REVISTIA

EJMN

EUROPEAN JOURNAL OF MEDICINE AND NATURAL SCIENCES

July - December 2020

Volume 3, Issue 2

ISSN 2601-6397 (Print)

ISSN 2601-6400 (Online)

REVISTIA
PUBLISHING AND RESEARCH

EUROPEAN JOURNAL OF
MEDICINE AND NATURAL SCIENCES

July - December 2020
Volume 3, Issue 2

Typeset by Revistia

ISSN 2601-6397 (Print)
ISSN 2601-6400 (Online)

Address: 11, Portland Road, London, SE25 4UF, United Kingdom
Tel: +44 2080680407
Web: https://ejmn.revistia.com
Email: office@revistia.com

Indexed in Elsevier's Mendeley, WorldCat, RePEc & Ideas, Google Scholar, Microsoft Academics, Crossref

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Influence of Coronary Artery Disease over Exercise Systolic Blood Pressure in Men with Hypertension

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Abstract

Aim: Disclosing coronary artery disease by analyzing the rates of systolic blood pressure response to workload during exercise stress test. **Methods**: 53 males with hypertension underwent exercise stress test on bicycle ergometer and coronary angiography within one month .rates of systolic blood pressure to workloads in the first stage peak exercise, second, fourth and sixth minute of recovery were analyzed and compared .Also basic characteristics of patients involved in the study were also analyzed. **Results**: All systolic blood pressure to workload rates during exercise and recovery resulted higher in males with coronary artery disease and hypertension compared with hypertension but no coronary artery disease. **Conclusion**: High levels of systolic blood pressure to workloads rates in males with hypertension reveal the diagnosis of coronary artery disease despite the ECG variations during exercise stress test and this are not influenced by other basic characteristics of the patients.

Keywords: Coronary Artery Disease, Exercise Systolic Blood Pressure, Men, Hypertension

Introduction

There is much interest in correlation between blood pressure response during exercise in patients with coronary artery disease (CAD). Some of the studies have documented that the abnormal response of systolic blood pressure (SBP) post exercise in patients with angina pectoris was a predictor of severe ischemia of the myocardium during exercise and can be the cause of increasing stroke volume of the left ventricle in the setting of increased peripheral vascular resistance and sympathetic tone (Amon 1984, Hashimoto 1993, Bourque 2015, Grogan 1993, Naimark 1992, Lin 2015, Kontsas 2013). Also has been shown that abnormal post exercise blood pressure response of SBP can be useful in detecting the CAD in patients with and without high blood pressure (HBP)(Lin 2015). In our point view is not the peak systolic blood pressure that determines the SBP response during recovery but, instead it is the workload (WL) which provokes the SBP response during exercise and as a consequence also during the recovery. In this study we have investigated rates of systolic blood pressure response to workloads during exercise but also during recovery in men with hypertension.

Methods

In the study were included 53 men patients with hypertension from 40 to 60 years old. All patients underwent a progressive maximal or symptom limited exercise stress test (EST) with stages lasting 3 minutes each. EST were performed with ergometric bicycle. All the patients underwent coronary angiography within one month. According to coronary angiography result patients were divided in two groups. The first group 17 individuals with normal coronary arteries and the second group 36 with CAD.

The following parameters are analyzed.

1. Rate between SBP in the third minute of the first stage of exercise to the workload at that stage.

2. Rate of peak SBP to the peak workload.

3. Rates of the SBP in the second, fourth and sixth minute of recovery to peak workload.

Statistical analyses

All the variables are compared between two groups with *t* test .To determine the role that other independent factors to SBP is used stepwise regression analyses.

Results

Basic characteristics of hypertensive man with or without CAD as age , height , body mass index (BMI) ,ejection fraction of the left ventricle and blood pressure during rest ,different stages od exercise and recovery do not show significant difference statistically. Table 1. While workload in the first stage 39 to 31 watt p<0.0018 and peak workload 139 to 103, p 0.0025 watts were significantly higher in males with normal coronary arteries in comparison with those with CAD .On the other hand the percentage of achieved heart rate was significantly higher in hypertensive males with normal coronary arteries in comparison to the hypertensive man with CAD 84.3 to 71.9 % p<0.0007.

Characteristics	Normal coronary angiography Mean (SD)	P-Value	Abnormal coronary angiography Mean (SD)
Age, y	47.8 (7.4)	0.054	52.3 (7.7)
Weight, kg	80.4 (10.4)	0.16	76.6 (8.1)
Height, m	1.72 ((0.05)	0.0	1.72 (0.03)
Body mass index	27.3 (2.8)	0.1	26.0(2.6)
Ejection fraction, %	0.73 (0.09)	0.5	0.64 (0.13)
Systolic blood pressure at rest, mm Hg	146 (11.4)	0.56	148 (15.9)
Systolic blood pressure at the end of 1st exercise stage, mm Hg	190 (20.8)	0.48	181.5 (18.1)
Peak systolic blood pressure, mm Hg	206 (27.8)	0.18	196 (21.3)
Systolic blood pressure at recovery minute 2	160 (18.6)	0.88	160.8 (19.3)
Systolic blood pressure at recovery minute 4	145.6 (14.9)	0.38	149.9 (16.5)
Systolic blood pressure at recovery minute6	136.9 (16.1)	0.076	145.2 (12.3)
Starting work load, watt	39.0 9(11.1)	0.0018	31.0 (6.5)
Peak work load, watt	139.0 (39.7)	0.0025	103.0 (37.4)

Table 1: Characteristic of both hypertensive men with normal and abnormal coronary angiography

Differently from SBP the rates of SBP to workloads during exercise and recovery were significantly higher in males with hypertension and coronary artery disease Tab 2 .So the mean difference between the rates of SBP to workload in the first stage was 1.047 (CI 95 % 0.283 −1.81 p=0.0082) .

The mean difference of peak SBP / WL was 0.668 (CI 95 %, 0.16 −1.176, p=0.011)

The mean difference of SBP / WL in the second minute of recovery was 0.587 (CI 95 %, 0.146 −1.027, p=0.01).

Table 2. Systolic blood pressure to workload rates (SBPR) in hypertensive men with normal and abnormal coronary angiography

Systolic blood pressure rate (SBPR)	Normal coronary angiography Mean (SD)	P-Value	Abnormal coronary angiography Mean (SD)
Starting SBPR	4.461 (1.399)	0.0082	5.507 (1.241)
Peak SBPR	1.582 (0.578)	0.011	2.251 (0.921)
Recovery minute 2nd SBPR	1.253 (0.422)	0.0101	1.840 (0.850)
Recovery minute 4th SBPR	1.130 (0.454)	0.009	1.718 (0.802)
Recovery minute 6th SBPR	1.041 (0.315)	0.0038	1.652 (0.765)

The mean difference of SBP / WL rate in the fourth minute of recovery was 0.587 (CI 95 %, 0.154 −1.021, p=0.01).

The mean difference of SBP / WL rate in the sixth minute of recovery was 0.612 (CI 95 %, 0.208−1.015, p=0.0038).

Analyses for sensitivity, specificity and correctness of the test for first stage SBP/WL was 80, 60.7 and 47.2 % respectively.

Analyses for sensitivity, specificity and correctness of the test for peak SBP/WL was 87.5, 65.9 and 64.6 % respectively.

Analyses for sensitivity, specificity and correctness of the test for SBP/WL in the fourth minute of recovery was 71, 75 and 72.3 % respectively.

The criterion of positivity of the stress test according to ECG was 85.3, 72.2 and 66.7 % for sensitivity, specificity and correctness of the test respectively.

This shows that higher levels of SBP to WL rates can detect CAD independently from the ECG changes during stress test in this subset of patients.

Stepwise regression analyses showed that age, weight, height, body mass index, heart rate and diastolic pressure do not have any influence on the SBP to WL rates. Table 3.

Table 3. Determining factors in hypertension men with normal and abnormal coronary angiography

SBP / WL Rates	Normal coronary angiography		Abnormal coronary angiography	
	Coefficient (SE)*	Adjusted R2	Coefficient (SE)*	Adjusted R2
Starting SBPR				
Intercept	5.213 (0.623)		4.475 (0.83)	
Starting SBP	0.024 (0.0.004)	0.96	0.033 (0.004)	0.86
Starting workload	-0.118 (0.006)		-0.114 (0.011)	
Peak SBPR				
Intercept	2.27 (0.483)		2.833 (0.653)	
Peak SBP	0.006 (0.002)	0.84	0.009 (0.003)	0.82
Peak workload	-0.013 (0.002		-0.023 (0.002)	
Recovery 2 SBPR				
Intercept	2.58 (0.208)		3.877 (0.22)	
Peak workload	-0.01 (0.001)	0.76	-0.02 (0.002)	0.75
Recovery 4 SBPR				
Intercept	2.609 (0.208)		3.656 (0.203)	
Peak workload	-0.01 (0.001)	0.78	-0.019 (0.002)	0.76
Recovery 6 SBPR				
Intercept	2.215 (-0.16)		3.539 (0.192)	
Peak workload	-0.008 (0.001)	0.88	-0.018 (0.002)	0.79

*SE, is standard error

Discussion

In normal individuals systolic blood pressure response is directly connected to the increase of the workload (WL). But this is partially true when there is CAD .There is no consensus which are the values of peak SBP that can be considered exaggerated response. Different investigators have considered as such the increase of peak SBP over 220 mmHg for males and 190 mmHg for females (Matthews 1998, Ha 2002). Exaggerated increase of SBP during exercise is related mostly with the prediction of having high blood pressure in the future (Jae 2015, Grossman 2014) and only weakly with the presence of CAD or mortality (Matthews 1998, Ha 2002, Hedman 2020). According to the fact that increasing blood pressure response is stimulated from the workload we have supposed that also the decrease of blood pressure during recovery is connected directly to the workload and not to peak SBP (Kamberi 1984). As a consequence this could be shown by the rate of SBP to workload. In previous studies has been shown that individuals with normal stress test and

those with positive test did not show any change in peak SBP. Our results show that although the peak SBP and recovery SBPs don't show any difference between hypertensive men with or without CAD. Their peak workload was significantly different being significantly lower with those with the presence of CAD. Tab 1. It is evident that the increase of SBP in hypertensive males with CAD is disproportionate to the increase of the workload. This disproportionate increase of SBP to workload was evident in first stage SBP/WL rate and in the peak SBP/WL rate (tab. 2) .So the increase of SBP should be considered exaggerated not based on the measured SBP values but from the value of SBP to workload rate. This study documents that higher levels to SBP to workload rates can detect the presence of CAD in hypertensive males with at least the same accuracy as ECG changes during stress test.

In special occasions the first stage SBP to WL rate can be of special importance because there are people that cannot perform more than one stage. In most of these cases stress ECG is normal and this SBP/WL rate in first stage is the only parameter that allows us to show the presence of CAD. Also our study shows that the slow SBP decrease during recovery can show the presence of CAD. But the rates of SBP to workload are more certain even if the peak SBP cannot be measured correctly. On the other hand the rates of SBP to WL represent sensitivity, specificity and test accuracy totally comparable with ECG depression of ST segment during stress test. Stepwise regression analysis show that for the exercise SBP to workload rates only the starting workload and starting SBP and peak workload and peak SBP were determining factors meanwhile for the SBP to workload rates in recovery the only determining factor was the peak workload .This is a strong prove of our hypothesis that in normal people not only the increase of SBP during exercise but also the decrease of SBP during recovery are dependent on the workload .is very important to emphasize that in hypertensive males with or without CAD rates of SBP to workload are not influenced by age, BMI, heart rate and systolic and diastolic blood pressure in rest. This surely increases the importance of rates of systolic blood pressure to workloads.

Conclusion

High levels of systolic blood pressure to workloads rates in males with hypertension reveal the diagnosis of coronary artery disease despite the ECG variations during exercise stress test and these findings are not influenced by other baseline characteristics of the patients.

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The Factors that Influence in Human Resources Management at the Clinical Hospital in Tetovo

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Abstract

Human Resource Management within healthcare institutions is an important part of their organization and as such, it is quite complicated, complex and dynamic. The interest in managing with human resources is crucial all around the world, since the success of daily activities as well as the welfare of the functioning of healthcare centers largely depend on the mode of human resource management within those institutions. The aim of this paper is to analyze the factors that influence in successfulness and efficiency of human resource management at the Clinical Hospital in Tetovo which in turn directly influences the improvement of the quality of medical services provided by the medical staff and to analyze the organizational structure at this public healthcare institution. During the first quarter of 2018 interviews with employees in some of the wards of this hospital were done related to their daily activities, services they provide, problems and challenges they face. Also, the level of satisfaction from the assessment of their work by the institution has been measured. Some of the major problems that were emphasized in all of the groups of interviewees had to deal with low salaries and the lack of additional compensations that can significantly motivate them in the more successful realization of their daily duties and activities. The stimulation and motivation of the medical staff for professional development and continuous education through various different professional development workshops, seminars, conferences, symposiums, etc. has a great impact on the overall performance of the employees. The adequate equipment of wards with the most modern items and devices is more than crucial for a smooth realization of daily activities and it also has a direct impact on the achieved results. Successes and achievements in the field of medicine are closely related to the scientific advancements in general. Healthcare institutions at all levels should treat their personnel better by providing them more reasonable salaries and rewards for their good performance as well as additional financial support for their further professional development. Competent bodies within the Ministry of Healthcare should actively monitor the quality of provided healthcare services by the medical personnel, encourage, and invest in their efficient distribution and dissemination.

Keywords: organizational structures within healthcare institutions, human resource management, leadership, motivation, quality assurance and professionalism

Introduction

Human Resource Management within healthcare institutions is an important part of their organization and as such is quite complicated, complex and dynamic. The interest in managing with human resources is crucial all around the world, since the success of daily activities as well as the welfare of the functioning of healthcare centers largely depend on the mode of human resource management within those institutions.

Parallel experiences clearly show that traditional leadership patterns, which appear as inflexible forms, now lose the importance of functioning and are largely replaced with more contemporary and sophisticated leadership models, more flexible, humanistic and more practical models, namely the contemporary management of human resources.

The health system in general, guided by this system and its development, is increasingly attracting the attention of society. Prior to the institutional leaders there's a great challenge to understand in a transparent way the world we live in today and be able to contemplate the future and the possible changes in it.

Today, with the new legal decisions in the health institutions, the decision to run with two directors should be implemented. This increasingly strengthens the need for comprehensive implementation of health management and all this is accomplished through an adequate organizational structure of the health system in general, which is of paramount importance in the health care of patients through the provision of great quality to the health services.

These changes, however, should be added to the beginning of the health system transformation process and privatization in the health sector, which implies change in several levels and in many segments of the overall health system. The primary goal of this process is to improve the quality of health services, one of which is the increase of the satisfaction of the users of these services, while the ultimate goal is to provide a more efficient, accessible, social and solid health system for all, which will work at estimated and controlled costs. All this means greater responsibility of health institutions and medical personnel in achieving institutional goals and in achieving high professional performance.

Aim

The health system is considered to be one of the most complex systems in society; therefore, its successful functioning represents a great and necessary need. The aim of this paper is to analyze the factors that influence the successfulness and efficiency of human resource management at Clinical Hospital in Tetovo, which directly influences the improvement of the quality of medical services provided by medical staff and to analyze the organizational structure of this public healthcare institution.

Through the given health indicators to define the existing situation and then consider the possibility of drafting an adequate health policy with the preparation of certain plans, programs and activities that should be implemented through appropriate decisions both in the institution concerned and in the system health as a whole.

Methodology

The subject of this paper was the assessment of the success of the daily activities of the medical staff of some departments at the Clinical Hospital of Tetovo. During the first quarter of 2018, interviews with employees in some of the wards of this hospital were made related to their daily activities, services they provide, problems and challenges they face. Also, the level of satisfaction with the assessment of their work by the institution has been measured, the level and difficulties they face in their work either as a result of the lack of equipment and equipment or the materials and tools necessary for realization of their activity with success.

Results

This study was conducted in seven departments of the Tetovo Clinical Hospital:

Surgical Department;

Urology Department;

Orthopedic Department;

Gynecological - Obstetrics Department;

Internistic Department of Internal Diseases;

Pediatric and

Neurological Department.

Personnel employed in these units as specialist doctors, secondary doctors, nurses as well as auxiliary and sanitary personnel were interviewed through questionnaires prepared in advance. Responses given by employees clearly show that one of the major problems in all of the abovementioned groups is the low wage but also the absence of additional compensation such as bonuses, awards or acknowledgments that have a significant impact on their motivation for achieving as much most successful daytime activities.

Lack of stimulation and promotion of medical staff for professional upgrading and continuous education, which is accomplished through the pursuit of training courses, symposiums, congresses or scientific conferences, is also another element that has a significant impact on the professional preparation and with this also in the successes shown at work.

The adequate equipment of the aforementioned units with the modern equipment and instruments necessary for the realization of daily activities, which in most cases is far from optimal, is also another factor which hampers the work of the medical staff and has a direct impact on the achieved results.

According to the study conducted and analyzes made - a very important factor that affects the successful management of human resources is also the character of the leader. As a matter of fact, a good leader must possess professional qualities such as self-confidence, sustainability, professionalism, communication skills and loyalty to the work and the staff employed, for the purpose of successful realization of his leadership activity.

Conclusions

The human factor should be accounted for as one of the most important health care links.

Managers of health institutions at all levels should treat the medical staff as best as possible by offering them not only reasonable wages but at the same time motivating them with bonuses, awards or acknowledgments for any good result in their work that differentiates from that of other colleagues.

The establishment of a long-term national strategy for human resource management in healthcare institutions and the provision of financial means necessary for the permanent advancement of medical staff in certain directions remains a factor of particular importance for the quality and success of medical services**.**

Competent bodies within the Ministry of Health or hospital departments should actively monitor the quality of services provided by the medical staff and promote and invest in the effective distribution of this staff. They should also build flexible and appropriate organizational structures for dynamic and complex environmental changes.

Harmonization of medical services across the country is of special importance and necessary for the success of the health institution.

Taking into account the daily activities of the institutional manager, it is required to be more innovative, more flexible, to respect the knowledge and experience of employees at all levels of the institution, to advance teamwork, to advance communication between departments and units and reward the employees for the quality work accomplished.

The principle of equality and justice must be enforced by the medical staff during the provision of health services, which is carried out in such a way that each citizen, depending on the form and the character of his medical requirements, can simultaneously fulfill his health requirements. First and foremost, it is about the published transparent waiting lists.

Successes in the field of medicine are closely and directly related to the pursuit of achievements in science. Therefore, with the change of the system of the undergraduate education of medical staff and its harmonization with the system that dominates in the European Union, especially with the postulate that the healthcare professional has an obligation to permanently acquire new information, skills and knowledge; to be allowed to be supplied with newest tools (most modern medical technology); adaptation and functional health area and a reasonable and effective human resource policy that enables greater efficiency; in the future it will be necessary to gradually harmonize the way of realization and verification of the specialization, so that it is identical to the one proposed by the European health associations, i.e. it should be harmonized with those currently implemented in the European Union.

It should be ensured that all healthcare activities are carried out in all areas where the health service and medical activities are applied, in a qualitative atmosphere and manner, ranging from the way patients behave (applying all national and international rules the rights of patients that are in effect) to the application of internal rules in the performance of workplace duties at health centers and institutions.

Taking into account the nature of the work in health institutions, healthcare as an activity is often counted as a place where, due to negligence and professional failure, there often occur health damages, loss of patient life or loss of life medical personnel. That is why it is mandatory to establish legal rules for adequate medical devices according to the examples of member countries in the European Union. The greatest deviation from the normal functioning of the individual in the collective and his inability to perform daily tasks occurs during the loss of health or injury. These situations in most cases are the reasons for the greatest number of other consequences (financial problems, inability to work, need for help from others). Every activity, event, segment of the process and the outcomes that have to do with the health condition should still be recorded.

On the other hand, taking into account the rules in contemporary medicine, due to the possible digitization of all these phenomena, not only must they be recorded, but they must be adequately memorized but always be at the disposal of those who are authorized to make certain decisions, ranging from decision-making health bodies that define rules, concepts, follow up the realization and carry out the ongoing supervision of the activity; to medical personnel who must necessarily be informed of any work done for the patient, in any segment of the patient's healthcare system, which is subject to attention and care; and to the insurance institutions who justify and take over all the health insurance costs. Today, with the rapid development of computer technology, it is wise to immediately (on-line) access all data and cases related to all therapeutic interventions.

Good and continuous communication between staff at all levels of the health system and especially the division of work between them, governed and managed fairly, will enable the successful functioning of all parts of the levels of this system.

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What Can We Learn from the Islamic Tradition About the Pandemic?

Emine Öztürk

Abstract

First of all, we must explain this, there is a big literature about pandemies in Islamic religious literature. So, there a lot of things we can learn about pandemy from Islamic literature. Once a day prophet Mohammed said that about pandemy, if there is a pandemy anybody doesn't go out form there, and if there ıs pandemy in anyplace outside don't go into that place untıll pandemy stops. This verse of prophet Mohammed tells us everything about pandemy. Beacuse this verse is about isolatıon. And also prophet Mohammed says cleanliness is the half of belief. And also he says cleanliness comes from beleif. So there are a lot of things in Islamic literature about pandemy that we can learn. So, we hope that we can tell some important points about pandemy approcah of Islam. We hope we can do some contributes about thıs subject. Of course, this ıs not the last word about this subjcet but it is a word about thıs subject that we can learn some important points form Islamic literature. [1]

Keywords: Islamic tradition, Pandemic

Introduction

In dictionaries there are many words which are related with pandemic. First word which related with pandemic is epidemic; it means outbreak, contagious and epidemic. And the other word with pandemic is epidemiology; it means the branch of modern medicine which is related with incidence and distribution. Anda there are epidemic diseases some of them are flu, influenza, grippe, cold, commmon cold, mumps, parotitis, cholera, malaria, ague, jungle fever, intermittent fever, marsh fever, varicella, chicken pox, swine pox, plague, pestillence, Black Death, pest, fowl pest. But all of these epidemic diseases does not mean that it is impossible to counterwork the distribution of these diseases. But some of these diseases are nor only epidemic but they are also pandemic, likewise cholera, malaria, ague, jungle fever, intermittent fever, marsh fever, varicella, chicken pox, swine pox, plague, pestillence, Black Death, pest, fowl pest. The diseases like cholera, malaria, ague, jungle fever, intermittent fever, marsh fever, varicella, chicken pox, swine pox, plague, pestillence, Black Death, pest, fowl pest are not only distributed in one country, they are distributed allover the world. We must konw that pandemic means a disease which is distributed all over the world. So now Covid -19 as the othername Choronavirus is distributed all over world. So, Choronavirus is a pandemic.

During the history there are many pandemics have seen all over the world. For example plague, pestillence, Black Death, pest, fowl pest. The first pandemic which is emerged in Europe in sixth century is the Plague of Justinian, and the other is Black Death, which is emerged in Europe in 1347 wtih Genoeses' arrival by following the sea route in Italy, it has been moved to Europe. Ibn Khaldun says that one year later after 1347 I have lost my father beacuse of the Black Death in 1348.

That is why we transferred the word to Ibn Khaldun because he is a Muslim Sociologist but he lived in Europe when he was a child. This means that pandemic not only affects not only Europe but it also affects whole the world and also the IsLamic world and Muslims. The people and the scholars who are listenning to me now, I think they know everything about the History of Pandemic of Europe. But we have to see that, there are many places and nations and religions on the earth that must ask question about this subject? What are the other nations and religions are doing about pandemic?

Let's have look about the History of Pandemic in Islamic Tradition. "Because of the Plague of Justinian, in Constantinople six thousand people died in an day in sixth century. During the Anatolian Seljuks there are mnay pandemics have emerged because of the military expeditions, sieges and famine. Because the military expeditions, sieges and famine have caused the people to loose the resistances of their bodies. And then they got diseases. Under the reign of the First (I) Suleyman

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Shah in 1078 during the four months sixth hundred thousand people have died. Duirng the first crusade and throughout the siege of Antakya in 1098 100.000 people died only form the Frank's army. In the period when Melik Mohammed, the ruler of the Danishmend, ruled Malatya, there had been an epidemic which killed first of all poultry then at the begining little children, and after a lot of people. In the period of Mesut the First, in 1153, during the Chukurova expedition, under the reign of Kılıcarslan the second, in the Seljuks army, following the famine, a plague emerged in Syria, Iraq, Diyarbakır and Ahlat. Because of the plague the people were unable to bury the bodies. Duirng the reign of Alaeddin Keykubad after the famine which emerged 1244 in Malatya and 1259 in Syria. Anatolia during the Mongolian sieges a plague emerged because of famine in Mardin and Silvan and it caused a great destruction."[1]

Now by the time we have to ask this question

How can Muslims deal with or overcome pandemic during historical pandemic processes? We can explain these two questions in several numeric answers:

First of all, there are verses from the Qur'an regarding cleaning and hygiene.

One of them is the verse of Maidah 6: Let's look, what the verse Maidah 6, tells us about celarness and hygen. "O you who have believed, when you rise to [perform] prayer, wash your faces and your forearms to the elbows and wipe over your heads and wash your feet to the ankles. And if you are in a state of janabah[2], then purify yourselves. But if you are ill or on a journey or one of you comes from the place of relieving himself or you have contacted women and do not find water, then seek clean earth and wipe over your faces and hands with it. Allah does not intend to make difficulty for you, but He intends to purify you and complete His favor upon you that you may be grateful."[3]

In this version, Allah tells us to take ablution and to be cleaned before the prayer to himself. And a Muslim have to ablution five times in a day. And a person who takes ablution in a day, he or she could not be dirty, beacuse he or she washes the parts of his or her body five times in day os he or she could not be dirty. Washing some parts of the body five times in a day give a person spaciousness and roominess and reprieve that person during all of the day. So this spaciousness, roominess and reprieve protects you from stress and viruses and also choronavirus.

2-Second iti is very important in Quran that the things people eat in the daily life must be clean, not only celan but also halal[4]. Maidah 88 is about the cleanliness of the things we eat. "And eat of what Allah has provided for you [which is] lawful and good. And fear Allah, in whom you are believers."[5] And there are many other verses which tells us about cleanliness in Qur'an.[6]

There are 49 verses in Qur'an which tells about clear and halal food. And there are 2 verses in Quran about body cleanliness.[7] So, cleanliness is very important in Islam.

3-And also prophet Mohammed has many hadiths about cleanliness. A few of them are these:

1-"Cleanliness is the half of the faith."[8]

[1] Bayat, Ali Haydar; *History of Medicine*, Merkezefendi Traditional Medicine Association, İstanbul, 2010, s.267.
[2] Literally, "distance." The state of one under obligation to perform *ghusl* (a complete bath) due to having had sexual intercourse or ejaculation.
[3] 5/al-Maidah/88
[4] Halal means lawfull.
[5] 5/al-Maidah/88
[6] These verses are those. 2/al-Baqarah/57, 125, 168, 172, 222, 267; 4/an-Nisa/43,160; 5/Maidah/4,5,6,87,88,100; 6/al-An'am/145; 7/al-A'raf/31,32,82,157, 160; 8/al-Anfal/26,37,69; 10/Yunus/93, 11/Hud/78; 16/an-Nahl/3, 66,72, 97, 114; 17/al-Isra/70; 18/al-Kahf/19; 20/at-Taha/81; 22/al-Hajj/26,29; 23/al-Mu'minun/50,51; 24/an-Nur/26; 25/al-Furqan/48; 27/an-Naml/56; 38/as-Sa'd/29; 40/al-Mu'min/64; 45/al-Jathiyah/16; 47/al-Mohammed/15; 56/al-Vaqıah/79; 74/al-Muddaththir/4,5; 76/al-Insan/21; 91/ash-Shams/9.
[7] Look for these verses. *The Qur'an English Meanings*, Saheeh International, Jeddah, Abu'lqasım Publishing House,1997- al-Muntada al-Islamı- 2004.
[8] Müslim, Ebu'l-Hüseyin Müslimu'bnu'l-Haccac el-Kuşeyri en-Niysaburi, *Sahihi Müslim,* Verification: Muhammed Fuâd Abdülbâkî, Beyrut: Dâru İhyai't-Türasi'l-Arabi, 1956, Lustration, I.

2-"Allah is clean, accepts only clean. Whatever Allah commanded his prophets, he commanded the beleivers. Allah Almighty to the Prophets, "O prophets eat things that are clean and halal, do good and usefull work. And to the beleivers " Oo you who beleive, Eat one of the clean ones of the susters we gave you."[1]

3-"When a Muslim or beleiver takes ablution, while he is washing his face, his sins which he done with his face are poured with ablution water(or the last drop of water). When he washes his hands, the sins he commits with his hands are poured with ablution water(or the last drop of water). When he washes his feet, his sins which he has done with his feet flow through the ablution water (or the last drops of the water). Finally he will be completely free from all of his sins."[2]

4-"When one of you will fast, open it with dates; because dates are abundant. If he cannot find dates; open his fast with water; because his water is clean."[3]

5-"If a person takes ablution, and if he is cleaned as much as he can, and he crawls from his own special smell or the fregnance in his house and leaves his house as this way; does not enter between two people, then he performs his obligatory prayer on him; if he is silent and listens to him while reading the sermon, their sins from Friday are forgiven."[4]

6-" If a person is cleaned beautifully in his house; and then goes to one of the houses of Allah; each of these steps will wipe out a sin; and the other step raises him one another degree."[5]

7-"Whoever gets ablution on Friday; what it is good; especially he gets big ablution."[6]

8-"If I had not worried about putting my ummah (or my people) into trouble; I would have ordered them to clean their teeth with miswak every time of prayer."[7]

We can take these massages below about daily cleanliness from all these hadiths.

Cleanliness is the half of the faith.

Allah is clean, accepts only clean.

Ablution cleans the person in terms of two size; one size is material, and the other is spiritual.

Water is clean, poen your fast with water.

Taking ablution cleans you in terms of two size; one size is material, and the other is spiritual.

Cleaning beautifully and going the house of Allah; saves you form all sins, and gives you spiritual degrees.

Celaning your teeth gives you Lord's consent.

And also, Muslims cope wtih or overcome with the pandemic also by quarantine.

And also, there are some hadiths of Prophet Mohammed about quarantine in basic Hadith Books. Before we look to these quarantine hadiths, let's learn about what is quarantine and then let's look at these hadiths about quarantine. Quarantine is not to enter the place, human beings and animals, where the infectus disease is seen from outside, and also human beings and animals, is not to go out from inside, where the infectus disease is seen, to the outside. There is isolation in quarantine. The intact willnot come close to the sick. So protection is essential. The quarantine applicaiton started with the advice applicaitons of the Prophet Mohammed (peace be upon him). It has forbidden others from entering and leaving the areas where infectious diseases are seen. Here, the Prophet (peace be upon him) has revealed that the diseases are not destiny and not bad luck. He also stated that we should be protected from these diseases. It has been seen that quarantine

[1] Muslim, Alms, 65.
[2] Muslim, Lustration, 32.
[3] Tirmizî, Ebu İsa Muhammed bin İsa bin Sevre es-Sülemi et-Tirmizi, *Sünen-i Tirmizi*, Verification: Ahmad Mohammed Shakir, al-Maktabatul-Islamiyya, Alms, 26.
[4] Buhârî, Ebû Abdillâh Muhammed b. İsmâîl b. İbrâhîm Cu'fî Buhârî, Sahih-i Buhari, Kahire: Mustafa el-Babi el-Halebi, 1953, Friday Prayer; 6, 19.
[5] Müslim, Masajid, 282.
[6]Tirmizî, Friday Prayer; 5.
[7] Buhârî, Friday Prayer; 8; Hope, 9; Fast, 27; Müslim, Lustration, 42.

is mandatory in other parts of the world and has been started to be applied partially from the 14th century. Millions of people have died from infectious diseases. Quarantine started to be implemented by the World Health Organization since 1952.

Now let's look at these hadiths about quarantine. One of these Hadiths is this.

1-"In the history of Islam, when Majesty Omar (God bless him) was the caliph, he was going to Damascus. It was learned that there was a Black Death or plague disease in Damascus. Abdurrahman bin Avf said to caliph Omar (God bless him) : Prophet Mohammed said that "Do not enter the place where there is plague or Black Death. If plague is seen in your place, do not leave there.[1]" At that time, Abu Ubeyde said to caliph Omar: "O Omar! Are you running away from Allah's accident?"

Upon saying:

- "Yes. I escape and beg from Allah's accident to his destiny." He gave the answer to Abu Ubeyde."[2]

And the second hadith is on the below.

2-"If you hear that there is a plague somewhere, do not go there. If plague occurs at your location, do not leave."[3]

And the third hadith is on the below:

3- "There is a danger of being close to the disease."[4]

And the fourth hadith is on the below:

4- "Do not put the sick animal next to the flat, which is solid."[5]

And the fifth hadith is on the below:

5- "Escape from leper as if escaping from the lion."[6]

And the sixth hadith is on the below:

6- "Also about allegiance from the Sakif tribe coming to Madinah a leper in a delegation

When he heard that he was there, he said, "Come back, We accepted your allegiance." is known to have sent."[7].

As, it is understood from al these hadiths, Prophet Mohammed is the only and the first person, who advises quarantine and isolation against pandemic in the history. Now let's look at the history of Islamic Medicine. And then let's look about what did Muslim doctors except cleenliness and aquarantine in Islamic history against pandemies during the Islamic Medicine History.

"Islamic civilization revived the classical culture that descended almost everywhere in medieval times. The reason for this success is that it can adapt existing cultures and is open to all kinds of ideas. For example, more VIII. In the 19th century, Câbîr wrote that the universe would tear the secret of the glaze, create living and inanimate beings, at least this is theoretically possible. It is very important that he can express them at that time. Without being influenced by any religious official opinion, the knowledge has spread thanks to scholars who can conduct research in various languages. Thus, Islamic science gathered the sciences of the ancient world in itself, translated its works, added new information and transferred them to the West with the will that triumphed on the courage and a strong sense of self while choosing the useful elements."[8]

[1] Ahmad b. Hanbal - Şuayib el-Arneut, *Musnad*; Müessesetu'r-risale, 1999, 42: 53 (25118); Ebu Dâvud, Süleyman b. el-Eş'as, *Sünenu Ebî Dâvud*, İstanbul: Çağrı Yayınları, 1992, "Funerals", 6.
[2] İbn Kesîr, Ebü'l-Fidâ' İmâdüddîn İsmâîl b. Şihâbiddîn Ömer b. Kesir el-Kureyşi ed-Dımeşki. *al-Bidâyah va'n-nihâyah*, Verification: Abdullah b. Abdulmuhsin et-Türki, Dâru'l- Hicre, 1998.c. X, s. 172.
[3] Ahmad b. Hanbal, *Musnad*, 42: 53 (25118); Ebu Dâvud, "Funerals", 6.
[4] Ebu Davud, Sünen,3923.
[5] Buhari, Medicine, 31.
[6] Buhari, Medicine, 16.
[7] Ibn Mace, Ebu Abdullah Muhammed bin Yezid er-Rebei el-Kazvini İbn Mace, *Sünen,* Delhi: Matbaatu'n-Nizami, 1905; Medicine, 44.
[8] Bayat, *History of Medicine*, s.205.

"The art of medicine, which is among the primary sciences (ulûmu'l-evâil) in Islamic culture, has developed in a short time. This movement took place in 2 stages:"[1]

"Accepting Period: With the encouragement of religion, the ancient culture and medicine on which Islamic geography rested were adopted; Hospital and medical education in Cündişapur was taken as an example; Scientific books of Ancient Greek and Indian medicine were translated in Beytü'l-Hikmah, which was established in Baghdad during the Abbasid period, within 200 years."[2]

"Creative Period: After learning ancient medicine information, with new medical knowledge obtained through observations and experiments, XII. In the 19th century, as the science historian Hartner put it, the idea of reliance on medieval fashion old authorities that would endanger the thought was abandoned, and the originality of scientific thought reached an unprecedented point until then. In this creative period, Muslim physicians dominated the world of scientific medicine for 600 years with their books. It has become. It is necessary to examine the institutions that reveal this brand new understanding of science and medicine in more detail."[3]

Gundeshapur Medical School And Commencement of Medical Translations

"The city of Gundeshapur, founded by the Persian Sassanid ruler of Iran, [241-73] on the road connecting Sûs and Hemedan, has long been recognized as the science and art center of the region. Gundeshapur, where a large group of artists, scholars and workers in Syria, together with the prisoners, was placed in the war where the First Emperor destroyed the Roman emperor Valerian. It was also a shelter for the Nesturians expelled from Anatolia. Husrev I (Anûşirvân) [531-79] sent a delegation of culture to India and brought many Indian scholars to Gundeshapur. Doctors named Berziye and Sencehl, whose books were later translated into Arabic in Beytü'l-Hikmah, are two of them. Again in his period, the New Platonic teachers of Athens were accepted to this city after the academy was closed in 529. Thanks to the school founded by Husrev I, the city has become the science center of the region. Large physician families, who grew up in this region where Greek-Indian-Iranian medical knowledge was synthesized, have contributed greatly to the advancement of scientific medicine in Islamic civilization with the medicine and the medicine books they translated. After Iran came under Muslim rule in 638, the scientific institutions here were not touched, and scientists -especially physicians- were respected by the Abbasid dynasty, and physicians trained in Gundeshapur worked in the palace, and scientists in translation schools."[4]

"At the time of Islam, there were powerful science and philosophy centers in the north of Arabia. Arab armies encountered a developed medical school and hospital [638] in Gundeshapur, and the scientific legacy of Ancient Egypt and Greek civilization in Alexandria, a major science and research center [642]. Also, Antakya and Edessa (Urfa) were important science centers."[5]

"Buhtişû family, one of the physicians of Gundeshapur Hospital, for 4 generations (Curcîs bin Cibrâîl [d. 769], Buhtişû bin Curcîs [d. 801], Cibrâîl bin Buhtişû [d. 828], Buhtişû' bin Cibrâîl [d. 870]. On the other hand, he worked as a private doctor of the Baghdad palace and on the other hand he was engaged in translation works. Book translations from Greek to Pahlevi (ancient Persian), which started before Islam in Gundeshapur, Alexandria and Edessa, continued during the Umayyad period, [661-750], scattered from Greek and Pahlevi to Arabic."[6]

"The original translation period started in the first period of the Abbasid state [750-860] with Beytü'l Hikmah. Created by Caliph Mansur [754-74], Beytu'l Hikmah gained wide space and regular functioning in the time of his grandson Hârûn er-Reşîd [786-809]. became like that. The number of books collected in Beytü'l-Hikmah has reached a level that cannot be compared to anywhere else in the medieval world. Beytü'l Hikmah was later withdrawn from the history scene, leaving its place to the daru'l-ilm/daru'l-kutubs established in Mosul, Bust, Basra, Baghdad, Shiraz, Rey, Cairo and Kayravan."[7]

"Medical studies in Beytü'l-Hikmah started with the coming of Baghdad with many scientific works of Indian physicians brought by caliph Mansur from Gundeshapur. IX. In the early part of the century, John bin Masselay, Jibrâîl bin Buhtişû

[1] Bayat, *History of Medicine*, s.205.
[2] Bayat, *History of Medicine*, s.205.
[3] Bayat, *History of Medicine*, s.205.
[4] Bayat, *History of Medicine*, s.205-206.
[5] Bayat, *History of Medicine*, s. 206.
[6] Bayat, *History of Medicine*, s. 206.
[7] Bayat, *History of Medicine*, s. 206-207.

'and Huneyn bin İshâk translated many medical works in Beytü'l-Hikmah with the suggestions of physicians from Gundeshapur. Indian physician Mankah and Sâlih bin Bahle, who healed Hârûn er-Reşîd's uncle, carried the Indian medicine to Baghdad palace."[1]

"He brought books from the important cities of Byzantium and asked the Cypriot judge to send the books in his hand as war compensation; Mutasim brought the valuable books [838] to Baghdad under the conquest of Ankara and Amorium. Sometimes it was necessary to travel long to find a book. Huneyn bin Ishaq stated that Galenus traveled Iraq, Syria, Palestine and Egypt for his book about the pulse and finally found it in Damascus. Collected works, Hunayn bin İshâk [d. 873], his son İshâk bin Hunayn, al-Kindî [d. 870], Shabbin bin Kurra and Kosta bin Luka [d. 912] has been translated by people who know Arabic-Greek-Syriac very well. The translators were paid by the weight of the books. Those who wrote on thick papers and large letters for heavy suffering were complained by the treasury minister, and the caliph ordered that the treasure will not be impoverished by the gold given to scientists and spent on the science path."[2]

"During this period of 200 years, Greek such as Hippocrates, Galenus, Ephesus Rufus, Dioskorides, Oribasius; The works of Indian physicians such as Susruta, Caraka, Vagbhata, Zantâh and Canakya were transferred to 37 Arabic. 64 works of Galenus, 13 of Hippocrates, and 20 of Rufus of Ephesus were translated. Thus, the loss of ancient medicine books was prevented and it was provided to be read in very remote areas. Muslim physicians who absorb the medical heritage of antiquity, adding their experiments, observations, knowledge and experience to the books, original works. They have become the leader of medicine in the East and West for nearly 600 years throughout the Middle Ages with the medical education they have provided in the health institutions they have established."[3]

Some of Hippocrates's Works Translated into Arabic[4]

"Although it is mentioned in some sources that the first Muslim hospital was built in 707 by the Umayyad Caliph Velid bin Abdülmelik in Damascus, this is a structure that was modeled by the Byzantine nosocomium and was established as a shelter for the lepers and the blind. The first full-fledged Islamic hospital was established in Baghdad in around 800, during the Abbasid period, by Hârûn ar-Raşîd and was managed by one of the Gundeshapur, physicians, Cibrâll bin Buhtişû. This hospital has set an example for other hospitals to be established in Baghdad and other major Islamic cities. IX-XVII. Between the centuries, many dharüşşifas were established in a wide geography from Andalusia to India, in Umayyads, Abbasids, Seljukies, Mamlukies, Ilkhanids, Timurids, Aqquyunlus and Ottoman countries."[5]

"Among the first İslamic hospitals we can count, these are the below,

1-the haospital which is built in Baghdad by Harun ar-Raşid and Bermekids;

2-the hospital which is built by the bridesmaid of the caliph Mutavakkil [847-61] Turk al-Fath bin Khakan [d. 861] in Cairo under the name of Mâristânü'l-Magafîr;

3-the hospital which is built in Cairo in 874 by Ahmad bin Tolun who is one of the Tolunids, 4-the hospital which is built by Abubakir Mohammed bin Togac(842-942) who is one of the Ikhshidies in Eygpt,

5-the hospital which is built by Bedrü'l-Mutaddîd Gulâm in in Baghdad in 902;

6-the hospital which is built by caliph Mukhtadir in (908-32) in the door of the Damascus;

7-the hospital which is built by vizier Ali ibn al-Furat (d.924) in Baghdad in Dâru'l Mufaddala,

8- the hospital which is built in Baghdad in 940 by Amîr Ebû'l-Hasan Baghâm et-Türkî who is one of the commanders of the caliph al-Muktefî (902-08),

9-the hospital which is built in Baghdad in 966 by Mu'izzüddevle who is one of the Buvayhid kings;

[1] Bayat, *History of Medicine*, s. 207.
[2] Bayat, *History of Medicine*, s. 207.
[3] Bayat, *History of Medicine*, s. 207.
[4] Bayat, *History of Medicine*, s. 208.
[5] Bayat, *History of Medicine*, s. 209.

10- the hospital which is built in Baghdad in 982 by Adûduddevle who is one of the emirate of the emirates of Buvayhids which was named The Bimaristan of Adudi;

11- the hospitals which are built in Basra by a slave who is borught from Anatolia in the period of caliph Nasr li-Dinillah (1180-1225);

12- the hospital which is built in 957 by the one of the kings of Ikhshids Kafur which is named Maristani Kafuri,

13- and last hospital which is opened by Sinan bin Sabit who is the surgeon general of caliph Mukhtadir which is named the Bimaristan of Sayyidah."[1]

"Other than these; it is known that;

1-in X.th century there are 4 hospitals in Rey, Zerend, Isfahan, Marv and Nishapur;

2-in XI.th century there are 4 hospitals in Vasıt(1022) and Mayyakafirin(1031);

3- in XII.th century there are 4 hospitals in Mosul, and 2 hispitals in Edessa; and one each in Nusaybin, Haleb and Hama."[2]

And there are many hospitals in also Andalusia[3] taht w can not count them in here because of our reserach's volume. And let's look at some doctors which are studied in those hospitals.

Abu Ubayd ac-Cuzcani wrote a poem about the ancient doctors. This poet is on the below.

"There was no medicine, Hippocrates found.

He was dead, Galenus resurrected.

Blind, Huneyn bin Ishaq opened his eyes.

Râzî collected his mess.

Ibn Sina completed his deficiencies and matured."[4]

Abu Ubayd ac-Cuzcani

"Physicians and their works in Islamic civilization have an important place in the history of medicine. Although Muslim, Christian, Jewish, Magi or Ethnic Arab, Iranian, Turkish physicians, who lived in a wide Islamic geography and wrote their works in Arabic, made some provisions about their nationality, it is difficult to make a definite judgment since the understanding of the ummah was dominant in this period. There are hundreds of physicians enlightening the Eastern and Western worlds with their works in the Middle Ages."[5] Here are some Mulsim Physicians who is studied about Medicine in classical Islamic World.

"Ali bin Rabben et-Tabari(d. After 861); el-Kindî (d. 873), Hunayn bin Ishaq (d.810-73); Abûbakir er-Râzî (d. 865-925), İbnü'l-Cezzâr (d. 979); Ali bin Abbâs el-Magi (d. 994), Ammâr bin Ali (d. 1010); Abu'l-Qasım Zahrâvî (d. 1013); Avicenna (980-1037); Ali bin Îsâ (d. 1038), İbn Zühr (ö. 1162); Maimonides (d.1204); İbnu'l-Baytâr (d. 1248) and there are many other physicians which they studied about medicine."[6]

And let's have a look about Turkish-Islamic Medicine. Turkish Medicine, in Historical Period seperates into four period;

"1-One and first of period of Turkish Medicine is the Peirod of Turkish Medicine Before the Islamic Medicine

2-Second period of Turkish Medicine is the Peirod of Turkish Medicine After the Islamic Medicine

3-Third period Turkish Medicine is the Peirod of Ottoman Turkish Medicine

[1] Bayat, *History of Medicine*, s. 209-210.
[2] Bayat, *History of Medicine*, s. 210.
[3] Bayat, *History of Medicine*, s. 210.
[4] Bayat, *History of Medicine*, s. 215.
[5] Bayat, *History of Medicine*, s. 213.
[6] Bayat, *History of Medicine*, s. 213-230.

4-Fourth period of Turkish Medicine is Modern Turkish Medicine."[1]

And from now on, we will try to tell about the second period because in this period Turkish physicians had kneaded the Turkish medicine knowledge and European medicine knowledge with Isamic medicine knowledge and they used this new medicine knowledge to built a new Turkish Islamic Medicine. And also they used this new medicine Turkish Islamic Medicine Knowledge in public service in the hospitals(Daru'sh-shifas) that Seljukies have built in Anatolia. Now let's look at these hospitals names. There are amny hospitals which Seljukies built in Anatolia.

"1-The Hospital of Mardin Nacmaddin Ilghazi

2-The Hospital of Kaysari Gavhar Nasiba Medical University and Hospital

3-Syvas Izzaddin Qayqavus Hospital

4- Divriği Turan Melek Hospital

5-Konya and Aksaray Hospitals

6- The Hospital of Çankırı Camaladdin Farruh

7-Tokat Muinuddin Scholomon Hospital

8-Kastamonu Ali bin Scholomon Hospital

9- Amasya Anber Bin Abdullah Hospital"[2]

After we have explained about Turkish-Islamic Medicine and Hospitals in Anatolia in Middle Ages. Now let's look at he treatment methods whcih are used in these hospitals. There are many classical treatment methods which Muslim Physicians used in these hospitals. Of course we can not explain all the methods. But we think two of these methods are very important. Let's look at what are they.

One of them is using water and music in treatment of psychological illnesses. This method is called water and music treatment.

"Each substance has its own vibration (frequency). Our body also has a vibration frequency. The disease is the disruption of cellular vibration in the body. For treatment, the disrupted vibration needs to be rearranged. The two compatible frequencies interact with each other to form a "resonance". In physics, resonance is the event that the first vibration initiates a second vibration that is compatible with it. In order to benefit from the healing effect of sound on the body and mind, it is aimed to rearrange the distorted body rhythm with the frequency of the voice played from the outside, to a sick body whose rhythm (vibration) is impaired or to an organ that is vibrated. In the Seljuk and Ottoman Darushshifas, the patients were made to listen the music which was played together with the sound of water. The sounds of water rising from the fountain -which has sprikler around it- in the middle of the courtyard provided the patients to relax and calm, thus increasing the healing effect of music. We know that it is used in Gavhar Nasiba Hospital Darushshifa and also this music and water treatment is used in Edirne Bajazid II. Darushshifa."[3]

And let's have a look how was Europe were healing the persons who have phsycological illnesses while Turkish Pyhsycisians were healing these persons with music and sound of water in the Middle Ages. Micheal Foucault tells about the treatment methods of pyhsicians that they apply for treating the phsycological illnesses in Europe in the Middle Ages. Foucault tells about a table which shows a ship named the Ship of Madness People which is painted by Hieronymus Bosch. This table is about the madness people who are closed, externalized and marginalized to a ship and suddenly there had been a fire in the ship and madeness people and many other disabled people died by burning in that ship. And Hieronymus Bosch painted these people and has shown how these people died in that ship by burning.[4]

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[1] Bayat, *History of Medicine*, s. 236-267.
[2] Bayat, *History of Medicine*, s. 267-271.
[3] Sancak, Leyla*; The Psychological Treatment Methods in the Turkish-Islamic Civilization and Comparison of Previous Period Musical Therapy with Today's Music Therapy Practices*, Unpublised Master Thesis, Nisantasi University, Institute of Social Sciences, Supervisor: Assist. Prof. Dr. Sera Çetingök; İstanbul, 2019, s.34-35.
[4] Foucault, Micheal; *History of Madness*; translation: Mehmet Ali Kılıçbay; İstanbul, 2006; s. 23-85.

And I leave the comparison to you about the treatment methods of Europe and Islamic Societies for healing phsycological illnesses in the Middle Ages.

And the other treatment method is healing pandemies by using thermae and healing hot waters and also by using hammams. In the Middle Ages there are many thermae and hammams in Anatolia. In the period of Turkey Seljuk State a hundreds of healing hot water resources nad thermae, which Homeros, Galenus and Strabon mentioned about them, have been used for healing the pandemic illnesses and many other new ones have been built. Let's look at the names of these thermae, hot water resources and hammams.

"According to one of the XIV. th century's writers, Omarî, there were more than 300 hot springs in Anatolia where the people went to find healing for various problems.

1-The most famous of these the thermal spring of Ilgın, which has been built by Alauddin Qayqubad,

2-Futher from this the thermal spring of Ankara Haimana and The Red Hammams;

3-Eskişehir; The Spring of Pergola;

4- Erzurum; The Spring Of Ilıca;

5-Kırşehir, The Spring of Karakurt(Blackwolf);

6-Kütahya, The Spring of Yoncalı;

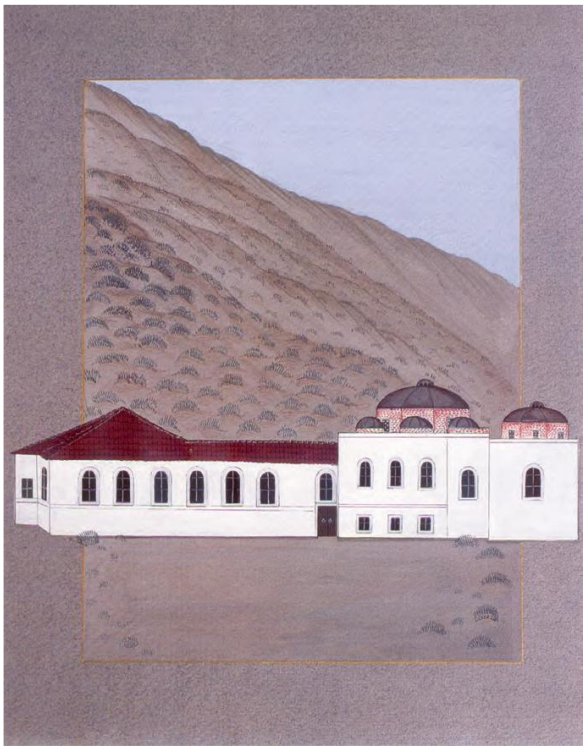
7-Havza, The Spring of Kızözü and Aslanagzı;

8-Ayash, The Spring of Karakaya."[1]

The Table of The Ship of Madness[2] is in above.

[1] Bayat, *History of Medicine*, s. 267-268.
[2] https://tr.pinterest.com/pin/555772410260741282/?autologin=true, The Date of Access: 07.05.2020

Turkish baths or hammams, which have been built by sultans and statesmen during the Seljuk period, have an important place among the Public Health Works. These hammams have like function for that societies like a Public Healthcare Centers.[1]



The Table of Spring of Konya Ilgın[2] is in above.

Conclusion

As a result; we can say about Turkish-Islamic Medicine Tradition; Muslim and Turkish doctors coped with or overcome with the pandemies in historical period with three methods;

1.Firtsly, being clean all the time and taking care of being cleanliness all the time both in terms of body cleanliness and cleanliness of food as Quranic verses and the hadiths said.

2.Secondly, applying qauarantine and isolation seriously when a Pandemic occurs in a place as it is said in Prophet's hadiths.

3.And thirdly using thermae and hot water resources and hammams for healing pandemies like plague and leprosy.

And as we have seen that there was big difference in the comprehension of healing and treating the illnesses especially pandemies in the Middle Ages between Europe and Islamic Counties. Let's come to today. Now today this difference in comprehension we have seen again in the pandemic of Choronavirus. Because Turkey is more succesfull than other countires because of this three healing and treatment methods and also because of this different comprehension.

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Calcium, Phosphorus and PTH in Patients with End Stage of Chronic Kidney Disease, Undergoing Hemodialysis

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Abstract

Renal hyperparathyroidism (rHPT) is a common complication of chronic kidney disease characterized by elevated parathyroid hormone levels secondary to derangements in the homeostasis of calcium, phosphate, and vitamin D. Patients with rHPT experience increased rates of cardiovascular problems and bone disease. The Kidney Disease: Improving Global Outcomes guidelines recommend that screening and management of rHPT be initiated for all patients with chronic kidney disease stage 3 (estimated glomerular filtration rate, < 60 mL/min/1.73 m**2**). Since the 1990s, improving medical management with vitamin D analogs, phosphate binders, and calcimimetic drugs has expanded the treatment options for patients with rHPT, but some patients still require a parathyroidectomy to mitigate the sequelae of this challenging disease.

Keywords: Calcium, Phosphorus and PTH in Patients with End Stage of Chronic Kidney Disease, Undergoing Haemodialysis

Introduction

Renal hyperparathyroidism (rHPT) is a common complication of CKD characterized by derangements in the homeostasis of calcium, phosphorus, and vitamin D.

rHPT is classically broken into 2 types on the basis of the patient's serum calcium level. Secondary hyperparathyroidism (2° HPT) is the elevation of parathyroid hormone (PTH) in response to hypocalcemia induced by phosphate retention and reduced calcitriol synthesis as a consequence of reduced renal function[1]. In 2° HPT, all the parathyroid glands become enlarged owing to parathyroid hyperplasia. Because 2° HPT is a compensatory mechanism of the parathyroid glands, it commonly resolves with normalization of calcium and phosphorus homeostasis (eg, renal transplantation). Tertiary hyperparathyroidism (3° HPT) is seen when a patient with longstanding 2° HPT develops autonomous PTH secretion, often associated with hypercalcemia. This is observed in up to 30% of patients with ESRD, who then undergo renal transplant[2].11 3° HPT is classically thought to have come from parathyroid hyperplasia, but some studies have suggested that up to 20% of patients may have single or double adenomas[3]

Since the 1990s, improving medical management with vitamin D analogs, phosphate binders, and calcimimetic drugs has expanded the treatment options for patients with rHPT, but parathyroidectomy remains necessary for many patients.

Normal Calcium and Phosphorus Homeostasis

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Calcium and phosphorus homeostasis is maintained through a complex relationship between the bones, intestine, kidneys, and parathyroid glands. PTH is probably the most important regulator of calcium metabolism and functions primarily via 3 mechanisms:

1. PTH is thought to stimulate PTH receptors mainly on osteoblasts, which then, through multiple cell-to-cell mechanisms, stimulate osteoclast formation and bone resorption, leading to increased serum calcium and phosphorus levels.

2. PTH activates 1-α-hydroxylase in the kidney, which catalyzes the conversion of nonactive 25-hydroxy (25-OH) vitamin D to activated 1,25 dihydroxy (1,25-OH) vitamin D. This leads to increased absorption of calcium and phosphorus in the gut.

3. PTH increases reabsorption of calcium and decreases reabsorption of phosphorus in the kidney.

Recently, there has been much interest in the role of fibroblast growth factor 23 (FGF-23), a protein secreted by bone in response to hyperphosphatemia, which functions primarily in maintaining phosphorus homeostasis. FGF-23 stimulates phosphorus excretion in the kidney mainly through reduced action of sodium-phosphate co-transporter in the proximal tubule. It also decreases 1-α-hydroxylase activity, leading to reduced 1,25-OH vitamin D levels.14,15 In CKD, FGF-23 levels progressively rise and are initially thought to be beneficial, given the phosphaturic effects. However, increasing FGF levels are also associated with increased cardiovascular mortality in patients with CKD[1].

Pathogenesis

The pathogenesis of rHPT is complex and incompletely understood (Figure 1).

An increase in PTH levels typically develops when the glomerular filtration rate (GFR) drops below 60 mL/min/1.73 m2. Abnormalities in serum levels of phosphorus and calcium tend to occur much later in the course of CKD (typically when the GFR drops below 40 mL/min/1.73 m2)[2].17 Initially, the elevated PTH levels serve to increase renal phosphorus excretion. However, as the GFR declines further, serum phosphorus levels start to rise and induce hypocalcemia by binding bioavailable calcium as $CaHPO_4$, which indirectly leads to a further rise in PTH production. CKD also leads to decreased activity of 1-α-hydroxylase, thereby decreasing 1,25- OH vitamin D. A lack of 1,25-OH vitamin D inhibits gastrointestinal absorption of calcium and also directly stimulates the parathyroid glands[3],[4].

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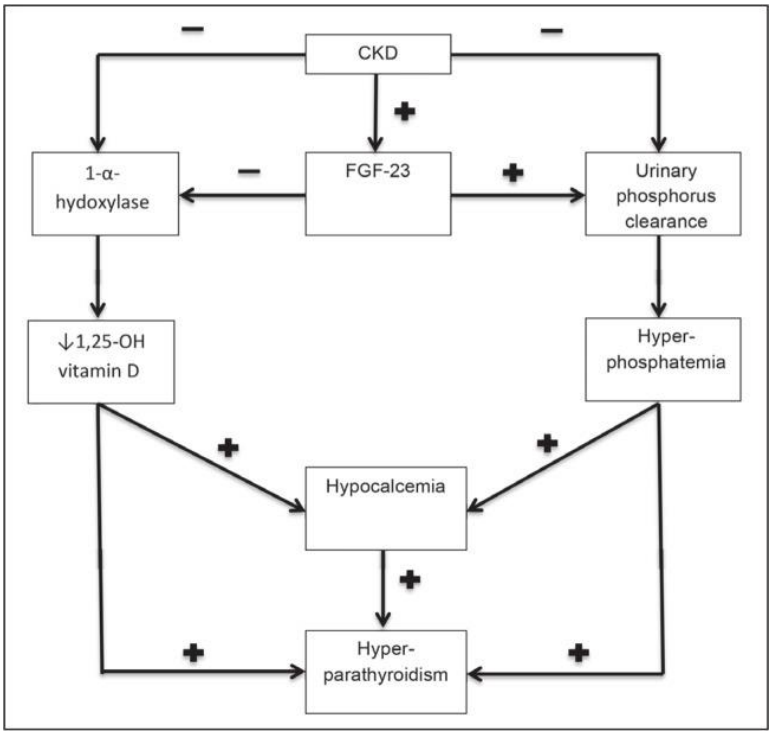

In CKD, chronic stimulation of the parathyroid glands triggers diffuse polyclonal hyperplasia. As the chronic stimulation of CKD continues, the parathyroids begin to develop monoclonal nodules within a background of parathyroid hyperplasia. These nodules demonstrate increased resistance to vitamin D and calcimimetic medications and may be the etiology of the loss of negative feedback seen in 3° HPT[1,2].

Clinical Manifestations

Renal osteodystrophy refers to a group of bone disorders caused by dysregulation of mineral metabolism in CKD, including osteomalacia, adynamic bone disease, and osteitis fibrosa cystica. Osteomalacia is a state of low bone turnover leading to poor mineralization. Adynamic bone disease is also a low-turnover pathology with normal mineralization that probably results from a low PTH state. The incidence of adynamic bone disease increasing is likely secondary to PTH oversuppression from vitamin D agents, calcimimetics, and phosphate binders[3,4]. Osteitis fibrosis cystica is a high-turnover bone disease that stems from elevated PTH concentrations stimulating osteoclast activity, bone breakdown, and resorption. This can lead to subsequent bone pain and fractures[5]. With longstanding bone resorption, patients may develop localized regions of bone loss that are then replaced by fibrous tissue, resulting in a brown tumor. These "tumors" appear as well-defined, lytic lesions on radiograph and may be mistaken for metastasis (Figure 2).

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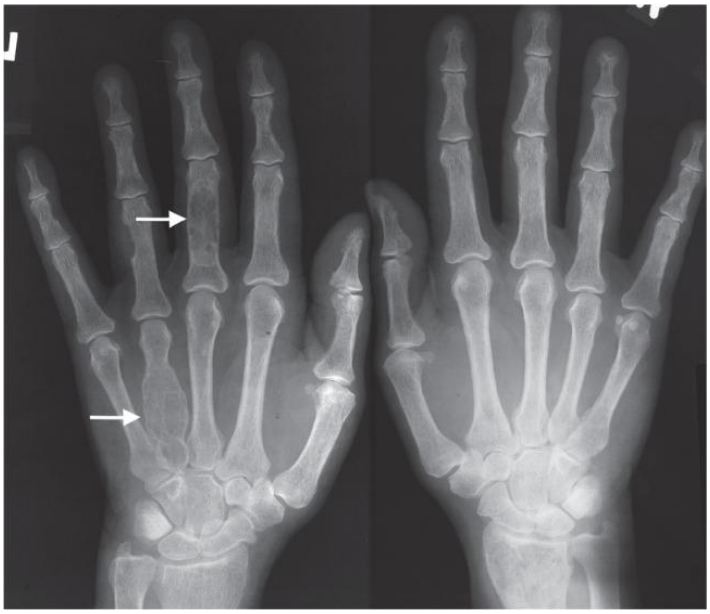

Figure 2.

Radiograph of the hands of a 55-year-old patient with renal osteodystrophy and brown tumors of the fourth metacarpal and third phalanx of the left hand (arrows).

The derangements in calcium and phosphate that result from rHPT may accelerate vascular calcification, including coronary artery calcification. Calcification of the cardiovascular tissue can affect the myocardium, atrial-ventricular conduction, and valvular function[12]. Furthermore, coronary calcification may put patients at an increased risk of cardiovascular events and death[3]. It is difficult to distinguish the unique detrimental effects of rHPT from those of hyperphosphatemia, which is also associated with cardiovascular disease in patients with CKD. Some studies have suggested that FGF-23 may induce arterial smooth muscle myocytes to change into osteoblast-like cells that lead to vascular calcification[4]. Moderate to severe hyperparathyroidism (PTH concentrations ≥ 600 pg/mL) may increase risk of cardiovascular death,7 though the causality of this association is debatable.

There is an association between CKD and medial calcification in the arterioles of the skin and soft tissue leading to vascular compromise and ulceration. This constellation of complications was formerly called calciphylaxis but is now termed calcific uremic arteriolopathy, and it is associated with an eight-fold increase in mortality rate. Tumoral calcinosis is an uncommon complication of longstanding rHPT and is classically associated with high serum levels of calcium and phosphorus. In tumoral calcinosis, the patient can develop soft-tissue calcium deposits that can appear to be soft-tissue malignant tumors on imaging studies

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Evaluation of Phospho-Calcic Metabolism

1. Levels of intact calcium, phosphorus and parathyroid hormone (PTH) should be dosed in all patients with CKD and FG <60 mL / min / 1.73 m2. The frequency of these doses should be based on the stage of chronic renal disease. (Table 1).

Stage of CKD	GFR (ml/min/1.73m2)	Measurements of PTH	Measurements od calcium/phosphorus
3	30-59	Every 12 months	Every 12 months
4	15-29	Every 3 months	Every 3 months
5	<15 ose dialize	Every month	Every month

2. These doses should be performed more frequently if the patient is being treated with concomitant therapy for disorders of plasma calcium, phosphorus or PTH levels.

3. Plasma PTH dosage may be repeated over a longer period of time in those patients with PTH values within the lower limit of target values.

4. The limits of the target values of plasma levels of intact PTH at different stages of CKD are given in Tab.2. Limits of target values of plasma intact PTH according to CKD stages

CKD stages (pmol/L])	GFR (ml/min/1.73m2)	Intact pth RANGE (pg/ml)
3	30-59	35-70 [3.85-7.7pmol/L] opinion
4	15-29	70-110 [7.7-12.1pmol/L]
5	<15 or hemodialysis	150-300 [16.5-33.0pmol/L] evidense

Evaluation of Phosphoric Plasmatic Levels[1].

1. In patients with CKD (St. 3 and st.4) plasma phosphorus level should be maintained at or below 2.7 mg.dL (0.87 mmol / L) and not more than 4.6 mg / dL (1.48 mmol / L)

2. In patients with CKD st.5 and in those treated with hemodialysis or peritoneal dialysis, the plasma phosphorus level should be maintained between 3.5-5.5 mg / dL (1.13-1.78 mmol/ L).

Hyperphosphatemia leads to secondary hyperparathyroidism and elevated levels of PTH through:

a) lowering the levels of ionized calcium;

b) intervention in the production of vit.D;

c) directly affecting the secretion of PTH[2].

This process leads to high-turnover bone disease.

Prolonged hyperphosphatemia causes vascular and soft tissue calcifications resulting at least in part from an increase in calcium x phosphorus product[3] and is associated with an increase in morbidity and mortality[4]. In the case of vascular calcifications, hyperphosphatemia has a direct calcifying effect on the cells of the vascular smooth muscle. Calcification of coronary arteries, cardiac valves and pulmonary tissue causes cardiac disease, the leading cause of death in patients with CKD. It is therefore very important to prevent hyperphosphatemia and to maintain phosphorus levels within normal limits.

Among the factors contributing to secondary hyperparathyroidism in patients with CKD are phosphorus retention and / or elevated plasma phosphorus levels.

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To prevent morbidity and mortality, it is recommended that plasma phosphorus levels should be maintained between 2.7-4.6 mg / dl (0.87-1.49 mmol / L) in patients with CKD st.3 and 4, and between 3.5-5.5 mg / dl (1.13 -1.78 mmol / L) in patients with CKD st.5

Plasma Calcium and Calcium-Fosfor Product[1]

In patients with CKD stage 3 and 4:

Plasma levels of corrected total calcium should be kept within the values of the laboratory rate used In patients with CKD stage 5:

Plasma levels of corrected total calcium should be kept within the laboratory norm values used, preferably within the minimum limit (8.4-9.5 mg / dL [2.10-2.37 mmol /L]).

In cases where the plasma level of corrected total calcium exceeds 10.2 mg / dL (2.54 mmol / L), the medications that cause the increase in calcium should be modified as follows.

a. Patients receiving calcium-based phosphorus binders, the dose should be reduced, or switched to a calcium-based, non-calcium-based phosphorus binder aluminum, not magnesium based.

b. In patients receiving active vitamin D, we should reduce its dose, or discontinue therapy until plasma levels of total calcium are corrected within the target range (8.4-9.5 mg / dL [2.10-2.37 mmol / L]).

c. If hypercalcemia (plasma levels of total corrected calcium> 10.2 mg / dL [2.54 mmol / L]) persists despite modification of vitamin D therapy and / or disruption of calcium-based phosphorus binders, low-concentration dialysis may be used. of calcium in dialysate fluid (1.5-2 mEq / L) for 3-4 weeks.

In patients with CKD st. 3-5:

1. The total dose of calcium taken (including that obtained with the diet and that obtained with calcium-based phosphorus binders) shall not exceed 2000 mg / day.

2. The calcium-phosphorus product must be kept <55 mg2 / dL2. This is best achieved by controlling the plasma levels of phosphorus within the range of target values.

3. Patients whose plasma total calcium levels are below the minimum values of the laboratory values used (< 8.4 mg / dL [2.10 mmol / L]) should receive plasma calcium therapy if:

a. Have clinical symptoms of hypocalcemia such as paresthesia, Chvostek-Trousseau syndrome, bronchospasm, laryngospasm, tetany, and / or convulsive crisis;

b. The plasma level of intact PTH is below the target values for the CKD stage

4. Treatment for hypocalcemia should include calcium salts such as calcium carbonate and / or vitamin D oral.

The total dose of calcium taken in patients with CKD should not exceed 2000 mg / day. In these patients the fraction of calcium absorbed in the duodenum and jejunum is reduced because this process depends on the year. D, and in CKD this vitamin is lowered. However, passive calcium uptake, which depends on the gradient, may increase if we increase the dose of calcium obtained.

Patients with CKD who have been treated with vit D or calcium supplements tend to develop hypercalcemia, especially in those with adenamic bone disease.

Hypercalcemia, together with hyperphosphatemia, or each individually may be responsible for increased Ca-P product. Since plasma phosphorus levels in patients with CKD are usually increased by a larger factor (from 3.5mg / dl [1.13mmol / L] to 7mg / dl [2.26mmol / L] giving a factor of 2), compared to calcium (from 9.5 mg / dl [2.37 mmol / L] to 11 mg / dl [2.74 mmol / L], giving a factor of 1.2), the relative importance of plasma phosphorus levels in the delivery of a high Ca x P

[1] Guidelines for mineralococcal abnormalities in CKD, Albanian group authors

product, is given as mg2 / dL2, it is greater than plasma calcium levels. Also, plasma calcium levels can be critical[1] if plasma phosphorus levels are too high, as is the case of patients with CKD st.5.

In the presence of a high Ca x P product in the blood, soft tissue calcifications are common but the latter are not always associated with high Ca x P, since many factors are involved in the genesis of these calcifications.

It is important that patients with CKD have normal values of corrected total calcium, as it is known that chronic hypocalcemia causes secondary hyperparathyroidism, has adverse effects on bone mineralization and may be associated with increased mortality.

Caution should also be exercised in the dose of calcium taken because it can be switched to hypercalcaemia. Spontaneous hypercalcemia can occur in patients with CKD.

The total calcium level should be adjusted based on the level of albumin through the formula:

Corrected calcium (mg / dl) = total calcium (mg / dl) + 0.0704 x [34-plasma albumin (g / L)]

A simpler formula is used for routine clinical interpretation of plasma calcium:

Corrected total calcium (mg / dl) = total calcium (mg / dl) + 0.8 x [4-plasma albumin (g / dl)]

Patients with FG <60 ml / min / 1.73m2 (CKD st.3) usually, but not always, have significant decreases in plasma levels of total and free calcium. Plasma calcium levels decline further with impaired renal function.

In advanced CKD, the total calcium fraction associated with complex compounds increases; therefore the free calcium fraction decreases, despite the level of total calcium being normal. Acidosis on the other hand can increase the level of free calcium. When hemodialysis begins, plasma calcium levels normalize. It should be borne in mind that dialysis does not play a role in improving calcium absorption.

It is recommended that the daily dose of calcium intake in CKD st.3 be 1.5-2 g / day and in st. 4 and 5 (patients not on dialysis), to be 1.5-1.8 g / day.

Calcium supplements should be started in patients with CKD st.2 when PTH begins to increase, FG <60 ml / min / 1.73 m2

An association between high Ca x P product and death risk was observed, so for every 10-fold increase, an 11% increase in relative risk of death was observed.

If the product Ca x P exceeds 55, then the risk of developing calculations increases and survival decreases. Therefore the target level of the product Ca x P should be <55.

Low Phosphorus Diet

A low phosphorus diet is recommended for patients with CKD and 2° HPT with hyperphosphatemia[2]. Dietary restriction of phosphorus in patients without elevated levels of phosphorus, but with elevated PTH levels only, is controversial. Unfortunately, this is very difficult given the high prevalence of phosphorus in Western diets. Dietary phosphorus comes from 2 sources: 1) protein-rich food groups such as meat and milk; and 2) phosphorus additives, which are used to process meats and cheeses. Phosphorus used as an additive is often only implied in the ingredients list, and not individually reported on the food label. Therefore, the true amount of phosphorus contained in a product may be underestimated.14 Patient education regarding this distinction may help them avoid phosphorous-rich foods.

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Phosphate Binders

Because of the difficulty in maintaining a low phosphorus diet, phosphate binders are usually an essential part of medical therapy for patients with CKD. Phosphate binders have been shown to decrease serum phosphorous and PTH levels.

Several phosphate binders are available, including aluminum hydroxide, calcium salts, sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate. In general, aluminum hydroxide should be limited to a short period because of the risk of aluminum toxicity. Newer agents such as lanthanum have unknown long-term effects of bone deposition. Iron-based binders such as sucroferric oxyhydroxide are also available to lower serum phosphorous. The Kidney Disease Outcomes Quality Initiative recommends for patients with CKD stages 3 and 4, that phosphate binders be used if phosphorus levels cannot be controlled within the target range despite dietary phosphorus restriction. In patients who remain hyperphosphatemic despite initiation of a single phosphate binder, combination therapy can be used[1]. It is interesting to note that lanthanum, being a heavy metal, commonly shows up as radiopaque in noncontrast radiologic studies of the gastrointestinal tract.30

Vitamin D Analogs

As described above, 1,25-OH vitamin D deficiency is a major mechanism of rHPT, and vitamin D replacement has been shown to effectively suppress PTH secretion[2].Several forms of vitamin D are available, including ergocalciferol (which requires activation in the kidney to 1,25-OH vitamin D), as well as activated forms such as calcitriol, paricalcitol, and doxercalciferol. Although observational studies have suggested improved survival in patients treated with vitamin D analogs, a 2007 meta-analysis showed no difference in mortality, bone pain, vascular disease, or rate of parathyroidectomy when comparing patients on vitamin D analogs versus those not taking vitamin D.

The Kidney Disease: Improving Global Outcomes work group recommends that in patients with CKD stages 3 to 5 (not on dialysis), attempts to control hyperphosphatemia, hypocalcemia, and vitamin D deficiency be made first. If PTH remains elevated or is progressively rising, treatment with calcitriol or vitamin D analogs is suggested. Close attention must be paid to serum levels of calcium and phosphorus, which if greater than 10.2 mg/dL and 4.6 mg/dL, respectively, may warrant modification in therapy. In patients with CKD stage 5 on dialysis, active vitamin D sterols (such as calcitriol, paricalcitol, or doxercalciferol) are used to control hyperparathyroidism.

Calcimimetics

Cinacalcet HCL is a calcimimetic agent that exhibits allosteric modulation of the calcium receptor on the parathyroid gland, increasing sensitivity to extracellular calcium and thereby suppressing PTH secretion.36 The effectiveness of cinacalcet in lowering PTH concentrations in ESRD patients has been demonstrated in multiple studies. Combined analysis of these studies showed that cinacalcet decreases rates of parathyroidectomy, fractures, and cardiovascular hospitalization. Patients receiving cinacalcet treatment rather than placebo also have improvements in self-reported physical function and less bodily pain.[3]

In 2012, the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events Trial randomized patients with ESRD and moderate to severe rHPT to cinacalcet or placebo and found that cinacalcet did not significantly reduce overall or cardiovascular mortality[4]. A recent Cochrane review corroborated these findings but did find that patients taking cinacalcet had a significant increase in the rate of nausea, vomiting, and hypocalcemia, suggesting that the potential risks associated with cinacalcet use in ESRD patients may outweigh the benefits. These clinical uncertainties further bring into question the costs of cinacalcet treatment. Currently the US spends $260 million annually on cinacalcet, accounting for the largest single drug cost in dialysis patients. Despite maximal medical interventions, surgical parathyroidectomy is still required for many patients.41

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Indications for Surgical Treatment

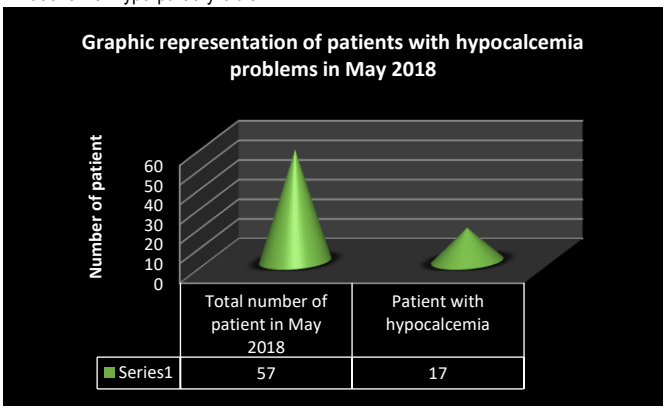
As stated in the *Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease,* published in 2003 by the Kidney Disease Outcomes Quality Initiative, the indications for parathyroidectomy are not well defined. High-quality studies are currently lacking to evaluate which patients might benefit from parathyroidectomy. In lieu of such data, the National Kidney Foundation recommends that the criteria in the Sidebar: Indications for Consideration for Parathyroidectomy be used to merit referral to an experienced surgeon for evaluation[1].

Indications for Consideration for Parathyroidectomy Medical management of rHPT > 6 months with Hypercalcemia or hyperphosphatemia
PTH > 800 pg/mL
Calciphylaxis with documented elevated PTH levels
Osteoporosis (T-score > 2.5 SD below mean), pathologic bone fracture
Symptoms/signs
Pruritus
Bone pain
Severe vascular calcifications
Myopathy

PTH = parathyroid hormone; rHPT = renal hyperparathyroidism, SD = standard deviation

Statistical data

Total number of patient in May 2018	57
Patient suffering from hypocalcemia	37
Patient suffering from hyperphosphatemia	17
Patient with hyperparathyroidism	27



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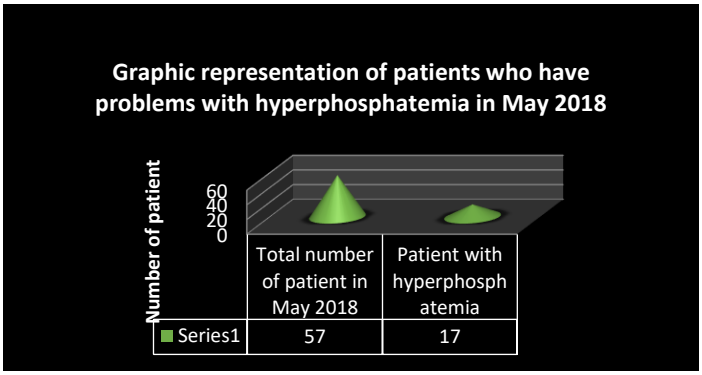
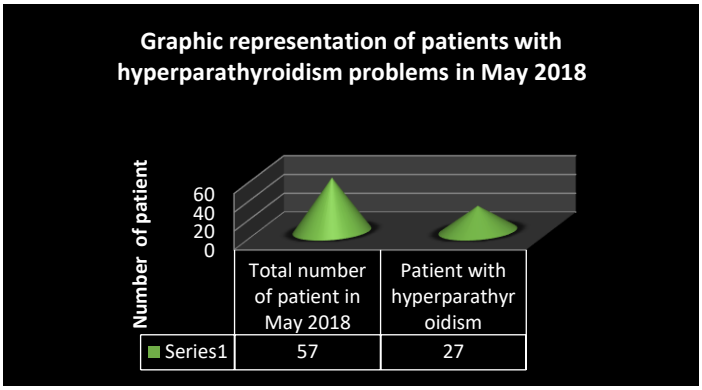
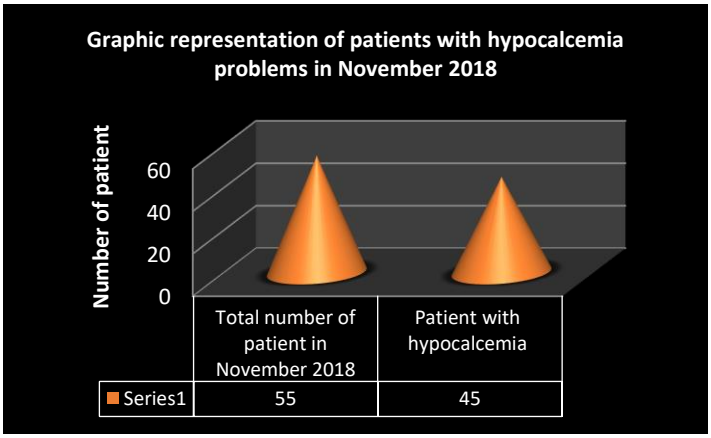
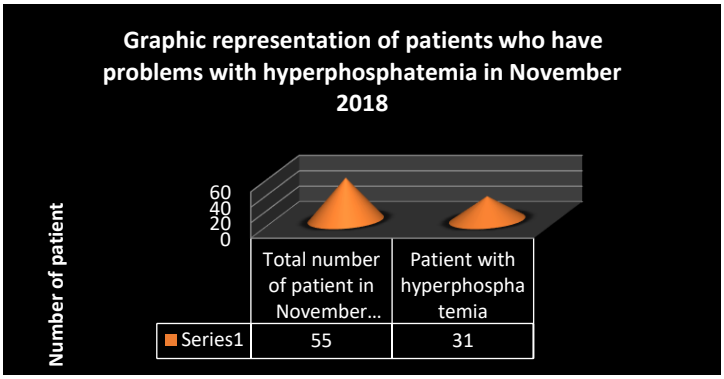
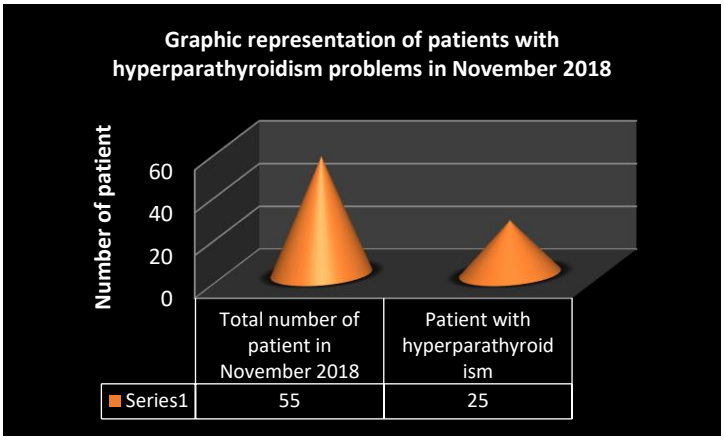




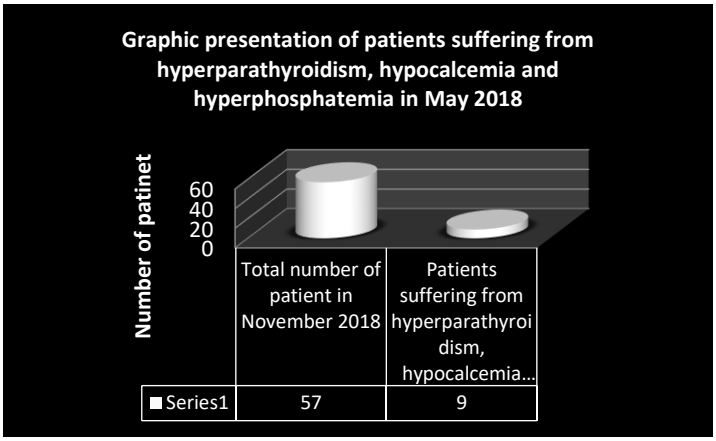
Total number of patient in November 2018	55
Patient with hypocalcemia	45
Patient with hyperphosphatemia	31
Patient with hyperparathyroidism	25







Total number of patient in May 2018	**57**
Patients suffering from hyperparathyroidism, hypocalcemia and hyperphosphatemia in May 2018	9



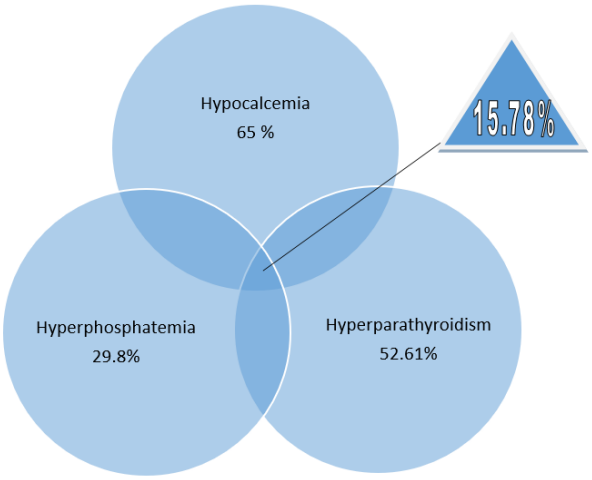
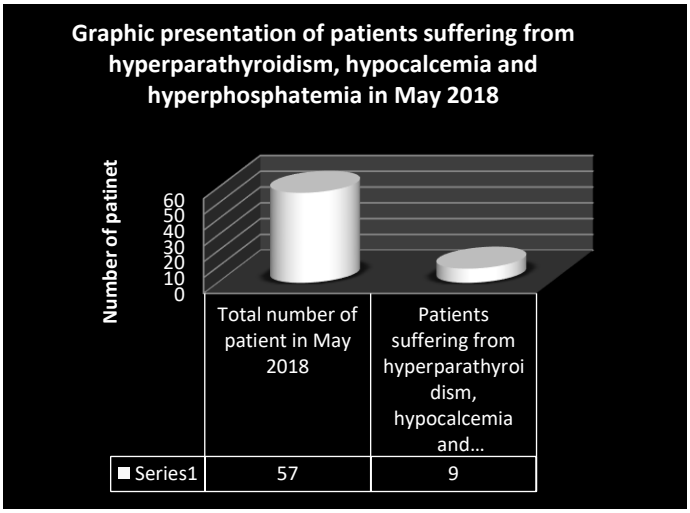
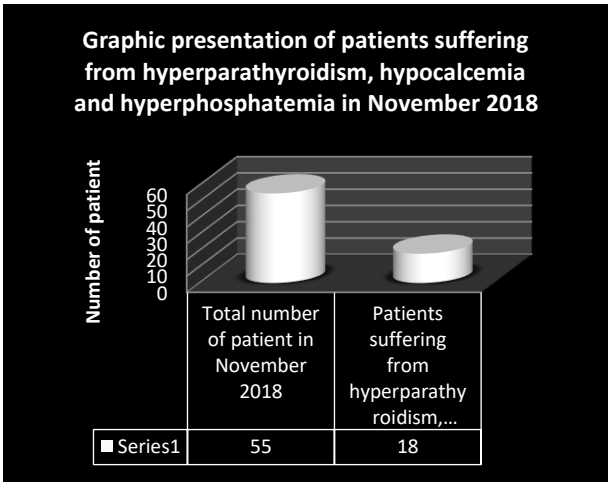


Diagram 1

Presents the percentage of patients suffering from renal hyperparathyroidism, hypocalcemia and hyperphosphatemia for the first 6 months of 2018

Total number of patient in November 2018	**55**
Patients suffering from hyperparathyroidism, hypocalcemia and hyperphosphatemia in November 2018	18





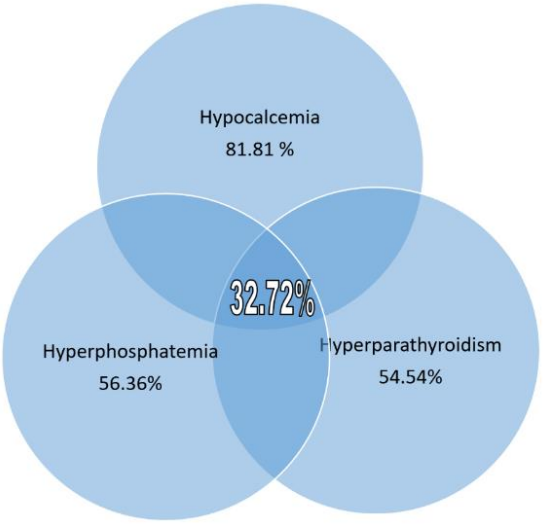


Diagram 2

Presents the percentage of patients suffering from renal hyperparathyroidism, hypocalcemia and hyperphosphatemia for the second half of 2018

Conclusions

It is difficult and multidisciplinary to treat these patients and prevent complications.

The best way to treat this is to begin with the awareness of the patient who, in the early stages of chronic renal disease, should maintain a strict dietary schedule and strictly follow the recommendations given by the physician.

Prevention of these complications should also be done by the physician who should closely follow the patient by recommending examinations according to world guidelines, the results of the examinations should be accompanied by appropriate therapy.

It is worth noting that the therapy for these patients is costly and unfortunately the patients in our country are not reimbursed for all the necessary medications, as a consequence the patients fail to be properly treated leading to an acceleration of renal hyperparathyroidism.

Our study shows that the majority of patients, respectively, 54.38% have hyperparathyroidism above target values for the first 6 months of 2018 and 54.54% have hyperparathyroidism values higher than the target values for the second half of 2018 .

With hypocalcemia there are about 63.15% of patients in the first 6 months of 2018 and about 81.8% in the second half of 2018.

With hyperphosphatemia are about 29.82% of patients for the first 6 months and 56.36% for the second 6 months of 2018.

From reviewing the above data in the two six months of 2018 we have an increase in the number of patients who have undergone hypocalcemia, hyperphosphatemia and hyperparathyroidism, a growth which is very significant as it results in almost doubling the number of patients.

Although detailed examinations are being conducted and patients are recommended strict diet and regular medication therapy it is noted that we have not achieved this goal as patients need to be more understandable and respect the doctor's advice and increase the role of the state in reimbursement. of drugs for these patients.

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Pharmaceutical Uses of Chitosan in the Medical Field

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Abstract

Two of the considerably versatile and promising biomaterials are chitin and chitosan. Chitin is known to be the most abundant natural amino mucopolysaccharide, produced annually almost as much as cellulose, and it is found in the structure of a wide number of intervertebrates (crustaceans' exoskeleton, insects' cuticles) functioning as a structural component that provides strenght and protection to the organisms, and the cell walls of fungi, among others. On the other hand, chitosan only occurs naturally in some fungi (mucoraceae). The composition of chitin is based on β(1→4)-linked 2-acetamido-2-deoxy-β-D-glucose (N-acetylglucosamine). Due to their natural origin, both chitin and chitosan are defined as a family of polymers which present a high variability in their chemical and biological properties such as biocompatibility, biodegradability, mucoadhesion, anticholesterolemic, antitumoral, hemostatic and antimicrobial effect. These characteristics of chitin and chitosan have a major influence on the their properties and depending on the DD (degree of dezacetilation) and Mw (molecular weight), they are used in a variety of medical applications such ascosmetics, artificial skin, wound-dressings, water engeneering, opthalmology, drug-delivery system. The aim of this review is to highlight the physicochemical properties of chitin and chitosan used in the wound healing process.It is known that in the last years, the number of pacients suffering from wounds and burns difficult to treat and heal has increased. During the wound healing process, the dressing protects the injury and contributes to the recovery of dermal and epidermal tissues. Due to their high biocompatibility, biodegradability and similarity to the human body macromolecules these natural polysacharides (chitin and chitosan) are extensively used in wounds and burns management.

Keywords: chitosan, chitin, wound dressing, natural polymer, biomaterials

Introduction

A major interest in modern medicine is represented by the biometerials with marine origins. Among these, chitin and chitosan received special attention in the medical fields due to their unique properties.

Chitin and its deacetylated derivative, chitosan are natural polymers composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). Both chitin and chitosan can not be defined as a unique chemical structure, but as a family of polymers, due to their natural origin, and also present a high variability in their chemical and physical properties. This variability is related not only to the origin of the samples but also to their method of preparation. So, a complete characterization of the samples is necessary.[1]

For chitin, there are known three crystalline forms: α-, β-, andγ-chitins. Chitosan is also crystalline and presents polymorphism depending on its physical state. The residual crystalinity may vary considerably depending on the origin of the polymer and its treatment during extraction from raw resources.

In a recent study, the author, Rinaudo has reported that the origin of chitin influences not only its crystalinity and purity but also its polymer chain arrangement, and its properties. [2]. Chitin and chitosan are used in various field of medicine, such as biomedicine, food industry, agriculture and cosmetics. The success of use of chitosan in all of these specific applications is directly linked to the detailed research of their physico-chemical properties.

Chitin is known to be the most abundant natural amino mucopolysaccharide, produced annually almost as much as cellulose, and it is found in the structure of a wide number of intervertebrates

(crustaceans' exoskeleton, insects' cuticles) functioning as a structural component that provides strenght and protection to the organisms, and the cell walls of fungi, among others. On the other hand, chitosan only occurs naturally in some fungi (*mucoraceae)*. The aim of this review is to highlight the physicochemical properties of chitin and chitosan used in the wound healing process.

Research Methods

The composition of chitin is based on β(1→4)-linked 2-acetamido-2-deoxy-β-D-glucose (N-acetylglucosamine). Due to their natural origin, both chitin and chitosan are defined as a family of polymers which present a high variability in their chemical and biological properties such as biocompatibility, biodegradability, mucoadhesion, anticholesterolemic, antitumoral, hemostatic and antimicrobial effect.

The main parameters that affect the polymer properties are DD, Mw, polydispersity and crystalinity.

The purity (ash content), the moisture, the content of heavy metals,endotoxin and proteins must be determined for applications related to human consumption such as food and medical applications.

It has been demonstrated that the DD is one of the most important chemical characteristics,which could influence the performance of chitosan in many of its applications. The influence of average Mw on the viscosity development of aqueos solutions plays a significant role in the biochemical and biopharmacological significance of chitosan [3]. Due to its low solubility chitin Mw is not easily determined.

Table 1. shows the various methods for the determination of chitin and chitosan characteristics.[4]

Table.1 Physicochemical Characteristics of Chitin and Chitosan and the Determination Methods

Physicochemical Characteristics	Determination Method
DD	Infrared Spectroscopy UV- spectrophotometry Nuclear magnetic resonance spectroscopy Potentiometric titration
Average Mw and/or Mw distribution	Viscosimetry Gel Permeation cromatography
Moisture content	Gravimetric analysis
Ash content	Gravimetric analysis
Protein	Bradford method

As is shown in Table.1 different result are obtained when using methods based on different principles. In present, even the best characterized chitosans available on the market are usually described olny with regard to their average degree of acetylation and their average degree of polymerization (DP), their ash content and the absence of contaminating bacteria [5].

Apart from the specific characteristics, which are specific fosr each application, there is a degree of consensus regarding general characteristics that must be present in chitosan samples to be used in the field of biomedical applications: moisture content %, ash content %, protein content %, insolubility%, turbidity NTU units, DD %.

For pharmaceutical applications, the chitosan requirements are: colour: white or slight yellow, particle size <0.3 mm, density 1.35-1.40 g/cm^3 , pH 6.5-7.5.

Results and Discussions

Chitin and chitosan are currently receiving a great deal of interest in the medical and pharmaceutical applications due to their interesting properties that make them suitable for use in the biomedical field, such as biocompatibility, biodegradability and non toxicity. Other properties such as analgesic, antitumor, hemostatic, hypocholesterolemic, antimicrobian and antioxidant properties have also been reported. A better understanding of the mechanism of these properties makes it necessary for chitosan to be well characterized and purified from accompanying compounds [6]. In addition chitin and chitosans derivatized in a variety of fashions can be used to prove molecular hypothesis for the biological activity. The parameter with a higher effect is the DD, because the majority of the biological properties are related to the cationic behaviour of the chitosan. In some cases, the Mw has a predominant role. Beside the DD and Mw, other properties such as chain conformation, solubility or degree of substitution have been studied. Chitosans produced by heterogenous deacetylation, with a block arrangement of acetylated units, have a tendency to form aggregates in aqueous solutions.

Table.2 shows the relationship between some chitin and chitosan biological properties and their physicochemical charateristics.[4]

Table.2. The relationship between some chitin and chitosan biological properties and their physicochemical charateristics

Property	Characteristic
Biodegradability	DD, distribution of acetyl groups Mw
Biocompatibility	DD
Mucoadhesion	DD, Mw (only chitosan)
Hemostatic effect	DD, Mw
Analgesic effect	DD
Adsorbtion enhancer	DD (only chitosan)
Antimicrobian effect	Mw
Anticolesterolemic effect	DD, Mw, viscozity
Antioxidant effect	DD,Mw

DD: deacetylation degree, Mw: molecular weight

1. Biodegradability

Chitin and chitosan are absent from mammals but they can be degraded *in vivo* by several proteases (lysozyme, papain, pepsin). Their biodegradation leads to the release of non-toxic oligosaccharides of variable length which can be subsenquently incorporated to glycosaminoglycans and glycoproteins, to metabolic pathways or be excreted. A degradation role on chitin and chitosan seems to play a non-specific protease present in all mammalian tissues- lysozyme. The lengths of the chains (Mw) affects the degradation rate [7]. The understanding and control of the degradation rate of chitin and chitosan-based devices is of great interest since degradation is essential in many small and large molecule release

applications and in functional tissue regeneration applications. Ideally, the rate of scaffold degradation should mirror the rate of new tissue formation or be adequate for the controlled release of bioactive molecules. Thus, it is important to understand and control both the mechanism and the rate

by which each material is degraded. The degradation rate also affects the biocompatibility since very fast rates of degradation will produce an accumulation of the amino sugars and produce an inflammatory response.

Chitosan samples with low DD induce an acute inflammatory response while chitosan samples with high DD induce a minimal response due to the low degradation rate.Degradation has been shown to increase as DD decreases. Kofuji *et al.* investigated the enzymatic behaviours of various chitosans by observing changes in the viscosity of chitosan solution in the presence of lysozyme [8]. They found that chitosan with a low DD tended to be degraded more rapidly. It can be concluded that it is impossible to estimate biodegradation rate from the DD alone.

2. Biocompatibility

Both chitin and chitosan show very good compatibility but this property depends on the characteristics of the sample (natural source, method of preparation, Mw and DD). Due to its higher versatility and biological properties the majority of the assays have been carried out on chitosan samples. Although the gastrointestinal enzymes can partially degrade both

chitin and chitosan, when both polymers are orally administered they are not absorbed. For this reason, they are considered as not bioavailable. Toxicity of chitosan is reported to depend on DD. It was reported that chitosans with DD higher than 35% showed low toxicity, while a DD under 35% caused dose dependant toxicity. On the other hand, Mw of chitosan did not influence toxicity. Residual proteins in chitin and chitosan could cause allergic reactions such as hypersensitivity. The protein content in a sample depends on the source of the sample and, especially, on the method of preparation.

3. Hemostatic Effect

Chitosan presents anticoagulant activity tested *invitro* [9]. The anticoagulant activity of chitosan seems to be related to its positive charge since red blood cells' membranes are negatively charged and chitin is less effective than chitosan. The hemostatic effect of chitosan is not related to the clasic coaulation pathways, but it can promote platelet agregation. The blood platelets play a very important role in the coagulation process and can lead to hemostatis and thrombosis. Besides platelets and erythrocytes, chitosan also accelerates thrombin generation.

4. Analgezic Effect

It was reported that both chitin and chitosan show analgesic effect. The analgesic effect of these biopolymers on inflammatory pain has been studied due to intraperitoneal administration of acetic acid. Chitosan showed a greater effect than chitin. This difference is due to the different action mechanism of the two polymers. It was demonstrated that themain analgesic effect of chitosan is the absorption of proton ions released in the inflammatory area.[4]

5. Antitumor Activity

An antitumor activity of chitosan has been claimed by inhibition of the growth of tumor cells mainly due to an immunevstimulation effect. chitosan oligomers possess antitumor activities tested both *in vitro* and *in vivo* [10].

Studies carried out using mice that had ingested low-Mw chitosan revealed significant antimetastatic effects of chitosan against Lewis lung carcinoma. Partially deacetylated chitin as well as chitin with a carboxymethyl group have also been effective to demote tumor progression. The suggested mechanism involves immunostimulating effects of chitin and its carboxymethyl derivatives via stimulation of cytolytic T-lymphocytes. This activity increases with smaller molecular sizes and it is suggested that they have immunostimulating effects that activate peritoneal macrophages and stimulate non-specific host resistance. However, higher Mw oligomers have also exhibited antitumor activity. The effect of chitosan on tumor growth and metastasis was studied. The activation of macrophages by chitosan is suggested to mediate its antitumor effects *in vivo*, while its angiogenic inducing properties may be the harmful effects of chitosan, such as promotion of tumor growth and invasion [11].

6. Anticholesterolemic Effect

There are several proposed mechanisms for cholesterol reduction by chitosan. The entrapment caused by a viscous polysaccharide solution is thought to reduce the absorption of fat and cholesterol in the diet. On the other hand,

the presence of the amino group in its structure determines the electrostatic force between chitosan and anion substances, such as fatty acids and bile acids. The interaction between chitosan and anionic surfaceactive materials (phospholipids, bile acids) depends on its three types of reactive functional groups: the amino group at the C2 position and primary and secondary hydroxyl groups at the C-3 and C-6 positions, respectively. Although great effort has been made to find a correlation between the physicochemical characteristics of chitosan and its fat-binding capacity, only some significant relationships have been demonstrated [4].

7. Antimicrobial Activity

The antimicrobial activity of chitin, chitosan, and their derivatives against different groups of microorganisms, such as bacteria, yeast, and fungi, has received considerable attention in recent years. Two main mechanisms have been suggested as the cause of the inhibition of microbial cells bychitosan. The first mechanism refers to the interaction with anionic groups on the cell surface. Due to its polycationic nature, it causes the formation of an impermeable layer around the cell, which prevents the transport of essential solutes. Electron microscopy demostratedthat the site of action is the outer membrane of gram negative bacteria. The permeabilizing effect has been observed at slightly acidic conditions in which chitosan is protonated, but this permeabilizing effect of chitosan is reversible [12]. The second mechanism involves the inhibition of the RNA and protein synthesis by permeation into the cell nucleus. In this case the Mw is the decisive property [13] Other mechanisms have also been proposed. Chitosan may inhibit microbial growth by acting as a chelating

agent rendering metals, trace elements or essential nutrients unavailable for the organism to grow at the normal rate. Chitosan is also able to interact with flocculate proteins, but this action is highly pH-dependent.

8. Antioxidative Activity

Chitosan has shown a significant scavenging capacity against different radical species, the results being comparable to those obtained with commercial antioxidants. Samples prepared from crab shell chitin with DD of 90, 75 and 50% where evaluated on the basis of their abilities to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, hydroxyl radical, superoxide radical and alkyl radical. The results revealed that chitosan with higher DD exhibited the highest scavenging activity [14]. Chitosans of different size as well as their sulphate derivatives were assayed against superoxide and hydroxyl radicals. A negative correlation was found between chitosan Mw and activity. The chitosan sulphated derivatives presented a stronger scavenging effect on peroxide radicals but the chitosan of lowest Mw showed more considerable ferrous ion-chelating potency than others [15].The chelation of metal ions is one of the reasons why chitosan may be considered as a potential natural antioxidant for stabilizing lipid containing foods to prolong shelf life. Chitosans may retard lipid oxidation by chelating ferrous ions present in the system, thus eliminating their prooxidant activity or their conversion to ferric ion.

Conclusion

- Chitin and chitosan present a great variety of properties, allowing them to have a large number of applications.
- Chitosan, a natural polysaccahridic cation, received a considerable attention as a functional, non-toxic, reneweable and biodegradable polymer in a wide field of applications, especially in the pharmaceutical, cosmetic fields and food industry.
- In the medical field, chitosan was not only used as artificial skin and wound healing accelerator, but also as physiological material, due to its antitumor, imunomodulator, antimicrobial and anticholesterolemic properties.
- It was revealed that these characteristics depend on the chemical structure and molecular weight. In conclusion, the applications of this natural polysaccharide are limited by its high molecular weight (Mw) and its low solubility in non-acidic aqueous media.

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Inovative Surgical Treatment for Intratubal Administration of Methotrexate

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Abstract

In patients where conservative medical treatment with methotrexate failed, surgical intervention was necessary. The personal surgical method was performed on a number of 9 patients; the surgical intervention was a conservative method – salpingorraphy. In order to prevent persistent gestational throphoblastic disease and tubal clogging, a polyethylene catheter is introduced in the oviduct until it reaches the ostium of the Fallopian tube, without exceeding it. In order to ensure a rigorous haemostasis, the Fallopian tube and the polyethylene catheter are sutured together. The level of HCG is measured in the fourth and seventh day postoperative: if the levels of HCG are higher than 1000 mUI/ml, if they plateau or if they have increased, methotrexate is administered intraluminally through the polyethylene tube, according to the following scheme: 50 mg of methotrexate are dissolved in 10 ml of physiological saline solution and injected through the polyethylene catheter, for 5 days. 10 mg per day in 2 doses (5 mg in the morning and 5 mg in the evening).If the values of HCG decrease to an adequate level and there is no risk of persistent throphoblastic disease, the polyethylene catheter is kept for 8-12 days, afterwards it is extracted by traction. If the values do not decrease accordingly, the intraluminal administration of methotrexate is resumed after a 3-day break. This method was used on a number of 9 patients; 4 of them had been treated with methotrexate before the surgical intervention and pertain to the study, and 5 of them had been operated on for complications of ectopic pregnancy and were suitable for this kind of surgical intervention. No postoperative complications or deaths were recorded.

Keywords: ectopic pregnancies, methotrexate, Human Chorionic Gonadotrophin Hormone.

Introduction

Regardless of the approach used, the patient must be followed by measuring the values of HCG, because of the persistent trophoblastic disease which continues to secrete placentary chorionic hormone and also continues to increase the rate of failure for methotrexate treatment.

Methotrexate can be used in the treatment of ectopic pregnancy in the following ways: systemic, in single dose of 50mg/m^2 of body surface area or multiple dose: 50mg/day in 4 doses, 1mg/kg body/day; it can be injected directly in the amniotic sac, using ultrasound or laparoscopy. All of these methods stop the evolution of extrauterine pregnancy.

Persistent gestational trophoblastic disease is not associated only with systemic treatment with methotrexate, but also with conservative surgical interventions performed through classic or laparoscopic methods. The patient must be followed by measuring HCG 7 days postoperative; if values of HCG are greater than 1000 mUI/ml or stay at a constant level, it is necessary to administer systemic methotrexate according to the known protocol schemes and to measure the level of HCG weekly until it lowers to under 10mUI/ml.

In certain situations (haemodynamic instability and/or haemoperitoneum due to tubal rupture), surgical intervention is necessary. If a conservative surgical procedure is elected – tubal milking, salpingectomy, salpingostomy – there is the risk of secondary bleeding due to the weak muscles of the oviduct or because of the remaining trophoblastic tissues (persistent trophoblastic disease) [1,2]. The surgical technique (conservative or radical) concerning the affected oviduct will be decided intraoperatively, according to the lesions found and to the patient's wish to have children or not [3]. Under these

circumstances, we have conceived an intraoperative surgical technique meant to solve the persistent trophoblastic disease through the intratubal administration of methotrexate using a polyethylene catheter. The polyethylene catheter, which is inserted in the oviduct, is used to inject methotrexate, guided by the values of HCG.

Late results are monitored by performing hysterosalpingography or contrast ultrasound at least 3 months after the surgical procedure, when the permeability of the ipsi- and contralateral tube is checked.

Tubal surgery and conservative surgery in general require a lot of patience and tenderness in gestures, a specialized surgeon, fine instruments and suture wires, atraumatic needles, a catheter of polyethylene. The best method in tubal plastic surgery is the one which least damages the mucosal lining [4].

Research Methods

Selecting the Cases

The patients were treated with methotrexate for ectopic pregnancy. Methotrexate therapy failed and surgery was required because of haemodynamic instability and complications.

The procedure can be used in patients not previously treated with methotrexate, in which disease became complicated, making the surgical intervention necessary.

Preoperative Preparation

Usually, surgery is a medical-surgical emergency, so there is no time for adequate preparation 2-4 before operation.

It is necessary and mandatory to get patient approval and a signed informed consent. The surgeon should warn the patient about the surgical intervention and about the therapeutic possibilities, according to the situation of the intraoperative lesions. The patient must know that the doctor will try to choose a conservative surgical procedure that will protect the pregnant tube, but the final decision will be made strictly intraoperatively, based on the lesions found in the internal genitelia. The situation becomes even more dramatic when the patient already has an ectopic pregnancy operated by radical procedure (salpingectomy).

Her obstetrical future depends on this new surgery and the risk of losing the only remaining tube is huge.

The patient must be aware and informed of the possibility of losing her only Fallopian tube, which will lead to her enrolment on a waiting list for in vitro fertilization.

In the fortunate event when the oviduct can be preserved, she must understand that conservative surgical procedures are based on strict anatomical principles, but there still remain unresolved physiological factors: muscular, epithelial, ciliary, hormonal, sperm migration, fertilization, migration of the zygote. The fact that the patient already has an ectopic pregnancy is the result of tubal morphophysiological disorders of the local and general aetiopathogenic factors, which surgery cannot solve.

The patient must know clearly before surgery all the aspects mentioned above and agree by signing an informed consent.

Anaesthesia

The type of anaesthesia, as well as the anaesthetic risk is determined by the anaesthetist. If the patient develops haemodynamic instability, the anaesthesia will be performed via orotracheal intubation. If the patient haemodynamically balanced, with normal blood pressure and pulse, without signs of haematological decompensation, a spinal anaesthesia or a peridural anaesthesia can be performed.

- Operative technique – surgical steps:
- Opening the abdominal wall;
- Inventory of lesions;
- Choice of surgical procedure

Opening the abdominal wall

Laparatomy using the Pfannenstiel incision is recommended for is aesthetic character and also because it provides an accessible way to the pelvic organs and abdominal wall closure has a low risk of eventration.

An autostatic retractor is positioned on the abdominal wall, the intestinal loops are isolated with soft sterile fields, the patient is placed in Trendelenburg position and, afterwards, the inventory of lesions is begun.

Inventory of the lesions

The condition of the uterus, the contralateral tube, the ovaries and the presence or absence of haemoperitoneum is checked, after which, the pregnant tube is investigated. In order to reveal the oviduct, a resorbable thread is applied on the bottom of the uterus, on the median line, which is tractioned using a Pean clamp. A second resorbable wire, handled with a traction clamp, is passed at the inferior pole of the ovary. If both wires are pulled, the tube's entire trajectory is revealed. The tube is checked from the fimbria to its insertion on the uterus. The following situations can be encountered, and these also represent the indications for the personal procedure:

- Tube is pregnant but intact;
- Tube is intact but the embryo is free in the peritoneal cavity (tubal abortion);
- Tube with tubal abortion but with little continuity solution without major bleeding;
- Tube pregnant in the ampullar/fimbrial region and/or isthmic region, unruptured;
- Tube pregnant in the ampullar/fimbrial region and/or isthmic region, ruptured, but with minor parietal damage and without heavy bleeding.

Contraindications of the personal procedure

- Tube pregnant in the ampullar/fimbrial region and/or isthmic region, ruptured, but with important mural destruction and heavy bleeding with haemodynamic instability – radical procedure is used – salpingectomy.

Results and Discussions

Electing the procedure

Description: A polyethylene catheter is introduced into the lumen of the tube, up to the level of the uterine ostium, without exceeding it. If the tube has minor lesions or if a linear salpingectomy was performed on the antimesometrial border of the oviduct, with the purpose of evacuating the pregnancy, a salpingorraphy with nonresorbable fine 4.0 wire is performed. In order to ensure a rigorous haemostasis, the Fallopian tube and the polyethylene catheter are sutured together. The exterior diameter of the polyethylene catheter must be between 1.2-1.7 mm, because thicker catheters lead to the atrophy of the tubal mucosa through compression [4].

After ensuring haemostasis through salpingorraphy, the polyethylene catheter is kept in the oviduct; towards the uterine ostium, it is put in place with a thin, resorbable, 4.0 wire, towards the abdominal ostium, the plastic tube is attached to the serosa of the fimbria with the same kind of wire.

The permeability of the polyethylene catheter is checked by introducing either a stylet or sterile substances (physiological saline solution, sterile methylene blue). The abdominal end of the tube is exteriorized to the abdominal wall in the right or left iliac fossa, through a contraincision. An abdominal lavage with warm physiological saline solution is performed. In order to avoid the forming of tubal adhesions, a solution of dissolved dexamethazone in 10 ml of physiological saline solution can be introduced in the polyethylene catheter. After cleaning the abdominal cavity and ensuring haemostasis, the abdominal wall is closed, layer by layer.

Postoperative care:

- Antibiotherapy 5 days;
- Prophylaxis of thromboembolic disease by administration of heparins with low molecular weight (Clexane 40-60 mg/day depending on patient weight) and early mobilization;
- Monitoring of urine output;
- Stimulation and the resumption of intestinal transit;
- Determination of HCG on the fourth and seventh day after surgery – if HCG levels are higher than 1000 mIU/ml, have remained in plateau or have increased, intraluminal methotrexate is administered in the polyethylene catheter, according to the treatment scheme:
- Methotrexate is administered daily through the polyethylene catheter for 5 days, in 2 doses (5 mg in the morning and 5 mg in the evening).

- The polyethylene catheter is kept 8-12 days after which it is extracted by simple traction, if the HCG levels drop there is no risk of persistent trophoblastic disease.
- If the values of HCG decrease to an adequate level and there is no risk of persistent trophoblastic disease, the polyethylene catheter is kept for 8-12 days, afterwards it is extracted by traction.

If the values do not decrease adequately, the intraluminal administration of methotrexate is resumed after a 3-day break. We administer methotrexate through the polyethylene catheter inserted in the oviduct, in order to avoid the adverse effects of its systemic administration. The methotrexate administered intraluminally is diluted and it is given in very small doses in order not to damage the tubal mucosa.

Table 1 – Late results after the surgical intervention through personal procedure.

Total number of operated patients	Lost from the study	Pregnancies			
		Intrauterine pregnancies			Extrauterine
		Full term	Premature	Abortion	
9	2	2	1	1	2

The general adverse reactions, decreased haemoglobin, platelets, leucocytes, the increase of transaminase, urea, creatinine, uric acid were insignificant.

If methotrexate is not required because the HCG levels drop satisfactory after surgical intervention (under 1000 mUI/ml), a solution containing antibiotics and cortisone can be given through the polyethylene catheter, 6 days after surgery, in order to avoid the forming of adhesions. 1 g of ceftriaxone (cephalosporin) and 8 mg of dexamethasone are dissolved in 10 ml of saline solution, after we have made sure the patient is not allergic. The solution is injected through the polyethylene catheter, after which we clamp the catheter to ensure that the instilled substances come into contact with the wall of the oviduct. Consecutively, the polyethylene catheter is unclogged.

The procedure can be repeated every 3 days because the cortisone may impede tubal scarring.

The procedure was used on a number of 9 patients, 4 of them had been treated with methotrexate before the surgical intervention and they pertain to the study, and 5 of them were operated for complications of ectopic pregnancy and were suitable for this type of surgical intervention.

No postoperative complications or death were recorded.

It is premature to draw conclusion after so few interventions of this kind, but the results have been encouraging. Of the 9 patients 2 were lost from the study. Tubal patency was tested on the remaining 7 patients by performing hysterosalpingography 3 to 6 months after surgery. Tubal patency was positive in 4 patients for tubes operated through the surgical procedure. The results of the operations are estimated by tubal pregnancy and not by obtaining tubal patency [4]. Out of the 7 patients, 5 remained pregnant with intrauterine pregnancies, of which: 2 delivered full term healthy babies, one had a premature delivery (34 weeks – foetus 2100 g) and 2 patients had a spontaneous abortion in the first trimester.

Two patients had a recurrent extrauterine pregnancy.

After intraluminal administrations of methotrexate, the values of HCG dropped under 1000mUI/ml after 12 days from the operation, and the values came back to normal in 23 to 31 days after the surgery. The decrease of the HCG level after conservative treatment takes more time than after the surgical intervention [5,6]. The procedure is similar to plastic tubal operations which ensure tubotubal anastomosis and/or tubo-uterine reimplantation surgeries.

Technical results proved in time will probably be higher than those offered by plastic tubing operations. According to Palmer, quoted by Sarbu, the results of tubal plastic surgery are:

- More than 40% success recorded in salpingolysis (55-75%) and tubal reanastomosis (40-66%);
- Around 30% successful in:
- Tubal reimplantation (27-38%);
- Lysis of adhesion (29-35%);
- Terminal neosapingostomy (26-32%).

Failures, even when the operation has managed to obtain patent tubes, shows that the mere restoration of permeability only partially resolves the functional disorders of the oviduct.

We have to compare this surgical procedure which uses a classic laparatomy to surgical laparoscopy which has taken a great momentum after 1980.The success rate for laparoscopic treatment varies with different studies: the success rate of treatment 88.1%, the conceiving rate post laparoscopic intervention 77.3%, and the rate for recurrent pregnancy 10.6% [1]. Out of the surgical procedures used in laparoscopy, we mention: salpingectomy, salpingotomy, salpingostomy, fimbrial aspiration, peritoneal fluid aspiration and lavage, lysis of ovarian and peritubal adhesions, partial ovary resection, hysterotomy, surgery of the contralateral oviduct [1].

The complications for conservative laparoscopic surgery are significantly higher than those of radical laparoscopic surgery. The rate of complications for laparoscopic surgery is higher than that for classic laparotomy [7].

After laparoscopic salpingotomy, persistent trophoblastic disease has a higher incidence, comparatively with classic salpingotomy [8].

Conclusion

- The rate for complications after laparoscopic salpingotomy is higher than the failure rate after salpingotomy performed via a laparotomy (15.5% as opposed to 1.8%) [7].
- In emergency cases, laparotomy remains the surgical procedure available to all obstetrical-gynaecology doctors.
- The attitude and mentality of experienced doctors has to be changed in the direction of conservative tubal surgery.
- This personal method of administration of methotrexate may protect a fragile and sometimes unique tube; it avoids the adverse effects of systemi administration and increases hopes for the patient's obstetrical future.
- If the HCG values do not require intratubal administration of methotrexate, this device can be used to prevent the forming of tubal adhesions by intraluminal administration of antibiotics and cortisone substances.
- The number of cases in which the personal procedure was used is relatively small, but the results obtained are encouraging and close to those of laparoscopic surgery.

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Methotrexate Therapy in Obstetrical Diseases

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Abstract

Our study is a rewiew of Methotrexate therapy in obstetrical diseases such us: hydatidiform mole, and medical abortion. In the medical world, methotrexate is a citostatic drug used in neoplastic diseases. The clinical pharmacology data regarding methotrexate is presented, alongside route of administration and therapeutic effects in malignant disease, hydatiform mole, and medical abortion. The use of methotrexate in medical abortion and ectopic pregnancy is a great accomplishment, as it replaces a surgical intervention marred by characteristic side effects, with similar results.

Keywords: Methotrexate, obstetrics, gynecology, tubal pregnancy, HCG human chorionic gonadotrophine hormon.

1. Introduction

In the medical world, methotrexate is a citostatic drug used in neoplastic diseases such as lymphoblastic leukaemia, leukaemic meningitis, Burkitt lymphoma, mycosis fungoides, osteosarcoma, as well as severe forms of psoriasis and rheumatoid arthritis.

Methotrexate was first used in obstetrics and gynaecology in the year 1956 for the treatment of trophoblastic gestational disease [1]. We present general data regarding methotrexate as a drug.

2. Methotrexate – General Pharmacology

Methotrexate is part of a citostatic group of drugs called antimetabolites. In the same group, we have 5-fluorouracil, an antimetabolite of uracil, and capecitabine, a prodrug of 5'-deoxi 5 fluoridine [2]. The chemical formula was first described in 1946. Methotrexate is an 8 amino 10 methyl pteroyglutamic acid (Fig.1).

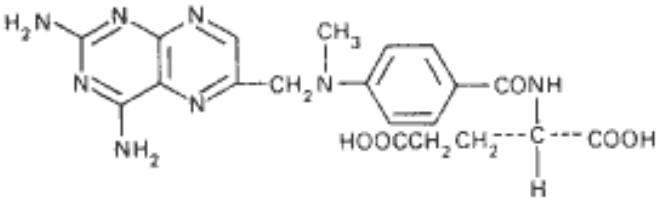

Fig. 1 The chemical formula of methotrexate (2)

The chemical name: (+)-*N*-[p-[[(2,4-Diamino-6-pteridinyl)methyl] methylamino] benzoyl]-L-glutamic acid; *N*-[4-[[(2,4-diamino-6 pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid.

Antimetabolites inhibit the synthesis of purine (guanine, purine) or pyrimidine (uracil) nucleotidic precursors or they compete with these in DNA or RNA synthesis. The maximym citostatic effect is specific of the S phase of the celular cycle. Folic acid is a structural metabolite of certain enzymes that take part in the synthesis of nucleic acids, followed by cellular division.

Pharmacodynamics

Cells with active proliferation (malignant cells of the bone marrow, oral, intestinal and bladder mucosa, and foetal cells) are generally more sensitive to the stopping of cellular division. When cell proliferation in malignant tissues is higher than in the majority of normal tissues, methotrexate can influence malignant growth, without irreversible effects on normal tissues [2].

Pharmacokinetics

Absorption. In adults, absorption following oral administration depends on the dose. The maximum serum concentration is obtained in 1-2 hours. At doses of 30 mg/m^2 or smaller, methotrexate is generally well absorped, with an average bioavailability of 60%. Absorption of doses higher than 80 mg/m^2 is significantly lower, possibly due to saturation effect [2].

Halving time. Halving time for methotrexate is 3-10 hours in patients who are administered less than 30 mg/m^2 or lower doses (in psoriasis or rheumatoid arthritis). In patients who are administered higher doses, halving time is around 8-15 hours.

Excretion. Renal excretion is the primary elimination pathway and it depends on dosage and the route of administration. Methotrexate is excreted unmodified in a percentage of 80-90% in the first 24 hours. There also exists a biliary excretion amounting to 10% or less of the administered dose. Renal excretion is accomplished through glomerular filtration and active tubular secretion [2].

Toxicity. The toxicity of the drug towards healthy tissues depends on the length of exposure to methotrexate. When a patient has a slow elimination of the drug due to renal ailments, accumulation in the serous tissues or due to other causes, the serum concentration can remain elevated for a long period of time. Toxicity due to high doses or slow excretion is reduced through the administration of calcium folinate (factor citrovorum) [2].

Overdose. To reduce the toxicity and counteract effects due to methotrexate overdose, treatment with calcium folinate is indicated. Administration must begin as early as possible. When the interval between the administration of methotrexate and that of calcium folinate is higher, the efficiency of folinate in alleviating methotrexate toxicity decreases.

Therapeutic guide regarding methotrexate and calcium folinate treatment

- **a.** The administration of methotrexate must be delayed if the leukocyte count is lower than 3000/mm^3; platelet count lower than 75.000, serum bilirubin higher than 1,2; TGP and TGO twice higher than normal, or if the patient presents with persistent pleurisy.
- **b.** Evaluation of renal function: serum creatinine must be normal, clearance higher than 60ml/min; if during treatment, creatinine grows by 50% or more, compared to the initial value, it is necessary to determine the creatinine clearance, which must be higher than 60mL/min.

c. Patient hydration and urine alkalinization: 1000ml/m^2 of intravenous fluid is administered 6 hours before the methotrexate i.v drip. Hydration with 125 mL/m^2/hour(3l/m^2/day) during the i.v. and 2 days after ending it. Urine is alkalized to obtain a pH higher than 7. Alkalinization can be achieved through the administration of oral or intravenous sodium bicarbonate.

Metotrexat – brand names

Abitrexate, injection 25 mg/mL- 2 mL; sol.inj. 25 mg/mL- 20 ml (Abic, Israel) **Antifolan**, tablets 2,5 mg; injection powder./perf. 50 mg (Sindan, Romania)

Methotrexat "Lederle", tablets 2,5 mg; tablets 10 mg; injection 25 mg/mL- 1 mL; injection. 25 mg/mL- 2 mL; injection. 25 mg/mL- 20 mL; injection 25 mg/mL- 40 ml; injection 25 mg/mL- 200 mL (Wyeth Lederle, Austria)

Methotrexat Ebewe, solution for injection and infusion 5 mg/mL- 1 mL; solution for injection and infusion 10 mg/mL-1 mL; solution for injection and infusion 10 mg/mL- 5 mL; solution for injection and infusion 100 mg/mL - 5 mL solution for injection and infusion 100 mg/mL- 10 mL; solution for injection and infusion 100 mg/mL- 50 mL; (Ebewe, Austria).

Trophoblastic gestational disease

Trophoblastic gestational disease is a complex clinical and anatomic pathology entity which defines a benign and malignant proliferation of the chorionic villi of the trophoblast during pregnancy. In partial mole, the trophoblastic hyperplasia is focal, with stromal inclusions, with a triploid karyotype 69XXX, 69XXY, 69XYY. The additional haploid set is usually of paternal origin [3]. If the foetus is present, it shows the signs of the triploidy: multiple foetal malformations, growth retardation, syndactyly, and hydrocephalus [4]. Complete molar pregnancy is characterized through the absence of embryonic or foetal tissue, chorionic villi show a general ballooning, trophoblastic hyperplasia is diffuse, stromal inclusions are absent, and the karyotype is 46XX and 46XY of paternal origin [5].

Results and Discussions

Treatment of persistent trophoblastic gestational disease

Mono-chemotherapy

The use of methotrexate and actinomycin D in the treatment of metastatic and non-metastatic persistent trophoblastic gestational disease with low risk has lead to the improvement of disease prognosis and to the obtaining of remission phases [6].

a. The use of methotrexate

There are several methotrexate admnistration protocols, with similar results.

- the most frequently used protocol is intra-muscular or intravenous 0,4mg/kg body weight for 5 days.
- a second option: 1-1,5 mg/kg body weight in 4 doses in the 1-3-5-7 days, followed by administration of folic acid (citrovorum acid) in doses of 0,1-0,14mg/kg body weight in the 2-4-6-8 days.

Literature first reported the association of methotrexate and folic acid in the treatment of trophoblastic gestational disease was in the years 1964 [7].

Starting with the year 1977, the combination methotrexate-folic acid has represented the first-choice treatment in persistent trophoblastic gestational disease [8].

First line chemotherapy – combined EMA/CO chemotherapy

Combined EMA/CO chemotherapy is used in patients with metastatic trophoblastic gestational disease and in those with a prognosis score with high risk. In all protocols for combined chemotherapy for trophoblastic gestational disease, etoposide is used alongside methotrexate and actinomycin D.

EMA/CO regimen, treatment scheme:

First session:

Day 1:

- etoposide 100mg/ m^2 ;
- methotrexate 100mg/ m^2 intravenous as loading dose, followed by 200 mg/m^2 intravenously for 12 hours;

Day 2:

- folic acid (citrovorum acid) 15mg intravenous, administered 24 hours after methotrexate and repeated 4 times at a 12 hour interval.
- actinomycin D 0,5 mg intravenous.

6 days break.

Second session:

Day 8:

- cyclophosphamide 600 mg/m^2 intravenous;
- vincristine 1 mg/m^2

The cycle is repeated every 2 weeks until 3 negative values of the human gonadotropin hormone (hCG).

Fertility after persistent trophoblastic gestational disease

In patients with persistent trophoblastic gestational disease successfully treated through chemotherapy, a normal future reproductive function is expected. Future products of concepts have a low risk of foetal abnormalities and malformations [9, 10].

Methotrexate in induced medical abortion. Classification

Medical abortion (induced) can be:

- *legal,* which is performed with the boundaries of the law by qualified medical personnel (specialized physicians);
- *illegal* – which is provoked through various methods. Known in literature as septic or unsafe abortion.

Legal abortion can be therapeutic in cases where:

- the foetus endangers the life of the mother;
- the pregnancy is a result of rape of incest (ethical abortion);
- the foetus has severe abnormalities or severe intra-uterine growth retardation (eugenic abortion).

In Romania, therapeutic abortion can be performed up to 24 weeks [11]. By request, abortion can be performed legally up to 14 weeks of gestational age.

In Romania, abortion has become possible as of 26 December 1989, through the abolishment of the communist decree. Between 1990-1992, the rate of requested medical abortion was of 200 abortions per 1000 fertile females with ages between 15 and 44, which corresponds to approximately 3 abortions for one live newborn and a total rate of 3,4 abortions per one fertile female between 15 and 44 years old. This rate was the highest in the world at the time [11, 12].

Induced abortion through medical treatment with methotrexate and misoprostol (see Fig 2)

Medical abortion induction methods as an alternative to surgical procedures first appeared in Europe and China starting with the year 1990 [13].

Inclusion criteria:

- haemodynamic stable patients;
- intra-uterine pregnancy 56-63 days old or less since the date of the last menstrual cycle;
- pregnancy age confirmed through trans-vaginal ultrasound;
- available blood tests;
- Rh factor – administration of antiD immunoglobulin if patients are RH negative and have no previous isoimmunization;
- complete blood count: RBC, WBC, PLT;
- hepatic enzymes: TGO, TGP;

- renal function: creatinine, uric acid, urea;
- signed informed consent regarding the drugs used, potential side effects, success and failure rate of the treatment as well as the potential need for surgical intervention.

Exclusion criteria:

- known alergies to the 2 compounds (methotrexate and misoprostol) ;
- haematological ailments: leukopenia (<3000/mm^3) or thrombocytopenia (<100000/mm^3)
- hepatic ailments;
- renal ailments;
- asthma or other pulmonary ailments;
- HIV or AIDS infection.

Protocol administration [13]

If the inclusion criteria are met, the drugs are administered as follows:

Day 1

Methotrexate administered systemically

a. single dose of 50 or 60 mg/m^2 body surface, intra-muscular. Raising the methotrexate dose does not increase success rate [14].
b. single oral dose, 25-50 mg with the same efficiency as intramuscular doses [15].

The patient is discharged from hospital. The patient returns for the remainder of the treatment in the 5-7 days.

Day 5 and 7:

Intravaginal misoprostol 800 μg, one of the two options:

1. 4 tablets of 200 μg inserted vaginally with a tampon that will be kept in for 12 hours;
2. 4 ovules of 200 μg inserted in the Douglas cul-de-sac.

Day 12 – Day 14 – according to the results of clinical and ultrasound investigations, the treatment will continue as follows:

a. If the ultrasound shows an incomplete abortions (ovular remnants in the uterine cavity), treatment consists of a surgical aspiration abortion.
b. If the ultrasound shows the existence of an intra-uterine sac with or without cardiac activity, an additional dose of 800 μg intravaginal misoprostol or a surgical aspiration, as the patient wishes.
c. If the ultrasound shows a complete evacuation of the product of conception, the treatment is considered successful.

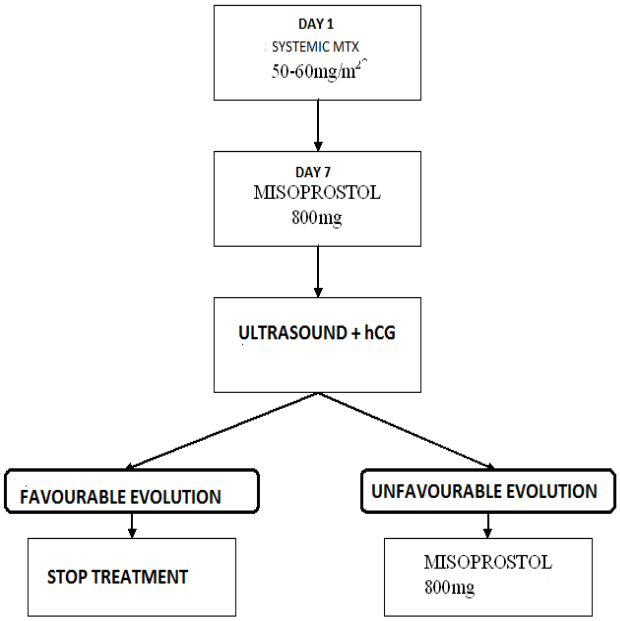

Fig.2 Treatment scheme for medical abortion with methotrexate-misoprostol

CONCLUSIONS

Treatment failure and success

Success is defined as the complete elimination of the product of conception within the first 7 days since the administration of the first misoprostol dose (days 7-14) or after the administration of the additional dose of misoprostol in days 12-14 (the interval 14-21).

Immediate success – complete abortion is obtained before the administration of misoprostol or during the first 24 hours since administration.

Late or delayed success – complete abortion is obtained after more than 24 hours since the administration of misoprostol.

Failure is defined as the incomplete elimination of the product of conception, even after the administration of the additional misoprostol dose, which leads to surgical resolution of the case. Literature studies show a success rate of 90% for pregnancies of 56 days or less [16].

In 12 to 35% of women, abortion is produced in the 20-30 days following administration of misoprostol.

Methotrexate was also used alone for abortion induction, but the success rate is smaller than in the case of combined therapy; abortion is produced 3 weeks following drug administration [17] Methotrexate, a drug used solely in neoplastic disease was also included in obstetrical therapy so as to prevent the transformation of hydatidiform mole in chorionic carcinoma with improvement in the vital prognosis of the patients. Its use in medical abortion and ectopic pregnancy is a great accomplishment, as it replaces a surgical intervention with all of its complications – including those related to anaesthesia – with similar results.

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