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Oestrogens and insulin secretion

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Abstract There is a persistent perception that oestrogens have an adverse effect on carbohydrate metabolism. It might therefore be expected that their use would result in a corresponding increase in the incidence of diabetes. Recent evidence from clinical trials suggesting that women on postmenopausal oestrogen hormone replacement therapy (HRT) have a reduced incidence of type 2 diabetes therefore appears paradoxical. Short-term supraphysiological oestrogen administration has an adverse effect on glucose tolerance, resulting from suppression of first-phase insulin secretion and increased insulin resistance. Oestrogen-induced increases in glucocorticoid activity could account for these effects. Oestrogen-induced deterioration in glucose tolerance is, however, accompanied by a reduction in fasting glucose, an effect that could be accounted for by glucagon antagonism. These short-term effects contrast with long-term preservation of insulin secretion and glucose homeostasis by oestrogens. In animal studies, ovariectomy is associated with decreased insulin secretion and increased risk of diabetes, whereas oestrogen administration protects against diabetes and increases the insulin response to glucose. The mechanism is uncertain, but direct effects on the pancreas via steroid receptors or indirect effects via oestrogen-induced glucagon antagonism and subclinical increases in glucocorticoids and growth hormone could all contribute. Recent evidence that HRT increases the risk of cardiovascular disease suggests that it should not be used for the prevention of diabetes, but the mechanism responsible for this benefit merits further investigation and might lead to new therapies.

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Abbreviations HRT: postmenopausal oestrogen hormone replacement therapy · NHANES: National Health and Nutrition Examination Survey

Introduction

Clinical administration of oestrogens has long had a poor reputation with regard to carbohydrate metabolism. This dates back to the 1960s, when glucose tolerance was seen to deteriorate in women on high-oestrogen oral contraceptives [1], some of whom developed a reduced early insulin response to glucose and diabetic plasma glucose levels [2]. Worsening glucose tolerance was confirmed with low-dose oral contraceptive use [3] and, depending on steroid composition and dose, postmenopausal oestrogen hormone replacement therapy (HRT) [4]. Accordingly, there is a persistent perception that oestrogens have an adverse effect on carbohydrate metabolism, and a corresponding increase in the incidence of diabetes might therefore be expected from their use.

Although no randomised controlled trials have examined oestrogens in relation to the incidence of diabetes, the Heart Estrogen Progestin Replacement Study and the Women's Health Initiative have explored their effects on cardiovascular disease [5, 6]. Both studies found no improvement in cardiovascular outcomes but—equally unexpected—also found a significantly lower incidence of diabetes. With regard to the latter, the authors of one report commented that 'We are unable to reconcile these findings with (the) expected physiological changes' [5].

This review will argue that the effects of oestrogens on carbohydrate metabolism may be more complex than previously imagined, and that oestrogens may have favourable long-term effects on glucose-induced insulin secretion, which—if confirmed—could explain the clinical trial observa-

tions and justify further research into the mechanisms involved. Particular attention will therefore be given to experimental effects of oestrogens on insulin secretion. The influence of oestrogens on diabetes development in animal models and in humans is then considered, and possible mechanisms discussed.

Effects of oestrogens on pancreatic islets and beta cell insulin secretion in animals

The effect of oestrogens on the pancreas was originally examined in the search for agents that might be effective in treating diabetes. Early work showed that administration of oestrogens increased the insulin content of the pancreas in rats [7]. Subsequently, during the 1940s, Bernardo Houssay and his team used a partially pancreatectomised rat model to show that administration of various oestrogens was associated with hypertrophy and regeneration of the islets [8]. Androgens had no such effects. These actions of oestrogen appeared independently of adrenalectomy or hypophysectomy. Moreover, subtotal pancreatectomy followed by implantation of an oestrogen pellet in the remaining pancreatic tissue resulted in localised islet regeneration, suggesting a direct effect of oestrogens on the pancreas. Similar islet regeneration was seen in the alloxan-diabetic rat [8, 9].

More detailed investigations of the effect of oestrogens on insulin secretion at the cell and tissue level followed in the 1970s. Ovariectomy in mice was associated with reduced insulin release from isolated islets stimulated with glucose, restored by oestradiol administration [10]. Oestradiol levels designed to simulate those seen in pregnancy increased insulin secretion from isolated islets, as compared with those from untreated rats [11].

Effects of oestrogens in animal models of diabetes

Houssay and colleagues used the partially pancreatectomised rat model to show that oestrogen administration minimised progression to diabetes [8, 12]. For example, oestradiol benzoate reduced progression by around 75% in intact or ovariectomised animals (Fig. 1) [12], whereas androgens had no effect. The frequency of diabetes was higher in male than female rats, and was reduced in males after castration and increased in females after ovariectomy, independently of any changes in food intake. These differences were subsequently confirmed in other models of diabetes [13].

Effects of oestrogens on insulin secretion in humans

The effects of oestrogens on insulin secretion in humans can to some extent be inferred from changes observed following natural or surgical menopause or administration of oestrogens.

Fig. 1 Development of diabetes in the subtotal-pancreatectomised rat model of diabetes: **a** intact, and **b** ovariectomised. Prevention of diabetes by daily administration of oestradiol benzoate for 6 months is shown. *Open bars*, subtotal-pancreatectomised rats not receiving oestrogen; *closed bars*, subtotal-pancreatectomised rats receiving oestrogen. Reproduced with permission from reference [12]. Copyright, The Endocrine Society. A single operator was responsible for pancreatectomy in control and treated animals at each oestrogen dose, but a different operator was responsible for each dose. The authors ascribed the lack of a dose effect to this difference in operators

Effects of menopause on insulin secretion The effect of ovariectomy on insulin secretion does not appear to have been studied in humans. The effects of a natural menopause are difficult to interpret because of associated menopausal changes and the age difference between pre- and postmenopausal women. Studies adjusting for this report unchanged plasma glucose, and no change or a slight increase in insulin [14]. The menopause may, however, influence insulin secretion in ways that are not reflected in glucose or insulin levels. Asymptomatic pre- and postmenopausal women were studied using an IVGTT, and age-standardised measures of insulin secretion and insulin elimination were derived [15]. Postmenopausal women had similar glucose and insulin levels to premenopausal women (Fig. 2), but produced 50% less insulin and eliminated it more slowly—thus compensating for reduced secretion and maintaining insulin at premenopausal levels. There is other evidence of compensation for insulin resistance and control of glucose tolerance via effects on insulin elimination [16], but whether

Fig. 2 IVGTT mean glucose AUC and insulin AUC, and mean net increment in insulin secretion and plasma insulin elimination rate derived by modelling analysis of IVGTT insulin and C-peptide concentrations (error bars show SEM). *Closed bars*: premenopausal women ($n=66$). *Open bars*: postmenopausal women ($n=92$). Data were standardised to the mean age and BMI for the group as a whole in each group separately to allow for differing effects of age in pre- and postmenopausal women. From data reported in reference [15]

a deficit in insulin secretion would emerge from a more physiological test such as a meal-tolerance test is not known.

Effects of menopause on diabetes prevalence Estimates should be viewed with caution since there are many potential confounders. For example, menopausal symptoms can lead to increased medical surveillance, with the result that diabetes is more likely to be diagnosed. Seige and Hevelke [17] did report a striking relationship between the onset of diabetes and the menopause but such an effect should be reflected in a discontinuity between men and women in diabetes incidence with age. There has been some evidence for this [18] and change in prevalence was seen in

the second US National Health and Nutrition Examination Survey (NHANES-II) 1976–1980 [19] (Fig. 3). However, this was not confirmed in NHANES-III 1988–1994 [20] (Fig. 3). Moreover, endocrine changes other than a reduction in oestrogen occur at the menopause, and are accompanied by physiological changes such as increasing adiposity. Careful study of the effect of menopause on diabetes incidence in which all potential confounders are taken into account is still needed.

Effects of oestrogens on insulin secretion in humans These may be considered in relation to use of HRT or oral contraceptives, but the two therapies are very different. HRT

Fig. 3 Prevalence of diabetes mellitus (DM) in relation to age in men (*broken line, open circles*) and women (*continuous line, closed circles*). **a** UK hospital case series 1956 (583 women, 370 men), data

from reference [18]; **b** NHANES-II population prevalence 1976–1980, data from reference [19]; **c** NHANES-III population prevalence 1988–1994, data from reference [20]

aims at restoration of premenopausal oestrogen levels, and the oral contraceptive aims at supraphysiological levels. Cagnacci and colleagues [21] reported changes consistent with improved insulin sensitivity, secretion and elimination (i.e. reversal of the effects of the menopause) during low-dose parenteral administration of the native oestrogen, 17-beta oestradiol. Subsequently, 13 studies of 20 groups of HRT users have evaluated all three aspects of insulin action and metabolism (see Electronic supplementary material). There was evidence of improved insulin secretion in response to glucose in 11 groups, increased insulin elimination in 12, and improved insulin sensitivity in four. Reduced insulin secretion was reported in three groups, but with no evidence of reduced insulin elimination or sensitivity in response to HRT. The balance of evidence, therefore, supports a reversal of the effects of menopause by oestrogen replacement with respect to insulin secretion and elimination, with little effect on insulin sensitivity.

Few studies have specifically considered insulin secretion in women using oral contraceptives. High-oestrogen oral contraceptives, as mentioned earlier, were associated with a reduced insulin response [2]. Combined oral contraceptives are associated with insulin resistance, even at low dose [22], but the insulin response appears inappropriately low for the degree of insulin resistance [23]. Nevertheless, a marked age-related increase in glucose AUC following an OGTT was seen in women not taking oral contraceptives, but was absent in current users of oral contraceptives [24]. The same analysis showed that the first-phase insulin response to the IVGTT declined with age in non-users, but was unchanged in users of oral contraceptives. These findings suggest that, despite adverse short-term effects on insulin secretion, sensitivity and glucose tolerance, oral contraceptives may benefit insulin secretion in the longer term.

Effects of oestrogens on diabetes incidence—observational studies Four studies have compared the incidence of diabetes in postmenopausal women taking or not taking HRT (Table 1). The largest of these by far, the Nurses' Health Study (422,991 person-years of follow-up), reported a reduced incidence in those on HRT [25]. Three smaller studies (3428–9752 person-years of follow-up) found a reduction in incidence [26–28], lost after adjustment for confounding variables—primarily weight or BMI. This suggests that any apparent protective effect of HRT was secondary to less adiposity in HRT users. These adjustments should be interpreted with caution, however, since HRT can itself have favourable effects on body fat distribution and could, therefore, act to reduce diabetes risk via this mechanism. Statistical adjustment for adiposity might then obscure a favourable effect of HRT.

The incidence of diabetes in users compared with non-users of oral contraceptives was analysed in the Royal College of General Practitioners' Study [29], the Oxford/Family Planning Association Study [29] and the Nurses' Health Study [30] (Table 1). Non-significant reductions in risk were apparent in each analysis.

Effects of oestrogens on diabetes incidence—clinical trials Observational studies may be confounded by a number of biases—in particular, selective prescribing. Two randomised, placebo-controlled trials examined the effects of a combination of 0.625 mg conjugated equine oestrogens and 2.5 mg medroxyprogesterone acetate daily on diabetes incidence [5, 6]. Neither trial had diabetes as its primary outcome, and one concerned only self-reported diabetes [6]. Nevertheless, both found a significant reduction in diabetes incidence (Table 1). These trials did not distinguish between the effects of conjugated equine oestrogens and medroxyprogesterone acetate. Medroxyprogesterone acetate does, however, possess glucocorticoid activity and induces insulin resistance [4], so the favourable effect on diabetes incidence more likely derives from the oestrogen.

Possible mechanisms underlying the effects of oestrogens on insulin secretion

The possibility that oestrogens might benefit insulin secretion has received little attention, but suggestive evidence from animal studies could justify more detailed investigation. It is important to distinguish between direct effects on the pancreas and the effects of oestrogens on other hormones which might themselves affect insulin secretion or action. Potential mechanisms—with evidence for and against—are summarised in Table 2. Key observations are considered below.

Direct effects of oestrogens on the pancreas Receptor binding for oestrogen is present in islets [31] and direct effects on insulin secretion from the isolated, perfused pancreas have been reported [32], but islets only show evidence of increased secretion when isolated from animals pretreated with oestrogens [11]. Incubation of isolated islets with oestrogen, even for durations employed when islet hyperplasia has been demonstrated in vivo, has no effect on insulin production [11, 33].

Oestrogen-induced changes in progesterone receptors Oestrogens increase islet progesterone receptor binding and could therefore make the pancreas more sensitive to the effects of progesterone [10]. These include, in isolated islets, an increased insulin response to glucose [11, 33].

Oestrogen-induced changes in corticosteroids Oestrogens increase glucocorticoid levels, especially at relatively high doses or potency [4]. No clinical signs of glucocorticoid excess have been reported in humans taking oestrogens, but glucocorticoids have a number of effects in animals that parallel those seen with oestrogens, including suppression of the early insulin response to glucose [34], pancreatic hypertrophy, an increased insulin response to glucose and prevention of diabetes [8]. Importantly, the enhanced insulin response to oestrogen is not seen in adrenalectomised animals, but is restored by glucocorticoid administration [35]. The extent to which these effects

Table 1 Prospective studies of postmenopausal oestrogen hormone replacement therapy (HRT) and oral contraceptive therapy on the incidence of diabetes

Study	Design	Treatment	Women— years of observation	Current users’ relative risk (95% CI)
Nurses’ Health Study, Manson et al. 1992 [25]	Observational 12-year follow-up of US occupation-based cohort	Any HRT	422,991	0.80 (0.67–0.96) (age- and BMI- adjusted)
Hammond et al. 1979 [26]	Retrospective observational follow-up of hypo-oestrogenic women in US hospital clinic	Any HRT	3844	0.29 (0.14–0.60) (unadjusted; non-significant after adjustment for weight)
Rancho Bernardo Health and Chronic Diseases Study, Gabal et al. 1997 [27]	Observational 11.5-year follow-up of US community-based cohort	HRT	9752	0.83 (0.43–1.63) (age-adjusted), 1.12 (0.56–1.37) (age- and BMI- adjusted)
STRONG Heart Study, Zhang et al. 2002 [28]	Observational 4-year follow-up of Native American communities cohort	Any HRT	3428	0.66 (0.39–1.12) (unadjusted), 1.11 (0.62–1.97) (adjusted)
Heart Estrogen Replacement Study, Kanaya et al. 2003 [5]	Randomised placebo-controlled trial of HRT in secondary prevention of cardiovascular disease in US postmenopausal women, with 5.7 years’ follow-up	0.625 mg/day conjugated equine oestrogens plus 2.5 mg/day medroxyproges- terone acetate	15,749	0.65 (0.48–0.89)
Women’s Health Initiative, Margolis et al. 2004 [6]	Randomised placebo-controlled trial of HRT in primary prevention of cardiovascular disease in US postmenopausal women, with 5.2 years’ follow-up	0.625 mg/day conjugated equine oestrogens plus 2.5 mg/day medroxyproges- terone acetate	81,333	0.79 (0.67–0.94)
Royal College of General Practitioners’ Study, Wingrave et al. 1979 [29]	Observational 10-year follow-up of premenopausal women registered with UK general practitioners	Any oral contraceptive	221,865	0.80 (0.43–1.25)
Oxford/Family Planning Association Study, Wingrave et al. 1979 [29]	Observational 9-year follow-up of premenopausal women attending UK family planning clinics	Any oral contraceptive	98,044	0.52 (0.15–1.86)
Nurses’ Health Study, Rimm et al. 1992 [30]	Observational 12-year follow-up of US occupation-based cohort	Any oral contraceptive	1,237,440	0.86 (0.46–1.61)

apply to oestrogen administration in humans has not been investigated.

Oestrogen-induced changes in growth hormone Oestrogen administration increases serum growth hormone in humans [36], but this is seen only with oral administration and is not accompanied by any increase in IGF [37]. The growth hormone increase, therefore, appears to be a compensatory response to hepatic growth hormone resistance induced by oestrogen use. It can be noted that the effects of oestrogen on the pancreas are unaffected by hypophysectomy [9]. Growth hormone does, however, stimulate insulin release and DNA synthesis in isolated islets [38] and stimulation of beta cell replication by growth hormone appears to be independent of IGF [39]. Growth hormone per se might, therefore, contribute to long-term survival of the pancreas.

Oestrogen-induced changes in glucagon sensitivity and secretion The effect of oestrogens on glucagon secretion and action has received little attention in humans. In animals, glucagon-induced hyperglycaemia was diminished by oestrogen [40] and enhanced by ovariectomy [41]. Ovariectomy also increased circulating glucagon [42], an effect reversed by oestradiol [42]. Portal vein glucagon levels were reduced relative to insulin in ovariectomised rats given oestrogens [43] and glucagon secretion from isolated islets was reduced by pregnancy [44]. Oestrogen, therefore, appears to induce glucagon resistance and to decrease glucagon secretion, changes that could account for reduced hepatic glucose production in response to oestrogens [45]. Although none of these effects have been investigated in humans, glucagon antagonism could provide a straightforward explanation for the consistent reduction in fasting

Table 2 Possible mechanisms by which oestrogens might exert a long-term beneficial effect on insulin secretion and protect against loss of beta cell function

Suggested mechanism	Supportive evidence	Contrary evidence
Direct effects of oestrogens on the pancreas	Receptor binding for oestrogen present in the pancreas [31] Exposure of perfused pancreas to oestrogen augments insulin release [32]	Exposure of isolated pancreatic islets to oestrogen does not affect insulin release [33]
Oestrogen-induced increases in pancreatic islet progesterone receptors	Receptor binding for progesterone present in the pancreas [10] Oestrogens increase receptor binding for progesterone in the pancreas [10] Exposure of isolated pancreatic islets to progesterone augments insulin release [33] Progesterone administration to animals augments isolated islet insulin release [11]	Exposure of perfused pancreas to progesterone does not affect insulin release [32] In vivo effects of progesterone on insulin secretion could be secondary to weight gain and insulin resistance
Oestrogen-induced increases in glucocorticoid activity	Glucocorticoid levels are increased in women taking oestrogens [4] Effects of glucocorticoids in humans on first-phase insulin release resemble those of oestrogens [34] Glucocorticoids have a trophic effect on the pancreas and diminish incidence of diabetes in animal models [8] Augmentation of insulin secretion by oestrogen is not seen in adrenalectomised animals but is restored by corticosteroids [35]	Suppression of first-phase insulin secretion by oestrogens is still apparent following adrenalectomy [35] Trophic effect of oestrogens on the pancreas is still apparent following adrenalectomy [8]
Oestrogen-induced increases in growth hormone activity	Growth hormone levels are increased in women taking oestrogens [36] Growth hormone stimulates insulin secretion and DNA synthesis in isolated islets [38]	Changes in growth hormone do not relate to changes in glucose metabolism [36] IGF levels are unaffected by oestrogens [37] Favourable effect of oestrogens on the pancreas is apparent following hypophysectomy [9]
Oestrogen-induced decreases in glucagon sensitivity and secretion	Glucagon-induced hyperglycaemia is diminished by oestrogens [40] Ovariectomy increases plasma glucagon concentrations and enhances the hyperglycaemic action of glucagon [41] Following ovariectomy, oestrogen administration decreases the hepatic portal vein insulin glucagon ratio [43] Following ovariectomy, oestrogen administration decreases the hyperglycaemic action of glucagon [41]	Oral contraceptive oestrogens do not affect plasma glucagon concentrations in humans [50]

Key references are given. Evidence is from animal studies, except where stated

plasma glucose observed in women taking HRT or oral contraceptives (see below), which might in turn be expected to have favourable long-term effects on islet function.

Oestrogen-induced changes in glycaemia and insulin sensitivity The most consistent effect of oral contraceptives and oestrogen replacement therapy is to lower fasting plasma glucose and to worsen glucose tolerance [2, 3, 6, 28, 46], also seen in the NHANES studies [47]. Basal insulin is unchanged or reduced, whereas glucose-stimulated insulin is enhanced. The weight of evidence favours the view that, in humans, oestrogen deficiency (resulting, for example,

from ovariectomy or the menopause) is associated with a relatively minor deterioration in glucose tolerance and increased insulin resistance [4]. Physiological oestrogen replacement is then associated with recovery from these effects. In contrast, oestrogen excess, as in oral contraceptive therapy or HRT with potent alkylated oestrogens or high-dose natural oestrogens, is associated with deterioration in glucose tolerance and insulin resistance. Interestingly, such gradations in response to oestrogens could be further determined at the level of insulin receptor gene expression [48].

Discussion

The sometimes conflicting effects of oestrogens on glucose homeostasis (Text box: Summary of effects of oestrogens on insulin secretion and related measures)

Summary of the effects of oestrogens on insulin secretion and related measures

- oestrogens induce pancreatic hypertrophy and hyperplasia and augment the pancreatic insulin response to glucose
- oestrogens protect against diabetes in animal models of diabetes
- menopause in humans is associated with a reduction in the pancreatic insulin response to glucose
- menopause in humans is associated with increased risk of diabetes
- oestrogen replacement in humans is associated with increased insulin secretion
- oestrogen replacement in humans is associated with decreased risk of diabetes
- oral contraceptive therapy protects against age-related deterioration in glucose tolerance and insulin secretion
- oral contraceptive therapy has no effect on the incidence of diabetes
- oral contraceptive therapy in humans is associated with deficient insulin secretion
- orally administered oestrogens increase growth hormone but not IGF concentrations
- oestrogens, particularly at high dose, increase glucocorticoid concentrations
- oestrogens inhibit glucagon secretion and oppose glucagon action
- oestrogen administration in humans is associated with reduced fasting glucose concentrations and deterioration in glucose tolerance
- oestrogen deficiency in humans is associated with deterioration in glucose homeostasis and insulin resistance
- oestrogen replacement restores glucose homeostasis and insulin sensitivity
- oestrogen excess in humans is associated with deterioration in glucose tolerance and insulin resistance

might be resolved if a distinction is made between the short-term and long-term effects of oestrogens. Short-term effects include suppression of insulin secretion, induction of insulin resistance and deterioration in glucose tolerance, particularly at high dose or potency, together with glucagon antagonism. These short-term effects are exemplified by the repeated observation of increased post-load but reduced fasting glucose concentrations in oestrogen users. The principal long-term effect of oestrogens, however, is preservation of the pancreatic insulin response to glucose.

The underlying mechanism is unknown. Nevertheless, as summarised in Table 2, there are several levels at which oestrogens could act on the pancreas—both direct, via islet steroid receptors, or indirect, via oestrogen-induced changes in other hormones, which might themselves affect the pancreas directly or favourably modify glucose homeostasis to reduce risk of diabetes. Further work will be needed to resolve these possibilities and to establish how these effects are mediated at the molecular level. Although oestrogens can sustain insulin secretion and there is clinical trial evidence for protection from diabetes by HRT, use in diabetes prevention is ruled out by the increased risk of cardiovascular disease [49]. Although the evidence for the latter largely relates to a single HRT combination (conjugated equine oestrogens and medroxyprogesterone acetate), com-

mensurately powerful evidence of benefit will be required before alternatives could be considered further. Nevertheless, if it can be confirmed that oestrogens offer protection from diabetes in humans, it would be important to explore the underlying mechanisms and to see if these could be exploited by the development of therapeutic agents.

Duality of interest

Over the past 5 years, the author has received honoraria for speaking at two meetings sponsored by manufacturers of oral contraceptives and HRT.

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