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The Metabolic Syndrome in Menopausal Women: No Links with Endogenous Intoxication

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The metabolic syndrome is a complex of interrelated risk factors for cardiovascular disease (CVD) and diabetes. The risk factors include raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), raised fasting glucose, and central obesity. The 101 postmenopausal women and 20 women without menopause were referred to the study. The level of endogenous intoxication investigated by test of the absorption ability of erythrocytes (AAE). Menopause caused high level of endogenous intoxication, determine by absorption ability of erythrocytes test, which correlate with triglyceride and LDL-cholesterol levels. There is no difference in level of endogenous intoxication in postmenopausal women with or without metabolic syndrome. New trials with evaluation of other parameters of inflammation are required.

Keyword: Metabolic Syndrome, Inflammation, Postmenopausal Women.

1. Introduction

Metabolic syndrome (MetS), also called "insulin resistance syndrome" [1], "death quartet" [2], or "syndrome X" [3], places an individual at risk for type 2 diabetes (T2D) and cardiovascular disease (CVD) [4]. MetS is becoming a worldwide epidemic as a result of the increased prevalence of obesity and a sedentary lifestyle, and the prevalence of MetS in the adult population is relatively high. The presence of MetS doubles the risk of developing CVD over the next 5-10 years and for 3-6 times increased risk of diabetes mellitus type 2. In addition, these patients have higher risk of mortality from CVD. According to the Framingham Heart Study, which included about 5,000 persons aged 18 to 74 years, a combination of 3 or more components of the metabolic syndrome increases the risk of coronary heart disease (CHD) in 2.4 times in men and 5.9 times in women [4].

Four elements comprising MetS have been identified: central obesity, dyslipoproteinemia (increased triglycerides and reduced high-density lipoprotein (HDL) cholesterol), hypertension, and glucose intolerance; however, the definitions used vary somewhat between ethnic groups. Namely, the National Cholesterol Education Program Adult Treatment Panel (ATP) III [5] defined MetS as the presence of three or more of the following conditions: waist circumference greater than 102 cm in men and greater than 88 cm in women (for Japanese, greater than 85 cm in men and greater than 90 cm in women), triglyceride level of at least 150 mg/dl, HDL level less than 40 mg/dl in men and less than 50 mg/dl in women, systolic/diastolic blood pressure (SBP/DBP) 130/85 mm Hg or higher, and fasting blood glucose level 110 mg/dl or higher. The metabolic syndrome is variably defined by the European Group for the Study of Insulin Resistance and the World Health Organization, especially because of different definitions of central obesity, although a so-called harmonized definition was presented in 2009 [6] (tab. 1).

Table 1: Clinical Criteria of the Metabolic Syndrome. (adapted from K. Alberti et al., 2009)

Measure	Categorical Cut Points
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

Remarks: The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose ω-3 fatty acids presumes high triglycerides. Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

Many studies showed the high prevalence of metabolic syndrome among postmenopausal women, which varies from 32.6% to 41.5% [7, 8]. Differences in genetic background, diet, levels of physical activity, age and sex structure all influence the prevalence of both metabolic syndrome and its components. Cardiovascular disease is one of the main reasons of death among women in the world [9]. The studies indicated that women aged more than 55 have a higher incidence of cardiovascular disease than younger women. The mechanism behind the role of menopausal risk factors in initiating cardiovascular disease remains unclear. Several trials have recently been demonstrated that the chronic inflammatory condition associated with morbid obesity is characterized by a continuous activation of the innate immune system [10].

2. The purpose of This Investigation was to study the level of endogenous intoxication as marker of system inflammation in postmenopausal women with MetS.

3. Materials and Methods: This cross-sectional study was performed in the Central Municipal Hospital of Ivano-Frankivsk, Ukraine (West part of Ukraine). The 101 postmenopausal women and 20 women without menopause were referred to the study. Postmenopausal women who had at least 1-year history of cessation of menses were included. All the included subjects provided an informed consent. At the point of study entry, all study participants were subjected to clinical and biochemical investigations. Data were collected by trained interviewers. Demographic information is achieved by a questionnaire. The exclusion criterion was the coexistence of any other serious illness which could influence for results. A venous blood sample was collected from all the subjects who came after 8–12 hours in the morning after an overnight fast. The serum was used for estimating fasting blood glucose, triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol concentrations, by biochemical kit using spectrophotometer techniques in central hospital laboratory. Postmenopausal women were considered to have metabolic syndrome if they had any three or more of the clinical criteria (see tab. 1). The level of endogenous intoxication investigated by test of the absorption ability of erythrocytes (AAE) [11]. This test based on ability of red blood cells absorb of vital pigment (Methylene blue) according level of endotoxicosis. Systolic and diastolic blood pressure was measured twice after 10 minutes resting in sitting position from the right hand. Two measurements were done all postmenopausal women at five-minute intervals and we used the average of the 2 measurements. Weight was then measured, while subjects were minimally clothed without shoes, using digital scales. Height was measured in standing position without shoes using tape meter while the shoulder was in a normal position. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared using BMI-calculator (http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmi-m.htm). 30 practically healthy persons randomized for age and sex were control group. The statistical analysis was done with MedCalc Version 12.7.2 software.

4. Results of Study and Discussion: The mean age of all observed postmenopausal women was 65.45±10.04 years, and the mean term of menopause was 15.22±3.40 years.

We didn't find any differences between data of AAE in premenopausal and postmenopausal women with metabolic syndrome: 39.90±4.63 % vs 37.35±4.51 % (p=0.43). The level of AAE in control group was significally lower - 33.63±1.47 % (p<0.001). We have found directly middle correlation between mentioned indicator of endogenous intoxication and level of triglycerides (r=0.48, p=0.03), and level of LDL-cholesterol (r=0.69, p=0.49) in postmenopausal women.

Table 2 shows the baseline data of postmenopausal women with and without metabolic syndrome.

Table 2: Baseline data of postmenopausal women (total subjects and subjects with and without metabolic syndrome).

Parameters	All postmenopausal women, n=101	Postmenopausal women with MetS, n=80	Postmenopausal women without MetS, n=21
Age, years	65.45±10.04	65.23±10.07	65.65±10.03
SBP, mm Hg	161.04±31.43	163.03±30.97	123.01±4.47**
DBP, mm Hg	94.35±16.74	95.21±16.65	78.01±8.37*
Heart rate, bpm	81.52±14.71	81.60±14.98	80.0±8.71
Glucose, mmol/l	5.67±2.49	6.74±2.27	4.59±2.50
TG, mmol/l	1.85±0.93	1.99±0.92	1.71±0.85*
Total Cholesterol, mmol/l	5.64±1.39	5.66±1.39	4.90±1.05*
LDL-Cholesterol	4.29±1.19	4.39±1.13	4.21±1.16
HDL-Cholesterol	1.37±0.26	1.23±0.21	1.43±0.19
VLDL-Cholesterol	0.97±0.25	0.98±0.21	0.96±0.22
AAE, %	37.35±4.51	37.32±4.60	37.35±2.31

Remarks: SBP – systolic blood pressure, DBP – diastolic blood pressure, AAE – absorption ability of erythrocytes; ** - p<0.001; * - p<0.05.

The mean systolic and diastolic blood pressure, and triglyceride and total cholesterol levels were significantly high among postmenopausal women with metabolic syndrome, but the mean HDL-cholesterol was low (P<0.05). There were no significant differences in the age, years since menopause, and parameters of LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, heart rate of postmenopausal women with and without metabolic syndrome. Also we didn't observe difference in level of endogenous intoxication (AAE-test) in both groups.

Its known, that inflammation is a physiological response of the organism to harmful stimuli, be they physical, chemical, or biological. The response provided usually conducts to the reestablishment of homeostasis. It involves the coordinated action of many cell types and mediators, whose intervention depends on the nature of the initial stimulus and ensuing responses thereafter. The inflammatory state that accompanies the metabolic syndrome shows a quite peculiar presentation, as it is not accompanied by infection or sign of autoimmunity and no massive tissue injury seems to have taken place. Furthermore, the dimension of the inflammatory activation is not large and so it is often called "low-grade" chronic inflammation. Other researchers have attempted to name this inflammatory state as "metaflammation", meaning metabolically triggered inflammation [12], or "parainflammation" as a term to define an intermediate state between basal and inflammatory states [13]. Obesity is associated with deregulated lipid and carbohydrate metabolism. An increase in either one of these substrates will also increase the demand on themitochondria and the utilization of the electron transport chain [14]. As inmetabolically active tissues undergoing increased demand, there is usually relative hypoxia, together with the increased need for nutrient oxidation. This generates unusual amounts of reactive oxygen species. Oxidative stress activates kinases like JNK, p38 MAPK, and IKK that may directly interfere with insulin signalling or indirectly via induction of NFκB and increased cytokine production [15]. Adipocytes as immune cells and are able to synthesize and release a huge amount of proinflammatory adipokines and cytokines including leptin, resistin, PAI-1, IL-6, TNFα, retinol-binding protein 4, IL-1β, monocyte chemoattractant protein-1 (MCP-1), CRP, macrophage migration inhibitory factor (MIF), chemokines from the CC and CXC families, and more other cytokines such as IL-18 and IL-33, most of which, if not all, are involved in insulin resistance [16]. Thus, chronic (latent) inflammation take an important part in MetS. For our opinion, similar data of AAE parameters in our study is result low grade of

endogenous intoxication, but couldn't disavowal links between inflammation and metabolic syndrome. New trials with evaluation of other parameters are required.

5. Conclusions

Menopause caused high level of endogenous intoxication, determine by absorption ability of erythrocytes test, which correlate with triglyceride and LDL-cholesterol levels. There is no difference in level of endogenous intoxication in postmenopausal women with or without metabolic syndrome. New trials with evaluation of other parameters of inflammation are required.

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