Sex Hormones, Insulin Sensitivity, and Diabetes Mellitus

Cristin M. Bruns and Joseph W. Kemnitz

Abstract

Sex differences and the role of gonadal hormones in modulating insulin sensitivity and glucose tolerance are of increasing interest and importance because of the increasing prevalence of type 2 diabetes mellitus and the metabolic abnormalities associated with aging. Body composition is closely associated with insulin sensitivity, and increased body fat, particularly in the visceral compartment, is a risk factor for developing type 2 diabetes mellitus. Sex differences in body composition and/or insulin sensitivity are evident in humans throughout the lifespan. Ovarian hormones influence insulin sensitivity across the menstrual cycle, during pregnancy, and in the menopausal transition. Similarly, estrogens and progestins used for contraception and hormone replacement therapy affect glucoregulation. Nonhuman primates and humans have similar life histories and reproductive characteristics. As a result, nonhuman primates provide a valuable model for investigating factors related to insulin sensitivity. Studies of nonhuman primates have contributed significantly to our understanding of sex differences and the influence of sex steroids in this context. This brief review surveys present knowledge of the sex differences in body composition, insulin sensitivity, and risk for development of type 2 diabetes mellitus derived from studies in humans and nonhuman primates. The influences of endogenous and exogenous gonadal steroids are emphasized.

Key Words: body size and composition; diabetes mellitus; gonadal hormones; insulin sensitivity; reproductive condition; sex differences

Introduction

The prevalence of type 2 diabetes mellitus (DM2[1]) is increasing at a dramatic rate, and the economic costs of caring for patients with diabetic complications are high. The increase in DM2 is closely associated with the epidemic of obesity in industrialized countries. Reduced physical activity is a contributing factor as sedentary lifestyles become more common. Increased body fat, particularly in the visceral compartment, is a strong risk factor for the development of DM2. Advanced age is an additional risk factor, and people are living longer in this country and in many others. Elucidation of such risk factors will lead to interventions that can delay the onset or protect against the development of DM2.

Sex differences, as well as the effects of gonadal hormones and drugs that mimic or antagonize the effects of these hormones, are factors that may also have an impact on the development of DM2. Knowledge of the risk associated with these factors is important to individuals for making lifestyle choices and to medical providers counseling patients who are considering hormone use for contraception or as replacement therapy.

Animal models have provided important insights into the pathogenesis of human diseases and new therapeutic approaches. Nonhuman primates are particularly valuable in this context, because many of their life history and reproductive characteristics are very similar to those of our own species. This article provides an overview of available information on sex differences in risk for developing insulin resistance and the influences of endogenous and exogenous sex hormones, emphasizing studies of women and nonhuman primates. Because body composition is very closely associated with insulin sensitivity, the similarities and differences between nonhuman primates in terms of growth and body fat are also described.

Development and the Emergence of Sex Differences

Pregnancy in Old World nonhuman primates shares many characteristics with humans. The length of gestation is relatively long and typically culminates in a singleton birth. In rhesus monkeys, the average length of gestation is virtually identical for male and female fetuses, namely 165 days (Kemnitz 1994). As is the case in human fetal development, there is very little fat accretion during the first 5 to 6 mo of

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[1]Abbreviations used in this article: BMI, body mass index; CEE, conjugated equine estrogens; DM2, type 2 diabetes mellitus; DXA, dual energy x-ray absorptiometry; FSIGTs, frequently sampled intravenous glucose tolerance tests; HRT, hormone replacement therapy; MPA, medroxyprogesterone acetate; NHANES III, Third National Health and Nutrition Examination Survey.

gestation. Rhesus monkeys are born at approximately 5½ mo after conception and have very little body fat at birth. In contrast, human fetuses add body fat at an exponential rate during the third trimester of pregnancy (Southgate and Hey 1976).

The islet cells of the fetal rhesus monkey pancreas are clearly distinguishable by 60 days after conception, but the maximal growth rate of the pancreas occurs during later phases of gestation (Hoar and Monie 1981). The fetal testes are distinguishable and secrete testosterone by the seventh week after conception (Resko et al. 1980). Ovarian development in rhesus monkeys closely parallels human ovarian development in that mitotic activity in oogonia is maximal at 4 mo after conception and the quantity of oogonia and oocytes is similar to humans during development and at birth (Baker 1966).

Alterations in the intrauterine environment and resultant effects on fetal characteristics, such as birth weight, have been implicated as risk factors for adult diseases, including DM2, as part of the so-called "thrifty phenotype" hypothesis (Hales and Barker 1992). Extremes in birth weight are associated with an increased risk of DM2 later in life (Godfrey and Barker 2000). Decreased maternal insulin sensitivity is a common finding during the later stages of normal human and rhesus pregnancies and may be due to increasing levels of progesterone and other endocrine changes (Freinkel 1980). Maternal insulin resistance in humans allows preferential transfer of carbohydrates to the fetal compartment, supporting rapid growth of the fetus during the third trimester (Buchanan 1991). In humans, the variance in maternal insulin sensitivity accounts for significant portions of variance in birth weight and body composition of the newborn (Catalano and Kirwan 2001). Women with low body mass index (BMI^1) in early pregnancy tend to have smaller infants than heavier women, and weight gain during pregnancy is also positively correlated with birth weight of the infant (Shapiro et al. 2000). Low birth weight has been linked to insulin resistance and reduced pancreatic beta-cell responsiveness during childhood (Li et al. 2001). High birth weight also appears to confer an increased risk of diabetes. In Pima Indians, a population with a high risk of DM2, high birth weight is associated with maternal diabetes during pregnancy and an increased risk of DM2 in the offspring (McCance et al. 1994).

In some individuals, the inability to compensate completely for the insulin resistance during pregnancy may lead to gestational diabetes (Buchanan 1991). In pregnancies complicated by diabetes, the increased transfer of glucose and other metabolic fuels across the placenta to the fetus stimulates the fetal pancreas to secrete increased amounts of insulin in an attempt to control glycemia. In utero, insulin functions as a growth-promoting hormone, resulting in macrosomia (Farrell et al 1982). Additionally, an increase in fetal fat mass related to macrosomia occurs in diabetic pregnancies (Farrell et al. 1982; Jovanovic-Peterson et al. 1993). The effects of insulin on growth have been demonstrated experimentally in a nonhuman primate model by delivering insulin directly to the rhesus fetus of nondiabetic mothers by an implanted minipump (Susa et al. 1979).

Similar to human pregnancies, maternal obesity in rhesus monkeys is associated with increased growth of the fetus. Pregnant rhesus monkeys with higher BMI at conception have exacerbated insulin resistance, indicated by higher fasting insulin concentration and lower glucose disappearance rates during an intravenous glucose tolerance test at day 125 of pregnancy, when compared with leaner pregnant females (Kemnitz et al. 1988). The incremental increase in insulin levels after intravenous glucose administration is directly proportional to BMI as shown in this study of more than 100 pregnancies, although some heavier gravidae are unable to compensate fully for the increased insulin resistance by increasing acute insulin secretion. Infants from these pregnancies are 12% heavier than expected for gestational age (Kemnitz et al. 1988). Whether this apparent increase in birth weight would have resulted in increased risk of DM2 in the offspring is unknown. Additionally, the association of extremes in birth weight with future risk of DM2 has not been studied in nonhuman primates.

Whether sex of the offspring has an impact on such changes during pregnancy and the resultant fetal consequences has not been fully explored in humans. Although male rhesus newborns weigh on average approximately 10% more than females (Goy and Kemnitz 1983; Kemnitz 1994), the birth weights of genetic females exposed to prenatal androgens are similar to birth weights of unexposed females (Goy and Kemnitz 1983). Additionally, sex differences in infant body composition have not been directly assessed in nonhuman primate models. The impact of sex differences in birth weight on future risk of DM2 has not been elucidated, because most studies of DM2 in rhesus monkeys have used males (Hamilton and Ciaccia 1978; Hansen and Bodkin 1986).

Juvenile and Peripubertal Period

Human females have greater fat mass and lesser fat free mass than males during the first 2 yr of life (Butte et al. 2000). There are few reports of sex differences in body composition and metabolism in immature nonhuman primates. Nutrient partitioning may differ between male and female infant baboons (Lewis et al. 1984). Male baboons gain more lean mass than females on a high calorie formula during the preweaning period whereas the increase in fat mass is approximately the same for both sexes. On a low calorie diet males gain more lean mass than the females, but females are more efficient at retaining calories in the form of fat (Lewis et al. 1984). The mechanism for this sex difference during early postnatal development and its implications for later development of DM2 are not clear.

Monkeys, like humans, have an extended juvenile growth period. Among prepubertal children, girls have greater total body fat and more subcutaneous fat as assessed by noninvasive imaging than boys, although visceral fat

content is not detectably different between the sexes at this stage of development (Arfai et al. 2002). Growth rates of male and female rhesus monkeys maintained on a standard laboratory diet are very similar during the juvenile period, but the small sex difference in absolute weight persists. Beginning at shortly before 2 yr of age, females undergo peripubertal acceleration of growth in body weight that is maximal at 30 mo of age and then declines as body weight plateaus during adulthood (Goy and Kemnitz 1983). The corresponding peripubertal increase in growth rate of males begins about 6 mo later than that of females and peaks at nearly 5 yr of age. It is both greater in magnitude and longer in duration than for females, resulting in the characteristically higher average body weights of males compared with females throughout adulthood (Goy and Kemnitz 1983; Hudson et al. 1996). Body composition and patterns of fat distribution have not yet been systematically studied during the juvenile period in monkeys.

It has been thought for many years that the timing of puberty is due in part to some metabolic signal to the central nervous system that body size and/or metabolic fuel reserves are sufficient to support reproduction (Cameron 1991). Because insulin levels often reflect energy reserve in the form of fat, insulin was thought to be a prime candidate for this role. Critical studies, however, have dissociated the changes in insulin levels from the activation of gonadotropin secretion, indicating strongly that insulin levels alone cannot be the critical link between peripheral metabolic status and reproductive hormone secretion (Cameron 1996).

A transient insulin resistance occurs during puberty in humans. During the transition from Tanner stage I to Tanner stage III, insulin sensitivity decreases by approximately 30% in both boys and girls (Goran and Gower 2001). This reduction is accompanied by increases in fasting glucose and insulin, and insulin increment in response to glucose. The decrease in insulin sensitivity is not statistically associated with changes in body fat, visceral fat, or levels of androgens or estradiol (Goran and Gower 2001). Androgen treatment in males with delayed puberty does not result in worsening insulin sensitivity, which provides additional evidence that the insulin resistance of puberty is not solely due to androgens in males (Saad et al. 2001; Wickman et al. 2002). Sex differences in leptin levels are evident during puberty and appear to be directly related to sex steroid concentrations. Girls exhibit higher levels of leptin than boys during puberty even after controlling for the increase in fat mass, and a marked rise in leptin during the transition from prepuberty to postpuberty is seen in females but not in males (Demerath et al. 1999). It is not clear how these differences in leptin levels during puberty translate to alterations in insulin sensitivity. Similar studies for nonhuman primates have not been reported.

Awareness of the metabolic changes during puberty is clinically important. Children who are already at risk for developing DM2 (e.g., related to obesity) may not be able to compensate fully for the additional insulin resistance of puberty (Goran et al. 2003).

Adulthood

For adults it is clear that insulin resistance is linked with obesity and particularly excessive abdominal body fat. Several studies demonstrate an increase in visceral fat mass in normal adult males compared with females, resulting in the typical "android" body type (Butte et al. 2000; Demerath et al. 1999; Despres et al. 2000; Hill et al. 1999; Lemieux et al. 1993; Snehalatha et al. 1997; Sumner et al. 2002). Analysis of data from the Insulin Resistance Atherosclerosis Study reveals that subcutaneous abdominal fat and visceral fat have both independent and combined effects on insulin sensitivity (Wagenknecht et al. 2003). Furthermore, this analysis shows that fat distribution also predicts insulin secretion. Therefore, sex differences in body composition are an important component of potential differences in insulin sensitivity in humans.

The sex difference in body weight of rhesus monkeys seen during adulthood also reflects differences in body composition. Evaluation of males and females representative of young adults (6-9 yr of age), middle-aged adults (15-19 yr), and older adults (26-30 yr) shows that males are heavier than females in all categories, and have greater crown-rump lengths and limb circumferences than females (Hudson et al. 1996). Males have greater absolute lean tissue mass than females, and females have a greater percentage of fat mass than males, as measured by dual energy x-ray absorptiometry (DXA[1]). The increase in lean body mass of males is likely a consequence of the anabolic effects of testicular androgens, particularly on skeletal muscle. Testosterone propionate administered to gonadectomized male and female rhesus monkeys induces a rapid increase in body weight and indices of muscle mass (Kemnitz et al. 1988). Body fat mass is greatest during middle age for both sexes, and lean tissue mass declines in later adulthood (Hudson et al. 1996; Ramsey et al. 2000).

Fasting insulin levels and insulin increment to glucose challenge are typically highly correlated with the amount of body fat in healthy adult humans. A similar relation is found in laboratory-housed rhesus monkeys (Gresl et al. 2001; Hansen and Bodkin 1986; Kemnitz 1984; Kemnitz and Francken 1986) and in free-ranging rhesus monkeys (Schwartz et al. 1993).

Interestingly, unlike humans, there is no evidence for a sexually differentiated pattern of fat deposition in macaques (Pond and Mattacks 1987). Both sexes accumulate excess fat predominantly in the abdominal region, as evidenced by trunk and limb circumferences, skin fold thickness, and DXA; but differences in the visceral compartment have not been systematically studied (Hudson et al. 1996; Kemnitz et al. 1989b). This observation, which merits more detailed study, has implications for interpretation of data on sex differences in insulin sensitivity and glucose tolerance when monkeys are compared with humans. When sex differences in these end points are identified, they are less likely to be complicated by differences in fat distribution.

Adult female rhesus monkeys tend to have improved

glucose tolerance and greater insulin increments to intravenous glucose challenge than males (Kemnitz et al. 1989b; Ramsey et al. 2000). Use of frequently sampled intravenous glucose tolerance tests (FSIGTs[1]), with evaluation of the data by minimal modeling, reveals enhanced insulin sensitivity and glucose effectiveness in females compared with males (Kemnitz et al. 1998). Importantly, disposition index, which reflects the combined influence of insulin secretion and insulin sensitivity, as well as the derived value of glucose effectiveness at zero insulin (reflecting the component of glucose effectiveness that is independent of insulin), are greater in females than in males.

These observations suggest that ovarian hormones contribute to the sex differences in glucoregulatory endpoints. Valdes and Elkind-Hirsch (1991) assessed insulin sensitivity in cycling women with FSIGTs and found a significant decrease in insulin sensitivity during the luteal phase of the menstrual cycle. To investigate whether this reduction occurs in monkeys, data from 14 FSIGTs conducted on females in the follicular phase of the menstrual cycle were compared with similar data from 13 FSIGTs from the luteal phase of the cycle (Kemnitz et al. 1998). Phases of the cycle were initially estimated by the typical changes in coloration of perineal skin and number of days from observed menstruation, and were subsequently confirmed by measurements of estradiol and progesterone in serum samples collected on the day of the FSIGTs. Plasma estrogen levels were approximately three-fold higher in the follicular phase compared with the luteal phase, whereas luteal phase progesterone levels were approximately 100-fold greater than follicular phase values. Results of the FSIGTs clearly indicate that both insulin sensitivity and disposition index are greater during the follicular than the luteal phase of the menstrual cycle. The reduced insulin secretion and action during the luteal phase are more likely due to elevated progesterone levels rather than waning estrogen levels (see below).

It is not likely that the sex differences observed in glucoregulatory end points are from testicular androgens. Billiar and colleagues (1987) treated intact cycling female rhesus monkeys with androstenedione for as long as 4½ yr, and they saw no change in circulating basal insulin, glucose tolerance, or plasma C-peptide concentration. Androstenedione can be aromatized to estrogen, which could explain the lack of effect on insulin sensitivity in the aforementioned study. In the study by Wickman and colleagues (2002), cited above, testosterone therapy given to boys with delayed puberty had no impact on insulin concentration. However, when testosterone was administered with an aromatase inhibitor, insulin concentrations decreased. This result suggests that androgens do not directly impair insulin sensitivity. Furthermore, Tyagi and colleagues (1999) treated intact male rhesus monkeys with 50 mg of testosterone enanthate bimonthly for nearly 3 yr and saw no change in glucose tolerance, although fasting insulin values decreased significantly after 27 mo of treatment and returned to baseline values within 3 mo after withdrawal of treatment. Islet cells of baboons contain receptors for estrogen and progestin, but not testosterone (Winborn et al. 1983, 1987a, 1987b), suggesting a direct role for ovarian but not testicular hormones in modulating insulin secretion. In further support of the hypothesis, female-to-male transsexual individuals treated with testosterone injections show no or only modest decrements in insulin sensitivity (Elbers et al. 2003; Polderman et al. 1994). The insulin resistance often seen in hyperandrogenic women with the polycystic ovary syndrome is associated with a more complex pathophysiology, as discussed elsewhere in this issue (Abbott et al. 2004). In conclusion, endogenous progestins impair insulin sensitivity, and endogenous estrogens and androgens appear to have minimal effects on glucoregulation. The basis for the sex differences in insulin sensitivity may therefore be more strongly associated with body composition and fat distribution, although this possibility merits further investigation.

Insulin resistance during pregnancy is discussed above in the context of an altered intrauterine environment. The effects of this insulin resistant state are also important for maternal health. Women who develop gestational diabetes, presumably from the inability to compensate for increased insulin resistance, have a significantly increased risk for future development of DM2. Prepregnancy BMI, blood glucose at diagnosis, and persistent hyperglycemia 2 mo after giving birth positively correlate with future diabetes risk (Coustan et al. 1993; Damm et al. 1992). To our knowledge, this phenomenon has not been studied in depth in nonhuman primates.

Later Life

Insulin resistance is often seen in older people, and there is increased risk of developing DM2 in later life (Muller et al. 1996). The potential role of changing levels of bioavailable gonadal hormones in this context is unclear. There is an increase in glucose and insulin levels associated with the menopausal transition (Carr 2003), which may be related to changes in body composition (Poehlman et al. 1995). Low testosterone levels in men and high testosterone levels in women predict insulin resistance and DM2 in older adults (Oh et al. 2002).

There are few reported studies of glucose tolerance and insulin sensitivity in older monkeys, largely due to the limited availability of these animals. Ramsey and colleagues (2000) compared 28- to 37-yr-old female rhesus monkeys and 23- to 37-yr-old males with younger adults. The older females were postmenopausal based on lack of menstruation and cyclic changes in sex skin coloration for at least 1 yr before study. Males had greater lean body mass than females, but there was not a significant sex difference in fat mass. Across all age groups females had greater values for glucose tolerance, and for acute and second phase insulin responses to glucose challenge, than males. There was a trend toward lower insulin responses in both older groups.

Older animals of both sexes had lower metabolic rates and decreased levels of physical activity compared with younger adults.

Contraceptive Agents

The effects of oral contraceptive agents on carbohydrate metabolism have been extensively studied in women, and this area continues to be actively investigated as new dosages and combinations of synthetic agents are evaluated and comparisons of different routes of administration are made. In general, studies of women indicate that the use of newer oral contraceptive formulations have minimal deleterious effects on glucose tolerance and insulin sensitivity and are not associated with an increased risk for development of DM2 (Adams et al. 1980; Chasan-Taber et al. 1997; Godsland and Crook 1994; Kim et al. 2002; Rimm et al. 1992; Vela and Yen 1969). As lower doses of estrogen and newer progestins with less androgenic activity and more specificity are coming into use, the side effects of oral contraceptives are further reduced (Godsland et al. 1990; Ludicke et al. 2002). Although oral, low-dose, progestin-only contraceptives have minimal metabolic effects (Godsland et al. 1990, 1992), parenteral administration of medroxyprogesterone is associated with worsening glucoregulation (Amatayakul et al. 1980), particularly with longer duration of use (Liew et al. 1985). Furthermore, Kim and colleagues (2001) reported an increased risk of developing DM2 in Navajo women using depot medroxyprogesterone for contraception. Differences in progestin formulation and route of administration may therefore be important variables with regard to metabolic effects. To our knowledge, newer transdermal contraceptives have not been studied in this context.

Surprisingly little work in this area using nonhuman primates has been published, and most of this was published more than 20 yr ago (Beck 1969, 1977; Beck et al. 1975; Goldzieher et al. 1978). A survey of glucose tolerance in zoo-housed orangutans revealed no difference between females with contraceptive implants and untreated females (Gresl et al. 2000).

Hormone Replacement Therapy

Although testosterone replacement therapy in hypogonadal men appears to have either a neutral (Tripathy et al. 1998) or a beneficial effect on insulin sensitivity (Simon et al. 2001), numerous studies of hormone replacement therapy (HRT[1]) in women have yielded variable results. Variations in the hormonal composition, doses, route of administration, and differences in study design likely account for the variable influence on insulin sensitivity.

HRT appears to attenuate the weight gain associated with menopause. Haarbo and colleagues (1991) reported that continuous oral estradiol either alone or in combination with cyproterone acetate or levonorgestrel prevents an increase in abdominal fat mass assessed by DXA in naturally postmenopausal Danish women compared with placebo. Similar findings have been reported with oral conjugated equine estrogen (CEE[1]) alone or in combination with medroxyprogesterone acetate (MPA[1]) (Reubinoff et al. 1995). Mattiasson and colleagues (2002) performed a more detailed analysis of body composition with computed tomography and found a reduction in visceral fat mass in postmenopausal women treated with estradiol and cyclic MPA.

Despite the attenuation of weight gain, several studies have reported worsening insulin sensitivity with oral HRT (Ryan et al. 2002; Soranna et al. 2002). In the Postmenopausal Estrogen/Progestin Interventions trial, HRT with continuous CEE alone or in combination with MPA or micronized progesterone was associated with an increase in glucose levels obtained 2 hr after an oral glucose load, whereas fasting glucose levels decreased slightly in the treatment groups (Writing Group for the PEPI Trial 1995). Similar results have been reported in American Indian women (Zhang et al. 2002). As with oral contraceptives, the dose of estrogen use may influence metabolic parameters. Lobo and colleagues (2001) reported that lower doses of CEE alone or combined with MPA have beneficial effects on lipid status, but only minimal dose-response changes are seen in carbohydrate metabolism. Additional studies examining dose-response are warranted.

Different formulations of estrogen may have varying effects on glucoregulation. Studies using estradiol have yielded conflicting results. The study by Soranna and colleagues (2002) cited above reported reduced insulin sensitivity in subjects randomized to continuous oral estradiol alone or in combination with dydrogesterone without concurrent changes in BMI or abdominal fat mass as estimated by the waist:hip ratio. However, in another study, insulin sensitivity was enhanced with oral estradiol, but the effect was negated when oral norethindrone acetate was added (Spencer et al. 2000). The latter result suggests that the addition of certain progestogens may be an important factor in reducing insulin sensitivity. This notion is consistent with the findings of decreased insulin sensitivity during the luteal phase of the menstrual cycle when progesterone levels are high. In further support of this hypothesis, oral estradiol in combination with MPA, but not estradiol alone, results in reduced insulin sensitivity in women with premature ovarian failure (Elkind-Hirsch et al. 1993). In other studies, treatment with CEE alone results in improved glucoregulation, and these effects are attenuated by the addition of a progestin (Lindheim et al. 1993; Lobo et al. 1994).

The route of administration of HRT may also influence glucoregulation because transdermal steroids do not undergo first pass metabolism by the liver (Ansbacher 2001). Transdermal estradiol tends to have a neutral or beneficial effect on insulin sensitivity in normoinsulinemic women (Cucinelli et al. 1999; Duncan et al. 1999; Godsland et al. 1993; Raudaskoski et al. 1999; Spencer et al. 2000). The addition of oral progestins with low androgenic potential

(Duncan et al. 1999; Godsland et al. 1993) or transdermal progestins (Stevenson et al. 1993) appear to have little effect on insulin sensitivity.

HRT appears to have a neutral or beneficial effect on glucose metabolism in women who have insulin resistance or diabetes. In the study by Cucinelli and colleagues (1999) cited above, a subgroup of hyperinsulinemic women had a significant reduction in plasma insulin and insulin area under the curve with transdermal estradiol alone or with combination therapy. Other studies have reported similar findings in insulin-resistant women treated with oral continuous combined HRT with CEE and MPA (Saglam et al. 2002; Sumino et al. 2003). Based on the Third National Health and Nutrition Examination Survey (NHANES III[1]), women with DM2 on HRT have lower fasting glucose levels than never users (Crespo et al. 2002). Another evaluation of NHANES III data shows a neutral effect on fasting glucose, and A1c, a marker of glucose control, although postchallenge glucoses are slightly higher in HRT users (Triusu et al. 2000). The two evaluations of the NHANES III used different inclusion criteria, therefore the sample sizes were different. Araujo and colleagues (2002) reported no deleterious effects on glucose metabolism in women with DM2 treated with oral CEE or transdermal estradiol combined with micronized progesterone. Additional studies show improvements in measures of glucose control in women with DM2 treated with oral estradiol alone (Andersson et al. 1997) and CEE alone (Friday et al. 2001) or in combination with MPA (Manning et al. 2001). Other small studies show improved glucoregulation in women with DM2 taking oral or transdermal estradiol as part of combination HRT (Borissova et al. 2002; Darko et al. 2001).

Despite this apparent beneficial effect on glucose metabolism, women with diabetes mellitus who used HRT had an increased risk of ischemic heart disease, myocardial infarction, and death compared with never users in a prospective observational study of Danish nurses (Lokkegaard et al. 2003). Although subjects with known cardiac disease at baseline were excluded, it is conceivable that women with asymptomatic heart disease participated in the study. In this case, the findings from this study are consistent with increased thrombotic events reported in secondary prevention trials (Hulley et al. 1998). A previous case control study showed no increased risk of myocardial infarction in diabetic women using HRT (Kaplan et al. 1998).

HRT is associated with a neutral or reduced risk of developing diabetes. The Rancho Bernardo Heart and Chronic Disease Study reported no altered risk of developing diabetes in women on HRT in a community-based cohort of postmenopausal Caucasian women (Gabal et al. 1997). Similar findings were demonstrated in the prospective study of a subgroup of mainly white, healthy postmenopausal women in the Nurses' Health Study (Manson et al. 1992). In the Heart and Estrogen/Progestin Replacement Study, combined HRT with CEE and MPA is associated with a reduced risk of developing diabetes in postmenopausal women with coronary disease (Kanaya et al. 2003).

The North American Menopause Society recommends that women with insulin resistance or diabetes who desire HRT for menopausal symptom relief should use continuous-cyclic HRT with a low-dose, oral micronized progesterone (NAMS 2003). Alternatively, vaginal or intrauterine progesterone may decrease the adverse metabolic effects associated with progesterone use.

Similar to HRT, the few examples in the literature of studies that have investigated the effects of the selective estrogen receptor modulator raloxifene provide inconsistent results with both neutral (Cucinelli et al. 2002) and negative effects on glucoregulation in nondiabetic postmenopausal women (Lee et al. 2003). Additional studies have reported neutral effects on glucoregulation in women with DM2 (Andersson et al. 2002; Barrett-Connor et al. 2003). Additional studies are needed in this regard.

Biases related to study design have made it difficult to draw conclusions about the risks and benefits of HRT in women as evidenced by the recent Women's Health Initiative study (Rossouw et al. 2002). Therefore, studies of HRT in nonhuman primates may provide useful information because many biases (e.g., self-selection) can be minimized. However, most studies of HRT in monkeys have been in the context of surgical menopause in younger monkeys, mimicking the postmenopausal condition. Whether surgical withdrawal of ovarian hormones, particularly in young monkeys, is an entirely appropriate model of menopause is a matter of some debate (Bellino and Wise 2003), but studies using this approach have generated useful data.

Middle-aged ovariectomized rhesus monkeys were studied during periods of treatment with estradiol alone, progesterone alone, and estradiol plus progesterone (Kemnitz et al. 1989a). In this study, there were no detectable effects of hormone treatment on fasting glucose levels or glucose tolerance during intravenous glucose tolerance tests, but progesterone treatment significantly increased insulin levels. Both fasting insulin concentration and insulin response to glucose challenge were increased by approximately 50% during treatments with progesterone alone or with the combination of estradiol plus progesterone.

Wagner and colleagues (1996) studied ovariectomized female cynomolgus monkeys fed a lipid-lowering diet and given no HRT, CEE alone, or CEE combined with MPA for 30 mo. Monkeys receiving combined hormone replacement had significantly higher fasting glucose and insulin levels and higher insulin responses to a glucose challenge compared with controls or those given estrogen alone. Monkeys given estrogen-only therapy had lower body weights, lower measures of abdominal adiposity, and decreased serum androgen concentrations.

Wagner and colleagues (1998) subsequently studied ovariectomized adult female cynomolgus monkeys fed a moderately atherogenic diet, with one of the following three treatments added to the diet: no treatment (control), CEE alone, or CEE combined with nomegestrol acetate, a progestin without androgenic activity. Insulin sensitivity was assessed after 10 wk of treatment. In contrast to their studies

of CEE and MPA, CEE plus nomegestrol treatment, although reducing the insulin sensitivity to less than that of the CEE only group, did not reduce the insulin sensitivity index to less than that of control monkeys.

Cefalu and colleagues (1994) studied surgically postmenopausal cynomolgus monkeys that were fed a moderately atherogenic diet for 12 wk and received no treatment (control), CEE, MPA, a combination CEE and MPA, or tamoxifen. Compared with control animals or CEE alone, insulin sensitivity was significantly decreased in animals treated with MPA or CEE combined with MPA. Although insulin sensitivity was decreased in the tamoxifen-treated animals, the difference was not statistically significant compared with the control or CEE-treated animals. These results suggest that progestins alone or in combination with estrogens can induce insulin resistance in postmenopausal monkeys.

More recently, Shadoan and colleagues (2003) investigated the effects of tibolone (a synthetic steroidal agent with estrogenic, progestogenic, and androgenic activity) on body weight, body composition, and fasting carbohydrate measures in surgically postmenopausal cynomolgus monkeys that were compared with those receiving CEE with and without MPA. Compared with controls, body weight significantly increased and abdominal soft tissue mass was greater in all but the CEE-treated group. They concluded that HRT with CEE combined with MPA or tibolone results in greater body weight, abdominal soft tissue, and insulin resistance compared with control-treated monkeys.

To summarize, although the human studies of oral HRT are inconsistent, HRT is not associated with an increased risk of DM2, and transdermal estrogens appear to have little impact on insulin sensitivity. HRT has neutral to beneficial effects on glucoregulation in women with diabetes, but additional studies are needed to investigate whether HRT alters cardiac endpoints in this population. The nonhuman primate studies indicate that deleterious effects of HRT on glucoregulation may be related more to the progestin than to the estrogen. Additional investigations of the effect of selective estrogen receptor modulators on insulin sensitivity are warranted.

Conclusion

There are striking similarities among macaques, baboons, and humans in body composition, insulin sensitivity, and development of DM2, which supports the use of the nonhuman primate model in this context. The nonhuman primate model holds particular value for assessing sex differences in factors related to insulin sensitivity as well as benefits and risks of hormonal treatment of adults during later life. In light of the recent reports of deleterious consequences of HRT on cardiovascular health in women, additional studies of nonhuman primates that explore new dosages, combinations, and routes of administration of hormones and selective estrogen receptor modulators are needed.

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