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Mini Review

The Interrelationship of Menopause and Type 2 Diabetes Mellitus

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ABSTRACT

Menopause is a critical time in a woman's life which heralds the cessation of reproductive competence. There is body fat redistribution which increases the risk of type 2 diabetes mellitus (T2DM). There is a complex interrelationship between menopause and T2DM; several variables like the timing of the menopause, the type of menopause and the symptomatology impact this relationship. The treatment of vasomotor symptoms with hormone replacement therapy may also impact glycemia both in women with and without pre-existing T2DM. We tried to examine this relationship based on current scientific evidence. We also suggested strategies to reduce the burden of T2DM in menopausal women.

Keywords
Menopause; T2DM; Hormone replacement therapy.

INTRODUCTION

Menopause is the cessation of menses for a year or more. The years preceding and succeeding this event are fraught with medical and psychological issues which greatly impact a woman's quality of life. Most women struggle with weight gain during this period. Whereas weight gain per se cannot be attributed to the menopause transition, the change in the hormonal milieu at menopause is associated with an increase in total body fat and an increase in abdominal fat.[1]

A retrospective study showed that weight increase around pregnancy and menopause correlated significantly with higher odds for the diagnosis of type 2 diabetes mellitus (T2DM) and/or hypertension, irrespective of the number of children.[2] Midlife women are at significant T2DM risk due to the high prevalence of excess adiposity, insulin resistance and disorders that contribute separately to T2DM risk such as sleep disorders and depression.[3]

It is well-known that there are gender differences in the burden of complications of T2DM. Large-scale meta-analyses, summarizing all the evidence available to date from the best quality epidemiological studies globally, have provided compelling evidence that T2DM confers a 44% greater excess risk of coronary heart disease (CHD)[4] and a 27% greater excess risk of stroke in women than in men, independent of sex differences in other major risk factors.[5]

Thus, weight redistribution with increase in total body fat may predispose a woman to T2DM; and the complications of T2DM tend to be more severe for women. Menopause is a golden window where early diagnosis of T2DM is feasible and this window must not be missed.

CHARACTERISTICS OF MENOPAUSE AND ITS TREATMENT WHICH INFLUENCE TYPE 2 DIABETES MELLITUS

The timing of menopause, the type of menopause, the treatment of vasomotor symptoms with hormonal therapy all impact T2DM. In the article, we address several of these questions.

1. Does early menopause increase the risk of T2DM?

2. Does type of menopause influence risk of T2DM- surgical *vs.* natural?

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3. Does T2DM lead to early menopause?

4. Does the severity of menopausal symptoms help predict T2DM?

5. What is the impact of hormone replacement therapy on T2DM?

6. What are the strategies for prevention of T2DM in menopausal women?

Does Early Menopause Increase the Risk of T2DM?

In the prospective, population-based Rotterdam Study,[6] Three thousand six hundred thirty-nine (3639) post-menopausal women were followed for a median duration of 9.2-years. Of these, 348 women were identified with incident T2DM. After adjustment for confounders, hazard ratios (HRs) for T2DM were 3.7 (95% confidence interval (CI) 1.8, 7.5), 2.4 (95% CI 1.3, 4.3) and 1.60 (95% CI 1.0, 2.8) for women with premature (<40-years), early (40-45-years) and normal (>45-years) menopause, respectively, relative to those with late menopause (p trend <0.001). The HR for T2DM per 1-year-older at menopause was 0.96 (95% CI 0.94, 0.98).

Further adjustment for body mass index (BMI), glycemic traits, metabolic risk factors, C-reactive protein, endogenous sex hormone levels or shared genetic factors did not affect this association. Thus, the early onset of natural menopause is an independent marker for T2DM in post-menopausal women.

The Dongfeng-Tongji cohort study[7] examined the association of earlier menopause (<45-years) with the prevalence of T2DM in 16,299 women. Seventeen percent of the study population had T2DM. The average age at menopause was 49.5±3.3 years. For each 1-year delay in menopausal age, the presence of T2DM was reduced by 2% (OR: 0.98, 95% CI: 0.97-0.99) after adjusting for potential confounding factors. Compared with those whose menopausal age was 46-52-years, the OR for T2DM was 1.20 (95% CI: 1.03-1.39) for those with an earlier menopausal age (≤45-years). The risk was small but discernible.

Findings from the China Kadoorie Biobank study in the Zhejiang area[8] in 17,076 post-menopausal women showed that 1,288 (7.54%) of the participating women had T2DM. In comparison with those with menopause at 46-52-years, women with menopause at a later age (≥53-years) were 1.21-fold (95% confidence interval 1.03-1.43) more likely to have T2DM.

An early age at natural menopause/surgical menopause was associated with a higher risk of T2DM, which exhibited a linear relationship (p for trend= 0.009) with HRs of 1.83, 1.02, 0.89, and 0.64 for ages <40, 40-44, 45-49, and >55-years, respectively.[9] This study did not find an increased risk of T2DM with later age at menopause, women > 55-years showed the least risk of T2DM.

Additionally, the duration of natural menses was positively associated with T2DM, with women who had fewer years of menstrual cyclicity having elevated risks, yielding HRs of 14.89, 5.41, 2.09, 0.51, and 0.31 for reproductive life span of <20, 21-25, 26-30, 36-40, and >40-years, respectively (p for trend <0.001).

In contrast, a study by Qiu et al[10] found no association of age at menarche or menopause with T2DM though higher menopause age was associated with decreasing cardiovascular disease (CVD) risk (p for trend 0.020) and earlier menopause (46-years) with significantly higher osteoporosis risk (odds ratio 1.59, 95% confidence interval, 1.072.36; p 0.023).

Thus, there is a definite trend of increased risk of T2DM with earlier menopause (<45-years). Some evidence suggests greater osteoporosis risk with early menopause. The evidence for risk of T2DM at a later age (>45-years) at menopause and lesser years of menstrual cyclicity is sparse and needs more study.

Women with earlier menopause require focused screening, appropriate counselling of this risk and strategies for prevention must be in place to prevent T2DM. It is well-known that early intensive glucose lowering reduces the risk of microvascular and macrovascular complications of T2DM.[11]

Does the Type of Menopause Affect Risk of T2DM-Surgical *vs.* Natural?

Data from a cohort of 2,597 post-menopausal women enrolled in the National Health and Nutrition Examination Survey I Epidemiologic follow-up study[9] with a median follow-up time of 9.2-years, found the incidence of T2DM (in cases/1,000 person-years) was 7.4 for women with no hysterectomy or bilateral salpingo-oophorectomy (BSO), 8.2 for hysterectomy alone, and 8.5 for hysterectomy with BSO. Hysterectomy status was associated positively with T2DM (HR 1.66, 95% CI 1.23-2.23). However, the elevated risk was restricted to women with both hysterectomy and BSO after adjustment for relevant confounders (HR 1.57, 95% CI 1.03-2.41).

Of 437 post-menopausal women, who participated in the Tehran Lipid and Glucose Study,[12,13] women with surgical menopause and 39 age-matched controls with natural menopause were selected. During the follow-up period, changes in metabolic and biochemical profiles were compared between surgical and natural menopause women. Odds of incidence of metabolic syndrome in surgical menopause women compared to natural menopause women, was 9.7 (95% CI 1.8-51.8).

The authors concluded that metabolic disturbances after menopause are highly influenced by type of menopause and are more prevalent in those undergoing surgical menopause. However, the study was small and definite conclusions are difficult.

Thus, surgical menopause confers a greater risk of T2DM with hysterectomy and bilateral salpingo-oophorectomy both as compared with hysterectomy alone or no hysterectomy. The preservation of ovaries if feasible mitigates the risk of T2DM to a certain extent and must be given due consideration prior to planning surgery.

Does T2DM Lead to Early Menopause?

In a study in a teaching, tertiary care hospital in Southern India,[13]

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600 post-menopausal (300 had T2DM, 300 did not) women were recruited over a period of 1-year. Average age of menopause among diabetic women was 44.65-years which is much earlier than the menopause in non-diabetic women (48.2-years). Out of the 600 women, 212 women had an early menopause (<45-years). Among them, 54 were non-diabetic and 158 were diabetic. The authors concluded that T2DM increases the risk of early menopause but patients with T2DM had greater BMI.

In the longitudinal and multiethnic Study of Women's Health Across the Nation (SWAN) bone study[13] (n=2171), women with T2DM near the beginning of the study experienced a significantly earlier age at their final menstrual period (FMP) than women without T2DM (at age 49.1 *vs.* 52.4; p=0.002). The study further noted that although all women in SWAN were premenopausal (54%) or early peri-menopausal (46%) at baseline, a significantly higher proportion of women with DM of any kind transitioned to early peri-menopause as compared to those without T2DM (58% *vs.* 45%, p<0.001)

These results are consistent with the findings of a study of women in Latin America[14] that reported a more than two-fold higher prevalence of early menopause among 40-44-year-old women with T2DM (n=410) as compared with women without (n=5669) (29% *vs.* 13.2%; OR 2.76: CI 1.32-5.34).[15]

In contrast, Lopez-Lopez et al[16] found that Mexican women with T2DM (n=409) experienced a similar age at menopause as compared with women without T2DM (n=404) (49.8 *vs.* 49.6; p not provided).[15]

The European Prospective Investigation into Cancer and Nutrition (EPIC)[17] investigated the impact of T2DM on age at natural menopause (ANM) in 258,898 women enrolled between 1992 and 2000.

Overall, no association between T2DM and ANM was found (HR=0.94; 95% CI 0.89-1.01). However, women with T2DM before the age of 20-years had an earlier menopause (10-20-years: HR=1.43; 95% CI 1.02-2.01, <10-years: HR=1.59; 95% CI 1.03-2.43) compared to non-diabetic women, whereas women with T2DM at age 50-years and older had a later menopause (HR=0.81; 95% CI 0.70-0.95). None of the other age groups were associated with ANM.

Thus, the question of T2DM predisposing to early menopause is not yet clear at this time.

Do Patients with T2DM Experience Different Symptomatology as Compared with Non-diabetic Women during Menopause?

A study of 100 women in Mexico[18] aged 45-72-years of age, 51 with and 49 without non insulin dependent diabetes mellitus (NIDDM) compared the physical characteristics, emotional symptoms and metabolic conditions of menopausal women with and without NIDDM. They found greater scores for depression and empty nest syndrome in NIDDM women.

A high quality cohort study by Herber-Gast et al[19] assessed the association between four distinct VMS profiles, (including the early severe profile characterized by symptoms reported in pre-menopause with a peak at menopause) in a population of 4895 healthy peri-menopausal women, with a baseline age of 45-50-years. Results show that women with an early severe VMS profile are more likely to have T2DM across a period of 15-years (odds ratio, 1.55; 95% CI, 1.11-2.17). This association is not explained by body mass index or other potential confounders.

There are several studies that reflect the greater severity of menopausal symptoms in diabetic women compared with non-diabetic women.

What is the Impact of Hormone Replacement Therapy on Type 2 Diabetes Mellitus?

Without pre-existing T2DM: Hormone replacement therapy is used to treat the severe vasomotor symptoms that accompany the menopause transition. It is now clear that hormone replacement therapy (HRT) can be safely given to early (<10-years) menopausal women, less than 60-years of age with low risk of breast cancer and cardiovascular disease and are willing to take HRT.[20] However, the Endocrine society guidelines for the treatment of symptoms of menopausere commend using systemic HRT with caution in women with T2DM.

In women without T2DM, use of menopausal hormone therapy (MHT) appears to reduce the risk of self reported T2DM and glycated haemoglobin (HbA1C).[21,22] In a meta-analysis by Salpeter et al[23] of 107 randomized trials comparing MHT to placebo or no treatment in women without T2DM, MHT was associated with a reduction in fasting glucose and fasting insulin that led to a 13% drop in insulin resistance, as calculated using the homeostatic model assessment of insulin resistance (HOMA-IR). This was associated with an estimated reduction of 30% in new-onset T2DM. In most randomised controlled trials (RCTs), the beneficial effects of estrogen on metabolism were attenuated by the addition of a progestogen.[23]

These RCTs confirm results from large observational studies such as the Nurses' Health Study, in which current users of MHT showed a 20% reduced incidence of T2DM compared with past users and women who had never used MHT, after adjustment for age and BMI.[24] The post-menopausal estrogen/progestin interventions (PEPI) study showed a small increase in post-challenge glucose but it did not affect the overall glycemic control.[25]

With pre-existing T2DM: In two placebo-controlled, randomized, cross-over trials of oral CE or Estradiol (E2) treatment in post-menopausal women with T2DM, estrogens reduced fasting glucose, HbA1c, and insulin resistance without affecting post-prandialglycemia.[26,27]

Similarly, in an RCT of oral E2 in post-menopausal women[28] with T2DM, E2 produced a decrease in HbA1C and significantly increased insulin suppression of hepaticglucose production (HGP). It should be noted, however, that these studies indiabetic post-menopausal women had fewer subjects, used estrogens alone,

and were performed over a shorter duration of time than studies in women without T2DM.[29]

Oral *vs.* transdermal? Oral estrogen therapy and CE, in particular, results in a stronger beneficial effect on insulin resistance (as assessed by HOMA-IR) than does transdermal E2 delivery.[23] The stronger effect of oral therapy on blood glucose probably results from the first-pass liver metabolism leading to a better suppression of HGP. Surprisingly, in the Kronos Early Estrogen Prevention Study (KEEPS),[30] an RCT to assess the effects of early initiation of oral or transdermal MHT *vs.* place boon rates of progression of atherosclerosis in post-menopausal women, serum insulin and the HOMA-IR score decreased significantly with transdermal E2 (50 mcg), but not with oral CE (0.45 mg) probably because of the smaller dose of CE used. In summary, both oral and transdermal E2 can lower blood glucose and improve insulin sensitivity, although oral CE demonstrates the more powerful effect at equivalent doses.[29]

Though HRT is not recommended for the prevention of T2DM, if HRT is needed for a woman for severe vasomotor symptoms, it can be safely used without fear of worsening T2DM.

The cardiovascular risk needs to be considered in women with T2DM prior to prescribing HRT and women with previous or current CVD, strong family history of cardiovascular disease, current or past smokers, HRT should be prescribed after weighing risks *vs.* benefits. There is also very little data on the effect of HRT on complications of T2DM. It may be prudent to use other non-hormonal alternatives like selective serotonin reuptake inhibitors (SSRI's) for the treatment of vasomotor symptoms.

Strategies for Prevention of T2DM in Menopausal Women

A unique opportunity presents itself when a woman consults her doctor for vasomotor symptoms. This visit can be used to sensitize a woman about the need for screening herself for T2DM, cautioning her about expected increase in weight and adiposity and what she can do to prevent the weight gain and T2DM.

Three randomized controlled trials have shown that systematic intervention with diet and lifestyle can offset much of the risk of T2DM in midlife women. The Da Qing study enrolled 557 middle-aged women and men with impaired glucose tolerance and followed them for 6-years.[31] Participants were assigned to control group or one of three interventions: dietary therapy, physical activity or a combination of the two. The cumulative incidence of T2DM was 68, 44, 41 and 46%, respectively, with a significant difference between each of the intervention groups and the control group, but no significant difference between each of the intervention groups.[31]

The next randomized trial to be conducted was the finnish diabetes prevention study.[32] Women participating in this study, most of whom were middle-aged, also had impaired glucose tolerance and were also overweight. If randomized to the intervention, participants received dietary counseling aimed towards reduction of total caloric content, particularly saturated fat content and increased fiberin take, along with 30 min of exercise per day. After 3-years, participants in the intervention group had a cumulative incidence of T2DM of 14 *vs.* 6% in the control group ($p<0.05$), even though less than half of the participants in the intervention group achieved their weight loss goals.[32]

The most recent study was the aforementioned diabetes prevention program (DPP), which enrolled 3,819 adults, approximately two-thirds of whom were women, and the majority of whom were middle-aged. Women participating in this study also had impaired glucose tolerance and were overweight, and if randomized to lifestyle change, were given weight loss targets, dietary counseling for calorie reduction and healthy calorie consumption, and moderate physical activity goals.[33]

The menopause transition is the perfect time to sensitize a woman to the hazards of weight gain, risk of T2DM and its complications. Regular exercise and dietary modification are clearly effective in reducing the risk of T2DM. Stress reduction strategies like yoga, meditation and deep breathing exercises not only help to better manage vasomotor symptoms but also help to control glycemia.

Menopause is a golden window of opportunity and all health care professionals attending women in this period of life must use it to actively increase awareness of T2DM and its prevention.

CONCLUSION

Women with earlier age at menopause (<45-years) have greater risk of T2DM. Women who undergo hysterectomy with BSO also have a greater risk of T2DM. Type 2 T2DM may predispose women to an earlier age at menopause, though this is not yet definite. Women with T2DM may possibly have more severe vasomotor symptoms. In women without T2DM, HRT initiation is found to reduce the insulin resistance, fasting plasma glucose and HbA1c. In women with pre-existingT2DM, there is no worsening of T2DM with either E alone or E+P. Oral estrogen used in appropriate doses possibly has a more favorable impact on insulin resistance and glycemia compared with transdermal estrogen. However, in women with T2DM, those with current or risk of cardiovascular disease or existing complications of T2DM need to evaluated more carefully prior to initiation of HRT. Non-hormonal alternatives would be better treatment options. Early intervention with lifestyle modification helps to prevent T2DM in midlife in women and offers a unique opportunity that should not be missed.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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TABLE 1

Table 1. *Summary–Interrelationship of Menopause with Type 2 Diabetes Mellitus*

Early menopause increases the risk of type 2 diabetes mellitus
Surgical menopause increases the risk of T2DM which is partially mitigated by the preservation of ovaries
There is conflicting evidence as to whether T2DM leads to early menopause
In women with severe vasomotor symptoms, it is safe to give hormone replacement therapy especially if they are less than 60-years of age within 10-years of menopause and are low risk of VTE, CVD and breast cancer
Hormone replacement therapy reduces the risk of T2DM in women without pre-existing T2DM
HRT does not worsen T2DM and may improve glycemia in women with pre-existing T2DM