Managing menopause in women with diabetes

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Abstract

The impact of the current diabetes pandemic on the menopause experiences and health outcomes of women with diabetes is under-researched and poorly understood.

Type 2 diabetes mellitus (T2DM) often emerges during midlife and, in women, frequently presents synchronously with menopause, which independently increases the cardiometabolic risk.

Recent interest in menopause has highlighted the lack of clinical evidence upon which to base menopause management recommendations for women with diabetes. Most evidence relating to safety and efficacy of menopause hormone therapy (MHT), the first-line treatment for menopause symptoms, is based mainly on Caucasian, socially advantaged women with low rates of co-morbidity. The dearth of data relating to MHT in women with diabetes means that much evidence for women with diabetes relies on extrapolation. A nuanced and judicious approach to the management of menopause in women with diabetes and associated co-morbidities is, therefore, crucial.

This review focuses on the postmenopausal health risks in women with diabetes and the impact of different types of MHT. It highlights areas of uncertainties and unmet need in menopause care for this cohort of women.

Introduction

Rates of diabetes across the world continue to rise.[1] With improved diabetes treatments, life expectancy for people with diabetes is improving,[2] and the prevalence of postmenopausal women with diabetes is increasing. However, the number of postmenopausal women with diabetes is unknown, compounded by the fact that more than 44% of people with type 2 diabetes, are likely to be currently undiagnosed.[3]

Most women worldwide experience symptoms during the menopause transition (perimenopause) or post-menopause. Symptoms are most pronounced during the first four to seven years but can persist for more than a decade, and genitourinary symptoms tend to be progressive. During the menopause transition changes in hormones and body composition increase a woman's overall cardio-metabolic risk, with the resultant increased predisposition to metabolic syndrome, obesity, T2DM and cardiovascular diseases (CVD).[4]

Existing data relating to menopause hormone therapy (MHT), which is considered the first-line treatment for menopause symptoms, are based on research which under-represents women with diabetes and other health issues associated with increased cardio-metabolic risk. There is therefore a dearth of data informing best practice for management of menopause in women with diabetes, with most

recommendations based on extrapolation and inference.[5]

This review aims to evaluate symptoms and health risks in women with menopause and diabetes, to explore the evidence base for managing menopause in women with diabetes, to synthesise existing evidence relating to MHT's clinical indications, efficacy and safety in women with diabetes and to highlight the limitations of existing data.

Menopause symptoms

The cardinal symptoms causally associated with menopause are vasomotor symptoms (VMS), menstrual changes, disrupted sleep and genitourinary symptoms.[6-8] Other common symptoms include mood fluctuations, cognitive changes, low sexual desire, musculoskeletal symptoms, bone loss, increase in abdominal fat and adverse changes in metabolic health.[8] These symptoms and signs can occur in any combination or sequence, and the link to menopause may be elusive. Symptoms associated with the menopause transition can last for several years, with most women experiencing symptoms, and for 25% of women the symptoms are clinically severe.[8]

For most women menopause symptoms are time-limited, but effective treatment support is welcomed by many women at a busy life stage where work, care roles, responsibilities and life stresses often intersect. Intrusive menopause symptoms can negatively impact physical, social, emotional and economic wellbeing and symptom relief can facilitate agency and empowerment.[9]

Management options and support for menopause in women with diabetes

Lifestyle approaches to prevent, treat and reverse chronic disease are essential considerations for both diabetes and menopause care independently, and embody good clinical practice.[10]

Just as T2DM may require medication, intrusive menopause symptoms may require treatment, even in women who have addressed lifestyle as best they can. MHT is considered the most effective currently available treatment for menopause symptoms, with good international consensus.[11]

Non-hormonal treatment options for menopause are offered second-line for women who are MHT-unsuitable.[8,12] Cognitive behavioural therapy has efficacy data for relieving menopause symptoms,[9] and has been endorsed by the National Institute for Health and Care Excellence (NICE). A new and novel treatment targeting the vasomotor menopause symptom mechanism in the hypothalamus has recently been regulator-approved in several countries,[13] and other similar medications are in the pipeline.[14]

Menopause and diabetes: specific health risks and impact of MHT

Dementia risk

Diabetes is independently associated with an increased risk of dementia,[15] and women over 60 are twice as likely to be diagnosed with dementia than men.[2] Given that rates of dementia are considerably higher in women than men,[16] postmenopausal women with diabetes present a high risk for future dementia. Furthermore T2DM is more strongly associated with dementia mortality compared to non-dementia-related mortality among postmenopausal women.[17]

Optimising glycaemic control and addressing cardiometabolic risks through lifestyle and targeted medication currently represent the mainstay of treatment, aiming to reduce future dementia risk post-menopause.[18]

The currently available, pooled overall data on dementia risk with MHT amongst generally healthy women show a null effect. No conclusions can be drawn in relation to MHT effect on dementia outcomes.[19]

Cardiovascular risk

There is a two to three times higher all-cause and CVD-specific mortality in women with diabetes compared to women without diabetes, independently of ethnicity.[20]

Modifiable factors that can contribute to increased vascular risk, including smoking, hypertension, hyperlipidaemia and obesity, should be discussed and addressed in all postmenopausal women.

A Cochrane database systematic review published in 2015 suggested that treatment with MHT in postmenopausal women neither increased nor decreased CVD events overall. However, subgroup analysis demonstrated that MHT started or used by women before the age of 60 years or within 10 years of menopause was associated with a lower mortality, inferring a time window for commencing MHT before vascular disease is established, which may reduce future vascular risk.

Women with multiple CVD risk factors have generally been excluded from MHT RCTs,[21] and are under-represented in observational studies, which carry healthy-user bias.[22] When high-risk women have been included, results have not demonstrated meaningful benefits for chronic disease outcomes and some have shown increased morbidity.[23,24] Biological vascular ageing is complex and women with significant risk factors may develop progressive vascular disease pre-menopause,[25,26] suggesting that estrogen may not be protective in high-risk women. Furthermore, MHT-related outcome data for women with diabetes are unknown, therefore age-related guidance on timing of initiation of MHT in relation to likelihood of concurrent established cardiovascular disease should be viewed with caution in women with diabetes.

Women using oral MHT (estrogen alone and estrogen with progestogen) are exposed to a 2–4 fold increased risk of venous thromboembolism (VTE) compared to non-users.[27-29] This is not true for transdermal estrogen-based MHT.[30,31] Oral estrogens undergo first-pass hepatic metabolism, activating the coagulation system and increasing liver biosynthesis of procoagulant factors. In contrast, the effects of transdermal estrogen on the liver proteins are neutral.[32] Based on accumulated data, the risk of venous thrombosis and embolism is not considered an association with transdermal estrogen-based MHT.[32-35]

Oral oestrogen is associated with a slight increase in the risk of stroke. Transdermal oestrogen at a dose equivalent to a 50 microgram/day patch does not appear to increase the risk of stroke above a woman's own background risk but doses above this have been associated with an increased stroke risk.[36] Therefore, transdermal oestrogen at the lowest effective dose is preferred for women at increased stroke risk.

Breast cancer risk

Women with diabetes have an increased risk of postmenopausal breast cancer.[37] Individual risk is also influenced by background breast cancer-associated genetic, environmental and lifestyle factors.[38] Postmenopausal obesity, high alcohol intake and smoking independently increase breast cancer risk, and regular physical activity reduces risk.[39]

Breast cancer risks associated with MHT vary by type, timing and duration of treatment.[40-43] MHT appears to have a lower impact on breast cancer risk in women with overweight/obesity and the greatest impact on breast cancer risk in women of normal weight women.[44,45] MHT-associated breast cancer risks appear lower with estrogen-only therapy,[40,42] with the most favourable data relating to the use of conjugated equine estrogens.[42] There appear to be further breast cancer risk differences based on the progestogen used. Micronised progesterone and dydrogesterone-based MHT combinations have been found to confer lower risks than other progestogen MHT combinations when used in licensed doses,[46] but data are limited. Tibolone is a gonadomimetic which is effective in managing menopause symptoms and has been associated with a lower risk of primary breast cancer than standard combined MHT.[47] It also has a lower associated risk of VTE than standard oral combined MHT and improves bone mineral density, but is associated with a high background risk of stroke.[36,47-50]

Topical vaginal estrogen does not appear to increase the risk of primary breast cancer.[40,43]

Endometrial cancer risk

Diabetes is associated with an increased risk of endometrial cancer.[51] The association between diabetes and endometrial cancer may in part relate to coexisting obesity.[52] Obesity is recognized as an independent risk factor for endometrial cancer and is associated with reduced overall survival.[53] Endometrial cancer incidence and mortality are rising, and this has been linked with the worldwide obesity epidemic.[53]

Women with an intact uterus require progestogen as part of MHT for endometrial protection. Some MHT regimens containing micronized progesterone, in regulator-approved doses, may not provide adequate endometrial protection in otherwise healthy women,[54] and may therefore be inadequate for endometrial protection in women with high endometrial risk, such as women with diabetes.[51]

The occurrence of an increase in MHT-associated unscheduled bleeding since a recent rise in MHT uptake outside clinical trials in the UK has necessitated a formal consensus guidance to support clinicians, involving several national UK responsible bodies.[55] This unexpected rise in unscheduled bleeding in UK women utilising MHT in recent years may relate to the increased use of micronized progesterone for endometrial protection. Another possible contributor is that the characteristics of women accessing MHT in clinical practice may differ from clinical trial participants, with a likely higher occurrence of co-morbidities, reflecting changes in population demography.[56] Furthermore, given the current high rates of obesity globally,[56] the presence of obesity and diabetes in women seeking MHT justifies a careful discussion regarding the choice of progestogen for endometrial protection.

Fracture risk

Postmenopausal fracture risk varies by ethnicity. When compared to Caucasian women, Black women have a lower risk and South Asian women a higher background risk of osteoporosis.[57] There is an overall increased fracture risk associated with diabetes.[58]

A meta-analysis of RCTs assessing fracture risk in women using oral and transdermal estrogens (with or without the addition of a progestogen) reported a 20% to 37% reduced risk of hip, vertebral and total fracture.[59] These data demonstrate unequivocal benefits of estrogen-based therapy on bone health. However, as previously stated, women, with complex co-morbidities are not well represented in MHT research, and therefore there are greater outcome uncertainties.[5] The risk-benefit ratio of MHT is complex, even in healthy women. Despite bone health benefits, MHT is not routinely recommended for disease prevention.[60,61] This nuance is particularly relevant in women with complex health issues, including many postmenopausal women with diabetes, who may have greater associated risks with MHT with longer-term treatment but also increased risk of osteoporosis and fracture.

Vaginal estrogen therapy

Local vaginal therapy may be used alone or in combination with systemic MHT for genitourinary symptoms, including symptoms of vulvovaginal atrophy (VVA), urinary urgency and recurrent urinary tract infections. Topical vaginal therapies have an overall superior safety and side-effect profile compared to systemic MHT.[8,62,63]

Systemic progestogen is not required with regulator-approved doses of vaginal estrogen therapy.

Additional considerations in women with diabetes and menopause

If MHT is deemed necessary for menopause symptom control in women with diabetes, judicious tailoring of MHT is essential. As stated in the previous sections, different MHT regimens carry different associated risks. Regimens containing oral estrogen and some systemic high-dose progestogens may increase risk of VTE and stroke, whereas regulator-approved doses of transdermal estrogen and most progestogens in doses approved for endometrial protection do not increase VTE.[28,64]

Women with multiple cardio-metabolic risk factors, which includes many women with diabetes, may benefit from MHT for treatment of intrusive

menopause symptoms. Recognising, candidly discussing and addressing underlying risk factors should be prioritised if MHT is to be deployed in such women.[65] Individual MHT-specific risks should be identified to inform the judicious use of tailored MHT regimens. Different MHT doses, formulations and routes of administration have different effects on target organs, allowing many options to minimise individual risks. For example, modest dose transdermal estrogen is neutral to VTE and stroke risk;[66,67] the transdermal estrogen route is therefore favoured in women with increased vascular risk. In women with diabetes, micronised progesterone may be considered a preferred progestogen for MHT due to its favourable VTE, stroke and breast cancer risk profile. However, such regimens may expose these women to greater endometrial risk.

Women with diabetes are not well represented in MHT research and therefore the long-term effects of modern MHT formulations on such women are unknown. These uncertainties should be shared with women to inform decision-making.

Addressing chronic disease burden through risk-reducing strategies and treatments, including optimising lifestyle, glycaemic and hypertension control, hyperlipidaemia and weight management, should arguably be considered an essential prerequisite in all women with menopause and diabetes, as a foundation for disease treatments, prevention and reversal.[20] Depending on specific symptoms and patient preference, non-hormone treatment options may be considered in women who are MHT-unsuitable.[68] Some women with diabetes may not want or need medication to manage menopause symptoms.

Menopause and diabetes uncertainties

Research evidence for efficacy and safety of MHT has generally been limited to selected groups of women with low overall health risks. Furthermore, the majority of MHT research has included a predominance of Caucasian, socio-economically advantaged women. There is therefore sparse evidence for efficacy and safety in women with high cardiometabolic risk, those from minority ethnic backgrounds and those experiencing socioeconomic adversity. Extrapolating data from historical research trials to the fundamentally higher-risk modern demographics of women may not be accurate, and some evidence suggests that selective interpretation of research is facilitating misinformation about menopause outcomes with MHT.[69-72]

There is an unmet need to assess menopause treatments and health outcomes in modern cohorts of women with diabetes accessing menopause care in clinical practice. Whether MHT may impact glycaemic control in women with diabetes is unknown. Optimal regimens of MHT for menopause symptoms in women with diabetes are also unknown. While VTE and stroke risk can be mitigated using selected MHT regimens which carry neutral vascular risk, uncertainties around possible increased breast and endometrial cancer risk in women with diabetes using MHT require further investigation.

Conclusions and future directions

During the last two decades menopause care advances have mainly related to MHT research in women with low rates of underlying disease. There is a dearth of data assessing symptoms or treatment outcomes in women with diabetes.

The recent increased awareness around menopause and greater prescribing of MHT in clinical practice have highlighted an unmet need to determine menopause-related quality of life, treatment efficacy and health outcomes in women with diabetes.

Large-scale randomised trials using modern formulations of MHT in women with diabetes are unlikely to be funded. Formal collection of real-word evidence through registry data therefore represents the best potential opportunity to capture the menopause experiences and outcomes of women with diabetes among other under-represented groups.[73]

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