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Body Fat distribution, Menopausal Hormone Therapy and Incident Type 2 Diabetes in Postmenopausal Women of the MESA Study

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Abstract

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Contributors

IAE proposed the study, researched data, and wrote and revised the manuscript.

KEW contributed to data interpretation and discussion, and reviewed, edited and approved the final version of the manuscript.

KGH contributed to data interpretation and discussion, and reviewed, edited and approved the final version of the manuscript.

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AGB contributed to data interpretation and discussion, and reviewed, edited and approved the final version of the manuscript.

Ethical approval

MESA's protocol was approved by the institutional review board at participating centers and informed consent was obtained from all participants.

Provenance and peer review

This article has undergone peer review.

Conflict of interest

The authors declare no conflicts of interest.

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Objectives—We investigated the association between menopausal hormone therapy (MHT) and incident type 2 diabetes in postmenopausal women, and explored the potential modifying role of body fat distribution on this association.

Methods—We included 2210 postmenopausal women without prevalent diabetes at recruitment (2000-2002) from the Multiethnic Study of Atherosclerosis. Cox proportional hazards models were used to examine associations of MHT and MHT types with incident diabetes, testing for variation according to body fat distribution.

Results—Over a median follow-up of 11.1 years, there were 226 incident cases of diabetes. There were no significant interactions with central or generalized body fatness. In fully adjusted models, current and past MHT use was associated with a greater risk of incident diabetes [HR: 1.66 (1.18-2.35) and 1.60 (1.11-2.30) respectively]. Estrogen only (ET) and combined progestin and estrogen (PET) formulations were similarly associated with a greater risk of incident diabetes [HR: 1.52 (1.03-2.24) and 1.77 (1.15-2.72) respectively].

Conclusions—In our observational study of middle-aged and older, non-diabetic postmenopausal women, a current or past use of MHT was independently associated with a greater risk of incident diabetes. ET and PET are associated with similar risks of incident diabetes in postmenopausal women. The association of MHT use with incident diabetes is the same irrespective of body mass index (BMI) or waist circumference.

Keywords

Body Fat; Menopausal Hormone Therapy; Diabetes

1. Introduction

Glucose abnormalities are common in the postmenopausal period, but, it is unclear whether or not menopause has a strong role on the risk of developing type 2 diabetes.[1, 2] The association of menopausal hormone therapy (MHT) with insulin sensitivity is also controversial and prior studies have produced inconsistent results.[2, 3] Some studies have suggested that the changes in blood glucose that occur after menopause are due to increases in body fat.[1] Fat deposition increases during the menopausal transition and persists into the postmenopausal period.[4-7] The effects of MHT on body composition after menopause are variable, but, most randomized controlled trials have shown a reduction in weight gain and central body fatness with its use.[3, 5]

Excessive body fat is associated with an increased incidence of diabetes.[8] Because MHT has been associated with reductions in central body fatness, we hypothesized that MHT is associated with a decreased risk of incident type 2 diabetes in postmenopausal women but this association would vary by body fat distribution, and would be greater in women with central body fatness. There are different formulations of MHT with some comprising of estrogen only (ET), while others consist of combined progestin and estrogen (PET). The addition of progestin to estrogen could result in a decrease in insulin sensitivity.[3] We also hypothesized that the association of MHT with a decreased risk of incident type 2 diabetes in postmenopausal women is greater in women who used or are using ET when compared to those who used or are using PET.

2. Research Design and Methods

2.1 Study population

MESA is a population-based study that included 6814 participants, aged 45-84 years without known cardiovascular disease (CVD) at recruitment (2000-2002). Fifty-three percent were women. Whites comprised 38% of the cohort, African-Americans 28%, Chinese-American 12% and Hispanics 22%. Participants were recruited from six regions in the US. The design and objectives of the MESA study have been reported.[9] MESA's protocol was approved by the institutional review board at participating centers and informed consent was obtained from all participants.[9]

2.2. Sample selection

Women were considered postmenopausal if they were older than 55 years of age or had undergone a bilateral oophorectomy and/or self-reported being postmenopausal or absence of menstrual periods in the preceding year. Of 3077 postmenopausal women, we sequentially excluded 377 women who had prevalent diabetes at baseline, 64 women with missing information on MHT use, 28 underweight women with body mass index (BMI) less than 18.5 kg/m², 291 women who reported extremes of daily caloric intake (less than 500 or greater than 4500 kilocalories) and 23 women with missing information on incident diabetes. We also excluded 84 women who had hysterectomy and were younger than 55 years of age, but self-reported being postmenopausal without bilateral oophorectomy. Our analytical sample comprised 2210 women.

2.3. Baseline Measurements

Standardized questionnaires were used to collect information on menopause, menstrual periods, ethnicity, educational status, cigarette smoking, number of live births, hypertension, diabetes, oophorectomy, hysterectomy, MHT including type of MHT and other medication use. There was no data on the route or dosage of MHT therapy. A woman was classified as a current, past or non user of MHT. Women were considered to be grand multiparous if they had given birth 5 or more times. BMI was calculated as weight divided by the square of height (kg/m²) and used to indicate generalized body fatness. Women were categorized as normal weight (BMI <25 kg/m²), overweight (BMI: 25-29.9 kg/m²) or obese (BMI > 30 kg/m²). Waist circumference (WC) was measured with a measuring tape at the umbilicus. Central body fatness was defined as WC greater than 88 cm.[10] Three measurements of resting blood pressure (BP) were obtained and the average of the second and third reading was used. Fasting plasma triglyceride and high density lipoprotein-cholesterol (HDL-C) were measured by a glycerol-blanked enzymatic method and cholesterol-oxidase reaction respectively.[11] Interleukin-6 was measured using an ultrasensitive enzyme-linked immunosorbent assay.[12] Fasting serum glucose and insulin were measured by an adaptation of the glucose-oxidase and radioimmunoassay methods respectively.[13] Insulin resistance (indicated by homeostasis model assessment, HOMA-IR) was calculated as fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5.[13]

2.4. Follow Up and Incident Diabetes Definition

The median follow-up was 11.1 years (interquartile range, 10.5-11.7 years) with a total of 21,985 person-years of observation. The study end-point was incident type 2 diabetes, defined as fasting glucose ≥ 126 mg/dl or use of insulin or oral hypoglycemic medications. The date of incident type 2 diabetes was defined as the first in-person follow-up exam in which a participant met the criteria for diabetes.[13] In-person exams were conducted in 2000-2002 (exam 1), 2002-2004 (exam 2), 2004-2005 (exam 3), 2005-2007 (exam 4) and 2010-2011 (exam 5). Follow-up time was calculated as the difference between the dates of the first examination and when diabetes was first identified in cases or between the dates of the first examination and time of last participant contact in non cases. Women were considered censored if they were lost to follow-up or failed to experience incident diabetes at the end of follow-up. Details of quality control measures that were conducted at the coordinating center, field centers and laboratories are available in the manual of operations at www.mesa-nhlbi.org.

2.5. Statistical Analysis

We calculated the incidence rates of type 2 diabetes per 1000 person-years of exposure in each MHT group. Data are presented according to (i) incident diabetes and (ii) MHT groups using means $\pm$ SD and percentages as appropriate. Logarithmic transformation was done for skewed variables. Comparisons were tested between (i) incident diabetes and (ii) MHT groups using Chi-square, student's T-test and one way ANOVA as appropriate. Using Cox proportional hazard models, we calculated the hazard ratios of incident type 2 diabetes for current and past users of MHT, using women with no prior use as reference. We sequentially adjusted for confounders and known risk factors for diabetes including smoking.[14] We initially constructed unadjusted models (model 1). Next, we adjusted for age and ethnicity (model 2). Model 3 included model 2 plus educational status, current cigarette smoking, intentional exercise, years since menopause and center. Model 4 consisted of model 3 plus central body fatness, systolic BP, antihypertensive medication use, triglyceride, HDL-C, statin use and interleukin-6. Model 5 included model 4 and HOMA-IR. We tested for the presence of multiplicative interactions using product terms between central body fatness and MHT use. We performed sensitivity analysis that replaced central with generalized body fatness. Interaction was determined when the multiplicative term was statistically significant at $p < 0.05$. In exploration, we calculated the hazard ratios of incident type 2 diabetes associated with ET and PET, using women with no prior MHT use as reference. We checked for proportionality of hazards by visually examining the log-log plots. Participants with missing data on a variable needed for a particular model were excluded from analyses. The percentage of missing data was $< 3\%$ for all variables, therefore, sample sizes may have varied slightly between the models. 2-sided p-values of < 0.05 were considered significant. Statistical analysis was performed using SAS enterprise guide version 5.1. (SAS Institute Inc, Cary, NC).

3. Results

Our study sample of 2210 women included 751 current users, 423 past users and 1036 non users of MHT. The average menopausal age was 47.9 ± 6.4 years for the entire cohort, and

48.6 $\pm$ 5.8 years and 44.6 $\pm$ 7.5 years for women with and without natural menopause respectively. We observed 226 cases of incident type 2 diabetes (79 in current users, 49 in past users and 98 in never users of MHT). The overall incidence of type 2 diabetes was 10.3/1000 person years, with incidence densities of 10.2/1000 person years, 11.7/1000 person years and 9.7/1000 person years in current users, past users and non users of MHT, respectively. Baseline characteristics of participants are presented according to incident diabetes status (table 1). Women who developed incident diabetes were younger and had a shorter duration of MHT use than those who did not. Baseline characteristics of participants are also presented according to MHT use (supplemental table). Current users of MHT were younger, more educated and less likely to be obese than past or non users. HDL-C and triglyceride levels were greater while interleukin-6 and HOMA-IR was lower in current users when compared to past and non users of MHT.

There were 193 and 33 events in women with and without central body fatness respectively. There were 34, 87 and 105 events in normal weight, overweight and obese women respectively. We did not stratify our results by central or generalized body fatness because the interaction terms of current and past MHT use with both central and generalized body fatness were not statistically significant (p for interaction, 0.19-0.92). The interaction terms of current and past MHT use with both age and years since menopause were also not statistically significant (p for interaction, 0.19-0.37). There was inadequate power for ethnic-specific analysis which was not prespecified for this study.

When compared with non users, both current and past MHT use was associated with greater hazards of incident type 2 diabetes in fully adjusted models (Table 2). Our estimates did not vary much when we replaced central with generalized body fatness (hazard ratios, 1.69 [1.20-2.39] and 1.62 [1.12-2.34]) for current and past users of HRT respectively. In exploratory analyses involving 1780 women with information on MHT type, we found that the risk of incident type 2 diabetes were similarly increased in women who had used (or were using) ET or PET when compared to non users of MHT (table 3). The estimates also appeared similar when we replaced central with generalized body fatness, with hazard ratios of 1.54 (1.04-2.27) and 1.81 (1.18-2.79) for women who had used (or were using) ET or PET respectively.

4. Discussion

In our retrospective observational study involving a multi-ethnic cohort of middle-aged and older, non-diabetic postmenopausal women, we have shown that a current or past use of MHT (either ET or PET) is independently associated with greater risks of incident type 2 diabetes. This association was the same irrespective of body fat distribution. The results from this study do not support our original study hypothesis but are consistent with findings reported by Ryan et al [15] in which greater insulin resistance was seen in postmenopausal women who were using MHT when compared to those who were not.

Past studies linking MHT use to incident type 2 diabetes have produced conflicting results. In randomized clinical trials like the Womens Health Initiative (WHI) [16], and the Heart and estrogen/Progestin Replacement Study [17], MHT use was associated with a reduced

incidence of type 2 diabetes in postmenopausal women without and with coronary disease respectively. In the Rancho Bernardo Heart and Chronic Disease Study, the trend towards a reduced incidence of type 2 diabetes with MHT use was reversed after adjusting for age, body weight and behavioral factors.[18] Gabal et al. suggested that the reduced risk of incident type 2 diabetes seen with MHT use in previous studies may have resulted from selection bias (unlikely in clinical trials) relating to MHT prescription, confounding factors or differential efforts in diabetes diagnosis.[18] In the Strong Heart Study, a longer duration of current MHT use was associated with an increased risk of type 2 diabetes in postmenopausal women of American Indian origin.[19] Although current use of MHT was associated with a reduced risk of incident type 2 diabetes in postmenopausal women of the Nurses' Health Study, the dose or duration of use was not related to diabetes incidence.[20]. In support of Gabal's theory of selection bias, current users of MHT in our study had more favorable metabolic profiles at baseline. We adjusted for more diabetes risk factors than were accounted for in previous studies and the risk of incident diabetes became greater for current and past MHT users after we accounted for these factors. There were no differences in the duration of MHT use across incident diabetes groups, therefore, duration of use was not included in our models.

The increased CVD risks associated with MHT use in the initial reports from the WHI investigators in 2002 [21] led to abrupt discontinuation of MHT among many postmenopausal women. It is conceivable that our study participants who were enrolled between 2000-2002 and using MHT at baseline may have stopped using MHT during follow up. However, we expected that discontinuation of MHT would likely bias our findings towards the null. Disparities in compliance and early discontinuation of MHT during follow up could account for differences reported amongst various studies. Subsequent reports from WHI which focused on age groups and timing from menopause have suggested that the increased CVD risks associated with MHT are applicable to older postmenopausal women who are greater than ten years into the postmenopausal period.[21] This concept of age effects and timing from menopause could also apply to diabetes risk. This was illustrated by Pereira et al.[22] in a randomized, crossover, placebo-controlled study. In that study, the actions of transdermal estradiol on glucose disposal was dependent on the time from menopause with apparent benefits early (6 years) and harm later (10 years) from menopause.[22] In our study, age and years since menopause were confounders but not effect modifiers of the association between MHT use and incident diabetes.

Our study differs from WHI in several ways. We utilized a multiethnic population consisting of middle-aged and older participants over a longer duration of follow-up. Participants in WHI on the other hand were mostly white, aged 50-79 years with an average follow-up of only 5.6 years. In the extended post intervention phase of WHI lasting 8.2 years, there were no differences in the incidence of diabetes amongst users and non users of MHT.[23] This would support the concept of timing as contributing to the differences between our study findings and those of WHI. WHI was a randomized trial with detailed information on types, routes and dosage of MHT. A disadvantage of clinical trials is that external validity tends to be lower [24] than observational studies.

MHT use attenuates the weight gain that is associated with the onset of menopause.[3, 5] Current MHT users were less likely to have central or generalized body fatness when compared to past and non users in our study. Our associations were independent of both central and generalized body fatness, thus, we concur with studies that have suggested that body fat does not account for the differences in insulin sensitivity between users and non users of MHT.[15, 25] We failed to demonstrate differences in our associations according to the presence or absence of central or generalized body fatness. Thus, we concluded that our associations were the same irrespective of body fat distribution.

Different formulations of MHT could have varying effects on glucose regulation [3] and insulin sensitivity.[25] Some studies have reported beneficial effects of ET on insulin sensitivity which is attenuated by the addition of progestin to estrogen.[3, 25, 26] In other studies, neither use of ET or PET was associated with an increased risk of diabetes.[20] In our study the risk of developing diabetes was similarly increased with ET or PET use. This finding did not support our a priori hypothesis. The mechanism by which estrogen could influence diabetes risk is not fully understood [19] because of its conflicting effects on glucose metabolism.[27] Short term effects are mostly diabetogenic and include suppression of insulin secretion, induction of insulin resistance, deterioration in glucose tolerance and glucagon antagonism.[19, 27] Longer term effects involve regulation of the pancreatic insulin response to glucose.[27] Estrogen exerts direct effects on the pancreas by binding to estrogen receptors and increasing progesterone receptor binding or indirectly by causing elevations in insulin antagonistic hormones such as growth hormones, glucocorticoids or catecholamines and affecting intestinal absorption of glucose.[17, 19, 20, 27]

Our study has numerous strengths. This is the first study to concurrently explore the potential modifying role of central and generalized body fatness on the association between MHT use and incident type 2 diabetes in postmenopausal women. MESA has a multiethnic population and data collection methods were highly standardized. The prospective study design allowed us to measure incident type 2 diabetes. We also acknowledge limitations. The postmenopausal state was determined by self report and hormonal levels were not measured. As in any observational study, our findings may have resulted from residual confounding due to unknown or unmeasured risk factors. We used baseline records of MHT use but participants may have stopped or started using MHT during follow up. Our analysis did not account for changes in body fat distribution during follow up. The route of MHT use could affect glucose regulation.[3] We had no information on routes and dosages of MHT and were unable to determine how these factors affected our study findings. We were limited by inadequate power for ethnic-specific analysis. We used single measurements of blood glucose and hemoglobin A1C was not measured or included in our definitions for incident diabetes. Our definition of incident diabetes included use of oral hypoglycemic medications which could also be used to treat prediabetes. We had inadequate power to perform separate analysis according to type of menopause (natural or surgical) particularly amongst current users where menopause resulted from surgical causes in 34% of women.

4.1. Conclusion

In our observational study involving a multiethnic cohort of middle-aged and older, non-diabetic, postmenopausal women, a current or past use of MHT is independently associated with greater risks of developing incident type 2 diabetes. The association of MHT use with incident type 2 diabetes is the same irrespective of body fat distribution. Both ET and PET are associated with similar risks of incident type 2 diabetes in postmenopausal women. Our findings which favor more regular monitoring for incident type 2 diabetes in postmenopausal women using MHT needs further evaluation in other cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Chae CU, Derby CA. The Menopausal Transition and Cardiovascular Risk. *Obstet Gynecol Clin N Am.* 2011; 38:477–88.
2. Szmuiłowicz ED, Stuenkel CA, Seely EW. Influence of menopause on diabetes and diabetes risk. *Nat Rev Endocrinol.* 2009; 5:553–8. [PubMed: 19687788]
3. Bruns CM, Kemnitz JW. Sex Hormones, Insulin Sensitivity, and Diabetes Mellitus. *ILAR J.* 2004; 45:160–169. [PubMed: 15111735]
4. Espeland MA, Stefanick ML, Kritz-Silverstein D, Fineberg SE, Waclawiw MA, James MK, et al. Effect of Postmenopausal Hormone Therapy on Body Weight and Waist and Hip Girths. *J Clin Endocrinol Metab.* 1997; 82:1549–56. [PubMed: 9141548]
5. Davis SR, Castelo-Branco C, Chedraui P, Lumsden MA, Nappi RE, Shah D, et al. Understanding weight gain at menopause. *Climateric.* 2012; 15:419–29.
6. Abdunour J, Doucet E, Brochu M, Lavoie JM, Strychar I, Rabasa-Lhoret R, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa new emerging team group study. *Menopause.* 2012; 19:760–7. [PubMed: 22395454]
7. Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Weber MH, et al. Adipokines, Inflammation, and Visceral Adiposity across the Menopausal Transition: A prospective Study. *J Clin Endocrinol Metab.* 2009; 94:1104–10. [PubMed: 19126626]
8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart Disease and Stroke Statistics--2014 Update: A Report From the American Heart Association. *Circulation.* 2014; 129:e28–e292. [PubMed: 24352519]
9. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. *Am J Epidemiol.* 2002; 156:871–81. [PubMed: 12397006]
10. Lean MEJ, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ.* 1995; 311:158–61. [PubMed: 7613427]
11. Paramsothy P, Knopp RH, Bertoni AG, Blumenthal RS, Wasserman BA, Tsai MY, et al. Association of Combinations of Lipid Parameters With Carotid Intima-Media Thickness and

- Coronary Artery Calcium in the MESA (Multi-Ethnic Study of Atherosclerosis). *J AM Coll Cardiol*. 2010; 56:1034–41. [PubMed: 20846602]
12. Lakoski S, Cushman M, Siscovick DS, Blumenthal RS, Palmas W, Burke G, et al. The relationship between inflammation, obesity and risk for hypertension in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Hum Hypertens*. 2011; 25:73–9. [PubMed: 20944659]
 13. Mackey RH, Mora S, Bertoni AG, Wassel CL, Carnethon MR, Sibley CT, et al. Lipoprotein particles and Incident Type 2 Diabetes in the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care*. 2015; 38:628–36. [PubMed: 25592196]
 14. Xie, X-t; Liu, Q.; Wu, J.; Wakui, M. Impact of cigarette smoking in type 2 diabetes development. *Acta Pharmacol Sin*. 2009; 30:784–7. [PubMed: 19434055]
 15. Ryan AS, Nicklas BJ, Berman DM. Hormone Replacement Therapy, Insulin Sensitivity, and Abdominal Obesity in Postmenopausal Women. *Diabetes Care*. 2002; 25:127–33. [PubMed: 11772913]
 16. Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, 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. [PubMed: 15252707]
 17. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, 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. [PubMed: 12513038]
 18. Gabal LL, Goodman-Gruen D, Barrett-Connor E. The Effect of Postmenopausal Estrogen Therapy on the Risk of Non-Insulin-Dependent Diabetes Mellitus. *Am J Public Health*. 1997; 87:443–5. [PubMed: 9096551]
 19. Zhang Y, Howard BV, Cowan LD, Yeh J, Schafer CF, Wild RA, et al. The Effect of Estrogen Use on Levels of Glucose and Insulin and the Risk of Type 2 Diabetes in American Indian Postmenopausal Women: the Strong Heart Study. *Diabetes Care*. 2002; 25:500–4. [PubMed: 11874937]
 20. Manson JE, Rimm EB, Colditz GA, Willett WC, Nathan DM, Arky RA, et al. A Prospective Study of Postmenopausal Estrogen Therapy and Subsequent Incidence of Non-Insulin-Dependent Diabetes Mellitus. *Ann Epidemiol*. 1992; 2:665–73. [PubMed: 1342318]
 21. Genazzani AR, Gambacciani M, Simoncini T. The latest elaboration of the Women's Health Initiative data on hormonal replacement therapy and cardiovascular disease in postmenopausal women. *Gynecol Endocrinol*. 2007; 23:183–5. [PubMed: 17505935]
 22. Pereira RI, Casey BA, Swibas TA, Erickson CB, Wolfe P, Van Pelt RE. Timing of Estradiol Treatment After Menopause May Determine Benefit or Harm to Insulin Action. *J Clin Endocrinol Metab*. 2015; 100:4456–62. [PubMed: 26425886]
 23. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal Hormone therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative randomized Trials. *JAMA*. 2013; 310:1353–68. [PubMed: 24084921]
 24. Rothwell PM. Factors That Can Affect the External Validity of Randomised Controlled Trials. *PLoS Clin Trial*. 2006; 1:e9.
 25. Brown MD, Korytkowski MT, Zmuda JM, McCole SD, Moore GE, Hagberg JM. Insulin Sensitivity in Postmenopausal Women. *Diabetes Care*. 2000; 23:1731–6. [PubMed: 11128342]
 26. Spencer CP, Godsland IF, Cooper AJ, R D, Whitehead MI, Stevenson JC. Effects of Oral and Transdermal 17b-Estradiol With Cyclical Oral Norethindrone Acetate on Insulin Sensitivity, Secretion and Elimination in Postmenopausal Women. *Metabolism*. 2000; 49:742–7. [PubMed: 10877199]
 27. Godsland IF. Oestrogens and Insulin Secretion. *Diabetologia*. 2005; 48:2213–20. [PubMed: 16193292]

Highlights

- A current or past use of menopausal hormone therapy is independently associated with a greater risk of incident diabetes.
- Estrogen only or combined progestogen and estrogen therapy is associated with similar risks of incident diabetes in postmenopausal women.
- The association of the use of menopausal hormone therapy with incident diabetes is the same irrespective of body fat distribution.

Table 1

Baseline characteristics of postmenopausal MESA women according to incident type 2 diabetes at the end of follow up

Characteristics	Incident diabetes present n=226	Incident diabetes absent n=1984	<i>p</i>
Age, years	62.8 (8.7)	65.2 (9.1)	<0.001
Ethnicity, %			<0.001
White	30.5	44.2	
Chinese American	15.5	11.4	
African American	27.4	25.5	
Hispanic	26.6	19.0	
More than high school, %	50.4	58.9	0.01
Current cigarette smoking, %	7.5	10.6	0.14
Years since menopause	15.3 (10.9)	17.4 (11.0)	0.007
Intentional exercise, %			0.008
105.0 Met-minutes/week	31.9	25.6	
105.0 - 735.0 Met-minutes/week	31.0	25.2	
735.0 - 1800.0 Met-minutes/week	18.1	23.8	
> 1800.0 Met-minutes/week	19.0	25.5	
Central body fatness, %	85.4	67.3	<0.001
Generalized body fatness, %			<0.001
Normal weight, kg/m ²	15.0	34.1	
Overweight, kg/m ²	38.5	36.3	
Obesity kg/m ²	46.5	29.5	
High density lipoprotein cholesterol, mg/dl	52.1 (13.0)	58.4 (15.7)	<0.001
Triglyceride *, mg/dl	133.9 (1.7)	110.1 (1.6)	<0.001
Interleukin-6 *, pg/ml	1.5 (1.9)	1.2 (1.9)	<0.001
HOMA-IR *	2.7 (1.8)	1.7 (1.7)	<0.001
Systolic blood pressure, mm hg	131.0 (22.3)	128.4 (23.3)	0.100
Antihypertensive medication use, %	48.2	37.5	0.002
Use of statins, %	21.8	14.3	0.003
Menopausal hormone therapy (MHT), %			0.45
Never used MHT	43.4	47.3	
Past use of MHT	21.7	18.9	
Current use of MHT	35.0	33.9	
Natural menopause, %	81.9	80.2	0.55
Duration of MHT use	4.3 (6.8)	4.8 (8.2)	0.33

Values are expressed as means (SD) unless otherwise indicated; missing values were less than 3%; *p*-values were determined using chi-squared and students T-test. Central body fatness was present if waist circumference was greater than 88 cm.

* Values are geometric mean of triglyceride, interleukin-6 and HOMA-IR.

Abbreviations: HOMA-IR, homeostasis model assessment for insulin resistance.

Table 2

Associations of menopausal hormone therapy with incident type 2 diabetes in postmenopausal MESA women

	Menopausal hormone therapy use		
	Current Users	Past Users	Non Users (referent)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	1.06 (0.79-1.42)	1.22 (0.86-1.71)	1.00
Model 2	1.17 (0.86-1.60)	1.32 (0.93-1.86)	1.00
Model 3	1.23 (0.89-1.69)	1.37 (0.96-1.94)	1.00
Model 4	1.43 (1.01-2.01)	1.55 (1.08-2.23)	1.00
Model 5	1.66 (1.18-2.35)	1.60 (1.11-2.30)	1.00

Model 1: Unadjusted

Model 2: Model 1 plus age and ethnicity

Model 3: Model 2 plus educational status, current cigarette smoking, intentional exercise, years since menopause and center

Model 4: Model 3 plus central body fatness, systolic blood pressure, antihypertensive medication use, high density lipoprotein cholesterol, triglyceride, use of statins and interleukin-6

Model 5: Model 4 plus HOMA-IR

Missing values were less than 3% for all variables.

Table 3

Associations of menopausal hormone therapy types with incident type 2 diabetes in postmenopausal MESA women

	Menopausal hormone therapy type		
	Estrogen Use only [*]	Estrogen + Progesterone Use [†]	Never Used (referent)
Model 1	1.06 (0.74-1.50)	1.18 (0.80-1.75)	1.00
Model 2	1.23 (0.86-1.76)	1.43 (0.95-2.15)	1.00
Model 3	1.28 (0.88-1.86)	1.46 (0.97-2.22)	1.00
Model 4	1.46 (0.98-2.16)	1.69 (1.10-2.58)	1.00
Model 5	1.52(1.03-2.24)	1.77 (1.15-2.72)	1.00

Model 1: Unadjusted

Model 2: Model 1 plus age and ethnicity

Model 3: Model 2 plus educational status, current cigarette smoking, intentional exercise, years since menopause and center

Model 4: Model 3 plus central body fatness, systolic blood pressure, antihypertensive medication use, high density lipoprotein cholesterol, triglyceride, use of statin and interleukin-6

Model 5: Model 4 plus HOMA-IR

Missing values were less than 3% for all variables.

^{*} Indicates current and past use of estrogen,

[†] indicates current and past use of progesterone and estrogen.