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Partner: University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca

SIGNIFICANCE OF MICROALBUMINURIA IN THE METABOLIC SYNDROME

SUMMARY OF PhD THESIS

PhD: MAIDANIUC (TRAIAN) Maria Gabriela

Scientific adviser: Prof. Dr. PETROVANU Rodica

IASI - 2013
KEYWORDS: metabolic syndrome, endothelium dysfunction, microalbuminuria, insulinoresistance, dyslipidemiae, circulating endothelial cells, progenitor endothelial cells, ankle arm index.

“Grigore T. Popa” University of Medicine and Pharmacy –Iasi Rector's decision for the appointment of the PhD Commission no. 9870 / 05.06.2013.

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Materials and method

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INTRODUCTION

Metabolic syndrome (MS) is an important public health problem, is the most aggressive cardiovascular risk factor (1). It overlaps the risk of association with type 2 diabetes, some cancers and a host of other comorbidities (2). If current trends continue, premature death and disabilities resulting from these degenerative conditions will bankrupt the national budgets of many countries, developed or developing.

The presence of metabolic syndrome causes three times higher risk of developing coronary heart disease and stroke, doubling mortality from these causes. The risk of sudden death is five times higher in patients with diabetes and two to three times higher in patients with metabolic syndrome (2). Cardiovascular disease is the leading cause of morbidity and mortality in developed countries and those in developing countries, through the process of atherosclerosis and endothelial dysfunction are key process in the pathogenesis of atherosclerosis and its complications. In the metabolic syndrome, all its components involved in the acceleration of atherosclerosis (8).

I. Description of study. Stages of study

1. Metabolic syndrome and endothelial dysfunction - the relationship with anthropometric parameters, biochemical and imaging.
2. Evaluation of microalbuminuria in quantifying the importance of endothelial dysfunction in metabolic syndrome correlated with circulating endothelial cells and endothelial progenitor cells.
3. New research directions in the prevention of obesity, insulin resistance and non-alcoholic liver disease. Assessment tool IKKE (inhibitor of nuclear factor kappa-B kinase subunit epsilon) on weight status and liver in ApoE knockout mice (ApoE-/-) are under Western type diet (high fat / low carbohydrates).

II. First stage. Metabolic syndrome and endothelial dysfunction - the relationship with anthropometric parameters, biochemical and imaging.

II.1. Purpose: Establish the anthropometric parameters, biochemical and imaging elements endothelial dysfunction correlated with metabolic syndrome.

II.2. Objectives

1. Identification of risk conditions in insulin-resistance syndrome
2. Identify feasible to quantify the anthropometric indicators of abdominal obesity in relation to insulin resistance, non-alcoholic liver disease and endothelial dysfunction.
3. Quantification of endothelial dysfunction using surrogate markers to identify an easy and feasible method in ambulatory practice.
4. Evaluation of insulin resistance and non-alcoholic liver disease non-viral (BHNA) in SM in the studygroup.
5. Correlation of microalbuminuria with the other diagnostic criteria of MS to assess the usefulness of placing it among the criteria.

II.3. Materials and methods

The research was conducted in the Specialty Ambulatoryt St. Spiridon Hospital Iasi, and included patients who were sent to Internal Medicine Cabinet, and meet the criteria for the selection of the lot. These are: age over 18 years, decision making capacity, metabolic syndrome diagnosed according to NCEP-ATP III definition modified in 2004 (National Cholesterol Education Program - Adult Treatment Panel III) (1).

For the diagnosis of metabolic syndrome have used NCEP-ATP III criteria, according to which diagnosis is made in the presence of at least three of the following:
1. Hypertension, BP ≥ 130/85 mmHg or antihypertensive treatment;
2. Triglycerides ≥ 150 mg / dl;
3. HDL-cholesterol <40 mg/dL for men and <50 mg/dl for women;
4. Waist circumference ≥ 102 cm for men and ≥ 88 cm for women;
5. Fasting plasma glucose> 100 mg/dl.

The study was conducted between January 2010 - December 2012 in the Specialty Ambulatory Hospital St. Spiridon. We included 600 patients per month, of which 300 initial (first visit). Of those diagnosed with metabolic syndrome have 95 patients / month, giving a total of 2850 patients with metabolic syndrome in the 3 years of study. Unfortunately, 165 were unwilling to participate in further investigation. 2685 batch of patients was performed a glucose tolerance test and glycosylated hemoglobin to detect people with undiagnosed diabetes. Thus, 698 (25.9%) patients were diagnosed with type 2 diabetes newly diagnosed. They were excluded from the study. Of the 1987 patients with non-diabetic metabolic syndrome but 247 did not wish any further (the distance, the time, etc.) and 141 patients were also not shown, the end group is thus made up of 1599 patients who were subjected to a full investigation.

The inclusion in the squad following data were recorded: demographic data, clinical data (family history, personal history, lifestyle), anthropometric data (height, weight, body mass index, waist circumference, hip circumference ratio waist / hip) complete physical examination, laboratory data (initial balance sheet that contained all necessary investigations to identify patients with metabolic syndrome, type 2 diabetes and associated cardiovascular risk factors evaluation and identify target organ damage, OGGT, ECG, ankle-brachial index).

Processing of medical data we performed using SPSS 16 (Statistical Package for Social Sciences) or Microsoft Office Excel to create a database (the program supports the import of data in SPSS). Determine the ranges of statistical indicators and hypothesis testing was performed with statistical confidence of 95% resulting in a significance level p = 0.05 (defined as sufficient in literature).

II.4. Ethical considerations. To study conducted prior to initiating its got the Committee of Ethics of the University of Medicine and Pharmacy "Gr T. Popa" Iasi.

II.5. Results

The group included 1599 patients with metabolic syndrome aged between 26-77 years. The average age group was 49.4 years [± 7.5]. The difference in the two sexes showed that women had a mean age of 49.8 years [± 7.6] and men 49.05 years [± 7.3], older women being 0.76 years difference with statistical significance (p=0.042).

Gender distribution of the study group showed a predominance of women in the study group, so a slightly higher frequency of MS in women.

Sources patients showed a predominance of patients in urban areas than those in rural areas.

Thus, the presence of macrosomia birth APP was identified in 191 patients (21.4%) and the presence of hypertension of pregnancy APP and APP PCOS were present in approximately equal percentages, 15.15% and 14.14% . APP gestational diabetes was not present in any of the patients.

The presence of male erectile dysfunction group was present in 4.3% of patients, the association with microalbuminuria was present in 87.1% of them, value highly statistically significant (p <0.001). Comparison of APP with ankle-brachial index as a marker of endothelial dysfunction showed a statistically significant 19.6% of people with fetal macrosomia APP (p = 0.024) and 14.2% of those with hypertension of pregnancy APP (p = 0.041). IGB disease was identified in 9.3% of women with PCOS APP, and 2.2% of men with erectile dysfunction, but
without statistically significant in any of the cases.

In our study we considered the following significant family history: type 2 diabetes, hypertension, dyslipidemia and obesity. Of all, the most frequent association was with history of hypertension (52.6%), followed by obesity (51.5%). Family history of dyslipidemia were recorded in 34.9% of cases and those of type 2 diabetes 30.5% of people. Family history were significantly associated with the presence of microalbuminuria, which is present in over 50% of patients with hypertension (p = 0.017). There was a high percentage of microalbuminuria in patients with a family history of type 2 diabetes but without statistical significance.

Correlation of positive family history (AHC) with IGB, revealed a significant association of this marker of endothelial dysfunction in hypertension AHC 56.6% of cases. As can be observed in Fig. 33), 53.2% of cases with pathological ABI (<0.9) had obesity AHC AHC and 32.2% had type 2 diabetes.

The lipid profile of the study group was quantified in combination with other cardiometabolic risk factors.

![Figure 40. Prevalence of pathological lipid distribution in the study group](image)

According to BMI in our study the highest percentage was found in patients with obesity grade I (49.2%):

![Fig. 48. Graphical representation of groups of cases divided according to BMI value](image)

I used to quantify abdominal obesity as indicators measuring abdominal circumference (AC) and the ratio waist / hip (T/S).
Comparison of waist circumference with the atherogenic index showed a statistically significant association between those with abdominal obesity and the atherogenic index of disease, but also with other lipid markers.

Correlating turn and abdominal circumference ratio T / S with insulin resistance defined by HOMA-IR noticed that just to associate statistically significant (p = 0.02) with insulin resistance, unlike the T/S which did not reach statistical significance.

Evaluation of microalbuminuria compared with the two defining abdominal obesity anthropometric indicators identified a highly significant association (p <0.001) for both waist circumference and the ratio T /S.
Fig. 67. Correlation of abdominal obesity with microalbuminuria

Non-alcoholic liver disease is the consequence of a non-viral complex etiopathogenic factors such as inflammatory, metabolic and idiopathic multiple other factors. Due to the involvement of lipid components in liver disease determinism we evaluated their association with BHNA. Thus, 97.7% of people BHNA showed an increase in LDL-cholesterol, high statistically significant association (p = 0.05), a factor known to be highly atherogenic. Triglycerides, one of the diagnostic criteria for MS was identified in 90.7% of patients with hepatic impairment (p = 0.003), which emphasizes the association of these metabolic abnormalities in the insulin resistance syndrome.

The distribution function of the value of microalbuminuria can be seen in Figure 89. It shows that most cases showed microalbuminuria at between 105-135 mg/24.

Fig. 89. Distribution of the study group based on the value of microalbuminuria

II.6. Discussions

Despite evidence supporting its ability to independently predict both type 2 diabetes and CVD, various definitions have been and are an extremely controversial topic (292) (293) (294). In the present study we evaluated patients in all aspects of cardiometabolic risk in outpatient settings. Thus, the duration of the study (30 months) I diagnosed with MS in 2850 patients (approximately 95 patients per month, or 31.6% of the patients were sent), which remained after a preliminary assessment only 1,599 people (excluded patients with diabetes and those who no longer wanted to participate).

Distribution by age group showed the highest frequency in the age group 46-55 years (46.4%), age at which events occur both inherited and acquired, both women and men. In the study group the most common disease in people with a personal history of female fetuses was the birth of macrosomia in a percentage of 21.4%. In order to establish a connection between medical
history and endothelial dysfunction, we compared the presence of microalbuminuria and pathological ankle-brachial index (<0.9). The most significant association was observed between PCOS and microalbuminuria in a proportion of 72.2% of cases. An approximately equal frequency occurred between hypertension of pregnancy (66.7%) and fetal macrosomia (69.1%) with the presence of microalbuminuria.

Abdominal obesity is an important cardiovascular risk factor. Because BMI does not specifically quantify visceral obesity, the cardiometabolic risk, we used two anthropometric indicators that quantify abdominal obesity. Large studies in recent years, with more than 25 000 participants showed that visceral obesity indicators such as waist circumference and ratio waist / hip correlates better with cardiovascular risk (314).

According waist circumference and the ratio T/S group 90% of patients had abdominal obesity. However, the distribution of abdominal obesity differentiated sexes showed a male predominance of its group, statistically significant difference (p = 0.002).

Microalbuminuria was associated with statistically significantly higher (p<0.001) with abdominal obesity measured by waist circumference measurement (73.9% of those with microalbuminuria showed pathological CA). In percentage roughly equal, microalbuminuria was correlated with specific dyslipidemia SM, hypertriglyceridemia (74.02%, p = 0.003) and lower HDL-cholesterol (73.5%, p=0.001). Microalbuminuria was found in 72.7% of cases with altered fasting plasma glucose. The only element that did not correlate significantly microalbuminuria was hypertension (73.2%, p=0.4). Thus, microalbuminuria is correlated significantly with four of the five criteria for the diagnosis of MS, which stresses the need for placing it among the elements of clinical diagnosis of MS.

III. Step 2: Evaluate the importance of microalbuminuria in quantifying endothelial dysfunction in metabolic syndrome correlated with circulating endothelial cells and endothelial progenitor cells.

III.1. Purpose: weighted rating microalbuminuria in quantifying endothelial dysfunction in metabolic syndrome correlated with circulating endothelial cells and endothelial progenitor cells. Algorithm for screening and prevention of the metabolic syndrome and their complications in primary care.

III.2. Objectives:

a. Quantification of circulating endothelial cells and endothelial progenitor cells in MS.
b. Establishing the relationship circulating endothelial cells and endothelial progenitor dysfunction.
c. Evaluation of circulating endothelial cells and progenitors in relation to insulin resistance.

III.3. Materials and methods

This case-control study was conducted between December 2012 - February 2013 and was the choice of 90 candidates, including 20 without metabolic syndrome or other pathology known (apparently healthy), and 80 with metabolic syndrome. They were evaluated in order to detect early endothelial dysfunction and microalbuminuria compared dosing using circulating endothelial cells and endothelial progenitor cells.

Criteria for inclusion in the pathological group: age over 18 years, metabolic syndrome according to ATP III, the absence of established cardiovascular disease, the absence of type 2 diabetes, microalbuminuria 30-299 mg/24 h, consumed by ethanol consent to participate in the study.

The control group consisted of patients without metabolic syndrome with inflammatory diseases, diabetes and without liver disease.

Initial evaluation of patients was performed identical to that of Phase 1 of the study, assessing personal data, family history, lifestyle, physical activity, anthropometric indicators, haematological,
biochemical, immunological and imaging.

Apart from the usual tests taken were taken and 5 ml peripheral blood in anticoagulant dosage of circulating endothelial cells and endothelial progenitor cells.

**Working protocol**

1. Optimization method for assessing cell viability (DAPI - 4 ',6-diamidino-2-phenylindole)
2. Lysis in the microvolum

Table. XXXVI. Marking immunological circulating endothelial cells (CEC) and endothelial progenitor cells (EPC)

<table>
<thead>
<tr>
<th></th>
<th>DAPI</th>
<th>CD45</th>
<th>KDR</th>
<th>CD146</th>
<th>CD133</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEC</td>
<td>- (viabile)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>EPC</td>
<td>- (viabile)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
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</table>

**III.4. Results**

![Graphical representation of study groups](image)

Table XXXIX. Anthropometric characteristics of the study group

<table>
<thead>
<tr>
<th>LOT</th>
<th>Media</th>
<th>Min</th>
<th>Max</th>
<th>St. Dev</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5%</td>
<td>25%</td>
<td>75%</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>NORMAL</td>
<td>84</td>
<td>52</td>
<td>101</td>
<td>14</td>
<td>58, 80, 94, 100</td>
</tr>
<tr>
<td></td>
<td>28.69</td>
<td>19.88</td>
<td>35.62</td>
<td>4.28</td>
<td>19.97, 27.81, 31.01, 35.08</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>65</td>
<td>112</td>
<td>13</td>
<td>66, 80, 98, 106</td>
</tr>
<tr>
<td></td>
<td>.792</td>
<td>.680</td>
<td>.920</td>
<td>.063</td>
<td>.68, .74, .84, .90</td>
</tr>
<tr>
<td></td>
<td>21.1</td>
<td>15.9</td>
<td>28.6</td>
<td>3.6</td>
<td>16.2, 19.0, 23.1, 27.7</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>79</td>
<td>130</td>
<td>14</td>
<td>86, 91, 109, 121</td>
</tr>
<tr>
<td></td>
<td>36.8786</td>
<td>30.9000</td>
<td>53.3900</td>
<td>4.6546</td>
<td>30.7500, 33.1200, 39.8100, 44.5800</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>80</td>
<td>149</td>
<td>13</td>
<td>83, 101, 116, 130</td>
</tr>
<tr>
<td>PATHOLOGIC</td>
<td>.89</td>
<td>.60</td>
<td>1.10</td>
<td>.094</td>
<td>.69, .87, .95, 1.03</td>
</tr>
<tr>
<td></td>
<td>30.6</td>
<td>21.6</td>
<td>48.4</td>
<td>5.1</td>
<td>23.4, 26.6, 33.1, 39.4</td>
</tr>
</tbody>
</table>

In the study group, CEC quantification revealed a broad range with 125.5 - 3169.1 CEC / ml with a mean of 628.1 CEC / ml [± 602.9]. CEP ranged from 0 to 70.3 / ml, with an average of 11 CEP / ml [± 11] (Table XLIV).
Table XLIV. Changes in CEC and CEP in the study group

<table>
<thead>
<tr>
<th></th>
<th>CEC (/ml)</th>
<th>CEP (/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>628.1</td>
<td>11.0</td>
</tr>
<tr>
<td>Median</td>
<td>387.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>125.5</td>
<td>.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>3169.1</td>
<td>70.3</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>602.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Standard Error of Mean</td>
<td>63.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Percentile 05</td>
<td>164.4</td>
<td>.0</td>
</tr>
<tr>
<td>Percentile 25</td>
<td>250.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Percentile 75</td>
<td>792.2</td>
<td>14.7</td>
</tr>
<tr>
<td>Percentile 95</td>
<td>1967.2</td>
<td>29.7</td>
</tr>
</tbody>
</table>

For the relevance of the results of CEC and CEP assays we assessed their variation compared between the control group and the pathological. In the control group, CEC ranged from 125.5 to 281.6 / ml with a mean of 201.5 CEC / ml [± 43.8] versus pathological group where values have for between 206.2 to 3169.1 / ml with an average of 750 / ml [± 632.8]. An overview of changes in circulating endothelial cells between the two study groups is shown in Figure 134. Obvious difference is observed (p < 0.001) between the two groups of CEC.

![Fig. 134. CEC variation between the two study groups](image1)

Fig. 134. CEC variation between the two study groups

In lotul cu sindrom metabolic se observă o acumulare a datelor corespondente unei microalbuminurii în intervalul 50-100mg/24h cu CEC în intervalul 300-500/ml. Deasemenea se conturează tendința de relație de directă proporționalitate între microalbuminurie și CEC în lotul patologic (fig 136).

![Fig 136. Correlation of circulating endothelial cells in the group with microalbuminuria with metabolic syndrome](image2)

Fig 136. Correlation of circulating endothelial cells in the group with microalbuminuria with metabolic syndrome

In assessing these cells in the context of metabolic syndrome we wanted to identify whether there is a link between CEC and abdominal obesity, we evaluated it by measuring waist circumference (proved in the first part of the sentence to be more faithful than the ratio waist / hip).
This correlation proved highly statistically significant association between CEC and abdominal circumference in metabolic syndrome (Figure 143).

![Fig 143. Correlation with waist circumference CEC](image)

Circulating endothelial cells were inversely associated with HDL. This shows that the decrease in HDL-cholesterol leads to an increase in the number of CEC, as a result of endothelial injury (p = 0.007) (Figure 144).

![Figure 144. Correlation with HDL-cholesterol CEC](image)

**III.5. Discussion**

Quantification of circulating endothelial cells are an innovative method for the determination of endothelial dysfunction. The study group consisted of 90 participants, 22.2% of apparently healthy persons and 77.8% of patients with metabolic syndrome according to ATP III criteria with microalbuminuria. In both groups there was a female preponderance, 58.6% in group pathology, and 55% in normal group.

In the entire study group CEC ranged between 125.5 and 3169.1 / ml, with an average of 628.1 / ml [± 602.9], extremely high variation, but 95% of subjects had more than 1900 CEC / ml. Endothelial progenitor cells had values between 0 and 70.3 / ml, with an average of 11/ml [± 11.2], 95% of people having about 30 CEP / ml. The CEC normal group had values between 125.5 and 281.6 / ml with a mean of 201.5 CEC / ml [± 43.8]. In patients with metabolic syndrome, CEC ranged between 206.2 and 3169.1 / ml, 750/ml with a mean [± 632.8]. Accumulation of risk factors present in metabolic syndrome are acting amplified determinism implicit endothelial dysfunction and cardiometabolic risk in these patients. The presence of high CEC significant share in the study group is an argument in favor of making them as early marker of subclinical endothelial dysfunction. Not
the same thing happens with CEP signifying advanced endothelial injury and thus loses its value as a marker early.

In the normal group, the number of CEC tended to associate inversely with urinary albuminuria value (which did not reach microalbuminuria, < 30mg/24h). The CEC pathological group were proportionally associated with microalbuminuria but without reaching statistical significance threshold. CEC were highly significantly correlated (p = 0.001) with microalbuminuria and varied in proportion to this, the entire study group. Aggregation of data from the two groups not only to emphasize the idea that pathology in patients with and without cardiometabolic risk factors, there is a minimum of endothelial dysfunction may be detected by quantification of circulating endothelial cells, determining equivalent dosage of microalbuminuria.

The study of circulating endothelial cells in metabolic syndrome in patients with microalbuminuria is one of the original elements of the thesis. Although difficult to achieve and costly, early evidence of endothelial dysfunction through CEC emphasized the role of microalbuminuria in determining early injury endothelium under cardiometabolic risk, capitalizing it as a surrogate marker.

**IV. Step 3: New research directions in the prevention of obesity, insulin resistance and non-alcoholic liver disease. Assessment tool IKKE (inhibitor of kappa-B kinase nucler factor subunit epsilon) on weight status and liver in ApoE knockout mice (ApoE-/+) are under Western type diet (high fat / low carbohydrates).**

**IV.1. Objective:** To evaluate the function IKKE (inhibitor of nucler factor kappa-B kinase subunit epsilon) on weight status and liver in ApoE knockout mice (ApoE-/+) are under Western diet (high fat / low carbohydrates) for 24 weeks.

**IV.2. Materials and methods**

The study was conducted during November 2011 - January 2012 to "HUMAN NUTRITION RESEARCH", Cambridge, UK. The research project was to assess the function IKKE / IKKE (inhibitor of nucler factor kappa-B kinase subunit epsilon) on the liver in ApoE knockout mice (ApoE-/+) are under Western diet (high fat / low carbohydrates) for 24 weeks. This project aims to identify a treatment method, or rather the prevention of obesity. The easiest way would be to identify the gene responsible for obesity, given that food is a necessary but not required. The results presented are only a small part of a vast project, still in progress.

This project was divided into two studies:

- **Study 1:** a follow liver function, namely the occurrence of hepatic steatosis compared between the two subgroups divided according to the presence or absence IKKE: ApoE - / - and IKKE-/ - versus ApoE-/ - and IKKE + / +.
- **Study 2:** they increased female mice knockout (ApoE-/ - and IKKE-/ -) and then were divided into two groups transplantându their bone marrow IKKE-/ - and IKKE + / +, following the evolution of liver steatosis compared between the two groups.

**IV.3. Substudy 1: Liver function and weight status by excluding ikke mice ApoE-/+**

**IV.3.1. Material and methods**

The study was performed on 30 Wistar rats aged 26 days and weighing about 60 g were divided according to sex and the presence or absence of IKKE. Ikke gene ablation was carried out by irradiation to form the two subgroups of the study.
IV.3.2. Results

Weight, which at baseline was approximately equal after 24 weeks of dietary Western was observed: an increase in weighted subgroup ApoE-/ - IKKE-/ - (dKO) compared to group ApoE-/ - IKKE + / +, predominant to sex female. Gas and liquid chromatography coupled with mass spectrometry showed an increase in fatty acid composition and in particular to the group ApoE-/ - IKKE-/ -, also more pronounced in women. The group IKKE + / + showed an increase in the level of fatty acids in the liver, which could be explained by the absence of ApoE.

IV.3.3. Discussion

ApoE gene ablation rats IKKE-/ -, causes weight gain and liver steatosis, particularly in the group of women under Western diet.

IV.4. Substudy 2: Evolution of fatty liver after bone marrow transplantation IKKE + / + mice ApoE-/ - IKKE-/ -.

IV.4.1. Material and methods

The study was conducted on 15 female Wistar rats ApoE-/ - IKKE-/ -, who received a Western diet for 17 weeks. They were divided into two groups and were identical bone marrow transplant group IKKE + / + and other IKKE-/ -, then comparing the two groups after 9 weeks.

Design group:
♂: ApoE-/ - IKKE-/ - n=8  ⇐ bone marrow transplant ApoE-/ - IKKE+/+
♀: ApoE-/ - IKKE-/ - n=7  ⇐ bone marrow transplant ApoE-/ - IKKE/-

IV.4.2. Results

Associated gas and liquid chromatography mass spectrometry revealed an increase in the proportion of fatty acids in the group IKKE-/ -, compared with group IKKE +/+.

Liver biopsy showed a reduction in the group receiving hepatosteatosis transplanted bone marrow IKKE +/+

IV.4.3. Discussion

Reactivation ikke weight causes stagnation and alleviate diet-induced steatohepatitis changes.

V. Conclusions

1. In our group the predominant age was between 46 and 55 years, the onset of cardiovascular disease. In this idea early diagnosis of endothelial dysfunction is useful for prevention.

2. Lipid profile is represented in metabolic syndrome by hypertriglyceridemia and decreased HDL-cholesterol. They have proven their value in our study, in association with all cardiovascular risk factors. Non-HDL cholesterol better quantify the risk of cardiovascular disease than LDL cholesterol in patients with hypertriglyceridemia in metabolic syndrome.

3. Uric acid correlates with all elements of the metabolic syndrome is useful in quantifying the metabolic risk.

4. Obesity is identified in most cases of metabolic syndrome is present mainly in males. Waist circumference is the most accurate anthropometric indicators in defining obesity with cardiovascular risk, irrespective of BMI, especially in women.

5. Insulin resistance is the central pathogenic element of metabolic syndrome, and it is correlated
with the surrogate markers of endothelial dysfunction, highlighting the usefulness of HOMA-IR in the diagnosis and prevention.

6. Non-alcoholic liver disease non-viral has a large share in the metabolic syndrome and is associated particularly with microalbuminuria and HOMA-IR.

7. Microalbuminuria was found to be the most useful marker of endothelial dysfunction quantification of metabolic syndrome compared with ankle-brachial index, in association with four of the five criteria of the clinical definition of the metabolic syndrome.

8. IKKE gene is necessary and sufficient to reduce diet-induced liver steatosis in rats ApoE-/- and IKKE-/- -. This particular gene IKKE may be the target of future drugs to treat obesity, fatty liver, prevent type 2 diabetes and coplicațiior them.

9. Circulating endothelial cells as a result of endothelial injury are expressed significantly increased in metabolic syndrome in the absence of clinically evident cardiovascular disease. Endothelial cells assets are correlated with the decrease in HDL-cholesterol and abdominal obesity measured by waist circumference. Highly significant correlation statistic between endothelial cells assets and microalbuminuria proving its usefulness and precocity latter in assessing endothelial dysfunction.

10. Endothelial progenitor cells were significantly associated with circulating endothelial cells in patients with metabolic syndrome.

11. Primary medicine is the component of the health care system most directly involved in the identification of the general population at risk and is able to initiate educational measures to change the lifestyle and risk reduction modern day heart.
VI. Selective bibliography
Final date

In the thesis were used XLIV tables, 157 figures and 362 bibliographic index. Tables and figures have kept the numbering of the summary thesis.

LIST OF SCIENTIFIC PAPERS ISSUED DURING THE PhD STUDIES


