Doctoral School of Medicine

Doctoral field: MEDICINE

DOCTORAL THESIS (ABSTRACT)

Contributions to the study of correlations between orodontal diseases and the metabolic syndrome

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Content

Current state of knowledge. Metabolic syndrome and the dysmetabolic profile

Metabolic disorders, classified today under the name "Metabolic Syndrome" (S Met) can be defined as a set of changes in the biological constants in the body, which have at their center an association of conditions including: obesity, especially abdominal obesity, arterial hypertension, hyperglycemia/dyslipidemia, and type 2 diabetes. Metabolic syndrome is increasingly being blamed today as a determinant factor for a number of diseases, foremost among which is type 2 diabetes and cardiovascular disease.

In addition to these, although the mechanisms of interaction and determination are not fully elucidated, other diseases such as: colorectal cancer, rheumatoid arthritis, psoriasis, premature births, periodontal disease, etc. are also blamed. All these conditions cause important changes in the body, manifested either by important functional disabilities or by conditions that put life at risk through a particular morbidity and mortality.

The current century is characterized, for a good part of the population, by a diet with caloric excesses or frequently unbalanced, associated with sedentary lifestyle and stress specific to modern life. These conditions are clinically manifested by a worldwide epidemic of obesity and its associated diseases, which affects both the quality of life and the costs of medical and social health rehabilitation services. The burden of these costs is increasingly difficult for any society to bear.

In numerous scientific approaches, from the last decades, a series of factors such as: insulin resistance, visceral obesity, arterial hypertension (HT), dyslipidemia and more recently their association with periodontal diseases are found. The interaction of these conditions, although frequently mentioned in studies, could not be fully elucidated.

Only some common links with periodontal disease were noted, with which it is associated in significant percentages. By controlling this disease as well as the risk factors of S Met we can expect a reduction of the risks and an improvement of the body's health.

For the care of patients with S Met it is necessary to evaluate a series of risk factors, which contribute to changes outside the biological limits for the constants of the body's homeostasis and today considered as normal values.

1.2 Brief history of Metabolic Syndrome

The first scientific reports on the changes produced in the human body, determined by the associations of some abnormalities, related to metabolism, date back more than 60-70 years. Thus, in 1923 associations between hyperglycemia, gout and hypertension are reported in the medical literature, and later, in 1956, in addition to these, links with android obesity and arteriosclerosis are also associated [1,2]. Despite this evidence, it was only in 1988 that GW Reaven defined for the first time a new syndrome, which he called syndrome X or the syndrome of acquired insulin resistance [3].

The recent definitions, elaborated by international scientific organizations, propose, within the definition of this syndrome, the association of changes in some physiological parameters of the body that reproduce the causal links as faithfully as possible, facilitate the diagnosis and facilitate the therapeutic approach. In this sense, the WHO in 1999 believes that at the center of the biological changes, triggered by S Met, the changes caused by the abnormal metabolism of carbohydrates must be placed. Risk factors involved in the production of S Met

Appreciation of S Met epidemiology is an essential step in cardiovascular risk assessment. Both obesity, diabetes and HTN as components of S Met know an increase in prevalence in recent decades both worldwide and in our country. Studies estimate that currently, about a quarter of the population of Western Europe could be diagnosed with S Met (23,28)

Data from the recent medical literature record that the risk factors implicated in S Met etiopathogenesis are multifactorial. They can be grouped by having the following common origins: genetic predisposition, uterine determinism and environmental influences.

1.5 Etiopathogenic factors incriminated in the production of S Met

1.5.1 Genetic predisposition

The global obesity epidemic has important consequences for society. There are a number of hypotheses that try to explain etiopathogenetic possible ways of occurrence. According to one hypothesis, the human body, initially having to face periods of food restrictions, naturally selected individuals with genes capable of saving energy and storing energy reserves and thus predisposing to obesity.

According to this hypothesis, called the "thrifty genotype" in the medical literature, it is considered that about 25% of the world's population shows a decrease in tissue sensitivity to the insulin hormone. The decrease in insulin secretion causes changes in the absorption and metabolism of carbohydrates at the cellular level. This genetic predisposition, thus gained, can manifest specifically, depending on the interaction of environmental risk factors [29 - 31].

1.5.2. Uterine determinism

The hypothesis of uterine determinism has been incriminated in the etiopathogenesis of S Met. This hypothesis was advanced following some epidemiological studies, carried out in 2005, which suggest that the low weight of the fetus at birth is the result of insufficient development of the maternal placenta. This favors the installation of a specific metabolic adaptation, which favors lipid deposits as an energy reserve in the child and then in the adult. These deposits can later favor the appearance of obesity. There are studies, which confirmed this hypothesis through some experiments carried out on animals, which were undernourished during the gestation period and which subsequently, shortly after birth, became obese [32-34].

1.5.3. Environmental influences

According to this hypothesis, dietary influences from the environment can very easily determine, against the background of a predisposed terrain, the accumulation of lipids in the cells. In this field, the lack of regular physical activities and sedentary lifestyle aggravates the insulin resistance of skeletal muscle tissues, favoring the preferential transformation of carbohydrates into lipids and their subsequent deposition in cells in the form of fatty acids. Their accumulation causes weight gain, even with moderate food consumption.

Other environmental factors that can aggravate insulin resistance are stress, smoking and alcohol. On the other hand, there are also studies that claim, paradoxically, that a moderate consumption of alcohol of up to two glasses of wine per day "the French paradox" can neutralize part of the factors that increase the risk of S Met installation [35].

Also in this context, another recent etiopathogenic concept, based on new technologies for studying the bacterial genome, assigns a major role to commensal bacteria in the intestine in the general control of nutrient absorption in the body favoring lipids. This theory tries to explain why some individuals are affected differently by obesity, although they are exposed to the same food and emotional stress as normal weight individuals [35].

And in the bacterial genome, recent research has issued three hypothetical directions that could determine S Met. Thus, a first research hypothesis starts from the study carried out on "germ free" animals which proves that of the over 1000 different bacterial species that colonize the intestine, Firmicutes and Bacteroidetes species represent over 85% of the intestinal microflora.

It is estimated that in the intestine of germ free mice the Bacteroidetes/Firmicutes ratio is 1/10, while in obese mice this ratio is 1/100. By losing weight following the diet, the return to the 1/10 ratio was found, similar to the flora of normal-weight individuals.   Based on this flora, richer in bacteria of the genus Firmicutes, the body is able, through important metabolic changes, to absorb in greater quantities the energy components from the food intake, which it then stores in the form of lipids stored intracellularly [35, 36].

The second hypothesis was launched after 2007, following the study of Cani et al [37]. This study is based on the assumption that a diet rich in lipids causes an increased serum concentration of LPL (lipoprotein lipases) which originate from the degradation of the wall of gram negative bacteria. Through the hyperlipidic diet, there is a qualitative change in the intestinal flora with the reduction of Bacteroidetes species. These changes simultaneously produce an alteration in the intestinal absorption function, which can lead to obesity, tissue resistance to insulin and the appearance of type 2 diabetes [38,39].

The third hypothesis is based on the possibility of determining a change in the intestinal flora with the help of prebiotics (represented by yeasts and bacteria derived from fermented foods) or with the help of prebiotics (oligosaccharides or short-chain polysaccharides from food fibers). Through their intake, the proportion of bacterial species such as Bifidobacteria and Lactobacillus significantly increases in the intestine. These bacteria allow the reduction of LPZ absorption and improve the absorptive function of the intestinal mucosa, making lipid absorption more difficult and therefore could have a protective role [39].

Despite these numerous hypotheses that try to explain the determination of S Met, none of them succeeds in fully explaining the etiopathogenesis and the cascade changes produced by the clinical entity defined by S Met.

2.1 Clinical consequences in patients classified as S Met

A goal of the "Metabolic Syndrome" concept is to identify subjects with increased waist circumference who are also at increased risk of developing type 2 diabetes and cardiovascular disease with thrombotic potential (40).

2.1.1 Cardiovascular risk

Current epidemiologic studies, performed on large cohorts, confirm that patients in the S Met category have a relatively increased risk of atheromatous cardiovascular disease [40-43]. In addition to morbidity, S Met is also implicated in increased mortality due to obstructive cardiovascular accidents [44].

In a large epidemiological study, performed on a sample of 172,173 subjects with S Met, the relative risk of cardiovascular events and death was particularly elevated, with a value of 1.78% in 95% of patients [45].

Other studies also find a high risk of stroke in patients with S Met, and the association of S Met components with HTN, hyperglycemia and a low level of HDL-cholesterol also increases the incidence of coronary accidents [46,47].

Numerous other studies reveal that the association of hyperglycemia, abdominal obesity, and an elevated triglyceride level is recognized as a predictor of cardiovascular risk. The higher the number of S Met associated factors, the higher the probability of cardiovascular accidents [48, 49].

2.1.2 The risk of type 2 diabetes

Numerous studies claim that the risk of type 2 diabetes is increased in S Met entity patients. This risk is estimated to be about 5 times higher compared to patients without S Met. It seems that the association of insulin resistance with S Met is the element that marks prediabetes. Other studies estimate that about 75-80% of those who show insulin resistance will develop type 2 diabetes in the near future [50-55].

2.1.3 Other pathologies associated with S Met

In other recent studies it is mentioned that in S Met patients there is a prothrombotic state in the blood due primarily to disturbances caused by endothelial dysfunction [56, 57]. Vascular manifestations can be extensive and are manifested by pathological changes of hypercoagulation and hypofibrinolysis, which increase the risk of cardiovascular accident [58,59].

There are also studies that attribute to this prethrombotic state the installation of changes of vascular origin in the vessels of the cerebral substance, which also seem to be involved in the etiopathogenesis of neuro-degenerative diseases such as Alzheimer's disease [60,61].

The installation of tissue insulin resistance leads to the achievement of a low-level inflammatory state, characterized by the increase in the values of some serum inflammatory markers such as: C-reactive protein, the increase in the number of leukocytes and the increase in the cytokines IL-6, IL-8, TNF-alpha and resistance [62-65].

2.1.4 Insulin resistance, abdominal obesity and inflammation

Adipose tissue is considered a true highly active endocrine organ. Its secretion changes in case of visceral obesity, producing cytokines, growth factors and hormones, which act on the vascular endothelium. The secreted peptides act either locally or at a distance. Among these, the best known are: TNF-α, IL-6, leptin, adiponectin, resistin, angiotensinogen, PAI 1 and tissue factor.

Their actions in the body are as follows:

- TNF-α the cell necrosis factor and IL-6 are mediators of insulin resistance in obesity. These factors inhibit insulin signal transmission and block glucose transport, stimulate lipolysis contributing to the increase of blood triglycerides.

- leptin is a hormone that binds to hypothalamic receptors and triggers the satiety reaction, thus controlling body weight. It is associated with insulin resistance, its dose being increased in the blood in insulin resistance. It seems that there is not only an increased secretion and even a resistance to leptin.

- adiponectin is a hormone that sensitizes insulin. Its blood level is low in S Met.

- resistin is a peptide that promotes insulin resistance. It is found in increased concentration in obese and diabetic patients.

-angiotensinogen is a hormone produced by adipose tissue that favors an increase in blood pressure. The antihypertensive treatment in S Met is also based on the inhibition of the receptors of this hormone.

- tissue factor and PAI 1 enzyme contribute to hypercoagulation and fibrinolysis. This representation of the pathophysiology induced by these substances is reproduced in a recent study from 2011[70].

2.1.5 Oral health and S Met

Recent studies incriminate in the pathophysiology of oral diseases the disruption of the oral biofilm with the predominance of pathogenic bacteria that can cause caries, gingivitis or periodontitis. The bacterial action seems to be complex not only at the odontal and periodontal level, being also attributed to a systemic immunological modulation effect (71-73).

2.1.6 Physiological functions of the oral cavity

The oral cavity is considered the first organ with a role in the body's nutrition and digestion. At its level, a series of functions are carried out that concern the choice of food, mastication and the formation of the food bowl and then swallowing.

Taste buds and sensory receptors in the oral cavity determine food choices based on the pleasure caused by a particular food or its taste. Through mastication and salivation, a first step in the mechanical and biochemical decomposition of food is ensured. At this level, other functions are carried out, such as: breathing, phonation and non-verbal expression, mimicry, smile, joy, etc. (27).

In addition to these roles, the oral cavity also plays an important aesthetic role. It can symbolize youth, well-being or physical decline, sadness or aging. It is also the main way of entry or exit of some pathogens. An important number of therapeutic substances can be administered through the oral cavity.

It is obvious, then, that a disruption of the integrity of the tissues at this level can have important consequences, on the vital functions related to nutrition, and can have some global repercussions on the general metabolism and the general state of well-being (27).

2.1.16 Association of cardiovascular diseases with periodontal disease

In recent decades, studies report an increase in the prevalence of cardiovascular diseases worldwide. This category includes a number of conditions such as: heart failure, acute myocardial infarction, systemic atherosclerosis and cerebral thrombotic accidents (56,58,86).

Current research confirms that the immune system is involved in the etiopathogenesis of periodontal diseases along with independent risk factors such as obesity, smoking, alcohol consumption and lack of physical activities (58).

The association of periodontal disease with obesity has been the subject of numerous studies that have found that there are frequent associations between these pathologies, both based on determined low-intensity systemic inflammation. Despite this evidence, the complete etiopathogenetic mechanism of these interactions could not be explained at the moment (65,87).

Numerous recent studies confirm the passage of bacteria from the oral biofilm into the blood circulation and their subsequent localization at the level of heart valves, at the level of the pericardium or atheromatous plaques at the level of arteries (56,57,88,89).

In addition, it seems that the general systemic inflammation found in patients with S Met and periodontal disease induces endothelial dysfunction, which generates, after a while, the acceleration of the atherogenesis process and the increased risk of thrombotic accidents (56,90)

Personal contributions

3.1 Introduction

Recent studies in the medical literature believe that the interrelationships between the conditions that define S Met - obesity, hypertension, diabetes or dyslipidemia, cause important cardio-vascular changes, with increased morbidity and mortality especially in the last decades.

Without being able to state with certainty, the importance of the dento-periodontal health status in determining the changes in biological parameters towards pathological values is mentioned in numerous studies, which found the frequent association of a poor dento-periodontal health status in S Met patients whose parameters they are outside biological limits (74-76).

Another motivation, of our study, was represented by the fact that early manifestations of S Met can affect cardiovascular risk and quality of life in the medium and long term.

3.2 The motivation for choosing the theme

In the current research we tried to bring new arguments regarding the interrelationships between periodontal health, lifestyle, periodontal care, dental control and biological parameters of the patient. In this regard, we sought to find out whether there are significant relationships between cardiovascular disease, periodontal health status and impaired quality of life.

Another objective of our study was to bring some clarifications regarding the epidemiology of the risk factors involved in the etiopathogenesis of S Met by examining groups of patients admitted to the Cardiology and Diabetes wards of the Sibiu County Emergency Clinical Hospital.

We want these results to be an alarm signal to influence the adaptation of medical treatment, personal self-care, diet and, last but not least, a sanogenic lifestyle, which could decrease the morbidity caused by S Met.

We also wanted to find out if the patients in the studied groups have knowledge/apply methods of periodontal disease prevention, which can be incriminated in determining a loco-regional inflammatory state with consequences at the level of the whole organism.

Finally, we wanted our study to be able to serve the implementation of health education programs regarding the links between dental-periodontal health, a sanogenic lifestyle and the control of risk factors incriminated in the etiopathogenesis of cardio-metabolic conditions.

3.3 Inclusion in research in the field

Considering that the prevalence of cardiovascular diseases and metabolic diseases in the last decades is in an increasing trend both on a European and worldwide level, we believe that the work can bring some clarifications regarding the prevention and control of risk factors.

In a recent observational study of a cohort of more than 3,300 middle-aged American adults over 8 years, it was found that the risk of developing new coronary heart disease or type 2 diabetes in people with S Met is difficult to appreciate. These risks were evaluated in the male gender as follows: 34% for cardiovascular diseases, 29% for coronary diseases and the highest percentage of 62% for diabetes type 2. These risks differ for the female gender as follows: 16% for diseases cardiovascular, 8% for coronary diseases and respectively 47% for type 2 diabetes [7, 8].

Another large study, carried out on a batch of more than 100,000 people in France between 1997 and 2000 in the age groups 18-80 years, finds a slightly different prevalence of S Met, as follows: 10% for men and 8% for women. In addition, the study considers that the pathologies related to S Met: HTN, dyslipidemia, visceral obesity, are present in only 13-14% of patients included in this syndrome [8,9,10].

3.5 Clinical study 1

The association of risk factors that determine the classification of patients in the S Met category

Our study was carried out in the period 2018 - 2022 and had in mind the formation of study groups from patients hospitalized in the Cardiology departments and the Diabetes and Nutritional Diseases section of SCJU Sibiu.

In a first study we aimed to study the incidence of S Met in patients who were hospitalized in the two wards of SCJU Sibiu, depending on the environment of origin, and in the context of economic and social factors regarding school education, family income as well as in the context of anthropometric data on height, weight and waist circumference.

The main objectives of this study were:

- to determine the incidence of S Met in hospitalized patients;

- determining the epidemiological involvement of risk factors in maintaining a low-intensity inflammatory state, which determined the association of metabolic conditions. This association, which is increasingly common today, can be due to numerous factors including inadequate lifestyle, hypercaloric diet and sedentary lifestyle.

- determination of possible epidemiological links between periodontal health and the association of symptoms that define S Met. We wanted to find out if the data from the literature regarding the association of periodontal lesions in patients with S Met are statistically significant also in patients admitted to the two wards of the SCJUS.

- to evaluate which of the pathologies included in S Met are more frequently associated with periodontal disease

- to evaluate ways of control/prevention that can interrupt the possible etiopathogenetic links with the general manifestations occurring in the body.

Secondary objectives were:

- determining the prevalence of detected risk factors,

- determining the involvement of socioeconomic and educational factors that can influence the installation of S Met.

3.5 Clinical study 2

The association of risk factors that determine the classification of patients in the S Met category

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- to evaluate which of the pathologies included in S Met are more frequently associated with periodontal disease

- to evaluate ways of control/prevention that can interrupt the possible etiopathogenetic links with the general manifestations occurring in the body.

Out of the total of 40,866 patients admitted to SCJU Sibiu, about 3,300 patients were admitted to the Cardiology and Diabetes clinical departments. Of these in 2019, only 173 (5.24%) presented the simultaneous association of at least three conditions/treatments necessary to be included in the consensus definition of S Met.

Our study included a number of 296 randomly selected patients, among patients hospitalized during 2019 in the Cardiology and Diabetes wards of SCJU Sibiu

The study group included patients who presented the association of at least three conditions/treatments incriminated in constituting the clinical entity of S Met. For this purpose we randomly selected a group of 168 people who could be included in this clinical entity (10).

Patients in the S Met group were aged between 45-88 years. Of these, 68 (40.48%) were male and 100 (59.52%) were female.

The control group consisted of 128 individuals without S Met. The patients included in this batch came from patients also hospitalized in the Cardiology and Diabetes departments of SCJU Sibiu, who did not present the association of at least three conditions/treatments, which would allow them to be classified in the S Met category. We applied the study exclusion criteria to this group as well as to the patients in the experimental group - with S Met.

The data recorded in the individual S Met patient records were stored in the Microsoft Excel database. From these sheets, the individual parameters were coded numerically, so that they could be processed statistically. For the statistical analysis we used the ANOVA test and the Chi2 test from the SPSS program version 26.0 for Windows.

3.5.2 Results

In order to analyze the statistical variance of the data specific to the group of patients classified as S Met, we resorted to the set of ANOVA statistical analyzes to find out if there are significant differences regarding the prevalence of S Met according to the age and gender of the subjects.

Following the analysis of the BMI risk factor, in the studied groups, we found an increased prevalence of BMI in both genders.

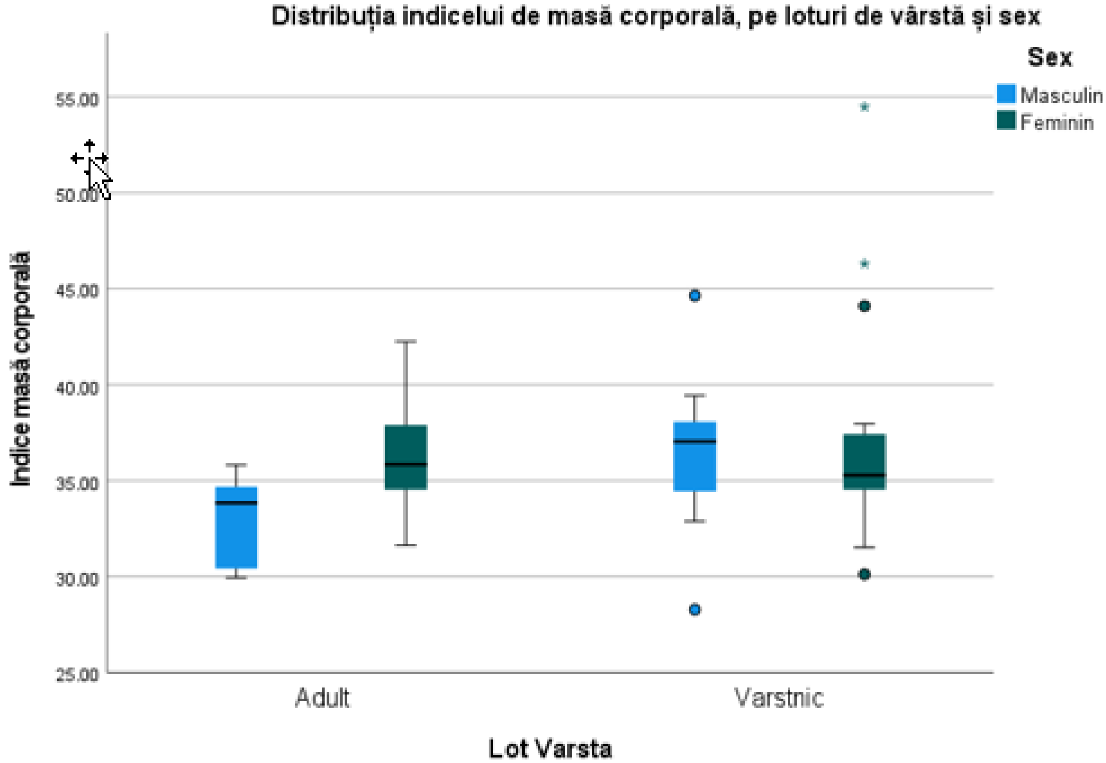
From the analysis of the statistical comparison, we can see that the ANOVA test does not provide the appropriate results to be able to reject the null hypothesis, formulated for the age subgroups considered (adults and elderly). Thus, in adults, the calculated value $F = 1.832$ is lower than the critical value (4.543) and the significance level $p = 0.197 > 0.05$.

Therefore, in the group studied by us, we could not state that there are statistically significant differences between the two genders, within the group of adults, between the average ages of the patients.

Also, for the elderly subgroup, the calculated value $F = 1,352$ is lower than the critical value (4,242) and the significance level $p = 0, 256 > 0.05$. Thus we can conclude that even in this batch there is no statistically significant difference in the average ages between the two genders.

In conclusion, we can state that the study groups made up can be considered homogeneous, without statistically significant differences regarding the ages and genders of the subjects.

In order to suggestively highlight the prevalence of BMI in the groups included in the study, we compiled a suggestive statistical representation of the average values of BMI, according to the gender and the average age of onset of the metabolic syndrome. This distribution can be shown suggestively, graphically, by figure 11.



Obs: Linia neagra = media; dreptunghiul conține 95% dintre valori

Figure 11 - Distribution of the BMI index in the studied subgroups, according to the age and gender of the subjects.

We considered that increased values of waist circumference represent an important risk factor involved in the prevalence of metabolic syndrome. And in this case we considered conducting the study according to the age and gender of the subjects. The data obtained, after the measurements, were processed statistically by the ANOVA method.

3.5.4 Conclusions

1. In the groups we studied, we found a different prevalence of S Met according to age and gender. Thus, in the age group under 65 years, in the male gender, the average age of onset of S Met was 58 years, and in the female gender, the average age was 60 years.

2. With increasing age (age group over 65 years old) the prevalence of S Met reverses slightly so that in males it occurs at around 72 years and in females at 70 years.

3. The links established between BMI and S Met are strong links with statistical significance for both genders. The most important statistical value we found exists for the female gender - 36.30% vs. 33.09% for the male gender.

4. We also found a statistically significant relationship between waist circumference and metabolic syndrome for both genders and for both age groups. With age these differences fade and disappear.

5. The distribution of the metabolic syndrome according to the geographical environment of living and age is different. Thus, in the age group under 65, S Met is 2 times more frequent in females compared to males in rural areas. In the age group over 65, the presence of S Met is reversed, being 1.53 times more frequent in rural males than in females.

6. The educational level, quantified by secondary education/higher education, influences the prevalence of S Met, it being encountered about 1.8 times more frequently in females with secondary education compared to males in the age group under 65 years. And these differences fade with age.

7. Regarding the correlation of S Met with income/family member, the observed prevalence of S Met is about 3.5 times higher among those with income <1500 lei/family member and prevails in rural areas. The results obtained in our research are comparable to those reported by other similar studies (9,18,103).

8. Risk factors present in the contemporary lifestyle, such as hypercaloric diet, which causes obesity, low level of education, low income/family member, low physical activity in association with family genetic predisposition may influence the prevalence of S Met.

3.6. Clinical study 2

Correlations established between the general state of health, the medical therapy administered and the lifestyle adopted by patients with S Met

3.6.1 Motivation of the study

Through this study, we wanted to find out if the state of general health, quantified by the values of some biological parameters involved in cardio-metabolic diseases: HTN, BMI, CT, LDL-cholesterol, HDL-cholesterol, triglycerides, have significant links with the state of oro-dental health , with the food preferences and in general with the lifestyle of the patients in the studied groups.

We considered that drug treatments, applied to patients included in S Met, have a more favorable effect if the patients follow and/or apply preventive measures regarding the sanogenic lifestyle, with a normocaloric diet without excess salt, regular physical activity, practicing physical activities in nature for at least 30 minutes daily to combat sedentarism.

We also considered it important to maintain the health of the oro-dental structures, which are the first entry gate for food into the body, but also a potential reservoir of pathogenic bacteria in the case of periodontal infections.

In the studied groups, we wanted to find out if there are statistical correlations in patients affected by S Met between the blood glucose values of the age and gender of the subjects

We also wanted to find out if the relationship S Met-fasting blood glucose can be influenced by the age of the subjects in the studied groups. For this, we also used the statistics provided by the ANOVA method in this case

Another risk factor, taken into account in our study, was the blood level of triglycerides, considering those under 150 mg/dl as normal values and those greater than 150 mg/dl as elevated values. Their individual values were taken from the clinical observation sheets and then recorded for statistical processing. We wanted to study if the interrelationship between serum triglyceride levels, age and gender of patients has a statistically significant relationship with the presence of S Met.

In this case we used the Chi2 test as a statistical method.

Figure 12 - Incidence of hypertriglyceridemia in the studied groups

We considered that the normal values, beneficial to the body, for the total cholesterol component are the lowest of 155 mg/dl. Above these values, we consider that the patient presents an increased cardiovascular risk, which must be monitored and, if necessary, treated with medication (40,43,45).

The recorded values from the clinical observation sheets were taken into Excel tables for statistical analysis

A suggestive graphical representation of the statistical values of the S Met-high blood cholesterol correlation, in the studied groups, can be suggestively shown in the graph in figure 13.

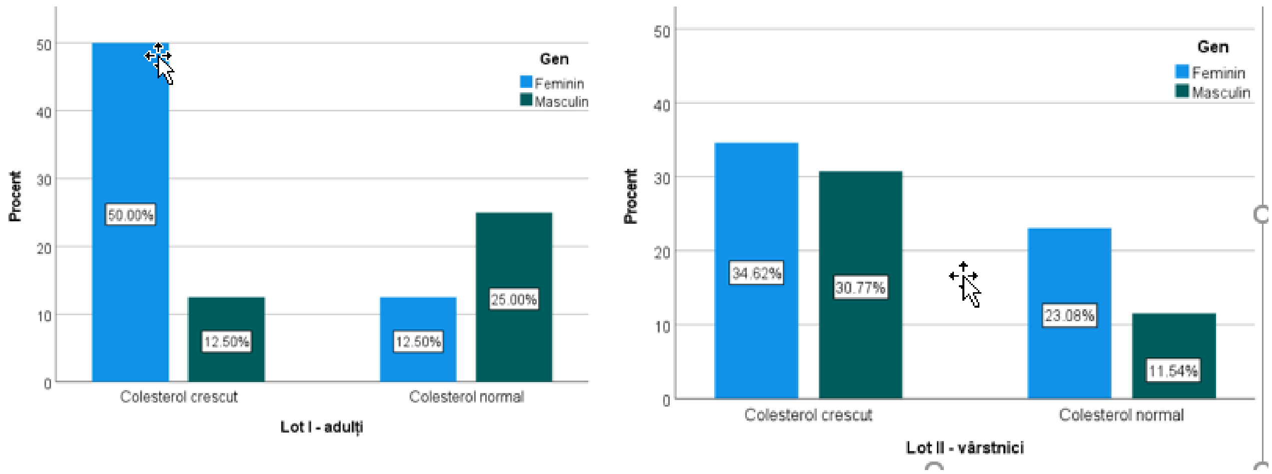


Figure 13 - Distribution of subjects with S Met according to hypercholesterolemia, in age groups according to gender of subjects

Another risk factor included in this study was the low level of HDL-cholesterol in the blood, considering values above 40 mg/dl as normal values, and those below this value as unfavorable for the body. For the purpose of our research, the values of this biological parameter were recorded from the patients' clinical observation sheets. I also used the Chi2 statistical analysis method in this case

The representation of the statistical distribution of the HDL-cholesterol level, in patients with S Met, depending on the age and gender of the subjects, can be suggestively represented graphically by figure 14.

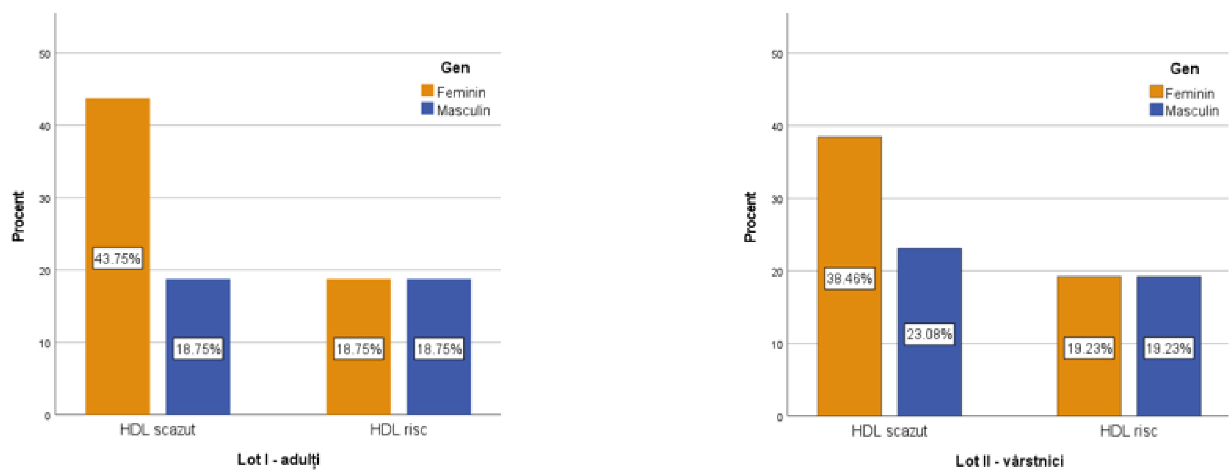


Figure 14 – Statistical distribution of the level of HDL-cholesterol in the studied groups

Another risk factor, pathogenically involved in S Met distribution, is the increased level of the lipid component LDL-cholesterol. We considered normal values below 160 mg/dl, and those above 160 mg/dl a pathological factor. This increased component is frequently incriminated in the determination of cardiovascular thrombotic risk.

A suggestive graphic representation of the differences found between genders, regarding the distribution of the LDL-cholesterol values found, is shown in figure 15.

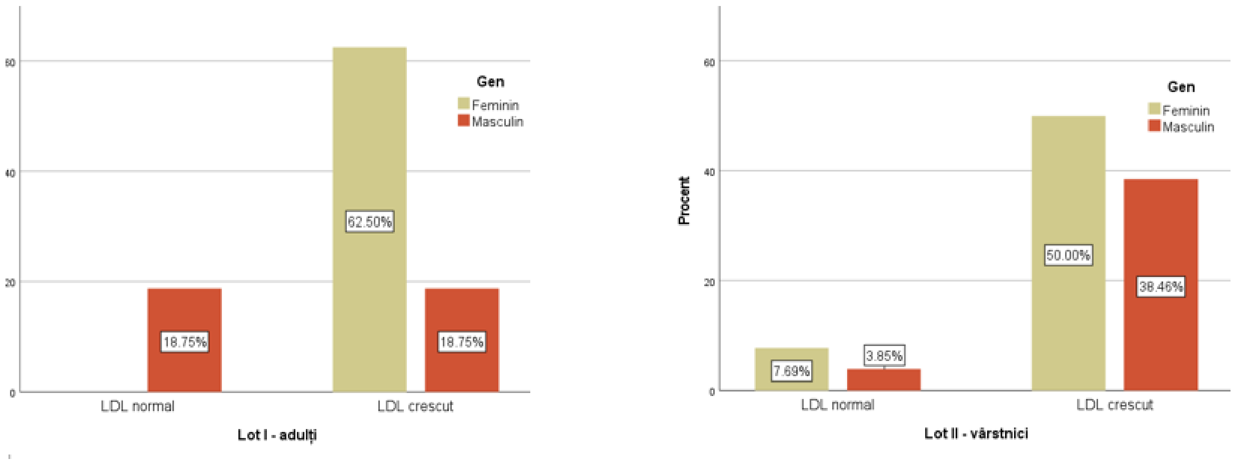


Figure 15 – Distribution of LDL-cholesterol values in the studied groups according to the age and gender of the subjects

At the end of this study, regarding the impact of different risk factors, we wanted to find out which of them has the closest interaction in determining S Met.

To determine the interaction of these factors, we resorted to a statistical analysis that is able to estimate these links. The result of the analysis is presented in figure 16 and confirms that in the studied groups the closest connection is established between BMI and SBP. For this purpose, we used a cubic regression model (according to the equation Y = b0 + (b1 * t) + (b2 * t**2) + (b3 * t**3)). Following this analysis we obtained a BMI-SBP correlation graph.

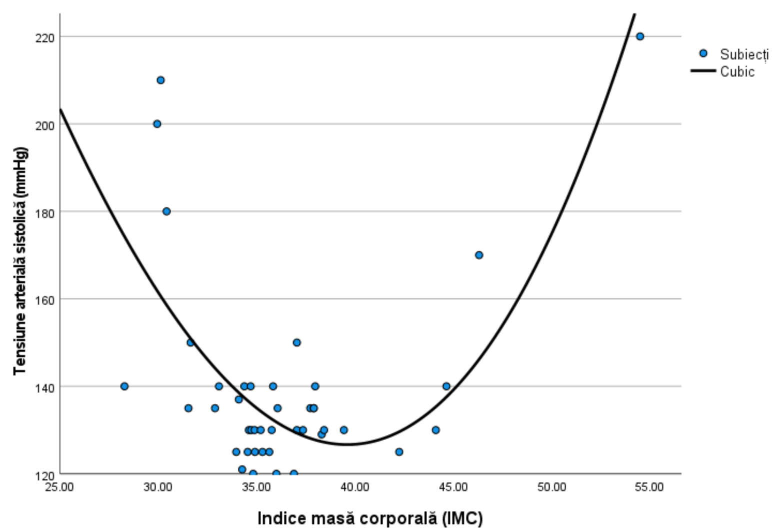


Figure 16 - Correlation established between BMI - SBP in patients with S Met

Conclusions

1. The biological parameter blood hyperglycemia of jeune is present in both males and females without statistically significant differences, confirming the fact that this risk factor is present and acts equally in both genders and age groups.
2. The increased values of blood triglycerides in the female gender (100%) are statistically confirmed compared to the values found in the male gender (33.3%) by the value p=0.003. It is confirmed, in this case, that the relative risk (RR) is about 3 times higher to determine S Met in the female gender.
3. Another important risk factor implicated in S Met determination is total cholesterol level. The values of this parameter are statistically significantly higher in the female gender (50%) and the age group over 65 compared to the male gender (12.5%), which may suggest that the female gender is more exposed to this syndrome.
4. Since the □2 test applied to HDL-cholesterol values in this case does not provide conclusive results in verifying the hypothesis that proclaims a correlation between the gender of the subjects and the level of risk represented by low HDL-cholesterol values, we can conclude that these results suggest the hypothesis that this factor of risk is equally plausible for patients of both sexes.
5. We found that with regard to LDL-cholesterol values, we found that they are higher in the female gender 50.0% compared to 38.5% in the male gender, although we did not find statistical significance (p=0.738) we can conclude that the action of this factor can be considered consistent in both genders, in the determination of S Met.
6. In the studied groups, we identified a close interaction between BMI and SBP risk factors in determining S Met. The link between the risk factors was formalized by a cubic regression model that was used to approximate the non-linear relationship between the independent variable BMI and the dependent variable SBP. The evaluation of the regression model was carried out by calculating R2, the value obtained being 0.6. Therefore, 60% of the variation in SBP is due to BMI, which demonstrates a good performance of the model fit on the analyzed data.

3.7 Clinical study 3

The impact of cardio-metabolic risk factors and oro-dental health in the etiopathogenesis of S Met

3.7.1 Introduction

Frequently, severe periodontal disease is associated with poor dental hygiene and tobacco smoking. In addition to this association, a series of chronic conditions such as type 2 diabetes, obesity, hypertension and some liver diseases can determine particular forms of periodontal disease manifestation.

Worldwide, the prevalence of periodontal disease also seems to be influenced by a number of factors such as socio-economic factors that determine social inequalities, income per family member, living environment or level of education.

3.7.2 Study objectives

The main objectives of this study were:

- to find out if there are epidemiological links between periodontal health and S Met according to age, gender, diet adopted, alcohol consumption and smoking habit,

- to find out, to what extent modifiable cardiovascular risk factors are significantly involved in the etiopathogenesis of S Met,

- to find out if food preferences in the diet are important in the etiopathogenesis of S Met,

- to find out if dental health has significant associations with S Met,

- to find out if periodontal health contributes to the low-intensity inflammatory state, frequently found in the body, in people who can be classified as S Met

- to find out whether regular dental control can have an effect on the control parameters of type 2 diabetes and on influencing the quality of life.

- to create a prediction model for S Met, considering several independent variables, which characterize the patients' lifestyle.

3.7.4 Results

From the data obtained, following the statistical processing by the mentioned method, we could find that the strongest association is the one established between systolic hypertension and BMI.

To be able to make the prediction in this statistical analysis we used performance metrics based on the confusion matrix.

Thus, using the confusion matrix, various metrics can be calculated to evaluate the performance of machine learning algorithms, in data classification and implicitly of prediction models based on these algorithms.

A first modifiable risk factor that we studied was the regular consumption of alcohol/day in a quantity greater than 100 ml of alcohol/day in men and about 50 ml of alcohol/day in the female gender.

Another risk factor studied was the involvement of smoking in S Met distribution. In the studied groups, the data recorded through anamnesis were processed statistically using the Chi2 method. Following this processing, we found the following distribution, depending on the age and gender of the subjects.

Regarding the realization of the proposed prediction model, the values of the performance metrics of the prediction model are presented in table 31. They correspond to the confusion matrices described in figure 17. Values close to 1 of the respective metrics correspond to a performing prediction model. From the total number of predictions made, only two cases were classified in the false positive category (FP), the rest of the cases being correctly classified (TN and TP, respectively).

Figure 17 - The confusion matrices obtained in training and testing the prediction model

Following the application of the prediction program, we obtained a classification of the importance of the involvement of risk factors in the determination of S Met. The values obtained allowed the creation of a graphic representation that can be shown suggestively in figure 18.

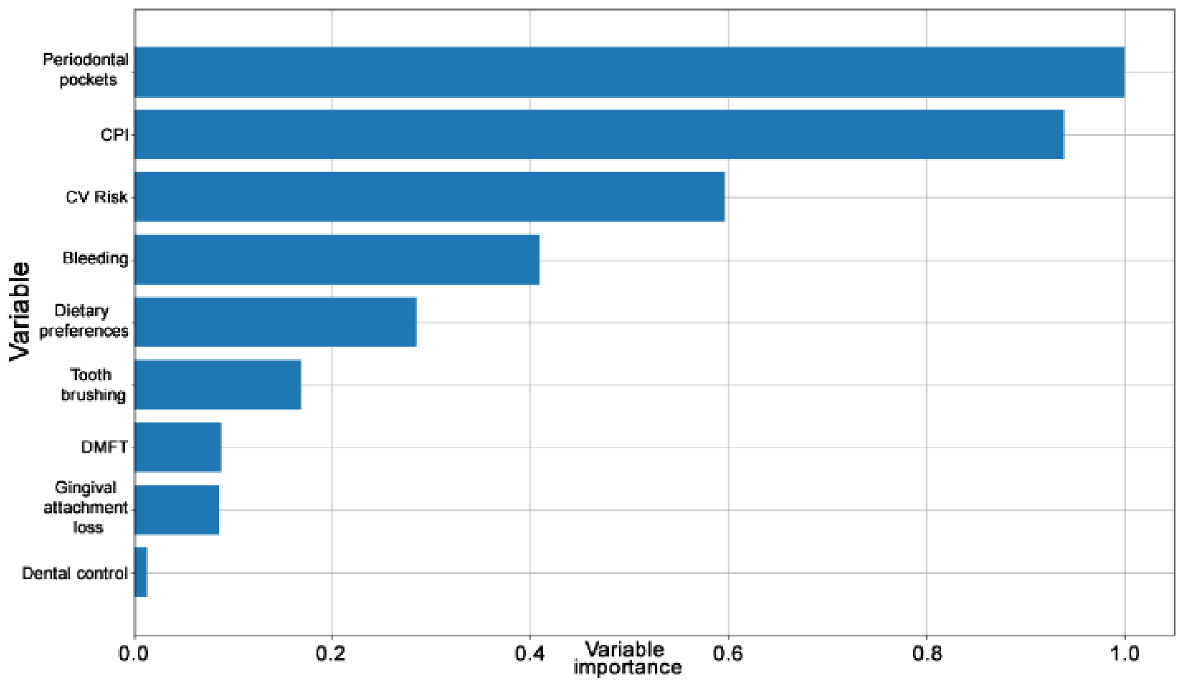


Figure 18 - Importance of different variables in determining S Met according to the Distributed Random Forest (DRF) model

We can see, from this graphic representation, that periodontal pockets have the greatest influence in the appearance of S Met, followed by the CPI index, CV risk, gingival bleeding and food preferences.

A suggestive representation of the relative importance of these risk factors working together to determine S Met can be rendered by the SHAP plot. This plot marks the contribution of features (independent variables) for each instance (dataset record / subject). We considered the sum of feature contributions to be equal to the gross model prediction.

In the created diagram, the SHAP value is represented on the x-axis, and all the characteristics (the independent variables) are represented on the y-axis. The positive (high) SHAP value has the meaning of a positive impact on the prediction, which can be interpreted that the model can predict variant 1 ie S Met. The negative (small) SHAP value means negative impact, which can be interpreted as the model predicting 0 i.e. no S Met.

Each point on the chart is a SHAP value for a prediction and a feature. Red color means a higher value of a feature. Blue color means lower value of a feature. The suggestive graphic presentation of this statistic is shown in figure 19.

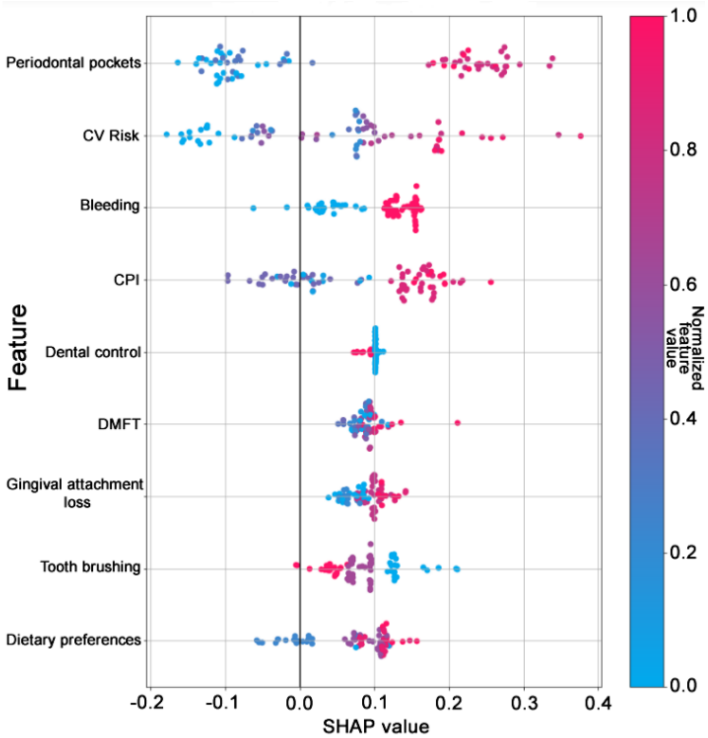


Figure 19 - SHAP chart regarding the involvement of risk factors in the determination of S Met according to Distributed Random Forest (DRF)

For the purpose of an in-depth analysis of risk factors, we applied the □2 test to study the relationship between the occurrence of S Met and the following categorical variables:

• the dimensions of the periodontal pockets;

• the existence of gingival bleeding;

• the frequency of dental perlage;

• existence of dental control;

• food preferences.

We also applied the ANOVA test to evaluate the null hypothesis between the means of the data series corresponding to the dependent variables:

• DMF-T score;

• community periodontal index (CPI);

• loss of gingival attachment;

• CV risk.

These values are grouped according to the existence or not of the metabolic syndrome (the independent variable).

3.6.6 Conclusions

1. From the analysis of the data expressing the distribution of S Met according to the risk factors age and the risk factor alcohol consumption in increased quantities, we can see that the relative risk (RR) of developing S Met is higher in the case of female subjects , who consume alcohol in the subgroup of adults (age <65 years) in relation to the male gender. From the same age group

2. Another conclusion, which we can make, is that in the adult subgroup, S Met in the group of subjects who consume alcohol is 1/0.056 = 18 times more common in men CI 95% (0.004 □ 0.81), and in the elderly subgroup , S Met in the group of subjects who consume alcohol is 1/0.13 = 8 times more common in the male gender CI 95% (0.02 □ 0.86), in relation to the female gender.

3. Regarding the involvement of the risk factor tobacco smoking, we can see that the relative risk (RR) is higher in the case of male adult smokers 1/0.6 = 1.66 compared to elderly male smokers 1/0.63 = 1.59 in relation to the female gender.

4. In adults, the distribution of S Met in the group of smoking subjects is 1/0.33 = 3 times more common in men, and in the elderly, S Met in the group of smoking subjects is 1/0.38 = 2.6 times more common in men, in relation to gender female.

5. There is a statistically significant correlation ($p < 0.001$) between S Met and periodontal pockets. Thus, 57% of subjects with S Met have periodontal pockets >3.5 mm. Among subjects without S Met, 59.4% have no periodontal pockets, and 40.6% of them have periodontal pockets with reduced depth <3.5 mm.

6. There is a statistically significant correlation ($p < 0.001$) between S Met and the existence of gingival bleeding. We can note that 79.2% of subjects with S Met present gingival bleeding. Among subjects without S Met, 84.6% do not have gingival bleeding. The relative risk (RR) of S Met is 5.15 times higher in subjects with gingival bleeding. The OR (odds ratio) refers to the probability of S Met occurring when gingival bleeding is reported. Thus, we could find that S Met is 20.9 times more common in subjects with gingival bleeding.

7. There is a statistically significant correlation ($p < 0.001$) between S Met and the frequency of dental perlage. The extent of the variation is demonstrated by the fact that 47.6% of subjects with metabolic syndrome brush their teeth only occasionally. Among subjects without metabolic syndrome, 50.0% have a frequency of dental pearlization 2 times a day.

8. We did not find a statistically significant correlation between S Met and the existence of dental control ($p=0.074 > 0.05$). However, S Met is 3.17 times more common in subjects who do not perform regular dental check-ups.

9. The results of our research allow us to state that there is a strong correlation with statistical significance ($p < 0.001$) between S Met and food preferences. The extent of variation is demonstrated by the fact that 92.9% of subjects with S Met exhibit hypersodium, hyperprotein, or hyperlipidic (or combinations thereof) dietary preferences. Among subjects without S Met, 53.1% have food preferences that fall within the normal caloric regime.

10. We found that there is a statistically significant difference ($p < 0.001$) between subjects presenting S Met and those who do not manifest this syndrome in terms of the community periodontal index (CPI). Thus, the average of this index is significantly higher in subjects with metabolic syndrome (2.98 vs 1.84).

11. In the case of gingival attachment loss, the ANOVA test provides results with statistical significance ($p = 0.003 < 0.05$) regarding the mean of the gingival attachment loss quantification variable which is significantly higher in subjects with S Met compared to those without S Met (2.93 vs 1.84).

12. We found that there is a statistically significant difference ($p < 0.001$) between subjects with S Met and those without this syndrome in terms of CV risk. Thus, the mean of this index is significantly higher in subjects with S Met (8.95 vs 2.22).

13. We could find, from our research, that periodontal pockets have the greatest influence on S Met distribution, followed by CPI, CV risk, gingival bleeding and food preferences. Considering the numerical values associated with the independent variables, it is observed that high values of the variables: periodontal pockets, CV risk, bleeding, CPI, DMF-T, loss of gingival attachment, food preferences, correspond to positive (high) SHAP values, so they correspond an increased likelihood of metabolic syndrome.

14. We can interpret that the high values of the variables tooth brushing, dental control (represented in the graph by red points) in opposition to the low values of SHAP (represented in the graph by blue points), can be followed by the decrease of the probability of occurrence of S Met.

15. The established links between periodontal disease and general health are complex and still only partially understood. There are numerous studies, which signal the frequent association with numerous diseases such as type 2 diabetes, obesity, S Met, CV diseases, stroke.

16. The prevention of periodontal diseases is based on two principles of treatment which consist on the one hand in optimizing oral hygiene (in this sense there are gingival-periodontal brushing techniques and auxiliary means of hygiene), and on the other hand it is possible to detect and control / neutralize individual risk factors.

17. For the DMF-T score (dependent variable), the ANOVA test does not provide adequate results to reject the null hypothesis for the study group. Thus, $F = 2.325$ is lower than the critical

value and the level of significance $p = 0.132 > 0.05$. Therefore, it cannot be stated that between subjects with/without metabolic syndrome, the means of DMF-T scores show significant differences. In other words, we can say that in the batches in our study the intensity of the dental caries effect did not influence the installation of S Met.

18. Social considerations such as education level, occupational status, income level can influence the prevalence of periodontal disease.

3.8 Clinical study 4.

Correlations between the clinical picture of S Met patients and the impairment of quality of life.

3.8.1 Introduction

Numerous recent researches indicate, through different means of quantification, the strong impact on the individual psychological level of some ailments capable of altering the state of well-being. The loss of masticatory units on the one hand affects the trituration and digestion of food and on the other hand it has an impact on the participation of individuals in social life.

3.8.2 Study objectives

Through this study, we wanted to find out to what extent patients are affected by a series of parameters that quantify the quality of life. These objectives can be succinctly expressed as follows:

- to find out if, following the installation of S Met, the quality of life of the patients was affected,

- if individual conditions such as: biological parameters, age, gender and living environment influence the quality of life of these patients,

- if socio-economic conditions regarding professional training and income per family member influence the quality of life,

- if individual medical parameters such as: BMI, blood pressure, type 2 diabetes, serum cholesterol level can influence the quality of life,

- if the general state of health perceived by the individual is influenced by the presence of S Met

-if some measures/programs can be undertaken at the collective level to improve/improve the quality of life of S Met patients.

3.8.3 Material and method

In order to start the study, we obtained the written consent of the Ethics Commission of SCJU Sibiu with the number 10948 of 2018, and the departments where the research was carried out had the research accreditation from the CNCSIS medical commission.

For inclusion in this study, patients were informed about the conditions of the study and signed the informed consent prepared by the ethics committee of the SCJUS. The personal data of the patients included in the study were protected according to the legal regulations in force. Patients who did not sign the agreement or who did not fully fill out the questionnaire were excluded from the study.

To find out the impact on the quality of life, we used the version that allows a detailed assessment of the impact on the quality of life based on 5 levels of assessment. This variant of the EQ-5D questionnaire (EQ-5D-5L) was introduced by the EuroQol Group in 1990.

The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, personal care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems and extreme problems. In our data, we considered the phrase "some problems" to mean moderate problems.

The numbers for the five dimensions can be combined into a 5-digit number that describes the patient's health status. Scores for these five dimensions were converted into a single utility index using the R language and the eq5d package (86,87)

The EQ-VAS component, often referred to as the “thermometer model” because it resembles the thermometer scale with values from 0 to 100, records the patient's self-rated health status on a vertical visual analog scale, where a score of 100 means the best health status. health you can imagine. The VAS can be used as a quantitative health outcome measure that reflects the patient's own judgment of health impairment (86,87).

To facilitate descriptive statistical analyses, ranges of values for health status scores/biological parameters were associated with selected variables named as follows:

Scorul EQ-VAS	
<70	scăzut
70-80	mediu
>80	normal

Tensiunea arterială	
<120	scăzută
120-150	normală
>150	crescută

HDL colesterol	
<40	deficitar
40-59	scăzut
>=60	normal

For statistical evaluations, we used the Chi2 (□2) test to assess whether the BMI, HDL-cholesterol and EQ-VAS scores vary according to the gender of the subjects.

We also aimed to perform the test, □2 to assess whether S Met scores varied according to parameters: BMI, blood pressure, HDL-cholesterol, EQ-VAS and type 2 diabetes.

A Chi2 statistic is a way of showing what relationship there is between two categorical variables. The Chi2 statistic is a unique number that quantifies the difference between the number observed and the number expected if there was no relationship in the population.

A small value for Chi2 (□2) (less than the critical value in the Chi2 table) means that there is a high correlation between the two data sets. (Obtained Chi2 < Tabulated Chi2 means statistical significance).

The p-value can also be used to quantify statistical significance. Small p-values (below 5%) usually indicate that there is a high correlation between the analyzed data sets and implicitly that the test results are significant.

One-way analysis of variance (ANOVA) was also performed for the EQ-5D and EQ-VAS measures, categorized by the following groups: BMI, blood pressure, type 2 diabetes, HDL cholesterol, and metabolic syndrome.

ANOVA tests the null hypothesis that the samples in all groups are drawn from populations with the same mean values. Groups or levels are different groups within the same independent variable. ANOVA analysis produces an F statistic, the ratio of the variance calculated between the means to the variance within the samples analyzed.

The critical value is the number that the test statistic must exceed to reject the test at the p% level of significance. If F is greater than the critical value, the null hypothesis is rejected, concluding that there is strong evidence that the means of the independent (unrelated) groups are unequal.

All statistical analyzes were performed in SPSS version 26, and a p value of 0.05 was considered statistically significant.

3.8.4 Results

Socio-demographic characteristics collected in our survey included age, gender, level of education, area of residence, and monthly income per family member. These socio-demographic data of the studied patients were classified as can be seen in table 10.

We wanted to study other variables associated with S Met such as BMI, arterial hypertension, HDL cholesterol values and EQ-VAS index were compared with each other

Other possible correlations, in the studied groups, were analyzed according to the presence of type 2 diabetes, HDL-cholesterol and the EQ 5D index.

The scores representing the mean value and standard deviation for the EQ-VAS measure were classified according to the following risk factors: BMI, blood pressure, diabetes, HDL-cholesterol, respectively S Met

Mean diff scores were calculated by performing a one-way analysis of variance (ANOVA), where the mean EQ-VAS scores for the "normal" category of patients in each group were compared to the mean EQ-VAS scores for patients in each of the other categories within the same group.

Scores representing the mean and standard deviation for the EQ-5D-5L measure were categorized according to the following characteristics: BMI, blood pressure, diabetes, HDL-cholesterol, and S Met, respectively.

Mean diff scores were calculated by performing a one-way analysis of variance (ANOVA), where the mean EQ-5D-5L scores for the "normal" category of patients in each group were compared to the mean EQ-5D scores -5L for patients in each of the other categories in the same group.

A suggestive graphic representation of the values from the contingency table is shown in figure 20. In it, the average values obtained of the EQ-VAS and EQ-5D-5L scores for the five BMI categories are graphically represented:

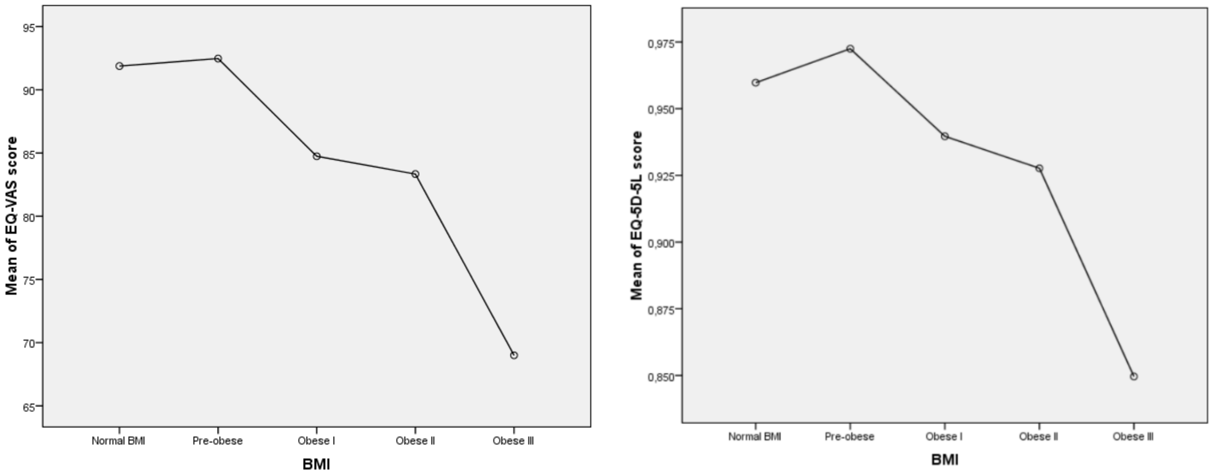


Figure 20 - Comparative graphic representation of the obtained values

A suggestive graphic representation of the response options coded by a number made up of the five assigned numerical values can be graphically displayed intuitively by figure 21

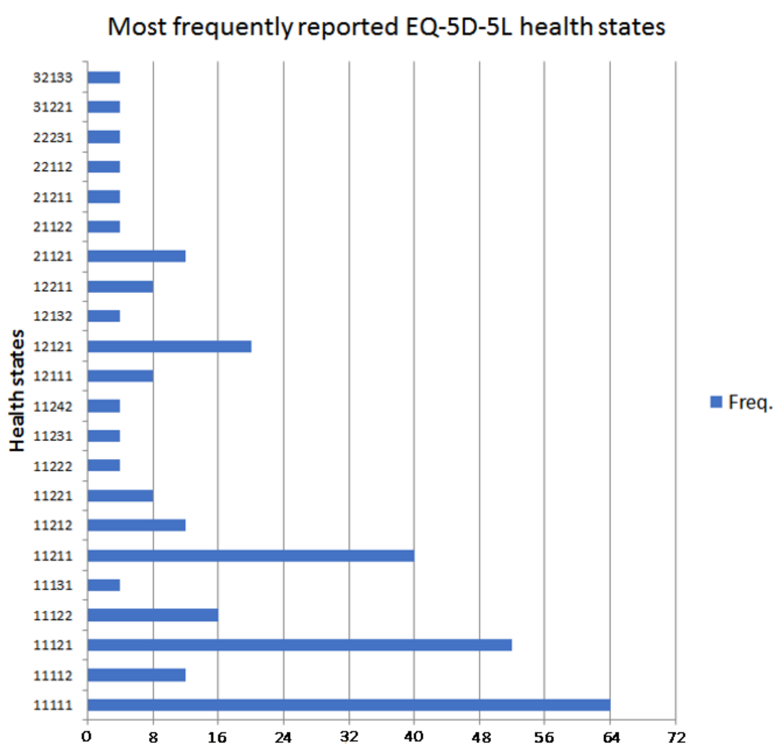


Figure 21 - Graphic representation of EQ-5D-5L scores

For a presentation of the variation of the average EQ-VAS scores obtained for the most frequently reported subjective health conditions EQ-5D-5L we resorted to the graphic representation of these values.

The suggestive graph represented in figure 22.

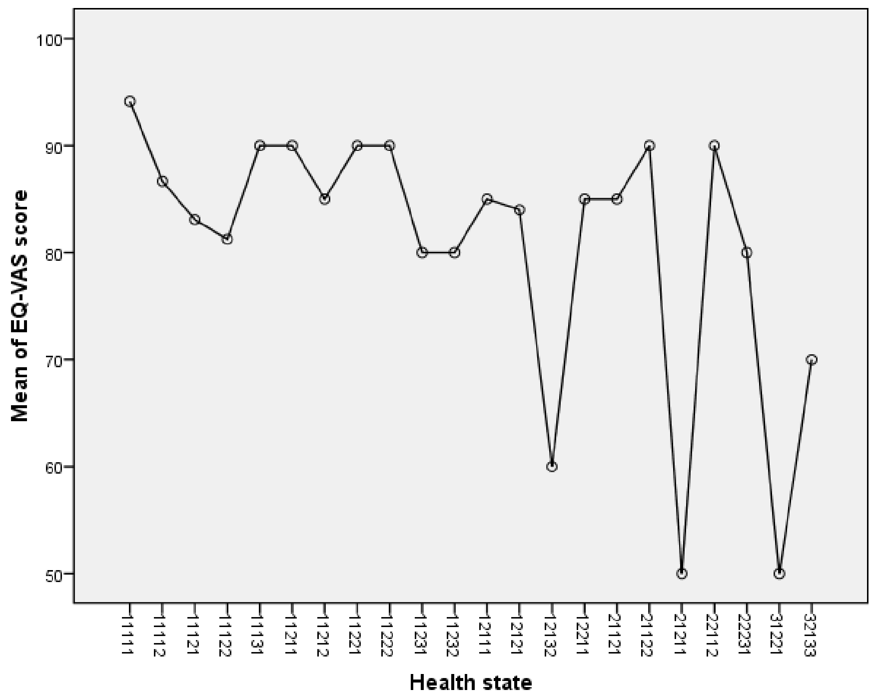
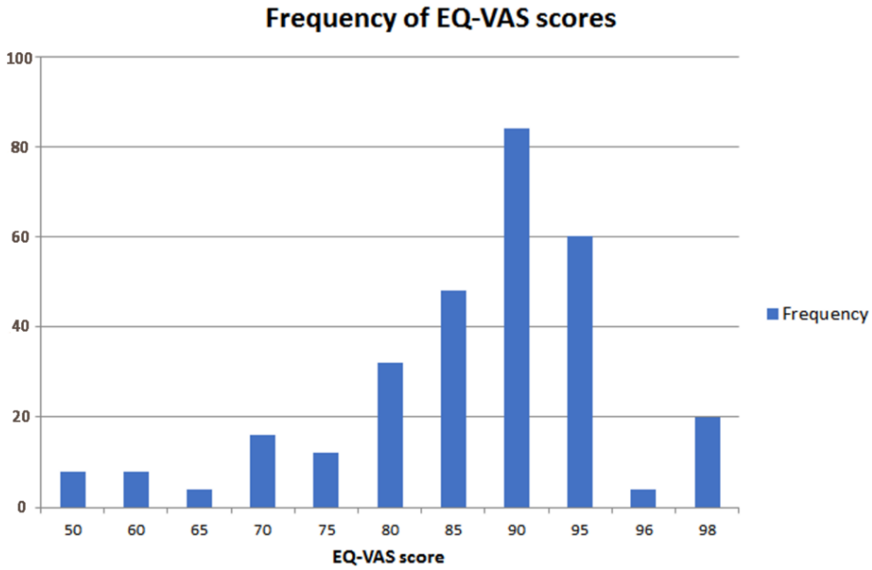


Figure 22 – Graphical representation of the variation of EQ-VAS scores encoding health status

The frequencies of responses encoded by the five-digit number representing the patient's health status according to the five dimensions of the EQ-5D-5L descriptive system are shown in figure 23.



3.8.6 Conclusions

1. Measuring the impact on quality of life in people with S Met-related morbidities is a feasible method to capture the impact of personal physical and mental impairment.

2. In this study we were able to determine that the lowest values of the pain/discomfort dimension are found especially in the 55-64 age group, and of the mobility and self-care dimension are found in the 65-74 age group .

3. The metabolic syndrome has the ability to influence the quality of life especially through the dimensions of physical mobility and through the pain and discomfort caused by self-care activities, especially in the female gender.

4. We also found in our research that the anxiety/depression dimension appears to be less important in influencing quality of life.

5. We can consider that these values can be explained in part by the sufficiently detailed possibilities that allow the adaptation of the answer variants of the questionnaire, to the 5 possible degrees of impairment: reduced impairment, medium impairment respectively severe impairment of the 5 categories of conditions that determine the reliability of the overall quality of life assessment indicator.

6. We can therefore state, following this study, that the mean values of the EQ-5D index are lower in women than in men. A possible explanation for this variation, according to gender, may be that the female temperament is more willing to notice changes in health status, while men, on the other hand, seem more confident in their ability to control their conditions and for this reason may show less depressive or anxiety phenomena

7. There is still a need for some differentiation of understanding in the Romanian language between the terms of appreciation for a more accurate rendering of the changes in the quality of

life in cases of health impairment. In this regard, new studies on larger groups are needed that can accurately capture the changes caused by S Met that may affect quality of life.

3.9 General conclusions

1. In this research we found a different frequency of S Met according to the age and gender of the subjects. Thus, in the age group under 65 years old, the average age of onset of S Met in males was 58 years, and in females the average age was 60 years.

2. With increasing age (age group over 65 years old) the frequency of S Met reverses slightly so that it is found in males at about 72 years and in females at 70 years.

3. The links established between BMI and S Met are strong links with statistical significance for both genders. The most important statistical value we found is that there is 36.30% for the female gender vs 33.09% for the male gender.

4. We found a statistically significant relationship between waist circumference and metabolic syndrome for both sexes and for both age groups. With advancing age these differences fade and even disappear.

5. The distribution of S Met according to the geographical environment of living and age is different. Thus, in the age group under 65, S Met is 2 times more frequent in females compared to males in rural areas. In the age group over 65, the presence of S Met is reversed, being 1.53 times more frequent in rural males than in females.

6. The educational level, quantified by secondary education/higher education, influences the prevalence of S Met, it being encountered about 1.8 times more frequently in females with secondary education compared to males in the age group under 65 years. And these differences fade with age.

7. Regarding the correlation of S Met with income/family member, the observed prevalence of S Met is about 3.5 times higher among those with income <1500 lei/family member and prevails in rural areas. The results obtained in our research are comparable to those reported by other similar studies (9,18,103).

8. Risk factors present in the contemporary lifestyle, such as hypercaloric diet, which causes obesity, low level of education, low income/family member, low physical activity in association with family genetic predisposition can influence the prevalence of S Met.

9. In the adult subgroup, S Met distribution in the group of subjects who consume alcohol is 18 times more common in men, and in the elderly subgroup, S Met is 8 times more common in males than in females.

10. Regarding the involvement of the risk factor tobacco smoking, we can see that the relative risk (RR) is higher in the case of male adult smokers 1/0.6 = 1.66 compared to elderly male smokers 1/0.63 = 1.59 in relation to the female gender.

11. The distribution of S Met in the group of smoking subjects is 1/0.33 = 3 times more common in men, and in the elderly, S Met in the group of smoking subjects is 1/0.38 = 2.6 times more common in men, in relation to the female gender .

12. There is a statistically significant correlation ($p < 0.001$) between metabolic syndrome and periodontal pockets. Thus, 57% of subjects with metabolic syndrome have periodontal pockets >3.5. Among subjects without metabolic syndrome, 59.4% have no periodontal pockets, and 40.6% have periodontal pockets <3.5.

13. Regarding gingival bleeding we found that there is a statistically significant correlation ($p < 0.001$) between S Met and the existence of gingival bleeding. 79.2% of subjects with metabolic syndrome have gingival bleeding. Among subjects without S Met, 84.6% do not have gingival bleeding. The relative risk (RR) of S Met is 5.15 times higher in subjects with gingival bleeding. We could find that S Met is 20.9 times more common in subjects with gingival bleeding.

14. There is a statistically significant correlation ($p < 0.001$) between S Met and the frequency of dental perlage. The extent of the variation is demonstrated by the fact that 47.6% of subjects with metabolic syndrome brush their teeth only occasionally. Among the subjects without S Met, 50.0% have a frequency of dental pearlization 2 times a day.

15. We did not find a statistically significant correlation between S Met and the existence of dental control ($p=0.074 > 0.05$). However, metabolic syndrome is 3.17 times more common in subjects who do not perform regular dental check-ups.

16. The results of our research allow us to state that there is a strong correlation with statistical significance ($p < 0.001$) between S Met and food preferences. The extent of variation is demonstrated by the fact that 92.9% of S Met subjects show preferences for high-sodium, high-protein, or high-lipid diets (or combinations thereof). Among subjects without S Met, 53.1% have food preferences that fall within the normal caloric regime.

17. We found that there is a statistically significant difference ($p < 0.001$) between subjects presenting S Met and those who do not manifest this syndrome in terms of the community periodontal index (CPI). Thus, the mean of this index is significantly higher in subjects with S Met (2.98 vs 1.84).

18. In the case of gingival attachment loss, the ANOVA test provides results with statistical significance ($p = 0.003 < 0.05$) regarding the mean of the gingival attachment loss quantification variable which is significantly higher in subjects with S Met compared to those without S Met respectively 2.93 vs 1.84.

19. We found that there is a statistically significant difference ($p < 0.001$) between subjects with S Met and those without this syndrome with respect to CV risk. Thus, the mean of this index is significantly higher in subjects with S Met (8.95 vs 2.22).

20. We could find, from our research, that periodontal pockets have the greatest influence on S Met distribution, followed by CPI, CV risk, gingival bleeding and food preferences. Considering the numerical values associated with the independent variables, it is observed that high values of

the variables: periodontal pockets, CV risk, bleeding, CPI, DMF-T, loss of gingival attachment, food preferences, correspond to positive (high) SHAP values, so they correspond an increased likelihood of metabolic syndrome. We can interpret that the high values of the variables tooth brushing, dental control (represented in the graph by red dots) in opposition to the small SHAP values (represented in the graph by blue dots), can be followed by the decrease of the probability of occurrence of S Met .

21. The established links between periodontal disease and general health are complex and still partially understood. There are numerous studies, which signal the frequent association with numerous diseases such as type 2 diabetes, obesity, S Met, CV diseases, stroke.

22. The prevention of periodontal diseases is based on two principles of treatment which consist on the one hand in optimizing oral hygiene (in this sense there are techniques of periodontal gingival brushing and auxiliary means of hygiene), and on the other hand it is possible to detect and control/ neutralize individual risk factors.

23. Social considerations such as education level, occupational status, income level can influence the prevalence of periodontal disease.

25. From the analysis of the data expressing the distribution of S Met according to the risk factors age and alcohol consumption in increased quantities, we can find that the relative risk (RR) of developing S Met is higher in the case of female subjects, who consume alcohol in the subgroup of adults (age <65 years) in relation to the male gender.

26. In the adult subgroup, the distribution of S Met in the group of subjects who consume alcohol is 18 times more common in men, and in the elderly subgroup, S Met is 8 times more common in males than in females.

27. Regarding the involvement of the risk factor tobacco smoking, we can see that the relative risk (RR) is higher in the case of male adult smokers $1/0.6 = 1.66$ compared to male elderly smokers $1/0.63 = 1.59$ in relation with the female gender.

28. In adults, the distribution of S Met in the group of smoking subjects is $1/0.33 = 3$ times more common in men, and in the elderly, S Met in the group of smoking subjects is $1/0.38 = 2.6$ times more common in men, in relation to gender female.

29. There is a statistically significant correlation ($p < 0.001$) between metabolic syndrome and periodontal pockets. Thus, 57% of subjects with metabolic syndrome have periodontal pockets >3.5. Among subjects without metabolic syndrome, 59.4% have no periodontal pockets, and 40.6% have periodontal pockets <3.5.

30. Regarding gingival bleeding we found that there is a statistically significant correlation ($p < 0.001$) between S Met and the existence of gingival bleeding. 79.2% of subjects with metabolic syndrome have gingival bleeding. Among subjects without metabolic syndrome, 84.6% do not have gingival bleeding. The relative risk (RR) of metabolic syndrome is 5.15 times higher in subjects with gingival bleeding. We could find that S Met is 20.9 times more common in subjects with gingival bleeding.

31. There is a statistically significant correlation ($p < 0.001$) between S Met and the frequency of dental perlage. The extent of the variation is demonstrated by the fact that 47.6% of subjects with metabolic syndrome brush their teeth only occasionally. Among subjects without metabolic syndrome, 50.0% have a frequency of dental pearlization 2 times a day.

32. We did not find a statistically significant correlation between S Met and the existence of dental control ($p=0.074 > 0.05$). However, S Met is 3.17 times more common in subjects who do not perform regular dental check-ups.

33. The results of our research allow us to state that there is a strong correlation with statistical significance ($p < 0.001$) between S Met and food preferences. The extent of the variation is demonstrated by the fact that 92.9% of the subjects with metabolic syndrome show hypersodic, hyperprotein or hyperlipidic food preferences (or their combinations). Among subjects without metabolic syndrome, 53.1% have food preferences that fall within the normal caloric regime.

34. We found that there is a statistically significant difference ($p < 0.001$) between subjects presenting S Met and those who do not manifest this syndrome in terms of the community periodontal index (CPI). Thus, the average of this index is significantly higher in subjects with metabolic syndrome (2.98 vs 1.84).

35. In the case of gingival attachment loss the ANOVA test provides results with statistical significance ($p = 0.003 < 0.05$) regarding the mean of the gingival attachment loss quantification variable which is significantly higher in subjects with S Met compared to those without S Met (2.93 vs 1.84).

36. We found that there is a statistically significant difference ($p < 0.001$) between subjects with S Met and those without this syndrome with respect to CV risk. Thus, the mean of this index is significantly higher in subjects with S Met (8.95 vs 2.22).

37. We could find, from our research, that periodontal pockets have the greatest influence on S Met distribution, followed by CPI, CV risk, gingival bleeding and food preferences. Considering the numerical values associated with the independent variables, it is observed that high values of the variables: periodontal pockets, CV risk, bleeding, CPI, DMF-T, loss of gingival attachment, food preferences, correspond to positive (high) SHAP values, so they correspond of an increased probability of occurrence of S Met.

We can interpret that the high values of the variables tooth brushing, dental control (represented in the graph by clusters of red dots) in opposition to the small values of SHAP (represented in the graph by clusters of blue dots), can be followed by the decrease of the probability of occurrence of S Met

38. The established links between periodontal disease and general health are complex and still only partially understood. There are numerous studies, which signal the frequent association with numerous diseases such as type 2 diabetes, obesity, S Met, CV diseases, stroke.

39. The prevention of periodontal diseases is based on two principles of treatment which consist on the one hand in optimizing oral hygiene (in this sense there are techniques of periodontal

gingival brushing and auxiliary means of hygiene), and on the other hand it is possible to detect and control/ neutralize individual risk factors.

40. Economic-social considerations such as education level, occupational status, family income level can influence the prevalence of periodontal disease, respectively its association with S Met..

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