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Menopause and diabetes: EMAS clinical guide

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ABSTRACT

Introduction: Whether menopause increases the risk of type 2 diabetes mellitus (T2DM) independently of ageing has been a matter of debate. Controversy also exists about the benefits and risks of menopausal hormone therapy (MHT) in women with T2DM.

Aims: To summarise the evidence on 1) the effect of menopause on metabolic parameters and the risk of T2DM, 2) the effect of T2DM on age at menopause, 3) the effect of MHT on the risk of T2DM, and 4) the management of postmenopausal women with T2DM.

Materials and methods: Literature review and consensus of experts' opinions.

Results and conclusion: Metabolic changes during the menopausal transition include an increase in and the central redistribution of adipose tissue, as well as a decrease in energy expenditure. In addition, there is impairment of insulin secretion and insulin sensitivity and an increase in the risk of T2DM. MHT has a favourable effect on glucose metabolism, both in women with and in women without T2DM, while it may delay the onset of T2DM. MHT in women with T2DM should be administered according to their risk of cardiovascular disease (CVD). In women with T2DM and low CVD risk, oral oestrogens may be preferred, while transdermal 17β-oestradiol is preferred for women with T2DM and coexistent CVD risk factors, such as obesity. In any case, a progestogen with neutral effects on glucose metabolism should be used, such as progesterone, dydrogesterone or transdermal norethisterone. Postmenopausal women with T2DM should be managed primarily with lifestyle intervention, including diet and exercise. Most of them will eventually require pharmacological therapy. The

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selection of antidiabetic medications should be based on the patient's specific characteristics and comorbidities, as well on the metabolic, cardiovascular and bone effects of the medications.

1. Introduction

Diabetes mellitus (DM) is a public health problem, especially in developed countries. It affects about 9.1% of the adult population in Europe and 13.3% in the United States of America [1]. The greater prevalence of DM in developed countries is broadly associated with ageing of the population [2]. Between 2015 and 2030, the world population aged over 60 years is projected to increase by 56%, from 901 million to 1.4 billion; by 2050 it is expected to reach nearly 2.1 billion [3]. These data suggest that the number of postmenopausal women with DM will grow substantially. The management of menopause in women with type 2 diabetes mellitus (T2DM) is challenging, as the precise nature of the risks and benefits of menopausal hormone therapy (MHT) in women with T2DM are still unclear.

The aim of this clinical guide is to summarise the evidence on 1) the effect of menopause on metabolic parameters and the risk of T2DM, 2) the effect of T2DM on age at menopause, 3) the effect of MHT on the risk of T2DM, and 4) the management of postmenopausal women with T2DM.

2. Metabolic changes during the menopausal transition

Menopause is the permanent cessation of menses due to oocyte depletion. The result is an abrupt decrease in endogenous oestradiol (E_2). During the transition to menopause, women undergo phenotypical, metabolic and biochemical changes which increase the risk of T2DM. Whether these changes are independent of ageing itself has been a matter of debate [4].

Women gain weight during the menopausal transition. While this may be influenced by age rather than menopause *per se* [5], the menopausal transition is independently associated with an increase in fat mass, especially in the abdominal region [6,7]. Perimenopausal women, furthermore, undergo a decrease in lean body mass and a significant reduction in energy expenditure, mainly from fat oxidation, which favour an increase in total body and visceral fat, without major changes in energy intake [6,7]. Visceral adiposity augments the production of proinflammatory cytokines, increases circulating free fatty acids and promotes the generation of reactive oxygen species, contributing to the development of insulin resistance [8]. On the other hand, menopause is a state of relative androgen excess: the postmenopausal ovary continues to secrete androgens, with higher bioavailability, due to the decrease in sex hormone-binding globulin (SHBG) seen during the transition. These hormonal changes further increase insulin resistance [9]. The prevalence of the metabolic syndrome, therefore, increases steeply after menopause, to between 30% and 70%, compared with 14–45% in women of reproductive age [8,10]. The metabolic syndrome has its pathogenetic origin in insulin resistance and is characterised by abnormal glucose metabolism, hypertension, central obesity and dyslipidaemia [11–14].

Beyond the metabolic changes triggered by menopause, experimental studies suggest that decreased E_2 concentrations, as well as decreased oestrogen receptor-α (ERα) activity, can cause insulin resistance in peripheral tissues [15,16]. Pancreatic β-cells have to compensate for insulin resistance to maintain glucose homeostasis; only when β-cell dysfunction coexists with insulin resistance does T2DM ultimately develop. Animal studies suggest an adverse effect of hypogonadism on insulin secretion. Ovariectomised rodents consistently present impaired β-cell function, while decreased E_2 action via ERα and ERβ seem to affect the survival of β-cells and the secretion of insulin, respectively [17–19].

3. Effect of menopause on the incidence of T2DM

Given the adverse metabolic changes associated with the menopausal transition, menopause is associated with an increased risk of T2DM. The Study of Women's Health Across the Nation (SWAN) suggested that lower E_2 concentrations resulted in a 47% higher risk of T2DM during the menopausal transition [20]. This finding was different from the initial results, which had suggested that the glucose dysregulation observed during menopause was associated with age and not with the decline of ovarian function [21,22]. Furthermore, the European Prospective Investigation into Cancer (EPIC)-InterAct, after following women for 11 years, showed that menopause before the age of 40 years was associated with a 32% greater risk of T2DM [23]. Another observational study, from China, provided evidence that menopause before the age of 45 years was associated with a 20% greater risk of T2DM compared with the average age of menopause [24]. In accordance with these findings, studies in women after ovariectomy have reported that their risk of T2DM is up to 57% higher than for women who have not undergone ovariectomy [25,26]. A recent analysis of data from the Women's Health Initiative (WHI) study, examining 124,379 postmenopausal women, concluded that women with a reproductive lifetime (difference between age at menarche and age at last period) of less than 30 years had a 37% higher risk of T2DM than women with a reproductive lifetime of 36–40 years. These results were reached after adjustment for chronological age [27]. Data from the same population showed that the report of any climacteric symptom was associated with an 18% increase in the incidence of T2DM (hazard ratio (HR) 1.18, 95% confidence interval (CI) 1.14–1.22). The risk increased in parallel with the severity and duration of symptoms, independent of obesity [28].

4. Effect of DM on age at menopause

Several studies have indicated an earlier age at menopause in women with type 1 diabetes mellitus (T1DM) than for women without T1DM. The prevalence of premature ovarian insufficiency in patients with T1DM is also higher, which might be related to the fact that both conditions are associated with autoimmunity [29,30]. The Familial Autoimmune and Diabetes study showed that women with T1DM experienced menopause at an earlier age (41.6 years) than their sisters (at age 49.9) or unrelated controls without diabetes (at age 48 years) [29]. Similarly, the European Prospective Investigation into Cancer and Nutrition (a cohort study) found that onset of diabetes before the age of 20 was associated with menopause at a younger age [30].

In contrast, other studies do not support an effect of diabetes on age at menopause. In the Ovarian Ageing in type 1 Diabetes mellitus (OVADIA) study, age at menopause was similar for women with and without the disease (49.8 years) [31]. Similarly, the results of the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which is a follow-up of the Diabetes Control and Complication Trial (DCCT), reported that age at menopause was not related to the therapy regimen or glycaemic control [32]. In a large population-based Finnish study of women with childhood-onset diabetes, the median age at menopause in the patient group was similar to that in the general population. Only the presence of advanced microvascular complications, such as renal disease and proliferative retinopathy, was associated with earlier menopause [33].

Furthermore, T2DM may accelerate the onset of menopause [30]. A study of 6079 middle-aged women from 11 Latin American countries showed that the proportion of middle-aged women with T2DM who had been through the menopause was three times that in the women without T2DM [34]. Moreover, women with a later onset of T2DM

(over 50 years) tended to have a later age of menopause, but this could have been associated with their higher body mass index (BMI) [34].

5. Impact of MHT on the risk of T2DM

MHT has a beneficial effect on various metabolic parameters, including a decrease in abdominal fat deposition, an increase in lipid oxidation and enhancement of energy expenditure [35,36]. Evidence also suggests that oestrogens improve insulin sensitivity through a direct effect on ERs in liver, muscle and adipose tissue [37,38]. Studies in rodents have shown that oestrogens may augment insulin secretion in pancreatic β-cells too [17].

A large body of evidence indicates that MHT reduces the risk of T2DM. The incidence of T2DM in the MHT arm was reduced by 35% in the Heart and Estrogen/progestin Replacement Study (HERS) [39], and by 21% in the Women's Health Initiative (WHI) study [40]. The same effect was reported in two prospective observational studies, the Nurses' Health Study (NHS), where the use of MHT resulted in a 20% reduction in the incidence of T2DM [41], and the Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N), where the incidence of T2DM was 25% lower in women on MHT [42]. A meta-analysis of 107 trials showed that MHT reduced insulin resistance by 13% and new-onset T2DM by 30% [43].

Most large trials have assessed women on treatment with conjugated equine oestrogens (CEE) combined with medroxyprogesterone acetate (MPA); there are limited data regarding other types of MHT. Among the E3N cohort of 63,624 postmenopausal women, 1220 new-onset T2DM cases were identified, and the use of oral MHT was associated with a lower risk of new-onset T2DM than the use of transdermal MHT [42]. Because of the first-pass metabolism in the liver, oral CEE has stronger beneficial effects on insulin resistance, suppression of hepatic glucose production and cholesterol concentrations [43,44]. However, CEE increases the hepatic synthesis of triglycerides, C-reactive protein (CRP) and coagulation factors, and may increase the risk of thrombosis [45]. Furthermore, progestogens have been associated with the development of insulin resistance; in most trials, the beneficial effects of oestrogens were decreased by the addition of a progestogen, in a dose-dependent manner. Progesterone, norethisterone acetate (NETA) and dydrogesterone are likely to be more neutral than MPA and levonorgestrel, which are more androgenic [46–51].

6. MHT in women with T2DM

In women with T2DM, MHT improves glycaemia, insulin resistance and other components of the metabolic syndrome [43]. Despite this, the frequency of MHT use among women with T2DM is about 50% lower than in the general population. This is probably because T2DM was broadly considered in the past to be a CVD equivalent [52], and this rationale still deters many clinicians from prescribing MHT to patients with T2DM. However, given the beneficial effects of MHT on glycaemic control, an individualised approach in treating menopausal symptoms should be considered. Women with T2DM may be excellent candidates for MHT, after careful evaluation of their CVD risk [35,53–55]. In peri- or recently postmenopausal women with T2DM and low CVD risk, oral oestrogens may be preferred. In obese women with T2DM or in any woman at moderate risk of CVD, transdermal 17β-oestradiol is the preferred treatment. In any case, a progestogen with minimal effects on glucose metabolism should be used, like progesterone, dydrogesterone or transdermal norethisterone [35,53–56].

7. Management of T2DM in women during and after menopause

Many of the adverse metabolic consequences of the menopause can be countered by lifestyle changes, such as optimal diet, increase in physical activity, cessation of smoking and decrease in alcohol consumption. Lifestyle intervention should be the cornerstone of management in women with T2DM entering the menopause. Weight loss is very important, not only for the treatment of T2DM but also for its prevention [57]. However, as bone health and sarcopenia are important concerns during the postmenopausal period, only gradual and modest weight loss (5–7% of initial body weight annually) should be recommended [58,59]. Specific clinical nutritional recommendations include consumption of mono- and polyunsaturated fat rather than saturated forms, reduction in the total amount of carbohydrates and a preference for those deriving from fruits and whole grains, as well as protein intake being mainly from fish, poultry or skimmed dairy products. Nutrition programmes that provide 1200–1500 kcal/day or that create an energy deficit of 500–750 kcal/day can result in the desired weight loss. Consumption of nuts and seeds, appropriate intake of calcium and vitamin D, and low intakes of alcohol and sodium are additional crucial dietary changes. The recommended calcium and vitamin D daily intakes for women older than 50 years with a risk of fracture are 1000–1200 mg and 600–800 IU, respectively [58–62].

Physical exercise prevents weight gain and muscle atrophy, and improves bone quality and glycaemic ontrol. Women with T2DM should be encouraged to engage in regular aerobic physical activity – at least 150 min per week of moderate exercise or at least 75 min of vigorous exercise per week. Anaerobic activities targeting major muscle groups should also be performed. Physical activity increases muscle mass and because muscle is denser than fat it may limit weight loss despite fat reduction. In that case, women should be informed that this is still excellent for their health and the indicator to be checked should then be waist circumference [57,60].

Smoking represents an important risk factor for many diseases associated with menopause and ageing, such as CVD, osteoporosis and cancer. Therefore, smoking discontinuation should be an essential part of routine clinical consultation [60].

Most postmenopausal women with T2DM will eventually require pharmacological therapy. Metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-dependent glucose transporter-2 inhibitors (SGLT-2i) and insulin are the most commonly used medications. They have different metabolic, cardiovascular and bone effects [63–65], and the most suitable agent for any particular woman should be selected according to these different effects after taking into consideration the woman's specific characteristics and comorbidities. Metformin should be used as the first-line treatment, while DPP-4i and GLP-1RA may be useful second-line options because of their beneficial (or at least neutral) effects on bones. TZDs should be avoided in women with osteoporosis and increased fracture risk, as should canagliflozin, an SGLT-2i; other SGLT-2i are not well-validated options [58,63–65].

8. Conclusions

Menopause is associated with an adverse metabolic profile and possibly an increase in T2DM risk. MHT has a favourable effect on glucose homeostasis both in women with and in women without T2DM. Women with T2DM can receive MHT after careful assessment of their CVD risk. They should also be managed with lifestyle interventions, including diet, exercise, smoking cessation and decrease in alcohol consumption, with a combined focus on metabolic, cardiovascular and bone health. The most suitable antidiabetic agents should be selected according to the individual's cardiometabolic and fracture risk.

Contributors

R. Słopień, A. Rogowicz-Frontczak, B. Męczekalski, D. Zozulińska-Ziółkiewicz, J.D. Jaremek and E. Wender-Ożegowska prepared the initial draft, which was revised by Irene Lambrinoudaki, Panayotis Anagnostis and Stavroula A. Paschou. The revised paper was circulated to all other named authors (EMAS board members) for comments and approval; production was coordinated by Irene Lambrinoudaki and Margaret Rees.

Conflict of interest

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12 Alfred Mueck, in the past 5 years, has received research funding by various pharmaceutical companies who produce and/or sell products used as hormone therapy in peri- and postmenopausal women; as well as lecture fees from various pharmaceutical companies for lectures on hormone therapy or other issues of menopause.
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