Original Article

Effects of Sex and Hormone Replacement Therapy Use on the Prevalence of Isolated Impaired Fasting Glucose and Isolated Impaired Glucose Tolerance in Subjects With a Family History of Type 2 Diabetes

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Impaired fasting glucose (IFG) is more prevalent in men and impaired glucose tolerance (IGT) more prevalent in women. To explore whether this sex difference is related to female sex hormones, we performed a cross-sectional analysis of data from 2,164 (1,329 women and 835 men) first-degree relatives of individuals with type 2 diabetes. Subjects were categorized based on a 75-g oral glucose tolerance test. Sex and hormone replacement therapy (HRT) effects on the distribution of glucose tolerance were assessed using multinomial logistic regression corrected for familial clustering. Compared with men, women were more likely to have isolated IGT (relative risk 1.8 [95% CI 1.3–2.5]) and less likely to have isolated IFG (0.5 [0.3–0.7]) adjusted for ethnicity, age, waist, fasting insulin, and early insulin release ($\Delta I_{0-30}/\Delta G_{0-30}$). To evaluate HRT effects, postmenopausal women using (n = 238) or not using (n = 378) HRT were compared. HRT users were more likely to have isolated IGT (2.2 [1.2–4.0]) after adjustment, but the prevalence of isolated IFG did not differ by HRT status. Based on the influence of sex and HRT on the prevalence of isolated IFG and isolated IGT, we conclude that female sex hormones may play an important role in the pathogenesis of IFG and IGT. *Diabetes* 55:3529–3535, 2006

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FPG, fasting plasma glucose; GENNID, Genetics of Type 2 Diabetes; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HRT, hormone replacement therapy; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

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The reclassification of glucose tolerance in 1997 included the subdivision of impaired glucose regulation into both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (1). When first defined, these both were expected to represent states of increased risk for developing type 2 diabetes and thus frequently have been referred to as pre-diabetes. Since that time, it has become clear that these two states do not always occur in the same individuals and that their pathogenesis may be different (2–6).

In line with the fact that IFG and IGT may independently occur and may differ in their etiology, it has been reported that the prevalence of IFG and IGT differs by sex, with IFG being more prevalent in men and IGT more prevalent in women (6–12). The reason(s) for this sex difference in glucose metabolism has not been explored, but some studies suggest that female sex hormones may contribute. In the Women's Health Initiative, when compared with placebo, the combination of estrogen and progesterone was associated with a decreased incidence of diabetes (13) and there was a trend for a decreased incidence of diabetes in the estrogen-only arm (P = 0.07) (14). After the 1st year of treatment, both the combination of estrogen plus progesterone and the estrogen-alone groups demonstrated decreased fasting plasma glucose (FPG) and decreased insulin resistance, as measured by the homeostasis model assessment of insulin resistance (13,14). Similarly, the Heart and Estrogen/Progestin Replacement Study showed a lower incidence of diabetes in women using combination hormone replacement therapy (HRT) (15). However, neither the Women's Health Initiative nor the Heart and Estrogen/Progestin Replacement Study performed oral glucose tolerance tests (OGTTs) to determine the effect of treatment on postchallenge plasma glucose. Studies that have measured both fasting and 2-h plasma glucose levels have shown that the beneficial effects of HRT on the fasting glucose were accompanied by adverse effects on the 2-h glucose (16–18), while others failed to see an effect on glucose metabolism (19–21).

While IFG and IGT both are known to increase the risk of developing diabetes, there are a number of other factors that also influence progression to hyperglycemia, including a family history of type 2 diabetes (22,23). As the

prevalence of type 2 diabetes increases (24), the number of people with a family history of type 2 diabetes, and thus an increased risk of developing diabetes, will also increase. We therefore examined the prevalence of impaired glucose status in first-degree relatives of individuals with type 2 diabetes, specifically addressing the effect of sex and HRT use on the prevalence of isolated IFG and isolated IGT.

RESEARCH DESIGN AND METHODS

The Genetics of Type 2 Diabetes (GENNID) study was conducted between 1993 and 2002 at multiple centers in the U.S. The design and methods used in this study previously have been described (25). Briefly, families with at least two siblings with type 2 diabetes were recruited. At each site, the study was approved by the local institutional review board, and written informed consent was obtained from each participant.

Details on a total of 7,234 subjects were available in the GENNID study database. This included 270 subjects who were historical subjects and did not have a study visit and 307 subjects who had no family history of diabetes. Thus, there were 6,657 subjects who either had diabetes and were listed as the proband or had a first-degree relative with type 2 diabetes and had laboratory and medical questionnaire data available. Subjects with no prior history of diabetes underwent a standard OGTT. A total of 2,164 of these subjects had sex, FPG, and 120-min glucose data available. Data on age (n = 2,161), ethnicity (n = 2,164), waist circumference (n = 1,901), fasting insulin (n = 2,152), and the early insulin response (n = 1,907) were available in a majority of subjects. Thus, for the current analysis, we examined data from 2,164 (835 men and 1,329 women) subjects from 864 families. Subjects also completed a self-reported medical/family history questionnaire, underwent anthropometric measurements, and had other laboratory data collected.

Postmenopausal women were subdivided into two groups based on self-reported HRT use. The group using HRT reported current use of HRT (HRT users; n = 238), while the group that was not using HRT (non-HRT users; n = 378) consisted of those who reported that they had never used HRT (n = 290), those who had used HRT in the past but not currently (n = 83), and those who did not report never versus past use (n = 5). Information regarding the type of HRT used, length of treatment, or route of administration was not available. However, 148 of 184 women on HRT reported having had a hysterectomy an average of 18.0 ± 10.5 years before enrolling in the study. These women were presumed to have been on estrogen alone.

A standard 75-g OGTT was performed in the morning after a 10-h overnight fast. Subjects were told to refrain from smoking and did not take medications on the morning of the test. Blood samples were drawn at baseline and at 30 and 120 min after glucose ingestion. These samples were collected in EDTA and were separated and stored at −20°C before being assayed. Glucose was measured in duplicate using a hexokinase method (Glucose/HK; Boehringer Mannheim, Indianapolis, IN), and insulin was measured by radioimmunoassay (Linco Research, St. Louis, MO). Height, weight, and waist circumference were measured three times using a common protocol (25). The average of the three measurements was used. The self-reported medical/family history questionnaire that each subject completed was used to determine age, menopausal status, and HRT use.

Classification of glucose tolerance. Using the 2003 American Diabetes Association criteria for fasting and 2-h plasma glucose concentrations (26), subjects were categorized as having normal glucose tolerance (NGT) (FPG <5.6 mmol/l and 2-h plasma glucose <7.8 mmol/l), isolated IFG (FPG 5.6–6.9 mmol/l and 2-h plasma glucose <7.8 mmol/l), isolated IGT (FPG <5.6 mmol/l and 2-h plasma glucose 7.8–11.0 mmol/l), or both IFG and IGT or diabetes (FPG ≥7.0 mmol/l and/or 2-h plasma glucose ≥11.1 mmol/l).

Calculations and statistical analysis. Insulin resistance was estimated by fasting insulin. The early insulin response to oral glucose was calculated as the ratio of the change in insulin to the change in glucose over the first 30 min of the OGTT ($\Delta I_{0-30}/\Delta G_{0-30}$): (30-min insulin − fasting insulin [pmol/l])/(30-min glucose − fasting glucose [mmol/l]).

Statistical analysis was performed using STATA version 9.0 (StataCorp, College Station, TX). Comparisons of variables between men and women and between HRT users and non-HRT users were performed using regression analysis corrected for familial clustering. Variables that were not normally distributed were ln transformed to achieve a normal distribution. To test the effect of sex and HRT use on glucose tolerance, four different multinomial logistic regression models were used. The first model contained either sex or HRT as the independent variable. The second model added ethnicity and age. Model 3 added waist circumference to model 2. Model 4 added fasting insulin and $\Delta I_{0-30}/\Delta G_{0-30}$ to model 3. For each model, the glucose tolerance categories were the dependent variables. To determine whether sex and hormonal differences in IFG and IGT extended to the diagnosis of diabetes by either fasting or 2-h glucose, a similar analysis was performed with the diagnostic criterion for diabetes diagnosis (by FPG alone, 2-h plasma glucose alone, or both) as the dependent variable. All multinomial logistic regression analyses were corrected for familial clustering using the generalized estimating equation approach (27).

Data that were normally distributed are presented as means ± SD. Non–normally distributed data are presented as median (interquartile range). For the multiple regression models, the relative risks (RRs) and the 95% CIs are provided. A $P < 0.05$ was considered statistically significant.

RESULTS

The study group was composed of 2,164 subjects (835 men and 1,329 women). Among these individuals, 701 (32.4%) were categorized as having NGT, 191 (8.8%) as having isolated IFG, 369 (17.1%) as having isolated IGT, 292 (13.5%) as having both IFG and IGT, and 611 (28.2%) as having diabetes. The ethnic background of the population was diverse, with 41.6% being of Caucasian origin, 35.1% Hispanic, 16.1% African American, and 7.2% other.

Effect of sex on the distribution of glucose tolerance. The characteristics of men and women by glucose tolerance category are shown in Table 1. Overall, whereas BMI was greater in women ($P < 0.001$), waist circumference was larger in men ($P < 0.01$). FPG was higher in men ($P < 0.001$), but there was no significant difference in 2-h glucose by sex. As illustrated in Fig. 1*A*, isolated IFG was more frequent in men than in women (13.1 vs. 6.2%), whereas isolated IGT was more frequent in women than in men (20.7 vs. 11.3%). The distribution of NGT, IFG and IGT, and diabetes did not show major differences by sex.

Multinomial logistic regression corrected for familial clustering confirmed that when compared with NGT status, isolated IGT was more likely to occur in women and isolated IFG was less likely (model 1; Table 2). Age was an additional determinant of the distribution of isolated IGT, the combination of IFG and IGT, and diabetes but not of isolated IFG. Ethnicity did not affect the distribution of isolated IFG or isolated IGT. Waist circumference was independently associated with an increased risk of isolated IFG, isolated IGT, the combination of IFG and IGT, and diabetes. Both fasting insulin and $\Delta I_{0-30}/\Delta G_{0-30}$ were independently associated with isolated IFG and isolated IGT. However, the sex difference in IFG and IGT remained significant even after adjustment for all of the above variables (model 4; Table 2). When isolated IGT and isolated IFG were directly compared, women were more likely to have isolated IGT than isolated IFG relative to men, even after adjustment (model 1: RR 3.89 [95% CI 2.68–5.64], model 2: 3.94 [2.71–5.71], model 3: 4.07 [2.68–6.17], and model 4: 4.03 [2.62–6.18]).

A total of 611 subjects (372 women and 239 men) were diagnosed with diabetes: 3.8% (3.8% women and 3.8% men) by FPG alone, 51.7% (56.4% women and 44.3% men) based on the 2-h glucose alone, and 44.5% (39.8% women and 51.9% men) based on both the fasting and 2-h glucose. By multiple logistic regression analysis corrected for familial clustering with diagnosis by 2-h glucose as the comparison group, men were more likely to be diagnosed using both FPG and 2-h glucose relative to women (RR 1.66 [95% CI 1.20–2.30]), and this effect remained significant after adjustment for age, ethnicity, and waist circumference (1.75 [1.22–2.50]) but was lost when fasting insulin and $\Delta I_{0-30}/\Delta G_{0-30}$ were added to the model. There was no significant sex difference in the diagnosis by FPG alone.

TABLE 1
Characteristics of the glucose tolerance categories by sex and by HRT use in postmenopausal women

	Men (n = 835)						Women (n = 1,329)					
	All	NGT	Isolated IFG	Isolated IGT	IFG + IGT	Diabetes	All	NGT	Isolated IFG	Isolated IGT	IFG + IGT	Diabetes
n (%)	835 (38.6)	264 (31.6)	109 (13.0)	94 (11.3)	129 (15.5)	239 (28.6)	1,329 (61.4)	437 (32.9)	82 (6.1)	275 (20.7)	163 (12.3)	372 (28.0)
Age (years)	53.1 ± 15.8	47.8 ± 16.7	48.0 ± 13.9	59.1 ± 16.5	52.7 ± 14.7	59.2 ± 12.7	52.9 ± 15.4	47.4 ± 15.4	53.2 ± 13.4	54.2 ± 15.8	53.3 ± 15.5	58.3 ± 13.4
BMI (kg/m^2)	29.3 ± 6.6*	28.6 ± 8.1	28.9 ± 5.1	27.9 ± 5.8	29.6 ± 5.4	30.5 ± 6.2	31.0 ± 11.6	28.9 ± 7.8	31.2 ± 7.4	30.4 ± 8.1	34.8 ± 23.7	32.2 ± 9.3
Waist circumference (cm)	100.8 ± 13.8†	97.7 ± 15.4	100.2 ± 13.9	98.0 ± 11.5	102.5 ± 12.5	104.4 ± 12.7	98.6 ± 16.5	93.0 ± 16.2	100.4 ± 16.6	97.6 ± 15.0	104.7 ± 16.5	102.7 ± 16.1
FPG (mmol/l)	6.1 ± 1.9*	5.0 ± 0.4	5.9 ± 0.3	5.2 ± 0.3	6.1 ± 0.4	7.9 ± 2.7	5.8 ± 1.8	5.0 ± 0.4	5.8 ± 0.3	5.1 ± 0.3	6.0 ± 0.3	7.4 ± 2.6
2-h plasma glucose (mmol/l)	9.4 ± 4.3	5.8 ± 1.2	6.3 ± 1.0	9.1 ± 0.9	9.2 ± 0.9	14.9 ± 3.8	9.6 ± 4.0	6.2 ± 1.1	6.7 ± 0.9	9.1 ± 0.9	9.5 ± 1.0	14.7 ± 3.8
Fasting insulin (pmol/l)	63.7 (60.7)	48.0 (46.4)	66.3 (66.7)	53.5 (57.5)	69.0 (59.1)	83.7 (76.7)	61.8 (59.3)	45.5 (38.4)	63 (60)	55.6 (47.1)	83.5 (67.3)	90.0 (73.6)
$\Delta I_{0-30}/\Delta G_{0-30}$ ([pmol/l]/[mmol/l])	106.5 (97.0)	114.5 (127.2)	96.7 (86.7)	88.4 (87.8)	78.6 (88.2)	32.6 (41.6)	84.6 (99.8)	121.3 (132.5)	127.6 (98.7)	94.6 (95.6)	90.6 (73.7)	43.9 (53.6)

	Postmenopausal women only											
	Non-HRT users (n = 378)						HRT users (n = 238)					
	All	NGT	Isolated IFG	Isolated IGT	IFG + IGT	Diabetes	All	NGT	Isolated IFG	Isolated IGT	IFG + IGT	Diabetes
n (%)	378 (61.4)	94 (24.9)	27 (7.1)	64 (16.9)	50 (13.2)	143 (37.8)	238 (38.6)	55 (23.1)	11 (4.6)	69 (29.0)	29 (12.2)	74 (31.1)
Age (years)	65.7 ± 10.7*	63.9 ± 11.0	65.6 ± 7.0	65.7 ± 12.4	66.2 ± 10.3	66.7 ± 10.4	61.8 ± 9.0	58.6 ± 9.4	61.7 ± 5.2	64.1 ± 8.3	61.4 ± 8.3	62.3 ± 9.4
BMI (kg/m^2)	31.3 ± 17.1	28.8 ± 8.5	30.3 ± 8.1	30.7 ± 7.7	37.8 ± 41.9	31.0 ± 8.4	29.8 ± 7.6	29.5 ± 6.9	31.9 ± 7.6	29.0 ± 7.7	30.9 ± 5.8	30.2 ± 8.7
Waist circumference (cm)	100.7 ± 14.2	97.2 ± 15.6	103.4 ± 15.3	100.2 ± 12.9	103.8 ± 15.3	101.6 ± 13.2	98.6 ± 16.1	95.9 ± 16.4	103.4 ± 18.1	96.9 ± 16.6	103.3 ± 14.0	99.6 ± 15.8
FPG (mmol/l)	6.1 ± 1.9*	5.0 ± 0.4	5.9 ± 0.3	5.1 ± 0.3	6.0 ± 0.3	7.3 ± 2.6	5.6 ± 1.1	5.0 ± 0.3	5.8 ± 0.2	5.1 ± 0.4	6.0 ± 0.3	6.5 ± 1.5
2-h plasma glucose (mmol/l)	10.4 ± 4.4	6.1 ± 1.0	6.4 ± 1.0	9.0 ± 0.8	9.8 ± 0.9	14.7 ± 3.9	10.0 ± 3.4	6.3 ± 1.1	7.0 ± 0.9	9.4 ± 0.9	9.5 ± 0.9	13.9 ± 2.7
Fasting insulin (pmol/l)	66.96 (56.1)*	49.1 (42.96)	60.0 (57.1)	58.3 (35.5)	81.48 (56.3)	89.1 (68.5)	54.3 (41.5)	43.8 (32.9)	54.0 (38.0)	47.5 (31.0)	71.1 (45.5)	60.0 (67.2)
$\Delta I_{0-30}/\Delta G_{0-30}$ ([pmol/l]/[mmol/l])	76.1 (73.0)	109.4 (111.2)	112.8 (75.4)	87.4 (60.5)	72.1 (56.1)	47.8 (54.8)	64.7 (72.5)	74.8 (127.2)	63.7 (84.7)	70.1 (67.6)	102.5 (76.7)	39.9 (53.3)

Data are means ± SD or median (interquartile range). *$P < 0.001$; †$P < 0.01$.

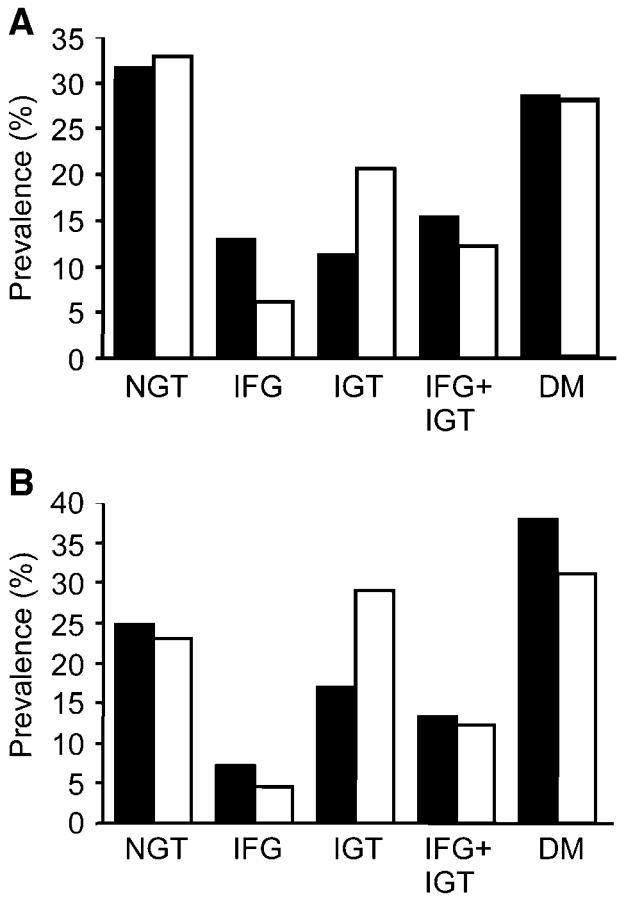

FIG. 1. Distribution of glucose tolerance categories in 2,164 subjects subdivided by sex (■, 835 men; □, 1,329 women) (*A*) and HRT use (■, 378 non-HRT users; □, 238 HRT users) (*B*). The statistical analysis corrected for familial clustering is presented in the text.

Effect of menopausal status on the distribution of glucose tolerance. There were 443 premenopausal and 632 postmenopausal women. As expected, postmenopausal women were older (64.2 ± 10.3 vs. 37.3 ± 8.9 years). The uncorrected prevalence values for postmenopausal versus premenopausal women were 24.4 vs. 46.2% for NGT, 6.2 vs. 6.6% for isolated IFG, 21.5 vs. 19.2% for isolated IGT, 12.6 vs. 11.1% for IFG plus IGT, and 35.3 vs. 16.9% for diabetes. Relative to premenopausal women, using multinomial logistic regression corrected for familial clustering with NGT as the comparison, postmenopausal status was associated with an increased risk of isolated IFG (RR 1.79 [95% CI 1.08–2.98]), isolated IGT (2.13 [1.47–3.08]), IFG plus IGT (2.17 [1.44–3.28]), and diabetes (3.96 [2.81–5.57]). When age and ethnicity were included in the model, postmenopausal status was no longer associated with an increased risk, in keeping with age being a very strong confounder. The findings were similar when postmenopausal women on HRT were excluded (data not shown).

Effect of HRT on the distribution of glucose tolerance. To determine whether HRT use altered the distribution of the glucose tolerance categories, postmenopausal women who were using HRT were compared with postmenopausal women who were not. The group of nonusers also contained past users, but excluding them from the analysis did not change the results (data not shown). The demographic and phenotypic characteristics of the women based on whether they were or were not using HRT are listed in Table 1. Women who were using HRT were slightly younger ($P < 0.001$) and had lower FPG ($P = 0.001$) and fasting insulin levels ($P < 0.01$) than non-HRT users. HRT users had a lower prevalence of isolated IFG (4.6 vs. 7.1%) but a higher prevalence of isolated IGT (29.0 vs. 16.9%; Fig. 1*B*) when compared with women not using HRT.

By multinomial logistic regression analysis corrected for familial clustering with NGT as the comparison group, women using HRT were more likely to have isolated IGT (model 1; Table 2) than women who were not using HRT. HRT use remained associated with an increased risk of isolated IGT, even after adjusting for age, ethnicity, waist circumference, fasting insulin, and $\Delta I_{0-30}/\Delta G_{0-30}$ (models 2, 3, and 4; Table 2).

When the prevalence of isolated IGT and isolated IFG was compared directly, women using HRT were more likely to have isolated IGT (RR 2.65 [95% CI 1.22–5.74]), and this difference remained significant even after adjusting for age and ethnicity (2.80 [1.27–6.19]) but was lost when waist circumference was added to the model (2.40 [0.91–6.36]).

A total of 217 postmenopausal women were diagnosed with diabetes based on the OGTT results (HRT users versus non-HRT users: 2.7 vs. 2.8% by FPG, 71.6 vs. 53.8% by 2-h glucose, and 25.7 vs. 43.4% by both). By multiple logistic regression analysis corrected for familial clustering with diagnosis by 2-h glucose alone as the comparison group, HRT users were less likely to be diagnosed by both the FPG and the 2-h glucose relative to non-HRT users (RR 0.45 [95% CI 0.24–0.83]), and this decreased risk remained even after adjustment for age, ethnicity, waist circumference, fasting insulin, and $\Delta I_{0-30}/\Delta G_{0-30}$ (0.27 [0.10–0.71]). There was no significant HRT difference in the diagnosis by FPG alone.

DISCUSSION

Our results show that in a population of first-degree relatives of subjects with type 2 diabetes, there is a significant sex difference in the prevalence of isolated IFG and isolated IGT, with isolated IFG being more prevalent in men and isolated IGT more common in women. To better understand this sex difference in early dysglycemia, data on postmenopausal women were analyzed by use of HRT. HRT use in postmenopausal women was associated with a lower fasting glucose level and an increased RR of isolated IGT, suggesting that the observed sex differences in the prevalence of isolated IFG and IGT may be mediated by female sex hormones. These differences by sex and HRT use extended also to the diagnosis of diabetes with men and non-HRT users being more likely to be diagnosed by both the fasting and the 2-h glucose values compared with women and HRT users who were more likely to be diagnosed by the 2-h glucose value alone.

Our study is, to our knowledge, the first to examine possible reasons for the sex difference in the prevalence of isolated IFG and isolated IGT. Other studies that have examined both the fasting and 2-h glucose levels support our observations. In the Postmenopausal Estrogen/Progestin Intervention study, estrogen administration was associated with a modest decrease in the fasting glucose concentrations and a modest increase in the 2-h plasma glucose concentrations, and this change was not affected by addition of progesterone (16). In both the Third Na-

tional Health and Nutrition Examination Survey (17) and the Strong Heart Study (18), postmenopausal estrogen use was associated with lower fasting glucose levels and higher 2-h glucose levels, but the effect of therapy on categorization of glucose tolerance was not addressed. Other studies (13,15,28,29) have examined the effect of estrogen on the fasting glucose but not postprandial glucose levels and have also found that estrogen therapy decreases fasting glucose. Our observations therefore extend all these findings by highlighting that HRT in postmenopausal women alters the distribution of isolated IFG and isolated IGT.

The underlying mechanisms whereby estrogen is associated with decreased fasting glucose are not clear. While our study is a cross-sectional epidemiologic study and thus is unable to make conclusions about cause or effect, other studies suggest that estrogen may be influencing fasting glucose levels by impacting insulin sensitivity. Pima Indians with isolated impaired fasting glucose have been shown to have increased basal endogenous glucose production (30), suggesting that impaired fasting glucose is due to inadequate basal insulin that is required to suppress endogenous glucose production. There are little data on the effects of hormone therapy on hepatic insulin sensitivity in humans. In one study (31), treatment of menopausal women with oral estrogen plus progesterone versus placebo did not result in differences in basal endogenous glucose production or improvement in hepatic insulin sensitivity. Thus, whether the decrease in FPG associated with female hormones is due to effects of estrogen to improve hepatic insulin sensitivity is not yet clear.

Likewise, the mechanism(s) underlying the association between female hormones and increased postprandial glucose has not been well explored, but there are some data suggesting that HRT use is associated with decreases in whole-body glucose uptake. Oral estrogen plus progesterone treatment versus placebo was shown to result in decreased whole-body insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp technique (31). This decrease in insulin sensitivity was not accompanied by changes in fat mass or intra-abdominal fat as measured by a computed tomography scan and was reversed to the level of the placebo-treated group 1 year after the trial ended (31). This suggests that estrogen may have direct effects on insulin sensitivity. Insulin sensitivity, as measured by the clamp technique, was also demonstrated to be 31% lower in women on oral estrogen and 26% lower in women on estrogen plus progesterone compared with women not on HRT who were matched for age, weight, and BMI (32). However, others have not demonstrated changes in insulin sensitivity with either oral (33,34) or transdermal (19,35) hormone treatment.

Our study was limited to a cohort of individuals who are at increased risk of developing type 2 diabetes, as they had a first-degree relative with the disease. This group of individuals will only increase further over time as the prevalence of diabetes is expected to increase worldwide from 2.8% in 2000 to 4.4% in 2030 (24). In our cohort, which was recruited between 1993 and 2002, we found a very high prevalence of previously undiagnosed diabetes (27.7%), a proportion that exceeds that of both diagnosed and undiagnosed diabetes in the general U.S. population (36). However, in this at-risk group, we observed that the sex-based differences in isolated IFG and isolated IGT were similar to those previously reported for other groups (6–12) and that HRT appeared to have a similar effect on glucose as reported in other populations (16–18). This effect was independent of the fact that we had sampled families, as we corrected our analyses for familial clustering. Thus, we believe our findings are applicable to the general population when considering the role of female sex hormones on glucose tolerance.

There are several limitations to our study. First, it was cross-sectional and thus we are unable to determine cause and effect. However, the Postmenopausal Estrogen/Progestin Intervention study found that HRT treatment for 3 years was associated with reduced fasting and increased 2-h glucose levels (16), which would be predicted to increase the prevalence of IGT. Second, we used self-reported data to determine menopausal and HRT status, and we did not have information to be able to discern possible differential effects of estrogen with or without progesterone or possible differential effects of oral versus transdermal estrogen. In the Postmenopausal Estrogen/Progestin Intervention study, no effect of progesterone above and beyond that of estrogen was observed (16). Inclusion of women using transdermal estrogen would have made it more difficult for us to detect differences, as transdermal estrogen would be expected to have fewer effects on glucose metabolism, given its lack of a first-pass effect in the liver. Third, we do not have data on the phase of the menstrual cycle in which premenopausal women were studied. However, we do not believe this to be a confounder as the sex-related differences in the prevalence of isolated IGT and isolated IFG remained significant even after adjusting for both fasting insulin and the insulin response, parameters that possibly may have been affected by the phase of the menstrual cycle (37). Finally, there may have been a selection bias in the analysis of diagnosis of diabetes by FPG, 2-h glucose, or both FPG and 2-h glucose, as subjects with previously diagnosed diabetes (most commonly diagnosed in the community by an elevated fasting blood glucose value) did not undergo an OGTT test and thus were not included in the analysis.

The findings based on HRT use in our study are important for understanding the underlying pathophysiology of impaired glucose regulation but have little relevance to clinical practice in terms of HRT use, given the concerns about long-term safety raised by the Women's Health Initiative. However, even though the prevalence of diabetes in men and women in our study was similar, suggesting that the observed sex differences in isolated IGT and isolated IFG equilibrate during the progression to diabetes, the increased prevalence of isolated IGT in women does mean that more women who are at high risk for developing diabetes will be missed if just an FPG is used for screening, and this may have clinical implications. Perhaps of more clinical importance is that approximately half the subjects diagnosed with diabetes were diagnosed based on the 2-h glucose alone and would have been missed with just a FPG.

In summary, we observed a sex-based difference in the distribution of isolated IFG and isolated IGT in individuals with a family history of type 2 diabetes. This difference was also observed in postmenopausal women who were or were not using HRT, suggesting that female sex hormones may mediate differences in glucose tolerance. Further studies in humans are needed to better understand whether and in what manner female hormones may impact glucose regulation.

TABLE 2
Multinomial logistic regression models for the relationship between the glucose tolerance categories and sex and HRT use

	Isolated IFG	Isolated IGT	IFG + IGT	Diabetes
Sex				
Model 1				
Sex	0.45 (0.33–0.63)	1.77 (1.34–2.34)	0.99 (0.57–1.71)	0.94 (0.75–1.17)
Model 2				
Sex	0.45 (0.33–0.63)	1.78 (1.34–2.36)	0.76 (0.58–1.00)	0.95 (0.75–1.20)
Ethnicity	1.04 (0.90–1.20)	1.06 (0.93–1.20)	1.15 (1.01–1.32)	1.30 (1.16–1.47)
Age	1.01 (1.00–1.02)	1.04 (1.03–1.05)	1.02 (1.01–1.03)	1.05 (1.04–1.06)
Model 3				
Sex	0.43 (0.30–0.63)	1.76 (1.30–2.38)	0.78 (0.58–1.07)	1.00 (0.77–1.30)
Ethnicity	1.01 (0.86–1.18)	1.03 (0.91–1.18)	1.10 (0.95–1.27)	1.26 (1.11–1.44)
Age	1.01 (0.99–1.02)	1.04 (1.03–1.05)	1.03 (1.02–1.04)	1.06 (1.05–1.07)
Waist circumference	1.02 (1.01–1.03)	1.01 (1.00–1.02)	1.04 (1.03–1.05)	1.04 (1.03–1.05)
Model 4				
Sex	0.45 (0.30–0.67)	1.81 (1.32–2.49)	0.81 (0.58–1.15)	1.27 (0.88–1.82)
Ethnicity	0.96 (0.82–1.13)	1.03 (0.90–1.19)	1.03 (0.89–1.20)	1.03 (0.88–1.22)
Age	1.01 (0.99–1.02)	1.03 (1.02–1.05)	1.02 (1.01–1.03)	1.06 (1.05–1.07)
Waist circumference	1.01 (0.99–1.02)	1.01 (0.99–1.02)	1.02 (1.00–1.03)	1.01 (0.99–1.02)
ln(fasting insulin)	3.17 (2.02–4.98)	2.34 (1.76–3.11)	7.38 (5.07–10.73)	24.43 (15.14–39.43)
$\ln(\Delta I_{0-30}/\Delta G_{0-30})$	0.50 (0.36–0.69)	0.43 (0.33–0.56)	0.19 (0.13–0.26)	0.05 (0.03–0.07)
HRT use				
Model 1				
HRT use	0.70 (0.33–1.48)	1.84 (1.14–2.98)	0.99 (0.57–1.71)	0.88 (0.58–1.35)
Model 2				
HRT use	0.76 (0.35–1.61)	2.12 (1.28–3.52)	1.09 (0.63–1.89)	1.00 (0.66–1.53)
Ethnicity	0.94 (0.72–1.24)	0.94 (0.74–1.20)	0.98 (0.76–1.62)	1.09 (0.88–1.33)
Age	1.02 (0.99–1.05)	1.04 (1.01–1.07)	1.03 (0.99–1.05)	1.03 (1.01–1.05)
Model 3				
HRT use	0.84 (0.32–2.19)	2.01 (1.16–3.48)	1.24 (0.68–2.28)	0.94 (0.59–1.52)
Ethnicity	0.89 (0.63–1.26)	0.91 (0.70–1.18)	0.94 (0.72–1.24)	1.07 (0.86–1.34)
Age	1.02 (0.99–1.06)	1.03 (1.00–1.06)	1.03 (1.00–1.06)	1.03 (1.01–1.06)
Waist circumference	1.03 (1.00–1.06)	1.01 (0.99–1.03)	1.03 (1.01–1.05)	1.02 (1.00–1.04)
Model 4				
HRT use	0.95 (0.35–2.57)	2.18 (1.19–3.96)	1.31 (0.63–2.73)	1.24 (0.66–2.32)
Ethnicity	0.83 (0.58–1.19)	0.85 (0.64–1.11)	0.79 (0.58–1.07)	0.81 (0.61–1.08)
Age	1.04 (0.99–1.08)	1.04 (1.01–1.08)	1.06 (1.02–1.10)	1.06 (1.03–1.10)
Waist circumference	1.02 (0.98–1.05)	1.01 (0.98–1.03)	1.01 (0.99–1.03)	0.99 (0.97–1.02)
ln(fasting insulin)	3.53 (0.93–13.39)	2.42 (1.36–4.32)	13.68 (6.56–28.51)	21.62 (9.59–48.75)
$\ln(\Delta I_{0-30}/\Delta G_{0-30})$	0.59 (0.29–1.20)	0.50 (0.29–0.86)	0.16 (0.08–0.34)	0.06 (0.03–0.15)

Data are RR (95% CI). All models were corrected for familial clustering. For all models, NGT is the comparison group. The reference group for sex is men. The reference group for HRT use is non-HRT users.

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