Diabetes Ther (2019) 10:2313–2320
https://doi.org/10.1007/s13300-019-00695-y

BRIEF REPORT

Type 2 Diabetes Mellitus and Menopausal Hormone Therapy: An Update

Stavroula A. Paschou · Nikolaos Papanas

Received: August 7, 2019 / Published online: September 24, 2019

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.

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.9851339.

S. A. Paschou
Division of Endocrinology and Diabetes, "Aghia Sophia" Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

N. Papanas (✉)
Diabetes Centre, Second Department of Internal Medicine, University Hospital of Alexandroupolis, Medical School, Democritus University of Thrace, Alexandroupolis, Greece
e-mail: papanasnikos@yahoo.gr

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

[2–4, 20]. 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

Table 1 MHT: suggestions for use in women with T2DM

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

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Stavroula A. Paschou 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.

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.

REFERENCES

1. Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal hormone therapy and type 2 diabetes prevention: evidence, mechanisms, and clinical implications. Endocr Rev. 2017;38:173–88.

2. Paschou SA, Anagnostis P, Pavlou DI, Vryonidou A, Goulis DG, Lambrinoudaki I. Diabetes in menopause: risks and management. Curr Vasc Pharmacol. 2018. https://doi.org/10.2174/1570161116666180625124405 **(Epub ahead of print)**.

3. Szmuilowicz ED, Stuenkel CA, Seely EW. Influence of menopause on diabetes and diabetes risk. Nat Rev Endocrinol. 2009;5:553–8.

4. Paschou SA, Marina LV, Spartalis E, et al. Therapeutic strategies for type 2 diabetes mellitus in women after menopause. Maturitas. 2019;126:69–72.

5. Paschou SA, Anagnostis P, Goulis DG, Lambrinoudaki I. Diet and lifestyle for post-reproductive health: focus on diabetes. Case Rep Women's Health. 2018;18:e00056.

6. EMAS care on-line Section 7: hormone therapy in women with coexisting medical conditions. http://www.emas-online.org/guidelines/88/57/emas-care-online.html. Last Accessed 01 Aug 2019.

7. Slopien R, Wender-Ozegowska E, Rogowicz-Frontczak A, et al. Menopause and diabetes: EMAS clinical guide. Maturitas. 2018;117:6–10.

8. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2019;42(Suppl 1).

9. Lambrinoudaki I, Brincat M, Erel CT, et al. EMAS position statement: managing obese postmenopausal women. Maturitas. 2010;66:323–6.

10. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. JAMA. 2015;314:1021–9.

11. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol. 2009;54:2366–73.

12. Matthews KA, Gibson CJ, El Khoudary SR, Thurston RC. Changes in cardiovascular risk factors by hysterectomy status with and without oophorectomy: study of Women's Health Across the Nation. J Am Coll Cardiol. 2013;62:191–200.

13. Park SK, Harlow SD, Zheng H, Karvonen-Gutierrez C, Thurston RC, Ruppert K, et al. Association between changes in oestradiol and follicle-stimulating hormone levels during the menopausal transition and risk of diabetes. Diabet Med. 2017;34:531–8.

14. Brand JS, van der Schouw YT, Onland-Moret NC, et al. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. Diabetes Care. 2013;36:1012–9.

15. Shen L, Song L, Li H, et al. Association between earlier age at natural menopause and risk of diabetes in middle-aged and older Chinese women: the Dongfeng–Tongji cohort study. Diabetes Metab. 2017;43:345–50.

16. Malacara JM, Huerta R, Rivera B, Esparza S, Fajardo ME. Menopause in normal and uncomplicated NIDDM women: physical and emotional symptoms and hormone profile. Maturitas. 1997;28:35–45.

17. Appiah D, Winters SJ, Hornung CA. Bilateral oophorectomy and the risk of incident diabetes in postmenopausal women. Diabetes Care. 2014;37:725–33.

18. Anagnostis P, Christou K, Artzouchaltzi AM, et al. Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. Eur J Endocrinol. 2019;180:41–50.

19. LeBlanc ES, Kapphahn K, Hedlin H, et al. Reproductive history and risk of type 2 diabetes mellitus in postmenopausal women: findings from the Women's health initiative. Menopause. 2017;24:64–72.

20. Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab. 2003;88:2404–11.

21. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clin Nutr. 1992;55:950–4.

22. Svendsen OL, Hassager C, Christiansen C. Age- and menopause associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. Metabolism. 1995;44:369–70.

23. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Disord. 2000;24:226–31.

24. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab. 2009;94:1104–10.

25. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes. 2008;32:949–58.

26. Rogers NH, Perfield JW 2nd, Strissel KJ, Obin MS, Greenberg AS. Reduced energy expenditure and increased inflammation are early events in the development of ovariectomy-induced obesity. Endocrinology. 2009;150:2161–8.

27. Heine PA, Taylor JA, Iwamoto GA, Lubahn DB, Cooke PS. Increased adipose tissue in male and female estrogen receptor-alpha knockout mice. Proc Natl Acad Sci USA. 2000;97:12729–34.

28. Xu Y, Nedungadi TP, Zhu L, et al. Distinct hypothalamic neurons mediate estrogenic effects

on energy homeostasis and reproduction. Cell Metab. 2011;14:453–65.

29. Martinez de Morentin PB, González-García I, et al. Estradiol regulates brown adipose tissue thermogenesis via hypothalamic AMPK. Cell Metab. 2014;20:41–53.

30. Saito K, He Y, Yang Y, et al. PI3K in the ventromedial hypothalamic nucleus mediates estrogenic actions on energy expenditure in female mice. Sci Rep. 2016;6:23459.

31. Paschou SA, Anagnostis P, Goulis DG, Lambrinoudaki I. Androgen excess and post-reproductive health. Maturitas. 2018;115:115–6.

32. Lindheim SR, Buchanan TA, Duffy DM, et al. Comparison of estimates of insulin sensitivity in pre- and postmenopausal women using the insulin tolerance test and the frequently sampled intravenous glucose tolerance test. J Soc Gynecol Investig. 1994;1:150–4.

33. Walton C, Godsland IF, Proudler AJ, Wynn V, Stevenson JC. The effects of the menopause on insulin sensitivity, secretion and elimination in non-obese, healthy women. Eur J Clin Invest. 1993;23:466–73.

34. Toth MJ, Sites CK, Eltabbakh GH, Poehlman ET. Effect of menopausal status on insulin-stimulated glucose disposal: comparison of middle-aged premenopausal and early postmenopausal women. Diabetes Care. 2000;23:801–6.

35. Riant E, Waget A, Cogo H, Arnal JF, Burcelin R, Gourdy P. Estrogens protect against high-fat diet-induced insulin resistance and glucose intolerance in mice. Endocrinology. 2009;150:2109–17.

36. Alonso A, Gonzalez-Pardo H, Garrido P, et al. Acute effects of 17 beta-estradiol and genistein on insulin sensitivity and spatial memory in aged ovariectomized female rats. Age (Dordr). 2010;32:421–34.

37. Zhu L, Brown WC, Cai Q, et al. Estrogen treatment after ovariectomy protects against fatty liver and may improve pathway-selective insulin resistance. Diabetes. 2013;62:424–34.

38. Kim JH, Meyers MS, Khuder SS, et al. Tissue-selective estrogen complexes with bazedoxifene prevent metabolic dysfunction in female mice. Mol Metab. 2014;3:177–90.

39. Ribas V, Nguyen MT, Henstridge DC, et al. Impaired oxidative metabolism and inflammation are associated with insulin resistance in ER{alpha} deficient mice. Am J Physiol Endocrinol Metab. 2010;298:E304–19.

40. Bryzgalova G, Gao H, Ahren B, et al. Evidence that oestrogen receptor-alpha plays an important role in the regulation of glucose homeostasis in mice: insulin sensitivity in the liver. Diabetologia. 2006;49:588–97.

41. Ribas V, Drew BG, Zhou Z, et al. Skeletal muscle action of estrogen receptor alpha is critical for the maintenance of mitochondrial function and metabolic homeostasis in females. Sci Transl Med. 2016;8:334ra334.

42. Ribas V, Drew BG, Le JA, et al. Myeloid-specific estrogen receptor alpha deficiency impairs metabolic homeostasis and accelerates atherosclerotic lesion development. Proc Natl Acad Sci USA. 2011;108:16457–62.

43. Davis KE, Neinast M, Sun K, et al. The sexually dimorphic role of adipose and adipocyte estrogen receptors in modulating adipose tissue expansion, inflammation, and fibrosis. Mol Metab. 2013;2:227–42.

44. Tiano JP, Mauvais-Jarvis F. Importance of oestrogen receptors to preserve functional beta-cell mass in diabetes. Nat Rev Endocrinol. 2012;8:342–51.

45. Mauvais-Jarvis F. Role of sex steroids in β cell function, growth, and survival. Trends Endocrinol Metab. 2016;27:844–55.

46. Kahn SE, Andrikopoulos S, Verchere CB, Wang F, Hull RL, Vidal J. Oophorectomy promotes islet amyloid formation in a transgenic mouse model of Type II diabetes. Diabetologia. 2000;43:1309–12.

47. Le May C, Chu K, Hu M, et al. Estrogens protect pancreatic beta-cells from apoptosis and prevent insulin-deficient diabetes mellitus in mice. Proc Natl Acad Sci USA. 2006;103:9232–7.

48. Gray KE, Katon JG, LeBlanc ES, et al. Vasomotor symptom characteristics: are they risk factors for incident diabetes? Menopause. 2018;25:520–30.

49. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. Circulation. 2011;123:1243–62.

50. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab. 2006;8:538–54.

51. Espeland MA, Hogan PE, Fineberg SE, et al. Effect of postmenopausal hormone therapy on glucose and

insulin concentrations. Diabetes Care. 1998;21:1589–95.

52. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo controlled trial. Ann Intern Med. 2003;138:1–9.

53. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's health initiative hormone trial. Diabetologia. 2004;47:1175–87.

54. Anagnostis P, Galanis P, Chatzistergiou V, et al. The effect of hormone replacement therapy and tibolone on lipoprotein (a) concentrations in postmenopausal women: a systematic review and meta-analysis. Maturitas. 2017;99:27–36.

55. Manson JE, Rimm EB, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin-dependent diabetes mellitus. Ann Epidemiol. 1992;2:665–73.

56. de Lauzon-Guillain B, Fournier A, Fabre A, et al. Menopausal hormone therapy and new-onset diabetes in the French Etude Epidemiologique de Femmes de la Mutuelle Generale de l'Education Nationale (E3N) cohort. Diabetologia. 2009;52:2092–100.

57. Duncan AC, Lyall H, Roberts RN, et al. The effect of estradiol and a combined estradiol/progestagen preparation on insulin sensitivity in healthy postmenopausal women. J Clin Endocrinol Metab. 1999;84:2402–7.

58. Mattiasson I, Rendell M, Tornquist C, Jeppsson S, Hulthen UL. Effects of estrogen replacement therapy on abdominal fat compartments as related to glucose and lipid metabolism in early postmenopausal women. Horm Metab Res. 2002;34:583–8.

59. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med. 1991;325:1196–204.

60. Elkik F, Gompel A, Mercier-Bodard C, et al. Effects of percutaneous estradiol and conjugated estrogens on the level of plasma proteins and triglycerides in postmenopausal women. Am J Obstet Gynecol. 1982;143:888–92.

61. Cefalu WT, Wagner JD, Bell-Farrow AD, et al. The effects of hormonal replacement therapy on insulin sensitivity in surgically postmenopausal cynomolgus monkeys (Macaca fascicularis). Am J Obstet Gynecol. 1994;171:440–5.

62. Godsland IF, Gangar K, Walton C, et al. Insulin resistance, secretion, and elimination in postmenopausal women receiving oral or transdermal hormone replacement therapy. Metabolism. 1993;42:846–53.

63. Kimmerle R, Heinemann L, Heise T, et al. Influence of continuous combined estradiol-norethisterone acetate preparations on insulin sensitivity in postmenopausal nondiabetic women. Menopause. 1999;6:36–42.

64. Spencer CP, Godsland IF, Cooper AJ, Ross D, Whitehead MI, Stevenson JC. Effects of oral and transdermal 17beta-estradiol with cyclical oral norethindrone acetate on insulin sensitivity, secretion, and elimination in postmenopausal women. Metabolism. 2000;49:742–7.

65. De Cleyn K, Buytaert P, Coppens M. Carbohydrate metabolism during hormonal substitution therapy. Maturitas. 1989;11:235–42.

66. Crook D, Godsland IF, Hull J, Stevenson JC. Hormone replacement therapy with dydrogesterone and 17 beta-oestradiol: effects on serum lipoproteins and glucose tolerance during 24 month follow up. Br J Obstet Gynaecol. 1997;104:298–304.

67. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100:3975–4011.