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Relationship between serum sex hormones and glucose, insulin, and lipid abnormalities in men with myocardial infarction

(diabetes/estradiol-17β/testosterone/cholesterol/triglyceride)

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ABSTRACT **Fifteen patients who had had a myocardial infarction before the age of 43 were compared with thirteen age-matched normal subjects. Twelve of the patients and three of the controls had a delayed glucose and insulin peak in the glucose tolerance test. Curves with delayed peaks defined larger mean glucose and insulin areas than normal curves. When the measurements of the four patients with the largest areas under the glucose tolerance curve were separated, significant correlations were observed in the remaining patients and controls. The ratio in serum of the concentrations of estradiol-17β to testosterone (E/T) correlated with serum glucose area ($r = +0.69$, $P < 0.001$), insulin area ($r = +0.80$, $P < 0.001$), and the ratio of insulin area to glucose area (I/G) ($r = +0.64$, $P < 0.005$) in the glucose tolerance test. Serum cholesterol concentration correlated with E/T, insulin area, and I/G, and serum triglyceride concentration correlated with glucose area, I/G, and serum cholesterol concentration. The hypothesis is presented (*i*) that in men who have had a myocardial infarction, an abnormality in glucose tolerance and insulin response and elevation in serum cholesterol and triglyceride concentrations are all part of the same defect (glucose–insulin–lipid defect), (*ii*) that this glucose–insulin–lipid defect when glucose intolerance is present is the "mild diabetes" commonly associated with myocardial infarction but is based on a mechanism different from that of classical diabetes, (*iii*) that this glucose–insulin–lipid defect is secondary to an elevation in E/T, and (*iv*) that an alteration in the sex hormone milieu is the major predisposing factor for myocardial infarction.**

An abnormality in glucose tolerance, insulin response, serum lipid or lipoprotein concentrations, or some combination of these has been reported to occur in 80–96% of patients with coronary heart disease (1–7). In a previous study (8), a high incidence of hyperestrogenemia was observed in men under 44 years of age with myocardial infarction. The present report describes further investigations carried out on the patients and normal subjects of that study in order to determine whether the hyperestrogenemia was related to the glucose, insulin, and lipid abnormalities. The results of these investigations show a high level of correlation between the degrees of the glucose and insulin defects and the ratio of the weight concentrations in serum of estradiol-17β to testosterone (E/T). The degree of the glucose–insulin defect was also found to correlate with the serum cholesterol and triglyceride concentrations, suggesting that an elevation in the concentrations of these lipids is part of the same defect (glucose–insulin–lipid defect). These observations raise the possibility that this glucose–insulin–lipid defect is secondary to an elevation in E/T and that a disturbance in the relationships of serum sex hormones is the major predisposing factor for myocardial infarction in men.

Abbreviations. E/T, estradiol/testosterone weight concentrations in serum; G.T.T., glucose tolerance test; I/G, insulin area/glucose area of curves in the G.T.T.; % MDW, % maximum desirable body weight.

PATIENTS AND METHODS

The patients and normal subjects (controls) studied were described previously (8). They were between 33 and 43 years old at the time of study. The patients had had a myocardial infarction before the age of 43 and were studied at least 4 months after that. None of the patients were left with any complication of the myocardial infarction or had any other serious disorder. No patient or normal subject had a history of alcoholism or was regularly taking any drug. A glucose tolerance test (G.T.T.) was performed using 75 g of glucose in 300 ml of water flavored with fresh lemon juice and blood samples were drawn when the subject was fasting and at ½, 1, 2, and 3 hr. The areas under the glucose and insulin curves in the G.T.T. will hereafter be referred to as *glucose area* and *insulin area*, respectively, and the ratio of the insulin area to glucose area as *I/G*. The hormone and lipid determinations were carried out on the sample taken when the subject was fasting. Serum glucose, insulin, growth hormone, and cortisol concentrations were measured on all of the samples. One of the normal subjects was excluded from this study because he had no response in the G.T.T., his serum glucose values at 0, ½, 1, 2, and 3 hr having been 82, 75, 70, 73, and 54 mg/dl, respectively. The possibility of an absorptive defect was considered. Another normal subject was discovered to have not been fasting before his G.T.T. His serum hormone and lipid studies were carried out in the fasting state subsequently but because the G.T.T. could not be repeated until 9 months after these measurements, he was also excluded from this study. Inclusion of his data, however, would have had little effect on any of the correlation coefficients and would have increased the significance of the correlations of both glucose area and insulin area with serum testosterone concentration and E/T. His glucose and insulin curves in the G.T.T. peaked at ½ hr. Thus, the 15 patients and 13 of the 15 control subjects of the previous study (8) were included in this study. The percent of maximum desirable body weight (% MDW) was determined using Metropolitan Life Insurance Co. tables (9). No control was over 114% MDW. One patient, although he did not appear obese, was 127% MDW (obese patient). None of the other patients was over 111% MDW.

All measurements were made on serum. Glucose was measured by a glucose oxidase method and lipid and lipoproteins as described previously (8). Sex hormones were estimated by radioimmunoassay (8). Insulin (10) and growth hormone (11) were measured by double antibody radioimmunoassay and cortisol by competitive protein-binding radioassay (12).

To obtain the mean correlation coefficient, the correlation coefficients (r) for the patient and control samples were compared and combined using the Fisher z transformation (13). The significance of the difference between two means was determined by using Student's t test.

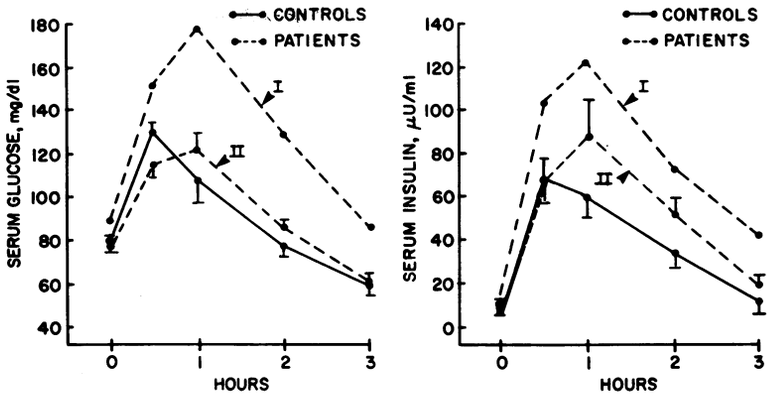

FIG. 1. Glucose tolerance and insulin response curves. I, four Group I patients. II, ten Group II patients. Values are means + or − standard errors.

RESULTS

When the four patients with the largest areas under the G.T.T. curve, who were the four patients with abnormal values in the G.T.T., were treated as a group (Group I) separate from the other 11 patients, significant correlations became evident. Because of the effect of obesity itself on insulin area and serum triglyceride concentration (14), the one obese patient was considered separately, leaving 10 patients in Group II. The G.T.T. and insulin response curves of these two groups of patients and controls are shown in Fig. 1. One Group I patient would be classified as having unequivocal diabetes mellitus (diabetes) by conventional criteria (15). Two of the other Group I patients had elevated 1-hr serum glucose concentrations of 175 and 179 mg/dl in the G.T.T. and the third had an elevated 2-hr serum glucose concentration of 142 mg/dl, the other values in the test being in the normal range in these three patients (15). Although the mean glucose area of Group II patients was similar to that of the controls, the peak mean value was at 1 hr in the patients compared to ½ hr in the controls. This delayed glucose peak was observed in 7 of the 10 Group II patients and 3 of the 13 controls. The insulin curves conformed to the glucose curves in all patients and controls except in two control subjects with a normal glucose and delayed insulin peak. The shapes of the mean glucose and insulin curves of the Group II patients were similar to those of the Group I patients. All of the Group I patients and the obese patient showed a delayed glucose and insulin peak. The delay in the glucose and insulin peak correlated with glucose and insulin area, respectively. The mean ± standard deviation glucose area (305 ± 39 mg-hr/dl) of the Group II patients and controls together with a 1-hr peak was significantly higher ($P < 0.02$) than in those with a ½ hr peak (264 ± 38 mg-hr/dl). The corresponding values for the mean insulin area, 175 ± 59 and 99 ± 48 μunit-hr/ml, were also significantly different ($P < 0.005$). I/G in those with the delayed peak was significantly higher whether considered on the basis of the peak-time of the glucose ($P < 0.02$) or insulin ($P < 0.02$) curves.

Combining the data of the 10 Group II patients and 13 controls as described above revealed significant mean correlations (Table 1). The glucose area correlated negatively with serum testosterone concentration and positively with E/T (Fig. 2). The correlation between glucose area and E/T was also significant for the data of the controls calculated separately ($r = +0.75$, $P < 0.01$). The insulin area appeared to correlate to a higher degree and in the same direction with serum testosterone concentration and E/T (Fig. 2), and significant correlations were found when the data were calculated separately for insulin area and serum testosterone concentration in the patients ($r = -0.77$, $P < 0.01$) and for insulin area and E/T in both the patients ($r = +0.89$, $P < 0.01$) and controls ($r = +0.71$, $P < 0.01$). Although the glucose and insulin areas correlated with each other in the combined samples, and for the data of the controls

Table 1. Mean correlation coefficients between serum factors*

	Estradiol	Testosterone	Estradiol/ testosterone	Glucose area	Insulin area	Insulin area/ glucose area
Glucose area	+0.28	−0.49 $P < 0.02$	+0.69 $P < 0.001$	—	+0.60 $P < 0.005$	+0.27
Insulin area	+0.13	−0.64 $P < 0.005$	+0.80 $P < 0.001$	—	—	+0.93 $P < 0.001$
Insulin area/glucose area	+0.07	−0.55 $P < 0.01$	+0.65 $P < 0.005$	—	—	—
Cholesterol	+0.25	−0.36	+0.44 $P < 0.05$	+0.32	+0.50 $P < 0.02$	+0.49 $P < 0.02$
Triglyceride	+0.16	−0.36	+0.40	+0.54 $P < 0.01$	†	+0.43 $P < 0.05$
β-Lipoprotein	+0.40	−0.34	+0.52 $P < 0.02$	+0.53 $P < 0.01$	+0.49 $P < 0.02$	+0.40

* Correlations include the 10 Group II patients and 13 controls. Correlations are not significant where no P value is given.
† The two separate correlations were found to be significantly different.

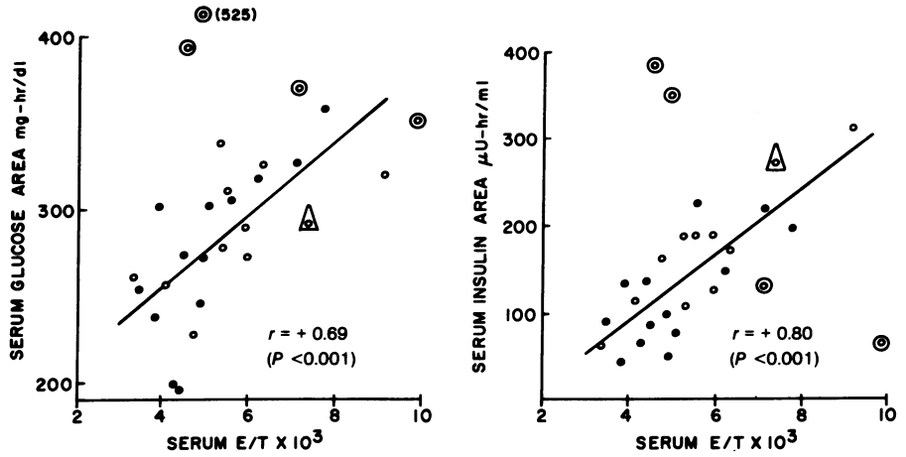

FIG. 2. Relationship of serum glucose area and insulin area with E/T. ●, Controls; ○, Group II patients; ⊙, Group I patients; ▲, obese patient. Serum glucose area–E/T, $y = 173 + 20.6x$. Serum insulin area–E/T, $y = -61 + 38x$.

calculated separately ($r = +0.61$, $P < 0.05$), they did not rise equally, as evidenced by the high degree of positive correlation between insulin area and I/G. I/G in turn correlated with E/T for the combined samples (Fig. 3) and for the data of the patients calculated separately ($r = +0.81$, $P < 0.01$). The values for the four Group I patients and the obese patient are also shown in Figs. 2 and 3. The two Group I patients with the highest glucose areas had the highest insulin areas.

The serum cholesterol concentration correlated with E/T, insulin area, and I/G. A significant correlation was also found for the data of the controls alone between serum cholesterol concentration and insulin area ($r = +0.68$, $P < 0.02$) and I/G ($r = +0.67$, $P < 0.02$). The serum triglyceride concentration correlated with glucose area and I/G and for the data of the controls alone with insulin area ($r = +0.79$, $P < 0.005$) and I/G ($r = +0.68$, $P < 0.02$). Serum cholesterol and triglyceride concentrations correlated with each other in the combined samples ($r = +0.79$, $P < 0.001$) and for the data of the patients ($r = +0.64$, $P < 0.05$) and controls ($r = +0.84$, $P < 0.005$) calculated separately. The serum β-lipoprotein concentration correlated with the serum cholesterol concentration ($r = +0.82$, $P < 0.001$) and with E/T, glucose area, and insulin area. The serum α-lipoprotein and pre-β-lipoprotein concentrations did not achieve significant correlations with any of the factors in Table 1 except between pre-β-lipoprotein concentration and serum triglyceride ($r = +0.89$, $P < 0.001$) and β-lipoprotein ($r = +0.48$, $P < 0.05$) concentrations.

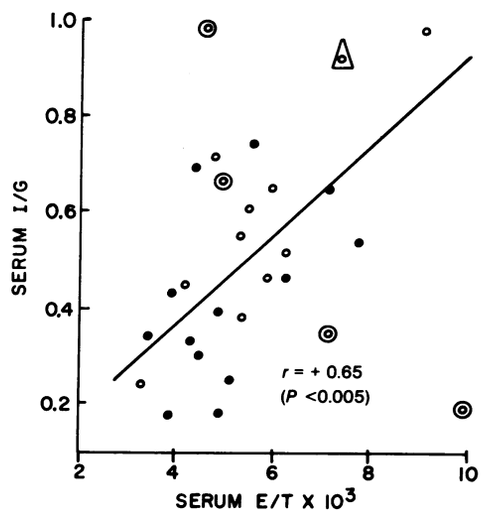

FIG. 3. Relationship of serum I/G with E/T. ●, Controls; ○, Group II patients; ⊙, Group I patients; ▲, obese patient. $y = -0.007 + 0.093x$.

The % MDW correlated in the combined samples with serum triglyceride concentration ($r = +0.49$, $P < 0.02$) and in the controls alone with serum triglyceride concentration ($r = +0.68$, $P < 0.02$), E/T ($r = +0.55$, $P < 0.05$), glucose area ($r = +0.57$, $P < 0.05$), insulin area ($r = +0.76$, $P < 0.01$), and I/G ($r = +0.58$, $P < 0.05$). These correlations occurred even though no patient was over 111% MDW and no control over 114% MDW and the mean ± SD % MDW was 99.9 ± 6.1% in the Group II patients and 99.3 ± 7.0% in the controls. Exclusion of the control with 114% MDW lowered the r between % MDW and serum triglyceride concentration in the combined samples to +0.28 and in the controls to +0.40, and the r between % MDW and I/G in the controls to +0.39, but the correlations between % MDW and E/T, glucose area, and insulin area in the controls remained significant. These results suggest that over even a modest range of % MDW, % MDW was related to serum triglyceride concentration, E/T, glucose area, insulin area, and I/G in the controls. Inclusion of the obese patient had little effect on the major correlations, decreasing the significance of the correlation between glucose area and insulin area by <2%, and increasing the significance of all the other correlations among glucose area, insulin area, I/G, serum estradiol concentration, serum testosterone concentration, and E/T by <6%. Thus, overweight did not appear to be a significant factor in the relationship between the serum sex hormone concentrations and the glucose–insulin defect in the patients or in the combined samples.

No other significant correlations were found among these factors or between these factors and systolic or diastolic blood pressure or serum growth hormon or cortisol concentrations.

In order to determine whether the abnormal glucose and insulin curves in the patients might have been related to an abnormality in serum growth hormone or cortisol levels, the serum concentrations of these hormones were determined during the G.T.T. in patients and controls. No significant difference was found between Group I patients, Group II patients, and controls in either mean serum growth hormone or cortisol concentrations at any time in the test. Nor were significant differences in the mean concentrations of these hormones observed when patients and controls were grouped together and compared on the basis of the peak-time. The "total" serum cortisol (sum of 5 values in G.T.T.) and "total" serum growth

hormone (sum of first 4 values in G.T.T.) correlated ($r = +0.51$, $P < 0.02$) in the combined samples and in the patient group alone ($r = +0.71$, $P < 0.05$).

DISCUSSION

Although an abnormality in glucose tolerance may occur in the majority of patients who have had a myocardial infarction (3, 6, 16, 17), an increased insulin response to glucose administration has been reported to have an even higher incidence in such patients (14, 18, 19). But the present study suggests that if the delay in the glucose peak in the G.T.T. were used as a criterion of abnormality, the incidence of abnormality in glucose tolerance and in insulin response would be similar. The time of the peak in the glucose curve coincided with that in the insulin curve in every patient and control except two. The delay in the peak, furthermore, correlated with an increase in the area under the glucose or insulin curve, suggesting that shape and area were both manifestations of the same phenomenon. That patients with this glucose-insulin defect have a true hyperinsulinemia is suggested by the high degree of positive correlation between the insulin area and I/G.

When the four patients with the largest glucose areas were excluded, glucose area, insulin area, and I/G correlated negatively with serum testosterone concentration and positively and to a higher degree with E/T. The two patients with the largest glucose and insulin areas had the lowest serum estradiol concentrations of the patients and E/T values less than the mean value of the patients or controls. These observations suggest that the glucose–insulin defect in these two patients is based on a mechanism different from that in the other patients and controls. The other two of these four patients had among the highest serum estradiol concentrations and E/T values, but one of them did not fit the regression lines because of a low insulin response in the G.T.T. The possibility arises that this patient did not fit the correlations because of a defect in insulin secretion. That the glucose–insulin defect in the remaining patients is based on a mechanism different from that of classical diabetes is supported by the reports in patients who had had a myocardial infarction of (*i*) hyperinsulinemia after intravenous glucose (2, 5), (*ii*) a normal decline in serum free fatty acid concentration after administered glucose (1, 17, 19), and (*iii*) the finding in this study and others (4–6) of a family incidence of diabetes no greater than that of controls. The observation that 3 of the 13 normal subjects in the present study had this glucose–insulin defect is consistent with the findings of others (7, 14) and suggests that this defect, which when glucose intolerance is present is the "diabetes" most often associated with myocardial infarction, is much commoner than classical diabetes in the general population.

The high degree of correlation among glucose area, insulin area, and E/T suggests that the three are related. The high degree of correlation between I/G and E/T indicates that the degree of hyperinsulinemia is a function of E/T. Whether the glucose–insulin defect and elevation in E/T are causally related or are both secondary to another factor cannot be concluded from this study. However, the observation that the two patients with the largest glucose and insulin areas in the present study had E/T values that were lower than the mean value of the patients or controls suggests that decreased glucose tolerance with increased insulin response does not cause an elevation in E/T. Studies in women on contraceptive medication, on the other hand, suggest that an alteration in sex hormone relationships can produce decreased glucose tolerance with increased insulin response (20). A high incidence of this type of glucose–insulin defect has also been observed in men with cirrhosis of the liver (21) and with Klinefelter's syndrome (22), disorders associated with an elevated E/T (23, 24). It seems likely, therefore, that the glucose–insulin defect of patients who have had a myocardial infarction is secondary to the hormonal alterations.

The serum cholesterol concentration correlated with E/T, insulin area, and I/G, and the serum triglyceride concentration correlated with glucose area and I/G, as well as with the serum cholesterol concentration. Others have noted a correlation between serum triglyceride concentration and insulin area (14). An increase in serum triglyceride concentration has been reported in men administered estrogen (25). These observations suggest that an increase in the serum concentrations of these lipids is also part of the glucose–insulin defect and may contribute importantly to the incidence of hyperlipidemia in patients with myocardial infarction.

Although the mean serum estradiol concentration was significantly higher in the 15 patients than in the 15 controls as previously reported (8), the increase in E/T in the patients was not significant. Thus, myocardial infarction correlated with serum estradiol concentration while the degree of the glucose–insulin–lipid defect correlated with E/T. The highly significant correlation ($r = +0.55$, $P < 0.005$) between serum estradiol concentration and E/T in patients and controls combined, however, could explain the correlation between myocardial infarction and the glucose–insulin–lipid defect. If this is the case, myocardial infarction would be expected in the absence of the glucose–insulin–lipid defect and vice versa, a hypothesis consistent with the data in this and other studies (1, 2, 14). Because of the small size of the present series of patients, however, the possibility arises that myocardial infarction may actually correlate better with E/T or some related pattern of serum sex hormones than with serum estradiol concentration.

The high incidence of the glucose–insulin–lipid defect in men who have had a myocardial infarction, the possibility that this defect is secondary to an elevated E/T, and the observation that estrogen administration to men increases the incidence of myocardial infarction (26) suggest that an alteration in the pattern of serum sex hormones may be the major predisposing factor for myocardial infarction in men. Because only men were included in the present study, it is not known whether any of these relationships apply to women. That the marked increase in the incidence of myocardial infarction after the menopause has not been explained by known risk factors (27), however, suggests that a change in the sex hormone milieu may also be the major predisposing factor for myocardial infarction in women.

A high incidence of this type of glucose–insulin–defect has been reported in patients with peripheral vascular disease (4, 14, 28), stroke (3), hypertension (29), obesity (14), and impotence (S. Deutsch, personal communication) and suggests that an elevation in E/T and perhaps hyperestrogenemia may be operative in these disorders. Administration of estrogen appears to increase the likelihood of stroke in patients who have already had one (30) and may produce hypertension in women (31). Evidence for a similar incidence of the glucose defect in patients with angina (4, 7) and with coronary artery disease without myocardial infarction (7) shows that the defect is not secondary to the infarction and implies that hyperestrogenemia may act not merely by provoking thrombosis but also by promoting the atherosclerotic process itself. Finally, the report of an increasing serum estradiol and decreasing serum testosterone concentration with aging in men (32) is consistent with the increasing incidence of myocardial infarction observed with aging (33)

and may also explain at least in part the decreasing glucose tolerance (34) with increasing insulin response (35), increasing serum cholesterol and triglyceride concentrations (34), increasing blood pressure (36), impotence, tendency to obesity (37), and perhaps other concomitants of aging as well.

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