UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
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DOCTORAL THESIS

SUMMARY

CARDIOVASCULAR IMPLICATIONS OF ENDOCRINE AND
METABOLIC DISORDERS IN OBESITY

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KEY WORDS
Obesity, hypothyroidism, hypercorticism, insulin resistance, dyslipidemia, sugar diabetes, arterial hypertension, ischemic heart disease, cardiovascular risk, statistical analysis

INTRODUCTION
Defined as an excess of body fat mass, obesity has known in the last years a plus of attention from researchers, along with emphasizing its impact on atherogenesis and placing the abdominal obesity as a necessary criterion of metabolic syndrome.

Globally, the prevalence of obesity is ever-growing. In 2005 the World Health Organization assessed that at worldwide level there were over 400 million obese people (9.8% of the adult population) and estimated that in 2015 their number will exceed 700 million.

Increased body weight is associated with total mortality and morbidity increase also by cardiovascular disease (partly averaged by the AT and cholesterolemia increase), HDL cholesterol decrease and increased probability of sugar diabetes onset.

STUDY OBJECTIVES
The performed study aims to:
- clinically evaluate obese patients and establish the obesity degree according to BMI and obesity type based on anthropometric indices;
- research endocrine and metabolic modifications in the patients included in the study;
- establish the prevalence of cardiovascular pathology;
- analyze the correlation between endocrine and metabolic modifications and their implications in the pathogeny of cardiovascular diseases.

MATERIAL AND METHODS
The study has a prospective character and was in progress over 6 years (2005-2010) in the Clinic of Cardiology of the Filantropia Town Clinical Hospital in Craiova.

1. Research protocol
The study was based on the method of observation of a batch of obese patients over 6 years, having a prospective character.

The criteria of inclusion in the study were:
- age over 18;
- presence of obesity defined by the BMI value ≥ 30 kg/m²;
- presence of abdominal obesity (abdominal circumference ≥ 94 cm in men, abdominal circumference ≥ 80 cm in women);
- presence of suggestive accusations of cardiovascular disease.

The patients’ criteria of exclusion from the study were the following:
- patients with known inflammatory infections or diseases;
- non-cooperant patients.

2. Casuistry evaluation protocol
The data gathering was done for each hospitalized patient in the study enlistment interval, who met the criteria of inclusion in the research, in a data base made in EXCEL, which is compatible with all the statistical analysis programs I have used for interpreting the information.

The study batch included a number of 172 patients with different obesity degrees, all presenting abdominal obesity, hospitalized in the clinic specifically accusing cardiac pathology.

The cases were investigates by anamnesis, clinical examination and by paraclinical examinations.

Clinical evaluation
Each patient in the study was drafted a typical card, which comprised information regarding: identity data, age, sex, residence, profession, heredo-collateral and personal antecedents, alimentation, drinking, smoking, physical activity. There were recorded the height, weight, size of abdominal circumference, BMI was calculated.
The clinical examination of cardiovascular apparatus included measuring the AT, AV, heart auscultation, determining the pulse at the radial, posterior tibial and pedious arteries level.

The endocrine clinical examination consisted of:

a) clinical examination of the hypothalamus
b) clinical examination of the thyroid
c) clinical examination of the cortical suprarenal
d) gonadic clinical examination (ovarian and andrologic).

Paraclinical investigations

Biohumoral exploration consisted of:

- Hormonal measurings - TSH, FT4, serum cortisol, ACTH, basal insulinemia;
- Metabolic explorations - fasting glycemia (TTGO in selected cases), total serum cholesterol, LDL cholesterol, HDL cholesterol, tryglicerides, uric acid;
- Measuring of inflammatory - C - reactive protein (highly sensible) markers, fibrinogen.

Evaluation of the cardiovascular function in patients with obesity

The evaluation of the cardiovascular function consisted in measuring the AT, the peripheral pulse, heart auscultation, performing the ECG track (12 derivations, the effort ECG tossue in the selected cases, the carotid Doppler echocardiography and echography, determining the ankle - arm index.

The statistical significance of relation between various clinical was based on statistical analysis (Chi square test, lambda (λ) test, Cramer test, the arithmetic mean and dispersion of individual values).

RESULTS AND DISCUSSIONS

Characteristics of participants in the study

In the present study there were comprised 172 patients, 118 women (68.60%) and 54 men (31.40%), who were hospitalized in the Clinic of Cardiology of the Filantropia Hospital in Craiova. In order to evaluate the endocrine status of these patients I have collaborated with the Clinic of Endocrinology of the County Emergency Hospital in Craiova.

The patients’ selection criterion was the weight excess associated with manifestations specific to cardiovascular disease.

The average age was 60.22 years (with a standard deviation of 8.86). The minimal age of the patients in this study was 40 years and the maximum one was 81. All the women included in the study were at menopause age.

According to the presence of endocrine disorders and their type, patients were divided in 3 batches:

- batch 1: patients without endocrine disorders (89 patients);
- batch 2: patients with primary hypothyroidism (61 patients);
- batch 3: patients with reactive hypercorticism and secondary hypothyroidism (22 patients).

The endocrine status was evaluated by studying the thyrotropic and corticotropic axis.

The average TSH value in the studied batch was 2.62 µU/l at a standard deviation of 1.63 and the average FT4 value was 13.53 pmol/l at a standard deviation of 4.05.

Regarding the corticotropic axis, in the studied batch I have determined an ACTH average value of 29.09 pg/ml at a standard deviation of 11.89 and a cortisol average value of 356.39 nmol/l at a standard deviation of 117.59.

For the patients in batch 1 I have registered a TSH average value of 1.89 µUI/ml, a maximum value of 4.1 µUI/ml and a minimal value of 0.4 µUI/ml at a standard deviation of 1.03.

In batch 2 I have highlighted a TSH average value of 4.43 µUI/ml, a maximum value of 6.1 µUI/ml and a minimal value of 3.6 µUI/ml at a standard deviation of 0.52.

For the patients in batch 3 I have registered a TSH average value of 0.56 µUI/ml, the maximum value was 1.9 µUI/ml and the minimal one 0.18 µUI/ml at a standard deviation of 0.38.

By comparing the averages in the three batches I have obtained a value of p<0.0001, which shows that the averages of the three batches differ among them in a highly significant statistical way.
For the patients in batch 1 I have highlighted a FT4 average value of 16.58 pmol/l (normal value being comprised between 12 and 22 pmol/l), a minimal value of 10.4 pmol/l and a maximum value of 21 pmol/l.

In batch 2 I have registered a FT4 average value of 10.54 pmol/l, a minimal value of 7.7 pmol/l and a maximum value of 20 pmol/l;

For the patients in batch 3 the FT4 average value was 9.44 pmol/ml, the minimal value 7.4 pmol/l and the maximum one 12 pmol/l. At the FT4 measuring significant differences were found statistically between the values obtained in the 3 batches, at a chi - square of 117.795 having a p<0.001.

In batch 1 I have registered a cortisol average value of 342.57 nmol/l, the maximum value was of 530 nmol/l and the minimal one 180 nmol/l at a standard deviation of 112.39;

For the patients in batch 2 I have highlighted a cortisol average of 311.21 nmol/l, a maximum value of 520 nmol/l and a minimal value of 190 nmol/l at a standard deviation of 79.68;

In batch 3, the cortisol had an average value of 537.54 nmol/l, the maximal value was 566.8 nmol/l and the minimal value was 499 nmol/l at a standard deviation of 19.88.

Also after the cortisol measuring for the patients in the 3 batches, statistical significant differences resulted. For a chi - square of 95.883 I had p<0.001.

ACTH values in the 3 batches were: in batch 1 I have registered an average value of 26.31 pg/ml, the maximum value was 45.8 pg/ml and the minimal value was 6.8 pg/ml; in batch 2 I have highlighted an average value of 27.67 pg/ml, a maximum value of 43 pg/ml and a minimal value of 8.3 pg/ml; in batch 3 I have determined an average value of 44.27 pg/ml, a maximum value of 51.2 pg/ml and a minimal value of 39 pg/ml.

By comparing ACTH averages between the three batches I have obtained a value of p<0.0001, which shows that the averages of the three batches differ among them in a highly significant statistical way.

In the case of the patients in batch 3, who had increased cortisol and ACTH values, for the differentiation of reactive hypercorticism from Cushing syndrome the inhibition test with dexamethasone. Patients were administered 2 mg of dexamethasone for 2 days and the cortisol plasmatic was measured before and after administration. Following this test all the patients in batch 3 had cortisol values smaller with 50%. After performing this test patients were diagnosed with reactive hypercorticism.

Between batches 1 and 2 (patients without endocrine disorders and patients with primary hypothyroidism) there were no significant differences of their average age (60.65 years for batch 1 and 61.28 years for batch 2). Instead, the average age of patients in batch 3 (with reactive hypercorticism) was lower - 55.55 ani.

Among the patients included in the study, 34.30% presented 1st degree obesity, 44.19% 2nd degree obesity and 21.51% 3rd degree obesity.

The percentage of patients with 1st and 2nd degree obesity in batches 1 and 2 was similar and 3rd degree obesity was encountered in 15.73% of the patients of batch 1 and 22.95% of the patients in batch 2. Instead, none of the patients in batch 3 presented 1st degree obesity, here I encountered a percentage of 59.09% patients with 2nd degree obesity and 40.91% patients with 3rd degree obesity.

44 patients had sugar diabetes type 2, 20 patients having alteration of glucose tolerance; 11 patients had alteration of fasting glycemia. Sugar diabetes type 2 was more frequently associated with 3rd degree obesity (40.54%), whereas a percentage of 21.05% from the patients with 2nd degree obesity and 13.56% from the patients with 1st degree obesity had sugar diabetes type 2.

Arterial hypertension was present in 146 patients (84.88%), 18 patients (10.47%) had normally high arterial tension and 8 patients (4.65%) had normal values of the arterial tension.

From this study there resulted an increase of the arterial tension values along with the increase of the obesity degree and especially with the value of abdominal circumference (66.10% of the patients with 1st degree obesity had HTA, 92.11% of the patients with 2nd degree obesity had HTA and 100.00% of the patients with 3rd degree obesity were hypertensive).

Ischemic coronary disease was present in 109 patients (101 patients had modifications on resting ECG and for 8 patients with symptomatology specific to pectoral angina, but without modification on resting ECG, the diagnosis was given after performing the effort test).
Epidemiology of obesity
In the current study, the prevalence of obesity increased with the age advancement, from 8.72% in the persons in the forth decade of life, to 43.02% in the fifth decade, followed by a percentage of 31.98% in the sixth decade. The obesity prevalence decreased to 12.79% in the seventh decade of age. In patients with ages over 80, the obesity prevalence decreased to 3.49%.

The tendency of increase of obesity frequency paralleled with age advancement was also observed in other populations. NHANES III study revealed that for the USA population, the obesity prevalence increased from 6.7%, in persons in their third decade of life, to 43.5% for those with ages between 60 and 69 years and decreased after the age of 70.

The patients in this study, 20.35% women and 26.16% men, presented low HDLc and 95.93% of the patients presented hypertriglyceridemia. For 97 (56.40%) of the 172 patients there were registered glicemias <110 mg/dl and 44 patients (25.58%) had sugar diabetes type 2.

The threshold values used for the USA population for evaluating abdominal obesity are: abdominal circumference ≥ 88 cm in women and abdominal circumference ≥102 cm in men.

In my own research I have applied the threshold values recommended by IDF 2005 for European population. In our study, in the case of men I have used the threshold value of abdominal circumference ≥94 cm and for women abdominal circumference ≥80 cm.

The main factors that influenced the obesity prevalence were represented by age, sex, value of lipid metabolism parameters, AT and abdominal circumference values, data that are concordant with those encountered in the professional literature.

Insulin resistance
We observe that insulin resistance was significantly higher in patients with reactive hypercorticism, followed by patients with obesity, but without endocrine disorders.

Also, the HOMA-IR index was significantly higher in women with abdominal circumference > 80 cm and in men with abdominal circumference >94 cm, which confirms the fact that obesity and especially abdominal obesity represents a risk factor for IR and, implicitly, for the onset of metabolic syndrome (MS).

The IR accentuation is responsible at least partially for the increase of HTA prevalence, hyperglycemia and dyslipidemias along with the age advancement.

Glucoregulation disorders
It results from this study an important tendency (p<0.001) of increase of glycemia values along with the increase of obesity degree and the abdominal circumference increase. The distribution of sugar diabetes according to the obesity degree was the following: 13.56% of the patients with 1st degree obesity, 21.05% of the patients with 2nd degree obesity and 40.54 % of the patients with 3rd degree obesity have sugar diabetes type 2. These results show that obesity is an important risk factor for sugar diabetes type 2.

Alteration of lipid metabolism in obese patients
We observe from this study the correlation between high cholesterol level and obesity degree (and the directly proportional increase of cholesterol with the increase of abdominal circumference). The patients included in the study had in put obesity, the nutritional anamnesis showing a diet rich in fats, especially from animal origin, but also rich in hydrocarbons (bread and concentrated sweets) and poor in nutritive fibers. It results from this study a hypo-HDL cholesterolemia at a higher percentage in men, compared to that of women (increased risk for atherosclerosis).

In conclusion, the obesity degree and abdominal obesity represent a risk factor for hypo-HDL cholesteralemia.

Patients in batches 2 and 3 presented higher LDL values, being known the fact that the patients with hypothyroidism have increased cholesterol (especially LDL) and triglyceride values. Also in the case of LDL we observe an increase in its obesity degree and an increase in the abdominal circumference.

Abdominal obesity represented a risk factor for hypertriglyceridemia.

It was observed at the patients included in the study an important tendency (p<0.001) of increase of TG values along with MBI and abdominal circumference increase. This fact explained the nutritional habits of the patients with obesity (excessive consumption of cream cakes, chocolate and pastry in women and excessive consumption of bread and fat meat,
associated with drinking in men) responsible for an excessive input of calories and an increased content of TG in the diet.

**Purine metabolism**

By comparing averages in the three batches I have obtained the value of $p=0.012$, which shows that the averages of the three batches differ among them significantly in a statistical way.

Diet rich in content of nucleic acids has a significant effect on the serum urate. From the anamnesis of studied patients it resulted that most of them had a hyperprotidic nutritional diet.

**Arterial hypertension**

In the present study I have found a prevalence of HTA of 84.88% (higher compared to that reported in the professional literature). The high percentage of hypertensive patients is mainly due to the fact that the study took place in a department of cardiology, but also to the presence of obesity in all the patients in the study.

There are multiple epidemiological studies in which the relationship obesity - HTA and sugar diabetes - HTA is proven [43, 114, 122]. It is estimated that 55% of the hypertensive people have obesity and approximately 50% of the obese patients are hypertensive.

In the current study, the prevalence of normally high arterial tension cumulated on the 3 batches was of 10.47%, of 1$^\text{st}$ degree HTA was of 15.70%, of 2$^\text{nd}$ degree HTA was of 38.95% and of 3$^\text{rd}$ degree HTA was of 30.23%. Only a percent of 4.65% of the patients were normotensive.

Regarding the distribution on batches of hypertension degrees, it was not statistically significant ($p>0.05$), in all the 3 batches prevailing the proportion of patients with 2$^\text{nd}$ and 3$^\text{rd}$ degree HTA.

Also, I mention that in the case of patients in batch 2, arterial hypertension presented high values (especially of the minimal), resulting a tucking of differential tension. Within the performed study I have seen an increase of HTA prevalence according to obesity degree. It results from this study an increase of the arterial tension values directly proportional with the obesity degree and with the increase of abdominal circumference.

**Ischemic heart disease**

In the performed study I have highlighted 34.88% patients with painful ischemic heart disease and 23.84% patients with painless ischemic heart disease, diagnosed based on the clinical picture and the resting ECG. After performing the effort ECG test, another 4.65% of the patients were diagnosed with ischemic heart disease. Regarding the distribution of ischemic heart disease on batches there were no significant differences ($p>0.05$).

It results from this study the higher proportion of painless ischemic coronary disease in patients with sugar diabetes type 2, being followed by increased proportion of painless ischemic heart disease in persons with morning glucose tolerance decrease, on the last position as proportion of painless ischemic heart disease being the patients with normal glycemias (<110 mg/dl).

It results an increased prevalence of painless ischemic heart disease in patients with increased insulin resistance (hence abdominal circumference increase in the patients with abdominal obesity).

**Cerebrovascular disease in the batches of study**

I specify that most of the patients with CVA sequelae in this study were patients with 2$^\text{nd}$ and 3$^\text{rd}$ degree obesity, present for at least 5 years, big dyslipidemic patients and with increased prevalence of sugar diabetes type 2.

**Prevalence of peripheral arteriopathy in the studied batches**

Prevalence of patients with peripheral arteriopathy did not vary significantly ($p>0.05$) in the 3 batches. The number of male patients with peripheral arteriopathy was higher than that of women, this being explained by the fact that there more smokers among men than among women.

**Relation inflammatory markers and cardiovascular risk**

Prospective studies have shown that C-reactive protein is an important predictor of the prognostic of cardiovascular events not only for healthy persons, but especially for patients with stable angina or with acute coronary syndrome with or without over change of ST-T segment [189, 210, 232]. The C protein level proved to be useful for stratifying the risk regarding recurrent ischemia and the decease of patients with stable and instable angina, of those who had incisive angioplasty, but also
for estimating the myocardial heart failure, cerebrovascular accident, peripheral arterial disease and sudden death [30, 45, 133].

By comparing averages between the three batches I have obtained a value of $p$ of 0.0014, which shows that the averages of the three batches differ among them in a highly significant statistical way.

The prevalence of moderate/increased risk for cardiovascular events increases significantly ($p<0.001$) with the obesity degree and especially abdominal circumference increase.

Plasmatic fibrinogen is included among the new cardiovascular risk factors because: it influences greatly the plaque aggregation; it increases blood viscosity; it interacts with plasminogen binding; in combination with thrombin, it mediates the final phase of thrombosis formation [133, 134, 190].

After the fibrinogen measuring for the whole studied batch it was highlighted a correlation with high significance statistically speaking ($p<0.001$) between its increased values and the presence of ischemic coronary disease (for patients with painful ischemic coronary disease as well as for those with painless ischemic coronary disease).

**CONCLUSION**

1. In the studied batch, concordant with the data in literature, I have seen a tendency of increase of the prevalence of obesity paralleled with age advancement, from 8.72% in the forth decade of age, la 43.02% in the fifth decade and of significant decrease (12.79%) after the age of 70.

2. Endocrine disorders associated with obesity were present at almost half of the patients of the total batch (48.26%), being represented by primary hypothyroidism at 35.47% of patients and by reactive hypercorticism with secondary hypothyroidism at 12.79%.

3. Insulin resistance (estimated by the HOMA - IR index) was significantly higher ($p<0.01$) in patients with reactive hypercorticism, followed by patients with obesity, but without associated endocrine disorders; patients with primary hypothyroidism presented the lowest HOMA - IR index.

4. IR severity correlates positively with the obesity degree and abdominal circumference size, which confirms the fact that obesity and especially abdominal obesity represents a risk factor for insulin resistance and implicitly for the onset of metabolic syndrome; these results reveal the importance of determining BMI and abdominal circumference in current medical practice, allowing to identify the persons with increased cardiometabolic risk who could benefit from intensive therapeutic measures.

5. It results from this study an important tendency ($p<0.001$) of increase of glycemia values paralleled with the increase of obesity degree and abdominal circumference increase, proving the fact that obesity and especially abdominal obesity is an important risk factor for the onset of sugar diabetes type 2.

6. Patients with obesity and hypothyroidism (batches 2 and 3) presented significantly higher statistical values ($p<0.05$) of total cholesterol (especially LDL) and triglycerides, what proves that in the absence of thyroid hormones the lipid profile is of anabolic type.

7. It is noted a significant tendency ($p<0.01$) of increase of the total cholesterol and LDL, along with the BMI increase, as well as an important tendency ($p<0.001$), of increase of the triglycerides level, proportionally with the obesity degree and abdominal circumference size; the repartition on sexes of hypo - HDL - cholesterolemia is procentually higher in men (26.16%) in regard to women, confirming the fact that men present an increased risk to develop atherosclerosis.

8. In the present study, the HTA prevalence was of 84.88%, bigger than the one reported in the professional literature, the explication being that the study took place in a clinic of cardiology, all the studied patients being obese; the distribution on batches of hypertension degrees was not statistically significant ($p>0.05$).

9. BMI and abdominal circumference values seem to be involved not only the increase of HTA prevalence but also its degree, fact suggested by a significant tendency ($p<0.001$) of increase of TA values proportionally with the obesity degree in the performed study; in this sense we consider that in subjects with obesity and metabolic syndrome the notion of „normally high” AT must be considered real HTA.

10. In the performed study painful ischemic heart disease was present (based on the clinical picture and the resting ECG modifications) in 34.88% of the patients and the painless form in 23.84%;
following the effort test another 4.65% of the patients were diagnosed with ischemic heart disease, without existing significant differences of its distribution (p>0.05) on the 3 analysed batches.

11. It results from this study the higher proportion of the painless form of ischemic heart disease in patients with sugar diabetes type 2 (51.22%), being followed by an increased proportion in persons with modification of basal glycemia (29.27%), on the last position as proportion of painless ischemic heart disease being the patients with normal glycemia.

12. Prevalence of moderate/increased risk for cardiovascular events (estimated by determining hs CRP) increases significantly (p<0.001) with the obesity degree (especially the abdominal circumference increase).

13. It was highlighted a correlation with high statistical significance (p<0.01) between increased fibrinogen values and the presence of ischemic heart disease, which confirms the fact that obese patients present a proinflammatory and procoagulant status, which implies an increased risk of coronary disease.

14. Long term objectives of the prophylaxis of cardiovascular diseases which appear in the context of obesity with endocrine and metabolic disorders are: reducing the body weight and decreasing the risk factors. For achieving this challenge we plede for combining a poor fat diet, well dosed physical exercise and using pharmacological preparations with the least adverse reactions.

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