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Содржина/Contents

I. Оригинални трудови/ Original Articles

II. Приказ на случај/Case report

Мак Мед Прегled 2019; 73(3): 131-134

ММР

Original article

A SURVEY OF SECONDARY PREVENTION OF FRAGILITY FRACTURES BY ORTHOPAEDIC SURGEONS

ИСЛЕДУВАЊЕ ЗА СЕКУНДАРНА ПРЕВЕНЦИЈА НА КРЕВКИ СКРШЕНИЦИ ОД ОРТОПЕДСКИТЕ ХИРУРЗИ

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Abstract

Introduction. Osteoporosis is a disease characterized by low bone mass and deterioration in the microarchitecture of bone tissue, leading to an increased risk of fracture. Orthopaedic surgeons are often the first physicians to see these fracture patients; hence, they have an important role in the secondary prevention of fragility fractures. The aim of this study was to carry out an audit and telephone survey to determine whether secondary prevention of fragility fractures is being implemented by orthopaedic surgeons. The survey was performed at the University Clinic for Orthopaedic Surgery in Skopje.
Material. A total of 270 patients treated surgically for hip fragility fracture (124 males and 146 females, aged 60-89) were investigated.
Method. A retrospective audit of drug charts and discharge summary of these patients for the period January 2017-December 2017 was performed. In the year 2018 (from June to December) a telephone survey was performed among all patients.
Results. The discharge summaries showed that 13% of the patients received recommendation for calcium and vitamin D supplement by an orthopaedic surgeon and Bisphosphonate therapy was recommended for 6% of the patients. The telephone survey showed that of the 270 patients, 11 patients died 6 months after the hip fracture. Of the remaining 259 patients, 12 patients suffered further fragility fracture. Six months after the hip fracture, supplement therapy are receiving 12% of the patients, and bisphosphonate therapy 9% of the patients. DXA scan was performed in 3% of the patients.
Discussion. Systems with a dedicated post-fracture coordinator at their heart have transformed post-fracture osteoporosis care, resulting in significantly lower refracture rates and enormous cost savings.
Conclusion. We feel that this model can be implemented with success in our healthcare system. Of course, this requires a close collaboration between medical professionals and health policy makers.

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Keywords: osteoporosis, secondary prevention, fragility fracture

Апстракт

Вовед. Остеопорозата е заболување, кое се карактеризира со ниска коскена маса и пореметување во микроархитектурата на коскеното ткиво, и со тоа предизвикува зголемен ризик од скршеници. Ортопедските хирурзи се честопати првите лекари, кои ги прегледуваат овие пациенти со скршеници и затоа тие имаат важна улога во секундарната превенција на фрагилните (кревки) фрактури. Целта на оваа студија е да изведе ревизија и телефонска анкета за да се одреди дали се применува секундарна превенција на кревките фрактури од ортопедските хирурзи. Истражувањето е изведено на Универзитетската клиника за ортопедски болести-Скопје.
Материјал. Вкупно без иследувани 270 пациенти со хируршки третирана кревка скршеница на колкот (124 мажи и 146 жени, на возраст од 60 до 89 години).
Методи. Спроведена беше ретроспективна ревизија на температурните листи, како и отпусните листи на овие пациенти за периодот јануари-декември 2017 година. Следната година (во периодот од јуни до декември, 2018 година) беше изведена телефонската анкета кај сите пациенти. Од отпусните листи се дознава дека 13% добиле препорака за суплемент на калциум и витамин Д од ортопедски хирург. Бисфосфонатна терапија е препорачана кај 6% од пациентите во отпусните листи. Телефонската анкета покажа дека од 270 пациенти, шест месеци по скршеницата на колкот, починале 11 пациенти. Од останатите 259 пациенти, 12 се здобиле со следна фрагилна скршеница. Суплементарна терапија, шест месеци по скршеницата на колкот, примаат 12% од пациентите, а бисфосфонатна терапија само 9%. ДЕКСА скен е направен кај 3% од пациентите.
Дискусија. Системите со наменски постфрактурен координатор во центарот ја трансформирале постфрактурната терапија кај остеопорозата, што резул-

тира со сигнификантно намалување на рефрактури и огромна заштеда.
Заклучок. Сметаме дека овој модел може да се примени со успех и во нашиот здравствен систем. Секако, тоа ќе бара блиска соработка меѓу здравствените работници и здравствените власти.

Клучни зборови: остеопороза, секундарна превенција, фрактура на кршливост

Introduction

Osteoporosis is a disease characterized by low bone mass and deterioration in the microarchitecture of bone tissue, leading to an increased risk of fracture [1]. Osteoporosis occurs when the bone mass decreases more quickly than the body can replace it, leading to a net loss of bone strength. As a result, the skeleton becomes fragile, so that even a slight bump or fall can lead to a fragility fracture [1]. These fractures, also referred to as low or minimal trauma fractures, usually occur as a result of a fall from standing height. Fragility fractures are common; 1 in 2 women over 50 years of age will suffer one, as will 1 in 5 men [2]. Globally, during the year 2000, there were an estimated 9 million new fragility fractures, of which 1.6 million were at the hip. Hip fractures are associated with a higher risk of death-20% of those who suffer a hip fracture die within 6 months after the fracture [3]. Patients who have sustained previous fragility fractures are at an increased risk of future secondary fractures [4,5]. Science has provided us with a broad spectrum of effective pharmacological agents to reduce the risk of future fractures [6]. These medicines have been shown to reduce fracture rates amongst individuals with and without fracture history, and even amongst those that have already suffered multiple fractures [6-8]. For patients presenting with fragility fractures there is an opportunity for secondary fracture prevention. Orthopaedic surgeons are often the first and only physicians to see these fracture patients; hence, they have an important role in the secondary prevention of fragility fractures [9,10].
The aim of this study was to carry out an audit and telephone survey to determine whether secondary prevention of fragility fractures is being implemented by orthopaedic surgeons in the case of patients admitted with hip fracture to an orthopaedic clinic.

Material and methods

The survey was performed at the University Clinic for Orthopaedic Surgery in Skopje. Patients were selected based on the clinical history for fragility hip fracture. A total of 270 patients treated surgically for hip fragility fracture (124 males and 146 females, aged 60-89) were investigated. A retrospective audit of drug charts and discharge summary of these patients for the period January 2017- December 2017 was performed. Analysis of drug charts was performed to find out whether these patients were started on treatment in the form of calcium and vitamin D3 for osteoporosis. In the discharge summary we were looking for surgeons' recommenddations regarding calcium and Vitamin D3, DXA scan referral and/or bisphosphonate therapy. In the year 2018 (from June to December) a telephone survey was performed among all patients.

Table 1. Questionnaire used for patient interview after hip fracture

Is there a subsequent fracture?
Do you receive supplement therapy (calcium and vitamin D)?
Do you receive bisphosphonate therapy?
Have you undergone DXA scan after the hip fracture?
Was there a prior fracture?

They were all interviewed with a specially designed questionnaire approximately 6 months after surgery (Table 1). A statistical analysis was performed on all data and the results of the audit and telephone survey.

Results

Of the examined 270 patient's records, according to the drug charts only 27 patients (10%) were treated with calcium and vitamin D supplement, including patients who were already on calcium and vitamin D. The discharge summaries showed that further 13% of the patients received recommendation for calcium and vitamin D supplement by an orthopaedic surgeon. Bisphosphonate therapy was recommended for 6% of the patients in the discharge summary.
The telephone survey showed that of the 270 patients, 11 patients died 6 months after the hip fracture. Of the remaining 259 patients, 12 patients suffered further fragility fracture (3 hip fracture, 2 wrist fracture, 7 vertebral fracture). Six months after the hip fracture, supplement therapy are receiving 12% of the patients, and bisphosphonate therapy 9% of the patients. DXA scan was performed in 3% of the patients. In 23% of the patients there was prior fragility fracture.

Discussion

Harrington described osteoporosis care of fragility fracture patients as "…a Bermuda Triangle comprised of orthopaedic surgeons, primary care physicians and osteoporosis experts, into which the fracture patient disappears" [6]. There is a significant care gap between the first fragility fracture and secondary fractures [11-13]. Osteoporosis treatment of fracture patients can reduce the overall incidence of hip fracture by 20-25% [14,15]. Regrettably, by missing the opportunity to respond to the first fracture, healthcare systems around

the world are failing to prevent the second and subsequent fractures. Numerous audits of secondary prevention show that the majority of fragility fracture patients never learn about the underlying cause of their fracture, or receive treatment to prevent it from happening again. Two meta-analyses concluded that a prior fracture at any skeletal site is associated with a doubling of future fracture risk [16,17]. Thus, fracture begets fracture.

Our results show that, if left to the orthopaedic surgeon, most of the patients would not undergo a DXA scan, and only small percentage would receive recommendations for supplement and/or bisphosphonate therapy. This may be due to the healthcare system organization which convinces the surgeon that further investigation for osteoporosis and supplement and /or bisphosphonate therapy will be recommended and prescribed to the patient by the primary care physician. The primary care physician, on the other hand, is convinced that since this therapy is not recommended by the surgeon, there is no need for further investigation or osteoporosis therapy.

All patients who have suffered a fragility fracture should undergo a comprehensive clinical assessment for osteoporosis. In 2011, the Fracture Working Group of the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) published a position paper on coordinator-based systems for secondary prevention in fragility fracture patients [2]. The paper consolidated knowledge of the development, effectiveness and common factors that underpin successful clinical systems designed to close the secondary fracture prevention care gap. A systematic literature review found that two thirds of such systems employed a dedicated coordinator who acts as the link between the orthopaedic team, the osteoporosis and falls services, the patient and the primary care physician. Exemplar service models have been referred to as 'Fracture Liaison Services', 'Osteoporosis Coordinator Programs' or 'Care Manager Programs' [16,18-20].

Orthopaedic surgeons need be more pro-active in highlighting at-risk patients and inform the primary care physician of the need to prevent further fractures. However, the presence of a coordinator would facilitate this process and make it more successful.

Conclusion

For half of hip fracture patients, their hip fracture will be their first clinically apparent fracture. These individuals are at high risk of a second hip fracture. Accordingly, secondary prevention must be routine care for hip fracture patients. Innovators in many countries have tackled this healthcare delivery challenge and created systems that close the current care gap. Systems with a dedicated post-fracture coordinator at their heart have transformed post-fracture osteoporosis care, resulting in significantly lower re-fracture rates and enormous cost savings. We feel that this model can be implemented with success in our healthcare system. Of course, this will ask for close collaboration between the medical professionals and the health policy makers.

Conflict of interest statement. None declared.

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Original article

INTRACAPSULAR FEMORAL NECK FRACTURES IN YOUNG ADULTS AND GARDEN INDEX

ИНТРААРТИКУЛАРНИ СКРШЕНИЦИ НА ВРАТОТ НА БУТНАТА КОСКА КАЈ МЛАДА ПОПУЛАЦИЈА: ВРЕДНОСТА НА ГАРДЕНОВИОТ ИНДЕКС

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Abstract

Introduction. Intracapsular femoral neck fractures in the young population are rare and difficult injuries to be treated. Surgical management with osteosynthesis represents an imperative for their treatment. Femoral neck fractures in the young population are associated with a high percentage of complications such as osteonecrosis and non-union. The percentage of these complications in the literature ranges from 12 to 86%. Surgery to rescue the femoral head, such as a valgisation osteotomy, does not work best. Arthroplasty surgical procedures, on the other hand, are not the ideal choice in the treatment of young people seeking high levels of activity.
Aim. The primary objective of this study was to determine the quality of life through the SF-36 score system up to 1 year after injury. A secondary objective of this retrospective study was to determine the complications that occurred after surgical treatment of these fractures treated with closed (most commonly) or open repositioning with internal fixation and determining the risk factors that led to these complications (avascular necrosis).
Methods. This was a retrospective study. It was conducted at the University Clinic for TOARILUC, involving 56 patients aged 33-55 years who were treated surgically. The SF-36 score was used to determine patients` quality of life. Patients were divided into two groups depending on the type of fracture: group 1 undisplaced (Garden 1 and 2) and displaced group 2 (Garden 3 and 4).
Results. The results of this study in the first group 1 (undisplaced) showed that quality of life in patients with intracapsular femoral neck fracture after closed repositioning and screw fixation showed good results and similar to those of the general population. Their physical health (PCS) was 53.2, while their physical health was 49.8. In the group of displaced Garden 3 and 4 fractures the results showed lower quality of life values, especially in 6 patients where GAI was unsatisfactory. Their mental and physical health were lower than in the first group PCS 49.2 MCS 47.5. In 2 of them there was screws breaking and in 1 patient pseudoarthrosis, and conversion to total endoprosthesis was made.
Conclusion. Results from the first group (undisplaced Garden 1 and 2) with a good Garden Index showed a better quality of life for both mental and physical health as measured by the SF-36 score. The results were almost identical to those of the healthy population. In this group, complications for one year of follow-up, such as non-union and avascular necrosis, were not observed. In these patients, anatomic repositioning and internal fixation with cannulated screws showed good healing and return to daily activities. This technique has proven to be the most appropriate surgical treatment for this type of patients and fractures.
The second group of displaced Garden 3 and 4 fractures showed slightly worse results with lower SF scores for both mental and physical health. The complications that have occurred are correlated with the achieved repositioning of the GAI index. Therefore, the surgeon should strive to achieve as much as possible the normal values of the GAI index.

Keywords: Garden index, SF-36 score

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Апстракт

Вовед. Интраартикуларните скршениците на вратот на бутната коска се ретки и нивните компликации се добро документирани. Хируршкиот третман со интерна фиксација претставува генерален консензус, како кај нас, така и ширум светот. Фрактурите на вратот на фемурот кај младата популација се поврзани со висок процент компликации, како што се: остеонекроза и незараснување. Процентот на овие компликации во литературата се движи од 12 до 86 проценти. Реоперациите, кои се прават за спасување на главата на фемурот, како што е валгизациска остеотомија, не даваат најдобри резултати. Артропластичните хируршки процедури, од друга страна, не се идеален избор како примарна про-

цедура во третманот на младите, кои бараат високо ниво на активност.

Цел. Примарната цел на оваа студија беше да се одреди квалитетот на живот преку SF-36 бодовниот збир до една година од повредата. Секундарна цел на оваа ретроспективна студија беше да се одредат компликациите, кои настанале по хируршкиот третман на овие скршеници, лекувани со затворена (најчесто) или со отворена репозиција со внатрешна фиксација и интерна фиксација и одредување на ризик факторите, кои довеле до овие компликации (аваскуларна некроза и незараснување)

Методи. Студијата е од ретроспективен карактер, таа беше спроведена на Универзитетската клиника за ТОАРИЛУЦ, а во неа беа вклучени вкупно 56 пациенти на возраст од 33 до 55 години, коишто беа хируршки третирани. За одредување на квалитетот на живот на пациентите беше користен бодовниот збир SF-36. Пациентите беа поделени во две групи, во зависност од типот на скршеницата, и тоа група 1-недислоцирани (Garden 1 и 2), и дислоцирани-група 2 (Garden 3 и 4).

Резултати. Резултатите од оваа студија во првата група 1 (недислоцирани), покажаа дека квалитетот на живот кај пациентите со интракапсуларна скршеница на вратот на бутната коска по затворена репозиција и фиксација со шрафови покажаа добри резултати и слични со тие од општата популација. Нивното физичко здравје (PCS) изнесуваше 53.2, додека нивното физичко здравје изнесуваше 49.8. Во групата-дислоцирани скршеници Гарден 3 и 4 резултатите покажаа пониски вредности на квалитет на живот, особено кај шест пациенти, каде што GAI беше незадоволителен. Нивното ментално и физичко здравје беше пониско за разлика од првата група PCS 49.2 MCS 47.5. Кај две од нив се јави дезинсерација (кршење на шрафовите), а кај еден пациент псевдоартроза и беше направена конверзија во тотална ендопротеза.

Заклучок. Резултатите од првата група (недислоцирани Garden 1 и 2) со добар Гарденов индекс покажаа подобар квалитет на живот, како ментално, така и физичко здравје, мерено по SF-36 бодовниот збир. Резултатите, беа речиси идентични, како кај здравата популација. Во оваа група компликациите за следење во текот на една година, како незараснување и аваскуларна некроза, не се забележани. Кај овие пациенти анатомската репозиција и интерната фиксација со канулирани шрафови покажаа добро зараснување и враќање на пациентите во секојдневните активности. За оваа група, таа техника се покажа како најадекватен хируршки третман кај ваквиот тип пациенти и скршеници.

Во втората група дислоцирани скршеници Garden 3 и 4 покажаа нешто полоши резултати со пониски вредности на SF-збирот, како за менталното, така и за физичкото здравје. Компликациите што се случија се во корелација со постигнатата репозиција на GAI индексот. Заради тоа, хирургот треба да се стреми да ги постигне, колку е во можност, нормалните вредности на GAIиндексот.

Клучни зборови: Гарденов индекс, SF-36

Introduction

Intracapsular femoral neck fractures in the young population are difficult injuries to be treated [1,2]. A large number of studies have demonstrated that the complications such as aseptic necrosis of the femoral head and non-union (psudoarthrosis) are found in about 20-30% of cases [3-5]. Undisplaced fractures (Garden 1 and 2) [6] are successfully healed, whereas displaced Garden 3 and 4 are associated with a large number of complications. Many studies have reported good results with early internal fixation [1,6,7]. Others have debated on the issue of open reposition under direct vision of the reposition. A large number of authors [8] suggest closed reposition with internal fixation as a method of choice since it is minimally invasive, requires shorter time for its performance and is associated with less blood loss. Upadhyay *et al.* [9] showed that radiographic poor reposition is associated with a larger percentage of non-union of these fractures. Liporace *et al.* [10] presented several treatment variations that play a role in the final outcome, including the fixation time (early *versus* routine), method of reposition (open *versus* closed) and choice of the implants (cannulated screws *versus* dynamic screw-DS).

The primary aim of this study was to determine the quality of life in young adults with femoral neck fracture treated with reposition and fixation at the University Clinic for Traumatology, Orthopedic Diseases, Anesthesiology, Resuscitation and Intensive Care and Emergency Center. The secondary aim of this study was to detect the risk factors that have influence on the complications such as: avascular necrosis, failure of the osteosyntheric material and non-union as the most common postoperative complications in young patients with femoral neck fractures.

Material and method

A retrospective study comprising 56 patients with femoral neck fractures at the age of 30-55 years was conducted at the University Clinic of Thoracic Surgery, Faculty of Medicine, Ss Cyril and Methodius University in Skopje. Patients were divided into two groups depending on the dislocation of the fracture: group 1 of undisplaced fractures (Garden 1 and 2) and group 2 of displaced fractures (Garden 3 and 4). Garden classification was used as the most widely accepted and cited classification in our country and worldwide.

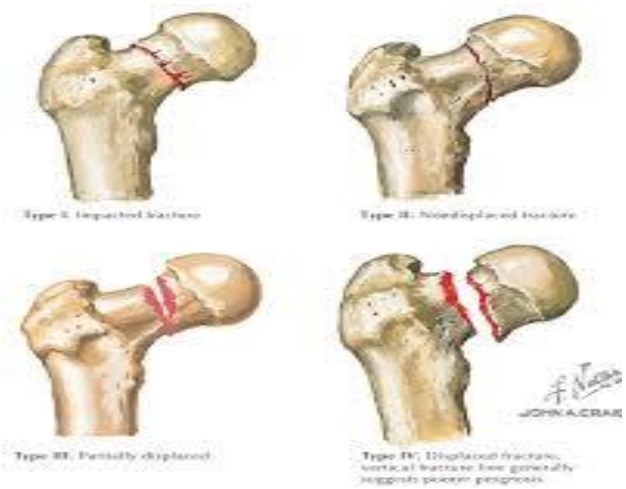

Fig. 1. Garden classification: Type 1 incomplete, impacted fracture; Type 2 complete fracture without displacement; Type 3 complete fracture with displacement; Type 4 displaced fracture withshortening

Diagnosis was made in each patient according to the following diagnostic protocol: clinical signs, physical status and radiographic evaluation including radiography of the pelvis with both hips and radiography of the injured hip in two planes-AP and profile. If patients did not have all secure and insecure signs of fracture, and if it was not possible to see the fracture with radiography, then they underwent computed tomography for more detailed evaluation and for diminishing the possibility of fracture to be overlooked. Also, Garden's alignment index was preoperatively determined in each patient.

All patients were surgically treated under the same conditions. Spinal anesthesia was usually administered, and the patient was in a supine position on a traction chair. Traction and rotation were made for reposition controlled by x-ray fluoroscopy. Roentgenoscopy was used for fracture classification and for evaluation of the accomplished reposition.

The grade of reposition was defined according to Garden alignment index (GAI) in two views – AP and profile (Figure 2).

Garden alignment index presents in fact assessment of the position of fractured and repositioned fragments of the hip shown on the x-ray in two views: anterio-posterior and profile. After reposition in AP, the normal angle

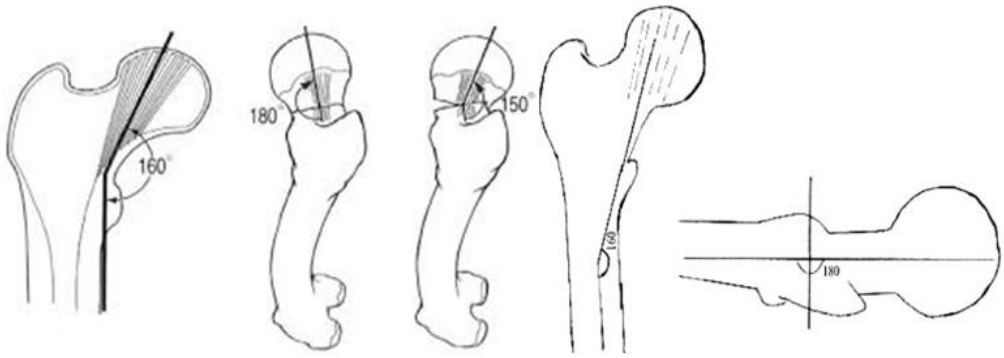

Fig. 2. Garden alignment index

of the diaphysis with the femoral neck has to be 160-180 degrees, and in profile 180 degrees. The quality of reposition based on Garden alignment index was defined using the criterion described in three groups: type 1-excellent reposition in both planes, type 2-accepted reposition in one view and type 3-unaccepted reposition in both views. If closed anatomic reposition was not an option, then the capsule was opened and closed reposition under direct vision was made. As soon as anatomic reposition was accomplished, screw placement was done as follows: the first screw was the supporting one in the internal-caudal position to prevent varus position, and the second screw provided fixation from dorsal to medial. This is the critical zone of head stabilization in the sagittal plane. The third screw was positioned cranial ventral against the second one. Compression is guaranteed only if the screws are positioned parallel between themselves.-

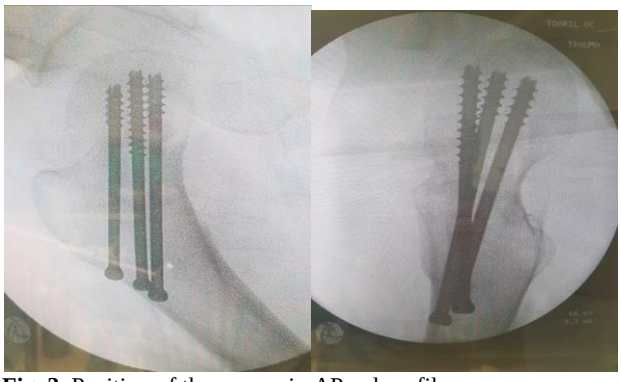

Fig. 3. Position of the screws in APand profile

The surgery lasted between 30 to 80 minutes, and hospitalization from 3 to 7 days. The follow-up period of each patient was in the first 6 weeks, at 6 months and at 12 months. The quality of life was evaluated with SF-36 score, which is a multi-item scale consisting of

8 elements, having in mind both the physical and mental health of the patient that is of extreme importance in this type of injured people. Concepts included in the SF score are aimed at assessment of: 1. Physical functioning, 2. Social activities, 3. Physical health problems, 4. Bodily pain, 5. General mental health, 6. Emotional problems, 7. Vitality and 8. General health perceptions.

Results

This study comprised 56 patients, of whom 32 males and 24 females. The major mechanism of injury in all included patients was higher energy force, and majority of patients were aged up to 55 years. Patients with initial or advanced osteoporosis and metabolic diseases were excluded from the study. According to the type of the fracture, 39 were undisplaced, and 17 displaced. Regarding the preoperative reposition, an excellent one was achieved in 40 patients (Garden index in both planes-AP 170, profile 180 degrees), and acceptable reposition in 10 patients (small Garden index variations), whereas unsatisfactory reposition with larger Garden index variations in 6 patients. Patients stayed in the hospital for 3 to 7 days.

In forty patients excellent reposition according to Garden index was achieved with small variations in the antero-posterior plane: 170±5.6 degrees and profile: 180±4.2 degree. Patients from this group showed the best score in the mental and physical health measured by SF-36.

Table 1. Distribution of patients according to the fracture type and preoperative reposition

Gender	**Males 32 Females 24**		**Physical and mental health**	
Fracture type	undisplaced	39	PCS 53.2	MCS 49.8
	displaced	17	PCS 49.2	MCS 47.5
Quality of	excellent	40	PCS 55.8	MCS 51.2
preoperative	good	10	PCS 52.9	MCS 50.3
reposition	unsatisfactory	06	PCS 46.8	MCS 45.2
Posterior communication		8 patients		
Days				

A good preoperative reposition was achieved in 10 patients along with good Garden index-AP 160±8.3 degrees and profile 165±7.4. This group had poorer results regarding physical and mental health the first group. Due to bad reposition in one patient, there was failure of the osteosynthetic material and total endoprosthesis was implanted in this patient.

Closed reposition was not possible to be made in the third group of patients, and hence in 3 of 6 patients capsulotomy and open reposition was performed. The results of the mental and physical health were the worst in this group of patients. Two patients experienced non-union and one patient had aseptic necrosis of the femoral head. Surgical intervention was realized 4 days after admission to hospital. All of these 3 patients are candidates for total endoprosthesis.

Discussion

The results obtained in this study have clearly demonstrated that the quality of life in the first group of patients with femoral neck fractures (Garden 1 and 2) surgically treated with anatomic reposition and internal fixation with cannulated screws were similar to the results obtained in the healthy population. Also, a satisfactory healing with high PCS (53.2) and MCS (49.8) was achieved in all patients. These results speak in favor of the surgical treatment indicated in undisplaced fractures in order to retain the anatomic condition and keep the fragments in proper contact, which, on the other hand, provides rapid return to daily activities, early mobility and solid healing. Therefore, this type of surgical approach has been estimated as the most adequate since it yields excellent results and avoids complications (avascular necrosis and non-union).

In 80% of patients from the second group (displaced Garden 3 and 4 fractures) anatomic reposition and solid fixation was achieved resulting in good scores at PCS (49.2±5.2) and MCS (47.5±4.2). However, in this group the following complications were registered: non-union in 4 patients with PCS 39±4.7 and MCS 42±5.2, malunion with PCS 39±4.7 and MCS 44.4±5.6, and osteonecrosis withPCS 42.2±8.2 and MCS 52.8±6.2.

Worse results regarding the physical health against mental health were registered in these patients. Similar results have been presented and described by Gerard P. Slobogen during his two-year follow-up of injured patients [4]. Collinge *et al.* found a lower SF-36 score in patients with higher percentage of complications (osteonecrosis and non-union) [11]. The correlation of osteonecrosis and non-union with the poorer quality of life presented with SF lower score has been described by several authors [4,7]. Their results showed that lower SF-36 score was associated with post-fixation complications.

The results presented in this studyhave confirmed the prognostic factors identified by other authors [11-13]. Displaced fractures inadequately repositioned at least in one projection are the cause of bad outcome. Dis-

placed Garden 3 and 4 fractures have shown lower PCS SF-36 due to the complications that developed (non-union and avascular necrosis). The association between radiographic reposition and fracture malposition with the poor fracture healing has been described by many authors [9,11]. In the series presented by Colanger the fracture displacement was associated with the incidence of avascular necrosis and degree of the femoral head necrosis in young adults [11]. Upadhay *et al.* published their radiographic criteria for prevention of non-union of femoral fracture [9]. The results of this study revealed different effect at PCS and MCS of these factors at the SC-36 scale. Worse results were observed at PCS than at MCS. This difference was registered in patients who developed complications such as non-union and avascular necrosis.

Conclusion

The results obtained in this study have shown better quality of life (both, physical and mental) measured with SF-36 score. The results were equal to those found in the healthy population; there were no complications such as non-union and avascular necrosis of the femoral head.

Closed anatomic reposition and stable internal fixation with cannulated screws resulted in excellent healing and return to normal everyday activities. Thus, this treatment is recommended as the most adequate surgical option for femoral neck fractures.

On the other hand, the results obtained for the displaced femoral neck fractures showed good results in both, physical and mental health in a larger number of patients, but with lower SF-36 score.

In this group of patients the following complications were registered: non-union, failure of the osteosynthetic material and aseptic necrosis of the femoral head. A total uncemented endoprosthesis was implanted in all patients.

Conflict of interest statement. None declared.

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Original article

ASSOCIATIONS BETWEEN BURNOUT AND SUBJECTIVE MUSCULOSKELETAL COMPLAINTS IN SURGICAL HEALTH PROFESSIONALS

АСОЦИЈАЦИИ МЕЃУ СИНДРОМОТ НА СОГОРУВАЊЕ И СУБЈЕКТИВНИТЕ ТЕГОБИ ОД МУСКУЛО-СКЕЛЕТНИОТ СИСТЕМ КАЈ ЗДРАВСТВЕНИТЕ РАБОТНИЦИ ОД ХИРУРШКАТА ДЕЈНОСТ

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Abstract

Aim. The objective of the actual study was to determine the predictive value of burnout for the occurrence of subjective musculoskeletal complaints in surgical health professionals (HPs).

Methods. A cross-sectional study analyzing different profiles of surgical HPs (30 surgeons, 30 surgical nurses, 30 physicians (non-surgeons), 30 non-surgical nurses, and 30 administrative and technical workers). Burnout was assessed by the Maslach Burnout Inventory. Hospital Experience Scale was applied for the assessment of job demands. Determination of predictive value of different factors for the occurrence of subjective musculoskeletal complaints included testing of various models of logistic regression.

Results. Participants with high/medium emotional exhaustion morefrequently complained about back pain (46.2% *vs*. 22%; χ^2=8.97; p=0.003) and lower limb pain (30.8% *vs*. 15.3%; χ^2=4.64; p=0.031) compared to participants with low emotional exhaustion. Participants with burnout compared to those who didnot have this syndrome, more frequently complained about back pain (54.5% *vs*. 29.2%; χ^2=8.57; p=0.003) and upper limb pain (20.5% *vs*. 3.8%; χ^2=10.93; p=0.001). The occurrence of back pain was predicted by physical demands (exp b=2.27, 95%CI 1.06-4.87, p<0.05) and emotional exhaustion (exp b=1.06, 95%CI 1.02-1.09, p<0.01) and the occurrence of upper limb pain by physical demands (exp b=4.31, 95%CI 1.3-14.26, p<0.05) and depersonalization (exp b=1.18, 95%CI 1.08-1.29, p<0.001).

Conclusion. Both job demands and burnout predict the occurrence of subjective musculoskeletal complaints. Adequate management of job demands can lead to prevention of burnout and musculoskeletal complaints in surgical HPs.

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Keywords: burnout, job demands, musculoskeletal, surgery, health professionals

Апстракт

Цел. Целта на оваа студија е да се утврди предиктивната вредност на синдромот на согорување за појава на субјективни мускуло-скелетни тегоби кај здравствените работници (ЗР) од хируршката дејност.

Методи. Студија на пресек, која ги анализира различните профили на ЗР од хируршката дејност (30 хирурзи, 30 инструментарки, 30 доктори, кои не се хирурзи, 30 медицински сестри, кои не се инструментарки и 30 административни работници). Синдромот на согорување е анализиран со Maslach Burnout Inventory. Прашалникот Hospital Experience Scale е употребен за проценка на барањата на работното место. Одредувањето на предиктивната вредност на различните фактори за настанување субјективни мускуло-скелетни тегоби вклучи тестирање на различни модели на логистичка регресија.

Резултати. Испитаниците со висока/средна емоционална исцрпеност почесто се жалат на болка во грбот (46,2% *спрема* 22%; χ^2=8,97; p=0,003) и долните екстремитети (30,8% *спрема* 15,3%; χ^2=4,64; p=0,031), во споредба со испитаниците со ниска емоционална исцрпеност. Испитаниците со синдром на согорување, во споредба со испитаниците, кои го немаат овој синдром, почесто се жалат на болка во грбот (54,5% *спрема* 29,2%; χ^2=8,57; p=0,003) и рацете (20,5% *спрема* 3,8%; χ^2=10,93; p=0,001). Појавата на болка во грбот е условена од физичките барања на работното место (exp b=2,27; 95%CI 1,06-4,87; p<0,05) и емоционалната исцрпеност (exp b=1,06; 95%CI 1,02-1,09; p<0,01), а појавата на болка во рацете од физичките барања (exp b=4,31; 95%CI 1,3-14,26; p<0,05) и негативниот став кон работата (exp b=1,18; 95%CI 1,08-1,29; p<0,001).

Заклучок. Барањата на работното место и синдромот на согорување имаат предиктивна вредност во нас-

танувањето субјективни мускуло-скелетни тегоби. Соодветното справување со барањата на работното место може да ја превенира појавата на синдромот на согорување и мускуло-склетните тегоби кај ЗР во хируршката дејност.

Клучни зборови: синдром на согорување, барања на работното место, мускуло-скелетни тегоби, хирургија, здравствени работници

Introduction

Work-related or job stress can be defined as hazardous physical or emotional response to job pressures and demands that are present at the workplace and which do not correspond to the knowledge, abilities, capacities and the needs of the worker [1,2]. On the other hand, burnout syndrome is a psychological syndrome that results from a prolonged response to chronic emotional and interpersonal workplace stressors [3,4], such as high job demands (physical, social, emotional, cognitive, and organizational aspects of the work that require prolonged mental or physical efforts) and lack of resources, resulting in withdrawal behavior (depersonalization) and disengagement [5,6]. The three components of burnout syndrome are emotional exhaustion, depersonalization, and reduced personal accomplishment [1,2,7-9].

Scientific literature has shown that the core dimensions of burnout are emotional exhaustion and depersonalization, taking into consideration the evidence that the last component (reduced personal accomplishment) usually demonstrates much weaker correlations with the other two dimensions.

The high job demands, working under pressure, prolonged and/or unpredictable working hours, lack of control over the working activities, lack of skills, reduced possibilities for promotion at the workplace, organizational factors, and low social support at work, make healthcare professionals (HPs) especially vulnerable to job stress and characterize hospital settings as an ideal environment for the development of distress, burnout and psychosomatic problems, usually deteriorating the quality of life and service provision [10-13]. Both job stress and burnout, as a potentially pathogenic mechanisms, can lead to negative health effects, including psychological changes, such as emotional manifestations (anxiety, depression, feelings of hopelessness), cognitive problems (difficulties in learning new things or decision making) and behavioral changes (negative attitudes towards people, life, and work), but also somatic manifestations, increasing the risk for cardiovascular mortality and morbidity, development of malignant diseases and development of musculoskeletal disorders (MSDs) [1,14,15].

MSDs are conditions that affect the muscles, nerves, tendons, joints, cartilage, and spinal discs, and they are associated with certain symptoms, such as pain, swelling, stiffness, and tingling. The most common MSDs include: carpal tunnel syndrome, muscle strains, sprains and tears, lower back pain, and injuries. Work-related MSDs can develop as a result of the factors from the working environment, working conditions and/or by the work performance, and if those factors persist at the workplace, the MSDs can worsen over time [16,17].

The healthcare sector is one of the most affected with an incidence of MSDs varying from 50% to 98%, globally [18-21]. Among HPs, the majority of work-related MSDs occur due to biomechanical exertion caused by:

- Manual handling, lifting, and movement of patients from beds or wheelchairs (the most commonly reported trigger),
- Prolonged periods of sitting or standing with awkward and static postures together with prolonged and repetitive hand/finger movements (e.g., surgery) and
- Moving of equipment/heavy loads (e.g., pushing heavy carts or beds) [16,22,23].

Apart from these, many studies emphasize the contribution of psychosocial factors and job stress in the development of MSDs. Work stressors have been proved to adversely affect workers' health, quality of life, and work performance, identifying them as important risk factors for MSDs [24-27]. Due to the high incidence, the MSDs are highly associated with absenteeism, loss of productivity, as well as increased health care and employers' compensation costs, estimated to be over $20 billion annually around the world [17,18]. Various interventions exist in practice for the prevention of work-related MSDs in HPs and they include: workers' education programs, physical conditioning or exercise programs, disability management, organizational policies, and use of mechanical lifts or other patient transfer equipment [28-32].

The actual study analyzes HPs working in a general hospital in Skopje, Macedonia,providing health care to the general population at a secondary and tertiary level. Changes in the health care system in the RN Macedonia in the recent years, together with social reforms aimed at EU accession, have led to increased job demands in hospital HPs. The main purpose of the present study was to examine the associations between burnout and its dimensions with the subjective musculoskeletal complaints in surgical HPs. More specifically, the objective was to determine the predictive value of burnout dimensions for the development of subjective musculoskeletal complaints in surgical HPs. The other objectives of the study were to detect differences between study groups according to: demographic and job characteristics, burnout dimensions, job demands, actual health complaints (including subjective musculoskeletal complaints).

Methodology

Study population

The **first group** consisted of HPs directly involved in surgical activities. Inclusion criteria for the first group were: physicians-surgeons; nurses directly involved in surgical activities (in the following text: surgical nurses). Exclusion criteria forthe first group were: physicians who were not surgeons; nurses who were not directly involved in surgical activities; administrative workers; respondents with pre-diagnosed mental illness.
The **second group** included HPs who were not directly involved in surgical activities. Inclusion criteria for the second group were: physicians who were not surgeons and nurses who were not directly involved in surgical activities. Exclusion criteria forthe second group were: physicians-surgeons; surgical nurses; administrative workers; respondents with pre-diagnosed mental illness.
The **third group** involved employees who were not HPs (administrative and technical staff). Inclusion criteria for the third group were administrative workers. Exclusion criteria forthe third group wereHPs and respondents with pre-diagnosed mental illness.
The first group consisted of 60 HPs directly involved in surgical activities (30 physicians-surgeons and 30 surgical nurses). The second group included 60 HPs not directly involved in surgical activities (30 physicians-non-surgeons and 30 nurses who were not surgical nurses). The third group consisted of 30 employees who were not HPs (administrative and technical staff).

Assessment of demographic and job characteristics data

We used a specially designed "Demographic and Job Characteristics Questionnaire" for the assessment of demographic variables (age, gender, marital status, and level of education) and job characteristics (work profile, hospital tenure, unit tenure, type of employment contract, working hours during the week, and night shifts work) of the examined subjects. By the application of this Questionnaire we identified the workplace stress factors related to job characteristics (work profile, hospital tenure, unit tenure, working hours during the week, and night shifts work), which, according to the WHO classification of work-related stress factors [2], are related to the following categories: physical workload and pace of work; working hours; and the role in the working organization. Additionally, to this Questionnaire, we added questions for the assessment of the health status of the participants, specially addressing subjecttive complaints by MSDs as well as other health problems.

Assessment of burnout and job demands

Burnout was assessed using the Maslach Burnout Inventory (MBI) [9]. In this study, emotional exhaustion (nine items) and depersonalisation (five items) subscales were used, and measured with a 7-point Likert scale (0=never to 6=every day). Emotional exhaustion refers to the feelings of overwhelming exhaustion and depletion of emotional resources. Depersonalization refers to the feelings of frustration, anger, and cynicism. It represents interpersonal dimension of burnout and it is described as an excessively detached response to other people. Emotional exhaustion was assessed by questions, such as "I feel emotionally drained from my work" and "I feel burned out by my work", and depersonalization with questions, such as "I feel I treat some patients as if they were impersonal objects". Responses wereadded to form a score for each subscale, thus giving each participant scores for the two components of burnout. The higher the score in one dimension means the higher level of burnout. The participants with the score of emotional exhaustion equal to 27 or higher and the score of depersonalization equal to 13 or higher were labelled as burntout.
Hospital Experience Scale (HES), which was constructed and developed for the FP7 ORCAB Project (http://orcab.web.auth.gr/) within the actual study, was applied for the assessment of job demands. The items were categorised into four subscales: physical workload (seven items, e.g., "I am responsible for too many patients in hospital rounds"), organisational (six items, e.g., "The roles in my department are not clear/ambiguous"), emotional (six items, e.g., "I have to deal with verbally abusive patients") and cognitive (five items, e.g., "I have to make decisions when I don't have all the information I need") job demands. Participants indicated their level of agreement with the items on a 5-point Likert scale (1=never to 5=always), and points for statements relating to each of the job demands types were averaged to derive the four types of job demands. The higher mean score means the higher perceived level of particular job demands type.
This cross-sectional study analyzed different profiles of surgical HPs. The research was conducted in a general hospital with different medical specialties. Respondents were categorized into three groups according to their job activities: whether they were HPs or they worked as an administrative (or technical) staff and whether HPs were directly involved in the surgical activities or not.
With the defined study sample and the determined methodology of the research, we obtained data about the factors (job demands and burnout) that might influence the occurrence of subjective musculoskeletal complaints in HPs directly involved in surgical activeties. The participation in the research was voluntarily and anonymous and the participants were informed about the study. The instrument of the survey was distributed among the participants and it contained all the questionnaires necessary for assessment of the objectives of the study.

In the actual study, the questionnaires were filled immediately after the distribution, and not at home. The instrument was distributed in envelopes in a hard copy. The research was anonymous and the HPs were informed about the aim of the study and how their data wouldbe kept and used.

With the analysis for reliability used in the study for the assessment of the internal consistency of the questionnaires, the following consistency coefficients (Cronbach alpha) were determined:

Questionnaire for the assessment of job demands:

- physical demands, Cronbach alpha = 0.736
- organizational demands, Cronbach alpha = 0.761
- emotional demands, Cronbach alpha = 0.738
- cognitive demands, Cronbach alpha = 0.736

Maslach Burnout Inventory:

- emotional exhaustion, Cronbach alpha = 0.913
- depersonalization, Cronbach alpha = 0.820

The Statistical Package for the Social Sciences (SPSS) statistics (Chicago USA 2011, version 19) was used for the statistical analyses. Continuous variables were presented as mean values with standard deviation, and the nominal variables as absolute numbers and percentages. *P* values below 0.05 were considered as statistically significant.

Results

The obtained data showed that within the analyzed hospital the five groups of participants were not significantly different according to age (about 40 years), hospital and unit tenure, as well as the average number of working hours during the week (slightly above 40 hours per week).

In Table 1 demographic characteristics of participants (gender, marital status, and education) and job characteristics (type of employment contract and night shifts work) are shown.

Table 1. Demographic characteristics of participants (gender, marital status, and education) and job characteristics (type of employment contract and night shifts work)

Characteristic	Group	*n*	%	χ^2 (*p*)
Gender (women)	surgeons (N = 30)	16	53.3	**26.92 (<0.001)**
	other physicians (N = 30)	18	60	
	surgical nurses (N = 30)	26	86.7	
	other nurses (N = 30)	28	93.3	
	administrative workers (N = 30)	26	86.7	
Marital status (married)	surgeons (N = 30)	18	60	4.96 (0.291)
	other physicians (N = 30)	19	63.3	
	surgical nurses (N = 30)	20	66.7	
	other nurses (N = 30)	23	76.7	
	administrative workers (N = 30)	20	66.7	
Education (universityeducation or higher)	surgeons (N = 30)	30	100	**52.65 (<0.001)**
	other physicians (N = 30)	30	100	
	surgical nurses (N = 30)	13	43.3	
	other nurses (N = 30)	14	46.7	
	administrative workers (N = 30)	17	56.7	
Type of employment contract (full-time contract)	surgeons (N = 30)	23	76.7	3.64 (0.457)
	other physicians (N = 30)	23	76.7	
	surgical nurses (N = 30)	25	83.3	
	other nurses (N = 30)	26	86.7	
	administrative workers (N = 30)	24	80	
Work in night shifts	surgeons (N = 30)	30	100	**25.15 (0.003)**
	other physicians (N = 30)	23	76.7	
	surgical nurses (N = 30)	23	76.7	
	other nurses (N = 30)	22	73.3	
	administrative workers (N = 30)	9	30	

As presented inTable 1, it was registered that:

- in the groups of surgical nurses (86.7%) and other nurses (93.3%), women were significantly more frequent than in the groups of surgeons (53.3%) and other physicians (60%), while in administrative workers (86.7%) females were significantly more often than in the surgeons group (χ^2=26.92; p<0.001),
- surgeons (100%) and other physicians (100%) had significantly more often completed a universityor higher education than surgical nurses (43.3%), other nurses (46.7%) and administrative workers (56.7%) (χ^2=52.65; p<0.001),
- significantly less frequently administrative workers (30%) worked night shifts in comparison to HPs (over 70%) (χ^2 = 25.15; p=0,003).

The following table presents the average values of the key variables of the survey within the total sample.

The above data and the methods for comparing mean values (ANOVA and the Post Hoc procedures of Gabriel and Games-Howell) showed that within the total sample:

Table 2. Average values of key variables within the total group of participants

Variable		Mean	SD	Welch *F* (*p*)
Burnout	Emotional Exhaustion	21.35	13.12	/
	Depersonalization	4.99	5.87	
Job demands	Physical	3.29	0.65	**45.23 (<0.001)**
	Organizational	2.58	0.83	
	Emotional	2.47	0.71	
	Cognitive	2.84	0.76	

- the mean value of physical job demands was significantly higher than the average values of all other job demands-organizational (mean diff.=0.72; $p<0.001$), emotional (mean diff.=0.82; $p<0.001$) and cognitive (mean diff.=0.45; $p<0.001$),
- the average value of cognitive job demands was significantly higher than the mean values of organizational (mean diff.=0.26; $p=0.017$) and emotional (mean diff.=0.37; $p<0.001$) job demands.

Medium or high level of emotional exhaustion was registered in 24(80%) surgeons, 24(80%) other physicians, 27(90%) surgical nurses, 14(46.7%) other nurses, and 2(6.7%) participantsfrom the administrative workers. Data showed that significantly more surgeons (80%), physicians who werenot surgeons (80%) and surgical nurses (90%) had medium or high level of emotional exhaustion (a sum of responses higher than 16) than other nurses (46.7%). In all examined groups of HPs a significantly higher frequency of participants with medium or high level of emotional exhaustion was registered in comparison to administrative workers (6.7%) ($\chi^2 = 59.34$; $p<0.001$).

Medium or high level of depersonalization was detected in 14(46.7%) surgeons, 13(43.3%) other physicians, 11(36.7%) surgical nurses, 5(16.7%) other nurses, and in 2 (6.7%) administrative workers. It was noticed that a significantly higher frequency of surgeons (46.7%), other physicians (43.3%), and surgical nurses (36.7%) hada medium or high level of depersonalization (a sum of responses higher than 6) than other nurses (16.7%) and administrative workers (6.7%) ($\chi^2=17.46$; $p=0.002$).

Burnout syndrome (for each of its two dimensions detected high or medium level) was registered in 14 (46.7%) surgeons, 13(43.3%) other physicians, 11(36.7%) surgical nurses, 5(16.7%) other nurses as well as in 1 (3.3%) administrative worker. These data have clearly shown that significantly more surgeons (46.7%), other physicians (43.3%), and surgical nurses (36.7%) had burnout syndrome compared to other nurses (16.7%) and administrative workers (3.3%) ($\chi^2=20.07$; $p<0.001$).

According to the Questionnaire data, actual health complaints were registered in 17(56.7%) surgeons, 16 (53.3%) other physicians, 23(76.7%) surgical nurses, 7 (23.3%) other nursesand in 16(53.3%) administrative workers. Accordingly, significantly smaller number of other nurses (23.3%) had actual health complaints when compared to the other groups of participants included in the study ($\chi^2=17.49$; $p=0,002$).

In the following table, the distribution of musculoskeletal complaints that show significant differences between different groups of participants is presented.

Table 3. Distribution of musculoskeletal complaints that show significant differences between different groups of participants

MS complaints	Group	*n*	%	χ^2 (*p*)
Back pain	surgeons	15	50	**12.34 (0.015)**
	other physicians	9	30	
	surgicalnurses	15	50	
	other nurses	12	40	
	administrative workers	4	13.3	
Shoulder and neck pain	surgeons	5	16.7	**10.29 (0.036)**
	other physicians	11	36.7	
	surgical nurses	15	50	
	other nurses	11	36.7	
	administrative workers	6	20	
Upper limb pain	surgeons	1	3.3	**9.77 (0.044)**
	other physicians	2	6.7	
	surgical nurses	4	13.3	
	other nurses	6	20	
	administrative workers	0	0	
Lower limb pain	surgeons	6	20	**10.62 (0.031)**
	other physicians	7	23.3	
	surgical nurses	12	40	
	other nurses	10	33.3	
	administrative workers	2	6.7	

The results presented in Table 3 show that:
- surgeons (50%), surgical nurses (50%) and other nurses (40%) significantly more often complained about **back pain** than administrative workers (13.3%) (χ^2=12.34; p=0.015),
- surgical nurses (50%) had**shoulder and neck pain** significantly more frequently than surgeons (16.7%) and administrative workers (20%) (χ^2= 10.29; p=0.036),
- -**upper limb pain** was significantly more frequent in other nurses (20%) than in surgeons (3.3%) and administrative workers (0) (χ^2=9.77; p=0.044), and
- significantly more frequently surgical(40%) and other nurses (33,3%) complainedon**lower limb pain** in comparison to administrative workers (6.7%) (χ^2=10.62; p=0.031).

Additionally, the data analysis indicated that participants who demonstrated a high or medium level of emotional exhaustion compared to participants with a low level of emotional exhaustion, significantly morefrequently complained about actual health problems (59.3% *vs*. 42.4%; χ^2=4.13; p=0.042), back pain (46.2% *vs*. 22%; χ^2=8.97; p=0.003),and lower limb pain (30.8% *vs*. 15.3%; χ^2=4.64; p=0.031). The participants with a high or medium level of depersonalization compared to participants with a low level of depersonalization significantly more frequently complainedonback pain (51.1% *vs*. 30.5%; χ^2=5.78; p=0.016),and upper limb pain (24.4% *vs*. 1.9%; χ^2=20.22; p<0,001). The participants from the analyzed hospital that had burnout syndrome compared to those who didnot have this syndrome significantly more frequently complained on back pain (54.5% *vs*. 29.2%; χ^2=8.57; p=0.003), and upper limb pain (20.5% *vs*. 3.8%; χ^2=10.93; p=0.001).

In order to determine the predictive value of different factors for the occurrence of health complaints (including subjective musculoskeletal complaints) in participants from the study hospital, we tested up to four models of logistic regression for every health complaint:
Model 1 - including the four types of job demands,
Model 2 - including the factor - working in night shifts,
Model 3 - with different work profiles, and
Model 4 - including burnout dimensions.

Table 4. Standardized exp *b*coefficients of significant independent predictors of subjective musculoskeletal complaints among study participants

Health complaints	Significant independent predictor	exp *b* (95% CI)	Cox & SnellR^2; NagelkerkeR^2	χ^2 of the model (*p*)
Health complaints-general	other doctors *vs*. administrative workers	5.65** (1.59-20.04)	0.1; 0.15	15.01 (0.011)
	other nurses *vs*. administrative workers	2.87* (1.2-6.89)		
Back pain	physical demands	2.27* (1.06-4.87)	0.11; 0.14	13.82 (0.02)
	emotional exhaustion	1.06** (1.02-1.09)	0.12; 0.17	17.56 (0.025)
Shoulder and neck pain	gender (women *vs*. men)	4.4* (1.17-16.58)	0.13; 0.18	17.55 (0.025)
	physical demands	2.19* (1.07-4.5)		
Upper limb pain	physical demands	4.31* (1.3-14.26)	0.13; 0.25	17.61 (0.024)
	depersonalization	1.18*** (1.08-1.29)	0.17; 0.34	25.81 (0.001)
Lower limb pain	not married *vs*. married	3.7* (1.29-10.61)	0.13; 0.19	17.57 (0.025)
	education (other *vs*.higher)	3.17* (1.16-8.64)		
	physical demands	2.37* (1.12-5.01)		
	not married *vs*. married	3.77* (1.38-10.3)	0.12; 0.17	17.43 (0.026)
	age	1.07* (1.01-1.15)	0.15; 0.22	22.45 (0.008)
	not married *vs*.married	4.85** (1.64-14.34)		
	surgical nurses *vs*. administrative workers	9.31** (2.29-37.91)		
	other nurses *vs*. administrative workers	3.78* (1.28-11.19)		

*p<0.05; **p<0.01; ***p<0.001

Every group of factors which predictive value was analyzed (job demands, night shifts work, work profile, and burnout dimensions) was integrated into a separate hierarchical model. These models also involved age, working hours during the week, hospital and unit tenure, gender, marital status, and education as a potentially confounding variables.

The factors: age, working hours during the week, and hospital and unit tenure were included in the first step of regression; the factors: gender, marital status, and education in the second step; and concrete specific variables which predictive value was the objective of analysiswere included in the third step. Within every single step, the variables were included in one block.

The following table demonstrates the standardized exp *b* coefficients of significant independent predictors of subjective musculoskeletal complaints.

The results from Table 4 show that the demographic characteristics of the participants, the stress factors from the workplace (job demands and work profile) and dimensions of burnout syndrome, in different combinations and relationships, presented significant predictors for the onset of subjective musculoskeletal complaints among the participants of this study.

Discussion

This study involved 150 HPs that demonstrated certain differences in demographic (i.e., women significantly more frequent in the groups of nurses than in physicians groups; physicians significantly more often completed a universityor higher education than nurses) and job (i.e., significantly less frequently administrative workers worked night shifts in comparison to HPs) characteristics.

Contrary to previous studies conducted in hospital HPs, the actual study showed lower average emotional exhaustion (21.4) and depersonalisation (4.99) scores [13]. Increased job demands that are reported by the HPs from this hospital [33], according to the JD-R Model, could result in increased compensatory efforts in HPs (in order to maintain performance level and higher levels of job engagement) as well as in reduced physiological and psychological costs (lower levels of depersonalization) [33]. Additionally, hospital "protective factors" (e.g., support from superiors, independence in decision making), previously emphasized by the hospital HPs [34], could also have an important role.

Participants from the analysed hospital emphasized physical workplace stressors (i.e., time pressure, excessive workload, and lack of staff and supplies) as particularly demanding aspects of their work life. Cognitive work demands (i.e., lack of receiving feedback on performance as well as training new staff) were also characterised as important and demanding workplace factors. Within the energetic process of overtaxing, high job demands could both exhaust the worker's energy (leading to emotional exhaustion) and downward adjustment of performance targets (resulting in cynical attitudes towards work, depersonalization, and disengagement). However, the presence of job resources (physical, psychological, social, or organizational aspects of the job) may be functional in achieving work goals, could reduce job demands and associated physiological and/or psychological costs (changes), and could stimulate personal growth, learning, and development of the worker [9,12]. Hence, the motivational process involves job recourses that enable dealing effectively with high job demands and prevents mental withdrawal or disengagement [5,35,36].

The actual study demonstrated that the frequencies of participants with medium/high levels of emotional exhaustion or depersonalization and burnout were very high in the groups of physicians and surgical nurses. The frequencies of these psychological phenomena were significantly lower in administrative workers. Similar findings have also been presented in other studies, clearly showing the high frequency of burnout in surgeons [37,38] and surgical nurses [39,40]. Shanafelt *et al.* in 2012 found that surgery department, together with emergency department, intensive care, and family medicine, represents a group of medical specialties with the highest frequency of burnout [41].

The risk of development of health complaints related to burnout is increased in HPs. Despite thisfact, there are only rare studies which have analyzed the associations between burnout, subjective health complaints, and workers' health behaviors [42,43]. The pool of studies analyzing these relationships in HPs or surgical HPs is even smaller [44,45].

Actual health complaints were reported by a large number of HPs (abovehalfof participants in all examined groups), especially in surgical nurses (above 75%). Surgical nurses were also characterized with significantly higher frequency of back, shoulder and neck pain, and lower limb pain compared to administrative workers. Health problems in surgeons and surgical nurses were reported in a wide range of studies, globally. Depression symptoms wereshown in a third of 7.905 examined USA surgeons [37].

The systematic literature review in surgeons in the UK highlighted several work-related problems: burnout, sharp injuries, and musculoskeletal diseases [46]. Musculoskeletal problems were reported in almost 80% of nurses and job stress was found to be one of the predictors for their manifestation [47]. These complaints were significantly more frequent in surgical nurses than in nurses from other departments [48].

The actual study also analyzed the associations of burnout and its dimensions with health complaints in participating HPs. Subjective musculoskeletal complaints were significantly more frequent in HPs with: 1. high/medium emotional exhaustion (back pain, and lower limb pain), 2. high/medium depersonalization (back pain, and upper limb pain), 3. burnout (back painand upper

limb pain), than in HPs with low emotional exhaustion, low depersonalization, and in HPs without burnout, respectively. Other studies similarly demonstrated that self-reported depression, anxiety, sleep disturbance, memory impairment, and neck and back pain were more frequent in workers with high emotional exhaustion and burnout [49]. It was also shown that burnout was correlated with MSDs and the prevalence of MSDs increased with the severity of burnout dimensions [50].

The actual study has shown that demographic characteristics of the participants, workplace stress factors (job demands, work profile) and dimensions of burnout syndrome, in different combinations and correlations, present significant predictors for the onset of subjecttive musculoskeletal complaints among the participants. It has been clearly demonstrated that in HPs who were exhausted, HPs who wereexposed to a wide range of job demands health problems were more frequent, as well as inHPs who worked in surgery department. The relationships between job stress (and especially burnout) and both physical and mental health problems in workers have been elaborated in different studies and burnout has been considered as a mediator in their development [49-53].

It has been detected that HPs with higher levels of burnout dimensions more frequently report health problems in comparison with HPs who reach low burnout levels. Available data have shown the strong association of altered health status with burnout in HPs [42].

Hence, it can be concluded that workplace characteristics (high job demands and reduced job resources) could predict the development of burnout, which in turn leads to health problems in workers. In that context, burnout acts as a mediator of the effects that high job demands and low job resources express on the physical and mental health [53]. Physical and emotional job demands as well as burnout have been found to be risk factors for the development of musculoskeletal problems [54,55].

As a support of the aforementioned findings, the prospective cohort study has detected associations between job demands/resources and neck pain. A significant relationship was found between neck pain and high job demands and low support from the colleagues [56].

In this study only job demands wereanalyzed. Further studies should also involve job resources (such as salary, team work, job security, participation in decision making, autonomy, performance feedback, etc.) that could reduce job demands, and protect HPs from disengagement and physical health problems. Special attention should be paid on the associations between different job and psychological characteristics of HPs and quality of patient care.

The data obtained can be used in the creation and implementation of specific organizational interventions in the analyzed hospital settings, guided by the effects of burnout and job demands on the occurrence of subjective musculoskeletal complaints. Specific strategies should be implemented in the hospital towards improvement of physical working conditions (e.g., reducing workload and time pressure through new employments as well as by purchasing new medical equipment and other supplies). Further building of the team work (e.g., forming teams to solve workplace problems, holding regular meetings to review progress, celebrating team successes publicly as well as building fun and shared occasions into the hospital's agenda) within the hospital settings can be used as a means with regard to improving the well-being ofHPs since team work was found to have buffering effect on the development of burnout. These issues should be presented to the policy makers especially in the context of health care reforms. Finally, it is important to notice that providing adequate job demands-resources interaction can lead to the prevention of work-related burnout and physical health complaints in HPs, and contribute positively to higher quality of patient care. These considerations are particularly meaningful since scientific evidence clearly demonstrates that burnout and impaired health in HPs lead to a reduced quality of care.

Various interventions could be implemented for the prevention of work-related MSDs in HPs [28-30]. The main effort focuses on early intervention by identifying and removing risk factors, as well as by implementing processes that could involve, for example, avoidance of repetitive patterns of work through job design and re-design (e.g., mechanization, job rotation, job enlargement and enrichment, or strengthening teamwork). Applying of organizational and individual strategies for the prevention of work-related stress has to be fostered, together with changes in regulations and policies at the workplace as well as lifestyle changes, training and education of employees, modifying the individuals' stress responses, and assistance or counseling programs [31,32]. The inclusion of key stakeholders, such as specialists in occupational medicine, occupational safety and health professionals, workers, employers, managers (especially, line managers), ergonomic consultants, or disability managers is needed for building an evidence platform for informed decision-making and making better choices towards prevention of work-related MSDs and job stress.

Conclusion

We can conclude that both job demands and burnout predict the occurrence of subjective musculoskeletal complaints. Participants with high/medium emotional exhaustion morefrequently complain about back and lower limb pain compared to participants with low emotional exhaustion. Participants with burnout compared to those who didnot have burnout more frequently complain about back and upper limb pain.The occurrence of back pain was predicted by physical

demands and emotional exhaustion and the occurrence of upper limb pain by physical demands and depersonalization. Adequate management of job demands can lead to prevention of burnout and musculoskeletal complaints in surgery HPs.

Conflict of interest statement. None declared.

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Original article

IODINE SUPPLEMENTATION AND THYROID STATUS IN HEALTHY PREGNANT WOMEN IN IODINE-REPLETE REGION

ЈОДНА СУПЛЕМЕНТАЦИЈА И ТИРОИДЕН СТАТУС КАЈ ЗДРАВИ БРЕМЕНИ ЖЕНИ ВО РЕГИОН СО ДОВОЛЕН ЈОДЕН ВНЕС

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Abstract

Introduction. Optimal iodine intake is essential for proper function of the thyroid in pregnancy, affecting thus the fetal development. Recent data worldwide have revealed insufficient iodine intake in pregnant women in certain countries with confirmed iodine sufficiency and raise the issue of iodine supplementation in this population. The objective of the study was to determine the effects of the iodine supplementation in pregnant women (PW) on their thyroid status and compare the findings with the data of pregnant women without iodine supplementation, all living under iodine sufficiency of general population.
Methods. The case control study was performed on total of 543 pregnant women (PW) (aged 15-40 years), 267 of which were taking iodine supplements. Iodine status was assessed as median urinary concentration and thyroid function tests (TFTs) were performed by chemiluminescence immunoassays. Data analysis was performed by descriptive and nonparametric statistics.
Results. The overall median urinary iodine concentration (UIC) in PW was 167.5 μg/L. The median value of the group with iodine supplementation was higher compared to non-supplementation group (180.5 μg/L *vs.* 160.2 μg/L), but the difference was not statistically signifycant. The median value was higher for thyroid stimulating hormone (TSH) in the group of PW with iodine supplementation (1.8 mIU/L *vs.* 1.6 mIU/L), while for thyroglobulin (Tg) in the group without iodine supplementation (11.4 μg/L *vs.* 10.5 μg/L). The difference in free thyroxin (FT4) results between the two groups was not statistically significant.
Conclusions. Living in a long-term iodine sufficient region, PW on iodine supplementation with 150 μg/day remained euthyroid, without evidence of increased incidence of iodine-induced thyroid disorders.

Keywords: pregnancy, iodine status, thyroid status, iodine supplementation, sustainable iodine sufficiency

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Апстракт

Вовед. Оптималниот внес на јод е неопходен за правилна функција на тиреоидеата во бременоста, што влијае и врз развитокот на фетусот. Некои скорешни светски податоци укажуваат на недоволен јоден внес кај бремените жени и во земји со потврден јоден суфицит и ја актуелизираат потребата од јодна суплементација кај оваа популација. Целта на оваа студија е да ги утврди ефектите од јодна суплементација кај бремените жени врз тироидниот статус и да ги спореди овие наодите со податоците од бремени жени без јодна супституција, во услови на јоден суфицит кај општата популација.
Методи. Оваа контролирана студија беше изведена на вкупно 543 бремени жени на возраст од 15-40 години, од кои 267 земаа јодна суплементација. Јодниот статус беше одредуван преку медијалната вредност на концентрациите на јод во урина, додека тестовите за тироидна функција беа изведувани со имуно хемилуминисцентни анализи. Податоците се анализирани со дескриптивна и непараметарска статистика.
Резултати. Медијаната на концентрацијата на јод во урина за сите бремени жени изнесуваше 167,5 мg/L. Оваа медијана за групата со јодна суплементција беше повисока во споредба со групата без суплементација (180,5 μg/L vs 160,2 μg/L), но разликата не беше статистички значајна. Медијалната вредност за TSH беше повисока во групата бремени со јодна суплементација (1,8 mIU/L vs. 1,6 mIU/L), додека за тиреоглобулинот во групата без суплементација (11,4 μg/L vs. 10,5 μg/L). Разликата во резултатите за FT4 добиени помеѓу групите не беше статистички

значајна.
Заклучок. Живеејќи во регион со долгогодишен јоден суфицит, бремените жени со јодна суплементација од 150 μg/ден останаа еутироидни, без евиденција за зголемена инциденца на тироидни пореметувања индуцирани со јод.

Клучни зборови: бременост, јоден статус, тироиден статус, јодна суплементација, одржлив јоден суфицит

Introduction

Iodine is an essential micronutrient for the thyroid hormones synthesis and consequently, adequate intake is important for maintaining the thyroid gland homeostasis. Recommended daily intake depends on age and physiological status. According to the WHO guidelines [1], infants up to 6 years old need 90 μg/day, growing children and adults 150 μg/day, and pregnant and lactating women 250 μg/day. Pregnant women (PW) are especially vulnerable population in regards to iodine intake-increased amount is needed due to increased thyroid stimulation and thyroid hormones production. On the other hand, increased glomerular filtration contributes to iodine loss, and together with transplacental iodine transfer to the fetus, results in lower plasma iodine levels in the first trimester [2]. Inadequate thyroxin (T4) synthesis in this trimester may lead to mother hypothyroxinemia which can affect the early fetal neurodevelopment [3]. T4 is essential for synapsis development, brain maturation and myelination up to the second childhood year [4,5]. For this reason, lactating women may need even more iodine than pregnant women [6].
With the past history of iodine deficiency (ID), Macedonia reached sufficiency in 2003, as confirmed by WHO/INICEF/ICCIDD, by increasing the amount of iodine for universal salt iodination [7]. Several survey studies performed in school-age children (SAC) afterwards confirmed the sustainability of the status in the general population. Nevertheless, the first study of pregnant and lactating women, performed in 2001, revealed insufficient iodine intake, with median urinary iodine concentration (UIC) of 140.4 μg/L [8]. The subsequent study undertaken in 2005/2007 showed an increase of the median UIC, with values in all trimesters within the recommended interval of 150-249 μg/L [9]. However, the proportion of individual UIC values below the lower recommended limit was 29% in the first trimester, 37% in the second and 39.1% in the third trimester.
These results were taken into consideration by the National Committee for Iodine Deficiency (NCID), which in 2014 advised all gynaecologists to actively recommend iodine supplementation in tablets containing 100 to 150 μg per day throughout pregnancy and lactation. In the past few years, as a result of this recommendation, the number of pregnant and lactating women taking iodine supplementation has increased. With all of the above, the importance of current status evaluation of iodine intake and thyroid function in pregnant women became evident. Furthermore, it was important to inspect the possible adverse effects of iodine supplementation on the thyroid function in pregnant women in our country.

Materials and methods

For the purpose of this study, a partnership was established between Institute of Pathophysiology and Nuclear Medicine (IPNM), Medical Faculty Skopje and University Clinic for Gynaecology and Obstetrics (UCGO). The study was approved by the Ethics Committee of the Medical Faculty in Skopje. UCGO participated in the process of recruitment of respondents and collecting biological samples for analysis, while IPNM performed the laboratory analyses for UIC and thyroid biomarkers. Spot urine samples were taken for assessment of UIC, and blood samples for thyroid function tests (TSH, FT4, thyroglobulin and thyroid autoantibodies). The samples were collected and analyzed between October 2017 and January 2018.

Study population

The study population was generated using a random sampling strategy, by recruiting pregnant women coming to the UCGO for consultation and examinations. To ensure representativeness of the sample, the recruiting was based on two main criteria: iodine supplementation (150 μg/day) and gestational age. Additionally, a number of exclusion criteria were also applied, such as: chronic health conditions, self-reported thyroid dysfunction, smoking and multipara pregnancies.
The study was designed for 600 healthy pregnant women of which half taking iodine supplementation in any form (iodine tablets or composite multivitamin preparations) and the other half not taking any iodine supplementation apart from regular diet. Within the two groups, recruitment was equally distributed between the trimesters, i.e. 100 women in each trimester. From the initially recruited population, after exclusion of the women with thyroid gland disorders according to the results of thyroid biomarkers [10], only 543 women (aged 15-40 years) were further evaluated. The main characteristics of recruited women are shown in Table 1.
Both urine and serum samples, if not analyzed the same day, were aliquoted and stored frozen at -20˚C.

Table 1. Study population-participants` characteristcs

Pregnant women				**N=543**
Iodine supplementation	No supplementation			276
	Supplementation with 150 μg per day			267
Gestational age	1st trimester			180
	2nd trimester			182
	3rd trimester			181
Iodine supplementation	*Gestational age*			
	1st trimester	2nd trimester	3rd trimester	Total
No supplementation	91	94	91	276
150 μg iodine per day	89	88	90	267
Total	180	182	181	543

Laboratory methods

UIC was assessed by the manual, colorimetric Method A, as classified by WHO/UNICEF/ICCIDD [11]. It is based on the Sandell-Kolthoff reaction, using ammonium persulfate for oxidative pretreatment of urine samples. The absorbance was measured on UNICO UV-2102 spectrophotometer with peristaltic pump (UNICO, USA), at 420 nm in 30 seconds interval. The results were calculated from standard curve derived by Multi Calc software package.

Analytical sensitivity was 7.2 μg/L, internal QC was performed with three-level in-house pools, and the proficiency was monitored regularly by EQUIP external quality scheme from CDC (Atlanta, USA).

Thyroid function tests were performed with routine competitive and non-competitive immunoassays, designed for the automatic chemiluminescence analyzer Immulite 2000 (Siemens Healthcare Diagnostics, USA). For internal QC we used commercial lyophilized sera in two levels and external quality assessment was performed with EQAS, BioRad.

Category criteria for iodine nutrition

The criteria for assessing iodine nutrition in pregnant women differ from the general adult population [12]. The data are related to median UIC obtained from survey studies as follows: <150 μg/L-insufficient, 150-249 μg/L-adequate, 250-499 μg/L-more than adequate and ≥ 500-excessive iodine nutrition.

Exclusion criteria based on the reference values for TFT

The results from FTFs for PW should be expressed as trimester specific reference values [13-15]. For TSH (as determined in the IPMN Lab) the reference interval was 0.35-3.4 mIU/L for all trimesters. For FT4 11.6-24.1 pmol/L for the first and 8.2-24.7 pmol/L for the second and third trimester, as declared by the manufacturer. For Tg, a-TgAb and a-TPOAb: <55 μg/L, <40 KIU/L and <35 KIU/L respectively, provided for the general population by the manufacturer.

Statistical methods

UIC and thyroid function tests were expressed as median, mean and standard deviation obtained by descriptive statistics, using Microsoft Excel. The Mann-Whitney U-test was used to compare the differences between groups, for a level of significance of $P<0.05$. Statistical analysis was performed using Statistica for Windows, Package 10.

Results

Iodine status

Out of total 530 urine samples, 261 were from PW taking iodine supplements and 269 from those not taking iodine supplements. The median UIC of both groups, overall UIC median and distribution of values are presented in Table 2.

Table 2. UIC and value distribution in pregnant women with and without iodine supplementation

Pregnant women	**Number of samples**	**Median UIC(μg/L)**	**p25**	**p75**
With iodine supplementation	261	182.5	112.07	252.45
Without iodine supplementation	269	160.2	108.00	240.60
Total	530	167.5	108.40	247.800

Legend: UIC, urinary iodine concentration

The median value of the group with iodine supplementation was higher compared to non-supplementation group (180.5 μg/L *vs*. 160.2 μg/L), but the difference was not significant (Mann-Whitney U-тест, p=0.093). In addition, both UIC median values fall within the interval of adequate iodine intake (150-249 μg/L).

Table 3. Distribution of values for TFTs in pregnant women with and without iodine supplementation

	FT4 (pmol/L)			TSH mIU/L		
Distribution of values	SD	p25	p75	SD	p25	p75
With iodine supplementation	2.31	9.8	12.15	1.04	1.2	2.50
Without iodine supplementation	2.27	9.7	11.22	0.95	1.1	1.70
Total	2.29	9.8	12.40	1.00	1.1	2.30

	Tg (μg/L)			*aTPO Ab (kIU/L)*			*aTg Ab (kIU/L)*		
Distribution of values	SD	p25	p75	SD	p25	p75	SD	p25	p75
With iodine supplementation	9.92	5.8	17.50	4.02	10.0	10.00	3.44	20.0	20.00
Without iodine supplementation	10.02	6.5	12.60	4.08	10.0	10.00	2.33	20.0	20.00
Total	9.96	6.2	17.50	4.05	10.0	10.00	2.92	20.0	20.00

Legend: TFTs, thyroid finction tests; FT4, free thyroxine; TSH, thyroid stimulating hormone; Tg, thyreoglobulin; aTPO Ab, anti thyroidperoxidase antibody; aTg Ab, anti thyroglobulin antibody

Thyroid function tests

The distribution of the total 543 sample results for the TFTs are depicted in Table 3. The data show overt differences between two groups of pregnant women only for TSH and Tg. The rest of TFTs in the groups had very similar 25th and 75th percentile values.

The TFTs results are presented as medians in Table 4. It is evident that the median values were higher for TSH in the group of PW with iodine supplementation (1.8 mIU/L *vs*. 1.6 mIU/L), while for Tg in the group without iodine supplementation (11.4 μg/L *vs*. 10.5 μg/L), but statistically significant were only the values for TSH (p =0.026).

Nevertheless, both TSH medians were within the laboratory reference interval. The median values for Tg, both below 13 μg/L are noteworthy since it is considered as a cut-off value indicating iodine deficiency in pregnant women [16]. In addition, we present the data obtained for thyroid antibodies, which were both exclusion criteria and an indicator of thyroid autoimmunity in pregnant women recruited for the study. As shown in Table 5, out of 578 samples, 41 or 7.1% were a-TPO Ab positive, while for a-Tg Ab the prevalence was 2.6%.

Table 4. Results for TFTs expressed as median in pregnant women with and without iodine supplementation

Pregnant women	Number of samples	FT4 (pmol/L)	TSH mIU/L	Tg (μg/L)	aTPO (kIU/L)	aTg (kIU/L)
With iodine supplementation	267	10.7	1.8	10.5	10.0	20.0
Without iodine supplementation	276	11.0	1.6	11.4	10.0	20.0
Total	543	10.8	1.7	11.1	10.0	20.0
Statistical difference between groups ($p < 0.05$)*		0.344	0.026	0.376	0.921	0.982

*Man Whitney U –тест

Table 5. Prevalence of positive anti-thyroid antibodies in pregnant women

Biomarker	No. of samples	% of total samples (n=578)
a-TPO Ab (+)	41	7.1
a-Tg Ab (+)	15	2.6

Legend: a-TPO Ab, anti thyroid peroxidase antibody; a-Tg Ab, anti thyroglobulin antibody

Discussion

Healthy pregnancy is a prerequisite for the well-being of the prodigy and requires specific dietary regime to ensure optimal nutrients intake for adequate fetal growth and development. Furthermore, it is often advised to women planning pregnancy in low-income countries to take supplements well before conception [17]. Multiple micronutrient supplements are usually comprised of iron, folic acid, vitamin A, vitamin B_{12}, vitamin D and also of variable amounts of iodine. However, these multiple supplements are not recommended by WHO for pregnant women to improve maternal and perinatal outcome [18], while recommendations of WHO are strong only for iron and folic acid. Regarding iodine intake during pregnancy, the optimal quantity of 250 μg/day is difficult to obtain by regular food intake, especially in regions with some degree of iodine deficiency. Iodine supplementation in pregnancy has been discussed by different researchers worldwide. Majority of published data refers to supplementation of mild to moderate iodine deficiency population [19-21]. Moreover, American Thyroid Association recommended supplementation with 150 μg iodine/day for all US pregnant women, despite the obtained median for UIC of 174 μg/L, that fell within the iodine sufficiency range [22].

The data from all iodine intake surveys in pregnant women from Macedonia revealed lower median UIC compared to data from school-age children [8,9,23], as shown in Table 6.

Table 6. UIC in SAC and PW in surveys in Macedonia from 2001-2017

SAC Med. UIC µg/L	Survey date	Iodine intake	PW Med. UIC µg/L	Survey date	Iodine intake
164.5	2001	adequate	140	2001	insufficient
241	2007	more than adequate	184.3	2005/2007	adequate
236	2016	more than adequate	167.5	2017	adequate

Legend: UIC, urinary iodine concentration; SAC, school age children; PW, pregnant women

These results are in compliance with most survey findings worldwide [24] presented in the IGN 2017 Scorecards. Iodine deficiency is still a persisting public health problem in Europe, as confirmed by publications of Zimmermann [25] and Lazarus *et al*. [26] who reported 11 European countries with iodine deficiency. Moreover, there is evidence that after a successful elimination of ID, some countries neglect this issue and the monitoring of iodine intake is diminished. Thus in Finland, the iodine status deteriorated from sufficient to deficient. Or, despite of adequacy in iodine nutrition in the general population, pregnant and lactating women remain iodine deficient, as found in USA, Australia and many of EU countries [27].

The last survey study of pregnant women in our country was undertaken a decade ago, and soon afterwards, gynecologists were recommending iodine supplementation of 150 µg/day. Being aware of the increasing median UIC trend for the general population within the more-than-adequate iodine intake interval (as displayed in Figure 1), we set the objective not only to assess the recent iodine status, but also the thyroid status in PW. Besides iodine deficiency, iodine excess can lead to increased thyroid impaired function risk [28]. The results of our recent study show decrease in the overall median value for UIC compared to the last PW survey (167.5 µg/L *vs*.184.3 µg/L). Moreover, we were able to compare the iodine intake category values of both groups - with and without iodine supplementation. As shown in Table 7, the percentage of insufficient iodine samples was higher in PW without supplementation in comparison to the supplemented group (42.7% *vs*. 37.4%). The percentage of iodine excessive samples was almost the same in both groups and very low (2.3 and 2.2 %, respectively).

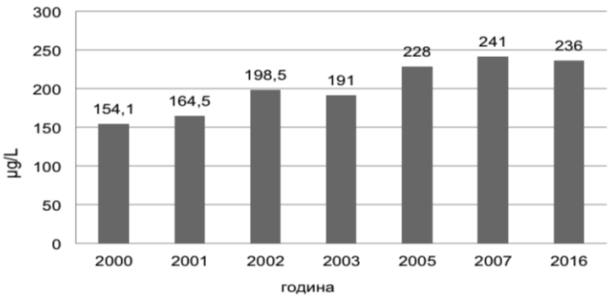

Fig. 1. Urinary iodine concentration (median) in 2000-2016 survey studies

Table 7. Categories of iodine intake in pregnant women with and without iodine supplementation

PW iodine suppl. (n= 259)	No of samples	%
UIC µg/L		
< 150	97	37.4
150-249	92	35.5
250-499	24.3	24.3
> 500	6	2.3
PW no iodine suppl. (n=267)		
< 150	114	42.7
150-249	89	33.3
250-499	56	21
> 500	6	2.2

In compliance with the low incidence of iodine excessive samples were the results of the thyroid autoantibodies. For both, the prevalence in unselected PW without clinical signs of thyroid dysfunction was within the values reported in the literature [29], which does not imply possible side effects, eg. iodine induced autoimmunity. The TFTs results in our study were not indicative for impaired thyroid function. However, the median values for thyroglobulin were both close to the cut-off value for iodine deficiency. Regarding thyroglobulin as a biomarker, it has been identified recently as sensitive for iodine status assessment in general population, reflecting the intermediate changing in iodine intake [30-32]. The cut-off value of <13 µg/L was suggested by Zimmermann *et al*., based on a large multicentric study of SAC. However, for PW such large observational study has not been undertaken so far. In the review paper of Ma [16] the authors summarized the results of several studies and concluded that typically reported median for Tg in PW was <13 µg/L, as well.

Our results for thyroglobulin and the relatively high proportion of samples with insufficient iodine intake raise the dilemma about the iodine supplementation in our population of pregnant women. As mentioned before, there are ambiguous recommendations in the literature on iodine supplementation, excessive and safety dose. In 2007 WHO/UNICEF/ICCIDD reached a consensus [1] according to which PW should not be recommended to take iodine supplementation if the general population had been in sufficiency for 2 years. The current iodine status in our population corresponds with this category. The WHO consensus from 2007 was validated by the review article of Andersen and Laurberg in 2016 [33].

The other approach on this issue, as suggested by ATA

in 2006, is iodine supplementation in all PW (even iodine-sufficient), which was accepted by US Endocrine Society as well [34]. Concerning the safety dose of iodine intake, the US Institute of Medicine (IOM) has set the upper tolerable dose of daily iodine intake at 1100 μg/day [35]. For the European Commission Scientific Committee on Food, the upper safe limit is 600 μg daily [36]. However, a large population study conducted on 7190 PW in iodine-sufficient regions in China revealed that in iodine-sufficient population UIC should not exceed 250 μg/L. They found that excessive iodine intake, with more than 500 μg/L UIC, increased the risk of isolated hypothyroxinemia by 2.85 fold. Similarly, more-than-adequate intake was 1.75 fold risks for subclinical hypothyroxinemia [37]. In compliance with these findings are the remarks by Monkayo *et al*. [14] who observed latent to overt hyperthyroidism in pregnant women in iodine–sufficient population, taking multivitamin preparations containing 200-220 μg iodine.
Macedonia is one of the few countries in the world with sustainable iodine sufficiency [38] obtained through universal salt iodination. However, considering the PW iodine needs, and the recent WHO agenda for decreasing the salt consumption in overall population [39], an adequate strategy should be reconsidered in order to ensure optimal iodine nutrition in our PW. Thus, regarding PW iodine supplementation, guidelines issued by ATA in 2017 recommend country-specific strategies of the national health authorities. The other important guidelines recommendation is not to initiate iodine supplementation in PW with thyroid disorders.

Conclusion

The recent evaluation of iodine and thyroid status of pregnant women in Macedonia revealed adequate iodine intake and normal thyroid function, irrespective of iodine supplementation with 150 μg per day in half of the survey group. However, this status requires awareness and frequent follow-up by national and subnational surveys, especially for the expected salt intake decrease, due to the general salt restriction initiative of WHO implemented in our country. So far, the recommended iodine supplementation in PW by the NCID has proved to be safe.

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Conflict of interest statement. None declared.

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Origiale article

CORRELATION OF SCORING SYSTEMS WITH HISTOPATHOLOGICAL FINDINGS AND THEIR IMPORTANCE IN REDUCING THE PERCENTAGE OF UNNECESSARY APPENDECTOMIES

КОРЕЛАЦИЈА НА СКОРИНГ СИСТЕМИТЕ СО ХИСТОПАТОЛОШКИОТ НАОД И НИВНОТО ЗНАЧЕНИЕ ВО НАМАЛУВАЊЕ НА ПРОЦЕНТОТ НА НЕПОТРЕБНИ АПЕНДЕКТОМИИ

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Abstract

Introduction. Acute appendicitis (AA) is one of the most common emergency surgical conditions, where emergency laparotomy is necessary. However, perforation rates and negative laparotomies during this procedure have not been reduced. The purpose of this paper was to evaluate the importance of the scoring systems in the differential diagnosis for setting an indication for appendectomy.
Method. Prospective comparisons of the values of 4 scoring systems were performed among 60 patients: Alvarado, Appendicitis Inflammatory Response (AIR), Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) and Tzanakis. Values for the scores were determined in all patients treated with lower right quadrant (LRQ) abdominal pain, under a differential diagnosis of AA. After the appendectomy (open surgery or laparoscopic), a correlation was obtained between the histopathologic findings (HP) and the corresponding latent values.
Results. In the study 63.33% of the patients were male. Distribution of patients according to the values of the three different systems (Alvarado, RIPASA and Tzanakis) showed that the largest number of patients had values higher than 8 and AIR values of 7- 8. In the study, 95% of the operated patients were positive for appendicitis compared to the histopathological finding. 80% of the surgeries included on-time appendectomy, 15% delayed diagnosis, and 5% were found to be with an unnecessary appendectomy. According to the HP findings of those with positive findings, 77.2% of the cases had appropriate preoperative ultrasonographic (US) diagnosis. A statistically significant association of the scores with HP findings (promptly phlegmonous, promptly gangrenous, late perforated and unnecessary) was found only for the Alvarado, AIR, Tzanakis, and no statistically significant associationwas found for the RIPASA score.
Conclusion. Scoring systems are useful diagnostic tools for appendectomy indication. Using one or a combination of two or more scoring systems reduces the percentage of unnecessary appendectomies.

Keywords: acute appendicitis, scoring systems, diagnosis, appendectomy

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Абстракт

Вовед. Акутен апендицитис (АА) е една од најчестите итни хируршки состојби, каде е индицирана лапаротомија. Сепак, при оваа состојба,стапките на перфорации и негативни лапаротомии не се намалени. Целта на трудот е да се процени значењето на скоринг системите во диференцијалната дијагноза за поставување на индикација за апендектомија.
Метод. Кај 60 пациенти, направено е проспективно компарирање на вредностите на 4 скоринг системи: Алварадо, Appendicitis inflammatory response (Апендицитис инфламаторен одговор-АИО), Raja Isteri Pengiran Anak Saleha Appendicitis-РИПАСА и Тзанакис. Вредноста за скоровите се одредени кај сите пациенти примени со болка во долен десен квадрант (ДДК) на абдоменот, под диференцијална дијагноза за АА. По апендектомија, (класична или лапароскопска), направена е корелација помеѓу добиениот хистопатолошки наод (ХП) и соодветните вредности на скоровите.
Резултати. Во студијата 63.33% од испитаници беа од машки пол. Дистрибуцијата на пациентите согласно висината на вредностите на трите различни (Алварадо, РИПАСА и Тзанакис) скора, покажа дека најголем број на пациенти се со вредности на скорот поголемо од 8, а кај АИОС за вредности на скорот 7-8. Во студијата, 95% од оперираните пациенти имаа позитивен патохистолошки наод во однос на АА. Кај 80% од оперираните се работеше за нав-

ремена апендектомија, кај 15% за закаснета дијагноза, а кај 5% најдено е непотребна апендектомија. Согласно добиениот ХП наод од тие со позитивен наод кај 77,2% од случаевите се работеше за соодветна предоперативна ултрасонографска (УС) дијагноза. Статистички сигнификантна асоцираност на скоровите со ХП наод (навремен флегмонозен, навремен гангренозен, закаснето перфориран и непотребна) се покажа само за скоровите Алварадо, АИО, Тзанакис, додека кај РИПАСА скорот асоцираноста остана несигнификантна.
Заклучок. Скоринг системите се корисни дијагностики алатки при индикација за апендектомија. Со користење на комбинација на два или повеќе скоринг системи може да се намали процентот на непотребни апендектомии.

Клучни зборови: акутен апендицитис, скоринг системи, дијагноза, апендектомија

Introduction

Acute appendicitis (AA) is the most common cause of acute abdominal pain and emergency abdominal surgery. AA can occur during any period of life of the general population, with the highest incidence in children and adolescents. Delayed treatment of AA is associated with prolonged hospitalization, increased percentage of perforations (34%-75%), operative wound infections (1%-11%), pelvic abscesses (2%-7%), and late intraabdominal adhesions [1-5].
The most commonly used methods for diagnosing AA are disease history, physical examination and laboratory blood analysis. Diagnosis of AA based only on clinical and laboratory data results in high negative rates of appendectomy and missed diagnoses with increased morbidity [6-8]. Atypical presentation is more difficult to diagnose, with additional diagnostic methods being used, such as US, computed tomography, and magnetic resonance imaging. However, early diagnosis is highly dependent on the experience of the surgeon [9-15].
AA therapy can be conservative and surgical. Early surgical intervention is the gold standard for preventing blind perforations. However, the high rate of unnecessary negative appendectomies leads to unnecessary morbidity and even mortality. Clinical scoring systems are inexpensive, repeatable, and easily applicable tools in the preoperative period of AA diagnosis developed to reduce the rate of adverse appendectomies. Today, more scoring systems are used for diagnosing AA, mostly Alvarado, Tzanakis, Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA), Appendicitis Inflammatory Response score (AIR), but new ones are emerging. Scoring systems incorporate different variables: demographic data (sex, age), clinical symptoms and signs, laboratory values (complete blood count, leukocytes, urine, C-reactive protein, etc.) and radiological examinations [16-19]. The Alvarado score is widely used in the diagnosis of AA because of its availability and low cost; it also avoids exposing the patient to radiation when using computed tomography. RIPASA score is a newer score that has more sensitivity and specificity than the Alvarado score. On the other hand, AIR and Tzanakis have recently used several clinical criteria and two simple laboratory tests (CRP and complete blood tests), but also US, which can lead to better and faster diagnosis of AA [16-19]. The gold standard in the diagnosis of AA is histopathological (HP) evaluation of the specimen after surgery. The purpose of this study was to correlate the values of different scoring systems with the histopathological finding and to evaluate their impact on reducing the percentage of unnecessary appendectomies.

Materials and methods

This prospective cohort study was conducted at the University Clinic of Surgical Diseases “St. Naum Ohridski”-Skopje, Macedonia. The ethical and legal requirement in accordance with the International Helsinki Protocol was received before the start of this study. Consent was obtained from all patients. The study included 60 patients over the age of 14, admitted in the hospital during the trial duration due to pain in the LRQ and suspected of AA. The preoperative diagnosis was established by disease history, clinical examination, and laboratory analysis that included total leukocyte count, neutrophil percentage, and CRP in the blood. All patients underwent preoperative US examination with appropriate criteria for AA: lumen diameter >6 mm, periappendiceal collection, appendicolith. Standardized demographic, symptom and symptom questionnaires, laboratory values, US findings and scoring data for Alvarado, AIR, Tzanakis, and RIPASA scoring system were completed for all patients. All patients underwent a classic or laparoscopic appendectomy. Each sample was sent for HP analysis. Patients without informed consent, with a previous history of urolithiasis, pelvic inflammatory disease, pregnant women and children under 14 years of age were excluded from the study. Table 1 shows all 4 examined scoring systems: Alvarado (8 parameters), AIR (7), Tzanakis (4) and RIPASA (18).

Table 1. Tracked scores

			Alvarado	AIR	RIPASA	Tzanakis
Parameters	Female				0.5	
	Male				1.0	
	Age/under 39,9				1,0	
	Age/ over 40				0.5	
Symptoms	Pain in the low right quadrant or right iliac fossa				0.5	
- signs	Migration pain in LRQ		1		0.5	
	Palpatory pain sensitivity in LRQ		2	1	1.0	4
	Rebound palpatory sensitivity in LRQ		1		2.0	3
	Rigid RLQ				1.0	
	Rowing / positive sign				2.0	
	Muscular defense/guarding	*Light*		1		
		Medium		2		
		Strong		3		
	Nausea / vomiting		1	1	1.0	
	Anorexia		1		1.0	
	Body temperature	*Raised*	1			
		>38.5 C°		1		
		37 - 39,5 C°			1.0	
	Time duration of	*< 48 hours*			1.0	
	the symptoms	*> 48 hours*			0.5	
Laboratory		*74- 84*		1		
values	Polymorphonuclear	*≥ 85*		2		
	leukocytes %	left shift of the neutrophils> 75%	1			
	Raised white blood cells	> 10000	2		1.0	
		10000 – 14999		1		
		> 12000				2
		≥ 15000 sv/sic		2		
	C - reactive	*10- 49 gr/l*		1		
	Protein	*≥ 50 gr/l*		2		
	Urinalysis	*Negative*			1.0	
Radiological m.	Ultrasonography	*Positive*				6
		Total value:	10	12	16.5	15

Guide for Scores Interpretation, Alvarado: <4-unlikely AAA; 4-7-suspected AA; > 7-AA definitive, AIR: 0-4-low probability of AA; 5-8 probability of AA; 9-12 high probability of AA, RIPASA: <5- most likely AA malabsorption; 5-7 low probability of AA; 7.5-11.5-probable AA; > 12-AA definitive, Tzanakis: <5 unlikely for AA; 6-10 probable AA; > 10 highly probable AA

Patients were monitored from the time of admission to the time of discharge. Patients were monitored twice daily for vital parameters. The HP findings were analyzed at the Institute of Pathology, Faculty of Medicine-Skopje. Statistical analysis was performed using the statistical software package Statistica for Windows 7.0 and standard statistical package (SPSS v 20). Results are presented with descriptive statistics, mean±SD. Student's t-test was used for comparison of the two groups. For comparison of 2 groups with categorical normal (nominal) variables X2 test was used. And for comparison of more than 2 groups ANOVA analysis was performed.

Results

In our study group of 60 operated patients, 63.33% were men and 36.67% women, with a mean age of 35.86± 15.15 years. Palpatory pain in the lower right quadrant was present in all 60 patients, anorexia in 54(90%), nausea and vomiting in 59(98.33%), and low right quad-

Table 2. Demographic, clinical and laboratory characteristics of the study population

Characteristics of the analyzed patients(N = 60)	
Age (years)	35.86±15.15(15 - 77)
Males	36.11±17.10 (63.33%)
Females	35.44±11.40 (36.67%)
Time of onset of symptoms (in hours)	42.616667(3-180)
Migration pain in RLQ	30(50%.)
Anorexia	54(90%)
Nausea / vomiting	59(98.33%)
Palpatory sensitivity in RLQ	60(100%)
Rebound palpatory sensitivity	34(56.67%)
Diffuse abdominal pain	16(26.6%)
Raised temperature (≥37.3°C)	24(40%)
Leukocytosis(10^9/ l)	14.01±3.7 (5.1-22.9)
Differential neutrophils (75% neutrophils)	76.41±15.98 (11.1-94%)
CRP (mg / l)	82.45±81.98 (0.2-320)
Ultrasonography	
Acute	78.33%
Normal	21.66%

rant pain in 14(23.33%) patients. Migration pain as the first symptom was present in 30 patients. Rebound palpatory pain was present in 34(56.67%) patients. Elevated body temperature (≥37.3°C) was present in 24(40%) patients (Table 2). Of the total number of respondents, 26(43.3%) underwent classical surgery, while the remaining 34(56.6%) underwent laparoscopic surgery.

Table 3. Histopathological findings

Histopathological findings	Number	Percentage %
Normal AA	3	5
Phlegmonous AA	32	53.3
Gangrenous AA	16	26.6
Phlegmonous perforated AA	2	3.33
Gangrenous perforated AA	7	11.6

Table 3 shows that 95% of operated patients were positive for AA in relation to HP finding. Eighty percentages of patients were operated on for timely appendectomy, 15% for delayed diagnosis, and 5% for unnecessary appendectomy.

Regarding leukocyte values, the highest mean was in timely gangrenous appendectomies (15.08±3.76), and the lowest in unnecessary appendectomies (7.90±2.43), while in the neutrophils, no statistically significant difference was observed. The highest mean value for CRP was in timely gangrene appendectomies (107.21± 83.10) and the lowest in unnecessary appendectomies (14.40±9.58) (Table 4).

Table 4. Association of inflammatory markers with histopathological finding

	Histopathological findings				
	On-time Phlegmonous N=32	On-time Gangrenous N=16	Delayed Perforated N=9	Unnecessary N=3	p
Leukocytes	13.97 ± 3.67	15.08 ± 3.76	14.29± 2.62	7.90 ± 2,43	0.020
Neutrophils	75.07± 19.35	82.10 ± 9.00	77.17 ± 6.66	58.10± 12.41	n.s.
CRP	72.05 ± 89.19	107.21 ± 83.10	98.16 ± 46.03	14.40 ± 9.58	0.011

Table 5. Ultrasonographic finding and scoring systems

	Ultrasonography		
	Negative N=13	Positive N=47	p
Alvarado	8.38 ±1.04	8.29 ±1.24	n.s.
AIR	8.07±1.75	7.94 ± 1.69	n.s.
RIPASA	10.42±1.45	10.67 ±1.89	n.s.
Tzanakis	7.85±1.52	12.91 ±1.84	0.000

Of the preoperatively performed US examinations, 77.2% of those with positive HP findings were diagnosed with appropriate and 22.8% had an inappropriate US diagnosis. Only at the Tzanakis score there was a statistically significant difference concerning positive and negative US findings (Table 5).

The distribution of patients according to the values of the four scoring systems (Table 6) showed that the largest number of patients (28) was in group of 7 to 8 in AIR, while in relation to the other three scoring systems, at the value of almost >8, 29 patients in Alvarado, 55 in RIPASA and Tzanakis.Of all four scoring systems, patients with scores <7 did not receive HP for delayed appendectomies, whereas only two (3.33%) had unnecessary appendectomy according to HP findings. Most patients with delayed appendectomies were in the group with 7-8 scoring values. According to the HP findings, the majority of patients were in the group of promptly appendectomies, and that was in the group with scores of >8 present in all three systems (Alvarado, RIPASA, and Tzanakis). Only in the AIR score the highest percentage of promptly appendectomy occurred at the value of score 7-8.

Table 6. Distribution of patients concerning recent histopathological finding

	Scores				Histopathological findings		
	Alvarado	AIR	Tzanakis	RIPASA	AA	late	unnecessary
< 7	4 (6.67%)	12 (20%)	5 (8.33%)	0	2 (3.33%)	0	2 (3.33%)
7– 8	27 (45%)	28 (46.67%)	0	5 (8.33%)	20 (33.33%)	6 (10%)	1 (1.66%)
> 8	29 (48.33%)	20 (33.33%)	55 (91.66%)	55 (91.66%)	26 (43.33)	3 (5%)	0

Table 7 shows that according to the obtained HP findings, there was a statistically significant difference in all three systems (Alvarado, AIR, Tzanakis) relative to the histopathological finding, with the highest values obtained in gangrene HP finding (for Alvarado 8.75±1.18, p=0.011; for AIR 8.56±1.67, n=0.007, and for Tzanakis 13.37±2.42, n=0.004), whereas in RIPASA there was no statistically significant difference in baseline values with HP findings.

Table 7. Association of scoring systems (Alvardo, AIR, RIPASA, and Tzanakis) with histopathological finding

	Histopathological findings				
	On-time Phlegmonous N=32	**On-time Gangrenous N=16**	**Delayed Perforated N=9**	**Unnecessary N=3**	**p**
Alvarado	8.34 ± 1.06	8.75 ± 1.18	8.11± 1.27	6.33 ± 0.58	0.011
AIR	7.93± 1.64	8.56 ± 1.67	8.00 ± 1.00	5.00± 1.00	0,007
RIPASA	10.64 ± 1.81	11.22 ± 1.89	10.00 ± 1.44	9.00 ± 1.00	n.s.
Tzanakis	11.34 ± 2.77	13.37 ± 2.42	10.67 ± 2.65	12.00 ± 1.73	0.004

Discussion

Appendectomy is one of the most common procedures in general surgery. The overall incidence of AA ranges around 8.6% for men and 6.7% for women. The lifetime risk of possible appendectomy is about 12% in men and 23% in women [1-3]. In our study, a higher percentage of the total number of patients was male (63.33%). Men do not differ significantly from women in the outcome of appendicitis as a definitive diagnosis based on a HP finding.

In our study, the average age of the patients was 35.86 ±15.15 years and correlated with the results found in the literature. Forty percentages of the patients were >39 years of age, which did not correspond to the distribution in other studies [20]. We consider that as a tertiary institution we take care of patients from both primary and secondary health care centers from where this adult population is most often referred to our facilities.

Concerning clinical manifestation, palpatory pain sensitivity in LRQ was present among all 60 patients, followed by nausea-vomiting in 59, and anorexia in 54. These data coincide with the data from the literature [2,3], confirming the fact that this triad of symptoms and signs (LRQ pain, anorexia, nausea and vomiting) should give rise to a suspicion of a AA diagnosis.

Acute appendicitis as a surgical problem is also associated with an acute-phase inflammatory response. Blood tests are often unclear. In our study higher values of the leukocyte >10,000 mm3 were present in 50(83.34%) patients. In relation to the histopathologic findings statistically significant highest leukocyte count of 15.08± 3.76 was found among the gangrenous appendectomies, while the lowest among the unnecessary appendectomies (7.90±2.43). A similar result was shown in the study of Zuhoor K. *et al.* [21].

The high value of CRP is associated with the highest percentage of inflamed appendixes. In our study, the high CRP value supported the surgical diagnosis. Significantly higher CRP was characteristic of promptly gangrene appendectomies, while the lowest for unnecessary appendectomies (107.21±83.10 g/l; 14.40±9.58 g/l, p=0.011). These results correlate with results in the literature regarding inflammatory appendectomies [11,22]. There are several studies in the literature about the importance of CRP value, which has undoubtedly high specificity and sensitivity. Yokohama *et al*. clearly confirm that CRP levels can predict the severity of AA and consequently the mode of treatment [23].

Preoperative US examination showed that 78.3% of patients had a positive AA, while 21.7% had a normal appendix. According to the obtained HP findings, in 77.2% of the cases it was appropriate and in 22.8% it was inappropriate US diagnosis. In terms of scores, however, only Tzanakis showed a statistically significant difference in negative versus positive US findings. The data in the study by Chafri S. *et al.* differ in the percentage of unnecessary appendectomies (15%) [24]. However, diagnostic modalities such as US or CT in developing countries can significantly increase healthcare costs [10-15].

The length of hospitalization in our study was 4.42±2.93 days with a shorter mean compared to literature data. In the Cochrane Database the mean length of hospital stay for unnecessary appendectomies is 21.4 and for delayed appendectomies 14.7 [25]. Thus, the overall hospital stay of patients with unnecessary appendectomies is longer than those with delayed appendectomies, which differs in our study where the median value of unnecessary was 3 days and that of delayed 4.11.

According to the HP findings, the majority of cases were with phlegmonous AA 48(80%), followed by a finding of perforated AA 9(15%), and the least with normal AA 3(5%). In the study of Arif E. *et al*.,of 1255 patients, 70.1% were phlegmonous, 11.8% were perforated, 6.06% were negative, and 12.03% with other pathology [26]. The study by Shafri S. *et al*, however, finds that it is not necessary to send all samples for HP analysis to avoid unnecessary expense, thereby reinforcing the need for a more accurate diagnosis. In our Institution per-protocol, each sample obtained as a result of appendectomy is sent for HP analysis. Our practice supports the study of Anel B. *et al*., according to which sending all samples for HP analysis enables the diagnosis of malignancy present in 1% of a patient who often presents as a neuroendocrine tumor of the appendix, adenocarcinoma or mucinous [27].

The scoring system should contain simple parameters to assist in the treatment decision-making process. The purpose of scoring systems is to make a difference between AA and non-specific abdominal pain.

Difficulties in the differential diagnosis of AA, especially in atypical presentations, lead to the risk of appendicular perforation and more severe infections (abscess,

sepsis), which increases morbidity and mortality [5-12]. On the other hand, due to inadequate diagnosis, negative or unnecessary appendectomies are on the rise, ranging from 20% to 40 % [5-7]. Good clinical assessment of the surgeon is considered an important prerequisite for the diagnosis of AA [13]. In our study regarding HP findings, the largest number of unnecessary appendectomies occurred in the group with values <7 (only in 2(3.33%) patients). Regarding the number of delayed appendectomies, the majority of patients were in the 7-8 group (6 patients), as well as three in the scoring group >8. The largest number of promptly appendectomies was in patients with a score of >8. Distribution of patients according to the height of the scoring values showed that in all 3 scales (Alvarado, RIPASA, and Tzanakis) the highest values were in the group of >8, except in the AIR score where the distribution was highest in the group of values of 7-8. Regarding the values of the scores according to the obtained HP findings, there was a statistically significant difference in all three scores (Alvarado, AIR, Tzanakis), with the highest values obtained in gangrene HP finding (for Alvarado 8.75±1.18, p=0.011; 8.56±1.67, n=0.007, and for Tzanakis 13.37±2.42, n=0.004) where as in RIPASA there was no statistically significant difference in the baseline values with the histopathological finding.

Most of the studies show dominance of Alvarado score and the same corresponds to our study, however when only using this scoring system, it shows some disadvantages. According to the study of Klan and Rehman [28], the Alvodaro score is a simple test that depends on the presence and absence of variables involved in the test. A more recent systematic review of S.A. Kabir *et al*. points to the fact that this test is difficult to apply to women of childbearing age and to children [7]. In many studies, as well as in the study of Karami *et al*., the RIPASA scoring system is more sensitive and specific than the Alvarado score, AIR and Tzanakis score where CRP and US are used in addition to clinical and laboratory parameters, providing better statistical data in the diagnosis of AA. However, the combined use of two or more scoring systems provides better statistics in reducing the percentage of unnecessary appendectomies. The importance of scoring systems is also seen in the fact that they are already incorporated into recommendations for the diagnosis of AA [29].

One of the limiting factors of our study is the analysis of a smaller number of patients, thus limiting the possibility for significant conclusions. Regarding the results of the US findings, the second limiting factor is that in our institution, patients are examined by different radiologists, with subjectivity present in their diagnosis, but a factor which, given the emergency of the condition, could not be limited to a single radiologist.

Conclusion

Scoring systems are useful in the early diagnosis of AA in the indication for appendectomy. The proper single or combined use of multiple scoring systems in the diagnosis of AA contributes to a decrease in the percentage of unnecessary and delayed appendectomies. The use of scoring systems, their simple design, and simple applicability, allows to reduce the rate of unnecessary appendectomies, as well as to enable faster diagnosis and reduction of delayed appendectomies.

Conflict of interest statement. None declared.

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Original article

SIGNIFICANCE OF IN EARLY DIAGNOSIS OF SPONDYLOARTHROPATHY

ЗНАЧЕЊЕ НА САКРОИЛЕИТИС ВО РАНАТА ДИЈАГНОЗА НА СПОНДИЛОАРТРОПАТИИ

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Abstract

Introduction. Very often late diagnosis in spondylitis ankylosans (SA) in the period between 5 to 10 years is due to unstandardized diagnostic method besides established diagnostic criteria. But, they are very restrictive and not practical for early diagnosis of SAbecause they are based on proved radiographic changes.
Aim. Sacroiliitis (SI) as a sole entity rarely exists, usually is a part of the diagnostic mosaic of SA and related spondyloarthropathies (SpA). Surely proved SI clinically and radiographically means sure diagnosis of SA, especially in the early stage of the disease.
Methods. A highly selective group of patients with SA was followed in the period of one year: group of 23 patients (pts) with unconvincing radiographic changes for SA from 1-2° and group of 21 pts without radiographic changes i.e. 0°. Beside SA, both groups fulfilled at least another from the listed conditions: 1.oligoarthritis; 2. enthesitis; 3. iridocyclitis; 4. positive family history for SA; 5. positive antigen HLA-B27 and 6. elevated ESR > 30mm/h.
Results. After one-year observational period 11/21 pts in group A were with SA. In group B only 6/23 pts were with SA; the others were transformed in different directions: 4/23 in the group of spondyloarthropathies (SpA)-2 pts with psoriatic spondyloarthropathy (PsSpA), 1 patient with Reiter syndrome (RS) and 1 patient with entericspondyloarthropathy (ESpA). The remaining 8/22 pts were still undefined SpA.
Conclusion. Our results showed that defining of SA was crucial in the diagnosis of SA. The fact that most of the cases with authentic SA were in group A with minimal radiographic changes from 1-2° in comparison with group B without radiographic changes showed the necessity of using other imaging techniques (scan, MRI) for earlier detection of SI in the so called preradiographic stage which lasts 2-4 years, when radiographic findings are absent. Clinical (symptomatic) SI without radiographic changes according to the findings of pts in group B gives a possibility for overlap to other entities in the group of SpA.

Keywords: spondyloarthropathies, sacroiliitis, spondylitis ankylosans

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Апстракт

Вовед. Доцна поставената дијагноза кај анкилозантниот спондилитис (АС), во период меѓу пет и десет години, често се должи на нестандардизирана дијагностичка постапка, и покрај востановените дијагностички критериуми. Но, тие се доста рестриктивни и непрактични за рана дијагноза на АС, бидејќи се базираат на сигурно докажани радиографски промени.
Цел. Сакроилеитисот (СИ) ретко постои како самостоен ентитет, а влегува во дијагностичкиот мозаик на АС и сродните спондилоартропатии (СпА). Сигурно докажан клинички и радиографски СИ значи и сигурна дијагноза на АС, особено во раната фаза на болеста.
Методи. Во период од една година проспективно беше следена висококоселектирана група на пациенти со СА: група од 23 пациенти со неубедливи Rtg промени за СА од 1-2ст и група од 21 пациент без Rtg промени, односно СА од 0ст. Покрај СА, двете групи исполнуваат барем уште еден од наведените услови: 1. oligoarthritis; 2. enthesitis; 3. iridocyclitis; 4. позитивна фамилна анамнеза за АС; 5. позитивен антиген HLA-B27 и 6. покачена Se> 30 mm/h.
Резултати. По опсервацискиот период од околу една година се покажа дека во групата А-11/21 од пациентите претставуваат сигурно докажани случаи на АС. Во втората група Б, само кај 6/23 е потврдена дијагнозата на АС, а останатите поминале во друг правец: 4/23 во групата спондилоартропатии (СпА)-(Псоријатична спондилоартропатија (ПсСпА)-2 пациенти; Рајтер-овиот синдром (РС)-1 пациент; и ентеропатската спондилоартропатија-(ЕнСпА)-1 пациент, и конечно 8/22 и натаму се водат како недефинирани СпА.

Заклучок. Нашите резултати покажаа дека дефинирањето на СА има пресудна дијагностичка ориентација кон АС. Податокот дека најголемиот број автентични случаи со АС има во групата А, со минимални Rtg промени од 1 до 2^{ст}, во однос на втората група Б без Rtg промени, укажува на потребата од користење други „imaging" техники (скен, CT, MRI) за порано детектирање на СИ, во т.н. прерадиографски стадиум, кој трае во период од две до четири години, кога се отсутни Rtg наодите. Клиничкиот-симптоматски СИ, но без Rtg промени, според наодите од пациентите во групата Б, дава можност за премин или „overlap" кон други ентитети од групата SpA.

Клучни зборови: спондилоартропатии, сакроилеитис, анкилозантен спондилитис

Introduction

Spondyloarthropathies (SpA) are group of diseases with common clinical features and are carriers of the genetic marker-antigen HLA-B27 in a high percentage. Main representative is spondylitis ankylosans (SA), but there are also Reiter syndrome-reactive arthritis (RS), psoriatic spondyloarthropathy (PsSpA) and undefined spondyloarthropathies (SpA). SA is a chronic progressive inflammatory disease with unknown etiology. It is usually seen in young people between 25 and 35 years of age with the domination of males. All these entities have similar clinical features and presence of the antigen HLA-B27 in a high percentage of 70-95%.

Material and methods

In patients included in this study disease diagnosiswas based on the modified New York criteria (1984), graded by Hart and Robinson, proposed by the American Association for Rheumatism (ARA) for diagnosis of SA. They are rather restrictive, based on secure radiographic changes. They are used for epidemiological studies and not for clinical use, because they donot encompass the whole spectrum of SA. Clinical assessment of the disease activity and disease diagnosis was made by a subspecialist. For diagnosis of psoriatic spondyloarthropathy diagnostic criteria by Moll-Wright for theclassification of psoriatic arthritiswere used. They were dermatologically tested, including examination of psoriatic changes, nails, psoriatic areas as well as an index for disease activity (PASI) and evaluation of peripheral and axial joints. The diagnosis of oligoarthritis was made when <5 joints were involved, polyarthritis when >5 joints were involved. The diagnosis of symmetric arthritis was made when there was a bilateral involvement of> 50% of joints.

This study included 23 pts (7 women, 16 men) with SI with unconvincing radiographic changes for SA from 1-2° and a group of 21 pts (9 women, 12 men) without radiographic changes i.e.SA-0°. The mean age in the first group was 27.28 years (±8,09) (range 25-40 years), while in the second group it was29.35 years (±9.24) (range 28-44 years).
Mean duration in months from the beginning of the disease was 7.27 (±6.12). Patients did not take any previous medication that would modify the course of the disease like sulfasalazine, methotrexate, leflunomide. The samples were collected in the period of one year. In the group of 23 pts with unconvincing radiographic changes for SA we expected to find authentic cases of SA in the early stages of disease.

Including criteria

In this study were included newly diagnosed patients suffering from sacroiliitis, aged 18-45 years, previously untreated.

Excluding criteria

All patients with diseases or conditions that could directly or indirectly affect the results were excluded from this study:

1. Pts with previous historyof diseases of the spleen, thyroid gland, liver damages, renal, hematological, heart, neurological, lung disorders, autoimmune diseases, AIDS, aged <18 years.
2. Pts with diabetes mellitus, acute infections, malignant diseases, febrile conditions.
3. Pts previously treated with antibiotics and salicylatesin the period less than 6 months from the beginning of the study.
4. Pts with hypertension, uric arthritis, urinary infections, SLE, Sjogren syndrome, mixed conective tissue disease, vasculitis.
5. Pts treated with antihypertensive drugs, antidiabetic medications and cardiological drugs.
6. Pts with history of blood transfusions and overweight pts.
7. Pts with medications from the baseline.
8. Pts with acute and chronic renal failure.

All patients voluntarily participated in this study, so the ethic criteria were fulfilled.

Laboratory assessment

For clinical assessment of the basic disease the following laboratory variables were necessary to be taken into account: complete blood count (CBC), differential blood count, reactants of the acute phase, ACPA antibodies, C-reactive protein (CRP), rheumatoid arthritis (RA), erythrocyte sedimentation rate (ESR), alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine ami-

notransferase (ALT), creatine kinase (CK), lactate dehydrogenase (LDH), serum urea, serum creatinine.
CRP was determined with agglutination test (Latex CRP test) (BioSystemS.A. reagent&instruments Costa Brava 30, Barcelona (Spain). Reference values for CRP in serum were <6 mg/L.
RF was determined with agglutination test (Latex CRP test) (BioSystemS.A. reagent&instruments Costa Brava 30, Barcelona (Spain). Reference values for RF in serum were < 30 IU/ml.
For ESR quantitative Westergren.test was used. Reference values for men were 7-8 mm, for women 11-16 mm.
ACPA antibody was determined with the semi-quantitative/qualitative ELISA method, from the manufacturer Dia-stat™ (Axis-Shield Diagnostic), based upon detection of IgG antibodies in human serum/plasma directed towards synthetic cyclic citrullinated peptides that comprise modified arginine residua. Calculation and interpretation of the results for the quantitative protocol was estimated from the absorbent value (optic density) from positive and negative control, for every sample.

Absorbent value	**Interpretation of the results**
<0.95	negative
≥0.95≤1.0	Borderlinevalue
>1.0	positive

Statistical analysis

For testing the significance of differences between two arithmetic means, i.e. proportions in comparison of the values of certain numerical parameters between two groups Wilcoxon-matchedtestfor independent samples was used. Pvalue between 0.05 and 0.1 was considered statistically significant. Data processing was made with the statistical package Statistica, v.7.0

Results

In the group with 21 pts with SA 1 patient showed presence of ACPA antibodies, while RF was not found in any patient. In the group withsacroiliitis none of the patients was ACPA positive, while 1 patient was RF positive (Table 1).

Table 1. ACPA antibodies in spondylitis ankylosans and sacroiliitis

	Spondylitis ankylosans Group N°21 *Positive / Negative*	**Sacroiliitis GroupN° 23** *Positive / Negative*
ACPA+ ≥ 1,26	1/21	0/23
RF +30≥IU/ml	0/21	1/22
CRP +12 ≥ mg/L	16/5	7/16
ESR + ≥16	18/3	15/8

1. There was a statistical correlation using Wilcoxon-matched testbetween ACPA in SA and SI forp <0.05 (p=0.01). In the group with SA there was a statistical correlation between ACPA and RF for p<0.05 (p=0.00), ACPA and CRP (p=0.00).
2. There was no statistical correlation using Wilcoxon-matched testbetween ACPA in SA and age, disease duration in months, RF and CRP in the same group for p<0.05 (ACPA*versus* age p=0.04; ACPA *versus* disease duration in months, p=0.07, ACPA *versus* RF p=0.02, ACPA *versus* CRP, p=0.05 (Figure 1).

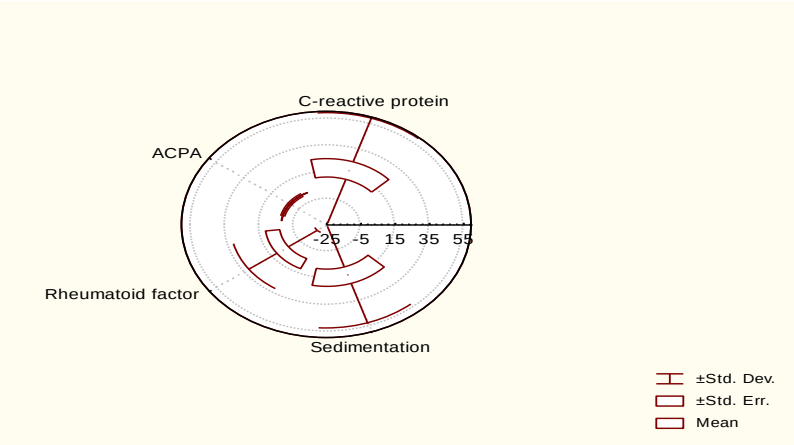

Fig. 1. Distribution of ACPA, RF and CRP in SI group

Discussion

According to the concept of the European study spondyloarthropathy group-ESSG (1991), the leading inclusion criterion is presence of spondylitis or oligoarthritis [1-7]. If this criterion is fulfilled follow: 1. Positive family history; 2. Dermatological changes such as psoriasis vulgaris; 3. Data for colitis or similar diseases (Crohn disease, Whipple disease); 4. Urethritis or cervicitis; 5. Diarrhea; 6. Alternate femoral pain (sacral); 7. Enthesopathy; 8. Radiological prove forsacroiliitis.
If the patients fulfill this clinical-diagnostic mosaic there is a possibility for "overlap" syndrome i.e. transition from one into other spondyloarthropathy.
This basic concept in 1995 was accepted by the international expert group, formally for study of SA, later renamed ASAS (Assessment of SpondyloArthritis International Society) orInternational group for estimation of spondyloarthritis. It is obvious that the term spondyloarthritis prevail over the term SpA, but time will show whether this will remain so.
In the last decade the international ASAS group (Germany, France, Netherlands, Mexico and Canada) supported by the bodies of EULAR (European Rheumatology Association) took a leading role in sublimation of all new knowledge in the field of SpA. Although main targets are in better definition of SA as a prototype or synonym for the group of SpA, of no less importance is the research of undefined SpA.
There was a try to reevaluate the current qualification criteria for diagnosis of SA and other SpA. A special accent was put on defining the inflammatory pain in the lumbar region and its distinction from mechanical pain in the same region. It would be the "key" in the detection of the early forms of SA [8-14].
Because the laboratory findings, including determination of the antigen HLA-B27, have not crucial diagnostic significance, the focus is made on the novel "imaging" techniques, among them nuclear magnetic resonance (MRI) has a dominant place.
The group Bathfrom Great Britain in their epidemiologic and clinical research in the period 1994-98included one series of 5 questionnaires-indexes for SA, referring the follow-up of the disease activity, functional capacity, radiographic progression and the effect of applied therapy. The validity of these questionnaires was proved by several authors, but their application is not yet widely accepted. They are not used in routine examination, and also not used in our country [15-21].
Similar tries and modifications of Bath indexes were made recently the ASAS group in terms of follow-up the SA activity, and especially in the management of therapy and follow-up of qualitative and quantitative aspect. This especially relates to the follow-up of the effects of biological therapy in SA as a turning point to the present insight that the disease is incurable and has its own natural course, upon which it is not possible to interfere (Figure 2, 3 and 4).

Fig. 2. Normal sacroiliac joints

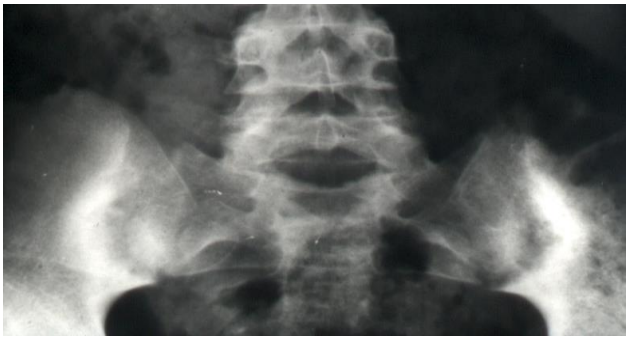

Fig. 3. Bilateral sacroiliitis

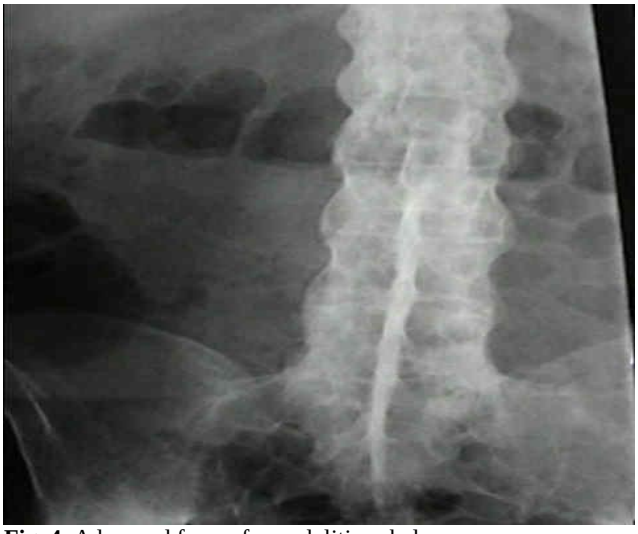

Fig. 4. Advanced form of spondylitis ankylosans

With this sophisticated therapy patients would have better control, stabilization of the process and stopping the disease in long term. All the new recommendations proposed by the experts ofthe ASAS group throw new light in the study of SpA as a significant segment in rheumatology, but time will show how wide will be the consensus for their acceptance/ application.

Conclusion

The fact that the prevalence of SpA is approximately 1% in common population with tendency to increase, shows the focus of interest towards this group. It affects mostly the young active population between 20-40 years of age with important implications in the functional capacity, working capacity and quality of life. Therefore, better knowledge of SpAis of crucial importance as well as the useof contemporary diagnostic and therapeutic approach.

Conflict of interest statement. None declared.

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Original article

ACR20 AND ACR50 CRITERIA FOR THE ASSESSMENT OF TREATMENT RESPONSE IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH METHOTREXATE

ACR20 И ACR50 КРИТЕРИУМИ ЗА ПРОЦЕНКА НА ТЕРАПИСКИ ОДГОВОР ОД МЕТОТРЕКСАТ КАЈ ПАЦИЕНТИ СО РЕВМАТОИДЕН АРТРИТИС

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Abstract

Introduction. Multiple comparative studies have assessed the therapeutic effect of methotrexate (MTX) and have shown that it is the leading disease modifying anti-rheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA). A quantitative appraisal of the therapeutic response of this drug in a set period of time is of great importance.

Aim. To make an assessment of the therapeutic response to MTX, by using the American College of Rheumatologists (ACR), ACR20 and ACR50 criteria, for a fixed time period, in patients with rheumatoid arthritis and long disease evolution.

Methods. In this prospective study we examined 60 patients with RA, of which 30 with disease evolution less than one year (average disease duration 5.1+/-2.8 months, 2-11 months), and 30 with disease duration over 5 years (average disease duration 7.9+/-1.8 years, 5-12 years). They were treated with an average dose of 7.5mg MTX weekly and non-steroid anti-inflammatory drugs (NSAID) as needed. In patients with early RA, MTX was used for the first time. At baseline all patients had active disease. ACR20 and ACR50 were assessed in all patients for the duration of the study.

Results. After one year 26 (86.7%) of patients with early RA had satisfied ACR20 criteria compared to 18 (62.1%) of the patients with late arthritis. After two years this changed to 25 (83.3%) *vs*. 20 (69%) patients, respectively. ACR50 criteria after one year of treatment were satisfied in 12 (40%) patients with early arthritis and 8 (27.6%) with late arthritis, over 5 years of disease evolution. After two years data showed 21 (70%) *vs*. 10 (34.5%) patients, respectively.

Conclusion. Early application of MTX in patients with arthritis allows for significantly better improvement in patients with RA compared to the use of the same treatment in those with a longer evolution of the disease.

Keywords: rheumatoid arthritis; methotrexate, ACR20 criteria, ACR50 citeria

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Апстракт

Вовед. Компаративни студии кои го проценуваат терапискиот ефект од Метотрексат (MTX) укажуваат дека е водечки лек од групата на ДМАРД слекови (Disease Modifying Anti Rheumatic Drugs) во лекување на Ревматоидниот артритис (РА). Квантитативна процена на тераписки одговор во одреден временски период е од значење за процена на ефект од лекување.

Цел. Процена на тераписки одговор од MTX, со ACR20, ACR50 критериуми во одреден временски период кај пациенти со ран РА vs пациенти со долга еволуција на болеста.

Методи. Во проспективна студија беа проследени 60испитаника со РА од кои 30 со ран РА со еволуција до 1 год. со просечно времетраење од 5,1± 2,8 месеци (2 мес-11 мес) и 30 со еволуција на РА над 5 години со просечно времетраење од 7,9± 1,8 год. (5 год-12 год.) лекувани со средна доза на MTX од 7,5 мг. и НСАИЛ. Кај пациенти со ран РА, MTX беше воведен прв пат. Во 0 време сите испитаници имаа активен РА. Кај секој пациент беа анализирани ACR20, ACR50 критериуми.

Резултати. По 1 год. од лекувањето 26(86.7%) испитаници со ран РА ги исполнија ACR20 критериумите vs 18(62.1%) со РА над 5 години а по 2 год. 25 (83.3%) vs 20(69.0%). ACR50 критериумите по 1 год. ги исполнија 12(40%) испитаници со ран РА vs 8 (27.6%) со РА над 5 години, а по 2 год. 21(70%) vs 10(34.5%).

Заклучок. Рано воведување на MTX кај ран РА овозможува поголемо % подобрување од лекувањето vs

подоцнежно воведување на MTX при долга еволуција на болеста.

Клучни зборови: ревматоиден артритис, метотрексат, ACR20 критериуми, ACR50 критериуми

Introduction

Early treatment in patients with RA is of great importance in order to achieve quick and maximal results [1-3]. However, it is also very important to choose the right drug regarding the level of disease activity and progression in the individual patient [4-6]. Disease modifying anti-rheumatic drugs (DMARDs) not only reduce pain in patients, but they inhibit the inflammatory process and prevent joint damage, thus modifying the course of the disease. By preventing structural damage of the joints, it prevents functional damage and disability [7]. Methotrexate is the leading DMARD used in the treatment of patients with RA. Comparative studies of the effectiveness of MTX as monotherapy, or in combination with biologic DMARDs, as well as comparison of MTX *vs.* other synthetic DMARDs show that this drug is still essential in the treatment of this disease [8,9]. A quantitative assessment of the therapeutic response of MTX use in patients with RA is of use in the planning of long-term treatment for these patients. The American College of Rheumatology (ACR) criteria are used for the assessment of the effectiveness of treatment. ACR20 detect minimal significant changes in inflammatory synovitis [10-12].

Aim

The aim of this study wasto quantifiably assess the therapeutic response of patients with early RA compared to those with a longer disease evolution, treated with MTX, by using the ACR20 and ACR50 criteria in a period of two years.

Material and methods

In this prospective study conducted at the University Clinic forRheumatology we examined 60 patients with RA, of which 30 with disease evolution less than one year (average disease duration 5.1+/-2.8 months, 2-11 months), and 30 with disease duration over 5 years (average disease duration 7.9+/-1.8 years, 5-12 years). They were treated with an average dose of 7.5mg MTX weekly and non-steroid anti-inflammatory drugs (NSAID) as needed. In patients with early RA, MTX was used for the first time. At baseline all patients had active disease. ACR20 and ACR50 were assessed in all patients at baseline, at year one and year two. We examined the number of swollen and tender joints (out of 28). Any positive finding was scored with 1, and non-involved joints were scored 0. Thus, score for tender and swollen joins was between 0 and 28 (Figure 1). Sedimentation rate was also assessed, by using Westegren's method with reference values of 4/10; modified health assessment questionnaire (MHAQ) was used to assess the condition/functional disability/ functional capacity. This questionnaire has questions regarding 8 areas of everyday life, scored 0-3 points. Cumulative score is 21 and it is divided by 8 to give the final HAQ score. Likert's scale was used to assess disease activity by the doctor, scored from 1 to 5: asymptomatic, mild, moderate, severe and very severe. ACR20 criteria assess ≥20% improvement in erythrocyte sedimentation rate (ESR), number of swollen (SJC) and tender (TJC) joints, HAQ and Likert scores. ACR50 assess ≥50% improvement in the respective variables.

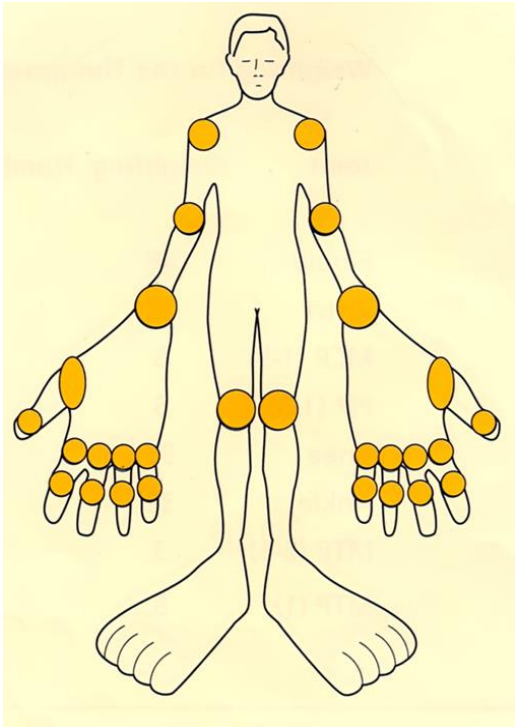

Fig. 1. Joints assessed, tender and swollen

Statistical methods

We used the following statistical methods:
Analysis of numerical data was done with SPSS v.19, Chicago, IL, USA, by using descriptive statistics (average values, standard deviation).
Comparative statistics wereconducted with X2-test, significance between the two groups wasassessed with the Student's t-test. Testing of significance between the two means (dependent samples) wasdone with Wilcoxon Matched Pairs Test.

Results

At baseline the patients with early RA had tender and swollen joints on examination, ESR, functional capacity

and disease activity according to the doctor (Table 1). At year 1 and 2, we registered a lower number of tender and swollen joints, as well as lower ESR and an improvement in functional capacity and disease activity (Table 1).

At one year of MTX treatment, 26(86.7%) patients fulfilled ACR20 criteria, and at two years 25(83.3%) had achieved the same (Table 2). Regarding ACR50, data showed 12(40%) and 21(70%) fulfilled these criteria, respectively.

Table 1. Assessment of disease activity in patients with RA with disease evolution less than 1 year (early arthritis)

Time interval	TJC	SJC	ESR	MHAQ	Likert scale
Baseline	12.4±5.1	6.9±2.8	59.9±27.7	1.396±0.966	4.3±0.568
Yearone	5.1±4.6	2.5±1.6	31.4±17.4	0.354±0.362	2.9±0.432
Yeartwo	2.9±2.7	1.9±2.2	25.0±11.6	0.229±0.334	2.1±0.536

Table 2. Number of patients that achieved ACR20 and ACR 50 criteria, set of five variables

ACR20	TJC	SJC	MHAQ	ESR	Likert scale	No. patients
Year-one	26	26	29	27	26	26 (86.7%)
Year-two	29	27	29	25	25	25 (83.3%)
ACR50	TJC	SJC	MHAG	ESR	Likert scale	No. patients
Yearone	22	20	25	12	12	12(40%)
Yeartwo	27	24	28	21	21	21(70%)

The patients with disease evolution over 5 years, at baseline had a higher number of swollen and tender joints, out of 28 assessed, higher ESR, lower functional capacity and higher disease activity compared to the early arthritis group. At year one and year two, all assessed elements showed improvement (Table 3). However, even after 2 years the patients in the late arthritis group still had higher SJC, TJC, ESR, disease activity, as well as lower functional capacity compared to those in the early arthritis group.

Table 3. Assessment of disease activity in patients with disease evolution over 5 years

Visit	TJC	SJC	ESR	MHAQ	Likert scale
Baseline	13.6±5.2	9.2±3.2	60.4±16.9	1.491±0.727	4.4±0.448
Yearone	8.5 ± 5.1	5.4±3.8	43.3±20.5	0.810±0.441	3.7±0.532
Yeartwo	7.9±5.6	4.9±3.5	36.6±21.1	0.732±0.391	3.1±0.378

Table 4. Number of patients reaching ACR20 and ACR50 criteria, late arthritis group

ACR20	TJC	SJC	MHAQ	ESR	Likert scale	No. patients
Year-one	25	18	19	24	18	18 (62.1%)
Year-two	20	23	22	23	20	20 (69%)
ACR50	TJC	SJC	MHAQ	ESR	Likert scale	No. patients
Yearone	15	14	12	8	12	8(27.6%)
Yeartwo	10	17	11	14	11	10(34.5%)

At year-one with MTX treatment, 18(62.1%) patients with disease evolution over 5 years achieved ACR20, and at yeartwo this was achieved by 20(69%) patients. Regarding ACR50 in this group, this was achieved by 8(27.6%) and 10(34.5%) patients, respectively (Table 4).

Discussion

Treatment with disease modifying anti-rheumatic drugs (DMARDs) has a significant advantage compared to more conservative treatments. Modern rheumatologists call for early diagnosis and aggressive treatment of patients with RA. This caused many clinicians to reassess the advances to date, such as the validity of anti-CCP antibodies, practical use of RF testing, as well as developing new methods for early diagnosis and effective treatment ofpatients with early RA [13].

In the last few years the definition of early RA has changed, so that it now usually refers to disease of no more than 3 months from onset of initial symptoms. The goal is to aggressively treat these patients in order to slow or stop disease progression, achieve low disease activity or remission, keep functional capacity and stop/slow joint damage [14-16].

Besides treating early and aggressively, it is crucial to choose the best DMARD in order to achieve a sufficient therapeutic response. Most rheumatologists believe that MTX is the drug of choice for continuing treatment of patients with RA [14,17], and that it is superior to the other synthetic DMARDs.

It is very important to identify the specific factors which could be negative predictive factors in the treatment of these patients. Thus, an assessment of the markers present at disease onset could be used to predict therapeutic response and influence the choice of the prescribed drug [2,5,6]. Long disease duration, previous DMARD use and low functional capacity are negative predictive factors for treatment response [17,18]. In this study we have confirmed the conclusions of previous studies that the use of MTX in patients with RA has satisfactory effects. We used ACR20 and ACR50 criteria [19] to assess the therapeutic effect of MTX on patients with early and late RA and showed that more patients with early RA achieved these criteria. These patients had lower TJC and SJC compared to patients with disease evolution over 5 years. The patients with early arthritis (disease duration less than one year) had better functional index as assessed by MHAQ. Based on the quantitative assessment of tender and swollen joints, acute phase reactants (ESR), functional status (MHAQ) and Likert scale for global evaluation of disease activity in patients with different duration of disease, actively treated with MTX, we can conclude that early treatment with immunomodulation such as methotrexate shows rapid and adequate treatment response, and preserves functional capacity. This is more pronounced in the early arthritis group compared to the patients with disease duration over 5 years [20].
ACR criteria allow for objective quantitative evaluation of treatment response.

Conclusion

Early initiation of MTX in patients with early RA leads to a rapid treatment response and greater improvement in comparison to the use of MTX in patients with longer disease evolution.

Conflict of interest statement. None declared.

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Original article

RHINOMANOMETRY AS A METHOD FOR OBJECTIFICATION OF NASAL AIR RESISTANCE IN SELECTING PATIENTS FOR SEPTORHINOPLASTY

РИНОМАНОМЕТРИЈАТА КАКО МЕТОД ЗА ОБЈЕКТИВИЗАЦИЈА НА НАЗАЛНА ВОЗДУШНА РЕЗИСТЕНЦИЈА ПРИ ИЗБОР НА ПАЦИЕНТИ ЗА СЕПТОРИНОПЛАСТИКА

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Abstract

Aim of the study. To objectify the nasal air resistance (nasal obstruction) using rhinomanometry while selecting patients for septorhinoplasty.
Methods. This is a prospective, non-randomized study which compriseda totalof 100 patients experiencing deviations of the nasal septum (*deviatioseptinasi*) aloneor along with deformities of the nasal pyramid: rhinokyphosis, rhinoscoliosis, rhinolordosis ("saddle nose"), and "functional tension nose". The examined patients were added to the list for surgical septo/rhinoplasty procedures performed at the ENT Clinic at the University Hospital Center in Skopje and the General Hospital "Remedika", during the period of 2014-2019. The rhinomanometry examinations were performed at the General Hospital "Remedika" in Skopje.The examined groups were divided according to several parameters.Based on the degree of nasal obstruction, patients were divided into 3 groups:Group IA had a severe degree of nasal obstruction (severe degree of nasal resistance); Group IB had a moderate degree of nasal obstruction (moderate degree of nasal resistance); Group II had a mild degree of nasal obstruction (mild degree of nasal resistance), and this group was clinically monitored for a year when a decision was made onperforming a surgical intervention.
Results. Despite dividing patients into three groups and the one-year follow-uppeiodofpatients with a mild degree of nasal obstruction, all patients underwent septoplasty. The results obtained enabled us to differentiate and grouppatients who were truly in need of septo/rhinoplasty and patients whowere to be monitored and treated with medication.
Conclusion. Rhinomanometry allows classification of patients forurgent intervention according to the results on the degree of nasal obstruction as well as the degree of nasal symptomatology.

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Keywords: nasal septal deviation, nasal air resistence, rhinometry, rhino/septoplasty

Апстракт

Цел на студијата. Да се објективизира назалната воздушна резистенција (назална опструкција) преку риномanометрија при избор на пациенти за септоринопластика.
Методи. Авторот истакнува дека ова е проспективна и нерандомизирана студија при што е спроведена статистичка анализа на вкупно 100 пациенти со девијација на носната преграда (deviatio septi nasi) одделно или во склоп со деформитети на носната пирамида: ринокифоза, риносколиоза, ринолордоза (седлест нос), и „долг нос" (анг. functional tension nose). Испитуваните пациенти беа ставени на оперативна листа за септоринопластика на ЈЗУ Клиника во Универзитетскиот клинички центар во Скопје и Општата болница „Ремедика" во периодот од 2014 до 2019 година. Риномanометриските испитувања се вршеа во Општата болница „Ремедика" во Скопје. Испитуваните групи беа поделени според неколку параметри: според степенот на назална опструкција, пациентите беа поделени во 3 групи: група IA-пациенти со тежок степен на назална опструкција (тежок степен на назална резистенција), група IB-пациенти со среден степен на назална опструкција (среден степен на назална резистенција), Група II-пациенти со лесен степен на назална опструкција (лесен степен на назална резистенција), а кои се опсервирани клинички една година, по што е донесена одлука за оперативна интервенција.
Резултати. И покрај поделбата на три групи и едногодишното чекање на пациентите со лесен степен на назална опструкција кај сите пациенти беше реализирана септопластика. Резултатите ни овозможија да направивме дистинкција и ги групираме пациентите на кои навистина им е потребна септоринопластика и пациентите што треба да бидат следени или третирани медикаментозно.

Заклучок. Риноманометријата ни овозможува да ги класифицираме пациентите по итност на интервенцијата спрема добиените резултати за степенот на назалната опструкција, како и степенот на назалната симптоматологија.

Клучни зборови: назална септална девијација, воздушна назална опструкција, ринометрија, рино/септопластика

Introduction

Nasal obstruction is one of the most common symptoms of diseases of the nose and paranasal sinuses. Most of the cases when patients are referred to ENT clinics or specifically rhinology are attributable to this nasal obstruction. According to Wengraf *et al*., 15% of patients treated at ENT clinics across Great Britain presented with nasal obstruction as the predominant symptom. In a Finnish study conducted by Vainio-Matiila, out of 200 randomly selected patients, 33% presented with symptoms of nasal obstruction [1-3]. The causes of nasal obstruction include allergic rhinitis, nasal polyposis as well as vasomotor rhinitis that are the most common causes with concurrent prevalence of mucosal inflammation. Deviation of the nasal septum is the prevalent structural deformity leading to nasal obstruction. In the study realized by Vainio-Mattila, 26% of the patients studied presented with a clinically significant deformity of the nasal septum. There are many causesfor deviations of the nasal septum, but they can also be asymptomatic. In our practice, patients undergoing septoplasty suffer from persistent nasal obstruction, rhinorrhea, recurrent sinusitis, nasal pain as well as frequent epistaxis as symptoms of nasal pathology. Mild deviations of the nasal septum in the frontal portions of the nasal septum near the nasal valves cause clear symptoms of nasal obstruction of weak-intensity, unlike severe deviations in the hind bony, nasal septum particles which cause a severe degree of nasal obstruction [4].
On the other hand, the results obtained from objective measurements in patients are significant as opposed to the subjective symptoms they often complain about [5-7]. There are many publications on the role of rhinomanometry in objectification of the degree of nasal obstructtion, but all of them are more scientifically-based, with very few being done on purely clinical trials related to surgicaltechniques. Our study is one of the latter.
We present the results of the rhinomanometry performed, a method used to determine the degree and severity of nasal obstruction [8].

Material and methods

At the University Ear, Nose and Throat Clinic and the Private General Hospital “Remedika”, a total of 100 patients-candidates for septorhinoplasty were studied in the period from 2014 to 2019. The degree of nasal obstruction in all patients was assessed through objective rhinomanometric measurements. Active frontal rhinometry was the method of choice.
According to the degree of nasal obstruction, the patients were divided into 3 groups:
Group IA were patients with a severe degree of nasal obstruction (severe degree of nasal resistance): Group IB were patients with a moderate degree of nasal obstruction (moderate degree of nasal resistance): Group II were patients with a mild degree of nasal obstruction (mild degree of nasal resistance), clinically monitored for a yearwhen a decision was made on perfroming a surgical intervention.After the surgical intervention, a survey was conducted to find out how satisfied the patients were with the correction performed, whereby patients were offered 5 scores, i.e. modalities: 1-very satisfied, 2-satisfied, 3-undecided, 4-dissatisfied and 5-extremely dissatisfied.
Over a one-year period, the patients had check-ups and were monitored for persistent subjective symptoms following the surgical intervention, whether they continued to use any of the medications for reducing nasal obstruction such as topical nasal steroids (Table 1).

Table 1. Division of patients-candidates for surgical intervention based on rhinomanometric findings

	N	%
Underwent surgical intervention	110	78.57
Check-ups (1 year)	30	21.43
Total	140	100

Results

All patientsbased on theirrhinomanometric findings were divided into three groups:
Group IA patients with a severe degree of nasal obstruction (severe degree of nasal resistance) included 55 or 39.3% of candidates for septorhinoplasty.
Group IB included the same number of subjects, 55 patients with a moderate degree of nasal obstruction (moderate degree of nasal resistance) or 39.3%.
Group II included 30 (21.4%) of patientswith a mild degree of nasal obstruction (mild degree of nasal resistance) who were clinically monitored for a year when a decision was made on performing a surgical intervention (Table 2).

Table 2. Distribution of patients based on obtained rhinomanometric findings

Degree of nasal obstruction	N	%
Group IA-severe degree	55	39.28
Group IB-moderate degree or other specific indications for nasal obstruction	55	39.28
Group II-mild degree	30	21.44
Total	140	100

The group of patients with severe degree of nasal obstruction consistedpredominantly of 40(72.7%) subjects with unilateral nasal air resistance of the nasal airflow of the *cavumnasi* greater than 200 Pal/s. The remaining 10(18.2%) subjects presented with total nasal resistance greater than 90 Pal/s (Table 3).

Table 3. Distribution of patients with severe degree of nasal obstruction

Severe degree - Objective nasal obstruction	N	%
Unilateral resistance >200Pa(1/s)	40	72.72
Total nasal resistance >90(Pa(1/s)	10	18.18
Total	55	100

Table 4 and Figure 4 show the distribution of indications for nasal obstruction in patients with severe degree of nasal air resistance. The deviations of the nasal septum with severe deformity of the nasal septum were reported as an indication in the largest number and percentage of patients of the group with severe degree of nasal obstruction - 20 patients (36.4%).

Table 4. Distribution of indications for nasal obstruction in patients with severe degree of nasal air obstruction

Severe degree - specific indications for nasal obstruction	N	%
Deviated septum with severe nasal septal deformities	20	36.36
Facial or nasal pain associated with deformity of the nasal pyramid or deviated septum	10	18.18
Septum deviation compressing the middle nasal concha and the osteomeatal complex	15	27.28
Septal pathology assessed from objective rhinoscopic findings treated conservativelywith medications for over 4 months, without improvement	10	18.18
Total	55	100

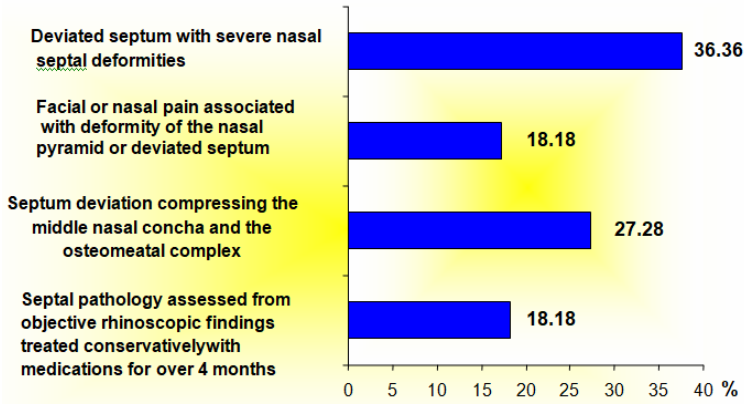

Fig. 4. Distribution of indications for nasal obstruction in patients with severe degree of nasal air obstruction

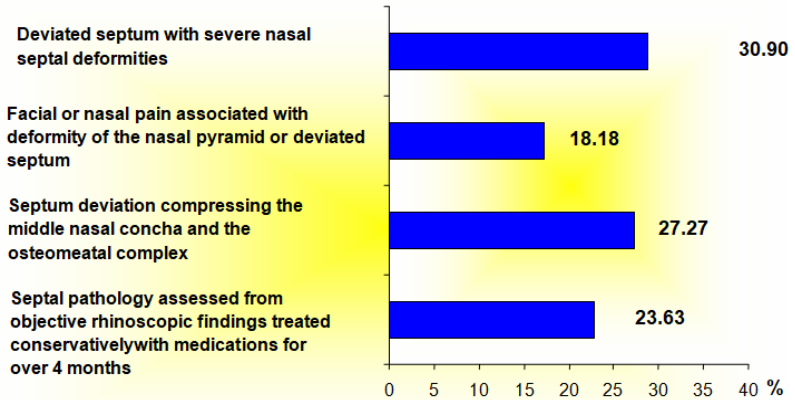

Fig. 5. Distribution of indications for nasal obstruction in patients with moderate degree of nasal air obstruction

The distribution of indications for nasal obstruction in patients with moderate degree of nasal air resistance is shown in Figure 5.

Group II consisted of 30 (21.4%) patients with a mild degree of nasal resistane (mild septum deviation). Even though this group of patients was monitored for one year, without medications or the use of nasal topical steroids, the nasal resistencepersisted, thus the recommenddation of septoplasty was unavoidable. Eighteen patients of this group presented with a mild degree of nasal resistance without any signs of nasal symptomatology, and hence there was no need for further treatment.

Sevenpatients underwent septoplastybecause they presented with symptoms of sinus pain or facial pain as well as sinusitis due to obvious deviations of the nasal septum. They received treatment with topical corticosteroids.

Symptoms in 5 patients of this group, in addition to nasal obstruction, included predominantly a subsequent hypertrophy and inflammation of the nasal mucosa followed by rhinorrhea, following the surgical intervention that was unavoidable in their case. This group also received treatment with topical corticosteroids. After the surgical intervention, the patients no longer had any symptoms of this type (Table 6).

Table 6. Distribution of indications for nasal obstruction in patients with mild degree of nasal air obstruction

Mild degree of nasal obstruction	N	%
Without symptoms	18	60.0
With sinus and facial pain	7	23.33
With hyperthropy and inflammation of concha nasalis	5	16.67
Total	30	100

Discussion

Our study hasshownthat rhinomanometry as an objective method hasa clinical benefit, and it can be used in clinical trials with patients-candidates for septorhinoplastiy as well as in routine procedures inpatients of this type. Studies of this kind are scarce, and therefore our study has proven that rhinomanometry is useful not only for scientific but also for clinical research [9-11].

In our study the benefit of rhinomanometry is the achievement of an important clinical goal: we have differentiated and grouped patients who really need septorhinoplasty and patients who need to be monitored and treated with medications [12-14].

Furthermore, we have made an indication for septoplasty in patients with a mild degree of nasal resistance (mild deviations of the septum) in whom, despite being monitored over a one-year-period, with no medications or nasal topical steroids, the nasal resistance persisted and consequently the recommendation to undergo septoplasty was unavoidable [15-17].

Our study is similar to thatof Dommerby*et al.*, done exclusively on postoperative results of patients with severe degree of nasal resistance (obstruction) as well as to the studyof Bohlin and Dahlqvist who confirmed that up to 85% of patients were satisfied with the postoperative results even 10 years after the surgical intervention [18-20].

Our study has confirmed the hypothesis that in some patients with nasal obstruction with predominant subsequent hypertrophy and inflammation of the nasal mucosa in addition to the nasal septum deviation, accompanied with rhinorrhea, after the surgical intervention there are no longer any symptoms of this type.

This was the case with patients of the II group where the surgical intervention was postponed for a year after a one-year follow-up. [21-23]

These findings suggest that a good rhinoscopic evaluation is needed preoperatively and the results obtained from rhinomanometry before and after applying a decongestive should be closely examined so as to determine the state of edema of the nasal mucosa as well the degree of nasal obstruction it causes.

Conclusion

Our study has allowed us to make a timely and accurate decision on the surgical intervention of the septum as well as the method by which it would be performed. Rhinomanometry allows us to classify patients by urgency of intervention according to the results obtained on the degree of nasal obstruction as well as the degree of nasal symtpomatology. Around 15% of patients in our study were not satisfied since they did not undergo surgical intervention immediately but after a one-year follow-upperiod. This is a result of our belief that surgical intervention of the nasal concha or septoplasty could be avoided by monitoring their condition or by using medications (such as nasal corticosteroids).

Conflict of interest statement. None declared.

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ММР

Case report

PATIENT WITH ANCYLOSING SPONDYLITIS - BECHTEREW'S DISEASE AND FRACTURE OF C4, C5 WITH PRIMARY QUADRIPLEGIA: CASE REPORT

ПАЦИЕНТ СО АНКИЛОЗИРАЧКИ СПОНДИЛИТ (M. BECHTEREW) И СКРШЕНИЦА НА ЧЕТВРТИ И ПЕТТИ ВРАТЕН ПРШЛЕН СО ПРИМАРНА КВАДРИПЛЕГИЈА - ПРИКАЗ НА СЛУЧАЈ

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Abstract

The ankylosing spine is usually prone to fracture after minor trauma. Our patient fell on ice in the skiing center Popova Shapka and he immediately felt severe pain in the cervical spine without neurological deficit in the first moments after injury. He was transported rapidly with a solid immobilization of the cervical spine on a special table to the University Clinic for Traumatology in Skopje. When he arrived in Skopje we detected a complete quadriplegia, and he was hospitalized at Trauma department. He was admitted at Intensive care unit where RTG investigation, CT-scan and MRI of the cervical spine were performed. We found a complete disruption on level C4, C5 with soft tissue compression on spinal canal from the posterior side. We prepared the patient for a posterior approach since in such cases the anterior approach is not possible because of the stiffness of the cervical spine. Also, the compression was posterior, and we used a special elastic cannula for intubation. We performed a decompression and posterior fixation. Synapsis system two levels above and two levels below was used. In such patients with ankylosing spondylitis -Bechterew's disease and fracture of cervical spine we can recommend posterior approach because of the stiffness of the cervical spine and limited chances for performing the anterior approach. We can also recommend decompression combined with aposterior fixation. Anesthesiologists have to use flexible cannulafor intubation. Chances for neurological recovery are bigger if decompression is immediately done.

Keywords: ankylosing spondylitis, Bechterew's disease, fracture, CIV, CV, primary quadriplegia

Апстракт

Анкилозирачкиот ’рбетен столб, вообичаено е склон кон скршеници по минорна траума, и како што е и вообичаено, нашиот пациент паѓа на мраз во скијачкиот центар Попова Шапка и се здобива со голема болка во пределот на вратниот ’рбет веднаш по повредата, но без невролошки испади во првиот момент по повредата. Тој е брзо транспортиран со солидна имобилизација на вратниот ’рбет на специјална даска до Клиниката за ТОАРИЛУЦ во Скопје. Кога пристигна во Скопје ние констатиравме комплетна квадриплегија и тој беше хоспитализиран на трауматолошкиот оддел со таа дијагноза. Пациентот беше примен во единицата за интензивна нега и направени му беа вообичаени рендген инвестигации: КТ и МРИ на вратниот ’рбет. Најдовме комплетна дисрупција на нивото CIV, CV, со мекоткивна компресија на спиналниот канал од задната страна. Пациентот беше подготвен за заден пристап, бидејќи кај вакви пациенти предниот пристап не може да се изведе поради вкочанетоста на цервикалниот дел од ’рбетниот столб, а исто така, и компресијата беше од задната страна, и употребивме специјална еластична канила за интубација. Направивме декомпресија и задна фиксација. Употребен беше SYNAPSIS систем на две нивоа, над и под местото на компресија. Кај вакви пациенти со анкилозирачки спондилит-Бехтерев и скршеница на вратниот дел од ’рбетниот столб, ние го препорачуваме задниот пристап, поради вкочанетоста на вратниот дел од ’рбетниот столб и ограничените можности за изведување на предниот пристап.

Исто така препорачуваме декомпресија, комбинирана со задна фиксација. Анестезиолозите треба да користат флексибилна канила за интубација на вакви пациенти. Шансите за невролошко опоравување се поголеми доколку декомпресијата е веднаш направена.

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Клучни зборови: Анкилозирачки спондилит-Бехтерев, фрактура на CIV,CV, примарна квадриплегија.

Introduction

The ankylosing spine is usually prone to fracture after minor trauma. Our patient fell on ice in the skiing center Popova Shapka and he immediately felt severe pain in the cervical spine without neurological deficit in the first moments after injury. He was transported rapidly with a solid immobilization of the cervical spine on a special table to the University Clinic for Traumatology in Skopje. When he arrived in Skopje we detected a complete quadriplegia, and he was hospitalized at the Trauma department with such a diagnosis.

Several authors have shown that patients with ankylosing spondylitis have a higher fracture risk compared to unaffected individuals. In these patients, fusion of sacroiliac joints and spine occurs due to chronic inflammation followed by a generalized stiffness of the spine. This disease is very rare and has a prevalence of 0.1-1.4% and usually affects males younger than 30 years, but our patient was 67 years old.

Case report

He was admitted at the Intensive care unit where RTG investigation, CT-scan and MRI of the cervical spine wereperformed. We found a complete disruption on level C4, C5 with soft tissue compression on spinal canal from the posterior side. Fractures in ankylosed spine are often unstable due to the ossification of supportive and elastic soft tissues and often they can cause neurologic deficit as a result of dislocation. Neurologic deficit after fracture is a well-known and feared complication in ankylosing spondylitis, therefore these patients should be handled with a great care even and especially when a fracture is suspected. We found a complete motor deficit in both legs and only limited movements in elbows and humeroscapular region. Sensitive sensations below mammillae line were absent. Babinski reflex was positive on both legs. Due to the spinal shock he was bradycardic.

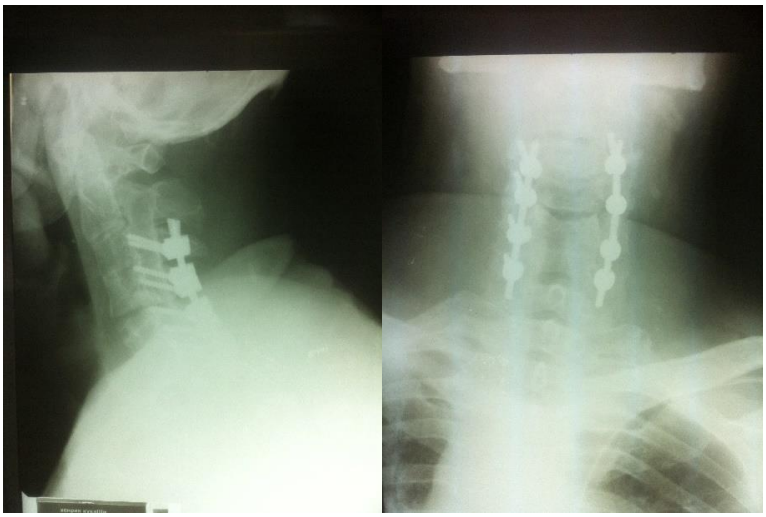
We prepared the patient for a posterior approach sincein such cases the anterior approach is not possible because of the stiffness of the cervical spine. Also, the compression was posterior, and we used a special elastic

A B

Fig. 1a. X ray: **A, B** - preoperative CT;

C D E F

Fig. 1b. C, D, E, F - preoperative MRI;



G H

Fig. 1c. G, H - postoperative X ray

cannula for intubation. We performed a decompression and posterior fixation.

After the operation we made a control MRI for visualization of the performed decompression. The patient was given thromboprophylaxis with LMWH according to ACCP. Also, he received cortical therapy according NASCIS II scale combined with high doses of gastro protective medications. Postoperatively, the patient was stable with sufficient breathing; there was no need for respiratory support. After two weeks he was transported to the town where he lived. For one month he had a high temperature of central origin without positive hemoculture (Figure 1a, 1b and 1c).

Discussion

There are uncommon complications of spinal fractures with ankylosing spondylitis described in the literature as aortic dissection, aortic pseudoaneurysm, tracheal rupture and most of them finish lethally, or postoperative wound infection, deep venous thrombosis, pneumonia and respiratory insufficiently. Overall mortality in the posttreatment phase described in the literature is 6.4% [1].

Also, there is a difference between patients surgically treated who have mortality of 4.9% and patients non-surgically treated where mortality is 7.9%. The most frequent cause of death in these patients is pneumonia and respiratory failure.

Conclusion

Patients with ankylosed spine have an increasing risk of fracture even after minor trauma.

Fractures of the ankylosed spine tend to be unstable, because ossified ligaments and surrounding tissue also fracture. An intrinsic unstable fracture configuration may lead to primary and secondary neurological deficit [2].

The clinical outcome of patients fracturing their ankylosing spine is worse compared to the general spine trauma population.

Surgical treatment may be favorable for patients with an ankylosing spine and spinal fracture, as this treatment option may be associated with lower complication and mortality rates and may lead to neurological improvement more frequently [3,4].

In patients with ankylosing spondylitis-Bechterew's disease and fracture of the cervical spine we can recommend a posterior approach due to stiffness of the cervical spine and limited chances for performing the anterior approach. We can also recommend decompression combined with a posterior fixation. Anesthesiologists have to use flexible cannula for intubation [5]. Chances for neurological recovery are higher if decompression is immediately done [6].

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ММР

Case report

DEEP VEIN THROMBOSIS IN A PATIENT WITH GENERALIZED PSORIASIS. THROMBOPHILIC MUTATIONS AND ITS ASSOCIATION WITH PSORIASIS: A CASE REPORT AND LITERATURE REVIEW

ДЛАБОКА ВЕНСКА ТРОМБОЗА КАЈ ПАЦИЕНТ СО ГЕНЕРАЛИЗИРАНА ПСОРИЈАЗА. ТРОМБОФИЛИЈА И НЕЈЗИНАТА АСОЦИЈАЦИЈА СО ПСОРИЈАЗА: ПРИКАЗ НА СЛУЧАЈ И ПРЕГЛЕД НА ЛИТЕРАТУРАТА

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Abstract

Introduction. Psoriasis is a complex immune-mediated disease, associated with cardiovascular risk, hypercoagulability markers and elevated homocysteine. Many observational reports suggest increased incidence of venous thromboembolic events in patients with psoriasis. In this report we present a patient with inherited thrombophilia and chronic diffuse psoriasis complicated with a deep venous thrombosis (DVT).

Case report. We report a case of a 30-year-old white man, referred to the Department of Dermatology for acute deep thrombosis in the left superficial femoral and popliteal vein. The physical examination showed an obese patient, with BMI 34.7 kg/m^2. His waist circumference was 100.5cm. Regarding his social history he is single, reported moderate alcohol use, cigarettes smoking one pack daily over the past 15 years and sedentary lifestyle. His past medical history included HTA. Dermatological history has been positive for plaque psoriasis for more than 12 years. Examination revealed extensive, diffusely distributed psoriatic lesion on the predilection places which covered more than 60% of the body surface. He reported worsening of psoriasis simultaneously with the onset of deep thrombosis. Blood sampling and DNA analysis indicated presence of heterozygosis of factor V Leiden mutation, also Factor XIII V34L, PAI -1 5G/4G and MTHFR A1298C polymerphism, which mutations are associated with increased risk for thromboembolism.

Conclusion. The present case report suggests a relation between chronic psoriasis and risk of venous thromboembolism. All patients with moderate to severe psoriasis should be taken in to consideration for being with a higher risk of venous thromboembolic event and should be managed appropriately.

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Keywords: psoriasis, venous thromboembolism, thrombophilia

АБСТРАКТ

Вовед. Псоријазата е комплексна имуно-посредувана болест, асоцирана со кардиоваскуларен ризик, маркери за хиперкоагулабилност и покачен хомоцистеин. Многу обсервациони студии сугерираат зголемена инциденца на венски тромбемболизам кај пациенти со псоријаза. Во овој приказ на случај презентираме пациент со наследна тромбофилија и хронична дифузна псоријаза комплицирана со длабока венска тромбоза (ДВТ).

Приказ на случај. Презентираме случај на 30-годишен белец, на одделот за дерматологија примен поради акутна длабока венска тромбоза во левата површна феморална и поплитеална вена. Физичкиот преглед покажа-обезен пациент, неговиот индекс на телесна маса (БМИ) изнесува 34,7 kg/m2. Неговиот обем на струкот беше 100,5cm. Во врска со неговата социјална анамнеза тој е самец, пуши една кутија цигари дневно во изминатите 15 години, пријавува умерен внес на алкохол дневно и седечки животен стил. Неговата медицинска историја е позитивна за покачен крвен притисок. Дерматолошката анамнеза е позитивна за плакарна псоријаза која ја има повеќе од 12 години. Испитувањето открило екстензивни, дифузно дистрибуирани псоријатични лезии на предилециони места кои засегнуваат повеќе од 60% на површината на телото. Тој известува за влошување на псоријазата истовремено со појавата на длабокота венска тромбоза. Анализата на ДНК укажува на присуство на хетерозиготност за фактор V Leiden мутацијата, како и за Factor XIII V34L, PAI-1 5G/4G и MTHFR A1298C полиморфизмите, кои мутации се поврзани со зголемен ризик за тромбемболични настани.

Заклучок. Приказот на овој случај укажува на асо

цијација помеѓу хроничната псоријаза и ризикот од венски тромбоемболизам. Сите пациенти со умерена до тешка псоријаза треба да се земе во предвид дека се со повисок ризик од венски тромбоемболизам и соодветно да се третираат.

Клучни зборови: псоријаза, венски тромбоемболизам, тромбофилија

Introduction

Venous thromboembolism (VTE) comprising deep venous thrombosis (DVT) and pulmonary embolism is a common medical problem, which can be predisposed by several medical conditions, for example: trauma, surgery, immobilization or cancer [1]. Recently there have been numerous studies about systemic chronic inflammation as a potential risk factor for VTE [2,3]. The relationship stems from the impact of the chronic inflammation on the aggregation of the platelets, activation of the coagulation cascade, and stimulation of the procoagulant activity of the inflammatory cytokines, decrease of the activity of the anticoagulant and fibrinolytic systems [2,3]. Therefore, some studies suggest that patients with elevated inflammatory markers, for example C-reactive proteins (CRP) and other inflammatory cytokines IL-6, IL-8 and TNF, have an increased risk of VTE [3,4]. This positive association between inflammatory makers and VTE is highly suggestive, but it is unclear whether the inflammation and its inflammatory cytokines are responsible and a causative component of generating a VTE event. In large epidemiologic studies several systemic inflammatory diseases have been linked with increased VTE risk, such as rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, systemic lupus erythematosus [5-8].

Psoriasis is a complex immune-mediated disease, associated with a variety of comorbidities [9]. A worldwide review revealed the prevalence of psoriasis ranging from 0.5-11.4% in adults and 0-1.4% in children [10].

Psoriasis is a chronic T immune-mediated inflammatory disease which activates both Th1 and Th 17 inflammatory pathways. It afflicts not only the skin and joints but involves the endothelium as well, and results in increased IL6 and TNF cytokines so the patients often have elevated CRP [11]. It is associated with cardiovascular risk, hypercoagulability markers and elevated homocysteine (Hcy). A cohort study conducted by Ahlehoff *et al.* in Denmark demonstrated age- and severity-dependent increase in risk of cardiovascular mortality in psoriasis patients [12]. There are limited data regarding association between psoriasis and VTE. In this report we present a patient with an inherited thrombophilia and chronic diffuse psoriasis complicated with a deep venous thrombosis (DVT).

Case report

We report a case of a 30-year-old white man of Macedonian nationality, who is a railway infrastructure worker. He was referred to the Department of Dermatology for a consultation and color Doppler ultrasound of the veins of the lower legs for persistent edema and pain in the left legin the past two weeks. The results revealed acute deep thrombosis in the left superficial femoral (VFS) and popliteal vein (VP). The physical examination showed an obese patient, withbody mass index (BMI) 34.7 kg/m^2. His waist circumference was 100.5cm. The left lower leg was tender, warm, and edematous with positive Homan's sign. Regarding his social history,

Fig. 1. Psoriatic plaques on the lower legs

Fig. 2. Diffuse extensive thick squamous plaques

he is single, reported moderate alcohol use, tobacco smoking one pack of cigarettes daily over the past 15 years and sedentary lifestyle. His past medical history included HTA diagnosed one year ago and treated with lisinopril 10mg daily. Dermatological history and examination revealed extensive, diffusely distributed

psoriatic lesion on the predilection places-the trunk and the limbs (Figures 1-4); extensive psoriatic plaques with infiltration, severe desquamation and persistent itching which covered more than 60% of the body surface. The patient has had plaque psoriasis for more than 12 years. He reported worsening of psoriasis simultaneously with the onset of deep thrombosis. His PASI score was 32.2.

Fig. 3. Psoriatic plaques on the upper part of the body

His vital signs on admission were remarkable except for his blood pressure which was 150/80 mmHg. Regarding laboratory findings, there were slightly elevated white blood cells (Le=11.2) and CRP (23.5). Rheumatoid factor (RF), antistreptolysin titer (ASO) was within normal range. The biochemistry parameters were within normal range. D dimmer level was 2.34, and fibrinogen 4.5. Chest X-ray and CT pulmonary angiography had no pathological signs. The patient did not have a history of recent trauma, immobilization, traveling long-distance, fever or history of cancer, but had a positive family history of thrombosis. The mother had two miscarriages and history of thrombophlebitis, and is set on a regular oral anticoagulant therapy. This was the reason why the specialist in transfusion medicine recommended thrombophilia panel. Blood sampling and DNA analysis discovered thrombophilic mutations. Blood test results are shown in Table 1.

Fig. 4. Psoriasis on the legs with squamous plaques

Table 1. Thrombophilic gene mutations

Gene (according to HGNC)	Reference sequence	Mutation		Genotype according to HGNC of the investigated mutations
		Standard nomenclature	Traditional nomenclature	
F5	NM_000130.4	c.1601G>A	Factor V Leiden	c.[1601G>A];[=]
		c.3980A>G	Factor V H1299R	[=];[=]
F2	NM_000506.3	c.97G>A	Factor II G20210AA	[=];[=]
F13A1	NM_000129.3	c.103G>T	Factor XIII V34L	C[103G.T];[=]
FGB	NM_005141.4	c.463G>A	FFB 455 G/A	[=];[=]
SERPINE1	NM_000602.4	c.816A>G	PAI-1 5G/4G	c.[-816A>G];[=]
MTHFR	NM_005957.4	c.665C>T	MTHFR C677T	[=];[=]
MTFHR	NM_005957.4	c.1286A>C	MTHFR A1298C	c.[1286A>C];[=]
MTRR	NM_002454.2	c.66A>G	MTRR A66G	[=];[=]
MTR	NM_000245.2	c.2756A>G	MTR A2756G	[=];[=]

The results indicate presence of heterozygosis of factor V Leiden mutation as well asFactor XIII V34L, PAI -1 5G/4G and MTHFR A1298C polymorphism, which mutations are associated with increased risk of thromboembolism.

Deep vein thrombosis and worsening plaque psoriasis were diagnosed. The patient was subjected to anticoagulant treatment with low molecular weight heparin, every 12 hours. He was screened for systemic treatment of the psoriasis, and phototherapy was also recommended. One year after monthly follow-up visits VFS and VP are completely recanalized and he is on regular oral anticoagulant therapy and local emollient treatment.

Discussion

The first one who recorded this association in the dermatological literature was Bunch [13]. Subsequentially,

many reports and growing evidence of VTE events in psoriasis appeared. A nation wide cohort study was conducted in Denmark from 1997-2006 [14], which indicated an increased risk of VTE in psoriasis patients. The highest risk was estimated in young patients with severe psoriasis [14]. A large prospective-population based study of almost 40.000 patients revealed that psoriasis is associated with 40% increased risk of incident VTE [15].

Still the pathogenesis is unknown. One of the proposed hypotheses is the process of systemic chronic inflammation, via genetic mechanism, producing inflammatory proteins. Elevated levels of inflammatory mediators like CRP and cytokines in psoriatic patients are related to the coagulation cascade and subsequently may lead to platelet aggregation and clot formation [11,16]. Also, the existing eosinophils in psoriasis act as thrombogenic factors regulated by the inflammation which lead to hypercoagulable or prothrombotic state [11]. The second hypothesis is elevated levels of homocysteine (Hcy) due to the condition or its treatment. Several mechanisms for hyperhomocysteinemia are proposed-Hcy is directly toxic to vascular and endothelial cells, decrease the NO bioavailability which contributes to thrombosis [17,18]. Moreover, it blocks the binding of tissue plasminogen activator which leads to decrease in plasmin production and extravascular fibrin deposition [17,18]. Another prothrombotic mechanism is related to decreased expression of thrombomodulin which is essential inactivation of the anticoagulant protein C. There are studies that demonstrate that deficiency in folic acid, Vit B12 and B6, which are involved in the synthesis of homocystein (Hcy), is the main reason for hyperhomocysteinemia [18].

Persons carriages of MTHFR polymorphism, are predisposed for elevated Hcy levels, because of their impaired ability to process folate [19]. The A1298C polymerphism in the MTHFR gene in one study showed an association with the risk of cardiovascular event and subclinical atherosclerosis in a patient with RA [19].

Thrombophilia is a defect in the blood coagulation that leads to a predisposition towards thrombosis [20]. Most commonly it is caused by mutation in the genes for coagulation factor II prothrombin and factor V Leiden and is associated with increased procoagulant activity [20]. On the clotting level, factor V Leiden is inactivated about 10 times slower than normal factor V and persists longer in the circulation, resulting in an increased generation of thrombin and a hypercoagulable state [20,21]. Factor V Leiden is the most common inherited disorder of blood clotting with incidence of 2-3% in Caucasian population [21]. Individuals homozygous for the factor V Leiden mutation have a slightly increased risk ofvenous thrombosis [21].

This test detects a polymorphism in the Factor XIII (FXIII) gene, Val34Leu, which has a small, but significant protective effect against venous thrombosis. It has also been associated with lower risk for stroke and myocardial infarction.

Plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of tissue type plasminogen activator (tPA). Increased plasma PAI-1 levels due to reduced fibrinolytic capacity play an important role in the pathogenesis of disorders associated with thrombosis. This polymerphism has been studied extensively. The prevalence of 4G allele was found to be higher in disorders like coronary artery disease, severe preeclampsia, type 2 diabetic nephropathy, pulmonary thromboembolism (PTE), and arterial thrombosis associated with hereditary protein S deficiency [22-26].

Psoriasis-related quality of life may lead to unhealthy behavior such as smoking, alcohol consumption, decreased physical activity and obesity, which are independent risk factors for cardiovascular diseases [27].

In this case report, the patient had a long history of psoriasis, treated only with topical creams. The patient was smoker, obese, hypertensive with metabolic Sy, heterozygous carrier of thrombophilic mutations which are associated with increased risk for thromboembolism, altogether risk factor for arterial and venous thrombosis. Still, it is not clear whether there is an association with psoriasis, thrombophilia and VTE events.

Due to the obvious risk factors, this patient should be under observation for future thrombotic events. The question is whether treatment of psoriasis can predispose thrombosis, and whichis the correlation between thrombophilia, thrombotic event and severe psoriasis. Does the cumulative effect of all of his comorbid conditions increase the risk? Thus, the conclusion is that patients with psoriasis, should be recommended cardiopreventive therapies, which also lowers the VTE risk [28].

Conclusion

In conclusion, the present case report suggests a relation between systemic inflammation and risk of venous thromboembolism, and it suggests that patients with even mild to moderate psoriasis may be at an elevated risk of a VTE event. Screening patients with psoriasis for additional risk factors that promote thrombosis should be considered. Until further evidence is available, all patients with moderate to severe psoriasis may be considered to be at a higher risk of venous thromboembolism and managed accordingly.

Conflict of interest statement. None declared.

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УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) листата на Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).
Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени vo Index Medicus):

а) ***статија во списание*** (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор*.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.

б) заеднички автор

GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.

в) ***без автор*** **-** анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).

г) ***поглавје во книга или монографија***

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

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