Metabolic Disorders in Menopause and their Correction

Dan Mircea Cheța* and Vlad Horia Chirilă

"N. C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

Abstract: Menopause represents a complex period in the women's life. Several disorders of nutrition and metabolism are accompanying it. The information on this topic is increasing.

The carbohydrate disturbances include impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM), but not only. The estrogen deficiency could be an essential contributor to the process of diabetogenesis. Other significant factors for the risk of T2DM are: ageing, obesity (with increasing incidence after menopause), lowering of physical activity, smoking, drinking, some drugs a.s.o.

Unfortunately, there are in the scientific literature a number of controversies regarding the relation menopause – diabetes. For instance, an important American study (Diabetes Prevention Program) pointed out that natural menopause did not associate with an increased risk of diabetes and did not influence the answer to the preventive strategy. On the other hand, a large European trial (EPIC – InterAct Study) concluded that early menopause has produced a higher risk for T2DM.

Referring to the control of diabetes in the menopause period, many studies emphasize on diet and improving lifestyle, with a major role of physical activity. It is interesting that metformin use in postmenopausal women with diabetes was associated with a lower incidence of invasive breast cancer.

Hormone Replacement Therapy (HRT), proposed for the correction of menopause, seems not to be adequate for the women with T2DM.

The increase in abdominal and, more particularly, visceral fat accumulation, is associated in menopause with a higher risk of developing an atherogenic lipid profile and an insulin-resistant state.

Elevation of total cholesterol, LDL-cholesterol, triglycerides and lipoprotein (a) levels and lowering of HDL-cholesterol levels are observed in the menopause.

There is an association between postmenopausal status and a substantial risk of the metabolic syndrome.

The cardiovascular risk is also significantly modified.

These disorders have a major impact on the quality and duration of life. Their control is in increasing attention of the medical staff.

Keywords: Dietary management, lipid disorders, metabolic syndrome, obesity, physical exercise, postmenopause, type 2 diabetes mellitus.

Motto: Menopause is associated with accelerated progression of vascular diseases. Ten to 15 years after menopause, women lose most or all of a lower risk for developing cardiovascular diseases compared with men [1,2].

1. INTRODUCTION

Step by step, the scientific literature collected various aspects regarding the metabolic modifications in menopause. We try now to synthetize the most interesting data and to add more information.

The term "menopause" has a Greek origin, coming from the words "meno(month)" and "pause (to end)" [3]. The best definition of the menopause is the absence of menses for 12 consecutive months [4]. The menstrual history seems to be the most adequate indicator of the menopausal state, as specific hormonal measures vary widely in that period [5].

The age of natural menopause goes from late thirties to late fifties with the range for most women being between 48 and 55 years. The most frequent symptom is hot flashes or flushes, reported by 60% of the subjects. Night sweats are reported by about 40% , and 41% of the women present trouble sleeping [3].

The so-called "perimenopause" is characterized as an interval of menstrual irregularity and hormonal variability starting when menstrual cycle length changes from an established pattern into more variable cycles, with an average duration of 4 years, ending 1 year after the final menstrual period. This means that women can expect to present menstrual disturbances for approximately 4 years before their final menses [4].

Therefore, the menopause represents a complex period in the women's life. Several disorders of nutrition

*Address correspondence to this author at the "N. C. Paulescu" Institute, 5-7 Ion Movilă street, 020475, Bucharest, Romania; Tel: +40-722 44 99 38; Fax: +40-21 211 02 71; E-mail: chetadan@gmail.com

E-ISSN: 2310-9971/16 © 2016 Synergy Publishers

and metabolism are accompanying it (Table **1**). For the beginning, we will discuss in detail the situation of type 2 diabetes (T2DM) in the context of menopause, including some controversial issues. Then we will comment the essential problems of obesity, of metabolic syndrome, of lipids and other metabolic disorders. The role of diet and physical activity will be presented in the final part of the article.

Table 1: The Main Metabolic Disorders Present During Menopause

Impaired Glucose Tolerance (IGT)
Type 2 Diabetes Mellitus (T2DM)
Obesity
Metabolic Syndrome
Lipid Disorders
Other Metabolic Disturbances

2. MENOPAUSE AND TYPE 2 DIABETES

The carbohydrate disturbances include impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM), but not only. Postmenopausal women are at high risk for developing type 2 diabetes mellitus due to many factors [6]. The estrogen deficiency could be an essential contributor to the process of diabetogenesis. Other significant factors for the risk of T2DM are: ageing, obesity (with increasing incidence after menopause), lowering of physical activity, smoking, drinking a.s.o.

However, there are in the scientific literature a number of controversies regarding the relation menopause-diabetes. For instance, an important American study (Diabetes Prevention Program) demonstrated that, among women at high-risk for diabetes, natural menopause was not associated with diabetes risk and did not influence the response to diabetes prevention strategy. In the lifestyle interventions, the authors noticed that bilateral oophorectomy was associated with reduced diabetes risk [7]. On the other hand, data obtained from the InterAct Study, a prospective case-cohort study nested within The European Prospective Investigation into Cancer and Nutrition (EPIC), concluded that early menopause has determined a higher risk for T2DM [8]. In 2015 Brand and his colleagues suggested that early-onset diabetes may accelerate menopause [9].

We mention that women with an early severe vasomotor menopausal symptoms (VMS) profile (including hot flushes and night sweats), are more likely to have diabetes across a period of 15 years. This association is not explained by body mass index (BMI) or other potential confounders [10].

In a study of a large number of female and male Japanese individuals (TOPICS 17), the postmenopausal status in women was significantly associated with the presence of type 2 diabetes and prediabetes, although the increased probability did not equal that in men. The postmenopausal status was also associated with prediabetic hyperglycemia independently of age and demographic and metabolic factors among women without diabetes. Menopause and older age might additionally influence the elevated probability of dysglycemia in Japanese women [11].

We know that low-grade chronic inflammation, as reflected by increased circulating levels of inflammatory cytokines, may promote insulin resistance in liver, skeletal muscle, and endothelium, ultimately leading to the clinical expression of T2DM and cardiovascular disease. The data published by Liu *et al*. in 2007 showed that high levels of interleukin (IL-6) and high-sensitivity C-reactive protein (hsCRP) were significantly associated with an increased risk of T2DM in postmenopausal women [12].

On the other hand, Chao *et al*. (2010) demonstrated in a multiethnic cohort of postmenopausal women (The Women's Health Initiative Observational Study) that evaluation of plasma markers for systemic inflammation and endothelial dysfunction contribute relatively little additional value in clinical T2DM risk prediction [13].

Several studies indicated that lifestyle interventions of weight loss and increased physical activity coupled with a low-fat dietary pattern reduced the risk of T2DM in subjects with IGT. But a study published by Tinker *et al*. in 2008 (The Women's Health Initiative Randomized Controled Dietary Modification Trial) showed that a low-fat dietary pattern among generally healthy postmenopausal women didn't find a reduction of T2DM risk after 8.1 years. Trends towards lower incidence were greater with greater reduction in total fat intake and weight loss. So, the weight loss, rather than macronutrient composition, may to be the main predictor of reduced risk of diabetes [14].

A moderate alcohol intake has been shown to be cardioprotective. Hyperinsulinemia and reduced insulin sensitivity (considered as risk factors for cardiovascular disease and T2DM) seem to be influenced by alcohol

intake. In a randomized controlled trial, Davies *et al*. demonstrated that a consumption of 30g/day of alcohol (2 drinks per day) had a beneficial effect on insulin and triglyceride concentrations and insulin sensitivity in nondiabetic postmenopausal women. As a consequence the risk of T2DM and cardiovascular disease is lower in this group of women. Unfortunately, there are in the same time modifications of the steroid hormones representing risk factors for breast cancer [15].

A number of large prospective studies have reported an inverse association between coffee consumption and risk of T2DM. A recent systematic review on this topic concluded that this association between the coffee intake and the risk of T2DM is consistent across age, obesity, and study location (U.S.A and Europe). Possible explanations for this association could include effects on insulin sensitivity and/or insulin secretion from a variety of minerals, antioxidants, and phytochemical compounds found in coffee.

Pereira *et al*. (2006) observed an inverse association between coffee consumption, especially decaffeinated coffee consumption, and the risk of T2DM over an 11-year period in 28812 postmenopausal women from the state of Iowa [16].

A group of studies evaluated the effect of phytooestrogens on the postmenopausal diabetes. Some of them suggested that a combination of soybean protein and isoflavones could have a positive influence on diabetes control, although isoflavones alone may not be efficient and not all studies are positive. It is not clear which component is active, and indeed it may be the soluble fibre alone that is useful [17,18].

Diabetes mellitus represents a common condition that has been associated with increased incidence of breast cancer [19]. Metformin is a well-known biguanide, used for the treatment of T2DM, that increases insulin sensitivity and improves glycemic control. On the basis of these properties and preclinical evidence of its inhibition of breast cancer development, metformin is under investigation for its anticancer effects. Metformin use in postmenopausal women with diabetes mellitus was associated with reduced incidence of invasive breast cancer. These good results can inform future research regarding the role of metformin in cancer management and prevention [19].

In 1997 Andersson *et al*. reported an improvement of glucose metabolism and plasma lipids in postmenopausal women with T2DM after replacement therapy with estradiol. These diabetic women were hyperandrogenic in comparison with nondiabetic women, confirming previous observations. After estradiol substitution, the level of sex hormone-binding globuline (SHBG) increased 4-fold, whereas free testosterone decreased [20].

Arterial hypertension and diabetes mellitus alone or together commonly result in renal microvascular damage. This is characterised by the development and evolution of proteinuria and the decrease of the glomerular filtration rate, usually measured by creatinine clearance. Proteinuria is not only an important indicator of nephropathy, but may also contribute to its progression [2,21]. An interesting paper published by Szekacs *et al*. in 2000 shows that hormone replacement therapy (HRT) may reduce proteinuria, and even improve creatinine clearance, in diabetic and hypertensive postmenopausal women. These benefits are additive to the nephroprotective treatment, and the mechanisms appear unrelated to conventional risk factors for vascular involvement, such as high blood pressure, high plasma glucose or serum cholesterol [2].

The utilization of statin medication in postmenopausal women is associated with an increased risk of diabetes mellitus, as demonstrated by Culver *et al*. in 2012 [22]. This may be a medication class effect. Further study by statin type and dose may reveal varying risk levels for new-onset diabetes in this population.

Cigarette smoking is associated with an increased risk of T2DM. However, smoking cessation is often accompanied by weight gain, which may explain the increased risk of diabetes that has been observed in several studies. A prospective analysis over 8 ½ years of following showed that the increased risk of diabetes associated with quitting is confined to a subgroup that gains at least 5 kg [23]. The data obtained from former smokers suggest that diabetes risk is likely to return to that in never smokers after 10 years, independent of more recent weight gain. Since weight gain after smoking cessation can be prevented by dietary modification and regular moderate physical activity, smokers should not be deterred from quitting by concerns about elevation in the risk of diabetes [23].

Smoking cessation was associated with a lower risk of coronary heart disease (CHD) among

postmenopausal women with and without diabetes. Weight gain following smoking cessation aweakened this relation, especially for women with diabetes who gained 5 kg or more [24].

3. MENOPAUSE AND OBESITY

The increase in overweight and obesity in postmenopausal period represents an important public health problem, but the reasons for this increase are not totally clear. Some researcher arguments that the absence of estrogens may be a strong obesity-triggering factor. Estrogens deficiency enhances metabolic dysfunction predisposing to T2DM, metabolic syndrome, and cardiovascular diseases [25].

The hypothalamus is an important region of the brain for the coordination of food consumption, body weight homeostasis and energy expenditure. Some areas of the hypothalamus, including the ventromedial (VNM), arcuate (ARC), and paraventricular (PVR) nuclei, regulate physiological control of the weight. The process by which estrogens influence the activity of the hypothalamic structures is complex [25].

Additionally, some chemicals and plant-derived compounds that regulate the activity of estrogen receptors are potential obesogens. Reffering to the hormone replacement therapy (HRT) during menopause, this will always be a mixture of benefits and risks [25].

The increase in abdominal, and more particularly, visceral fat accumulation that occurs at menopause is associated with a higher risk of developing an atherogenic lipid profile and/or an insulin-resistant state [26].

The data published by Mauriège *et al*. in 2000 showed that regional variation in subcutaneous adipose tissue metabolism is not observed in early phase of menopause. Additionally, once the concomitent variation in body fatness, body fat distribution, and adipose cell size is taken into consideration, the sample of pre- and postmenopausal women displays similar subcutaneous adipose tissue lipolysis and LPL activity. These observations suggest that regional fat distribution is an important factor for the evaluation of the age-related effects on adipose tissue metabolism in women [27].

Estrogen and HRT may improve fat distribution in postmenopausal women by preventing the increase in central body fat. However, the evidence concerning the effects of HRT on glucose homeostasis is controversial. A study of Ryan *et al*. (2002) demonstrated that overweight and obese women taking oral estrogen and those who combine estrogen plus progesterone are more insulin-resistant than non-hormone users, even when women are of comparable total body fat, abdominal obesity, intramuscular fat and physical fitness [28].

Excess body weight is connected with several health risks, including: insulin resistance, T2DM, dyslipidemia, hypertension, cholelithiasis, some forms of cancer, hepatic steatosis, gastroesophageal reflux, obstructive sleep apneea, gout, polycystic ovary syndrome (PCOS) etc. The main objective of obesity therapy is to low body weight, to reduce the risk of associate disorders and to prevent regaining the excess weight [29,30]. Some details referring to the obesity treatment will be offered at the end of this chapter.

Hot flushes are among the most frequent troubles during menopause and persist for five or more years after menopause in as many as one-third of women. These common symptoms can negatively affect women's quality of life by disrupting sleep, interfering with work and leisure activities, and exacerbating anxiety and depression. The mechanisms of hot flushes are poorly understood, although modifications in hypothalamic thermoregulation or endothelial function could play a role [31]. Among women who are obese and have bothersome hot flushes, an intensive behavioral weight loss intervention can improve the situation [31].

Van Gemert *et al*. showed that a modest weight loss of 6-7% resulted in a positive change in self-perceived health status in a population of healthy overweight and obese, inactive, postmenopausal women. This change was significantly larger when weight loss was produced mainly by exercise compared with diet alone [32].

4. MENOPAUSE AND METABOLIC SYNDROME

Amongst pre- and postmenopausal women the metabolic syndrome (MetS) ranges from 13.8% to more than 60.0% [33,34]. Weight gain has a strong influence on the increased prevalence of MetS in postmenopausal status and an increased risk of the metabolic syndrome was independent of normal aging, as demonstrated by Kim *et al*. [36].

Hyperinsulinemia, insulin resistance and visceral obesity are the main features of the metabolic syndrome, found in many postmenopausal women [34].

As testosterone progressively dominates the hormonal milieu in the menopause period, the prevalence of MetS increases, independent of aging and other important covariates. This may be a pathway by which cardiovascular risk increases during menopause [37].

According to Carr (2003), it is unclear whether the transition to menopause increases cardiovascular risk in all women or only in those who present features of the metabolic syndrome [4].

The utilization of hormone therapy seems beneficial for reducing many of the parameteres of the metabolic syndrome. Transdermal therapy may be preferable to oral therapy [34].

In 2016 Gurka *et al.* evaluated the progression of metabolic syndrome severity during the menopausal transition. They found that the progression of MetS is rapid in this period but slows afterwards among black women [35].

5. MENOPAUSE AND LIPID DISORDERS

Premenopausal women have a less proatherogenic plasma lipid profile compared with the men [38,39]. They have higher HDL-cholesterol level and lower LDL-cholesterol, VLDL-cholesterol and triglycerides levels (in fasted and fed conditions) than age-matched men. Both the concentration and average size of circulating VLDL are smaller, whereas the concentration of LDL is smaller but the average LDL is larger in women than in men. The concentration of circulating HDL does not differ, but women have larger HDL particles[39]. These differences account for at least part of the cardioprotective effect of female sex before menopause [40].

Postmenopausal women have higher total cholesterol, LDL-cholesterol, triglycerides, and lipoprotein (a) levels and lower HDL-cholesterol levels than premenopausal women [39,41] (Table **2**). LDL levels increase by 10-20% with menopause and LDL composition also changes with menopause. The prevalence of small, dense LDL is low in premenopausal women (10-30%), but increases to 30-49% in postmenopausal women. As we know, a preponderence of small, dense LDL is associated with an increased cardiovascular risk [42].

Increasing triglycerides with menopause may be related to the fact that triglycerides values are strongly correlated with increasing abdominal fat content and insulin resistance [4].

Table 2: Effects of Menopause on Lipid Metabolism (Modified after Carr, 2003)

Total Cholesterol ↑
LDL Cholesterol ↑
Triglycerides ↑
HDL Cholesterol ↓
Lipoprotein (a) ↑
Proteins of lipid metabolism
A more atherogenic lipid profile
Lipid lowering

Menopausal changes in HDL metabolism are more complex than the total HDL shows, because the more antiatherogenic HDL_2 levels decrease, whereas HDL_3 levels increase [4,43].

The perimenopausal modifications in lipid metabolism reveal a shift toward a more atherogenic lipid profile with higher LDL and triglycerides values, reduced HDL_2 concentration, and smaller, denser LDL particles, similar to the metabolic syndrome [4].

In a large study published in 2016, Chang *et al.* demonstrated that midlife women with high fasting plasma triglycerides had a 2-to-2.5-fold increased risk of non-traumatic fractures after controlling for other potential confounders. If the results are confirmed, high fasting plasma TG could be a modifiable risk factor and help to identify midlife women at risk of incident non-traumatic fracture [44].

6. OTHER METABOLIC ISSUES IN MENOPAUSE

Iron is stored in human body as a form of ferritin, and thus ferritin can be considered as an accurate indicator of the iron status. It has been suggested that a high level of serum ferritin is a potent oxidant, increasing oxidative stress and leading to various diseases [45,46]. The elevation of ferritin level in postmenopausal women has been involved in the pathogenesis of many diseases, such as cardiovascular diseases, diabetes mellitus and metabolic syndrome [47].

Ju and Ha from Korea (2016) demonstrated that age, obesity, drinking habit, and glucose were the most important factors for the elevations of serum ferritin values in postmenopausal women. To reduce the risk of high ferritin in postmenopausal women, the intake of plant based foods, especially whole grains and vegetables, may be useful [47].

Menopausal symptoms are common, but vary by body mass index (BMI), ethnicity, smoking status, and other lifestyle variables. The results of the Women's Health Initiative (WHI) have altered the idea that estrogen therapy could reduce cardiovascular risks that appear after menopause [48]. With the decline in prescription for estrogen, the potential role of micronutrients and phytochemicals in controlling menopausal troubles is of increasing interest. Vitamins and phytoestrogens (eg. black cohosh, soy) can be beneficial but studies have different results. Collaborative decision making can help women with hot flashes reduce such manifestations [48].

Breast cancer, especially postmenopausal, is the most frequent cancer in women worldwide. It represents a major public health problem [49]. Van Gemert *et al*. showed that one in four postmenopausal breast cancer cases in the Netherlands (a country with one of the highest incidence of this disease) was attributable to five strongly associated lifestyle-related risk factors (Table **3**).

Table 3: The Most Significant Lifestyle-Related Risk Factors for Postmenopausal Breast Cancer in the Netherlands (2010) – Adapted from van Gemert *et al*. [49]

Excess body weight
An inactive lifestyle
Alcohol consumption
Smoking
Low dietary fibre intake

7. WHAT ABOUT DIET?

An adequately prepared diet should meet all nutritional requirements in a suitable amount and proportion [30].

Basically, the methodology to prepare a low energy diet consists of the following stages:

1. Estimating energy requirement – calculating basal metabolic rate (BMR)

2. Estimating protein requirement (0.8 – 1 g/kg of adjusted ideal body weight [AIBW] or 20-25% of daily energy requirement).

3. Estimating fat requirement (20-25% of daily energy requirement).

4. Estimating carbohydrates requirements (supplementation of energy requirement about 40-45% of daily energy requirements).

5. Determing food rations.

6. Dividing daily rations into meals.

7. Planning a menu (4-5 meals) daily.

The followed low energy diet should also be a high fiber diet and eliminate high glycemic index foods (GI<75) [30].

Interesting observations were recently published by Luzia *et al.* [50]. They evaluated the effect of separate or combined (with vitamin E) supplementation with fish oil in dyslipidemic women of two ethnic groups transitioning through menopause. They observed that:

- Supplementation with fish oil alone increased thiobarbituric acid reactive substances (TBARS) concentrations.

- Combined supplementation with fish oil and vitamin E reduced total cholesterol, LDL cholesterol and anti-LDL autoantibodies.

- The effects observed in the intervention groups were independent of ethnic origin.

A cross-sectional study among Chinese postmenopausal women, published in 2016, revealed that dietary patterns featuring a low intake of processed foods and/or high intake of whole plant foods determined a low risk of depression and perceived stress[51].

8. ROLE OF PHYSICAL ACTIVITY IN MENOPAUSE

As we already commented, obesity represents an important health problem for menopausal women. Sedentary lifestyle and low physical activity have a major contribution to their weight gain. Blümel *et al*. confirmed in 2016 that a sedentary lifestyle is highly prevalent among middle-aged Hispanic Latin American women. Sedentary women are more likely to present severe menopausal manifestations and to be obese [52].

Regular physical activity is known to bring mental and physical benefits [53]. Dabrowska *et al*. (2015) demonstrated that menopausal women can manage their body mass and improve their health by changing their lifestyle and performing moderate physical activity

correlated with BMI in all domains. The study is going to be continued with additional factors such as diet, hormonal status and body composition [54].

There is a preferential loss of abdominal fat with aerobic exercise, as visceral adipocytes respond more quickly to exercise-induced weight loss than subcutaneous adipocytes [55]. Regular endurance exercise improves insulin sensitivity independent of total weight reduction [4].

9. CONCLUSIONS

Starting from type 2 diabetes, a long and increasing list of metabolic disorders can be described in association with menopause. Part of them include still controversial aspects and arise more questions for the next years.

Diet and physical activity have an essential role in treating and preventing such disturbances.

We are sure that the metabolic picture of the menopause will be better characterized in a not so distant future and this will be benefic for the women population.

REFERENCES

[1] Gorodeski GI, Utian WH. Epidemiology and risk factors of cardiovascular disease in postmenopausal women. In: Lobo RA, Ed. Treatment of the Postmenopausal Women. New York: Reaven Press, 1994; pp. 199-221.

[2] Szekacs B, Vajo Z, Varhiro S, *et al.* Postmenopausal hormone replacement improves proteinuria and impaired creatinine clearance in type 2 diabetes mellitus and hypertension. Brit J Obst Gynaec 2000; 107: 1017-1021. http://dx.doi.org/10.1111/j.1471-0528.2000.tb10406.x

[3] Wylie-Rosett J. Menopause, micronutrients, and hormone therapy. Am J Clin Nutr 2005; 81(Suppl): 1223S-31S.

[4] Carr MC. The Emergence of the Metabolic Syndrome with Menopause. J Clin Endocr Metab 2003; 88: 2404-2411. http://dx.doi.org/10.1210/jc.2003-030242

[5] Bringer HG, Dudley EC, Robertson DM, Dennenstein L. Hormonal changes in the menopause transition. Recent Prog Horm Res 2002; 57: 257-275. http://dx.doi.org/10.1210/rp.57.1.257

[6] Revis J, Keene S. Type II Diabetes in American Women over 40: Obesity and Menopause. The Internet Journal of Health 2006; 6(1).

[7] Kim C, Edelstein SL, Crandall JP, *et al.* Menopause and risk of diabetes in the Diabetes Prevention Program. Menopause 2011; 18(8): 857-868. http://dx.doi.org/10.1097/gme.0b013e31820f62d0

[8] Brand JS, van der Schouw YT, Onland-Moret NC, *et al.* Age at Menopause, Reproductive Life Span, and Type 2 Diabetes Risk. Results from The EPIC-InterAct study. Diabetes Care 2013; 36: 1012-1019. http://dx.doi.org/10.2337/dc12-1020

[9] Brand JS, Onland-Moret NC, Eijkemans MJC, *et al.* Diabetes and Onset of Natural Menopause. Results From the European Prospective Investigation Into Cancer and Nutrition. Hum Reprod 2015; 30(6): 1491-1498. http://dx.doi.org/10.1093/humrep/dev054

[10] Herber-Gast G-CM, Mishra GD. Early Severe Vasomotor Menopausal Symptoms Are Associated With Diabetes. Menopause 2014; 21(8): 855-860. http://dx.doi.org/10.1097/GME.0000000000000171

[11] Heianza Y, Arase Y, Kodama S, *et al.* Effect of Postmenopausal Status and Age of Menopause on Type 2 Diabetes and Prediabetes in Japanese Individuals: Toranomon Hospital Health Management Center Study 17 (TOPICS 17). Diabetes Care 2013; 36: 4007-4014. http://dx.doi.org/10.2337/dc13-1048

[12] Liu S, Tinker L, Song Y, *et al.* A Prospective Study of Inflammatory Cytokines and Diabetes Mellitus in a Multiethnic Cohort of Postmenopausal Women. Arch Intern Med 2007; 167(15): 1616-1685. http://dx.doi.org/10.1001/archinte.167.15.1676

[13] Chao C, Yiqing S, Cook N, *et al.* The Lack of Utility of Circulating Biomarkers of Inflammation and Endothelial Dysfunction for Type 2 Diabetes Risk Reduction Among Postmenopausal Women. Arch Intern Med 2010; 170(17): 1557-1565. http://dx.doi.org/10.1001/archinternmed.2010.312

[14] Tinker LF, Bonds DE, Margolis LK, *et al.* Low-Fat Dietary Pattern and Risk of Treated Diabetes Mellitus in Postmenopausal Women. The Women's Health Initiative Randomized Controlled Dietary Modification Trial. Arch Intern Med 2008; 168(14): 1500-1511. http://dx.doi.org/10.1001/archinte.168.14.1500

[15] Davies MJ, Baer DJ, Judd JT, *et al.* Effects of Moderate Alcohol Intake on Fasting Insulin and Glucose Concentrations and Insulin Sensitivity in Postmenopausal Women. A Randomized Controlled Trial. JAMA 2002; 287: 2559-2562. http://dx.doi.org/10.1001/jama.287.19.2559

[16] Pereira MA, Parker ED, Folsom AR. Coffee Consumption and Risk of Type 2 Diabetes Mellitus. An 11-Year Prospective Study of 28812 Postmenopausal Women. Arch Intern Med 2006; 166: 1311-1316. http://dx.doi.org/10.1001/archinte.166.12.1311

[17] Chandalia M, Garg A, Lutjohann D, *et al.* Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. NEJM 2000; 342: 1392-1398. http://dx.doi.org/10.1056/NEJM200005113421903

[18] Cassidy A, Albertazzi P, Nielsen IL, *et al.* Critical review of healthy effects of soybean phyto-oestrogens in post-menopausal women. Proceedings of the Nutrition Society 2006; 65: 76-92. http://dx.doi.org/10.1079/PNS2005476

[19] Chlebowski RT, McTiernan A, Wactawski-Wende J, *et al.* Diabetes, Metformin, and Breast Cancer in Postmenopausal Women. J Clin Oncol 2012. http://dx.doi.org/10.1200/JCO.2011.39.7505

[20] Andersson B, Mattsson L, Hahn L, *et al.* Estrogen Replacement Therapy Decreases Hyperandrogenicity and Improves Glucose Homeostasis and Plasma Lipids in Postmenopausal Women with Noninsulin-Dependent Diabetes Mellitus. J Clin Endocrinol Metab 1997; 82: 638-643. http://dx.doi.org/10.1210/jc.82.2.638

[21] Remuzzi G. Abnormal protein traffic through the glomerular barrier induces proximal tubular cell dysfunction and causes renal injury. Curr Opin Nephrol Hypertens 1995; 4: 339-342. http://dx.doi.org/10.1097/00041552-199507000-00009

[22] Culver AL, Ockene IS, Balasubramanian R, *et al.* Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative. Arch Intern Med 2012; 172(2): 144-152. http://dx.doi.org/10.1001/archinternmed.2011.625

[23] Luo J, Rossouw J, Tong E, *et al.* Smoking Cessation, Weight Gain, and Risk of Type 2 Diabetes Mellitus Among Postmenopausal Women (Research Letter). Arch Intern Med 2012; 172(5): 438-439. http://dx.doi.org/10.1001/archinternmed.2012.24

[24] Luo J, Rossouw J, Margolis KL. Smoking Cessation, Weight Change, and Coronary Heart Disease Among Postmenopausal Women With and Without Diabetes (Research Letter). JAMA 2013; 310(1): 94. http://dx.doi.org/10.1001/jama.2013.6871

[25] Lizcano F, Guzmàn G. Estrogen Deficiency and the Origin of Obesity during Menopause. BioMed Research International 2014; article ID 757461, 11. http://dx.doi.org/10.1155/2014/757461

[26] Björntorp P. The regulation of adipose tissue distribution in humans. Int J Obesity 1996; 20: 291-302.

[27] Mauriège P, Imbeault P, Prud'homme D, *et al.* Subcutaneous Adipose Tissue Metabolism at Menopause: Importance of Body Fatness and Regional Fat Distribution. J Clin Endocrinol Metab 2000; 85: 2446-2454. http://dx.doi.org/10.1210/jc.85.7.2446

[28] Ryan AS, Nicklas BJ, Berman DM. Hormone Replacement Therapy, Insulin Sensitivity, and Abdominal Obesity in Postmenopausal Women. Diabetes Care 2002; 25: 127-133. http://dx.doi.org/10.2337/diacare.25.1.127

[29] Mastorakos G, Valsamakis G, Paltoglou G, *et al.* Management of obesity in menopause: diet, exercise, pharmacotherapy and bariatric surgery. Maturitas 2010; 65: 219-224. http://dx.doi.org/10.1016/j.maturitas.2009.12.003

[30] Brończyk-Puzoń A, Piecha D, Nowak J, *et al.* Guidelines for dietary management of menopausal women with simple obesity. Prz Menopauzalny 2015; 14(1): 48-52. http://dx.doi.org/10.5114/pm.2015.48678

[31] Huang AJ, Subak LL, Wing R, *et al.* An Intensive Behavioral Weight Loss Intervention and Hot Flushes in Women. Arch Intern Med 2010; 170(13): 1161-1167. http://dx.doi.org/10.1001/archinternmed.2010.162

[32] van Gemert WAM, van der Palen J, Monninkhof EM, *et al.* Quality of Life after Diet or Exercise-Induced Weight Loss in Overweight to Obese Postmenopausal Women: The SHAPE-2 Randomized Controlled Trial. PLoS ONE 2015; 10(6): e01237520. http://dx.doi.org/10.1371/journal.pone.0127520

[33] Jouyandeh Z, Nayebzadeh F, Qorbani M, Asadi M. Metabolic syndrome and menopause. Journal of Diabetes and Metabolic Disorders 2013; 12: 1. http://dx.doi.org/10.1186/2251-6581-12-1

[34] Stachowiak G, Pertyński T, Pertyńska-Marczewska M. Metabolic disorders in menopause. Prz Menopauzalny 2015; 14(1): 59-64. http://dx.doi.org/10.5114/pm.2015.50000

[35] Gurka JM, Vishnu A, Santen RJ, DeBoer MD. Progression of Metabolic Syndrome Severity During the Menopausal Transition. J Am Heart Assoc 2016; 5: e003609. http://dx.doi.org/10.1161/JAHA.116.003609

[36] Kim HM, Park J, Ryn SY, Kim J. The Effect of Menopause on the Metabolic Syndrome Among Korean Women. The Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care 2007; 30: 701-706. http://dx.doi.org/10.2337/dc06-1400

[37] Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrell K. Menopause and the Metabolic Syndrome. The Study of Women's Health Across the Nation. Arch Intern Med 2008; 168(14): 1568-1575. http://dx.doi.org/10.1001/archinte.168.14.1568

[38] Magkos F, Mittendorfer B. Gender differences in lipid metabolism and the effect of obesity. Obstet Gynecol Clin North Am 2009; 36: 245-265. vii [PubMed:19501312]. http://dx.doi.org/10.1016/j.ogc.2009.03.001

[39] Wang X, Magkos F, Mittendorfer B. Sex Differences in Lipid and Lipoprotein Metabolism: It's Not Just About Sex Hormones. J Clin Endocrinol Metab 2011; 96(4): 885-893. http://dx.doi.org/10.1210/jc.2010-2061

[40] Freedman DS, Otvos JD, Jeyarajah EJ, *et al.* Sex and age differences in liporotein subclasses measured by nuclear magentic resonancy spectroscopy: the Framingham Study. Clin Chem 2004; 50: 1189-1200. http://dx.doi.org/10.1373/clinchem.2004.032763

[41] Jensen J, Nilas L, Christiansen C. Influence of menopause on serum lipids and lipoproteins. Maturitas 1990; 12: 321-331. http://dx.doi.org/10.1016/0378-5122(90)90012-U

[42] Carr MC, Kim KH, Zambon A, *et al*. Changes in LDL density across the menopausal transition. J Invest Med 2000; 48: 245-250.

[43] Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and liporoteins in healthy women. Atherosclerosis 1993; 98: 83-90. http://dx.doi.org/10.1016/0021-9150(93)90225-J

[44] Chang P-Y, Gold EB, Cauley JA, *et al.* Triglyceride Levels and Fracture Risk in Midlife Women: Study of Women's Health Across the Nation (SWAN). J Clin Endocrinol Metab 2016. http://dx.doi.org/10.1210/jc.2016-1366

[45] Vari IS, Balkau B, Kettaneh A, *et al.* DESIR Study Group Ferritin and transferrin are associated with metabolic syndrome abnormalities and their change over time in general population. Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care 2007; 30: 1795-801. http://dx.doi.org/10.2337/dc06-2312

[46] Cho GJ, Shin JH, Yi KW, *et al.* Serum ferritin levels are associated with metabolic syndrome in postmenopausal women but not in premenopausal women. Menopause 2011; 18: 1120-4. http://dx.doi.org/10.1097/gme.0b013e318217e172

[47] Ju SY, Ha AW. Dietary factors associated with high serum ferritin levels in postmenopausal women with the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V), 2010-2012. Nutrition Research and Practice 2016; 10(1): 81-88. http://dx.doi.org/10.4162/nrp.2016.10.1.81

[48] Wylie-Rosett J. Menopause, micronutrients, and hormone therapy. Am J Clin Nutr 2005; 81(Suppl): 1223S-31S. Available from: ajcn.nutrition.org

[49] van Gemert WA, Lanting CI, Goldbohm RA, *et al.* The proportion of postmenopausal breast cancer cases in the Netherlands attributable to lifestyle-related risk factors. Breast Cancer Res Treat 2015; 152: 155-162. http://dx.doi.org/10.1007/s10549-015-3447-7

[50] Luzia LA, Aldrighi JM, Damasceno NRT, *et al.* Fish oil and vitamin E change lipid profiles and anti-LDL-antibodies in two different ethnic groups of women transitioning through menopause. Nutr Hosp 2015; 32(1): 165-174.

[51] Liu Z-m, Ho SC, Xie YJ, *et al.* Associations between dietary patterns and psychological factors: a cross-sectional study among Chinese postmenopausal women. Menopause 2016. http://dx.doi.org/10.1097/GME.0000000000000701

[52] Blümel JE, Fica J, Chedraui P, *et al.* Sedentary Lifestyle in Middle-aged Women Is Associated With Severe Menopausal Symptoms and Obesity. Menopause 2016; 23(5): 488-493. http://dx.doi.org/10.1097/GME.0000000000000575

[53] World Health Organization (WHO). Global Recommendations on Physical Activity for Health. WHO, Geneva 2010.

[54] Dabrowska J, Dabrowska-Galas M, Naworska B, Wodarska M, Plinta R. The role of physical activity in preventing obesity in midlife women. Prz Menopauzalny 2015; 14(1): 13-19. http://dx.doi.org/10.5114/pm.2015.49252

[55] Despres JP, Pouliot MC, Moorjani S, *et al.* Loss of abdominal fat and metabolic response to exercise training in obese women. Am J Physiol 1991; 261: E159-E167.

Received on 05-07-2016 Accepted on 19-08-2016 Published on 09-09-2016

DOI: http://dx.doi.org/10.12970/2310-9971.2016.04.01.3

© 2016 Chețа and Chirilă; Licensee Synergy Publishers.
This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.