Sex Differences in Insulin Levels in Older Adults and the Effect of Body Size, Estrogen Replacement Therapy, and Glucose Tolerance Status

The Rancho Bernardo Study, 1984–1987

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OBJECTIVE — To determine if insulin levels vary with sex, independent of estrogen replacement therapy (ERT), differences in body mass index (BMI), waist-to-hip ratio (WHR), and glycemia.

RESEARCH DESIGN AND METHODS — In a population-based study of older adults, insulin levels were measured before and after a standardized oral glucose tolerance test in 673 men and 849 women, all free of known diabetes.

RESULTS — Age-adjusted fasting insulin levels were highest in men, intermediate in women not taking estrogen, and lowest in estrogen-treated women ($P < 0.01$). Differences between men and women not taking estrogen disappeared after adjusting for age and BMI, but not glycemia; estrogen-treated women had significantly lower fasting insulin levels than did men ($P < 0.01$) and women not taking estrogen ($P < 0.01$). The association of estrogen use with lower fasting insulin levels persisted after adjusting for age and WHR ($P < 0.001$) and was stronger among women with abnormal glucose tolerance. Age-adjusted postchallenge insulin levels were higher in women than in men ($P < 0.01$). The sex difference persisted after adjusting for age and BMI or glycemia. Postchallenge insulin levels did not vary by ERT.

CONCLUSIONS — Men have higher fasting insulin levels than do women, whether or not the women are using ERT. Differences between men and untreated women are explained by differences in BMI, but estrogen users have lower fasting insulin levels independent of BMI. Postchallenge insulin levels are higher in women than men and are independent of ERT, BMI, and glycemia. Clinical trials in women are needed to determine whether ERT can improve insulin and glucose metabolism.

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NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; BMI, body mass index; WHR, waist-to-hip ratio; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; ERT, estrogen replacement therapy.

Many epidemiological studies conducted during the last 20 years have established that, compared with men, women are protected from coronary heart disease; however, the sex difference is not entirely explained by differences in the distribution of the classical heart disease risk factors (1). Much of this female advantage is lost in women who have non-insulin-dependent diabetes mellitus (NIDDM) (1,2) and, again, the loss is not entirely explained by differences in the distribution of heart disease risk factors (3). It has been suggested that some of the sex difference in coronary disease experience could be explained by sex differences in insulin levels or in insulin sensitivity (4).

Evidence that women without diabetes are more insulin-sensitive than men without diabetes come from studies of insulin levels during an oral glucose tolerance test (OGTT) (4–6), studies of insulin sensitivity in muscle tissue using an insulin clamp (7) or forearm (8) technique, and studies of insulin-stimulated glucose oxidation, insulin-stimulated glucose transport in human adipocytes from the gluteal region (9), or the abdominal subcutaneous fat tissue (10). Only one study, using incremental intravenous infusion of insulin, showed the contrary (11).

It is known that women have higher mean plasma insulin levels after a glucose load than do men and that this sex difference in insulin levels is not completely explained by differences in glucose levels (4,12,13). In the only published population-based study of sex differences in insulin levels, women had higher postchallenge insulin levels than men, but subjects were not fasting when administered a 50-g oral glucose load, and insulin was measured only 1 h after the glucose challenge (13). None of these studies examined whether differences in body mass index (BMI), fat distribution, or estrogen use explained the observed sex differences.

We report the sex- and age-specific distribution of fasting and 2-h post-glucose load insulin levels in a population-based study of older adults and consider the effects of overall and central obesity and of estrogen use on the observed sex differences.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS— Between 1972 and 1974, 82% of Caucasian adults living in Rancho Bernardo, California, participated in a study of heart disease risk factors. All surviving subjects 30 to 89 years of age were invited to a follow-up clinic visit between January 1984 and February 1987; 84.5% of the men and 78.4% of the women participated (14). Standardized insulin assays were begun 4 November 1984. There were 1,577 consecutive participants who had fasted for at least 12 h and had an OGTT between 4 November 1984 and February 1987. Previously diagnosed diabetic patients (n = 55) were excluded to remove the confounding effect of therapy on insulin levels. Of the remaining 1,522 subjects (673 men and 849 women), fasting insulin levels were available for 1,520 subjects, and postchallenge insulin levels were available for 1,501 subjects.

Clinic visits were held between 7:00 and 11:00 A.M. after a requested 12-h fast. A 75-g OGTT was performed. Plasma glucose levels were measured by glucose oxidase assay both before and 2 h after glucose load. Fasting and 2-h postchallenge serum insulin levels were determined by a double-antibody radioimmunoassay in a diabetes research laboratory (15).

Demographic data, personal history of diabetes, behavioral factors (physical activity, alcohol consumption, and cigarette smoking), and current use of selected medications were determined by standardized interview. Medication use was validated by examination of prescriptions and pills brought to the clinic for that purpose. Height and weight were measured with subjects in light clothing without shoes; BMI was calculated as weight/height^2 (kg/m^2) and used as a measure of overall obesity. Waist circumference was measured at the bending point and hip circumference at the iliac crest; the waist-to-hip ratio (WHR) was calculated and used as a measure of central obesity. This ratio was highly correlated (r = 0.97) with the ratio based on measurements of minimum waist and maximum hip circumference.

NIDDM and impaired glucose tolerance (IGT) were defined by World Health Organization criteria (16). Newly diagnosed NIDDM was defined by fasting plasma glucose ≥140 mg/dl and/or 2-h postchallenge plasma glucose ≥200 mg/dl; IGT was defined as a 2-h postchallenge plasma glucose of 140–199 mg/dl in those with fasting plasma glucose <140 mg/dl. All others were considered to have normal glucose tolerance (NGT).

Statistical Analysis System (17) was used for all analyses. Because of the skewed distribution of fasting and 2-h insulin, these variables were log-transformed for all statistical analyses and re-exponentiated for tabular presentation. Linear regression models in each sex were used to examine the relation between age and insulin. A linear trend was used to test the association between age and 2-h insulin levels. Because a nonlinear relation between insulin and age was visually apparent, a quadratic trend was used to test the association between age and fasting insulin levels. To examine whether these associations were different between men and women, linear regression models were developed, including an interaction term between sex and age. Unadjusted and adjusted means were computed by analysis of variance and analysis of covariance, respectively, to test for differences by sex and estrogen replacement status among women, before and after stratifying for glucose tolerance status.

All probabilities are for two-tailed tests, with statistical significance defined as $P < 0.05$. No adjustments were made for multiple comparisons; rather, detailed P values are presented.

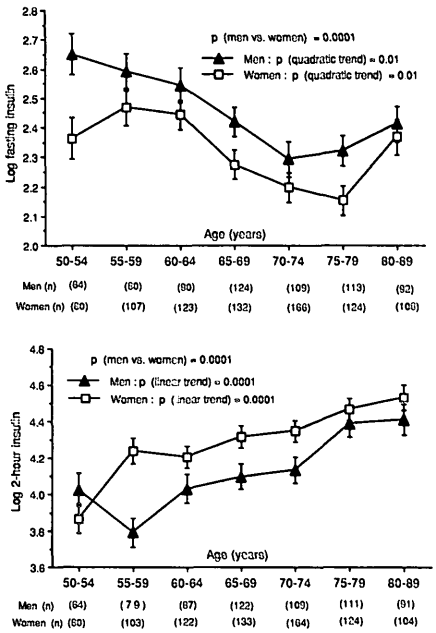

Figure 1—*Age- and sex-specific mean fasting and 2-h insulin levels and SE; Rancho Bernardo Study 1984–1987.*

RESULTS

RESULTS— The mean age of both men and women was 68 ± 9 years. All but 35 women were postmenopausal, with an average duration of 20 ± 10 years (means ± SD). Men had significantly higher mean fasting serum insulin levels than women (11.5 μU/ml vs. 10.1 μU/ml, P = 0.0001), and significantly lower mean 2-h serum insulin levels than women (62.9 μU/ml vs. 74.0 μU/ml; P = 0.0001). Figure 1 shows the age- and sex-specific mean fasting and 2-h serum insulin levels. In both sexes, there was a negative quadratic relation between age and fasting insulin (P = 0.01 for men and for women) and a positive linear relation between age and 2-h insulin (P = 0.0001 for men and for women). There was no evidence of an age-by-sex interaction for either fasting or 2-h insulin. Similar results were obtained after excluding 35 premenopausal women and 23 women with menopause duration of <2 years and when insulin levels were adjusted for menopause duration.

As shown in Fig. 2, there was a striking separation between the sex-spe-

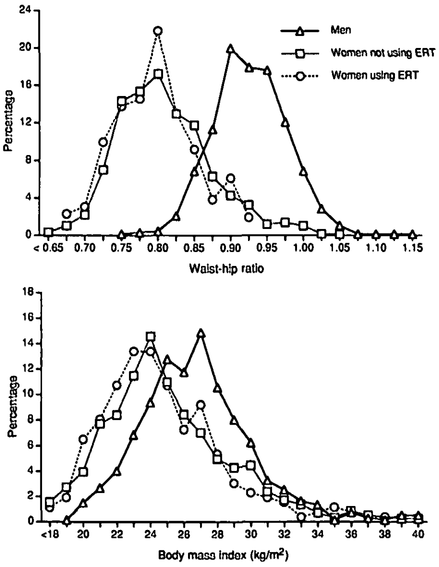

Figure 2—*Percent distribution of WHR and BMI by sex and ERT use; Rancho Bernardo Study 1984–1987.*

cific distributions of WHR, such that the 25th percentile among men was similar to the 90th percentile among women not using estrogen and to the 95th percentile among estrogen-treated women (levels of 0.880, 0.884, and 0.881, respectively). There was more overlap between the sex-specific distributions of BMI; the 25th percentile among men was similar to the 50th percentile among women using and not using estrogen (levels of 24.0, 23.9, and 23.7, respectively).

At the time of the clinic visit, 31% of the women were using estrogen replacement therapy (ERT) for an average of 14 years. As shown in Table 1, women not using estrogen were significantly older than men or estrogen-treated women. Age-adjusted means of fasting plasma glucose levels, BMIs, and WHRs were highest in men, intermediate in women not using estrogen, and lowest in estrogen-treated women; these differences were statistically significant ($P < 0.05$). Age-adjusted 2-h plasma glucose levels were significantly higher in women than in men, whether or not the women were taking estrogen.

To evaluate whether exogenous sex hormones explained the sex differences in insulin levels, analyses were performed comparing women not using estrogen with both men and estrogen-using women. Table 2 presents mean insulin levels by sex and estrogen replacement status, before and after adjusting for covariates. Because of the large difference in body fat distribution between men and women, adjustment for WHR between sexes is not possible. Thus men were excluded from analyses that compared age- and WHR-adjusted insulin levels of women using and not using estrogen. Fasting serum insulin levels were highest in men, intermediate in women not using estrogen, and lowest in the estrogen-treated women. Significant differences in fasting serum insulin levels between men and women not using estrogen remained after adjusting for age, and for age and fasting glycemia, but not after adjusting for age and BMI. After all these adjustments, estrogen-treated women had significantly lower fasting insulin levels than did men ($P < 0.01$) and women not using estrogen ($P < 0.01$). Also, after adjusting for age and WHR, estrogen-treated women had significantly lower fasting insulin levels than did women not using estrogen. Crude and adjusted 2-h serum insulin levels were significantly higher in women than in men whether or not the women were taking estrogen ($P < 0.001$). In women, the 2-h insulin levels did not differ by estrogen replacement status.

Because women using ERT had, on average, a shorter duration of menopause than did women not using ERT (17 ± 10 years vs. 21 ± 11 years; $P < 0.001$), insulin levels by estrogen use were recalculated after adjusting for menopause duration, and similar differences in fasting insulin levels between estrogen-treated women and women not using ERT were observed (data not shown). Finally, other analyses were performed to determine whether the observed differences in insulin levels were explained by physical activity, alcohol consumption, or cigarette smoking. Results were unchanged after stratifying or adjusting for these covariates (data not shown).

The prevalence of NGT, IGT, and NIDDM was (respectively) 67.6%, 23.9%, and 8.5% in men; 62.0%, 28.6%, and 9.4% in women not using ERT; and

Table 1—*Age and age-adjusted means of covariates of insulin by sex and ERT; Rancho Bernardo Study 1984–1987*

	Men	Women not using ERT	Women using ERT	P values	
				Sex	ERT
n	673	587	262		
Age (years)	68.4 ± 9.4	69.6 ± 9.8	65.4 ± 8.3	0.02	0.001
BMI (kg/m²)	26.2 ± 0.1	24.6 ± 0.2	24.0 ± 0.2	0.001	0.03
WHR	0.914 ± 0.002	0.796 ± 0.002	0.785 ± 0.004	0.001	0.01
Fasting glucose (mg/dl)	101.3 ± 0.6	98.8 ± 0.6	95.2 ± 1.0	0.004	0.002
2-h glucose (mg/dl)	128.5 ± 1.8	135.5 ± 2.9	137.2 ± 1.9	0.008	0.6

Data are means ± SD for age; data are means ± SE for age-adjusted covariates. *P* values for sex are for men vs. women not using ERT, and for ERT, they are for women using ERT vs. women not using ERT.

Table 2—*Mean insulin levels with adjustment variables by sex and ERT; Rancho Bernardo Study 1984–1987*

	Men	Women not using ERT	Women using ERT	*P* values	
				Sex	ERT
n	673	587	262		
Fasting insulin (μU/ml)					
Crude	11.5 (3–146)	10.4 (2–65)	9.4 (2–41)	0.004	0.02
Age	11.5	10.5	9.1	0.01	0.005
Age and BMI	10.8	10.9	9.8	0.8	0.013
Age and WHR	—	10.5	9.3	—	0.007
Age and fasting glucose	11.3	10.6	9.4	0.048	0.001
2-h insulin (μU/ml)					
Crude	62.9 (4–494)	76.1 (6–675)	69.5 (3–318)	0.001	0.1
Age	62.9	74.5	73.0	0.001	0.1
Age and BMI	59.6	76.9	78.3	0.001	0.7
Age and WHR	—	74.1	74.4	—	0.9
Age and 2-h glucose	64.4	73.4	70.2	0.001	0.6

Data are means (range). *P* values for sex are for men vs. women not using ERT, and for ERT, they are for women using ERT vs. women not using ERT. In age- and WHR-adjusted comparisons, men were excluded from analyses (see text).

61.4%, 30.2%, and 8.4% in estrogen-treated women. When fasting and 2-h mean insulin levels were compared after stratifying for glucose tolerance category, similar differences in insulin levels by sex and estrogen use were observed (Fig. 3). Men with NGT or newly diagnosed NIDDM had significantly higher fasting insulin levels than did women not using estrogen. Estrogen-treated women with IGT or newly diagnosed NIDDM had significantly lower fasting insulin levels than did women not using estrogen. The only occurrence of 2-h insulin levels differing significantly was in women with NGT not using estrogen compared with men. After adjusting for BMI, neither the difference in fasting insulin levels between men and women not using estrogen who had NGT, nor the difference between women using and not using estrogen who had diabetes were statistically significant (data not shown).

The observed differences in insulin levels also remained after adjustment for or stratification by current diuretic (thiazide) use, which was present in 17.4% of men, 21.7% of women not using estrogen, and 19.0% of estrogen-treated women (data not shown).

CONCLUSIONS— In this population-based study of older men and women who were free of known diabetes, men had significantly higher fasting and significantly lower postchallenge insulin levels than women did. Fasting insulin levels decreased significantly and 2-h postchallenge insulin levels increased significantly with increasing age in both sexes. The finding that fasting insulin levels decreased with age is consistent with the Israeli Study (M. Modan, personal communication), while the finding that postchallenge insulin levels increased with age is consistent with the Busselton Study (13).

In this cohort, nearly one-third of women were using ERT, primarily unopposed oral conjugated equine estrogen. Women not using estrogen had fasting insulin levels between those of men and estrogen-using women. Postchallenge insulin levels in women did not vary by estrogen use.

Sex differences in fasting insulin levels between women not using estrogen and men appeared to be mediated by sex differences in overall obesity. Adjusting for BMI removed the sex difference in fasting insulin levels between men and women not using estrogen. Others have demonstrated that fasting insulin levels are positively related to increased body fat in sex-specific analyses (18), and women typically have more body fat at any given BMI than men do (7,18,19). Adjusting for BMI does not entirely correct for differences in body fat, since obese men have higher fasting insulin levels than obese women after matching for amount of body fat (18). Apparently, women can accumulate 20–30 kg more fat than men before equality is established between the sexes for hyperinsulinemia (18). This may reflect the visceral or central location of male-pattern obesity, which is known to be more insulin resistant than the gluteal or femoral location of female pattern obesity (18,20). This problem is not really solved by adjusting for WHR because there is so little overlap in the distribution of WHR between the sexes (Fig. 2). In this cohort, WHR was a nearly sex-specific characteristic; controlling for WHR to test for differences between men and women would be equivalent to controlling for sex (21).

Sex differences in fasting insulin levels were still statistically significant after adjusting for fasting glycemia. This

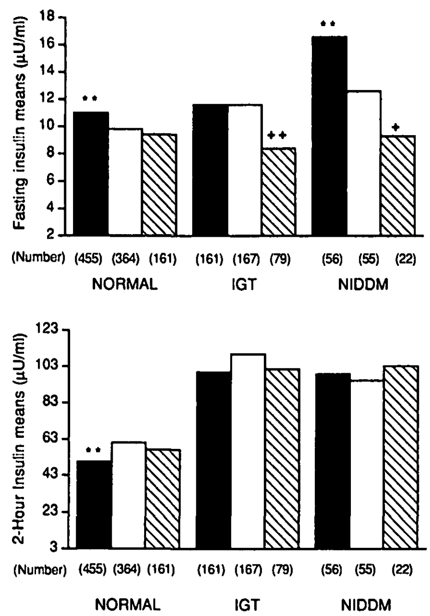

Figure 3—*Age-adjusted mean fasting and 2-h insulin levels by sex, ERT, and glucose tolerance status; Rancho Bernardo Study 1984–1987.* ■, *men;* □, *women not using ERT;* ▧, *women using ERT.* **P ≤ *0.001 for men vs. women not using ERT;* ++P < *0.001 for women using ERT vs. women not using ERT;* +P = *0.04 for women using ERT vs. women not using ERT.*

implies that women have lower fasting insulin levels than men for reasons other than plasma glucose. Because estrogen-treated women had even lower fasting insulin levels than did women not taking estrogen after controlling for all confounding factors, including BMI, it is possible that differences in plasma estrogen levels, whether of exogenous or endogenous origin, explain the sex difference in fasting insulin levels.

Consistent with previous studies (4,12–13), women had higher postchallenge insulin levels than did men. This sex difference is unlikely to be explained by endogenous estrogen (although estrogen is known to induce pancreatic β-cell hyperplasia and increase β-cell granulation [22]), because 2-h insulin levels did not differ by estrogen replacement status (Table 2).

Alternatively, sex differences in body composition could explain the observed sex differences in 2-h insulin levels. More than two-thirds of oral glucose is used in muscle (23,24), and less than 1% is taken up by adipose tissue (25). Since women have less lean body mass and more body fat than men, the higher postchallenge insulin levels observed in women, as compared with men, may reflect decreased peripheral metabolic clearance of insulin (26,27).

Because increased central adiposity decreases hepatic clearance of insulin (27,28), it is surprising that women had higher 2-h insulin levels than men despite less upper-body obesity. However, less than one-third of an oral glucose load is disposed of by the splanchnic tissue (24), which may explain why men had lower postchallenge insulin levels than women despite being heavier and more centrally obese.

Therefore, the sex difference in postchallenge insulin levels could be explained by sex differences in the amount of lean body mass or body fat. Since insulin secretion and action cannot be studied separately during an OGTT (29), it will be challenging to determine which of these mechanisms explains the sex differences in postchallenge insulin levels.

In this cohort, 74% of all ERT users were taking unopposed estrogen without progestin; >80% of all estrogen used was conjugated equine estrogen (30). The association of estrogen use with decreased obesity and central obesity is consistent with previous reports (30–34). The observation that postmenopausal women without diabetes who use ERT have significantly lower fasting insulin levels than do untreated women has been previously reported (35,36). The finding that estrogen use affected fasting but not postchallenge insulin is compatible with the thesis that ERT reduces insulin resistance in postmenopausal women. Fasting insulin is superior to postchallenge insulin as a marker for insulin resistance defined by insulin clamp techniques (37). When men and women were stratified for glucose tolerance status, the association of estrogen use with lower fasting insulin levels was stronger among women with IGT or NIDDM than among those with NGT. In this cohort, estrogen-treated women with IGT or NIDDM had lower fasting insulin and glucose levels than did nonusers, raising the possibility that ERT could reduce insulin resistance and improve glucose control in postmenopausal women with abnormal glucose tolerance.

These cross-sectional associations do not prove causality. In Rancho Bernardo women, current estrogen users were more likely to be lean and report behavior changes expected to decrease insulin resistance, such as increased physical activity and decreased dietary fat (38). Clinical trials will be necessary to determine whether the lower levels of fasting insulin and glucose in estrogen-treated women are mediated by estrogen use or by some other attribute leading to ERT. If estrogen has a favorable effect on insulin and glucose metabolism, this may explain in part the "female advantage" in cardiovascular disease and longevity.

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