SUMMARY OF PhD THESIS

CARDIOVASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS IN A RURAL FAMILY MEDICINE PRACTICE IN BACAU COUNTY

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GENERAL PART

Metabolic syndrome is an important risk factor for cardiovascular diseases and type 2 diabetes mellitus. Therefore, the metabolic syndrome might be useful as a practical tool to predict these two major metabolic disorders, its importance in the incidence of diabetes mellitus being often overlooked.

METABOLIC SYNDROME - A CONTINUOUS CHALLENGE

Metabolic syndrome is an aggregation of interdependent risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular diseases. Its main components are insulin resistance, hyperinsulinemia, visceral obesity, hypertension, dyslipidemia (high triglycerides and apolipoprotein [apo B], decreased high-density lipoproteins (HDL-C), prothrombotic state [increased plasma fibrinogen, increased plasminogen activator inhibitor-1 (PAI-1)], vascular abnormalities (high albumin urinary excretion, endothelial dysfunction), inflammatory markers and hyperuricemia. Metabolic syndrome is thought to be multifactorial, resulting from an aggregation of genetic and environmental factors.

PREVALENCE

The prevalence of metabolic syndrome varies among different populations. It is known to be increased in developed countries, due to physical inactivity and increased consumption of high calorie foods, thus leading to high rates of obesity. In the general population, the prevalence of the metabolic syndrome is estimated to be between 17% - 25%. In Europe, the prevalence of the metabolic syndrome varies between 12-26% and depends on the geographical area, urbanization and ethnic complex. The prevalence of the metabolic syndrome develops in parallel with: obesity, age, the presence of diabetes mellitus and hypertension. DM is associated with an increased risk of 2-4 times of developing atherosclerotic cardiovascular diseases, especially coronary artery disease and a risk 3-8 times higher of mortality due to CVD. High risk of CVD is highlighted by similar risks for future CVD events in people with DM without a history of previous myocardial infarction (MI), equal to people without DM with previous MI. Moreover, more than 50% of all deaths among diabetics are attributable to CVD complications. These facts, in general, were assigned to risk factors such as hypertension, obesity, smoking, hyperglycemia and dyslipidemia [elevated levels of fasting triglycerides, low levels of high density lipoprotein-cholesterol (HDL) and the presence of small, dense particles of very low density lipoprotein cholesterol (VLDL), many of which are associated with insulin resistance, resulting in a phenotype with high cardiovascular risk among people with DM.
PERSONAL PART

EPIDEMIOLOGICAL STUDY ON METABOLIC SYNDROME AND EARLY DETECTION OF DIABETES MELLITUS IN A RURAL FAMILY MEDICINE PRACTICE IN BACAU COUNTY

PURPOSE OF THE STUDY

This study is intended to provide an accurate statistical estimate of the data on morbidity of patients with metabolic syndrome, diabetes mellitus and cardiovascular complications in a rural population (Pancesti village - Bacău) in the adult population, aged 35-90 years old. Identification of the metabolic syndrome components in this type of population, less prone to epidemiological analysis, is important because they are related to an increased risk of cardiovascular disease and diabetes mellitus and other comorbidities like sleep apnoea syndrome, non-alcoholic fatty liver disease, polycystic ovarian disease, etc. By far the secondary metabolic and vascular complications of diabetes and atherosclerosis dominate the pathology and subsequently morbidity. The main objective of this study is to outline an epidemiological tool for early detection of diabetes mellitus and vascular complications in a rural population. Early detection of diabetes mellitus determines the adjustment of therapeutic targets and methods of primary prevention applicable to the rural population. In addition, the information obtained can be used to develop a prognostic on the long-term evolution of morbidity by cardiometabolic diseases for the studied population.

MAIN STAGES OF THE STUDY

1. STUDY I. DESCRIPTIVE EPIDEMIOLOGICAL STUDY OF METABOLIC SYNDROME COMPONENTS IN PANCESTI VILLAGE POPULATION

2. STUDY II. CLINICAL AND EPIDEMIOLOGICAL CORRELATIONS OF THE METABOLIC SYNDROME ELEMENTS IN THE STUDIED POPULATION

3. STUDY III. EARLY DETECTION OF DIABETES MELLITUS - CLINICAL SIGNIFICANCE

MATERIALS AND METHODS

STUDY I. DESCRIPTIVE EPIDEMIOLOGICAL STUDY OF METABOLIC SYNDROME COMPONENTS IN PANCESTI VILLAGE POPULATION

The study was conducted in the Family Medicine Practice of Pancesti village - Bacau County, with a registered population of 1,463 people aged 0-89 years old, insured and uninsured. The target population of the study was represented by subjects of both genders, aged between 35-89 years old.

The criteria for the selection of the group were the following:

- Age over 35 years;
- Decisional capacity;
- Wide abdominal circumference according to IDF criteria (≥80 cm in women and ≥94 cm in men);
- Informed consent of the patient.

The exclusion criteria include:

- Age over 35 years;
- Without decisional capacity;
- Lack of informed consent;
- Terminally ill patients.
The study was descriptive, transverse, the subjects being investigated in the family medicine practice during October 2011 - August 2012. The patients were selected by IDF diagnostic criteria of the metabolic syndrome (MS) (1,2). For the diagnosis of metabolic syndrome we have used the IDF criteria: - Abdominal obesity (AC ≥ 80 cm in women, namely ≥ 94 cm in men or BMI≥30 kg/m 2 ) + at least two of the following criteria:
- Elevated blood pressure: SBP ≥ 130 mmHg and / or DBP ≥85 mmHg or antihypertensive treatment previously established;
- Blood sugar ≥ 100mg / dl or previously diagnosed DM;
- Triglycerides ≥150 mg / dl or specific treatment for hyperTG;
- HDL-col ≤ 40 mg /dl in men or ≤ 50 mg /dl in women or specific treatment for this dyslipidaemia.

All subjects underwent anamnesis and complete clinical examination, measurement of abdominal circumference (soft tape) midway between the last rib and the iliac crest, while standing, waist and weight, determining blood pressure (twice in the right arm sitting down after 10 minutes of rest and the calculation of their average). We have scheduled a second visit for medical tests in a night fasting state: blood sugar, triglycerides, HDL-cholesterol, liver and kidney function tests. Then, we have extended the analysis including total serum cholesterol and LDL cholesterol for cardiovascular risk assessment. For detection of another co-existing risk factors we have directly questioned the subjects about: Alcohol consumption (yes or no and estimated quantities); Physical exercise (yes or no); Level of education: less than 8 classes or high school/college; family history of diabetes and hypertension (yes or no) with at least one first-degree relatives; Smoking (yes or no); Economic or social stress.

STUDY II. CLINICAL AND EPIDEMIOLOGICAL CORRELATIONS OF THE METABOLIC SYNDROME ELEMENTS IN THE STUDIED POPULATION

Patients with abdominal obesity AC were divided in turn into two groups, depending on the presence / absence of the metabolic syndrome MS according to IDF defining criteria 2012: - Group I- 330 cases consisting of patients with defined metabolic syndrome (abdominal circumference and at least two components of the defined metabolic syndrome).
- Group II - 285 cases consisting of subjects without a defined metabolic syndrome, but who have one or two components of the metabolic syndrome, abdominal circumference AC mandatory.

For the two groups, the comparison of the prevalence of metabolic syndrome elements and of other risk factors as well as the risk of ischemic heart disease (CIC) was performed.

STUDY III. EARLY DETECTION OF DIABETES MELLITUS - CLINICAL SIGNIFICANCE

Of the patients with metabolic syndrome, a study group was selected in which patients with fasting blood sugar of ≥ 100 mg/dl were included, threshold when blood sugar represents a factor of cardio-vascular risk, proven in recent studies, 204 cases, 132 women and 72 men. We reported this data to the population studied and the one with abdominal obesity and we have calculated the incidence data for glucosmetabolism disorders and prevalence of other risk factors. At the same time we have examined the risk of occurrence of diabetes mellitus and effectiveness within a year of clinical investigations of these subjects through a prospective study, intention to treat, with hygienic-dietary measures and therapeutic education. Thus, the participants in the study were monitored in a prospective study, of one year, targeting only hygienic-dietary and information measures on diabetes complications and the evolution of fasting glucose was assessed.
STATISTICAL PROCESSING. The medical data processing was performed using the SPSS 16 application (Statistical Package for Social Sciences) and Microsoft Office Excel to create the database (program compatible with SPSS in regards of data import).

Ethical considerations. For this study we have received prior to its commencing the approval of the Ethics Committee of the University of Medicine and Pharmacy "Gr. T. Popa" Iași.

CHAPTER I. DESCRIPTIVE EPIDEMIOLOGICAL STUDY OF METABOLIC SYNDROME COMPONENTS IN PANCESTI VILLAGE POPULATION

RESULTS I

The study group with ages between 35-89 years contained 969 subjects (66.23% of the population in the practice records) (fig. 1), of which 55.93% women (542 subjects), and 44.07% men (427 subjects).

According to IDF criteria (2, 6), the abdominal obesity criteria (abdominal circumference ≥ 80 cm in women and ≥ 94 cm in men) was fulfilled by a total of 615 people (63.47% of the total of 969 people) (Figure I-1, Table 21).

![Figure I-1. Organisation of the studied population](image)

<table>
<thead>
<tr>
<th>TOTAL POPULATION</th>
<th>1463p</th>
<th>35-90 years</th>
<th>969p</th>
<th>IDF framed, the first criterion, the abdominal circumference</th>
<th>615p</th>
<th>WOMEN</th>
<th>422p</th>
<th>MS +</th>
<th>222p</th>
<th>36.10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN 193p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MS +</td>
<td>108p</td>
<td>17.56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MS -</td>
<td>85p</td>
<td>13.82%</td>
</tr>
</tbody>
</table>

Table 21. Components of the studied population

This first study had as objective, as we stated above, only the epidemiological description of the selected population of 615 cases with abdominal obesity AC in conjunction with other elements of the metabolic syndrome and classic risk factors. We analysed a number of socio-anthropometric data, age, gender, which led to the following results. According to the descriptive analysis, the cases of the study group were 35 - 89 years of age, with an average of 66.49 years and standard deviation of 12.08 years. The distribution of age by groups of 10 years (decade) is shown in the
above table. The Gaussian distribution is observed and that the group is dominated by senior persons -60-70 and 70-80 years old. The two decades cover approximately 62.1% of the total cases totalling 383 cases (Figure I-2). The decade characterization of the risk factors studied is further useful for discovering the target populations in relation to age.

Abdominal circumference

IDF criteria defining the metabolic syndrome MS take into account the following features of abdominal circumference, AC: AC ≥ 94 cm for men, namely AC ≥80 cm for women (1,2). The statistical analysis emphasizes an average of the abdominal circumference of 99.36 cm and a standard deviation of 10.27 cm with a variance of 105.47 cm.

If we analyse further the distribution of the AC average per decade age groups, we note a relatively uniform distribution but with a predominance in the 50-60 years, 60-70 years and 70-80 years decades, which exceed 100 cm (fig I-3).

Gender

Figure 4 shows that the female population maintains its already described trend: high weight, with a significant statistical difference, for the 50-60 years group in relation to the group under 50 years of age and is maintained for the next two decades. This pattern is not
expressed as clearly by the male population where a more uniform distribution of AC averages is observed, without registering a statistically significant increase after 50 years. We also note also that the abdominal circumference calculated average for all age groups is higher in men (fig. I-4), fact which is also highlighted by the very definition of MS. (IDF criteria defining the metabolic syndrome MS take into account the following features of abdominal circumference, AC: AC ≥ 94 cm for men, namely AC ≥ 80 in women).

![Figure I-4. Relationship between abdominal circumference, age and gender](image)

**Estimated obesity by body mass index (BMI)**

Predicting obesity by body mass index (BMI) is useful and is often used in the diagnosis and definition of obesity. By statistically analysing the BMI distribution we wish to assess to what extent the data obtained are superimposable with the data relating to the abdominal circumference previously calculated. Thus, we find an average value of BMI for the studied population of 27.7967 +/-4.48 kg/sqm, with high extreme values of maximum and minimum [19.53-55.18]. Due to the large dispersion of the data, the analysed environments lose in part statistical significance. This is why we wish to analyse further the prevalence of cases with overweight (BMI between 25-30 kg/sqm) and obesity (BMI over 30 kg/sqm), in accordance with the definition of obesity using BMI. This characterization of this distribution is more significant (Figure I-5).

![Figure I-5. The distribution of the studied group based on BMI](image)

We analysed the distribution of overweight and obesity by age groups and a predominance of overweight is observed, between 35% and 46.9%. If in the majority of decades, the distribution of cases with normal weight and obese cases is balanced; in the 50-60 years decade obesity is predominant (37.8% obese in relation to 22.2% normal weight); in extreme decades, the group with normal weight is predominant (Figure I-6). The percentage of obese persons increases from 40 to 60 years from 25% to 37.8% in the 50-60 years decade and then
decreases to 12.5% for the final age group. For most age decade groups, overweight is the best represented and is more than 40%. The only exception is the 50-60 years group where obesity is near overweight, close to parity, 37.8% vs. 40%, according to Figure I-6.

![Figure I-6. The distribution of the studied group based on BMI and age](image)

**High blood pressure (HBP)**

We considered the HBP measured values for systolic blood pressure, SBP ≥ 130 mmHg and/or diastolic, DBP ≥ 85 mmHg. For the entire studied group (969 subjects), high blood pressure was present in 55% of subjects over 35 years (Figure 7).

![Figure I-7: Prevalence of high blood pressure in the studied group](image)

We have calculated the prevalence base on gender. We have obtained a statistically significant difference between specific prevalence calculated for the two sexes, the prevalence of the female population being higher than that of the male population (P < 0.05; fig.I-8)

![Figure I-8: Specific prevalence on gender of HBP in the studied group.](image)

At the same time, the group of patients with abdominal obesity AC (615 cases), meet the criteria for the definition of hypertension, 531 cases i.e. 86.3% of the group with abdominal obesity studied. As we can see from table 30, in the group of males (M) (7.8%), the percentage of normal BP is half in relation to the female group (F) (16.4%). Even if there is a difference in weight between the two genders, 353 cases of women in relation to 178 cases of men, the share of high blood pressure in men from the group with android
obesity maintains its statistical significance (fig. I-9).

**Figure I-9. The distribution of patients based on BP values in the group with abdominal obesity**

**High blood pressure in relation to age**

Further, we analysed the prevalence of HBP in relation with the studied patients’ age to discover some features. An analysis of the share of cases with HBP on age decades is expressed in Figure I-10 and presented the following characteristics. As shown in Figure 10, the increase in the HBP share has the same cut-off for groups after 50 years, but the differences are not as great as for AC. Moreover, high levels of HBP prevalence, within the age group, are registered in the group over 60 years, the percentage of HBP is increased around 90% compared to 77% for 40-60 years, respectively 30% than those under 40 years of age. The increased percentage is also maintained over 80 years (Figure 10). If we analyse the prevalence of HBP within the HBP group, the same increased prevalence can be observed, but focused on only two decades, 60-70 years, 70-80 years, 30.1% namely 35.2%.

**Figure I-10. The distribution of hypertensive patients based on age**

If we add the cases of hypertension treated with or without normal BP values we have the following epidemiological picture: from the 531 cases analysed as age decade prevalence we get to 559 cases. In the above statistical processing we have considered elevated BP values measured during the visit to the medicine practice. In the latter, I also taken into account treated patients regardless of thei BP value. As with the share of cases with high levels of BP and the expression of the distribution of HBP plus treated HBP (even if they have normal BP values) we can observe the same increase after 40 years, which is maintained until after the age of 80 (fig. I-11). Decade averages records percentages of over 90% after the age of 50 years (fig. I-11).
Measurement of triglyceride values

Measurement of triglyceride values shows an average of 115.13 mg/dl and a standard deviation of 65.464 mg/dl with a high variance of data: a maximum of 561 mg/dl and a minimum of 17 mg/dl; we also note a great standard error of 2.640. Comparison of average values on the two genders shows certain uniformity, without significant statistical differences. Triglyceride average values are comparable: 113.75 mg/dl vs. 118.16 mg/dl, women vs. men. The modest average values are influenced by the minimum values recorded in the group, 17 mg/dl which created great data dispersion, and great standard deviations, around 65 mg/dl. This great variance of data makes the interpretation of the obtained averages as having statistical significance difficult.

More significant is the share of increased values of triglycerides over 150 mg/dl. It is found that only 20% of the population has elevated triglyceride levels as described in table 35. With regard to gender distribution of elevated triglyceride values, we can observe a low increase of the hyper-triglyceridemia share in men: 24.4% male versus 18.0% in women.

Triglycerides in relation to age

I described the average values of triglycerides on age decades and I have obtained the following results.

Figure I-12. The average value distribution of TG based on age decades

An increase is observed in the average values of triglycerides in the decade of 50-60 years (from 93.15 mg/dl to 135.89 mg/dl) until the age of 60 years, after which a decrease from approximately 102.23 mg/dl in the decade over 80 years (Figure I-12). In addition, it is
observed that the average values, regardless of age decade, do not exceed the limit of 150 mg/dl. We note the significant increase, if we analyse the confidence interval of 95%, in the 50-60 years group. The statistical significance is very important. More statistically significant is the description of share on age groups of triglycerides values over 150 mg/dl. The decade analysis highlights a significant increase of the hyper-trigliceridemia share of 27.8% in the 50-60 years decade, the same observed in the average values. After 80 years, the share of hyper-trigliceridemia drops drastically, to 10.9% (Figure I-13). In Figure I-13 the same issue is expressed graphically, significantly increased prevalence of hyper-trigliceridemia cases for the 50-60 years decade.

Figure I-13. Hyper-trigliceridemia: percentage distribution by age decade

Measuring HDL cholesterol

The descriptive statistical study continued in the same form for the measurement of HDL-cholesterol: minimum, maximum, average, standard deviation, median. We also studied the average values of HDL-col by gender and age decades. The average of determined wales of the HDL-col ratio was 58.54 mg/dl with a standard deviation of 15.02 mg/dl (relative high standard deviation). The analysis of determined values of HDL-col shows a great dispersion of data (minimum 16 mg/dl versus maximum 163 mg/dl). Gender analysis of the distribution of average values of HDL-col shows comparable average values, without statistical differences between the two sexes, 58.14mg/dl, women vs 59.44 mg/dl, men and a standard deviation of 13.912 mg/dl vs 17.220 mg/dl. Unlike the average values of triglycerides, the standard error is smaller in both gender groups. The share of low values of HDL-col in the studied group is relatively small compared to those with normal values (report roughly equal to 1/4) (fig. 14).

Figure I-14. Distribution of HDL-col values in the studied group
Analysis of distribution by gender highlights the prevalence of low HDL-col in women: percentage of 24.2% compared to 8.8% in men. For a better characterization of the distribution of HDL cholesterol values, we have calculated the statistics descriptive indicators on age decades. Distribution of average values of HDL cholesterol on age decades shows a significant decrease for the 50-60 years decade (determined average of HDL-col for this decade being 56.93 mg/dl, with a 95% confidence interval between 54.59 and 59.28) (Figure I-15).

Figure I-15. Distribution of average values of HDL-col

However, the average HDL cholesterol does not have large variations, from a minimum of 56.85 mg/dl (for ages under 40 years), to a maximum of 59.44 mg/dl (in the 70-80 years decade), without statistical significance. We find the great dispersion of data on age extremes (fig. I-15). Frequency analysis of low HDL values with pathological significance, on the age decades shows a maximum of 28.1% in the over 80 years decade, followed by the 70-80 years decade, with 21.0% for pathological HDL cholesterol values and some uniformity within the age (Figure I-18).

We note that in the group with low HDL, a high prevalence is recorded in decade age groups 70-80 years and 60-70 years with 36.1%, respectively 24.4%.

Figure I-16. Distribution of normal and pathological values of HDL-col based on age

If we consider the age groups, the increased share of cases with low HDL cholesterol is relatively uniform 16-17% for middle ages (from 40 to 70 years). We note that after 70 years, the prevalence increases to 21% and is maximum after 80 years (over 28%) (see figure I-16).
Diagnosed mixed dyslipidemia

With regard to mixed forms of dyslipidemia, we note that 85.3% of women and 74.1% of men have a form of dyslipidemia, that is 360 women and 143 men from the 615 selected cases with abdominal obesity.

Distribution by age group shows increased prevalence in groups of 60-70 years and 70-80 years, totalling 318 cases, approximately 60%. With regard to age group, it is observed that dyslipidemia are predominant, approximately 80%, for all age groups (Figure I-17).

Increased fasting blood sugar (deteriorated) \( \geq 100 \text{ mg/dl} \)

The analysis of altered blood sugars shows that 37.9% (233 cases) of the total of 615 patients had blood sugars with pathological value (\( \geq 100 \text{ mg/dl} \)). Of these 152 are women and 81 men, representing 36%, namely 42%, within those two groups, women, respectively men. Further we examined the distribution of the altered values of blood sugar based on age decade and we noted, for all age groups the prevalence of normal values and gaussian distribution of decade shares. We note the obvious increase of this share in the 60-70 years and 70-80 years decades, over 40% (41.6%, namely 46.3%). The prior group is not to be neglected, the 50-60 years group with a percentage of 37.8% (Figure I-18).

The percentage of cases with fasting blood sugar levels increases from 40 to 80 years from 15% (for people between the ages of 35-40 years old) to 46.31% (for the 70-80 years decade), so over 2.5 times and remains high over 80 years (23.4%) (Figure I-18).
Diabetes Mellitus already treated and already diagnosed

As expected, the previous analysis needed some corrections, mostly related to patients already diagnosed with diabetes mellitus and treated for this disease. We note that they were included in both groups randomly, with altered blood sugar or not, depending on the determined value of blood sugar at the time of this study.

The known cases of diabetes mellitus have been identified and the statistical analysis was carried out. We found that in the study group, 45 patients were known to have diabetes mellitus and have been treated, a share of 7.3% within the subjects investigated. Of these, 31 cases were females (68.9% of diabetes cases), and 14 cases were males (31.1%). Analysis by age group shows that the majority of treated diabetes cases are included in the 50-80 years age groups, with a majority of 40 cases out of 45 (89.9%). Just like the blood sugar distribution, we have an increase in the percentage up to 80 years (46%) and for the last age group, this percentage decreases to half.

CHAPTER II. CLINICAL AND EPIDEMIOLOGICAL CORRELATIONS OF THE METABOLIC SYNDROME ELEMENTS IN THE STUDIED POPULATION

RESULTS II.

Analysis of metabolic syndrome elements. According to IDF criteria, 615 persons had an abdominal circumference ≥ 80 cm in women and ≥ 94 cm in men [63.47% of the total of 969 people]. The patients were divided into two groups, depending on the presence/absence of the metabolic syndrome: group I-consisting of 330 patients with defined metabolic syndrome (increased abdominal circumference, plus at least two elements of the metabolic syndrome) and group II- consisting of 285 subjects without a defined metabolic syndrome, but having one or two elements of the metabolic syndrome. Reference to the population of the study, 1462 cases, makes the incidence of discovered metabolic syndrome to be 23.52% and for the population with abdominal obesity, 615 cases, the incidence is 53.72%. Basically, out of the total patients analysed, we have selected the 330 patients with metabolic syndrome, MS. Of these, some were withdrawn from the group for objective reasons (death, lost). Thus, the study group analysed further included 301 patients.

<table>
<thead>
<tr>
<th>Table 48. Structure of the analysed study group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>f d</td>
</tr>
<tr>
<td>f p</td>
</tr>
<tr>
<td>Valid</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>m d</td>
</tr>
<tr>
<td>M p</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

F- female, m – male, fd/md – deceased women/deceased men, fp/mp – lost women/lost men from the study (withdrawn from the study)

Assessment of the number of elements of the MS has resulted in the following classification of cases: the prevalence of cases diagnosed with 2 elements is observed, besides abdominal obesity, 224 cases, 36.4%, with a great difference in relation to the 3 and 4 elements that represent the rest of MS cases, 17.4%. Assessment of the thus defined MS such in the second epidemiologic study, on age decades shows the same Gaussian appearance that we have described (figure I-20).
CARDIOVASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS IN A RURAL FAMILY MEDICINE PRACTICE IN BACAU COUNTY

Figure II-1. Prevalence of MS by age decade

Analysis of the associated diseases type to define MS

In the assessment of cases with defined metabolic syndrome MS we apply the notion of cluster (association of risk factors) and analyse this prevalence on the number of criteria and we name these criteria and their combinations. Thus we distinguish the following dominant associations: for 1 criterion, we have AC with HBP (231 cases, 94.7%), then glucosemetabolism and dyslipidemia disorders. For 2 criteria, HBP and glucosemetabolism disorders are prevalent (133 cases, 59.4%).

Table 51. Prevalence of the association of metabolic syndrome elements

<table>
<thead>
<tr>
<th>No. Elements</th>
<th>MS Elements</th>
<th>cases</th>
<th>% per no. elements</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Without a disorder (only AC)</td>
<td>39</td>
<td>100.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>1</td>
<td>Altered blood sugar or DM T/</td>
<td>5</td>
<td>2.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>Low HDL-col/</td>
<td>5</td>
<td>2.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>HBP or TA T/</td>
<td>231</td>
<td>94.7%</td>
<td>37.9%</td>
</tr>
<tr>
<td></td>
<td>Triglycerides ≥ 150/</td>
<td>3</td>
<td>1.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>2</td>
<td>Low HDL col./Altered blood sugar or DM T/</td>
<td>3</td>
<td>1.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>HBP or TA T /Altered blood sugar or DM T/</td>
<td>133</td>
<td>59.4%</td>
<td>21.6%</td>
</tr>
<tr>
<td></td>
<td>HBP or TA T/low/low HDL col./</td>
<td>43</td>
<td>19.2%</td>
<td>7.0%</td>
</tr>
<tr>
<td></td>
<td>HBP or TA T/Triglycerides ≥ 150/</td>
<td>42</td>
<td>18.8%</td>
<td>6.8%</td>
</tr>
<tr>
<td></td>
<td>Triglycerides ≥ 150 / Altered blood sugar or DM</td>
<td>1</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>Triglycerides ≥ 150 / low HDL col./</td>
<td>2</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>3</td>
<td>HBP or TA T/low/low HDL col./Altered blood sugar or DM T/</td>
<td>33</td>
<td>36.3%</td>
<td>5.4%</td>
</tr>
<tr>
<td></td>
<td>HBP or TA T/Triglycerides ≥ 150/ Altered blood sugar or DM T/</td>
<td>42</td>
<td>46.2%</td>
<td>6.8%</td>
</tr>
<tr>
<td></td>
<td>HBP or TA T/Triglycerides ≥ 150/ low HDL col</td>
<td>16</td>
<td>17.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>4</td>
<td>HBP or TA T/Triglycerides ≥ 150/low HDL col</td>
<td>17</td>
<td>100.0%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

The descriptive analysis performed above is expressed synthetically in the figure below and highlights once again the central place occupied by HBP associated to abdominal obesity AC in the definition of the metabolic syndrome (figure II-9).
CARDIOVASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS IN A RURAL FAMILY MEDICINE PRACTICE IN BACAU COUNTY

Figure II-9. The structure of subjects with metabolic syndrome based on the criteria that form it

We note, again, that the most important association is between AC and HBP, followed by altered blood sugar.

Statistical correlations between the prevalence of the metabolic syndrome, MS and prevalence of HBP

We redefine the metabolic syndrome and consider all the possible associations of its elements: AC + 2 of: elevated triglycerides; Low HDL (different for F/M); altered blood sugar, less HBP, according to IDF, and we analyse the relationship with HBP, namely CIC. Extraction of MS cases thus defined result in 198 cases of the 615 cases with abdominal obesity. We note the exclusion of HBP cases. We apply the qui² test for the analysis of the correlation between the defined MS and the association of HBP. In the correlation with MS with HBP we have statistical significance (p < 0.012). An increased ratio of HBP with metabolic syndrome is thus divided so a significant ratio.

Figure II-10. Linking the newly defined MS with the incidence of HBP

Linking MS, metabolic syndrome with HBP highlights that in cases of defined MS (34,1%), the incidence of HBP is significant (see figure II-10).

Statistical correlations between the prevalence of the metabolic syndrome, MS and prevalence of CIC

We also apply for the analysis of this correlation, between defined MS and CIC, the same statistical test, the qui² test for highlighting the power of this association, and a strong
association is established (p<0.0001), according to the table. We have statistical significance: increased proportion of CIC and metabolic syndrome (34,1%) (figure II-11).

![Figure II-11. Association of MS with CIC](image)

**Influence of classical risk factors: age, cholesterol, obesity-BMI, smoking upon ischemic cardiopathy (CIC) in the population studied by logistic regression.** Virtually all the variables proposed are important (because the significance level is below 0.05)-but there is a definite hierarchy of significance and score, which makes the step-by-step model to be built accordingly. The most appropriate factor to be introduced in the model is the age because it has the lowest significance and also the highest score.

At each step we have recalculated the significance of the remaining factors and we have chosen the most representative accordingly. We present below the influence of factors as predicting variables on the 3 working steps, using the model **If Term Removed**, i.e., after analysing a risk factor, it is removed and the following is analysed.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model Log Likelihood</th>
<th>Change in -2 Log Likelihood</th>
<th>df</th>
<th>Sig. of the Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-341,655</td>
<td>16,964</td>
<td>1</td>
<td>.000</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-337,177</td>
<td>19,526</td>
<td>1</td>
<td>.000</td>
</tr>
<tr>
<td>Obesity</td>
<td>-333,173</td>
<td>11,518</td>
<td>1</td>
<td>.001</td>
</tr>
<tr>
<td>Age</td>
<td>-334,414</td>
<td>18,605</td>
<td>1</td>
<td>.000</td>
</tr>
<tr>
<td>Step 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>-329,947</td>
<td>9,669</td>
<td>1</td>
<td>.002</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-327,414</td>
<td>4,604</td>
<td>1</td>
<td>.032</td>
</tr>
</tbody>
</table>

It appears that they have a significance below 0.05 in the moment they are removed from the model -this indicates that only Age, Obesity, and Cholesterol are important for ischemic heart disease prediction (CIC). Our data did not indicate that smoking would be useful in this prediction - maybe the threshold chosen in the definition of smoking is not well established. These are interpretations determined by logistic regression - the influence of the factors Age, increased Cholesterol and Obesity on the risk of having this disease, ischemic heart disease (CIC) is thus confirmed by our data.

**CHAPTER III. EARLY DETECTION OF DIABETES - CLINICAL SIGNIFICANCE FOR ITS TIMELY MANAGEMENT**

**RESULTS III.**

Further, we have selected from the remaining 301 patients in study, the group of patients with fasting blood sugar ≥ 100 mg/dl, limit when blood sugar represents a proven
factor of cardiovascular risk. Completion of these steps suggests the outlining of for clinical and epidemiological investigation of patients with glucose metabolism disorders and diabetes mellitus, using the tools available to the family doctor in a rural population. So we have studied a group consisting of 204 cases with blood sugar levels (initial) ≥ 100 mg/dl, discovered during the study. Of these, 132 cases are women (64.7%) and 72 cases (35.5%) men, according to table 63. We have reported this data to the population studied and the one with abdominal obesity and defined metabolic syndrome and we obtained data on the Incidence of glucose metabolism disorders in the studied population:

<table>
<thead>
<tr>
<th>A total of 1462 cases =&gt; incidence of 13.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>From a total of 615 cases with abdominal obesity =&gt; incidence of 33.1%</td>
</tr>
<tr>
<td>Of the total of 330 cases with MS= &gt; incidence is 61.81%</td>
</tr>
</tbody>
</table>

For a more thorough clinical and biological analysis of patients from the group with glucose metabolism disorders we have selected a number of 159 cases; the others did not want to continue with the study or were already known as having diabetic and being under treatment. The group thus formed consists of 101 women (63.5%) and 58 men (36.5%). The average age of the studied group was 68.23 +/-9.18 years with extremes of 37 years, i.e. 87 years. Within the same group, 11 cases had high blood sugar levels over 126 mg/dl, which defines diabetes mellitus DM (6.9%).

**Description of risk factors that define the metabolic syndrome MS**

**AC abdominal circumference**

Measuring abdominal circumference, within this group, 159 cases, shows an average of 100.76 +/-11.59 cm, with extremes between 72 cm and 134 cm. We compare it with the average obtained in group with abdominal obesity (615 cases) 99.36 +/-10.27 cm, with statistical significance (p = 0.05).

**Obesity reported by BMI (body mass index)**

Consideration of obesity as measured by body mass index, BMI, highlights an average of 28.25 ± 4.72 kg/sqm, with increased data variance, 22.31 kg/sqm what proves high dispersion of data. In the group with abdominal obesity (615), the average was 27.79 +/-4.48 kg/sqm. The difference is statistically significant (p = 0.05). In terms of category, dichotomisation of data by BMI groups that define normal weight, overweight and obesity, according to the table, we can observe a relatively homogenous distribution but with the prevalence of overweight and obesity groups (37.7%, 35.2%, compared to 27% those with a normal BMI). Together, overweight and obesity represent the dominant category of the studied group (116 cases representing 73% of the cases studied). Comparison of overweight/obesity groups for the group with glucose metabolism disorders/DM and one with abdominal obesity AC, shows a high prevalence of obesity and overweight in the population with glucose metabolism disorders compared to the one with AC (73% vs 46%)(figure III-1).
CARDIOVASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS IN A RURAL FAMILY MEDICINE PRACTICE IN BACAU COUNTY

Figure III-1. Prevalence of normal BMI, overweight and obesity among the two groups (with increased AC vs glucose metabolism disorders and MS)

From this finding, we analyse the possible relationship between overweight and obesity expressed by BMI over 25 kg/sqm and altered blood sugar using the Chi-square test in the population with abdominal obesity, 615 cases. Chi-square test accepts significance at a level of below 0.1, i.e. less than 10%. The data are consistent because we have the minimum expected value of 16.98 which is much over 5. We conclude that according to the value of $p = 0.087$ that we have significance and according to the percentages obtained, we have an increased proportion of DM in the group with obesity/overweight compared to the group with normal BMI.

Figure III-2. Distribution of glucose metabolism disorders and DM based on overweight/obesity in terms of BMI

Measurement of diastolic and systolic blood pressure (SBP and DBP)

Measurement of SBP highlights an average of 141.04 +/- 12.92 mmHg with a large variance of 67.11 mmHg. DBP has an average value of 84.53 +/- 7.62 mm Hg, with a variance of 158.16 mmHg. Considering the patients with HBP in terms of category according to the definition, we find that only 7 cases did not have HBP (4.4%) which means 95.6% of cases with MS and glucose metabolism disorders, as opposed to the prevalence of HBP in the group with abdominal obesity which is only 55%. Gender distribution of is balanced: 95% women and 96.6% men, without significant differences. In the group with abdominal obesity HBP is predominant in the male group, 92.2%.

Determination of serum lipoprotein profile

Measurement of serum triglycerides The measurement of serum triglyceride highlights an average of 123.11 +/- 68.55 mg/dl versus 115.13 +/- 65.46 mg/dl in the group with a significantly increased abdominal obesity ($p<0.003$). We note high DS and ES, proof of high dispersion of population data.
Measurement of HDL-cholesterol

The measurement of HDL cholesterol values shows an average of 57.58+/-17.11 mg/dl versus 58.54+/-15.02 mg/dl, with statistical significance (p<0.05).

Determination of other cardiovascular risk factors other than MS

Serum Cholesterol

Descriptively in the group of 159 patients, the measurement of serum cholesterol values shows a moderately increased average, 214.06=+- 49.92 mg/dl, the data being very dispersed (between 104 and 347 mg/dl).

LDL-cholesterol

The same thing is observed with regard to LDL cholesterol. The average is 115.58+/- 36.33 mg/dl.

Other cardio-vascular risk factors

Smoking is present in 35 cases (22%).
Alcohol consumption is present in 67 cases (42.1%). Patients with only elementary school total 140 cases (88.1%).

Presence of CIC

Prevalence of cases with established cardio-vascular disease (CIC, AVC) is significant. Ischemic cardiopathy is present in 33.3% and AVC in 3.8% of cases.

Report and prevalence of MS elements association

The statistical analysis is driven towards the notion of RF cluster, the base of cardio-metabolic risk definition starting from the exponential involvement of RF. Associating elements of metabolic syndrome shows a high prevalence for the association of abdominal obesity (increased CA), with HBP (30 cases, representing 18.9%) and the association as a third element, with obesity/overweight, expressed by BMI above 25 kg/sqm. This represents 58 of total cases, which represent 36.5%.

Comparative analysis of two groups with and without glucosemetabolism disorders

Further we compared the two groups: with glucosemetabolism disorders, blood sugar ≥ 100 mg/dl and without, 204 cases vs 107 cases in terms of the most commonly analysed RF belonging or not to MS. For this we have used the Mann-Whitney test.

Analysis of abdominal obesity expressed by AC

We a have statistical significance for the group with blood sugar levels over 100 mg/dl; AC is higher compared to the group with blood glucose levels lower than 100 mg/dl. The average is over 3 cm and the median is 2 cm. - according to our data (p < 0.041). The same thing is expressed graphically in Figure III-3.
**Analysis of obesity expressed by BMI**
Analysis of obesity by BMI reveals that there are not significant statistical differences.

**Analysis of systolic blood pressure values, SBP**
Further, we compared the average values of SBP for the two groups, to highlight the significance of SBP in the association with glucosemetabolism disorders. The table shows that the differences are not significant, regardless of the presence or absence of glucosemetabolism disorders; the average values of SBP do not have important differences. The same is discovered from Figure III-5. There are no statistical differences between the two groups, 140 mmHg vs 140 mmHg. However, an aggregation towards the value of 160 mmHg in the group without glucosemetabolism disorders can be observed, as opposed to group with glucosemetabolism disorders where the data are dispersed (Figure III-5).
CARDIOVASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS
IN A RURAL FAMILY MEDICINE PRACTICE IN BACAU COUNTY

Analysis of diastolic blood pressure values, DBP
Comparative analysis of DBP average values highlights the same lack of statistical significance between the two groups (figure III-6).

The analysis of total cholesterol values
As regards the total cholesterol values, comparative analysis of its values in the group with glucose metabolism disorders compared with the one with blood sugar below 100 mg/dl shows no significant differences. There is no statistical significance, meaning that the average value of cholesterol does not differ in the two groups. Comparison of average values is shown in Figure III-7 and shows the same lack of significance (210 mg/dl vs. 212 mg/dl).
Analysis of LDL cholesterol values

Comparative analysis of LDL cholesterol values has the same layout as in the case of average cholesterol values and shows no statistical differences (Figure III-8).

![Figure III-8. Comparative analysis of LDL cholesterol](image)

There are no statistical differences in the graphical representation, but we observe a high dispersion of data and increased values in the group without glucose metabolism disorders (Figure III-8).

Analysis of average triglycerides values

Measurement of average values of triglycerides and comparison with glucose metabolism disorders, by the same statistical method, Mann-Whitney, shows a statistically significant differences but in the group without glucose metabolism disorders (p<0,0001).

The same aspect is also expressed in graph III-9. We have statistical significance - triglycerides are higher in group with blood sugar levels < 100 mg/dl but an aggregation of values pretty high over the value of 260 mg/dl can be observed, quite a few over 300 mg/dl or even 400 mg/dl in the group with glucose metabolism disorders. On the other hand, the increased average in the group without glucose metabolism disorder is held up by some extreme values (561 mg/dl). Thus, the triglycerides average loses its significance. Elimination of biases could approach the average values to the comparison.
Figure III-9. Comparative analysis of triglycerides

Analysis of average HDL cholesterol values

Comparative analysis of average values of HDL cholesterol highlights the mirror effect of triglyceride analysis, which is what was expected. The same appearance is present in the graph from Figure III-10. We have statistical significance - lower HDL cholesterol in the group with blood glucose levels < 100 mg/dl.

Regression and correlation analysis: Because the correlation statistical analysis examined above does not satisfy us, we consider it opportune to analyse the various risk components for glucose metabolism disorders by regression and correlation. So, for the whole group of 311 cases we consider the dependent variable y = blood sugar levels and independent variables xi: BMI, AC, Age, SBP, DBP, Cholesterol, Triglycerides, HDL. We seek to determine a relationship between the blood sugar variable and possible predictors: BMI, AC, Age, SBP, DBP, Cholesterol, Triglycerides, HDL. We have two work methods: 1) regression model 2) characterization of the relationship through correlation. According to the proposed model, we find that only SBP and DBP have influence on blood sugar. It may be that some of the variables proposed as predictors of blood sugar be correlated and therefore negatively influences the model. To eliminate variables that do not have a role in the system, we apply the sequence method beforehand - so the factors that have maximum influence and significance will be added at each step of the optimization. By applying this method, we obtained significance for AC, SBP and DBP. The value of the coefficient of determination is 0.062 which shows that only 6.2% of the variation in blood sugar can be explained by the model. Such a low percentage is not accepted.

2) Analysis of associations through the correlation method. Because the linear regression
model was not statistically significant, we used the statistical association though the correlation method. Our data sets do not show a normal distribution of blood sugar. Correlation coefficient can be calculated using the Pearson method (parametric), namely the Spearman method (nonparametric - does not take into account the type of distribution). We calculate the correlation by both methods - we note that from a statistical viewpoint more appropriate is the Spearman nonparametric coefficient. According to the correlation method, we obtain directly proportional relationships for BMI, AC and SBP. In other words, an increase in BMI, or AC or SBP will lead to an increase in blood sugar. Other variables proposed for analysis do not have any statistical significance which shows a lack of influence on blood sugar - compliant with our data.

Comparison of fasting blood glucose at the initial time and after a year of clinical and biological monitoring. Comparison of fasting blood sugar levels, at a one year difference, shows significant differences: the initial average blood sugar is 110.38 +/-12.67 mg/dl versus the average blood sugar after a one-year clinical follow-up, 104.2 +/- 12.58 mg/dl, which is significantly low. We obtained statistical significance, p < 0.001. We can affirm that there is a decrease of blood sugar of about 6 units on average (between the old and new blood sugar levels).

GENERAL CONCLUSIONS
1. The majority of the target population, 615 cases with abdominal obesity, fall in the 50-, 60-70- decades, 76.8% of the total, so this is the group targeted in the application of the methods for detection and prevention of glucose metabolism disorders.
2. The results show a high percentage of the MS in the studied population with abdominal obesity (330 cases = 53.72%).
3. High blood pressure and obesity measured by BMI were the most common components (98.18% high blood pressure, 75.15% overweight and obese > 25 kg/sqm).
4. Altered blood sugar has a high frequency (68.18%) when detected in the population with MS, selected from the population with abdominal obesity.
5. The influence the Age, increased Cholesterol and Obesity factors is also confirmed by our data on the risk of having ischemic heart disease (CIC).
6. According to the correlation method, we obtain directly proportional relationships for BMI, AC and SBP. In other words, an increase in BMI, or AC or SBP will lead to an increase in blood sugar in the population with abdominal obesity.
7. Comparison of fasting blood sugar levels after one year indicate significant differences, 110.38 +/-12.67 mg/dl versus the average blood sugar levels after one year of clinical and biological follow-up, 104.2 +/- 12.58 mg/dl, p<0.001.

A. Limits and difficulties in research. However complex and based on arguments a scientific research might be, in addition to the results obtained and significant contributions which have been made, there are some limitations which are inherent, but which offer the possibility of continuing the scope of interest. In this research, we can identify the following limits: With regard to the study on the present state of knowledge we have experienced an extremely high amount of information, in terms of metabolic syndrome and endothelial dysfunction. Thus, it took a very careful review, in order not to become comprehensive. With regard to the study on the metabolic syndrome, as in any study on human subjects, the communication and identification of eligible patients to be included in the study was difficult. We also evaluated the elements considered to be personal, such as issues of sexual dynamics, consumption of ethanol, etc., for which we had to rely on the honesty of patients.
Due to the large number of patients included, it was quite difficult to capitalise the entire volume of information. As in most studies, the financial part was a limit.

**B. Originality and innovative contributions of the thesis.** This research aimed at quantifying aspects of endothelial dysfunction of the metabolic syndrome by valid, reliable, and easily reproducible methods in ambulatory practice. Multiple studies have been carried out over the last decade on the metabolic syndrome, but without reaching a clear and universally accepted definition of medical organizations. This makes difficult the comparison of studies as well as the implementation of preventive measures in general. Primary medicine represents the component of the health care system most directly involved in identifying persons among the general population at risk and the one which is able to initiate educational measures amending the life system and reducing cardiovascular risk. The originality of the thesis consists in a comprehensive study which demonstrates the extremely high prevalence of metabolic syndrome in the general population.

**SELECTIVE BIBLIOGRAPHY**


30. Alberti KG, Eckel RH, Grundy SM et.al. International Diabetes Federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the study of obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis society; and International Association for the study of obesity. Circulation, 2009;120(16):1640-5.


36. The IDF Consensus definition of the Metabolic Syndrome in childrens and adolescents. IDF 2007: 3–19


**WORK AND PAPER LIST**


- **Alamir Diaa,** Adorata Elena Coman, Elena Popa, Maria Gabriela Traian, Rodica Petrovanu. TREATING OBESITY IN PRIMARY CARE – AN ETHICAL APPROACH, acceptat pentru publicare in 2015 in REVISTA ROMANA DE BIOETICA – adeverinta atasata.
