARP has a poor prognosis as most patients die within 2 to 5 years[4]. MARP with a signet ring cell formation is rarely uncommon, and we consider it a sign of poorer prognosis as mucinous adenocarcinoma in the breast

or colon, with signet ring cell formation typically results in a significantly poorer prognosis[5,6]. As mentioned above, we observed local enlarged lymph nodes together with multiple lesions in the liver and lung but noted no progression of the disease three months postoperatively.

CONCLUSION

In this study, we reported a unique case of primary MARP with a signet ring cell formation, which may indicate a poor prognosis.

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Author's contribution: Wei Yongbao prepared the draft of manuscript. Cheng Hui and Li Tao participated in the case diagnosis and management and follow-up. Li Tao sponsored the study. All authors read and approved the final manuscript.

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Case Report

Spontaneous submucosal hematoma in the sigmoid colon causing complete intestinal obstruction in a patient with cerebral palsy

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ABSTRACT

Background: Intestinal submucosal hematoma (ISH) is often associated with coagulopathy and anticoagulant drug use. ISH is frequently seen in the esophagus, duodenum and rarely in small intestine in the gastrointestinal tract. It is very rare in the colon. In this case report, we present a 20-year-old male patient who developed intestinal obstruction due to spontaneous submucosal hematoma in the sigmoid colon. In the light of our English literature review, it was found that this was the first case in which spontaneous submucosal hematoma was detected in the sigmoid colon.
Case Report: In this case report, a 20-year-old male patient with a diagnosis of ileus with peroperative spontaneous submucosal hematoma was discussed. The patient had been suffering from inability to defecate and rectal bleeding with mucus for three days. The patient underwent laparotomy with the diagnosis of mechanical intestinal obstruction.
Conclusion: ISH is a clinical picture that frequently occurs due to anticoagulant use. It should be investigated in terms of ISH when prolonged international normalized ratio is detected in elderly patients applying with abdominal pain. Surgical treatment should be performed in the presence of unimpaired intestinal obstruction or peritonitis.

KEY WORDS: hematoma, intestinal, obstruction, spontaneous, submucosal

INTRODUCTION

Intestinal submucosal hematoma (ISH) was first reported by McLauchlan in 1838[1]. It is often associated with coagulopathy and use of anticoagulant drugs[2,3]. Apart from the use of anticoagulants, it may occur due to abdominal trauma, blood dyscrasias and iatrogenic causes[1,4-6]. In the gastrointestinal tract, it is frequently observed in the esophagus, duodenum, and rarely, in the small intestine. It is very rare in the colon[1,7]. The clinical symptoms typically include abdominal pain, intestinal obstruction and bleeding[1,8]. ISH is a rare cause of intestinal obstruction[2,9].

In this case report, a 20-year-old male patient who developed intestinal obstruction due to spontaneous submucosal hematoma in the sigmoid colon was examined. In the literature review, it was observed that this was the first case with spontaneous submucosal hematoma in the sigmoid colon.

CASE REPORT

In this case report, we discussed a 20-year-old male patient who was diagnosed with ileus and who showed spontaneous submucosal hematoma during operation. From the anamnesis, it was understood that the patient received ventilatory support in the home due to cerebral palsy. In this patient's history, rectal enema was not used for the last 10 days. The patient had been suffering from intestinal gas-obstructed defecation and rectal bleeding with mucus for three days. Patient was under follow-up in the intensive care unit and in

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the physical examination of general surgery, diffuse abdominal distension was noted and discharge in the form of strawberry jam was detected during rectal examination. Rectosigmoidoscopy was performed under sedation anesthesia in the intensive care unit. Rectosigmoidoscopy revealed necrotic mucosa and complete obstruction of the lumen at 15 cm from the rectum and there was no proximal transition. Figure 1 shows the endoscopic images of the patient.

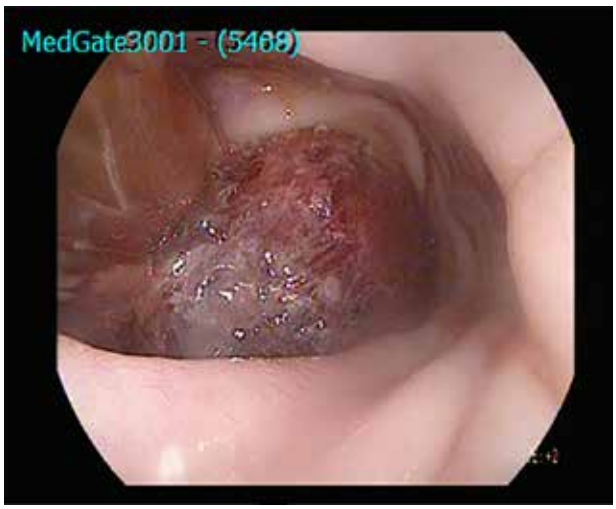

Fig 1: Endoscopic image of the patient

Computed tomography (CT) of the abdomen was performed and it was observed that rectal contrast agent did not pass through the proximal part of sigmoid colon and that the intestinal loops were dilated from the proximal part of the sigmoid colon. Abdominal CT image of the patient is shown in Figure 2.

The patient underwent laparotomy due to diagnosis of mechanical bowel obstruction. During the operation, it was observed that all colon segments were severely dilated from the proximal part of the sigmoid colon and that intestinal segment, measuring 15 cm, was necrotic and that its lumen was completely obstructed. The necrotic intestinal segment was totally excised up to the proximal and distal viability limits. During the operation, it was observed that necrosis and obstruction developed due to dissection associated with submucosal hematoma in the necrotic intestinal segment. After the resection, it was decided to perform end colostomy because of excessively dilated proximal colon segment. Distal segment was closed with stapler. Resected sigmoid colon segment is shown in Figure 3.

Fig 3: Image of resected colon segment

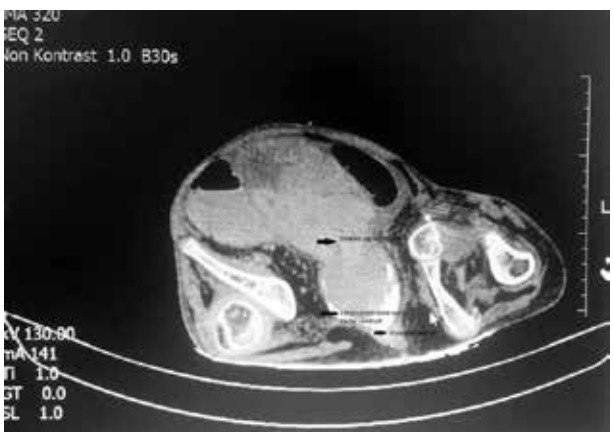

Fig 2: Abdominal CT image of the patient

DISCUSSION

ISH is a rare condition that was first described by McLauchan in 1838 and non-traumatic ISH, on the other hand, was first described by Sutherland in 1904[10]. It usually occurs in males and at an average age of 64 years. ISH occurs more frequently in the colon than the small intestine[1]. Possible pathophysiology is the bleeding caused by the rupture of the terminal artery originating from the mesenteric artery, which causes the dissection between the muscularis mucosa and the muscular layer[10]. The symptoms of ISH are nonspecific and may manifest with clinical symptoms ranging from mild abdominal pain to hemorrhagic shock[11]. Often, the initial symptom is abdominal pain with nausea and vomiting. Gastrointestinal bleeding

may occur as a result of rupture of the hematoma into the mucosa, or rupture into the abdomen may lead to peritoneal irritation[10]. In this case report, the patient had the symptoms of rectal bleeding and abdominal distention.

ISH often occurs as a complication to high-dose anticoagulant therapy. Other risk factors include hemobilia, idiopathic thrombocytopenic purpura, leukemia, lymphoma, myeloma, chemotherapy, vasculitis, pancreatitis, pancreatic cancer, trauma, and iatrogenesis[1,10]. In a study conducted by Kang *et al*[12] in 2018, they reported that there was a history of anticoagulant/anti-platelet drug use in 78.6% of 103 small bowel-induced ISH cases in the literature in the last 30 years. In the same study, it was detected that over 90% of patients had underlying cardiovascular co-morbidity such as hypertension and cardiac arrhythmia[12]. Yoldas *et al*[10] reported that 85.7% of the patients had a history of anticoagulant/anti-platelet drug use, and two patients with no drug use had a history of hypertension. The patient in this case report did not have anticoagulant / antiplatelet drug use and any trauma or comorbidity that could lead to bleeding. Although cases with colonic ISH due to an underlying disease, trauma or iatrogenic cause leading to anticoagulant use and coagulopathy have been reported in the literature, in the light of literature reviews, it was found that this patient was the first patient to have spontaneous ISH in the sigmoid colon without any use of anticoagulant/ anti-platelet drug or any underlying cause[8,13-15].

If a patient presents with the complaint of abdominal pain and he/she has history of prolonged international normalized ratio, ISH should be considered[10]. As the patient in this case report had no history of anticoagulant use or an underlying disease that could lead to coagulopathy, no prolongation in international normalized ratio was detected. In the diagnosis of ISH, barium enemas, ultrasonography (USG) and CT are used. USG sensitivity is reported as 71.4% and CT sensitivity as 80-100%. Among these, CT is the most useful examination. In addition, if the patient is stable and the diagnosis is not clear, endoscopic examination for tumor and hemorrhage discrimination can be performed[1,10]. In this case report, rectosigmoidoscopy was performed because of rectal bleeding, and mucosal necrosis and complete obstruction was observed in the lumen.

There are not enough studies for standard therapy of ISH. However, early diagnosis is very important for the success of medical treatment response[10]. The conservative approach is the first choice of treatment. In conservative treatment, anticoagulant / antiplatelet medication should be discontinued first. Coagulation parameters should be corrected with vitamin K and fresh frozen plasma, oral intake should be discontinued and nasogastric decompression should be performed[1,10]. In hemodynamically stable patients, if there is obvious arterial bleeding, endovascular methods should be preferred[15]. Surgical treatment is recommended in patients with hemodynamic instability, ineffective intestinal obstruction and intestinal necrosis or signs of peritonitis[8,15]. In this case report, the patient underwent surgical treatment because of the detection of mucosal necrosis and obstruction endoscopically, and the rectal contrast agent could not pass to proximal intestinal loop in CT. Resection+anastomosis or resection+end colostomy can be performed in surgical treatment[16]. In this case report, end-colostomy was performed as the intestinal loops in the proximal part were excessively dilated after segmental colon resection. Recently, several new treatment strategies have been reported as alternative to surgical treatment. These are percutaneous drainage under USG guidance and endoscopic incision and drainage. However, it should be known that there is a risk of intestinal perforation in these two treatment modalities. As the patient in this case report had total intestinal obstruction that prevented endoscopic passage, incision and drainage could not be performed[1,10].

CONCLUSION

In conclusion, ISH is a clinical picture that frequently occurs due to use of anticoagulants. For elderly patients who present with the complaint of abdominal pain, ISH should be considered if prolonged international normalized ratio is detected. However, as in this case report, it should be kept in mind that ISH and intestinal obstruction may develop without any underlying cause. Conservative treatment is the preferred choice and early diagnosis increases the success of conservative treatment. Surgical treatment should be performed in the presence of unimpaired intestinal obstruction or peritonitis. Current treatment modalities, such as percutaneous drainage and endoscopic drainage with USG should be considered as an alternative to surgery, but the risk of perforation should be taken into consideration.

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Case Report

Rare etiology of ischemic colitis in an Emergency Department: Phlebosclerotic colitis

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ABSTRACT

Among all types of colonic ischemia, phlebosclerotic colitis (PC) is a rare case in emergency departments (EDs). The prevalence of PC is unknown and the number of reported cases in the literature is few.
We encountered a 63-year-old female patient with PC in the ED last year and report our findings here. For patients with symptoms of recurrent colitis in the ED, awareness of this disease may allow more cases to be identified. Although colonic ischemia can be detected earlier than before due to the accessibility of abdominal CT at EDs, the emergency physicians should be familiar with the symptoms and imaging features of PC because early diagnosis is the key step in treating ischemic colitis.

KEY WORDS: herbal use, ischemic colitis, mesenteric phlebosclerosis, phlebosclerotic colitis

INTRODUCTION

Colonic ischemia is a serious, life-threatening medical condition that is often seen in the emergency department (ED). The overall mortality rate ranges from 29-50%[1-3]. The main cause of colonic ischemia is occluded or decreased blood flow of the mesentery artery[4], but it can also be related to mesenteric vein occlusion. Among all types of colonic ischemia that are related to mesentery venous occlusion, phlebosclerotic colitis (PC) is a highly rare case. The prevalence of PC is unknown and few cases have been reported in the literature[5,6].

CASE REPORT

A 63-year-old female patient with hypertension, type II diabetes mellitus and a history of using numerous herbal medications for more than 10 years visited a medical university hospital ED for nausea and a progressive dull pain over her periumbilical to right lower quadrant abdomen area. She had been discharged from our hospital for similar symptoms approximately one month previously and had been diagnosed with diverticulitis. Associated symptoms and signs included poor appetite and weight loss. No fevers, chills, vomiting, or stool color or habit change were reported. The initial presentation was acutely ill-looking with a body temperature of 36.3 °C, blood pressure of 151/83 mmHg, pulse rate of 80 beats/min, and respiratory rate of 16 breaths/min. The physical examination revealed a soft abdomen with mild distention and showed tenderness at the periumbilical–right lower quadrant region without rebound tenderness, in addition to hyperactive bowel sounds. Laboratory test results revealed a white blood cell count of 4910/mm^3, hemoglobin of 11.4 g/dL, platelet count of 249,000/mm^3, blood urea nitrogen of 15.8 mg/dL, creatinine of 0.8

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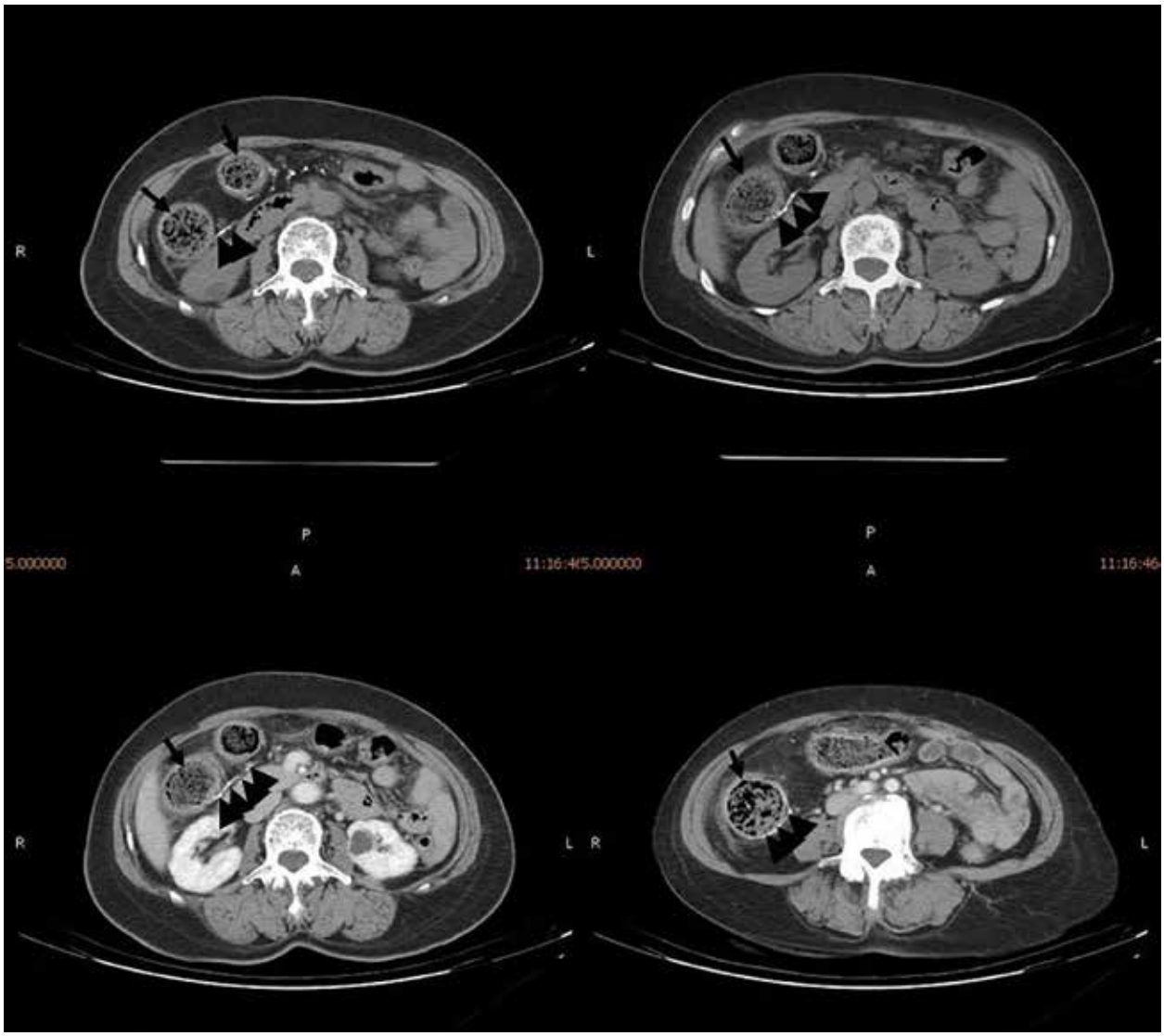

Fig 1: Image of abdomen CT; the images revealed thread-like calcifications along the colonic vessels (arrowheads), edematous thickening of the colonic wall from the terminal ileum to the hepatic flexure (arrow)

mg/dL and C-reactive protein of 0.54 mg/dL. Electrolyte levels were within normal limits.

The abdominal computed tomography showed abnormal dilatation of the small bowel region, especially distally and revealed that the transitional zone surrounded the ascending colon and extended to the transverse colon. The images also revealed thread-like calcifications along the colonic vessels (Figure 1, arrowheads), edematous thickening of the colonic wall from the terminal ileum to the hepatic flexure (Fig 1, arrow), and increased fat stranding around the ascending and transverse colon (Fig 1), which is compatible with PC.

A colonoscopy was performed without bowel preparation and revealed diffuse dark-purple discoloration with hyperemic change and ulcerations from the cecum to the splenic flexure. These changes were more severe from the cecum to the hepatic flexure and the terminal ileum was relatively normal. The biopsy of the terminal ileum revealed chronic inflammatory cell infiltration and lymphoid follicle formation in the mucosa. The biopsy of the ascending colon revealed an ulcer with necrotic debris and hemorrhage edema and collagen deposition in the colon mucosa, which is compatible with PC.

The patient was discharged about one week later without undergoing operation. However, right lower abdominal pain with poor appetite and general malaise were still noted at subsequent follow-ups; therefore, a surgeon was consulted and a colectomy was recommended. The operation with extended right hemicolectomy revealed a purple color from the cecum to the transverse colon with severe adhesion between the transverse colon and the liver.

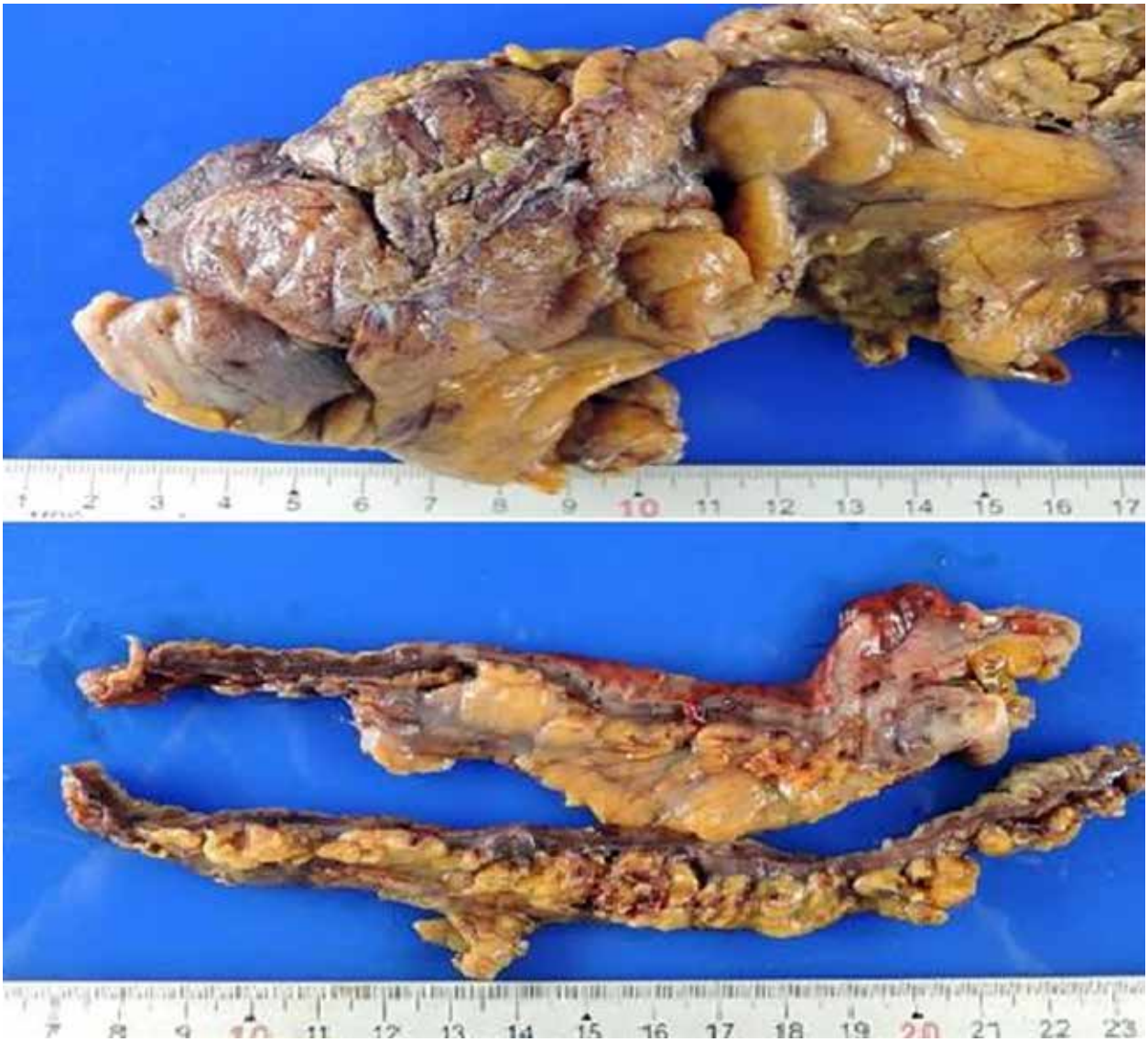

Fig 2: Gross pathology of the extended right hemicolectomy; A gross pathology of the extended right hemicolectomy showed a rough and focally fibrotic external surface of the mesocolon and some segments with erosion and hemorrhaging were seen on the mucosal surface, especially in the cecum and ascending colon.

A gross pathology of the extended right hemicolectomy showed a rough and focally fibrotic external surface of the mesocolon and some segments with erosion and hemorrhaging were seen on the mucosal surface, especially in the cecum and ascending colon (Fig 2). Focal stenosis in the middle portion of the colonic specimen were seen. On the cut section, focal erosion and hemorrhaging of the darkly stained mucosa and sclerosing change of the vessels throughout the specimen were noted, especially in the mesentery. Sclerosing change of the venous walls in the muscle wall, submucosal layer, and even in the mucosal lamina was also seen. These kinds of lesions were still present in the terminal ileum and its distal cut end but were not found in the appendix and the omentum. Focal fat necrosis around the venous wall and some hyaline globules were present and vacuolated degeneration in the muscle wall was also noted (Fig 3).

DISCUSSION

The symptoms of PC are nonspecific, including gradual right-side abdomen pain, diarrhea and tarry stool[5]. Diarrhea and tarry stool were not shown in our patient, but the symptom of chronic right-side abdominal pain was similar with that of previously reported patients. Although physical examinations in those patients could reveal right side abdominal tenderness with mild rebounding pain, which may indicate peritonitis, the duration of these symptoms is longer than that of peritonitis. It is usually noted in the ED as similar to appendicitis or diverticulitis but the pain could last from months to years[5].

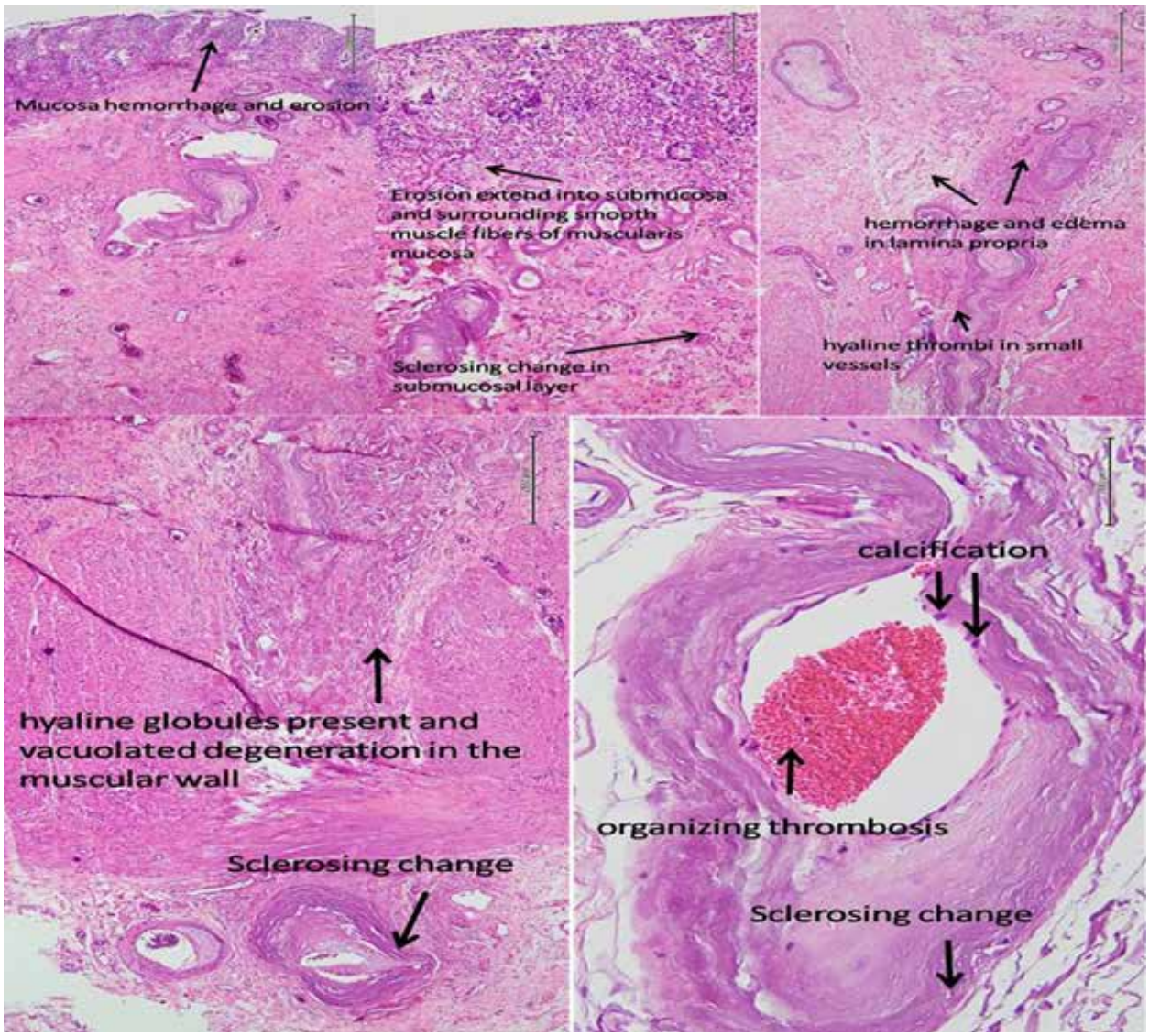

Fig 3: Histological finding; Focal erosion and hemorrhaging of the darkly stained mucosa and sclerosing change of the vessels were noted. Sclerosing change of the venous walls in the muscle wall, submucosal layer, and even in the mucosal lamina was seen. Focal fat necrosis around the venous wall and some hyaline globules were present and vacuolated degeneration in the muscle wall.

People of Asian descent are more vulnerable to PC, as has been noted in a larger study that included dozens of cases[7]. Our patient suffered long-term symptoms that conformed with the biopsy results of cases presented in 2006, in which the superior mesenteric vein distribution of the ascending and proximal transverse colon was affected. After three years, the lesions had extended to the proximal descending colon, suggesting a slow disease progression[7].

The pathophysiology of PC remains unclear. However, various studies are in agreement that dialysis, portal hypertension, diabetes and vasculitis are harmful to the vascular system. In Asia, the popularity of herbal medicines, such as with our patient, may relate to the higher prevalence in these countries. These substances and other chemicals are believed to be absorbed by the venous return from the proximal colon and then cause venous damage[8,9]. Hiramatsu *et al* reported that a commonly used herbal ingredient, sansisi, which is also known as geniposide that was hydrolysed and transformed to genipin by enteric bacteria in the caecum and the ascending colon, was correlated with PC[10]. One possible explanation is that genipin is a cross-linking reagent to collagen which may be associated with the thickening of collagen fibre at the involved vein[11].

There is still no definite treatment of PC. Most cases use conservative treatment with close follow-up. Surgery is considered for severe complications and for persistent symptoms following conservative management[12].

CONCLUSION

For patients with symptoms of recurrent colitis in the ED, awareness of this disease may allow more cases to be identified. Although colonic ischemia can be detected earlier than before due to the accessibility of abdominal computed tomography at EDs, the emergency physicians should be familiar with the symptoms and imaging features of PC because early diagnosis is the key step in treating ischemic colitis.

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Ethics approval and consent to participate: This study has been approved by expedited review process of the Taipei Medical University- joint Institutional Review Board in meeting #107-03-3(N201802011).

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Case Report

Acute hypertriglyceridemia and hyperglycemia related to mirtazapine: A case report

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ABSTRACT

A 42-year-old woman was hospitalized with depression and was started on mirtazapine 15 mg/day. Just one week after starting mirtazapine, severe hypertriglyceridemia and hyperglycemia were detected. Although these metabolic adverse effects have been reported before, to our knowledge this is the first case of hypertriglyceridemia and hyperglycemia occurring so early (just one week) after initiation of mirtazapine. The patient's glucose and triglyceride normalized nine days after discontinuation of mirtazapine. This case emphasizes the importance of regular glucose and triglyceride measurements at baseline and then regular monitoring in patients receiving mirtazapine treatment.

KEY WORDS: adverse effects, depression, hyperglycemia, hypertriglyceridemia, mirtazapine

INTRODUCTION

Two important neurotransmitters involved in the pathophysiology of depression are serotonin and noradrenaline[1]. Mirtazapine is an antidepressant from the piperazineazepine group, mainly used in the treatment of depression, which increases noradrenaline release by blocking alpha-2 autoreceptors[2]. This increase in noradrenaline levels facilitates cell firing by stimulating alpha-1 adrenoreceptors in the serotonergic cell body, which stimulates the release of 5-hydroxytryptamine (5-HT) in the synapses[3]. Increased serotonin in the synaptic space leads to increased transmission over 5-HT1 receptors, which is probably related to antidepressant and anxiolytic effects. In addition, mirtazapine blocks 5-HT2 and 5-HT3 receptors and acts as a 5-HT1A receptor agonist[4]. Mirtazapine has very weak muscarinic anticholinergic and histamine antagonist properties[5]. Common side effects associated with mirtazapine are somnolence (54%), dizziness (7%), increased appetite (17%), weight gain (8%), increased nonfasting serum cholesterol (15%) and increased serum triglyceride (6%) levels, elevated liver transaminases (52%), constipation (13%) and dry mouth (25%). Less commonly reported side effects (<1%) include activation of mania/hypomania, asthenia, agranulocytosis and neutropenia[6].

The European Atherosclerosis Society/ European Federation of Clinical Chemistry and Laboratory Medicine considers non-fasting triglyceride (TG) levels of >175 mg/dL and fasting TG levels of >150 mg/dL as upper limits while levels between 180-880 mg/dL, and above >880 mg/dL are considered mild to moderate and severe hypertriglyceridemia, respectively[7]. Fasting TG levels above 150 mg/dL can be considered as elevated TG levels, which is associated with an increased risk of atherosclerosis and cardiovascular diseases. Once TG levels increase above 500 mg/dL, and particularly above 1000 mg/dL, the most important clinical outcome is markedly increased risk of pancreatitis[8]. Here, we present a case with an elevation of TG levels three times the baseline level and elevation of glucose levels two times the baseline level, the elevation occurring within the first week of mirtazapine use.

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CASE REPORT

A 42-year-old Caucasian, married, housewife patient presented with a long-standing history of depression since the age of 25. Her history was notable for several visits to various psychiatric outpatient clinics over the course of eleven years due to anxiety, loss of motivation, feeling upset, hopelessness, pessimism, difficulty sleeping and "feeling sleepy all day''. She had a headache starting at the age of 20 but she was examined 5 years later by a neurologist and was started on amitriptyline, which she used for six months. The patient did not complain of the headache until the age of 31 years. Upon resumption of the depressed mood, anhedonia, early insomnia, feeling tired and being tearful all the time, she reported to the psychiatry outpatient clinic of another hospital. Although she continued her outpatient treatment, due to continuing complaints, she had been hospitalized three times and discharged with partial remissions until the age of 36 years. Despite taking several different medications including escitalopram, duloxetine, lamotrigine, sertraline, gabapentin, trazodone, venlafaxine, aripiprazole and lithium in various periods, the patient had never completely recovered. Due to the failure of symptom control in the outpatient setting, she was admitted to our hospital as an inpatient, which was overall her fourth admission. She was using metformin 1000 mg/day for her diabetes mellitus and nebivolol 5 mg/day for her hypertension. Her family history revealed major depressive disorder in her mother. She was a smoker, but she had never used alcohol or any other substance. The patient appeared to be overweight (weight: 72 kg, height: 160 cm, BMI:28.1). Her vital signs were as follows: blood pressure: 137/63 mmHg, heart rate: 105 beats/min and body temperature: 36.7 °C. Physical and neurological examinations were negative for any significant findings.

In the psychiatric examination, her mood was depressed and her affect was congruent with her mood. Her appetite was normal but she had early and middle insomnia. Based on these findings, she was diagnosed with depression. Her Hamilton depression rating scale score was 18 and Beck depression inventory score was 26. On the first day of hospitalization, a complete blood count, metabolic panel, hepatic and renal function tests and urine analysis were performed, which revealed the following abnormalities: A TG value of 572 mg/dL (normal: 50-150 mg/dL), fasting glucose level of 233 mg/dL (normal: 70-105 mg/dL), hemoglobin of 7.82 g/dL (normal: 12.2-16.2 g/dL). Her electrocardiogram showed sinus rhythm. HbA1c level was 5.1. Since she had impulse control problems, anxiety, early and middle insomnia, sertraline 50 mg/day, risperidone 1 mg/day and mirtazapine 15 mg/day were prescribed for her. Intravenous ferric carboxymaltose was administered for her anemia. On the seventh day of mirtazapine treatment, control blood tests revealed more than three-times increase in serum TG level (from 572 to 1637 mg/dL) and about two-times increase in serum fasting glucose level (from 233 to 432 mg/dL) for which fenofibrate 267 mg/day for

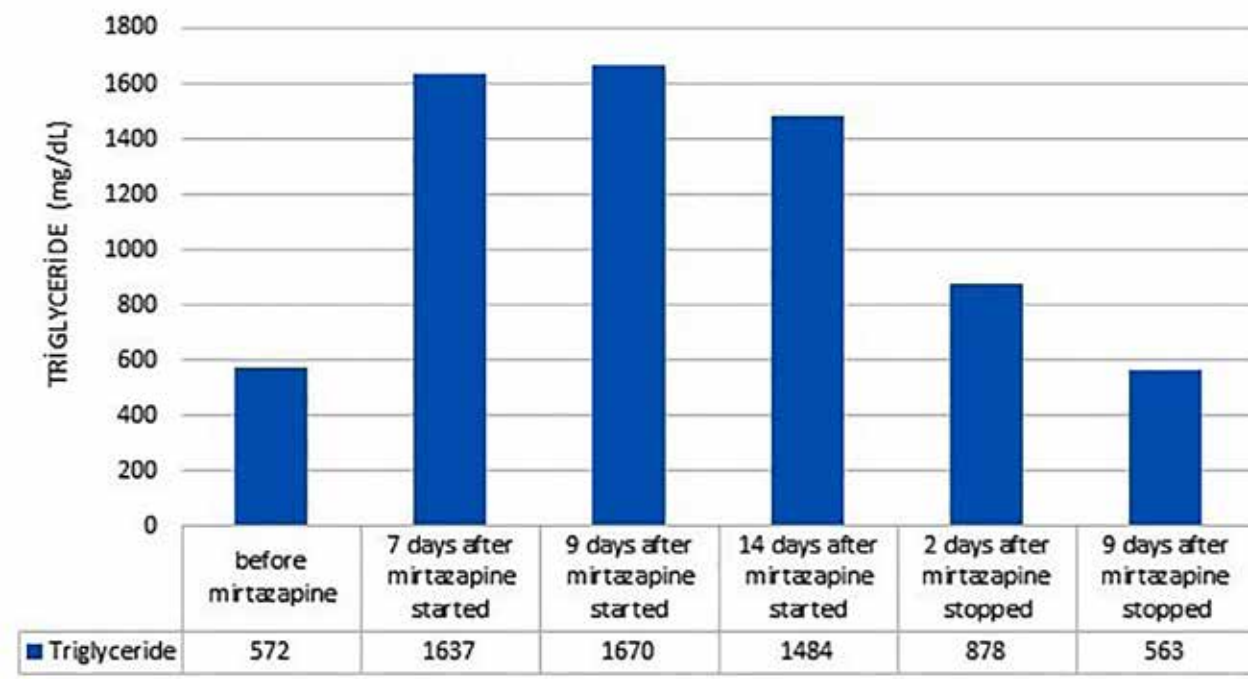

Fig 1: Serum fasting triglyceride levels before and after the initiation of mirtazapine.

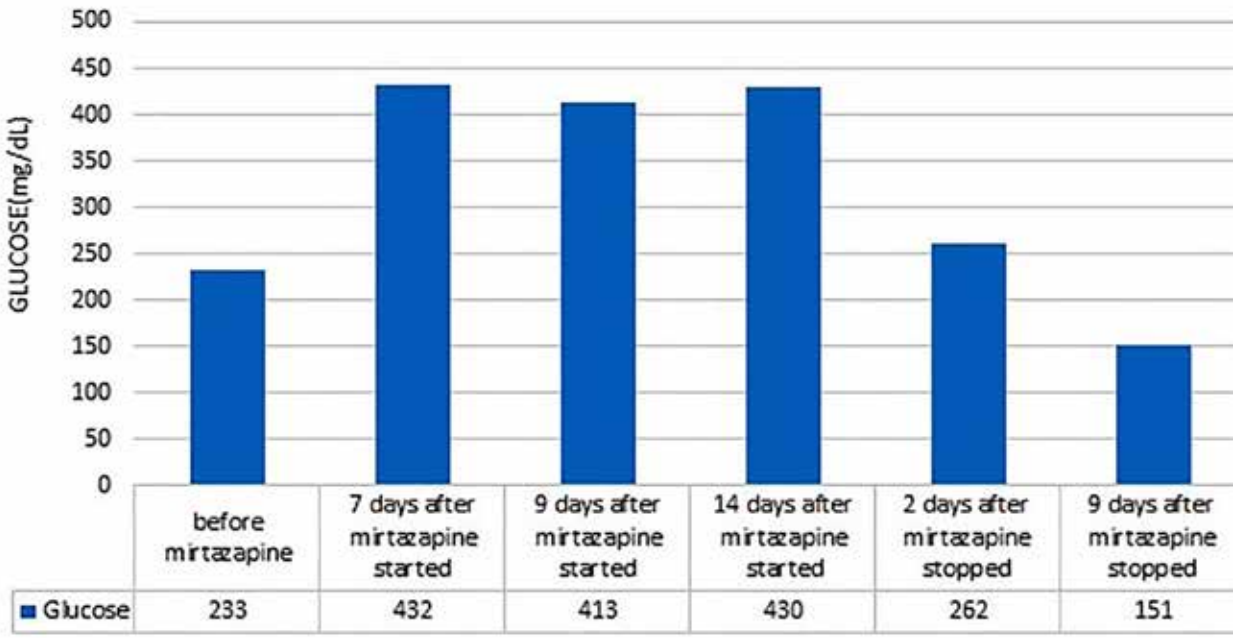

Fig 2: Serum fasting glucose levels before and after the initiation of mirtazapine.

hypertriglyceridemia and pioglitazone 30mg/day for hyperglycemia were started. Amylase and lipase were within normal limits. After two days, TG and glucose levels were still high (TG: 1670 mg/dl and glucose: 413 mg/dl). Mean capillary glucose measurements were 315 mg/dl for fasting and 330 mg/dl for nonfasting. Her impulse control disorder was in remission, therefore risperidone treatment was stopped. On the 14th day of admission, her weight was 0.7 kg less than her initial weight. The urine analysis was negative for ketones or protein. Her persistently elevated TG and glucose levels were suspected to be secondary to mirtazapine treatment, and therefore mirtazapine was stopped. Instead, the patient was started on trazodone for insomnia. Two days later, serum TG level dropped to 878 mg/dL and serum glucose level dropped to 262 mg/dL. Her psychiatric symptoms showed remarkable improvement and she was eventually discharged from the hospital. During her follow-up examination one week later, depressive symptoms were still in remission while her TG level was back to her baseline at admission (563 mg/dL on follow-up, 572 mg/dL on admission) and her serum glucose level had dropped to 151 mg/dL.

Figures 1 and 2 demonstrate the change in TG and glucose levels in chronological order, respectively.

DISCUSSION

The risk factors for hypertriglyceridemia include genetics, lifestyle and diet (*e.g.*, obesity, alcohol consumption and reduced physical activity), diseases and disorders (*e.g.*, metabolic syndrome, insulin resistance, diabetes mellitus, renal disease), and medications (*e.g.*, corticosteroids, estrogens, beta-blockers, thiazides, bile acid sequestrants and immunosuppressive agents)[8].

Various antidepressants like amitriptyline, clomipramine, fluoxetine, venlafaxine and citalopram have been associated with hypertriglyceridemia and/or acute pancreatitis[9-15]. In placebo controlled studies of the United States, nonfasting triglyceride increases to ≥500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline[6]. However, few cases have been reported about elevated serum triglyceride levels above 1000 mg/dL associated with mirtazapine in the literature. Bowers *et al* described a patient with hypertriglyceridemia induced pancreatitis for whom the suspected cause of dangerously elevated TG levels was mirtazapine[16]. Chen *et al* reported a 44-year-old woman with acute pancreatitis and diabetic ketoacidosis due to hypertriglyceridemia which started two months after mirtazapine treatment[17]. Similarly, Duncan *et al* reported a 75-year-old male patient who developed hypertriglyceridemia followed by hyperglycemia two months after starting to use mirtazapine[18].

Our patient had concomitant diabetes mellitus and hypertriglyceridemia, which might have put her in a more vulnerable position for mirtazapine-induced hypertriglyceridemia and hyperglycemia, although she did not gain weight and was not in diabetic ketoacidosis.

Literature was more plentiful about mirtazapine

Table 1: ADR probability scale

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

related pancreatitis cases, suggesting the elevated serum triglyceride levels as its possible explanation. In addition to Chen *et al* and Bowers *et al*, Navarro *et al*, Sommer *et al*, Hussain and Burke, Lankisch and Werner, and Stone and Puri reported acute pancreatitis cases secondary to hypertriglyceridemia in patients using mirtazapine[19-24]. However, our patient did not have the symptoms, signs or laboratory evidence of pancreatitis.

A research study observed significantly impaired glucose tolerance in acutely depressed patients compared to healthy controls. Although glucose tolerance improved under mirtazapine treatment, insulin sensitivity was still impaired and remained significantly lower in patients compared to controls[25].

Concerning 'mirtazapine' and 'hyperglycemia', Fisfalen described a patient who was on mirtazapine for appetite stimulation and who had severe hyperglycemia in addition to a 16-kg weight gain[26]. Chen *et al* reported hyperglycemia secondary to mirtazapine therapy in a 37-year-old man[27].

This patient had well-controlled diabetes before mirtazapine usage so we did not detect any diabetes complications. The antidiabetic drug metformin has not been related to hypertriglyceridemia, though it ameliorates obesity-associated hypertriglyceridemia in mice[28]. The antihypertensive drug nebivolol, which our patient was using, has not been shown to cause significant changes in insulin sensitivity and TG levels[29,30].

The Naranjo scale, shown in Table 1, evaluates the likelihood that an adverse effect is caused by a pharmacologic agent[31]. The Naranjo scoring system has been validated and is used in clinical practice. The probability that the adverse event was related to drug therapy was classified as Definite ≥ 9, Probable = 5-8, Possible = 1-4, Doubtful ≤ 0 that an adverse drug reaction was caused by a drug or some other factor.

A "definite" reaction was one that (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues; (2) followed a recognized response to the suspected drug; and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure. A "probable" reaction (1) followed a reasonable temporal sequence after a drug; (2) followed a recognized response to the suspected drug; (3) was confirmed by withdrawal but not by exposure to the drug; and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

In our patient, TG and glucose levels were found to be elevated only within the first week of mirtazapine treatment and were back to baseline shortly after the cessation of mirtazapine.

There are previous conclusive reports on this reaction (+1), the suspected event has appeared after the offending agent was administered (+2), adverse drug reaction improved when the offending agent was discontinued (+1), there are no alternative causes that could solely have caused the adverse drug reaction (+2). Naranjo adverse reaction scale score was "6" which corresponds to "probable causality".

CONCLUSION

In conclusion, depending on the possible association of mirtazapine and hypertriglyceridemia, serum glucose and TG levels should be measured before and shortly after starting mirtazapine treatment to ensure patient safety, especially in patients who are at high risk.

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Authorship criteria: All authors contributed to (1) history taking, physical and psychiatric examination and treatment of the case; the acquisition of laboratory data and interpretation of side effects; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

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Case Report

Pyelonephritis due to spontaneous massive steinstrasse and its treatment: A rare case report

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ABSTRACT

Spontaneous steinstrasse is rarely reported. We present a case of acute pyelonephritis due to spontaneous steinstrasse and obstructed kidney. A 74-year-old man was admitted with pyelonephritis. This patient, who had no risk factors, was made stone-free with ureterorenoscopic lithotripsy in two separate sessions. Steinstrasse can occur spontaneously or after extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy and can be treated effectively with ureterorenoscopic lithotripsy.

KEY WORDS: pyelonephritis, steinstrasse, stone street

INTRODUCTION

Steinstrasse or stone street means accumulation of stone fragments in the ureter. This can happen following extracorporeal shock wave lithotripsy (ESWL), following ureterorenal stone surgery and may also be seen in children who have distal renal tubular acidosis[1-3]. However, in patients with normal metabolic values, diet, inadequate fluid intake and environmental factors such as high temperatures may also lead to formation of steinstrasse[3]. Steinstrasse may present with acute clinical presentation such as loin pain, nausea, vomiting and fever. On the other hand, one third of the cases have no significant symptoms and present with permanent kidney damage[4].

Evaluation of patients consists of recording vital signs and assessment of general condition. Subsequently, imaging studies like plain x-ray of kidney, ureter and bladder, ultrasound examination of abdomen and pelvis and computed tomography urography are to be done to get an idea about the size, number and location of the stones, and whether there is back pressure effect to the kidney. Evaluation of renal function and urine culture need to be done and a decision taken on the treatment strategy. Conservative treatment and observation is the generally accepted treatment approach[5]. This involves treatment of pain with analgesics and using alpha blockers to facilitate spontaneous stone passage. If indicated, the treatment options are ESWL, percutaneous nephrostomy, ureterorenoscopy and stone disintegration, double pigtail ureteric stent insertion, percutaneous antegrade nephroureterolithotripsy, and in case the kidney is non functioning, laparoscopic nephroureterectomy.

We report a case of an adult male without any risk factors who presented with pyelonephritis due to spontaneous massive steinstrasse and it's management.

CASE REPORT

A 74-year-old male patient was admitted with complaints of left side pain, loss of appetite, nausea, vomiting and fever. He had a history of diabetes mellitus, coronary artery disease and had undergone transvesical open prostatectomy in the past. On clinical evaluation, he was found to have fever (39.7 ˚C) and the other vital signs were normal. There was tenderness on the left costovertebral angle. Laboratory analysis showed leukocytosis (18.4 k/uL); serum creatinine was

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Fig 1, 2: Left kidney stones and stone street

1.38 mg/dl; C-reactive protein: 40.25 mg/dl. Urine analysis showed significant pyuria. An X-ray of kidney, ureter and bladder showed multiple radiopaque shadows at the left renal area and along the distal ureter. An unenhanced computed tomography of abdomen and pelvis revealed a staghorn type of stone in the left kidney and multiple stones all along the left ureter starting from the ureteropelvic junction until ureterovesical junction. The size of stones varied from 8 to 9 mm (Figure 1,2). Urine and blood cultures were taken and third generation cephalosporin 2 gm/day as empirical antibiotic therapy was started. Under ultrasound guidance, two percutaneous nephrostomies were inserted into the left renal pelvis and left middle calyx. Urine culture was taken from the nephrostomy. Urine and blood cultures grew Enterococci and further antibiotic vancomycin 4.5 gm/day was given. Patient became afebrile and urine culture was repeated and detected to be sterile. Patient was subjected to left ureteroscopy (URS) using 7.5 Fr semirigid ureteroscope and the ureteric stones were disintegrated using pneumatic and holmium laser lithotripters. Double pigtail ureteric stent (28 cm, 4.8 Fr) was inserted into the left ureter. The nephrostomy catheter which was in the lower calyx was removed. The one which was localised into the renal pelvis was not removed. Two weeks later, computed tomography scan revealed many stones had migrated from the renal pelvis into the ureter and on second uretero-renoscopy, all the stones were removed. Patient was found to be stone free on follow up done a month later. Uretero-renoscopy can be applied in the treatment of steinstrasse and it's a safe treatment modality with high success rate. Consent was obtained from the patient to publish this case report.

DISCUSSION

Steinstrasse can occur in the upper or lower ureter and rarely in the whole length of ureter. Patients present with renal colic, dysuria, haematuria, pyelonephritis or even acute renal failure. Loss of renal function may be partial as in our case, or may result in total loss of renal function in the affected part. In the literature there is a report of nephroureterectomy done since the kidney was non-functional due to steinstrasse[3]. The risk of stone street after ESWL was reported to be 4-7%[6]. While the incidence of stone street after ESWL is high, it is much less after percutaneous nephrolithotomy and URS[7]. In our case, patient was diagnosed to have extensive steinstrasse without any history of undergoing ESWL, percutaneous nephrolithotomy or URS. The only etiology that could have possibly caused this pathology was lack of adequate fluid intake and dehydration.

The guidelines of initially establishing proximal drainage and parenteral antibiotic treatment in patients with obstructed infected kidney was followed in our case. In fact, we had to resort to put in two percutaneous nephorstomy tubes to make sure adequate proximal drainage was established. With parenteral antibiotic treatment, infection could be cleared and later with

two separate session of URS, total stone clearance could be achieved. On Technetium 99 mm dimercaptosuccinic acid renal scan showed that left kidney contributes 34% towards the total renal function, hence, effort was made to preserve this kidney, rather than do nephroureterectomy.

CONCLUSION

In the literature reviews, it was observed that there were no cases with the diagnosis of pyelonephritis after spontaneous steinstrasse. We think that this case will be significant and contribute to the literature. Lack of stone analysis and metabolic evaluation can be considered as the deficiency of our study.

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

Authors' contributions: Ekrem Güner, Ramazan Uğur and Kamil Gökhan Şeker conceptualized and planned the study, drafted the case report, did the data collection, revised the case report and consented to the as submitted.

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Case Report

A case with Fahr's syndrome who applied to the Emergency Department with convulsion complaint

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ABSTRACT

Fahr's syndrome is a rare calcium and phosphorus metabolism disorder. This disease is bilateral and symmetrical in brain hemispheres. In the emergency department (ED), it is mostly observed with neuropsychiatric symptoms and signs. This study presented a case with Fahr's syndrome, who applied to the ED with convulsion and tetany and had hypocalcemia, hyperphosphatemia and hypoparathyroidism, and in whose brain tomography hyperdense appearance was monitored in the globus pallidus, thalamus and cerebral hemispheres.

KEY WORDS: convulsion, Fahr's syndrome, tetany

INTRODUCTION

Fahr's syndrome was first described in 1930, and although its etiology is unknown, calcium metabolism disorders, genetic causes, hypoparathyroidism and pseudohypoparathyroidism were indicated among its main causes[1].

The clinical picture of Fahr's syndrome generally starts with weakness, unbalanced walking, speech disorder or slowing in speech, difficulty in swallowing or muscle cramps, and can be observed with neuropsychiatric symptoms such as psychosis and dementia[2]. It is usually observed in the fourth and fifth decades of life[1]. The diagnosis is made by brain tomography and the treatment is symptomatic and in the form of the correction of calcium metabolism.

We presented a case who applied to our clinic with convulsion and was hypocalcemic, and in whose brain tomography, bilateral common calcification that developed secondarily to hypoparathyroidism was detected in the basal ganglia and cerebral hemispheres.

CASE REPORT

A 43-year-old male patient who occasionally had convulsions and tetanies in the past 15 years applied to our Emergency Department with convulsion, tetany, and headache complaints.

In the examination and investigation of the patient, the following measurements were obtained: blood pressure: 140/90 mmHg; pulse: 94 pulse rate/minute; saturation: 97%; blood glucose: 140 mg/dL; calcium: 4.5 mg/dL; phosphorus: 5.76 mg/dL and parathormone: 2.1 pg/mL. His other biochemical markers were detected to be in the normal reference range and his electrocardiography was evaluated as normal sinus rhythm. There was no feature in his family history. In the cranial tomography (brain computerized tomography) of the patient, who had no history of any chronic drug use and surgery, hyperdense appearance was monitored in the globus pallidus, thalamus and cerebral hemispheres (Fig 1-2).

The patient was evaluated as Fahr's syndrome due to hypoparathyroidism according to the laboratory and radiological findings. For the patient, whose clinical findings improved with the administration of calcium replacement, internal medicine consultation was requested, and he was discharged by recommending him to come to the polyclinic control. In order to determine whether the disease was an

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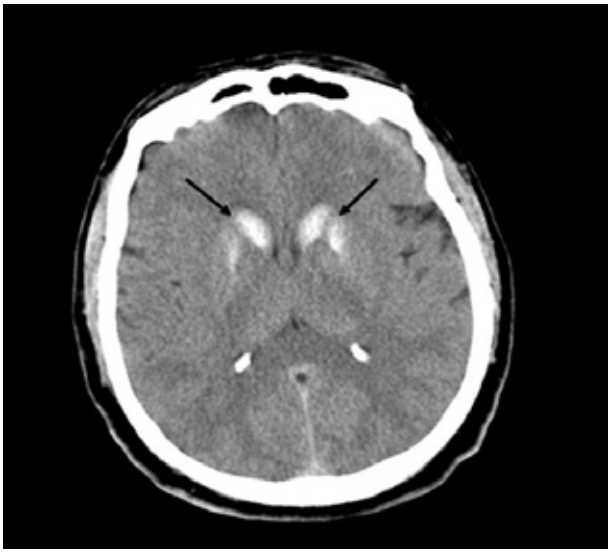

Fig 1: Bilateral calcification foci at the globus pallidus level in the patient's brain computerized tomography

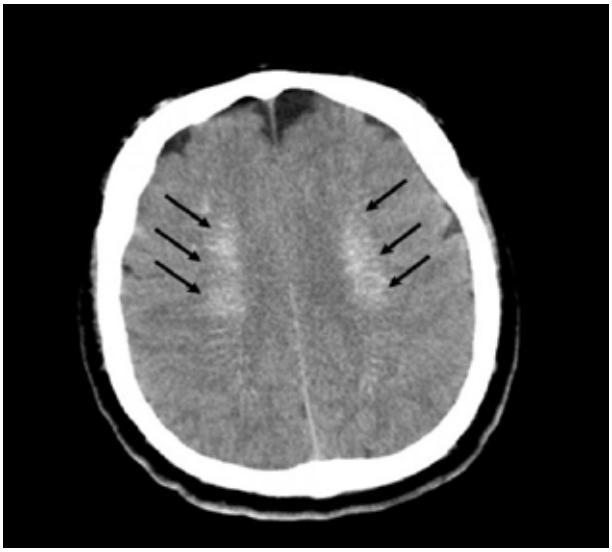

Fig 2: Calcification foci in the cerebral hemispheres in the patient's brain computerized tomography

autosomal dominant transitional form, which is the frequent familial transitional form of the disease, or an autosomal recessive transitional form, which has a very rare incidence, the patient was asked whether his first-degree relatives (the brother and the son) had similar symptoms and signs. We recommended the first-degree relatives of the patient to apply to the Emergency Department or internal medicine polyclinic, in order for the routine biochemical examinations to be carried out. Since the calcium, phosphate and other biochemical marker levels requested from the first-degree relatives of the patient who applied to the Emergency Department within the same week were in the normal reference range, the case was thought to be the rare autosomal recessive transitional form of Fahr's syndrome.

DISCUSSION

Fahr's syndrome is a syndrome that develops secondarily to many metabolic disorders, courses with calcifications in the globus pallidus, dental nucleus, thalamus, caudate nucleus, and cerebellum, originating from parathyroid diseases. In this case, in brain computerized tomography, calcification foci, which were dominant at the globus pallidus level in accordance with the literature, were also observed symmetrically in the cerebellar hemispheres[3]. Although iatrogenic cases are mostly observed in the literature, family-based cases were also reported, although they are rare[1,4].

In Fahr's syndrome, most of the cases apply to the hospital with neurological symptoms. Headache, vertigo, syncope, tetany and seizure are common neurological findings, but spasticity, personality changes, mental state disorders and mood disorders may be observed less frequently. In this case, the patient applied to our clinic with neurological symptoms, convulsion and tetany, compatible with the cases reported in the literature[1,4-5].

Besides, compatible with the literature, low parathormone levels, low calcium levels and hyperphosphatemia were detected in this case[6].

CONCLUSION

As a result, Fahr's syndrome can be overlooked because it is an uncommon disorder. Fahr's syndrome, which is usually observed with neuropsychiatric symptoms, develops depending on the disorder in calcium metabolism and of which cause is unclear, should be certainly considered in the differential diagnosis. The diagnosis of Fahr's syndrome can be made at an earlier stage with family screening in non-iatrogenic cases, and the progression of the disease can be prevented at the early stage by administering calcium replacement.

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The contributions of authors: The first author Dr. Turgut Dolanbay carried out diagnosis and treatment of the patient Fahr's Syndrome who applied to the Emergency Department with convulsion complaint.

The second author and responsible author, Dr. Hüseyin Fatih Gül studied and interpreted biochemical parameters requid from the emergency department. He also sent the manuscript to the journal.

The last author, Dr. Murat Aras, recorded the interventions to the patient in the emergency department and imaging results.

Finally, this observational work was written with the contributions of all the authors.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Accessibility to biologics and its impact on disease activity and quality of life in patients with rheumatoid arthritis in Kuwait

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OBJECTIVE
Biologics are indicated in rheumatoid arthritis (RA) in case of persistent high disease activity despite conventional disease-modifying anti-rheumatic drugs (cDMARDs) or patients with contraindications to cDMARDs or poor prognostic factors. The purpose of this study was to compare the prescription rates of biologics in Kuwaiti and non-Kuwaiti patients and to assess whether this had an impact on disease activity and quality of life in RA patients.

METHODS
Data were extracted from the Kuwait Registry for Rheumatic Diseases. Adult patients who satisfied the ACR classification criteria for RA from four major hospitals in Kuwait were evaluated from February 2013 through May 2018. The treatment agents, disease activity, and quality of life of Kuwaiti patients were compared with non-Kuwaiti patients.

RESULTS
A total of 1651 RA patients were included; 806 (48.8%) were Kuwaiti patients. Among Kuwaiti patients, 62.5% were on biologic drugs in comparison with 14% of non-Kuwaiti patients. In comparison with non-Kuwaiti patients, Kuwaiti patients had significantly lower numbers of swollen joints ($p < 0.001$) and disease activity score-28 scores ($p = 0.02$) and less steroid use ($p < 0.001$) yet a significantly higher health assessment questionnaire-disability index ($p < 0.001$). Regression analysis showed that DAS-28 scores were significantly associated with the treatment type ($p < 0.001$) and that nationality was significantly predictive of the treatment type ($p < 0.001$).

CONCLUSION
In the setting of easy accessibility to treatment for Kuwaiti patients, biologics were prescribed by rheumatologists at a higher rate than for non-Kuwaitis. This may explain the lower disease activity and the lower rate of steroid use in Kuwaiti patients than non-Kuwaitis.

KEY POINTS
• Significant discrepancies in the rates of prescribing biologic therapies between KP and NKP in Kuwait were observed. • Several treatment outcomes were significantly better in the KP group than in the NKP group even after adjustment of confounding factors. • The poor access to biologic therapies was suggested to limit the effectiveness of RA treatments in the NKP group.

Evaluation of disparities in multiple sclerosis risk by age, sex, and nativity in Kuwait:1980-2019

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OBJECTIVE
This cross-sectional cohort study quantified the disparities in MS risk by age, sex, nativity from 1980 to 2019 in Kuwait.

METHODS
Age-standardized MS incidence rate (ASIR) (per 100,000 person-years) overall and by subcohorts defined by cross-classification of the period (5-year groups) of diagnosis, age at onset, sex (female or male) and nativity (Kuwaiti or non-Kuwaiti) were computed and analyzed using multivariable negative binomial model.

RESULTS
Overall MS ASIR (per 100,000 person-years) was 3.41 (95% CI: 1.61, 5.21), which exponentially increased from 1980 to 2014 before drifting downward in 2015-2019 period. Compared with adults (age ≥ 40 years), males, non-Kuwaiti residents respectively, young adults (20-39 years), females and Kuwaiti nationals were significantly ($p < 0.05$) more likely to develop MS after adjusting for the period effect.

CONCLUSIONS
A high overall MS ASIR (per 100,000 person-years) was recorded with substantial temporal variation between 1980 and 2019. Young adults (20-39 years), females and Kuwaiti nationals constituted MS high-risk groups. The knowledge of underlying interface pathways between genetic and environmental factors may provide insights into MS pathogenesis and leads for future research.

Decreasing trend of imported malaria cases but increasing influx of mixed P. falciparum and P. vivax infections in malaria-free Kuwait

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Malaria still continues to be the most important parasitic disease worldwide, affecting 228 million people and causing 405,000 deaths each year. In this retrospective study during 2013 to 2018, we documented the incidence of imported malaria infection and evaluated the impact of malaria preventive measures in Kuwait, a non-endemic country. The epidemiologic and demographic data of all malaria cases was collected from the Infectious Diseases Hospital, Kuwait where all suspected cases of malaria are referred for confirmation and therapeutic intervention. The diagnosis of malaria infection was done by microscopy of Giemsa stained blood films. Selected samples were retested with BinaxNOW® Malaria rapid test and molecular assay to reconfirm the Plasmodium spp. or mixed infection. Overall, 1913 (25.9%) malaria cases were detected, 81.5% of which were among male subjects. Male subjects had higher incidence of P. vivax

malaria (113; 91.1%) and mixed infection with P. falciparum and P. vivax (1245; 90.0%) compared to females who had higher rate of P. falciparum infection (52.4%). An overwhelming majority of malaria cases (1895; 99.1%) were detected among expatriates from malaria-endemic countries; India (1012; 52.9%), Pakistan (390; 20.4%), Afghanistan (94; 4.9%) and African countries (313; 16.3%). Only 18 cases involved Kuwaiti nationals, all with a history of travel to African countries. The majority of malaria cases were detected during the summer and fall months (May-October). Our data showed that the incidence rate of imported malaria cases was stable during 2013 to 2018, however, the incidence of total malaria cases showed a declining trend over the years. This study confirms that the preventive program has been successful in reducing the incidence of imported malaria infections in Kuwait. The most striking finding of this study was high incidence of mixed infection with P. falciparum and P. vivax, with almost all (97%) cases among workers from India.

A matched case-control study of risk factors associated with multiple sclerosis in Kuwait

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BACKGROUND
Genetic and environmental factors seem to have etiologic roles in multiple sclerosis (MS). Kuwait is regarded as medium to high risk country for MS. However, there is a paucity of published data on the risk factors for MS in Kuwait. Therefore, this matched case-control study examined the association between various factors including family history, stressful life events, exposure to tobacco smoke, vaccination history, comorbidities and MS risk in Kuwait.

METHODS
Confirmed 110 MS cases and age (± 5 years), gender and nationality matched controls (1:1) were enrolled. A pre-tested structured questionnaire was used to collect the data through face-to-face interviews both from cases and controls. Conditional logistic regression was used to analyze the data.

RESULTS
Among both cases and controls, majority were Kuwaiti (82.7%), and female (76.4%). Multivariable model showed that cases compared to controls were significantly more likely to have had a family history of MS (adjusted matched odds ratio (mOR_{adj}) = 5.1; 95% CI: 2.1-12.4; $p < 0.001$) or less likely to have been vaccinated against influenza A and B viruses before MS onset (mOR_{adj} = %95 ;0.4 CI: 0.8-0.2; $p = 0.010$). None of the other variables considered were significantly related to MS status in this study.

CONCLUSIONS
Family history of MS had significantly direct, whereas, vaccination against influenza A and B viruses had inverse associations with MS status. Future studies may contemplate to verify the observed results.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2021; 53 (2): 218 - 220

European League against **Rheumatism** Congress 2021
Jun 02-05, 2021; Virtual conference
France
Event listing ID: 1408041
Event website: https://congress.eular.org/

IMCR - **Internal Medicine** Comprehensive Review and Update 2021
Jun 07-12, 2021; Live streaming
United States
Organizer: Harvard Medical School
Phone: 617-384-8600
Email: CEPrograms@hms.harvard.edu
Event listing ID: 1398518
Event website: https://internalmedicine.hmscme.com/

Lifestyle Medicine: Tools for Promoting Healthy Change
Jun 11-12, 2021; Live streaming
United States
Organizer: Harvard Medical School
Phone: 617-384-8600
Email: CEPrograms@hms.harvard.edu
Event listing ID: 1402130
Event website: https://lifestylemedicine.hmscme.com/

9th Congress of European **Microbiologists** 2021
Jun 11-15, 2021; Online
Germany
Event listing ID: 1407944
Event website: https://fems2021.org/

European **Human Genetics** Conference 2021
Jun 12-15, 2021; Virtual conference
United Kingdom
Event listing ID: 1407923
Event website: https://2021.eshg.org/

Biennial Congress of the International Organization of **Mycoplasmology** 2021
Jun 15-17, 2021
Israel / Tel Aviv-Yafo
Event listing ID: 1407921
Event website: https://iom2020.org/

DIABW0621 — **Diabetes** Update Refresher
Jun 17-18, 2021
Austria / Vienna
Contact: Veranstaltungskoordination
Phone: +43 225226326310
Email: info@fomf.at
Event listing ID: 1420422
Event website: https://www.fomf.at/diabetes-update-refresher-wien-0621?utm_source=koop&utm_medium=kalender_COMS&utm_campaign=DIABW0621

Rehabilitation Medicine Society of Australia and New Zealand 5th Annual Scientific Meeting 2021
Jun 22-25, 2021
Australia / Broadbeach
Event listing ID: 1408031
Event website: https://www.dcconferences.com.au/rmsanz2021/

AMF CME - Update CME - **Internal Medicine and Primary Care**: Live Stream
Jun 24-27, 2021; Live streamed conference
United States / Chicago
Organizer: American Medical Forum
Contact: CME Coordinator
Phone: 678 899 6444
Email: contact@amf-cme.org
Event listing ID: 1399868
Event website: https://amf-cme.org/event/june-2021-Live Stream-broadcast-live-qa/

31st European Congress of **Clinical Microbiology and Infectious Diseases** 2021
Jul 09-12, 2021
Austria / Vienna
Event listing ID: 1408008
Event website: https://www.eccmid.org/

IRIM - Intensive Review of **Internal Medicine**
Jul 25-Aug 01, 2021; Live streaming
United States
Organizer: Harvard Medical School
Phone: 617-384-8600
Email: CEPrograms@hms.harvard.edu
Event listing ID:1412514
Event website: https://irim.hmscme.com/

SAGES - Society of American **Gastrointestinal and Endoscopic** Surgeons
Aug 31-Sep 03, 2021
United States / Las Vegas
Organizer: SAGES
Phone: 310-437-0544x158
Email: michelle@sages.org
Event listing ID: 1418168
Event website: http://www.sages.org

European Forum for **Primary Care** Conference 2021
Sep 05-07, 2021
Norway / Bergen
Event listing ID: 1408025
Event website: http://euprimarycare.org/efpc-2021-bergen-conference-5-7-september-2021/

European Forum for Research in **Rehabilitation** 16th Congress 2021
Sep 23-25, 2021
Slovenia / Ljubljana
Event listing ID: 1389073
Event website: http://www.efrr2021.si/

6th Annual Emergency & Urgent Care Medicine for the **Primary Care** Provider 2021
Oct 01-03, 2021
United States / San Diego
Event listing ID: 1408068
Event website: https://www.cmemeeting.org/cme-conferences/san-diego-california-emergency-cme

Update in **Hospital Medicine** 2021
Oct 04-07, 2021 • Live streaming
United States
Organizer: Harvard Medical School
Phone: 617-384-8600
Email: CEPrograms@hms.harvard.edu
Event listing ID: 1404948
Event website: https://hospitalmedicine.hmscme.com/

11th Annual **Primary Care** Fall Conference 2021
Oct 11-15, 2021
United States / Lahaina, Hawaii
Event listing ID: 1408045
Event website: https://www.cmemeeting.org/cme-conferences/maui-hawaii-fall-cme-2021

Principles of **Medical Education**: Maximizing your Teaching Skills
Oct 18-20, 2021 • Live streaming
United States
Organizer: Harvard Medical School
Phone: 617-384-8600
Email: CEPrograms@hms.harvard.edu
Event listing ID: 1420029
Event website: https://medicaleducators.hmscme.com/

PCIM - Primary Care **Internal Medicine** 2021
Oct 18-22, 2021; Live streaming
United States
Organizer: Harvard Medical School
Phone: 617-384-8600
Email: CEPrograms@hms.harvard.edu
Event listing ID: 1421036
Event website: https://pcim.hmscme.com/

NanoMed 2021 - **NanoMedicine** International Conference 2021
Oct 20-22, 2021
Italy / Milan
Organizer: SETCOR conferences and events
Contact: Event coordinator
Phone: +33644101282
Email: info@setcor.org
Event listing ID: 1361871
Event website: https://www.setcor.org/conferences/nanomed-2021

American **Public Health** Association 149th Annual Meeting & Exposition 2021
Oct 23-27, 2021
United States / Denver, CO
Event listing ID: 1408109
Event website: https://www.apha.org/events-and-meetings/annual

Infectious Diseases in Primary Care
Oct 27-29, 2021; Live streaming
United States
Organizer: Harvard Medical School
Phone: 617-384-8600
Email: CEPrograms@hms.harvard.edu
Event listing ID: 1422001
Event website: https://idprimarycare.hmscme.com/

Diabetes and its Complications
Nov 04-06, 2021
United States / Boston
Organizer: Harvard Medical School and Beth Israel Deaconess Medical Center
Contact: Harvard Medical School
Phone: 617-384-8600
Email: ceprograms@hms.harvard.edu
Event listing ID: 1425244
Event website: https://hmsdiabetescourse.com/

18th Asia Pacific Congress of **Clinical Microbiology** and Infection 2021
Nov 11-13, 2021
Singapore
Event listing ID: 1408007
Event website: https://apccmi2021.com/

AIC2021 - Autumn **Immunology** Conference
Nov 19-22, 2021
United States / Chicago
Event listing ID: 695588
Event website: http://autumnimmunology.org/

Update in **Internal Medicine** 2021 | Live Stream
Dec 05-11, 2021
United States/ Boston
Organizer: Harvard Medical School and Beth Israel Deaconess Medical Center
Contact: Harvard Medical School
Phone: 617-384-8600
Email: ceprograms@hms.harvard.edu
Event listing ID: 1425210
Event website: https://updateinternalmedicine.com/

2nd Annual Medical Updates in **Primary Care** Conference Hawaii 2021
Dec 06-10, 2021
United States / Kohala Coast, Hawaii
Event listing ID: 1408000
Event website: https://www.cmemeeting.org/cme-conferences/big-island-hawaii-cme

WHO-Facts Sheet

1. Adolescent mental health
2. Breast cancer
3. Dementia
4. Mycetoma
5. Plague

Compiled and edited by
Vineetha E Mammen

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1. Adolescent mental health

Key facts

- One in six people are aged 10-19 years.
- Mental health conditions account for 16% of the global burden of disease and injury in people aged 10-19 years.
- Half of all mental health conditions start by 14 years of age but most cases are undetected and untreated(1).
- Globally, depression is one of the leading causes of illness and disability among adolescents.
- Suicide is the third leading cause of death in 15-19-year-olds.
- The consequences of not addressing adolescent mental health conditions extend to adulthood, impairing both physical and mental health and limiting opportunities to lead fulfilling lives as adults.

Introduction

Adolescence (10-19 years) is a unique and formative time. Multiple physical, emotional and social changes, including exposure to poverty, abuse, or violence, can make adolescents vulnerable to mental health problems. Promoting psychological well-being and protecting adolescents from adverse experiences and risk factors that may impact their potential to thrive are critical for their well-being during adolescence and for their physical and mental health in adulthood.

Mental health determinants

Adolescence is a crucial period for developing and maintaining social and emotional habits important for mental well-being. These include adopting healthy sleep patterns; taking regular exercise; developing coping, problem-solving, and interpersonal skills; and learning to manage emotions. Supportive environments in the family, at school and in the wider community are also important. An estimated 10-20% of adolescents globally experience mental health conditions, yet these remain underdiagnosed and undertreated*(1)*.

Multiple factors determine mental health outcomes. The more risk factors adolescents are exposed to, the greater the potential impact on their mental health. Factors that can contribute to stress during adolescence include a desire for greater autonomy, pressure to conform with peers, exploration of sexual identity, and increased access to and use of technology. Media influence and gender norms can exacerbate the disparity between an adolescent's lived reality and their perceptions or aspirations for the future. Other important determinants include the quality of their home life and relationships with peers. Violence (including harsh parenting and bullying) and socioeconomic problems are recognized risks to mental health. Children and adolescents are especially vulnerable to sexual violence, which has a clear association with detrimental mental health.

Some adolescents are at greater risk of mental health conditions due to their living conditions, stigma, discrimination or exclusion, or lack of access to quality support and services. These include adolescents living in humanitarian and fragile settings; adolescents with chronic illness, autism spectrum disorder, an intellectual disability or other neurological condition; pregnant adolescents, adolescent parents, or those in early and/or forced marriages; orphans; and adolescents from minority ethnic or sexual backgrounds or other discriminated groups.

Adolescents with mental health conditions are in turn particularly vulnerable to social exclusion, discrimination, stigma (affecting readiness to seek help), educational difficulties, risk-taking behaviours, physical ill-health and human rights violations.

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Emotional disorders

Emotional disorders commonly emerge during adolescence. In addition to depression or anxiety, adolescents with emotional disorders can also experience excessive irritability, frustration or anger. Symptoms can overlap across more than one emotional disorder with rapid and unexpected changes in mood and emotional outbursts. Younger adolescents may additionally develop emotion-related physical symptoms such as stomach ache, headache or nausea.

Globally, depression is the fourth leading cause of illness and disability among adolescents aged 15-19 years and fifteenth for those aged 10-14 years. Anxiety is the ninth leading cause for adolescents aged 15-19 years and sixth for those aged 10-14 years. Emotional disorders can profoundly affect areas like schoolwork and school attendance. Social withdrawal can exacerbate isolation and loneliness. At its worse, depression can lead to suicide.

Childhood behavioural disorders

Childhood behavioural disorders are the second leading cause of disease burden in young adolescents aged 10-14 years and the eleventh leading cause among older adolescents aged 15-19 years. Childhood behavioural disorders include attention deficit hyperactivity disorder (characterized by difficulty paying attention, excessive activity and acting without regards to consequences, which are otherwise not appropriate for a person's age), and conduct disorder (with symptoms of destructive or challenging behaviour). Childhood behavioural disorders can affect adolescents' education and may result in criminal behaviour.

Eating disorders

Eating disorders commonly emerge during adolescence and young adulthood. Eating disorders affect females more commonly than males. Conditions such as anorexia nervosa, bulimia nervosa and binge eating disorder are characterised by harmful eating behaviours such as restricting calories or binge eating. Eating disorders are detrimental to health and often co-exist with depression, anxiety and/or substance misuse.

Psychosis

Conditions that include symptoms of psychosis most commonly emerge in late adolescence or early adulthood. Symptoms can include hallucinations or delusions. These experiences can impair an adolescent's ability to participate in daily life and education and often lead to stigma or human rights violations.

Suicide and self-harm

An estimated 62 000 adolescents died in 2016 as a result of self-harm. Suicide is the third leading cause of death in older adolescents (15-19 years). Nearly 90% of the world's adolescents live in low-or middle-income countries and more than 90% of adolescent suicides are among adolescents living in those countries. Risk factors for suicide are multifaceted, including harmful use of alcohol, abuse in childhood, stigma against help-seeking, barriers to accessing care and access to means. Communication through digital media about suicidal behaviour is an emerging concern for this age group.

Risk-taking behaviours

Many risk-taking behaviours for health, such as substance use or sexual risk taking, start during adolescence. Risk-taking behaviours can be both an unhelpful strategy to cope with poor mental health and can severely impact an adolescent's mental and physical well-being.

Worldwide, the prevalence of heavy episodic drinking among adolescents aged 15-19 years was 13.6% in 2016, with males most at risk.

The use of tobacco and cannabis are additional concerns. Cannabis is the most widely used drug among young people with about 4.7% of 15-16-years-olds using it at least once in 2018. Many adult smokers have their first cigarette prior to the age of 18 years.

Perpetration of violence is a risk-taking behaviour that can increase the likelihood of low educational attainment, injury, involvement with crime or death. Interpersonal violence was ranked the second leading cause of death of older adolescent boys in 2016.

Promotion and prevention

Mental health promotion and prevention interventions aim to strengthen an individual's capacity to regulate emotions, enhance alternatives to risk-taking behaviours, build resilience for difficult situations and adversities, and promote supportive social environments and social networks.

These programmes require a multilevel approach with varied delivery platforms – for example, digital media, health or social care settings, schools or the community, and varied strategies to reach adolescents, particularly the most vulnerable.

Early detection and treatment

It is crucial to address the needs of adolescents with defined mental health conditions. Avoiding institutionalization and over-medicalization, prioritizing nonpharmacological approaches, and respecting the rights of children in line with the United Nations Convention on the Rights of the Child and other human rights instruments are key

for adolescents. WHO's mental health Gap Action Programme (mhGAP) provides evidence-based guidelines for non-specialists to enable them to better identify and support priority mental health conditions in lower-resourced settings.

WHO works on strategies, programmes and tools to assist governments in responding to the health needs of adolescents. Key resources are:

- Global Accelerated Action for the Health of Adolescents (AA-HA!): Guidance to support country implementation
- Global Strategy for Women's, Children's and Adolescents' Health 2030–2016
- Mental Health Action Plan 2020–2013
- Mental Health Gap Action Programme (mhGAP)

In the context of emergencies, WHO has developed tools for:

- assessment
- psychological first aid
- clinical management of mental disorders
- mental health system recovery

all of which consider issues related to young people.

1. Kessler RC, Angermeyer M, Anthony JC, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 2007; 6: 168–76

2. Breast cancer

Introduction

Breast cancer arises in the lining cells (epithelium) of the ducts (85%) or lobules (15%) in the glandular tissue of the breast. Initially, the cancerous growth is confined to the duct or lobule ("in situ") where it generally causes no symptoms and has minimal potential for spread (metastasis). Over time, these in situ (stage 0) cancers may progress and invade the surrounding breast tissue (invasive breast cancer) then spread to the nearby lymph nodes (regional metastasis) or to other organs in the body (distant metastasis). If a woman dies from breast cancer, it is because of widespread metastasis.

Breast cancer treatment can be highly effective, especially when the disease is identified early. Treatment of breast cancer often consists of a combination of surgical removal, radiation therapy and medication (hormonal therapy, chemotherapy and/or targeted biological therapy) to treat the microscopic cancer that has spread from the breast tumor through the blood. Such treatment, which can prevent cancer growth and spread, thereby saves lives.

Scope of the problem

In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. There are more lost disability-adjusted life years (DALYs) by women to breast cancer globally than any other type of cancer. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life.

Breast cancer mortality changed little from the 1930s through to the 1970s. Improvements in survival began in the 1980s in countries with early detection programmes combined with different modes of treatment to eradicate invasive disease.

Who is at risk?

Breast cancer is not a transmissible or infectious disease. Unlike some cancers that have infection-related causes, such as human papillomavirus (HPV) infection and cervical cancer, there are no known viral or bacterial infections linked to the development of breast cancer.

Approximately half of breast cancers develop in women who have no identifiable breast cancer risk factor other than gender (female) and age (over 40 years). Certain factors increase the risk of breast cancer including increasing age, obesity, harmful use of alcohol, family history of breast cancer, history of radiation exposure, reproductive history (such as age that menstrual periods began and age at first pregnancy), tobacco use and postmenopausal hormone therapy.

Behavioural choices and related interventions that reduce the risk of breast cancer include:

- prolonged breastfeeding;
- regular physical activity;
- weight control;
- avoidance of harmful use of alcohol;
- avoidance of exposure to tobacco smoke;
- avoidance of prolonged use of hormones; and
- avoidance of excessive radiation exposure.

Unfortunately, even if all of the potentially modifiable risk factors could be controlled, this would only reduce the risk of developing breast cancer by at most 30%.

Female gender is the strongest breast cancer risk factor. Approximately 0.5-1% of breast cancers occur in men. The treatment of breast cancer in men follows the same principles of management as for women.

Family history of breast cancer increases the risk of breast cancer, but the majority of women diagnosed with breast cancer do not have a known family history

of the disease. Lack of a known family history does not necessarily mean that a woman is at reduced risk.

Certain inherited "high penetrance" gene mutations greatly increase breast cancer risk, the most dominant being mutations in the genes BRCA1, BRCA2 and PALB-2. Women found to have mutations in these major genes could consider risk reduction strategies such as surgical removal of both breasts. Consideration of such a highly invasive approach only concerns a very limited number of women, should be carefully evaluated considering all alternatives and should not be rushed.

Signs and symptoms

Breast cancer most commonly presents as a painless lump or thickening in the breast. It is important that women finding an abnormal lump in the breast consult a health practitioner without a delay of more than 1-2 months even when there is no pain associated with it. Seeking medical attention at the first sign of a potential symptom allows for more successful treatment.

Generally, symptoms of breast cancer include:

- a breast lump or thickening;
- alteration in size, shape or appearance of a breast;
- dimpling, redness, pitting or other alteration in the skin;
- change in nipple appearance or alteration in the skin surrounding the nipple (areola); and/or
- abnormal nipple discharge.

There are many reasons for lumps to develop in the breast, most of which are not cancer. As many as 90% of breast masses are not cancerous. Non-cancerous breast abnormalities include benign masses like fibroadenomas and cysts as well as infections.

Breast cancer can present in a wide variety of ways, which is why a complete medical examination is important. Women with persistent abnormalities (generally lasting more than one month) should undergo tests including imaging of the breast and in some cases tissue sampling (biopsy) to determine if a mass is malignant (cancerous) or benign.

Advanced cancers can erode through the skin to cause open sores (ulceration) but are not necessarily painful. Women with breast wounds that do not heal should have a biopsy performed.

Breast cancers may spread to other areas of the body and trigger other symptoms. Often, the most common first detectable site of spread is to the lymph nodes under the arm although it is possible to have cancer-bearing lymph nodes that cannot be felt.

Over time, cancerous cells may spread to other organs including the lungs, liver, brain and bones. Once they reach these sites, new cancer-related symptoms such as bone pain or headaches may appear.

Treatment

Breast cancer treatment can be highly effective, achieving survival probabilities of 90% or higher, particularly when the disease is identified early. Treatment generally consists of surgery and radiation therapy for control of the disease in the breast, lymph nodes and surrounding areas (locoregional control) and systemic therapy (anti-cancer medicines given by mouth or intravenously) to treat and/or reduce the risk of the cancer spreading (metastasis). Anti-cancer medicines include endocrine (hormone) therapy, chemotherapy and in some cases targeted biologic therapy (antibodies).

In the past, all breast cancers were treated surgically by mastectomy (complete removal of the breast). When cancers are large, mastectomy may still be required. Today, the majority of breast cancers can be treated with a smaller procedure called a "lumpectomy" or partial mastectomy, in which only the tumor is removed from the breast. In these cases, radiation therapy to the breast is generally required to minimize the chances of recurrence in the breast.

Lymph nodes are removed at the time of cancer surgery for invasive cancers. Complete removal of the lymph node bed under the arm (complete axillary dissection) in the past was thought to be necessary to prevent the spread of cancer. A smaller lymph node procedures called "sentinel node biopsy" is now preferred as it has fewer complications. It uses dye and/or a radioactive tracer to find the first few lymph nodes to which cancer could spread from the breast.

Medical treatments for breast cancers, which may be given before ("neoadjuvant") or after ("adjuvant") surgery, is based on the biological subtyping of the cancers. Cancer that express the estrogen receptor (ER) and/or progesterone receptor (PR) are likely to respond to endocrine (hormone) therapies such as tamoxifen or aromatase inhibitors. These medicines are taken orally for 5-10 years, and reduce the chance of recurrence of these "hormone-positive" cancers by nearly half. Endocrine therapies can cause symptoms of menopause but are generally well tolerated.

Cancers that do not express ER or PR are "hormone receptor negative" and need to be treated with chemotherapy unless the cancer is very small. The chemotherapy regimens available today are very effective in reducing the chances of cancer spread or recurrence and are generally given as outpatient therapy. Chemotherapy for breast cancer generally does not require hospital admission in the absence of complications.

Breast cancers may independently overexpress a molecule called the HER-2/neu oncogene. These "HER-2 positive" cancers are amenable to treatment

with targeted biological agents such as trastuzumab. These biological agents are very effective but also very expensive, because they are antibodies rather than chemicals. When targeted biological therapies are given, they are combined with chemotherapy to make them effective at killing cancer cells.

Radiotherapy also plays a very important role in treating breast cancer. With early stage breast cancers, radiation can prevent a woman having to undergo a mastectomy. With later stage cancers, radiotherapy can reduce cancer recurrence risk even when a mastectomy has been performed. For advanced stage of breast cancer, in some circumstances, radiation therapy may reduce the likelihood of dying of the disease.

The effectiveness of breast cancer therapies depends on the full course of treatment. Partial treatment is less likely to lead to a positive outcome.

Challenges

Survival of breast cancer for at least 5 years after diagnosis ranges from more than 90% in high-income countries, to 66% in India and 40% in South Africa. Early detection and treatment has proven successful in high-income countries and should be applied in countries with limited resources where some of the standard tools are available. The great majority of drugs used for breast cancer are already on the WHO Essential Medicines List (EML). Thus, major global improvements in breast cancer can result from implementing what we already know works.

Global impact

Age-standardized breast cancer mortality in high-income countries dropped by 40% between the 1980s and 2020. Countries that have succeeded in reducing breast cancer mortality have been able to achieve an annual breast cancer mortality reduction of 2-4% per year. If an annual mortality reduction of 2.5% per year occurs worldwide, 2.5 million breast cancer deaths would be avoided between 2020 and 2040.

The strategies for improving breast cancer outcomes depend on fundamental health system strengthening to deliver the treatments that are already known to work. These are also important for the management of other cancers and other non-malignant noncommunicable diseases (NCDs). For example, having reliable referral pathways from primary care facilities to district hospitals to dedicated cancer centres.

The establishment of reliable referral pathways from primary care facilities to district hospitals to dedicated cancer centers is the same approach as is required for the management of cervical cancer, lung cancer, colorectal cancer and prostate cancer. To that end, breast cancer is an "index" disease whereby pathways are created that can be followed for the management of other diseases.

WHO response

The objective of the WHO Global Breast Cancer Initiative (GBCI) is to reduce global breast cancer mortality by 2.5% per year, thereby averting 2.5 million breast cancer deaths globally between 2020 and 2040. Reducing global breast cancer mortality by 2.5% per year would avert 25% of breast cancer deaths by 2030 and 40% by 2040 among women under 70 years of age. The three pillars toward achieving these objectives are: health promotion for early detection; timely diagnosis; and comprehensive breast cancer management.

By providing public health education to improve awareness among women of the signs and symptoms of breast cancer and, together with their families, understand the importance of early detection and treatment, more women would consult medical practitioners when breast cancer is first suspected, and before any cancer present is advanced. This is possible even in the absence of mammographic screening that is impractical in many countries at the present time.

Public education needs to be combined with health worker education about the signs and symptoms of early breast cancer so that women are referred to diagnostic services when appropriate.

Rapid diagnosis needs to be linked to effective cancer treatment that in many settings requires some level of specialized cancer care. By establishing centralized services in a cancer facility or hospital, using breast cancer as a model, treatment for breast cancer may be optimized while improving management of other cancers.

1. Age-standardization is a technique used to allow populations to be compared when the age profiles of the populations are quite different.

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3. Dementia

Key facts

- Dementia is a syndrome in which there is deterioration in memory, thinking, behaviour and the ability to perform everyday activities.
- Although dementia mainly affects older people, it is not a normal part of ageing.
- Worldwide, around 50 million people have dementia, and there are nearly 10 million new cases every year.
- Alzheimer's disease is the most common form of dementia and may contribute to 60–70% of cases.
- Dementia is one of the major causes of disability and dependency among older people worldwide.
- Dementia has a physical, psychological, social, and economic impact, not only on people with dementia, but also on their carers, families and society at large.

Dementia is a syndrome – usually of a chronic or progressive nature – in which there is deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not affected. The impairment in cognitive function is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation.

Dementia results from a variety of diseases and injuries that primarily or secondarily affect the brain, such as Alzheimer's disease or stroke.

Dementia is one of the major causes of disability and dependency among older people worldwide. It can be overwhelming, not only for the people who have it, but also for their carers and families. There is often a lack of awareness and understanding of dementia, resulting in stigmatization and barriers to diagnosis and care. The impact of dementia on carers, family and society at large can be physical, psychological, social and economic.

Signs and symptoms

Dementia affects each person in a different way, depending upon the impact of the disease and the person's personality before becoming ill. The signs and symptoms linked to dementia can be understood in three stages.

Early stage: the early stage of dementia is often overlooked, because the onset is gradual. Common symptoms include:

- forgetfulness
- losing track of the time
- becoming lost in familiar places.

Middle stage: as dementia progresses to the middle stage, the signs and symptoms become clearer and more restricting. These include:

- becoming forgetful of recent events and people's names
- becoming lost at home
- having increasing difficulty with communication
- needing help with personal care
- experiencing behaviour changes, including wandering and repeated questioning.

Late stage: the late stage of dementia is one of near total dependence and inactivity. Memory disturbances are serious and the physical signs and symptoms become more obvious. Symptoms include:

- becoming unaware of the time and place
- having difficulty recognizing relatives and friends
- having an increasing need for assisted self-care
- having difficulty walking
- experiencing behaviour changes that may escalate and include aggression.

Common forms of dementia

There are many different forms of dementia. Alzheimer's disease is the most common form and may contribute to 60–70% of cases. Other major forms include vascular dementia, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). The boundaries between different forms of dementia are indistinct and mixed forms often co-exist.

Rates of dementia

Worldwide, around 50 million people have dementia, with nearly 60% living in low- and middle-income countries. Every year, there are nearly 10 million new cases.

The estimated proportion of the general population aged 60 and over with dementia at a given time is between 5-8%.

The total number of people with dementia is projected to reach 82 million in 2030 and 152 in 2050. Much of this increase is attributable to the rising numbers of people with dementia living in low- and middle-income countries.

Treatment and care

There is no treatment currently available to cure dementia or to alter its progressive course. Numerous new treatments are being investigated in various stages of clinical trials.

However, much can be offered to support and improve the lives of people with dementia and their carers and families. The principal goals for dementia care are:

- early diagnosis in order to promote early and optimal management
- optimizing physical health, cognition, activity and well-being
- identifying and treating accompanying physical illness
- detecting and treating challenging behavioural and psychological symptoms
- providing information and long-term support to carers.

Risk factors and prevention

Although age is the strongest known risk factor for dementia, it is not an inevitable consequence of ageing. Further, dementia does not exclusively affect older people – young onset dementia (defined as the onset of symptoms before the age of 65 years) accounts for up to 9% of cases. Studies show that people can reduce their risk of dementia by getting regular exercise, not smoking, avoiding harmful use of alcohol, controlling their weight, eating a healthy diet, and maintaining healthy blood pressure, cholesterol and blood sugar levels. Additional risk factors include depression, low educational attainment, social isolation, and cognitive inactivity.

Social and economic impact

Dementia has significant social and economic implications in terms of direct medical and social care costs, and the costs of informal care. In 2015, the total global societal cost of dementia was estimated to be US$ 818 billion, equivalent to 1.1% of global gross domestic product (GDP). The total cost as a proportion of GDP varied from 0.2% in low- and middle-income countries to 1.4% in high-income countries.

Impact on families and carers

Dementia can be overwhelming for the families of affected people and for their carers. Physical, emotional and financial pressures can cause great stress to families and carers, and support is required from the health, social, financial and legal systems.

Human rights

People with dementia are frequently denied the basic rights and freedoms available to others. In many countries, physical and chemical restraints are used extensively in care homes for older people and in acute-care settings, even when regulations are in place to uphold the rights of people to freedom and choice.

An appropriate and supportive legislative environment based on internationally-accepted human rights standards is required to ensure the highest quality of care for people with dementia and their carers.

WHO response

WHO recognizes dementia as a public health priority. In May 2017, the World Health Assembly endorsed the *Global action plan on the public health response to dementia 2017-2025*. The Plan provides a comprehensive blueprint for action – for policy-makers, international, regional and national partners, and WHO as in the following areas: addressing dementia as a public health priority; increasing awareness of dementia and establishing dementia-friendly initiatives; reducing the risk of dementia; diagnosis, treatment and care; information systems for dementia; support for dementia carers; and, research and innovation

An international surveillance platform, the Global Dementia Observatory (GDO), has been established for policy-makers and researchers to facilitate monitoring

and sharing of information on dementia policies, service delivery, epidemiology and research. WHO is also developing a knowledge exchange platform to facilitate the exchange of good practices in the area of dementia.

WHO has developed *Towards a dementia plan: a WHO guide*, which provides guidance to Member States in creating and operationalizing a dementia plan. The guide is closely linked to WHO's GDO and includes associated tools such as a checklist to guide the preparation, development and implementation of a dementia plan. It can also be used for stakeholder mapping and priority setting.

WHO's *Guidelines on risk reduction of cognitive decline and dementia* provide evidence- based recommendations on interventions for reducing modifiable risk factors for dementia, such as physical inactivity and unhealthy diets, as well as controlling medical conditions linked to dementia, including hypertension and diabetes.

Dementia is also one of the priority conditions in the WHO Mental Health Gap Action Programme (mhGAP), which is a resource for generalists, particularly in low- and middle-income countries, to help them provide first-line care for mental, neurological and substance use disorders.

WHO has developed iSupport, a knowledge and skills training programme for carers of people living with dementia. iSupport is available as a hard copy manual, and is already being implemented in several countries. The online version of iSupport will be available soon.

4. Mycetoma

Key facts

- Mycetoma is a chronic, progressively destructive infectious disease of the subcutaneous tissues, affecting skin, muscle and bone.
- Mycetoma can be caused by different species of microorganisms, but almost always by bacteria or fungus.
- Mycetoma occurs in tropical and subtropical environments characterized by short rainy seasons and prolonged dry seasons that favour the growth of thorny bushes.
- Global burden is not known, but the disease is endemic; it has been reported from countries in Africa, Asia, Europe and Latin America.
- Mycetoma has numerous adverse medical, health and socioeconomic consequences for patients, communities and health services in affected areas.
- People living in or travelling to endemic areas should be advised not to walk barefoot, as footwear and clothing in general can protect against puncture wounds.

Mycetoma is a chronic disease usually of the foot but any part of the body can be affected. Infection is most probably acquired by traumatic inoculation of certain fungi or bacteria into the subcutaneous tissue.

The disease commonly affects young adults, mostly males aged between 15 and 30 years in developing countries. People of low socioeconomic status and manual workers such as agriculturalists, labourers and herdsmen are the worst affected.

Mycetoma has numerous adverse medical, health and socioeconomic impacts on patients, communities and health authorities. Accurate data on its incidence and prevalence are not available. However, early detection and treatment are important to reduce morbidity and improve treatment outcomes.

Mycetoma was first reported in the mid-19th century in Madurai, India, and hence was initially called Madura foot.

Distribution

The causative organisms of mycetoma are distributed worldwide but are endemic in tropical and subtropical areas in the so called 'Mycetoma belt', which includes the Bolivarian Republic of Venezuela, Chad, Ethiopia, India, Mauritania, Mexico, Senegal, Somalia, Sudan, Thailand, and Yemen.

Transmission

Transmission occurs when the causative organism enters the body through minor trauma or a penetrating injury, commonly thorn pricks. There is a clear association between mycetoma and individuals who walk barefooted and are manual workers.

Clinical characteristics

Mycetoma is characterized by a combination of painless subcutaneous mass, multiple sinuses and discharge containing grains. It usually spreads to involve the skin, deep structures and bone, resulting in destruction, deformity and loss of function, which may be fatal. Mycetoma commonly involves the extremities, back and gluteal region but any other part of the body can be affected. Given its slow progression, painless nature, lack of awareness, and scarcity of medical and health facilities in endemic areas, many patients present late with advanced infection where amputation may be the only available treatment. Secondary bacterial infection is common, and that may cause increased pain, disability and fatal septicaemia (severe infections involving the entire human system), if untreated. Infection is not transmitted from human to human.

Diagnosis

The diagnosis of mycetoma is based on clinical presentation and identification of the causative organisms which can be detected by directly examining the grains that are discharged by the sinuses. The samples can be obtained from any open discharging sinus by Fine Needle Aspiration (FNA) or surgical biopsy. Although grains microscopy is helpful in detecting the causative organism, it is important to further identify these by culture but even then misclassification occurs. Identification by Polymerase chain reaction (PCR) is the most reliable method but has high cost and lacks standardized techniques. There is no serological diagnostic test. Imaging techniques including X-rays, ultrasound, magnetic resonance and computer tomography can be used to assess the extent of lesions and planning the clinical management.

Treatment

The treatment depends on the causative organisms. For the bacterial type, it is a combination antibiotics whereas for fungal type it is combined antifungal drugs and surgery. The treatment is frequently unsatisfactory, has many side effects, expensive and not available in endemic areas.

Prevention & Control

Mycetoma is not a notifiable disease (a disease required by law to be reported) and global surveillance system is being developed. There are no control programmes for mycetoma yet, except for Sudan. Preventing infection is difficult, but people living in or travelling to endemic areas should be advised not to walk barefooted.

WHO and global response

To build national capacities on mycetoma, the Government of Sudan and WHO convened the First International Training Workshop on Mycetoma in Khartoum on 10–14 February 2019. Drawing on the expertise of the Mycetoma Research Centre in Khartoum, the workshop - attended by approximately 50 health staff from many mycetoma-endemic countries - provided a unique opportunity to share experiences and standardize practices relating to diagnosis, treatment and surveillance.

The workshop was followed by the Sixth International Conference on Mycetoma in Khartoum on 15-17 February 2019. The Conference adopted the 'Khartoum Call for Action on mycetoma' which calls on a wide range of actors to take specific public-health and policy measures to address the burden of mycetoma

Opportunities

Elaborating a public health strategy for the prevention and control of Mycetoma requires collection of epidemiological data on burden of disease, investment in research and product development, so that cost-effective prevention, diagnosis, early treatment and case management can be practiced in low-resource settings.

At present, active case-finding with early diagnosis and treatment with currently available tools is the most appropriate approach for lessening Mycetoma's disease morbidity and disability. However, important public health actions are required to tackling the burden of mycetoma. Some of these include:

- including mycetoma in national surveillance systems and establishing a registry in affected countries;
- Integrating mycetoma detection within the skin-NTDs approach to enhance early detection
- improving access to diagnostics and medicines and refinement of protocols for case-management;
- strengthening preventive measures (e.g. wearing shoes) to decrease incidence;
- reinforcing awareness among affected communities and building capacities of health staff.

Currently, the Drugs for Neglected Diseases initiative (DNDi) and other partners are investigating the safety and efficacy of fosravuconazole in treating eumycetoma in Sudan. In addition to an expected higher cure rate, if successful, the adoption of the results of this treatment would allow for a shorter therapeutic protocol, boosting compliance with treatment and saving financial resources.

5. Plague

Key facts

- Plague is caused by the bacteria Yersinia pestis, a zoonotic bacteria usually found in small mammals and their fleas.
- People infected with Y. pestis often develop symptoms after an incubation period of one to seven days.
- There are two main clinical forms of plague infection: bubonic and pneumonic. Bubonic plague is the most common form and is characterized by painful swollen lymph nodes or 'buboes'.
- Plague is transmitted between animals and humans by the bite of infected fleas, direct contact with infected tissues, and inhalation of infected respiratory droplets.
- Plague can be a very severe disease in people, with a case-fatality ratio of 30% to 60% for the bubonic type, and is always fatal for the pneumonic kind

when left untreated.

- Antibiotic treatment is effective against plague bacteria, so early diagnosis and early treatment can save lives.
- From 2010 to 2015 there were 3248 cases reported worldwide, including 584 deaths.
- Currently, the three most endemic countries are the Democratic Republic of the Congo, Madagascar, and Peru.

Plague is an infectious disease caused by the bacteria Yersinia pestis, a zoonotic bacteria, usually found in small mammals and their fleas. It is transmitted between animals through fleas. Humans can be infected through:

- the bite of infected vector fleas
- unprotected contact with infectious bodily fluids or contaminated materials
- the inhalation of respiratory droplets/small particles from a patient with pneumonic plague.

Plague is a very severe disease in people, particularly in its septicaemic (systemic infection caused by circulating bacteria in bloodstream) and pneumonic forms, with a case-fatality ratio of 30% to 100% if left untreated. The pneumonic form is invariably fatal unless treated early. It is especially contagious and can trigger severe epidemics through person-to-person contact via droplets in the air.

From 2010 to 2015, there were 3248 cases reported worldwide, including 584 deaths.

Historically, plague was responsible for widespread pandemics with high mortality. It was known as the "Black Death" during the fourteenth century, causing more than 50 million deaths in Europe. Nowadays, plague is easily treated with antibiotics and the use of standard precautions to prevent acquiring infection.

Signs and symptoms

People infected with plague usually develop acute febrile disease with other non-specific systemic symptoms after an incubation period of one to seven days, such as sudden onset of fever, chills, head and body aches, and weakness, vomiting and nausea.

There are two main forms of plague infection, depending on the route of infection: bubonic and pneumonic.

- **Bubonic** plague is the most common form of plague and is caused by the bite of an infected flea. Plague bacillus, *Y. pestis*, enters at the bite and travels through the lymphatic system to the nearest lymph node where it replicates itself. The lymph node then becomes inflamed, tense and painful, and is called a 'bubo'. At advanced stages of the infection the inflamed lymph nodes can turn into open sores filled with pus. Human to human transmission of bubonic plague is rare. Bubonic plague can advance and spread to the lungs, which is the more severe type of plague called pneumonic plague.
- **Pneumonic** plague, or lung-based plague, is the most virulent form of plague. Incubation can be as short as 24 hours. Any person with pneumonic plague may transmit the disease via droplets to other humans. Untreated pneumonic plague, if not diagnosed and treated early, can be fatal. However, recovery rates are high if detected and treated in time (within 24 hours of onset of symptoms).

Where is plague found?

As an animal disease, plague is found in all continents, except Oceania. There is a risk of human plague wherever the presence of plague natural foci (the bacteria, an animal reservoir and a vector) and human population co-exist.

- Global distribution of natural plague foci as of March 2016

Plague epidemics have occurred in Africa, Asia, and South America; but since the 1990s, most human cases have occurred in Africa. The three most endemic countries are the Democratic Republic of Congo, Madagascar, and Peru. In Madagascar cases of bubonic plague are reported nearly every year, during the epidemic season (between September and April).

Diagnosing plague

Confirmation of plague requires lab testing. The best practice is to identify Y. pestis from a sample of pus from a bubo, blood or sputum. A specific Y. pestis antigen can be detected by different techniques. One of them is a laboratory validated rapid dipstick test now widely used in Africa and South America, with the support of WHO.

Treatment

Untreated pneumonic plague can be rapidly fatal, so early diagnosis and treatment is essential for survival and reduction of complications. Antibiotics and supportive therapy are effective against plague if patients are diagnosed in time. Pneumonic plague can be fatal within 18 to 24 hours of disease onset if left untreated, but common antibiotics for enterobacteria (gram negative rods) can effectively cure the disease if they are delivered early.

Prevention

Preventive measures include informing people when zoonotic plague is present in their environment and advising them to take precautions against flea bites and not to handle animal carcasses. Generally people should be advised to avoid direct contact with infected body fluids and tissues. When handling potentially infected patients and collecting specimens, standard precautions should apply.

Vaccination

WHO does not recommend vaccination, expect for high-risk groups (such as laboratory personnel who are constantly exposed to the risk of contamination, and health care workers).

Managing plague outbreaks

- **Find and stop the source of infection.** Identify the most likely source of infection in the area where the human case(s) was exposed, typically looking for clustered areas with large numbers of small animal deaths. Institute appropriate infection, prevention and control procedures. Institute vector control, then rodent control. Killing rodents before vectors will cause the fleas to jump to new hosts, this is to be avoided.
- **Protect health workers.** Inform and train them on infection prevention and control. Workers in direct contact with pneumonic plague patients must wear standard precautions and receive a chemoprophylaxis with antibiotics for the duration of seven days or at least as long as they are exposed to infected patients.
- **Ensure correct treatment:** Verify that patients are being given appropriate antibiotic treatment and that local supplies of antibiotics are adequate.
- **Isolate patients with pneumonic plague.** Patients should be isolated so as not to infect others via air droplets. Providing masks for pneumonic patients can reduce spread.
- **Surveillance:** identify and monitor close contacts of pneumonic plague patients and give them a seven-day chemoprophylaxis. Chemoprophylaxis should also be given to household members of bubonic plague patients.
- **Obtain specimens** which should be carefully collected using appropriate infection, prevention and control procedures and sent to labs for testing.
- **Disinfection.** Routine hand-washing is recommended with soap and water or use of alcohol hand rub. Larger areas can be disinfected using 10% of diluted household bleach (made fresh daily).
- **Ensure safe burial practices.** Spraying of face/chest area of suspected pneumonic plague deaths should be discouraged. The area should be covered with a disinfectant-soaked cloth or absorbent material.

Surveillance and control

Surveillance and control requires investigating animal and flea species implicated in the plague cycle in the region and developing environmental management programmes to understand the natural zoonosis of the disease cycle and to limit spread. Active long-term surveillance of animal foci, coupled with a rapid response during animal outbreaks has successfully reduced numbers of human plague outbreaks.

In order to effectively and efficiently manage plague outbreaks it is crucial to have an informed and vigilant health care work force (and community) to quickly diagnose and manage patients with infection, to identify risk factors, to conduct ongoing surveillance, to control vectors and hosts, to confirm diagnosis with laboratory tests, and to communicate findings with appropriate authorities.

WHO Response

WHO aims to prevent plague outbreaks by maintaining surveillance and supporting at-risk countries to prepare. As the type of animal reservoir differs according to the region and influences the risk and conditions of human transmission, WHO has developed specific guidelines for the Indian sub-continent, South-America and Sub-Saharan Africa.

WHO works with ministries of health to support countries facing outbreaks for field control activities.