Type 2 Diabetes Mellitus and Menopausal Hormone Therapy: An Update

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ABSTRACT

During menopausal transition, various phenotypical and metabolic changes occur, affecting body weight, adipose tissue distribution and energy expenditure as well as insulin secretion and sensitivity. Taken together, these can predispose women to the development of type 2 diabetes mellitus (T2DM). Many women in midlife experience climacteric symptoms, including hot flashes and night sweats. Menopausal hormone therapy (MHT) is then indicated. MHT has a favourable effect on glucose homeostasis in both women without and with T2DM. T2DM was considered in the past as a cardiovascular disease (CVD) equivalent, which would suggest that women with T2DM should not receive MHT. This notion may still deter many clinicians from prescribing MHT to these patients. However, nowadays there is strong evidence to support an individualised approach after careful evaluation of CVD risk. In older women with T2DM (> 60 years old or > 10 years in menopause), MHT should not be initiated, because it may destabilise mature atherosclerotic plaques, resulting in thrombotic episodes. In obese women with T2DM or in women with moderate CVD risk, transdermal 17β-oestradiol could be used. This route of delivery presents beneficial effects regarding triglyceride concentrations and coagulation factors. In peri- or recently post-menopausal diabetic women with low risk for CVD, oral oestrogens can be used, since they exhibit stronger beneficial effects on glucose and lipid profiles. In any case, a progestogen with neutral effects on glucose metabolism should be used, such as natural progesterone, dydrogesterone or transdermal norethisterone. The goal is to maximise benefits and minimise adverse effects.

Keywords: Menopause; Menopausal hormone therapy; Type 2 diabetes mellitus

INTRODUCTION

Menopause is the permanent cessation of menses due to oocyte depletion [1, 2]. It is characterised by a substantial decrease in endogenous oestrogen production and
represents the end of female reproductive life. Women after menopause exhibit not only hormonal but also various phenotypical and biochemical changes, which can predispose them to the development of type 2 diabetes mellitus (T2DM) [1, 2]. The transition from pre- to post-reproductive life is associated with weight gain, especially with central obesity and an increase in waist circumference [1, 2]. Beyond central fat accumulation, menopause is associated with sarcopenia and decreased muscle mass, which further contribute to the change in body composition [1–3]. Whether these phenomena are not only the result of chronological aging, but also affected by ovarian aging has been a matter of scientific discussion [1–5]. A percentage of post-menopausal women present with climacteric symptoms and have an indication to receive menopausal hormone therapy (MHT) [6–9]. In the past, T2DM was considered an equivalent of cardiovascular disease (CVD), which would suggest that women with the disease should not receive MHT [8]. This notion may still deter many clinicians from prescribing MHT to these patients. However, nowadays there is evidence to support an individualized approach after careful evaluation of their CVD risk [2, 7].

The aim of this review is to analyse the risk of T2DM development after menopause and the potential use of MHT for the management of climacteric symptoms in these women. 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.

T2DM DEVELOPMENT AFTER MENOPAUSE

The prevalence of T2DM is increasing in western countries, indeed reaching epidemic proportions. This is broadly associated with aging and obesity, with diagnosed cases representing 5–10% of the general adult population [8, 10]. Initial findings of major studies suggested that impaired glucose metabolism after menopause was not related to decreased oestrogen concentration, but was merely the result of chronological aging [11, 12]. However, later analysis of data from the Study of Women’s Health Across the Nation (SWAN) concluded that the lower the oestradiol concentrations, the higher risk for T2DM development [13]. Other studies have confirmed that T2DM risk is indeed associated with a decline in ovarian function. The EPIC (European Prospective Investigation into Cancer)-InterAct study showed that premature ovarian insufficiency (before 40 years) was associated with a 32% higher risk for T2DM, after following up women prospectively for 11 years [14]. Another Chinese observational study including 16,299 women provided evidence that early menopause (before 45 years) was associated with a 20% higher risk for T2DM [15]. Similarly, studies with women after ovariectomy (surgical menopause), including data from the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study, reported increased risk (up to 57%) for the development of T2DM [16, 17].

A recent systematic review and meta-analysis [18] included 13 studies with 191,762 women in total, 21,664 of whom developed T2DM. Women with early menopause (40–45 years of age) or premature ovarian insufficiency (< 40 years of age) present increased risk for T2DM [odds ratio (OR): 1.12, 95% confidence interval (CI) 1.01–1.20, \( p = 0.02 \); \( p = 0.001 \) and OR: 1.53, 95% CI 1.03–2.27, \( p = 0.035 \); \( p = 0.001 \), respectively] [18]. Later analysis of 124,379 post-menopausal women from the Women’s Health Initiative (WHI) study showed that women with short reproductive lifetimes (< 30 years between the age of menarche and the age of the final period) had a 37% greater risk for the development of T2DM compared with those 36–40 years between the age of menarche and the age of the final period. Interestingly, this result was reached after adjustment for chronological age [19].

Indeed, menopause is accompanied by various consequences that could explain the increased T2DM risk [1, 2, 8]. One of the most prevalent changes is weight gain, associated with an increase in total body fat mass, especially with central abdominal fat accumulation and an increase in waist circumference.
With the use of dual-energy x-ray absorptiometry (DXA), computed tomography (CT) or other accurate body composition assessment techniques, it has been shown that the main parameter affected during menopause is the intra-abdominal fat [21–24]. When perimenopausal women were studied for 4 years, it was found that only those entering menopause exhibited increased visceral fat [25]. Additionally, menopausal women exhibited a significant reduction in energy expenditure from fat oxidation without important changes in energy intake [25]. Indeed, energy expenditure seems to be the earliest event, resulting probably from the decrease of the activation capacity of oestrogen receptor-α (ERα) [26, 27]. Such a relative loss of activation of the ERα can also affect the hypothalamic neuron activity as well as the ability of the sympathetic nervous system to regulate fat distribution through thermogenic activation in adipose tissue [28–30]. Menopause is also associated with sarcopenia and decreased muscle mass [22].

These changes in abdominal obesity and muscle mass may lead to physical and psychological morbidity [1, 2, 4]. A vicious cycle of subsequent excessive energy intake, sedentary lifestyle and stress may then start and further deteriorate the phenotypical and biochemical alterations of menopausal women [2, 4].

Abdominal fat deposition and decreased muscle mass due to sarcopenia after menopause lead to systemic low-grade inflammation [8]. Visceral adiposity augments the production of cytokines, contributing to the development of insulin resistance in the peripheral tissues [8]. Furthermore, menopause is a state of relative androgen excess. The post-menopausal ovary continues to secrete androgens, with higher bioavailability, because of the decrease in sex hormone-binding globulin (SHBG). These hormonal changes further increase insulin resistance [31]. There is also scarce evidence of the possible direct effect of menopause on insulin resistance, independently of body composition [31–34]. While relevant differences were not detected with the use of euglycaemic and hyperinsulinaemic clamps, the gold standard technique, insulin resistance was found to be increased in post-menopausal women with the use of intravenous glucose tolerance test (IVGTT) [32–34]. The insulin action may be affected by related changes in insulin metabolism, such as liver clearance [32, 33]. Moreover, experimental studies with female rodents and mice have provided evidence that both decreased oestradiol levels and decreased oestradiol action through the ERα could cause insulin resistance in skeletal muscle, liver and adipose tissue [35–43]. Pancreatic β cells need to compensate insulin resistance to maintain normal glucose levels. There is scarce data regarding the effect of menopause on insulin secretion, deriving mainly from animal studies [33]. Ovariectomy of rodents has been consistently shown to deteriorate β pancreatic cell function, while the decreased oestradiol action via ERα and ERβ seems to affect the survival of β cells and insulin secretion [44–47]. Of course, the genetic predisposition of β pancreatic cell dysfunction represents a crucial parameter for the ultimate development of T2DM [33, 44, 47].

### MHT IN WOMEN WITH T2DM

Some women after menopause present hot flushes or night sweats, known also as climacteric or vasomotor symptoms [1, 2]. MHT is indicated in such women, after evaluation of other comorbidities [1, 2, 6, 7]. Recently, such symptoms have been associated with increased risk of incident T2DM. A total of 150,007 women from the WHI study were prospectively examined for the potential association of T2DM with climacteric symptoms [48]. Interestingly, any vasomotor symptom was associated with an 18% increase in the risk of T2DM (hazard ratio (HR): 1.18, 95% CI 1.14–1.22) and this was independent of obesity. The more severe the symptoms and the longer their duration, the higher the risk for T2DM development is [48].

In the past, T2DM was broadly considered CVD equivalent, or at least as an important CVD risk factor for women [49], and this may still deter many clinicians from prescribing MHT to such women. However, there is strong evidence for beneficial effects of MHT in glucose homeostasis in women with or without T2DM. In women without T2DM, a meta-analysis of...
107 trials provided evidence that MHT can reduce abdominal fat, HOMA-IR by 13% and incident T2DM by 30% [50]. In women with T2DM, MHT exerts beneficial effects on fasting glucose and HOMA-IR. The reduction in insulin resistance, as represented by HOMA-IR, was 36%, even greater than in women without T2DM. This meta-analysis included very important studies and large randomised controlled trials (RCTs), such as the Post-menopausal Estrogen/Progestin Interventions (PEPI) study [51], the Heart and Estrogen/Progestin Replacement Study (HERS) [52] and the WHI Study [53]. On top of improved glucose homeostasis, MHT appears to improve other important CVD risk factors, such as blood pressure, LDL cholesterol, triglycerides, lipoprotein(a), adhesion and coagulation molecules [50, 54].

The favourable effects of MHT on glucose metabolism appear to extend beyond the correction of metabolic changes caused during menopausal transition. MHT decreases abdominal fat deposition [1] through the increase of lipid oxidation and enhancement of energy expenditure [1, 38]. However, reduced central obesity is not necessarily the main mechanism. Indeed, in HERS [52] and WHI trials [53] as well as NHS [55] and E3N [56] observational studies, the reduction in incident T2DM incidence was independent of the reduction in body weight and waist circumference. There is evidence that oestrogens may act directly on ERs in liver, muscle or adipose tissue, improving insulin sensitivity and contributing to improved glucose control and homeostasis [57, 58]. Furthermore, oestrogens may augment insulin secretion via a direct action on ERs in pancreatic β-cells, shown in experimental studies with rodents [44, 45].

Conjugated oestrogens (CEs) combined with medroxyprogesterone acetate (MPA) represent the type of MHT mostly investigated in large studies. CEs are available only in tablets, while 17β-oestradiol is available in both tablets and transdermal regimens. Oral oestrogens harbour stronger beneficial effects on insulin sensitivity, suppression of hepatic glucose production and cholesterol levels because of the first-pass metabolism in the liver [1, 2, 50, 59]. However, they increase hepatic synthesis of triglycerides, coagulation factors and other inflammatory markers [60].

Progestogens have been traditionally shown to decrease the beneficial effects of oestrogens on glucose metabolism. This phenomenon is dose-dependent and related to the development of insulin resistance [61, 62]. However, it appears that there are differences among various regimens. Indeed, MPA is known to have glucocorticoid activity, while levonorgestrel is a testosterone-derived product, both increasing insulin resistance. Conversely, natural progesterone, norethisterone acetate (NETA) and dydrogesterone are more neutral regarding glucose metabolism [63–66].

Given the beneficial effects of MHT on glycaemic control, an individualised approach in treating climacteric symptoms in post-menopausal women with T2DM should be considered, after careful evaluation of their CVD risk [1, 2, 7, 67] (Table 1). Women should be stratified according to their CVD risk. In older women with T2DM (> 60 years or > 10 years in menopause), MHT should not be initiated, as

| Women with T2DM | MHT use |
|-----------------|---------|
| > 60 years old  | NO      |
| or              |         |
| > 10 years in menopause |         |
| or              |         |
| High CVD risk   |         |
| Obese women     | YES     |
| or              |         |
| Moderate CVD risk | Prefer transdermal 17β-oestradiol |
| Peri- or recently | Prefer neutral progestogen |
| postmenopausal  |         |
| and             |         |
| Low CVD risk    |         |

MHT: menopausal hormone therapy, T2DM: type 2 diabetes mellitus, CVD: cardiovascular disease
such a therapy may destabilise mature atherosclerotic plaques, resulting in thrombotic episodes. In obese women with T2DM or those with moderate CVD risk, transdermal 17β-oestradiol could be used. Some experts recommend the use of the coronary artery calcium score to identify women with established but latent CVD [1, 2, 7, 67]. This route of delivery presents more beneficial effects regarding triglyceride concentrations and coagulation factors. In peri- or recently post-menopausal diabetic women with low risk for CVD, oral oestrogens can be used as they have the stronger beneficial effects on glucose and lipid metabolism profiles. In any case, a progestogen with neutral effects on glucose metabolism should be used, such as natural progesterone, dydrogesterone or transdermal norethisterone [1, 2, 7, 67].

CONCLUSIONS

Menopause is characterised by a substantial decrease in endogenous oestrogen concentrations and is associated with adverse metabolic profile and an increase in T2DM risk [1, 2]. MHT has a favourable effect on glucose homeostasis in both in women with and without T2DM. Although in the past women with T2DM would be excluded from MHT, nowadays there is strong evidence to support an individualised approach after careful evaluation of their CVD risk [1, 2, 7, 67].

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Compliance with Ethics Guidelines. 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.

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