Leading Article

Menopause and hormone therapy on risk of diabetes

Gooneratne MDP

Corresponding Author - *MDP Gooneratne (MBBS, FRCOG , FSLCOG),*
Consultant Obstetrician & Gynaecologist

Email - mdpg41@hotmail.com

Introduction

Prevalence of diabetes is increasing globally and specially in South Asia causing a major health problem and has reached epidemic proportions[1]. With demographic changes in Asian countries population of peri and postmenopausal women too is on the rise. In Sri Lanka, about 25% of women are around 50 years of age or above. There are many gender differences in relation to mortality and complications of diabetes[2]. Hence it is important to understand the effect of menopause and menopausal hormone therapy on the risk of diabetes and diabetic control among women who are already suffering from Type 2 diabetes.

Estrogen and glucose homeostasis

Menopause is associated with changes in body composition, with increased visceral adiposity and total fat mass independent of chronological age[3]. This is attributed to estradiol deprivation acting on the ventro-medial nucleus of the hypothalamus, thus reducing sympathetic activity and favouring visceral fat accumulation and reduced energy expenditure[4]. Further, possible effect of decreased ERα action on the liver, and impairment of insulin secretion by islet β cells of pancreas may contribute to impaired glucose homeostasis. These changes along with decreased lean body mass at menopause result in impaired insulin sensitivity predisposing menomenopausal women to type 2 diabetes.

Women with premature menopause and early menopause where there is prolonged estrogen deficiency, have a greater risk of developing type 2 diabetes, than women who develop menopause after 50 years[5]. Women who underwent bilateral oophorectomy have over 50% increased risk of developing diabetes when compared to women who had natural menopause[6]. Thus it is evident that prolonged estrogen deficiency leads to increased risk for type 2 diabetes.

Premenopausal women are at a lower risk to develop obesity, metabolic syndrome and type 2 diabetes when compared to age matched men[7]. Estrogen regulates insulin action by acting directly and indirectly on insulin sensitive tissues. Estrogen act through estrogen receptors nuclear ERα, ERβ, and membrane bound receptors, including G protein-coupled ER (GPER, also known as GPR 30). Animal experiments show that ERα plays an important role in insulin-glucose homeostasis[8]. ERα initiates insulin signalling mechanisms and expression of glucose transporter type 4 (GLUT4), which is involved in transportation of glucose across cell membrane, and primarily expressed in skeletal and adipose tissue[9].

Estrogen reduces gluconeogenesis and increases glycogen synthesis and storage in liver. Estradiol suppresses gluconeogenesis by inhibition of Foxo1, a transcription factor involved in hepatic glucose production[10].

Estrogen also maintains lipid and cholesterol balance by suppressing lipogenesis, lipid uptake, and cholesterol synthesis and promoting lipolysis and cholesterol removal.

Adipose tissue is involved in glucose and lipid metabolism, and produce bioactive adipokines. Postmenopausal women have increased adiposity

which can be reversed with estradiol treatment. Estrogen deficiency in menopausal women lead to increased lipolysis and resultant release of free fatty acids from adipose tissue. This lead to abnormal glucose metabolism, hyperinsulinemia, dyslipidemia and hypertension, correlating strongly with cardiovascular disease and type 2 diabetes. Further prolonged high levels of circulating free fatty acids inhibits insulin secretion from pancreatic beta cells and induce beta cell apoptosis.

Estrogen increases secretion of leptin which is an important metabolic hormone involved in reduced food intake and increased energy expenditure[11]. There is also evidence that estrogen suppresses proinflammatory cytokines, IL-6 and TNFα which play a role in obesity related insulin resistance. Estrogen exert protective effects against insulin resistance and obesity through the regulation of adiponectin production, leptin and proinflammatory cytokines[12].

Effect of menopausal hormone therapy on glucose control in non- diabetic women

Many observational studies have shown a reduced risk of diabetes in women using menopausal hormone therapy. In a large prospective study, postmenopausal hormone use was associated with 20% reduction of diabetes as compared with never users, after adjustment for age and body mass index[13]. In this study, dose, duration and whether estrogen was used alone or in combination with progestogen, did not alter the incidence of type 2 diabetes. In the WHI trial, 0.625mg conjugated equine oestrogen plus 2.5mg medroxyprogesterone acetate reduced the incidence of diabetes after one year when compared to placebo. Hazard ratio of 0.79 had not changed after adjustment for changes in BMI and waist circumference[14]. Previously the HERs study showed a 35% decrease of diabetes in postmenopausal women with Coronary heart disease who used the same therapy. In the E3N French cohort study, oral route of oestrogen administration was associated with a greater decrease in diabetes risk than a cutaneous route[15]. While these studies depended on self-reporting of diabetes, in the Rancho Bernard Study it was shown that plasma glucose levels, plasma insulin levels and proinsulin levels were reduced with postmenopausal hormone therapy[16]. Saltpeter, in a meta-analysis of 107 RCTs, concluded HRT reduced fasting glucose and Insulin resistance as calculated by homeostasis model assessment (HOMA-IR), which is a better assessment of βcell function and insulin sensitivity[17]. In a systemic review and meta-analysis, Xu et al found women taking combined estrogen and progesterone therapy, had significantly lower levels of fasting plasma glucose and HbA1c[18].

Antidiabetic effect of MHT depends on the type, dose, and route of administration. Many large RCTs like HERS, and WHI assessed the effect of CEE and MPA, while in other studies oral or transdermal estradiol and different progestogens were used. It has been demonstrated that oral CEE 0.625mg increased insulin sensitivity by about 25% while larger dose of 1.25mg decreased insulin sensitivity[19]. This difference may be because low concentrations of estradiol upregulates insulin receptor substrate 1, a protein which amplifies insulin receptor signal thereby increasing insulin sensitivity in peripheral tissues, while high concentrations downregulates this protein[20].

Oral administration of estrogen results in hepatic first pass effect resulting in many pharmacokinetic effects. Oral estradiol is metabolised to different estrogen conjugates having varying estrogenic activity. Due to high levels of estrogenic activity in the liver there is better suppression of hepatic glucose production, and unphysiological effect on liver protein synthesis. Thus oral therapy of estradiol is associated with increase in triglycerides, HDL fraction, many inflammatory markers, and coagulation factors. In contrast transdermal estradiol by avoiding first pass effect of oral administration provides a more physiological delivery of the hormone. In a cohort of French postmenopausal women, it was noted that cutaneous route

was associated with a lower decrease in diabetic risk when compared with the oral route[21]. In a placebo controlled study, Duncan and colleagues, using 50µg of 17β estradiol, observed no significant increase in insulin sensitivity after 6 weeks of transdermal treatment[22]. Thus it seems transdermal estrogen delivers unmetabolized estradiol mostly to non-hepatic tissues with lower suppression of hepatic glucose production.

In women with intact uterus, a progestogen is administered along with estrogen to protect the endometrium. Progesterone activates breakdown of glycogen leading to increased blood glucose levels[23]. It has also been suggested that it can act directly on pancreatic βcells to cause a decrease in insulin secretion. Many clinical studies support this action of progestogen on glucose metabolism. Salpeter in a meta-analysis on MHT, noted that in many RCTs progestogen attenuates the beneficial effects of estrogen on glucose metabolism[24]. This effect seems to depend on the dose, and more so on the structure of progestogen. MPA has glucocorticoid properties and when combined with estradiol, it blunts the effect of estradiol on insulin sensitivity[25]. Norethisterone acetate (NETA) appears to be more neutral. In a double blind study on postmenopausal women using 2mg E2/1mg NETA (high dose E2/NETA), 1mg E2/0.5mg NETA (low dose E2/NETA), or placebo it was shown that lower dose did not change the insulin sensitivity while the higher dose reduced it significantly[26]. Dydrogesterone, a potent orally active progestogen devoid of androgenic or oestrogenic activities, does not oppose the beneficial effects of estradiol on insulin sensitivity[27]. Tibolone which has estrogenic, and to a lesser extent progestogenic and androgenic properties, does not seem to affect glucose metabolism and may even improve peripheral insulin sensitivity[28]. Recently, in view of the adverse effects of oral estrogen and progestogen following WHI, Tissue Selective Estrogen Complex (TSEC) where conjugated estrogen is combined with bazedoxifene, is a newer method of treating menopausal symptoms with least side effects. In a pilot study on 12 obese postmenopausal women, CE/BZA has improved βcell function, and hence a promising combination[29].

Effect of menopausal hormone therapy on glucose control in diabetic women

Menopausal Hormone Therapy (MHT) has also shown to improve the glycaemic control in postmenopausal women with type II diabetes. In a cross over trial of 25 type II diabetic postmenopausal women, 0.625mg of CEE reduced fasting plasma glucose and HbA1C[30]. Salpeter in a meta-analysis involving a large number of participants, found that in women with diabetes, MHT reduced fasting plasma glucose by 11.5%, fasting insulin by 20.2%, and HOMA-IR by 35.8%[31]. This benefit was greater than in women without diabetes. In women with diabetes MHT improved other CVD risk factors like LDL cholesterol, triglycerides, lipoproteins and pro coagulation markers.

In a placebo controlled study, micronized 17 beta estradiol for six months in postmenopausal women with type II diabetes but with minimal vascular complications, had significantly reduced HbA1c, with improvements of lipid parameters[32].

Conclusion

Estrogen improved β cell insulin secretion and insulin sensitivity as measured by available laboratory tests. Clinical studies show estrogen containing MHT has beneficial effects on insulin sensitivity thus reducing the risk of type 2 diabetes in menopausal women. Use of MHT improves glycaemic control in postmenopausal women with type 2 diabetes.

In younger postmenopausal women or women within 10 years of menopause who had undergone hysterectomy, estrogen reduces the risk of developing type 2 diabetes. In similar type of women who have an intact uterus, estrogen along with an appropriate progestogen with minimal effect on coagulation factors and insulin sensitivity

will be beneficial. In younger women with type 2 diabetes MHT tend to improve glycemic control. However risk of developing atherosclerosis and cardiovascular disease should be considered in using MHT in these women.

Although MHT is not prescribed for the purpose of prevention of type 2 diabetes due to its complex balance of risks and benefits, it should not be withheld from women with increased risk of type 2 diabetes who seek treatment for menopausal symptoms. Further, it is noted that benefits are far outweigh the risks in newer combinations as TSEC.

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