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Diabetes and Menopause

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Abstract During menopause, women's body composition, sex hormone profile, and metabolic profile may change dramatically. In this review, we summarize studies examining whether the menopausal transition and physiologic factors characterizing the transition are associated with increased risk of diabetes. We review the evidence for estrogen therapy and diabetes risk and studies examining the relationship between diabetes and menarche, which represents an extension of the reproductive life span at the opposite end of the age spectrum. Although studied less extensively, the presence of type 1 or type 2 diabetes may increase the risk of ovarian failure, and we review this literature. In conclusion, we note that the evidence linking menopausal sex hormone changes with increased diabetes risk is weak, although rapid changes as observed with oophorectomy may increase risk. Further studies should investigate the contradictory effects of estrogen therapy upon hepatic and glucose metabolism in mid-life women.

Keywords Women · Menopause · Diabetes · Menarche · Estrogen therapy

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Introduction

Type 2 diabetes, like other disorders of metabolism, commonly manifests during the mid-life [1] and thus coincides with the timing of the menopausal transition in women. The menopausal transition is a period of rapid change in physiologic characteristics including endogenous sex steroid hormones, body composition and body fat distribution, and lipid and metabolic profiles [2•]. Thus, it has been hypothesized that these underlying changes represent a mechanistic link between diabetes and menopause [3]. This review will provide an overview of the menopausal transition and its association with diabetes risk. Further, the literature relating diabetes to variations in the timing of the menopausal transition will be examined. Finally, the burgeoning literature supporting a beneficial role for hormone therapy (HT) in reducing diabetes risk will be reviewed.

Pathophysiology and Characterization of the Menopausal Transition

While menopause (i.e., the postmenopause) is clinically defined by the cessation of menses for at least 12 months, the menopausal transition itself actually begins 5–10 years before and is characterized by menstrual cycle and hormone

variability [2•]. Utilization of longitudinal hormone data in combination with bleeding characteristics is accepted as the optimal methodology for staging menopause [2•]. As this data is not usually readily available, this is often impractical in the clinical setting. The recent 2011 International Stages of Reproductive Aging Workshop (STRAW+10) has defined the menopausal transition as an early and late stage preceding the final menstrual period (FMP) and postmenopause as an early and late stage following the FMP [2•]. Most clinical and research studies have implemented this paradigm with some simplification (see Fig. 1). The FMP can only be defined retrospectively after 12 months of amenorrhea, and anything after the FMP is designated as postmenopause. Perimenopause is the period before the FMP with menstrual cycle irregularity but before 12 months of amenorrhea. Premenopause occurs before perimenopause and is characterized by regular menses. Identifying a "natural" FMP can be complicated if women are using exogenous hormone therapy or if they have had a hysterectomy, bilateral oophorectomy, or both. Women who have stopped having menses due to surgical reasons are referred to as being in "surgical menopause."

Hormone variability during the menopausal transition can be attributed to the more rapid depletion of the ovarian follicle pool and loss of negative feedback loops for hormonal regulation due to aging of the hypothalamic-pituitary axis [4, 5]. Several epidemiologic studies have indexed changes in sex steroid hormone levels in relation to the timing of the FMP. As shown in Fig. 2, estradiol (E2), the hormone traditionally implicated in sex differences in disease risk, has fairly stable levels up until 2 years prior to the FMP, followed by a 4-year sharp decline until about 2 years after the FMP [5, 6]. Rising follicle-stimulating hormone (FSH) levels can be detected as early as 10 years prior to the FMP [4], and levels rise more rapidly approximately 2 years prior to the FMP and then stabilize 2 years after the FMP [6]. Because FSH increases precede changes in E2, it is a more widely used biomarker of endocrine change during the menopausal transition.

Anti-mullerian hormone (AMH) is a dimeric glycoprotein produced by the preantral or functional ovarian follicles [7]. AMH levels decline with age and are the most accurate

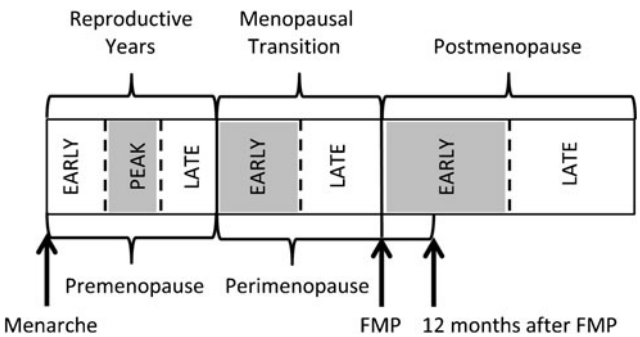

Fig. 1 Terminology of reproductive stages through the postmenopause and definition of the final menstrual period (*FMP*)

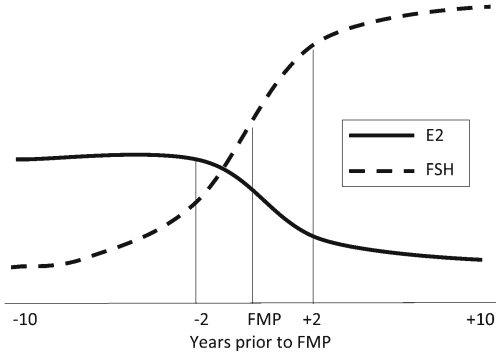

Fig. 2 Schematic of follicle-stimulating hormone (*FSH*) and estradiol (*E2*) changes around the final menstrual period (*FMP*)

marker of ovarian reserve [8, 9], particularly in late reproductive life before the onset of marked cycle irregularity [10]. AMH has primarily been used for risk stratification of women undergoing assisted reproductive technology interventions [11]. However, over the past decade, it has been increasingly applied to the diagnosis and management of endocrinopathies including polycystic ovarian syndrome [12] and to the prediction of the age at the FMP [7].

Menopausal Status and Diabetes Risk

Whether the increased prevalence of diabetes during the midlife is due to the menopausal transition independent of chronological aging is of great interest. In cross-sectional studies, evidence linking menopausal status with prevalent diabetes is mixed. Using a survey of more than 10,000 Japanese women, Heianza et al. reported that those with natural menopause had 40 % higher odds (odds ratio (OR) = 1.40, 95 % confidence interval (CI) 1.03–1.89) and women with surgical menopause had 59 % higher odds of diabetes (OR = 1.59, 95 % CI 1.07–2.37) as compared to premenopausal women [13]. Di Donato et al. reported a similar increase in the odds of diabetes among postmenopausal women as compared to premenopausal women (OR = 1.38, 95 % CI 1.03–1.84), a finding that persisted after adjustment for age [14]. Other cross-sectional studies have not found an association between menopausal status and several metabolic parameters including fasting plasma glucose, insulin, and insulin secretion rate or beta cell glucose sensitivity [15] or diabetes [16, 17]. Several longitudinal studies including the 6-year Pizarra Study [18], the 8-year Australian Longitudinal Study on Women's Health [19], and the 3-year Diabetes Prevention Program [20] found no association between natural postmenopausal status and diabetes risk.

Whether age at menopause is associated with diabetes risk has also been investigated with conflicting results. In both cross-sectional [21] and longitudinal [22, 23•, 24] studies, earlier age at menopause was associated with type 2 diabetes.

In the Study of Women's Health Across the Nation, diabetes was more prevalent among women with premature ovarian failure (cessation of menses before age 40), but this finding was not significant after adjustment for confounders [24]. However, in the InterACT Study, a subcohort of more than 8000 postmenopausal women nested within the larger European Prospective Investigation into Cancer and Nutrition (EPIC) study, women with early age at menopause (less than 40 years) had 32 % greater risk (95 % CI 1.04–1.69) of type 2 diabetes as compared to women with menopause at age 50–54 years [23•]. However, an analysis of all women in the EPIC study, the largest prospective study examining diabetes and age at natural menopause which includes women from France, Italy, Spain, the UK, the Netherlands, Greece, Germany, Sweden, Denmark, and Norway, found no association between age at natural menopause and diabetes risk [25••]. A lack of an association between menopause and diabetes risk was also reported in cohorts from Latin America [16], Italy [14], China [26, 27], Mexico [28], and Japan [17]. These studies suggest that the association between menopausal status or age at menopause and diabetes risk is not particularly strong, and at least part of the association is confounded by other factors (see Table 1 for hypothesized direct effects and confounders).

Unlike natural menopause whereby declines in E2 occur over several years, the event of a bilateral oophorectomy (known as surgical menopause) is a more abrupt end to a woman's reproductive capacity as the ovarian production of E2 is suddenly absent. Thus, studies of surgical menopause should be considered separately from those of natural menopause. Such studies have been more consistent regarding the impact of rapid and abrupt loss of E2 due to surgical menopause upon glycemic control. Two recently published longitudinal studies have reported an increased risk of diabetes among women with surgical menopause [22, 29]. Women in the NHANES I Epidemiologic Follow-up Study with both hysterectomy and bilateral oophorectomy had a 57 % increased risk (95 % CI 1.03–2.41) of developing diabetes as compared to women with natural menopause [22]. A deleterious effect of oophorectomy on insulin resistance and glucose tolerance has also been demonstrated in animal studies [30, 31].

Studies relating age at menarche to diabetes may also be informative given that an earlier age at menarche, like a later age at menopause, would extend a woman's reproductive life span. Further, like menopause, menarche is a period of change in the hormonal milieu. Despite different definitions of early puberty or early age at menarche, several studies have identified an increased risk of diabetes or metabolic dysfunction associated with early commencement of reproductive age [32–36]. In a study of Korean women, Baek et al. defined early age at menarche as less than 13 years and average age at menarche as 13–16 years; early menarche was significantly associated with prediabetes, diabetes, and hyperglycemia [32]. In a study of women in the USA, Chen et al. defined early menarche as ≤12 years and average age at menarche as 12–14 years of age and observed greater levels of fasting insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), and the homeostasis model assessment of beta cell function (HOMA-β) among women with early menarche as compared to those with an average age at menarche [33]. The association between decreased menopausal age with diabetes and decreased menarcheal age with diabetes suggests that factors aside from the reproductive-aged hormonal milieu may influence glucose metabolism as an early age at menarche and an early age at menopause have different impacts of the length of the reproductive lifespan.

Table 1 Hypothesized direct effects and confounders of menopause on diabetes risk

Hypothesized direct effects
↑ Testosterone, ↓ SHBG, ↑ androgenicity
Rate of E2 change
↑ Body fat, ↓ skeletal muscle mass
↑ Central deposition of fat
↑ Inflammation
↑ Hormone therapy use
Hypothesized confounders
Age
Smoking
Alcohol use
Physical activity
Education level
Parity

Mechanisms Linking Menopause and Diabetes Risk

Potential mechanisms linking menopause and diabetes include changes in body composition as well as sex steroids. While the mid-life is a vulnerable period for the development of obesity, longitudinal studies have shown that this increase in weight is due to chronological aging rather than reproductive aging [37–39] whereas changes in body composition and body fat distribution are related to both chronological and reproductive aging [39–41]. In the Study of Women's Health Across the Nation, FSH was positively correlated with fat mass and waist circumference change during the menopausal transition [41]. Further, obesity status is associated with differences in sex steroid trajectories during the menopausal transition; compared to women who are not obese, women with obesity have lower premenopausal E2 levels but higher postmenopausal E2 levels [6]. This may be due to the inhibitory effect of obesity on E2 production from the ovary prior to the

menopausal transition [42, 43] whereas after menopause, adipose tissue is the main source of postmenopausal estrogen [44, 45]. The changes in body fat distribution and elevated inflammatory cytokines [46, 47] that occur during the menopausal transition have been associated with decreased tissue insulin sensitivity and glucose tolerance [48–51]. However, the potentially beneficial effect of less rapid changes in menopausal E2 levels among obese women may be counteracted by the impact of excess adipose tissue on carbohydrate metabolism [52].

Unique to the menopausal transition, however, is a state of increased androgenicity during the postmenopause due to declines in ovarian production of estrogen [6], increased levels of testosterone [53], and decreases in sex hormone-binding globulin (SHBG) [53]. The combination of increased testosterone and decreased SHBG results in an increase in free circulating testosterone or greater overall androgenicity. Testosterone and SHBG levels have been associated with insulin resistance and diabetes. In the Rancho Bernardo Study, a prospective cohort study of older men and women, free testosterone was positively associated with fasting glucose, insulin, and insulin resistance among postmenopausal women [54] and SHBG was inversely associated with impaired glucose tolerance and diabetes incidence [55]. These findings have been replicated in other studies as well including the Multi-Ethnic Study of Atherosclerosis [56, 57], the Women's Health Study [58, 59], and the Study of Women's Health Across the Nation [60].

While estrogens are known to have insulin-sensitizing properties and to be protective for pancreatic beta cells [61], associations between estrogen levels and diabetes risk have been mixed. Among postmenopausal women, the Women's Health Study [58] and the Multi-Ethnic Study of Atherosclerosis [57] reported a significant association between higher levels of E2 and risk of diabetes, but this was not confirmed in the Rancho Bernardo Study [54] or among pre- or postmenopausal women in the Diabetes Prevention Program [62].

The autoimmunity characterizing type 1 diabetes may extend to other organ systems and co-existing thyroid autoimmunity is particularly common [63]. As premature ovarian failure may also be triggered by increased autoimmunity, investigators have examined whether women with type 1 diabetes are at risk for earlier menopause. Several studies have identified an earlier age at menopause among women with type 1 diabetes compared to women without diabetes [64–66], but whether these findings are generalizable to older cohorts is not clear. For example, using data from the Familial Autoimmune and Diabetes study of nearly 500 women, Dorman et al. [64] and Strotmeyer et al. [65] were the first to report a younger age at menopause (41.6 years) among women with type 1 diabetes as compared to their sisters without diabetes (49.9 years) or unrelated controls (48.0 years). Overall, the authors determined that this resulted in a 6-year relative reduction in reproductive lifespan among women with type 1 diabetes. However, given the length of follow-up of this study, only a small proportion of subjects reached natural menopause (10 %), thereby impacting the external validity of the study. Similarly, onset of diabetes before 20 years of age was associated with an earlier menopause in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort [25••]; although type 1 diabetes and type 2 diabetes could not be distinguished, the young age of onset is most consistent with type 1 diabetes [67]. However, other studies among women with validated diagnoses of type 1 diabetes have not confirmed an earlier age at menopause [68–70]. In a recently published analysis among more than 5000 women in the Ovarian Ageing in type 1 Diabetes mellitus (OVADIA) study, the age at natural menopause was identical among women with type 1 diabetes as compared to women without diabetes (49.8 years) [70].

Relative to type 1 diabetes, type 2 diabetes is a more heterogeneous disorder and usually not associated with autoimmunity. Interestingly, two studies have reported that women with type 2 diabetes have an earlier age at menopause than women without diabetes, consistent with the hypothesis that diabetes has an accelerating effect upon age at menopause [25••]. Data from a large multi-national Latin American study found that among 40–44-year-olds, the presence of diabetes was associated with a threefold risk of menopause before the age of 45 years [16]. In the longitudinal Study of Women's Health Across the Nation, women with diabetes had their FMP 3 years earlier than women without diabetes (49 vs. 52 years, respectively) [71]. In contrast, Brand et al. noted that women with later onset of diabetes (after age 50) tended to have later age at menopause. However, this finding may be due to misclassification of the timing sequence for diabetes onset and the FMP, as the two events likely occurred in close proximity to one another.

Exogenous Hormone Therapy and Diabetes Risk

For women who may be at an increased risk of diabetes due to surgical menopause, treatment with exogenous hormone therapy may be a reasonable treatment option to attenuate their risk profile as the results of a protective effect are encouraging. Data from both the Heart and Estrogen/progestin Replacement Study (HERS) and Women's Health Initiative (WHI) Hormone Trial, both large randomized controlled trials, showed a reduction in type 2 diabetes incidence associated with hormone therapy [72–74]. In the HERS study, women treated with 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate daily had a 35 % reduction in diabetes incidence versus women treated with placebo after 4 years of follow-up [72]. Similarly, the WHI trial which

utilized the same hormone therapy treatment as HERS found a 21 % reduction of incident diabetes after 5.6 years of follow-up [73]. Other RCTs [75] and observational longitudinal studies [76–78] further support a protective effect of HT on diabetes risk. A meta-analysis including data from 18 randomized controlled trials or crossover trials reported that postmenopausal hormone therapy was associated with a 30 % reduction in incident diabetes risk and reduced HOMA-IR, fasting glucose, and fasting insulin in diabetic and non-diabetic women [79]. These findings were repeated in a recent meta-analysis of articles published from 1997 to 2011; the pooled estimate suggested that postmenopausal use of combined estrogen replacement therapy reduced diabetes incidence by nearly 40 % and that women using estrogen replacement therapy had lower fasting plasma glucose and hemoglobin A1c [80••].

However, estrogen supplementation elevates postprandial glucose even as it suppresses fasting glucose. In the Postmenopausal Estrogen/Progestin Intervention Study, women randomized to estrogen had decreases in their fasting glucose and insulin levels while having increases in their postchallenge glucose and insulin levels [81]. The clinical implications of these postchallenge glucose elevations were unclear and suggest a differential effect on hepatic and peripheral insulin sensitivity. However, the majority of women in studies reporting a decreased risk of diabetes were diagnosed with the use of the fasting glucose. Thus, it is unclear whether the criteria used for diabetes diagnosis adequately captured postprandial glucose elevations. This is particularly an issue in aging women, who more commonly present with postchallenge glucose elevations than with fasting glucose elevations. More consideration of these potential differences is needed as the results from ongoing studies are being analyzed.

Due to concerns of increased risk for other chronic diseases including breast malignancy and thromboembolism, estrogen use is not currently recommended for diabetes prevention in postmenopausal women [82]. While estrogen is known to have insulin-sensitizing properties [83] and may improve insulin signaling and glucose transport, there is much to learn about the optimal treatment protocol, particularly the dosing and route of estrogen that would be most efficacious. Finally, it is well recognized that diabetes is a heterogeneous disorder, and affected individuals vary as to whether they have elevations in fasting glucose or postchallenge glucose. It is unclear whether the use of estrogen therapy would have different effects on these different populations of persons with diabetes. Confirmation of these potential differences should be a priority in future analyses of ongoing studies.

The so-called timing hypothesis regarding hormone therapy, whereby maximum benefit may be experienced with postmenopausal women who are treated within a certain time frame, has been suggested for cardiovascular health outcomes [84]. Now, a recently published small clinical study of the effectiveness of short-term treatment with transdermal E2 administration found that insulin-mediated glucose disposal rate was improved only among women in early menopause (≤6 years). In fact, glucose disposal rate worsened with E2 treatment among women in late menopause (≥10 years) [85••]. These findings highlight the importance of more careful consideration of HT as a treatment strategy for diabetes in mid-life women.

Conclusions

For women, the mid-life period, which coincides with the timing of the menopausal transition, is characterized by increasing levels of glucose and incidence of diabetes. The key characteristics of menopause, particularly decreases in estrogen and the presence of absence of bleeding, do not appear to have strong correlations with diabetes risk. However, the subtler changes in body composition that also occur during the transition may negatively influence glucose metabolism, as does the relative increase in androgenicity. Treatment with exogenous estrogen may decrease fasting glucose levels, and the application of this therapy to particular subpopulations with elevating fasting glucose levels should be explored. Finally, the interaction between diabetes and menopause on other comorbidities common in aging women, particularly cognitive function, cardiovascular conditions, and malignancy, has been infrequently examined. As the majority of women with diabetes are elderly and diagnosed during and after the menopausal transition, attention to the joint impact of these two extremely common conditions on other comorbidities is a critical public health priority.

Compliance with Ethical Standards

Conflict of Interest Carrie A. Karvonen-Gutierrez, Sung Kyun Park, and Catherine Kim declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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