Relationships in Men of Sex Hormones, Insulin, Adiposity, and Risk Factors for Myocardial Infarction

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That sex hormones, insulin, and obesity all correlate with the constellation of risk factors for myocardial infarction (MI) that has come to be known as "syndrome X," the "insulin-resistance syndrome," or the "metabolic syndrome" suggests that any one or more of them could underlie and link the risk factors to form the constellation. That sex hormones, insulin, and obesity also correlate with each other complicates their identification as an underlying link. To compare the likelihood of each being a link, we measured and determined the interrelationships of sex hormones, insulin, adiposity variables, and risk factors for MI in 80 apparently healthy men. Of the adiposity variables, visceral adipose tissue (VAT) correlated more strongly with the risk factors for MI than did body mass index (BMI), total adipose tissue (TAT), subcutaneous adipose tissue (SCAT), waist-to-hip ratio (WHR), and waist circumference (W). Controlling for VAT eliminated all of the other adiposity correlations that had been significant. VAT, therefore, was used as the measure of adiposity for further data analysis. VAT correlated more strongly with risk factors for MI than did sex hormones and insulin, and most of the correlations of sex hormones and insulin with risk factors for MI lost statistical significance after controlling for VAT. Testosterone and the ratio of estradiol-to-testosterone (E/T) correlated with insulin; on controlling for VAT, only the E/T-insulin correlation remained significant ($r = .38$, $P < .001$) and on multiple linear regression analysis, insulin was associated with estradiol ($P = .01$) and testosterone ($P = .04$) independently of VAT and age. In conclusion, (1) VAT in men may largely explain the correlations of sex hormones, insulin, and obesity with the risk factors for MI measured, (2) VAT may be the principal factor in men, independently of other measures of adiposity, that links risk factors for MI to form the constellation, and (3) estradiol may play a more important role in the sex hormone-insulin relationship in men than has generally been considered.

IT HAS BEEN observed that glucose intolerance, hyperinsulinemia, hyperlipidemia, and hypertension form a constellation of factors[1-3] that occurs not only with myocardial infarction (MI), but also with obesity, aging, and other clinical states.[1] That these risk factors for MI occur as a constellation in various clinical states, as well as with MI, suggested the presence of a common underlying factor linking them.[1] Because of the findings in non-obese men of correlations of sex hormones with insulin and risk factors for MI, it was hypothesized that an alteration in the sex hormone milieu might be this link.[1,4] It was also noted that this constellation could be reversed by weight reduction in the obese, and it was hypothesized that obesity could induce the constellation and be induced by sex hormones.[1]

The constellation of risk factors for MI has subsequently been named "syndrome X," the "insulin resistance syndrome," and the "metabolic syndrome," its composition has been variously redefined,[5] and insulin resistance and/or hyperinsulinemia[2,3] and obesity,[1,6,7] as well as an alteration in the sex hormone milieu,[1] have been suggested as possible links. Determining whether sex hormones, insulin, and/or obesity may link the risk factors to form the constellation is complicated by statistical associations between these 3 variables. The present study was performed in an attempt to discern which of the variables correlated best with the components of the constellation. To do this, sex hormones, insulin, 6 adiposity variables, ie, body mass index (BMI), total adipose tissue (TAT), subcutaneous adipose tissue (SCAT), visceral adipose tissue (VAT), waist-to-hip ratio (WHR), and waist circumference (W), and risk factors for MI were measured in a group of 80 apparently healthy men. The interrelationships among these variables were then determined.

PATIENTS AND METHODS

Eighty adult males recruited from a multiethnic community through advertisements were studied. Inclusion required that the subject be healthy, not regularly participating in vigorous physical activity training programs, not having gained or lost > 10% of body weight within the past year, not having a history of drug or alcohol abuse, and not taking medications known to influence serum lipid levels or body composition. The health of the subjects was determined by history, physical examination, and laboratory tests. Because blood pressure had not been measured according to standard procedure, blood pressure measurements were not analyzed. This study was approved by the institutional review board, and the subjects gave written informed consent.

BMI was calculated as weight/height (kg/m^2). For WHR, waist circumference was measured at the narrowest point between the lowest rib and the iliac crest, and hip circumference at the greatest protruberance of the buttocks. TAT, SCAT, and VAT were measured using whole-body multislice magnetic resonance imaging.[8] Venous blood samples were drawn between 8 and 10 AM afer a 12-hour overnight fast and the serum separated and stored at −20°C. Hormones were measured by radioimmunossay (RIA). Materials for the RIA of estradiol, estrone, and sex hormone–binding globulin (SHBG) were obtained from Diagnostic Systems Laboratories, Webster, TX, and for the RIA of total testosterone, free testosterone (FT) (nonprotein-bound testosterone), and insulin from Diagnostic Products, Los Angeles, CA. Because the reliability of the direct FT assay has been questioned,[9] FT was also determined by calculation using the total testosterone and SHBG values.[10] Serum cholesterol, triglyceride, and glucose were determined

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Table 1. Means, Standard Errors of the Means, and Ranges of Variables in 80 Men

Variable	Mean	SEM	Range
Age, (yr)	37.7	1.6	18-80
Body weight (kg)	81.0	1.4	51.6-108.2
Body mass index (kg/m^2)	25.9	0.4	17.8-38.6
Waist-to-hip ratio	0.87	0.01	0.78-1.04
Waist circumference (cm)	88.0	1.3	69.0-119.0
Total adipose tissue (kg)	20.2	1.0	6.0-43.4
Subcutaneous adipose tissue (kg)	17.7	0.8	5.8-36.1
Visceral adipose tissue (kg)	2.33	0.21	0.17-9.13
Cholesterol (mg/dL)	187	4	110-304
Triglyceride (mg/dL)	102	9	20-457
HDL-cholesterol mg/dL	48.4	1.4	26.0-89.0
Glucose (mg/dL)	85.3	1.2	61-120
Insulin (μU/mL)	8.9	0.5	2.8-21.0
Estradiol (pg/mL)	32.2	0.8	16.7-50.0
Estrone (pg/mL)	35.0	1.0	20.5-68.0
Testosterone (ng/mL)	5.08	0.16	2.22-8.80
Free testosterone (pg/mL)	18.5	0.6	7.8-30.9
Calculated free testosterone (pg/mL)	72.2	2.1	33.5-136.0
Estradiol/testosterone $\times$ 10^3	6.70	0.22	3.80-12.63
Sex-hormone binding globulin (nmol/L)	76.2	3.7	21.0-210.0

Abbreviations: SEM, standard error of the mean; HDL-cholesterol, high-density lipoprotein cholesterol.

enzymatically, as was cholesterol in the supernatant following phosphotungstic acid precipitation of serum in the measurement of high-density lipoprotein-cholesterol (HDL-C).

All statistical analyses were performed using SPSS version 10.0. Means $\pm$ SEM, Pearson and partial correlations, and multiple linear regressions were calculated. A 2-tailed P value of $\leq .05$ was considered significant.

RESULTS

The means, SEMs, and ranges of the variables measured in the 80 men are shown in Table 1.

Table 2 shows the Pearson correlation coefficients of measures of adiposity with risk factors for MI, insulin, and sex hormones. Because W and WHR correlated so similarly with these variables and with each other ($r = .86$, $P < .001$), the data on W are not shown. Although VAT correlated with BMI ($r = .65$), TAT ($r = .71$), SCAT ($r = .69$), WHR ($r = .78$), and W ($r = .81$), all $P < .001$, VAT correlated more strongly with each risk factor for MI, insulin, and the estradiol-to-testosterone ratio (E/T) than did the other adiposity variables. On multiple linear regression analysis with insulin as the dependent variable and age, VAT, and WHR as the independent variables, VAT was associated with insulin ($P = .002$) while WHR ($P = .54$), and age ($P = .13$) were not. VAT, WHR, and W correlated similarly, and more strongly than BMI, TAT, and SCAT with total testosterone and FT. On controlling for VAT, all of the correlations that had been significant of BMI, TAT, SCAT, WHR, and W with sex hormones, insulin, and risk factors disappeared except for testosterone-WHR. Estradiol and estrone did not correlate with any of the measures of adiposity. Thus, sex hormones, insulin, and the risk factors for MI all appeared to be more closely related to VAT than to fat located elsewhere.

Because VAT correlated more strongly than BMI, TAT, SCAT, WHR, or W with the risk factors for MI, insulin, and E/T, VAT was selected as the measure of adiposity for subsequent data analysis. To determine the influence of VAT on the correlations of sex hormones and insulin with risk factors for MI, these correlations were calculated before and after controlling for VAT (Table 3). There were numerous Pearson correlations between sex hormones, insulin, and risk factors for MI, but after controlling for VAT, insulin correlated only with glucose; estradiol and testosterone only with HDL-C; FT and calculated FT only with age; and E/T only with insulin. On the other hand, the correlations of VAT with the risk factors all remained significant after controlling for either testosterone, E/T, or insulin; eg, the VAT-triglyceride correlation stayed at the $P < .001$ level in each case.

Although after controlling for VAT, neither estradiol nor

Table 2. Correlation Coefficients of Measures of Adiposity With Risk Factors for Myocardial Infarction, Insulin, and Sex Hormones in 80 Healthy Men

	Pearson Correlation					Correlation Controlled for VAT			
Variable	BMI	TAT	SCAT	WHR	VAT	BMI	TAT	SCAT	WHR
Age	.27*	.38‡	.32†	.52‡	.55‡	−.14	−.11	−.11	.18
Cholesterol	.21	.27*	.24*	.25*	.32†	.01	.03	.03	.01
Triglyceride	.42‡	.47‡	.42‡	.36‡	.58‡	.07	.03	.03	−.16
HDL-cholesterol	−.32†	−.28†	−.24*	−.28†	−.37‡	−.11	.02	.03	.02
Glucose	.10	.28†	.23*	.31†	.42‡	−.25*	−.09	−.09	−.03
Insulin	.35‡	.44‡	.40‡	.40‡	.49‡	.05	.11	.11	.04
Estradiol	−.11	−.07	−.08	−.18	−.06	−.10	−.05	−.05	−.22
Estrone	.05	.08	−.10	−.15	−.05	.10	.19	.18	−.18
Testosterone	−.38‡	−.39‡	−.35‡	−.50‡	−.49‡	−.10	−.03	−.03	−.23*
Free testosterone	−.29†	−.27*	−.24*	−.37‡	−.36‡	−.09	.02	.01	−.16
Calculated free testosterone	−.20	−.23*	−.20	−.32†	−.32†	.01	.04	.03	−.12
Estradiol/testosterone	.32†	.36‡	.31†	.35‡	.47‡	.02	−.03	−.03	−.02
SHBG	−.24*	−.20	−.19	−.23*	−.20	−.15	−.07	−.07	−.12

Abbreviations: BMI, body mass index; TAT, total adipose tissue; SCAT, subcutaneous adipose tissue; WHR, waist-to-hip ratio; VAT, visceral adipose tissue; HDL-cholesterol, high-density lipoprotein cholesterol; SHBG, sex-hormone binding globulin.

*$P \leq .05$; †$P \leq .01$; ‡$P \leq .001$.

Table 3. Pearson and VAT-Controlled Correlation Coefficients of Insulin and Sex Hormones With Risk Factors for Myocardial Infarction

	Age	Cholesterol	Triglyceride	HDL-Cholesterol	Glucose	Insulin
Insulin	.15	.13	.36‡	−.33†	.38‡	—
Controlled for VAT	−.16	−.02	.11	−.18	.22*	—
Estradiol (E)	−.09	.01	−.17	.23*	.11	.16
Controlled for VAT	−.08	.03	−.16	.22*	.15	.21
Estrone	.02	.10	−.10	.21	.12	.08
Controlled for VAT	.06	.13	−.09	.20	.16	.12
Testosterone (T)	−.26*	−.22*	−.42‡	.38‡	−.16	−.31†
Controlled for VAT	.01	−.08	−.20	.26*	.05	−.11
E/T	.16	.26*	.35†	−.24*	.22*	.52‡
Controlled for VAT	−.14	.13	.10	−.08	.03	.38‡
Free testosterone (FT)	−.37‡	−.04	−.21	.26*	−.08	−.09
Controlled for VAT	−.22*	.08	−.01	.14	.08	.11
Calculated FT	−.46‡	−.00	−.04	.06	−.08	−.05
Controlled for VAT	−.36‡	.11	.19	−.06	.06	.13

Abbreviation: VAT, visceral adipose tissue; HDL-cholesterol, high-density lipoprotein cholesterol.
*$P \leq .05$; †$P \leq .01$; ‡$P \leq .001$.

testosterone correlated with insulin, E/T correlated highly significantly with insulin. To investigate this relationship further, multiple linear regression analysis was performed with insulin as the dependent variable (Table 4). With estradiol, testosterone, VAT, and age as the independent variables, estradiol, testosterone, and VAT were independently associated with insulin (Model 1). Of interest, the *P* value for estradiol was less than that for testosterone. E/T substituted for estradiol and testosterone was more strongly associated with insulin than was VAT (Model 2). The correlation of E/T with insulin is depicted in Fig 1.

Table 5 shows the results from the present study and the 4 previous studies reported from this laboratory[4,11-13] that tested the sex hormone and insulin correlation in men. Because VAT was not measured in the 4 previous studies, the correlations are all controlled for BMI and age. Testosterone correlated more strongly with insulin than did directly measured FT and calculated FT in the 4 studies in which FT was measured. Although estradiol did not correlate with insulin in any of the studies, E/T correlated with insulin more strongly than did testosterone or T/E (data not shown) in all of the studies and more strongly than did E/FT or FT/E (data not shown) in the 4 studies in which FT was measured.

DISCUSSION

Sex hormones, insulin, and obesity have all been reported to correlate with risk factors for MI in men.[11,14,15] Although a correlation does not by itself mean a cause and effect relationship or, if so, indicate which is the cause, each of these 3 variables has been suggested as the link that underlies the risk factors for MI to form the constellation.[1-4,6,7] In the present study, testosterone, FT, estradiol, estrone, insulin, 6 adiposity variables, and risk factors for MI were measured and their interrelationships compared in an attempt to discern whether sex hormones, insulin, or adiposity may be the most likely link.

To determine which adiposity variable correlated best with the risk factors for MI, we compared BMI, TAT, SCAT, VAT, WHR, and W. VAT correlated significantly and more strongly than did the 5 other adiposity variables with age, cholesterol, triglyceride, HDL-C, glucose, and insulin. On controlling for VAT, all of the significant correlations of the other adiposity variables with these factors disappeared; these findings suggest

Table 4. Multiple-Regression Analysis of Relationship of Insulin to Other Variables

Independent Variables		Regression Coefficients B	SE	*P* of t Value
Model 1	R^2 = .3242			
	Estradiol	.1657	.0643	.012
	Testosterone	−.7421	.3618	.044
	VAT	1.0563	.2937	<.001
	Age	−.0448	.0352	.208
Model 2	R^2 = .3530			
	E/T	.7795	.2309	.001
	VAT	.8789	.2867	.003
	Age	−.0374	.0344	.281

Abbreviations: VAT, visceral adipose tissue; E/T, estradiol-to-testosterone ratio.

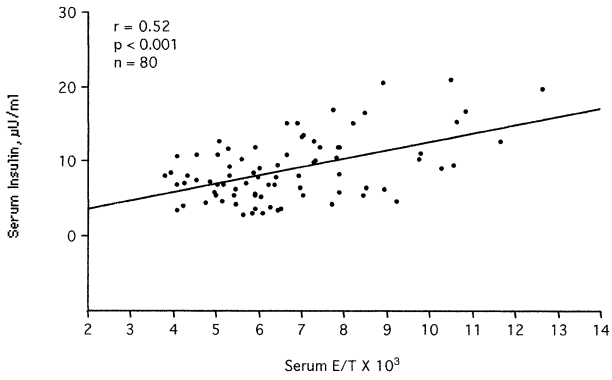

Fig 1. Scatterplot showing correlation of E/T and fasting insulin levels (80 men).

Table 5. Correlation Coefficients, Controlled for Age and BMI, of Present and Previous Studies in Men From This Laboratory

Reference	No. of Patients	Mean Age (yr)	Diagnosis	Partial Correlation Coefficients				
				E-Insulin	T-Insulin	FT-Insulin*	E/T-Insulin	E-T
4	23	39	MI	.05†	−.65†§	—	.76†‖	.38
				.08	−.58§	—	.69‖	.38
11	55	44	Obesity	.03	−.31§	−.24‡	.41‖	.30‡
12	30	53	Normal	.24	−.23	−.16	.68‖	.62‖
13	34	61	CAD	−.23	−.40‡	−.38‡	.41‡	.29
Present	80	38	Normal	.21	−.20	.04	.46‖	.42‖

NOTE. Values of references 4 and 12 were recalculated from the original data in order to control for age and BMI.

Abbreviations: BMI, body mass index; E, estradiol; T, testosterone; FT, free testosterone; MI, myocardial infarction; CAD, coronary artery disease.

*The calculated FT-insulin correlation was significant only in references 11 ($r = -.25$, $P < .05$) and 13 ($r = -.38$, $P < .05$).

†Insulin values used were insulin area under the glucose tolerance curve; all other insulin values in this table were fasting insulin.

‡$P \leq .05$; §$P \leq .01$; ‖$P \leq .001$.

that the correlations of BMI, TAT, SCAT, WHR, and W with risk factors for MI and insulin were explained by their VAT association. The correlation of obesity with risk factors for MI and insulin in men, therefore, may be largely a function of its VAT component. These findings are consistent with studies reporting that visceral fat differs metabolically from fat located elsewhere.[16] Previous studies have also reported that associations of adiposity with risk factors and insulin appear to be stronger with visceral than with subcutaneous fat.[14,17,18] The present study found that VAT was a stronger correlate of testosterone, FT, and E/T than was BMI, TAT, or SCAT and that controlling for VAT eliminated these correlations. Thus, because VAT appeared to be more closely related to the risk factors, sex hormones, and insulin than were other adiposity variables, VAT was selected as the measure of adiposity for further data analysis.

Most of the Pearson correlations of sex hormones and insulin with risk factors for MI in the present study lost statistical significance on controlling for VAT. Thus, the present study suggests a stronger relationship in men of VAT than of either sex hormones or insulin with the risk factors. In support of this finding are previous cross-sectional[6] and prospective[7] studies that found BMI[6,7] and WHR[6] to be more strongly related to risk factors than was insulin; neither VAT nor sex hormones were measured in these studies. However, a previous cross-sectional study in men that measured VAT showed that although Pearson correlations of testosterone with triglyceride and HDL-C/cholesterol were eliminated on controlling for VAT, on multiple regression analysis, insulin, but not VAT, was independently associated with triglyceride, HDL-C, and HDL-C/cholesterol.[19]

That VAT may induce risk factors for MI is suggested by the decrease in risk factors with weight reduction.[20] If VAT induces the risk factors and controlling for VAT eliminates the correlations of sex hormones and insulin with the risk factors, then sex hormones and insulin may relate to the constellation mainly through their association with VAT. Although in the present study, VAT did not correlate with estrogens, a strong positive correlation of estrogens and negative correlation of testosterone with body weight in men has been reported.[21-23] That obesity may induce these hormonal changes is suggested by their reversal toward normal in obese men with weight reduction.[24] Similarly, insulin decreases with weight reduction[20] and, as in the present study, has been shown to correlate strongly with VAT.[17] However, VAT was not measured in the weight reduction studies,[20,24] in which a change in diet could also have been a confounding factor. An increase in portal free fatty acids has been reported to increase insulin resistance[25] and may explain the strong positive correlation between VAT and fasting insulin level. Thus, VAT in men may link sex hormones and insulin with risk factors for MI by inducing an alteration in the sex hormone milieu and insulin resistance, as well as an increase in risk factors for MI.

It is also possible that sex hormones and/or insulin could relate to the risk factors by inducing VAT accumulation, which in turn induces the constellation. That a sex hormone alteration may lead to an increase in VAT is suggested by the observation in men that a low baseline testosterone level was prospective for VAT accumulation specifically, not for an increase in BMI or subcutaneous fat, over 7.5 years; the VAT accumulation in these subjects was independent of baseline VAT, BMI, subcutaneous fat, age, diabetes status, and fasting C-peptide; estradiol was not measured.[26] The decrease in testosterone and increase in VAT with age in men is consistent with this finding. Also consistent is that a low free[27] and total[28] testosterone level, controlled for baseline BMI[27,28] and waist circumference,[28] has been reported to be a prospective factor in men for type 2 diabetes, a disorder predicted by an increase in WHR in men[29]; VAT was not measured in these latter 3 studies. Moreover, testosterone undecanoate administration to men has been reported to decrease visceral, but not subcutaneous fat.[30] VAT appears to have a higher turnover rate of lipid than does adipose tissue elsewhere,[16] and testosterone has been reported to inhibit lipoprotein lipase activity.[31] That insulin could induce VAT is suggested by the report that a high fasting insulin was prospective for VAT accumulation.[32] Increased fasting insulin[33] and insulin resistance[34] have also been reported to be prospective for type 2 diabetes, which is predicted by an increase in WHR in men.[29] However, insulin resistance,[35] fasting insulin,[36,37] and insulin secretion[38] have been reported to be negatively associated with weight gain. Moreover, that low testosterone is prospective for VAT accumulation has been shown to be independent of baseline fasting C-peptide level,[26] whereas whether high insulin is prospective for VAT accumulation after controlling for baseline sex hormone levels has apparently not been

reported. Thus, it appears, at present, that a stronger argument can be made for a sex hormone alteration than for an insulin defect as underlying VAT accumulation. Other hormones, such as growth hormone[39,40] and cortisol,[39,41] have also been implicated in VAT accumulation.

It has been suggested that sex hormones may relate oppositely to risk factors for MI in men and women.[42-44] Because risk factors for MI appear to relate similarly to VAT in men and women,[45] the gender dichotomy may occur through the induction of VAT, ie, VAT might be induced by a decrease in testosterone and/or an increase in E/T in men and a decrease in estrogen and/or an increase in the ratio of testosterone-to-estrogen in women.

Whether it is a sex hormone alteration or an insulin defect that may underlie VAT accumulation, however, is further complicated by the relationship of the sex hormones with insulin. An inverse correlation of testosterone with insulin[4] or C-peptide[46] in men has been corroborated by other laboratories.[26,47-51] While E/T has seldom been evaluated by others, the present study and the 4 previous studies from this laboratory[4,11-13] that tested the sex hormone-insulin relationship found a positive correlation between E/T and insulin in men (Table 5). In the first of these studies, on non-obese men, it was reported that the insulin area, glucose area, and the ratio of insulin area-to-glucose area in the glucose tolerance test correlated negatively with the serum testosterone level, but more strongly and positively with E/T.[4] The insulin area/glucose area may be an estimate of insulin resistance in nondiabetic subjects.[52] Recalculation using fasting insulin gives similar results. In the 4 subsequent studies, the fasting insulin level, which has been reported to be a marker of insulin resistance,[53] was used. Although estradiol did not correlate with insulin in any of the 5 studies and estradiol correlated positively with testosterone in 3 of the studies, E/T correlated more strongly with insulin than did testosterone in all of the studies. Moreover, in 2 of the studies, while neither estradiol nor testosterone correlated with insulin, E/T correlated strongly with insulin ($P \leq .001$); in 1 of these studies, furthermore, the maximum BMI was 26.2,[12] suggesting that this correlation occurs also in men who are not overweight. All of the correlations in these studies (Table 5) were controlled for BMI and age. Because of the negative correlation of testosterone and positive correlation of estradiol with obesity reported in men[20-22] and the positive correlation of obesity with insulin,[17] controlling statistically for BMI or VAT prevents BMI or VAT from confounding a testosterone-insulin or E/T-insulin correlation. In the present study, on controlling for VAT, the testosterone-insulin correlation lost statistical significance; however, the E/T-insulin correlation did not ($P = .001$). The sex hormone-insulin relationship found in the present study is consistent with the finding of a high estradiol[54,55] and E/T[54] and low testosterone[56-58] level in men with type 2 diabetes, which is associated with insulin resistance and hyperinsulinemia.[59] Estradiol has apparently not been shown to correlate with insulin in men; however, that E/T correlated with insulin more strongly than did testosterone in each of the 5 studies from this laboratory and that E/T, but not testosterone, correlated with insulin after controlling for VAT in the present study, suggests that estradiol may play an important role in the sex hormone-insulin relationship. Further evidence for the contribution of estradiol to the sex hormone-insulin relationship was the significant and independent association in the present study of estradiol and insulin on multiple linear regression analysis.

But whether a high E/T or a closely related hormonal alteration might underlie the hyperinsulinemia, as hypothesized previously,[4] or vice versa, is speculative. That E/T and insulin correlated strongly independently of VAT in the present study suggests that VAT does not fully explain the E/T-insulin relationship. While we are unaware of studies in men implicating the insulin defect as underlying a decrease in testosterone or an increase in estradiol or E/T, there is evidence to support the hypothesis that a sex hormone alteration may underlie the insulin defect. An increased incidence of abnormal glucose tolerance with increased insulin response has been reported in men with hypogonadal disorders.[60-63] Administration of testosterone propionate[64] and 19-nortestosterone decanoate,[65] which is not aromatized primarily to estradiol, to normal men and testosterone undecanoate to abdominally obese men[30] have been reported to increase insulin sensitivity. Administration of ethinyl estradiol to normal men, moreover, has been reported to induce insulin resistance.[66] However, another study found no effect on insulin sensitivity of testosterone enanthate administration to normal non-obese men on a GnRH agonist to suppress endogenous testosterone secretion.[67]

While testosterone administration in men appears to decrease insulin levels, insulin infused in normal men so as to produce a wide range of plasma insulin concentrations has been reported to have no effect on the total testosterone[68,69] or free testosterone levels.[69] Administration of metformin, which has been reported to decrease hepatic glucose output and plasma insulin levels in patients with type 2 diabetes,[70] together with a hypocaloric diet to obese men with and without type 2 diabetes, was found to decrease rather than increase the testosterone level despite a decrease in BMI.[71]

Against the possibility that an increase in E/T may underlie the insulin defect in men are reports of a man with estrogen resistance owing to a mutation in the estrogen receptor alpha gene[72] and 2 men with low-estradiol levels and elevated testosterone levels owing to a mutation in the aromatase gene,[73,74] all of whom had evidence of insulin resistance and one of glucose intolerance.[72] These patients had, in effect, a very low E/T level with insulin resistance. Administration of oral conjugated estrogen[73] or transdermal estradiol[74] in the aromatase-deficient patients, furthermore, was associated with a decrease in insulin levels in 3[73,74] and 6[74] months despite a marked increase in the estradiol and decrease in the testosterone levels.[74] A third man with aromatase deficiency was reported to have a normal glucose tolerance and insulin response, a normal testosterone level, and a low-estradiol level with little, if any, change in the glucose and insulin levels after 6 months administration of either testosterone enanthate or transdermal estradiol despite marked changes in these hormone levels.[75] The apparent discrepancy among these findings and between these findings and the reports that testosterone[30,64,65] or estradiol[66] administration to normal men decreased or increased insulin resistance, respectively, is unexplained.

In conclusion, the present study suggests a stronger relationship in men of VAT than of either sex hormones or insulin with

risk factors for MI. However, that the testosterone level in men has been reported to correlate prospectively, independently, and negatively with VAT accumulation specifically, and testosterone administration to men has been reported to selectively decrease VAT, suggest that an alteration in the sex hormone milieu could underlie VAT accumulation. Furthermore, the strong correlation between E/T and insulin after controlling for VAT together with the observation in men that testosterone administration decreased and estrogen administration increased insulin resistance suggests that a sex hormone alteration may underlie the insulin defect, as well as VAT accumulation. Thus, it appears that a compelling argument could be made in men for a sex hormone alteration as underlying VAT accumulation and also the insulin defect both indirectly through the induction of VAT and directly; an alteration in the sex hormone milieu, therefore, could be the main underlying factor in the formation of the constellation by inducing insulin resistance and the VAT accumulation, which in turn links the risk factors for MI to each other and to insulin to form the constellation.

REFERENCES

1. Phillips GB: Sex hormones, risk factors and cardiovascular disease. Am J Med 65:7-11, 1978
2. Zavaroni I, Dall'Aglio E, Bonora E, et al: Evidence that multiple risk factors for coronary artery disease exist in persons with abnormal glucose tolerance. Am J Med 83:609-612, 1987
3. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988
4. Phillips GB: Relationship between serum sex hormones and glucose, insulin, and lipid abnormalities in men with myocardial infarction. Proc Natl Acad Sci USA 74:1729-1733, 1977
5. Meigs JB: Invited commentary: Insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. Am J Epidemiol 152:908-911, 2000
6. Cigoloni M, Seidell JC, Targher G, et al: Fasting serum insulin in relation to components of the metabolic syndrome in European healthy men: The European fat distribution study. Metabolism 44:35-40, 1995
7. Maison P, Byrne CD, Hales CN, et al: Do different dimensions of the metabolic syndrome change together over time? Diabetes Care 24:1758-1763, 2001
8. Gallagher D, Kovera AJ, Clay-Williams G, et al: Weight loss in postmenopausal obesity: No adverse alterations in body composition and protein metabolism. Am J Physiol 279:E124-E131, 2000
9. Vermeulen A, Verdonck L, Kaufman JM: A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 84:3666-3672, 1999
10. Sodergard R, Backstrom T, Shanbhag V, et al: Calculation of free and bound fractions of testosterone and estradiol-17β to human plasma proteins at body temperature. J Steroid Biochem 16:801-810, 1982
11. Phillips GB: Relationship between serum sex hormones and the glucose-insulin-lipid defect in men with obesity. Metabolism 42:116-120, 1993
12. Yang X-C, Jing T-Y, Resnick LM, et al: Relation of hemostatic risk factors to other risk factors for coronary heart disease and to sex hormones in men. Arterioscler Thromb Vasc Biol 13:467-471, 1993
13. Phillips GB, Pinkernell BH, Jing T-Y: The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 14:701-706, 1994
14. Pi-Sunyer FX: Health implications of obesity. Am J Clin Nutr 53:1595S-1603S, 1991
15. Ferrannini E, Haffner SM, Mitchell BD, et al: Hyperinsulinaemia: The key feature of a cardiovascular and metabolic syndrome. Diabetologia 34:416-422, 1991
16. Marin P, Andersson B, Ottosson M, et al: The morphology and metabolism of intraabdominal adipose tissue in men. Metabolism 41: 1242-1248, 1992
17. Bonora E: Relationship between regional fat distribution and insulin resistance. Int J Obes 24:S32-S35, 2000 (suppl 2)
18. Pouliot M-C, Despres J-P, Nadeau A, et al: Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes 41:826-834, 1992
19. Tchernof A, Labrie F, Belanger A, et al: Relationships between endogenous steroid hormone, sex hormone-binding globulin and lipoprotein levels in men: Contribution of visceral obesity, insulin levels and other metabolic variables. Atherosclerosis 133:235-244, 1997
20. Olefsky J, Reaven GM, Farquhar JW: Effects of weight reduction on obesity. Studies of lipid and carbohydrate metabolism in normal and hyperlipoproteinemic subjects. J Clin Invest 53:64-76, 1974
21. Glass AR, Swerdloff RS, Bray GA, et al: Low serum testosterone and sex-hormone-binding globulin in massively obese men. J Clin Endocrinol Metab 45:1211-1219, 1977
22. Schneider G, Kirschner MA, Berkowitz R: Increased estrogen production in obese men. J Clin Endocrinol Metab 48:633-638, 1979
23. Kley HK, Edelmann P, Kruskemper HL: Relationship of plasma sex hormones to different parameters of obesity in male subjects. Metabolism 29:1041-1045, 1980
24. Stanik S, Dornfeld LP, Maxwell MH, et al: The effect of weight loss on reproductive hormones in obese men. J Clin Endocrinol Metab 53:828-832, 1981
25. Randle PJ, Hales CN, Garland PB, et al: The glucose fatty-acid cycle: Its role in insulin sensitivity and the metabolic disturbance of diabetes mellitus. Lancet 1:785-789, 1963
26. Tsai EC, Boyko EJ, Leonetti DL, et al: Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. Int J Obes 24:485-491, 2000
27. Haffner SM, Shaten J, Stern MP, et al: Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. Am J Epidemiol 143: 889-897, 1996
28. Oh J-Y, Barrett-Connor E, Wedick NM, et al: Endogenous sex hormones and the development of type 2 diabetes in older men and women: The Rancho Bernardo Study. Diabetes Care 25:55-60, 2002
29. Ohlson L-O, Larsson B, Svardsudd K, et al: The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 34:1055-1058, 1985
30. Marin P, Holmang S, Jonsson L, et al: The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. Int J Obes 16:991-997, 1992
31. Rebuffe-Scrive M, Marin P, Bjorntorp P: Effect of testosterone on abdominal adipose tissue in men. Int J Obes 15:791-795, 1991
32. Boyko EJ, Leonetti DL, Bergstrom RW, et al: Low insulin secretion and high fasting insulin and C-peptide levels predict increased visceral adiposity. 5-year follow-up among initially nondiabetic Japanese-American men. Diabetes 45:1010-1015, 1996
33. Haffner SM, Stern MP, Mitchell BD, et al: Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. Diabetes 39:283-288, 1990
34. Lillioja S, Mott DM, Spraul M, et al: Insulin resistance and

insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective study of Pima Indians. N Engl J Med 329:1988-1992, 1993

35. Swinburn BA, Nyomba BL, Saad MF, et al: Insulin resistance associated with lower rates of weight gain in Pima Indians. J Clin Invest 88:168-173, 1991

36. Valdez R, Mitchell BD, Haffner SM, et al: Predictors of weight change in a bi-ethnic population. The San Antonio Heart Study. Int J Obes 18:85-91, 1994

37. Hoag S, Marshall JA, Jones RH, et al: High fasting insulin levels associated with lower rates of weight gain in persons with normal glucose tolerance: The San Luis Valley Diabetes Study. Int J Obes 19:175-180, 1995

38. Schwartz MW, Boyko EJ, Kahn SE, et al: Reduced insulin secretion: An independent predictor of body weight gain. J Clin Endocrinol Metab 80:1571-1576, 1995

39. Bjorntorp P: The regulation of adipose tissue distribution in humans. Int J Obes 20:291-302, 1996

40. Bengtsson B, Eden S, Lonn L, et al: Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J Clin Endocrinol Metab 76:309-317, 1993

41. Bujalska IJ, Kumar S, Stewart PM: Does central obesity reflect "Cushing's disease of the omentum"? Lancet 349:1210-1213, 1997

42. Phillips GB: Relationship of serum sex hormones to coronary heart disease. Steroids 58:286-290, 1993

43. Phillips GB: Sex hormones in male serum. Steroids 58:554-555, 1993 (comment)

44. Phillips GB, Pinkernell BH, Jing T-Y: Relationship between serum sex hormones and coronary artery disease in postmenopausal women. Arterioscler Thromb Vasc Biol 17:695-701, 1997

45. Imbeault P, Lemieux S, Prud'homme D, et al: Relationship of visceral adipose tissue to metabolic risk factors for coronary heart disease: Is there a contribution of subcutaneous fat cell hypertrophy? Metabolism 48:355-362, 1999

46. Seidell JC, Bjorntorp P, Sjostrom L, et al: Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. Metabolism 39:897-901, 1990

47. Lichtenstein MJ, Yarnell JWG, Elwood PC, et al: Sex hormones, insulin, lipids, and prevalent ischemic heart disease. Am J Epidemiol 126:647-657, 1987

48. Pasquali R, Casimirri F, Cantobelli S, et al: Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism 40:101-104, 1991

49. Simon D, Preziosi P, Barrett-Connor E, et al: Interrelation between plasma testosterone and plasma insulin in healthy adult men: The Telecom Study. Diabetologia 35:173-177, 1992

50. Haffner SM, Karhapaa P, Mykkanen L, et al: Insulin resistance, body fat distribution, and sex hormones in men. Diabetes 43:212-219, 1994

51. Tchernof A, Despres J-P, Dupont A, et al: Relation of steroid hormones to glucose tolerance and plasma insulin levels in men. Diabetes Care 18:292-299, 1995

52. Caro JF: Insulin resistance in obese and nonobese man. J Clin Endocrinol Metab 73:691-695, 1991

53. Laakso M: How good a marker is insulin level for insulin resistance? Am J Epidemiol 137:959-965, 1993

54. Phillips GB: Evidence for hyperestrogenemia as the link between diabetes mellitus and myocardial infarction. Am J Med 76:1041-1048, 1984

55. Small M, MacRury S, Beastall GH, et al: Oestradiol levels in diabetic men with and without a previous myocardial infarction. QJM 243:617-623, 1987

56. Ando S, Rubens R, Rottiers R: Androgen plasma levels in male diabetics. J Endocrinol Invest 7:21-24, 1984

57. Barrett-Connor E: Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. Ann Intern Med 117:807-811, 1992

58. Andersson B, Marin P, Lissner L, et al: Testosterone concentrations in women and men with NIDDM. Diabetes Care 17:405-411, 1994

59. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM. A balanced overview. Diabetes Care 15:318-366, 1992

60. Megyesi C, Samols E, Marks V: Glucose tolerance and diabetes in chronic liver disease. Lancet 2:1051-1056, 1967

61. Nielsen J, Johansen K, Yde H: Frequency of diabetes mellitus in patients with Klinefelter's syndrome of different chromosome constitutions and the XYY syndrome. Plasma insulin and growth hormone level after a glucose load. J Clin Endocrinol Metab 29:1062-1073, 1969

62. Epstein CJ, Martin GM, Schultz AL, et al: Werner's syndrome. Medicine (Baltimore) 45:177-221, 1966

63. Huff TA, Horton ES, Lebovitz HE: Abnormal insulin secretion in myotonic dystrophy. N Engl J Med 277:837-841, 1967

64. Talaat M, Habib YA, Habib M: The effect of testosterone on the carbohydrate metabolism in normal subjects. Arch Int Pharmacodyn Ther 111:216-226, 1957

65. Friedl KE, Jones RE, Hannan CJ Jr, et al: The administration of pharmacological doses of testosterone or 19-nortestosterone to normal men is not associated with increased insulin secretion or impaired glucose tolerance. J Clin Endocrinol Metab 68:971-975, 1989

66. Polderman KH, Gooren LJG, Asscheman H, et al: Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 79:265-271, 1994

67. Singh AB, Hsia S, Alaupovic P, et al: The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. J Clin Endocrinol Metab 87:136-143, 2002

68. Stuart CA, Prince MJ, Peters EJ, et al: Hyperinsulinemia and hyperandrogenemia: In vivo androgen response to insulin infusion. Obstet Gynecol 69:921-925, 1987

69. Ebeling P, Stenman U-H, Seppala M, et al: Acute hyperinsulinemia, androgen homeostasis and insulin sensitivity in healthy man. J Endocrinol 146:63-69, 1995

70. DeFronzo RA, Barzilai N, Simonson DC: Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. J Clin Endocrinol Metab 73:1294-1301, 1991

71. Ozata M, Oktenli C, Bingol N, et al: The effects of metformin and diet on plasma testosterone and leptin levels in obese men. Obes Res 9:662-667, 2001

72. Smith EP, Boyd J, Frank GR, et al: Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 331:1056-1061, 1994

73. Morishima A, Grumbach MM, Simpson ER, et al: Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 80:3689-3698, 1995

74. Herrmann BL, Saller B, Janssen OE, et al: Impact of estrogen replacement therapy in a male with congenital aromatase deficiency caused by a novel mutation in the CYP19 gene. J Clin Endocrinol Metab 87:5476-5484, 2002

75. Carani C, Qin K, Simoni M, et al: Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med 337:91-95, 1997