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REVIEW

Menopausal Hormone Therapy in Women with Type 2 Diabetes Mellitus: An Updated Review

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ABSTRACT

Menopause is accompanied by several metabolic adaptations, which are related to insulin resistance, increased total body fat mass, and central abdominal fat accumulation, predisposing women to type 2 diabetes mellitus (T2DM) development. Metabolic syndrome has a high prevalence in postmenopausal women, indicating the loss of estrogen protection on metabolic and cardiovascular health. Moreover, earlier age at menopause has been related to increased risk of T2DM. Menopausal hormone therapy (MHT) has favorable results in glucose metabolism. Indeed, it reduces the risk of T2DM in women without this condition and improves glycemic control in women with T2DM. Before MHT initiation in women with clinical indications, it is imperative to assess their cardiovascular disease (CVD) risk, using official electronic algorithms for score calculation. The latter will determine regimen, dose, and administration route of MHT. Oral estrogens are preferable in women with low CVD risk, while transdermal administration is indicated in those with moderate and high CVD risk, as the risk of stroke and venous thromboembolism (VTE) is increased with oral administration. Oral 17β-estradiol is usually preferred in women with T2DM, as this route has more beneficial effects on glucose metabolism. Oral estrogens are also suggested in perimenopausal or recently postmenopausal women with low CVD risk. Although oral estrogens have favorable effects when indicated, the risk of VTE or stroke should always be considered. Micronized progesterone, dydrogesterone, and transdermal norethisterone are the progestogens used in postmenopausal women with T2DM and intact uterus. MHT should not be initiated in women > 60 years or > 10 years in menopause, as there is an increased thromboembolic risk in women with established atherosclerosis and no additional cardiovascular benefit in women without atherosclerosis. In conclusion, MHT administration in postmenopausal women with T2DM can be safe and effective as long as the therapeutic regimen has been properly selected

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according to their cardiovascular, metabolic, and fracture risk.

Keywords: Diabetes; Menopause; Menopausal hormone therapy; MHT; Postmenopausal women; T2DM

Key Summary Points
Menopausal transition is accompanied by metabolic changes that predispose to type 2 diabetes mellitus (T2DM) development.
T2DM can affect ovarian ageing and lead to earlier menopause, while late-onset T2DM is associated with later age at menopause, mediated by obesity.
Menopause hormone therapy (MHT) is associated with reduced risk of T2DM development in women without this condition and improved glycemic control in women with T2DM.
Oral 17β-estradiol is preferred in women with low cardiovascular disease (CVD) risk or/and T2DM, as this route has more beneficial effects on glucose metabolism. The risk of venous thromboembolism or stroke should always be considered.
Women with moderate CVD risk or obesity and T2DM should receive transdermal 17β-oestradiol.
Oral natural micronized progesterone, oral dydrogesterone, and transdermal norethisterone acetate (NETA) have a more neutral effect on glucose metabolism and are indicated in women with T2DM.
Individualized care and appropriate MHT regimen should be offered to postmenopausal women according to their age and cardiovascular risk.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a pandemic with a global prevalence of 10.5% [1]. Ageing and increasing obesity rates constitute the primary causes of the T2DM worldwide spread. Moreover, ovarian ageing, resulting in menopause and the end of reproductive life, has a crucial effect on glucose metabolism [2]. Menopause is defined as the permanent cessation of menstruation owing to oocyte depletion [3]. During menopausal transition, various changes in body weight, muscle mass, fat distribution, and energy expenditure lead to cardiovascular risk acceleration [4]. In particular, increase in total adipose tissue mass and central adiposity is the most common finding during menopausal transition. The presence of hormonal fluctuations and ageing-related physiological changes form an impaired metabolic status, characterized by reduced insulin secretion, insulin resistance, increased total body fat mass, sarcopenia, and abdominal fat accumulation. Subsequently, these changes render women prone to T2DM development, while metabolic syndrome has a high prevalence in postmenopausal women [5].

Additionally, estrogen depletion leads to decreased bone mineral density (BMD), osteoporosis, and increased fracture risk later in life [6]. Menopausal hormone therapy (MHT) exerts a protective metabolic effect and may delay T2DM presentation. However, lifestyle changes (healthy dietary habits, physical activity, weight loss, smoking cessation) remain the cornerstone of T2DM prevention, as MHT is not indicated exclusively for T2DM prevention [7]. MHT should be individualized according to postmenopausal women's cardiovascular disease (CVD) risk, which is calculated by official electronic algorithms, such as the HeartScore, proposed by the European Society of Cardiology, and the ASCVD (Atherosclerotic Cardiovascular Disease) risk calculator, supported by the American College of Cardiology [8, 9]. Although T2DM was initially considered an equivalent of high CVD risk and a reason for exclusion from MHT, new evidence has confirmed that it can be safely administered after

patient assessment and CVD risk stratification to determine proper regimen, route, and optimal dose [10].

The aim of this updated review was to evaluate the relationship between menopause and T2DM and present the principles of MHT administration in women with T2DM. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. It provides an update of our previous publication [11].

TYPE 2 DIABETES MELLITUS AND MENOPAUSE

Metabolic syndrome has a high prevalence in postmenopausal women, indicating the loss of the favorable estrogen effects [12]. However, whether ageing or menopausal estrogen depletion (ovarian ageing) is related to the increased T2DM risk observed in this group has been a matter of controversy. The interplay between menopause and T2DM is mediated by the aforementioned metabolic changes in body composition, insulin action and secretion, and chronic inflammation [13].

In 2019, a systematic review and meta-analysis including 191,762 women demonstrated that early menopause and premature ovarian insufficiency (POI) were associated with increased risk of T2DM (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.01–1.20, $p=0.02$, and OR 1.53, 95% CI 1.03–2.27, $p=0.035$, respectively) [14]. Another meta-analysis including 14,445 women indicated that waist circumference and body mass index [BMI] were significantly elevated during menopausal transition (mean difference 4.12 cm and 0.94 kg/m^2, respectively) [15].

In addition, a higher risk for metabolic syndrome development has been observed in women with surgically induced menopause due to the abrupt decline in estrogen levels [16]. Weidlinger et al. [17] proved the protective metabolic effect of circulating estrogens, as their administration was associated with a significant increase in resting energy expenditure. Estrogen depletion was correlated with decreased energy expenditure, increased weight gain, and risk for obesity [17], the primary cause being a reduction in lipid oxidation [18].

Sarcopenia and central obesity have been associated with increased peripheral insulin resistance and low-grade systemic inflammation, given that fat accumulation between muscle cells disturbs the β-oxidation of fatty acids; free fatty acids promote the production of reactive oxygen species (ROS) and contribute to the oxidative stress and secretion of pro-inflammatory cytokines [19, 20]. Furthermore, the postmenopausal ovary still produces androgens, which decline at a lower rate, while the simultaneous decrease in sex hormone-binding globulin (SHBG) leads to a relative androgen excess [21]. The latter further exacerbates insulin resistance and contributes to an unfavorable cardiometabolic status [22]. Importantly, genetic predisposition as a primary factor affecting T2DM development should not be overlooked.

MENOPAUSAL AGE AND T2DM

The EPIC (European Prospective Investigation into Cancer and Nutrition)-InterAct study, a large European multicenter cohort study ($n=367,331$, 11 years of follow-up), concluded that diabetes may impact menopausal age. Women diagnosed with diabetes before the age of 20 entered menopause earlier, while menopause was delayed in women with late-onset T2DM; the latter can be attributed to obesity and premenopausal weight gain [23]. On the other hand, chronic hyperglycemia of early onset T2DM and type 1 diabetes mellitus (T1DM), which is commonly presented at younger age, accelerate ovarian ageing. In the French prospective cohort study (83,799 women, 22 years of follow-up), later age at menopause was related to reduced T2DM risk [24, 25]. A prospective analysis of the Women's Health Initiative (WHI) data ($n=124,379$) showed that women with shorter (<30 years) and longer (>45 years) reproductive lifespan had an increased risk of T2DM (37% and 23%, respectively) [26]. WHI showed that continuous combined conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA)

administration resulted in a significant reduction in the incidence of T2DM (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.70–0.94). CEE alone also resulted in a significant reduction in T2DM (HR 0.86, 95% CI 0.76–0.98).

Additionally, an Australian cohort study ($n = 6357$, 20 years of follow-up) concluded that women with shorter reproductive lifespan (< 35 years) exhibited a 30% increased risk of T2DM development [27]. Women with coexisting obesity had an even more pronounced risk for T2DM (HR 6.30, 95% CI 4.41–8.99) [27]. Furthermore, an analysis using data from the study of women's health across the nation (SWAN) documented a higher risk for T2DM in women with lower estradiol concentrations and a slower rate of FSH increase during menopausal transition after adjustment for age and obesity [28]. A later publication using a cohort of the SWAN study ($n = 3097$) followed up for 20 years concluded that women with multiple physical, psychological, and menopausal symptoms of moderate to high intensity had earlier onset of diabetes and metabolic syndrome [29].

MENOPAUSAL HORMONE THERAPY IN WOMEN WITH T2DM

MHT is the gold standard treatment for the management of menopausal symptoms and is also considered for the management of postmenopausal osteoporosis, as it prevents bone loss and osteoporotic fractures. There is strong evidence that MHT has a favorable metabolic effect in women with and without diabetes. It has been shown that MHT administration reduces the risk of T2DM development by 30% [30]. Moreover, MHT improves glycemic control and glycated hemoglobin in women with pre-existing T2DM [31]. MHT also has a beneficial effect on blood pressure, low-density lipoprotein (LDL) cholesterol, triglycerides, and lipoprotein (a) [32].

Epidemiological studies support that pre-menopausal women are at a lower risk of developing CVD compared with men of the same age. However, the CVD trajectories between genders align, as the female risk increases post-menopausally [33]. MHT is prescribed as estrogen monotherapy in women with a history of hysterectomy or as a combined estrogen–progestogen therapy in women with an intact uterus or endometriosis [34]. Progestogens are prescribed for endometrial protection from unopposed estrogen exposure [35]. Estrogens act through their binding to the estrogen receptor, subtype alpha (Era), which is located at the ventromedial nucleus of the hypothalamus. ERa is expressed mainly in reproductive tissues (uterus and ovary), breast, bones, white adipose tissue, liver, and kidney [36]. MHT is indicated in all women with primary ovarian insufficiency and early menopause until the age of natural menopause [37, 38]. It is individualized according to the risk factors in women with the following menopausal symptoms: hot flashes or night sweats (vasomotor symptoms), sleep disorders, mood swings, muscle and joint pain, or sexual dysfunction, women at high risk of osteoporotic fractures, and those presenting with genitourinary syndrome of the menopause (GSM) [37, 38].

CARDIOVASCULAR RISK AND MHT

Perimenopausal or recently menopausal women with low CVD risk may receive oral estrogens as they have the advantage of first-pass metabolism in the liver. Hence, they suppress hepatic glucose production and have a favorable effect on insulin resistance [39]. However, hepatic synthesis of triglycerides, coagulation, and inflammatory factors should be considered. On the other hand, women with obesity and T2DM or with a moderate CVD risk should receive transdermal MHT, as the risk of stroke and venous thromboembolism is lower; 17β-estradiol should be preferred. Although progestogens have been associated with insulin resistance development, oral natural micronized progesterone, oral dydrogesterone, and transdermal norethisterone acetate (NETA) have a more neutral effect on glucose metabolism and are indicated in women with diabetes [39].

MHT administration is not recommended in women with T2DM aged > 60 years old or > 10 years in menopause, because in women with established atherosclerosis it could destabilize mature atherosclerotic plaques and

predispose them to thromboembolic episodes [40]. This principle is based on the "timing hypothesis", which supports early MHT administration within 10 years since menopause to gain the optimal cardiovascular protection. Earlier administration protects the endothelium and deters the formation of atherosclerotic plaques, whereas later administration contributes to plaque erosion or rupture, leading to major adverse cardiovascular events [41]. In women without increased CVD risk, there is no additional benefit from MHT initiation beyond the age of 60 years. A Cochrane systematic review of randomized controlled trials (RCTs) including 40,410 postmenopausal women concluded that MHT administration within 10 years from the last menstrual period was related to lower mortality and coronary heart disease. However, these women were still at an increased risk of venous thromboembolism (VTE) (risk ratio [RR] 1.74, 95% CI 1.11–2.73) [42].

MENOPAUSAL HORMONE THERAPY COMPLICATIONS

Despite the multiple favorable effects of MHT, its side effects should also be acknowledged. Breast cancer, VTE, stroke, and myocardial infarction constitute the most common complications. The risk of breast cancer in women receiving MHT is small and is mainly attributed to progestogen addition, the type of progestogen, and therapy duration. Natural progesterone and dydrogesterone have been associated with a low risk of breast cancer. On the other hand, although MHT containing oral estrogens should be avoided in women with a history of thromboembolism, multiple studies have shown that transdermal estrogens, alone or combined with progestogens, are not associated with a significant VTE risk. The risk of stroke, though, remains significant with oral administration [43]. Conversely, oral estrogens are associated with an increased risk of stroke and VTE [44]. Thus, women with moderate to high CVD risk should receive transdermal MHT, because the risk of stroke and venous thromboembolism is increased with oral administration, due to an imbalance between coagulation and fibrinolysis. Moreover, a Korean study, including 58,060 postmenopausal women, showed that MHT is not associated with CVD or T2DM development [45].

CLIMACTERIC SYMPTOMS AND RISK OF T2DM

Although the association between climacteric symptoms and T2DM has been evaluated, the literature results remain inconsistent. An analysis using data from the WHI study (n = 150,007, 13 years of follow-up) showed that the presence of any vasomotor symptom was related to an 18% increased risk for T2DM (hazard ratio [HR] 1.18, 95% CI 1.14–1.22), after adjustment for obesity [46]. Another nationwide study (n = 6079) concluded that menopause was not related to T2DM presentation [47]. A recent review found that women with vasomotor symptoms during menopause share a specific cardiometabolic profile, including increased CVD risk, endothelial dysfunction, and atherosclerosis [48]. A meta-analysis of 107 RCTs, including the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, the Heart and Estrogen/Progestin Replacement Study (HERS) and the WHI Study, showed that MHT can reduce insulin resistance, abdominal fat, and the risk of T2DM development. In women without diabetes, MHT reduced new-onset diabetes (relative risk [RR] 0.7, 95% CI 0.6–0.9), abdominal fat (– 6.8%, 95% CI – 11.8 to – 1.9%), and homeostasis model assessment-estimated insulin resistance (HOMA-IR) (– 12.9%, 95% CI – 17.1 to – 8.6%). In women with diabetes, MHT reduced fasting glucose (– 11.5%, 95% CI – 18.0 to – 5.1%) and HOMA–IR (– 35.8%, 95% CI – 51.7 to – 19.8%). The underlying mechanisms include increased energy expenditure and lipid oxidation [30].

CONCLUSIONS

T2DM is a common comorbidity in postmenopausal women and can affect ovarian ageing, leading to earlier menopause. On the other hand, earlier age at menopause, including

premature menopause and primary ovarian insufficiency, predisposes to T2DM development in the future. MHT has been associated with reduced risk of T2DM development in women without this condition and improved glycemic control in women with T2DM. Postmenopausal women should receive individualized care and appropriate MHT regimen, according to their age and cardiovascular risk. Lifestyle modifications, including regular physical activity and healthy dietary habits, should always remain at the core of the therapeutic management.

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Declarations

Conflict of Interests. Nikolaos Papanas is a member of the Editorial Board for Diabetes Therapy. Nikolaos Papanas was not involved in the selection for peer reviewers for the manuscript, not any of the subsequent editorial decisions. Stavroula A. Paschou has participated in clinical trials sponsored by Novo Nordisk, Sanofi, and Eli Lilly, and has received honoraria for advisory board membership or lectures from Novo Nordisk, Sanofi, Bausch Health, and Abbott. Kleoniki I. Athanasiadou has no conflict of interest. Nikolaos Papanas has been an advisory board member of TrigoCare International, Abbott, AstraZeneca, Elpen, MSD, Novartis, Novo Nordisk, Sanofi-Aventis and Takeda; has participated in sponsored studies by Eli Lilly, MSD, Novo Nordisk, Novartis and Sanofi-Aventis; received honoraria as a speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elpen, Galenica, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Takeda and Vianex; and attended conferences sponsored by TrigoCare International, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Pfizer, and Sanofi-Aventis.

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