Glucose Tolerance, Serum Insulin and Lipid Abnormalities in Patients with Coronary Heart Disease

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SUMMARY

Blood glucose, free fatty acid and insulin responses to oral glucose and the fasting serum lipids were measured in 3 groups: 32 non-obese (mean age: 47.5 years) and 9 obese (mean age: 84.5 years), male patients with coronary heart disease and 12 non-obese male controls (mean age: 46.5 years). The oral glucose tolerance tests were repeated after 3 years in 16 of the non-obese patients with coronary heart disease.

The results were as follows:

1) Glucose tolerance was impaired in 19 of 32 non-obese patients (59.4%). There was a significant correlation between impaired glucose tolerance and hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia).

2) In obese patients FFA levels at 30, 60, and 120 min after oral glucose administration were significantly elevated and FFA decrease was delayed with a drop to minimum levels at 180 min.

3) The insulin response after oral glucose administration in the group of non-obese patients with normal glucose tolerance was similar to that of non-obese controls. In the group of non-obese patients with impaired glucose tolerance, serum insulin levels went up to normal levels, but the peak was delayed. The serum insulin levels in obese patients were significantly higher than those of controls at 0, 60, 120, and 180 min. After 3 years the change in insulin response to oral glucose was not related to anginal symptoms or ECG findings, but was related to body weight change in patients with minor changes in glucose tolerance.

4) The metabolic pattern in the non-obese group with impaired glucose tolerance resembled that of " mild diabetes " in delayed response of insulin and FFA, and mild hyperlipidemia.

These findings suggest that obesity may contribute to hyperinsulinemia in patients with coronary heart disease and that impaired glucose tolerance observed in patients with coronary heart disease is in part due to " latent diabetes ".

Additional Indexing Words:

Serum insulin Serum lipid Coronary heart disease Oral glucose tolerance Obesity

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IT is well known from a number of clinical studies that there is an increased incidence of coronary heart disease in patients with diabetes mellitus. Furthermore, many investigators have shown that glucose intolerance and hyperlipidemia are frequently found in those patients with coronary heart disease without clinical diabetes. However, no definitive causal relationship has been demonstrated between coronary heart disease and diabetes mellitus.[1]

Since the radioimmunoassay of insulin has become available, the serum insulin response to glucose in patients with coronary heart disease has been studied. Some investigators have advanced a hypothesis that could explain the mechanism of accelerated arteriosclerosis by insulin action.[2] However, any discussion of insulin response in humans must presuppose a proper selection of subjects because insulin response can be modified by disease states such as hypertension,[3] diabetes,[4] liver disease,[5] endocrine diseases, and also by physiological conditions such as aging,[6] sex,[7] obesity,[8] and nutrition.[9]

Combined analyses of clinical background and insulin response to glucose may help evaluate the role of abnormal insulin response in patients with coronary heart disease.

Consequently, the present study was designed to examine the fasting serum lipids and the blood glucose, insulin, and free fatty acid response to oral glucose in patients with coronary heart disease.

Subjects and Methods

The subjects were all males—32 non-obese patients with coronary heart disease, 9 obese patients with coronary heart disease, and 12 non-obese controls. Most were in their forties, but some were in their thirties and fifties. The non-obese patients with coronary heart disease (non-obese CHD group) ranged in age from 31 to 54 (mean 47.5) weighing not more than 11.1% above ideal body weight. Sixteen of them had experienced myocardial infarction and an equal number had angina pectoris. The obese patients with coronary heart disease (obese CHD group) ranged in age from 43 to 54 (mean 48.5) and weighed 25.5 to 37.3% above ideal body weight with average of 30.5% overweight. Of them, 4 had myocardial infarction and 5 had angina pectoris. Potential subjects were excluded if other factors which affect serum insulin levels, such as malnutrition, hypertension, diabetes, liver disease, clinically obvious endocrine disorders, or advanced age were present. Neither the subjects nor members of their families had history of diabetes mellitus and none of them had clinical diabetes mellitus. The members of the control group ranged in age from 43 to 53 (mean 46.3). All were healthy with a normal ECG, ophthalmologic examination, serum cholesterol, liver function tests, and blood pressure. All weighed not more than 10% above their ideal body weight.

The criteria for the diagnosis of coronary heart disease were (1) a clinically documented myocardial infarction and/or (2) angina pectoris with supporting electrocardiographic evidence or relief by nitroglycerin.

As the criteria for obesity, the ideal body weight was determined by Broca's formula: (body height in centimeters $-100) \times 0.9$ Kg. The difference between real body weight and ideal body weight divided by the ideal body weight was used to calculate the degree of obesity.

One hundred Gm oral glucose tolerance tests were performed after an overnight fast. Venous blood samples were taken at 0, 30, 60, 120, and 180 min intervals with measurements of blood glucose, free fatty acids (FFA), and serum immunoreactive insulin (IRI). The levels of triglyceride (TG) were measured in blood samples before glucose administration. The total fasting cholesterol concentration in serum (T-Ch) was determined within 3 weeks of the glucose tolerance test. Blood glucose was determined by the Hoffman method on the autoanalyzer;[10] FFA, by the modified Dole technique;[11] and IRI, by the two antibody method of Morgan-Lazarow.[12] The Zak-Hanley[13] method was used for T-Ch determination (normal levels: 170–240 mg/100 ml). The method of Eggestein and Kreutz[14] was used for the measurement of TG levels (normal level 74 to 172 mg%).

Out of 32 non-obese patients with coronary heart disease, 16 received a second 100 Gm oral glucose tolerance test 3 years later.

The criteria for impaired glucose tolerance was either a 60 min value greater than 170 mg/100 ml or a 120 min value greater than 130 mg/100 ml. These criteria are 10 mg/100 ml greater than those recommended by Japan Diabetic Society,[44] because our laboratory data showed the values of blood glucose by autoanalyzer and were approximately 10 mg/100 ml greater than the values by oxidase method.

Results

The mean blood glucose levels in the non-obese CHD group were slightly higher than those of the control group. In the obese CHD group the glucose levels were significantly higher at 30($P<0.05$), 60($P<0.01$), and 120 min ($P<0.01$) than those observed in the control group (Fig. 1a). The 32 non-obese CHD group was divided into 2 groups: 13 patients with normal glucose tolerance (Group A) and 19 patients with impaired glucose tolerance (Group B). The obese CHD group consisted of 3 patients with normal glucose tolerance and 6 with impaired glucose tolerance. Group A showed blood glucose curve following oral glucose similar to that of the control group, and blood glucose curve of Group B was similar to that of the obese CHD group (Fig. 1b).

The incidence of impaired glucose tolerance was 19/32 (59.4%) in the non-obese CHD group, 6/9 (66.7%) in the obese CHD group, and 25/41 (61.0%) for all the patients with coronary heart disease.

The mean FFA levels of the obese CHD were significantly higher than those of the control group at 0, 30, 60, and 120 min ($P<0.01$) and were still falling 180 min after glucose administration. The non-obese CHD group was little different from the control group, their FFA being lowest at 120

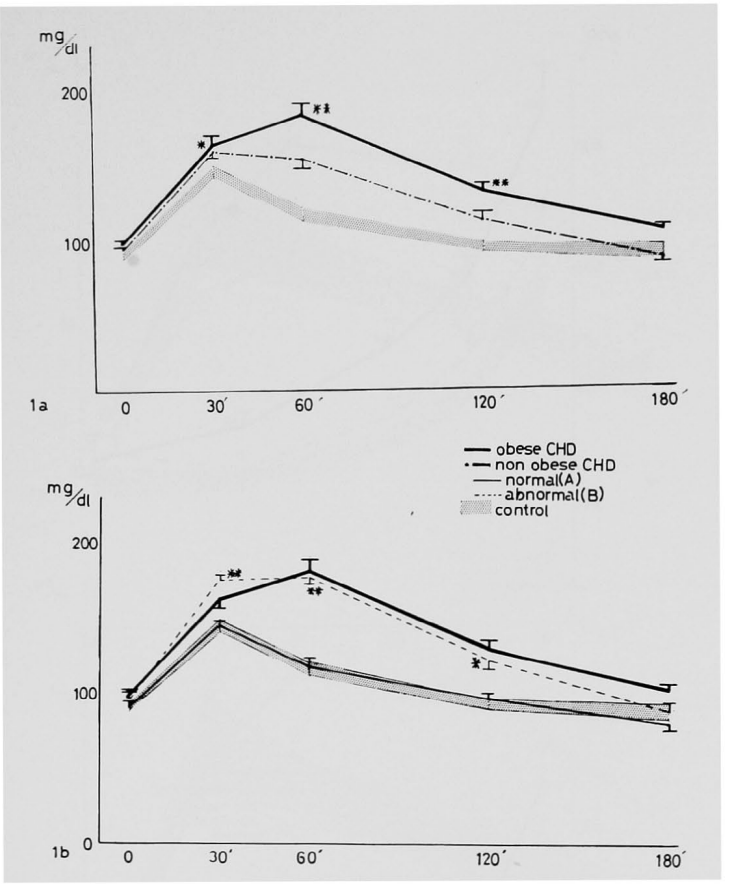

Fig. 1. Blood glucose levels (mean±SE) during 100 Gm oral glucose tolerance test. * $P<0.05$, ** $P<0.01$ compared with control.

min following glucose administration (Fig. 2a). In group B the mean FFA level was still falling 180 min after glucose administration (Fig. 2b).

The incidence of delayed fall (FFA level at 180 min continuing to fall) was 2/13 (15.2%) in Group A, 16/19 (84.2%) in Group B, and 8/9 (88.9%) in the obese CHD group.

In the control group the mean IRI level went up to its peak 30 min after glucose administration and then fell rapidly. In the non-obese CHD group, whose blood glucose level was at its peak at 30 min, the IRI levels went up slowly and reached a peak at 60 min, then fell slowly. In the obese CHD the IRI went up near the level of the peak IRI value of the control at 30 min, but continued to go up and reached a peak at 60 min and remained about the same level at 120 min. The IRI levels of the obese CHD group were significantly higher at 0($P<0.05$), 60($P<0.05$), 120($P<0.01$), and 180 min

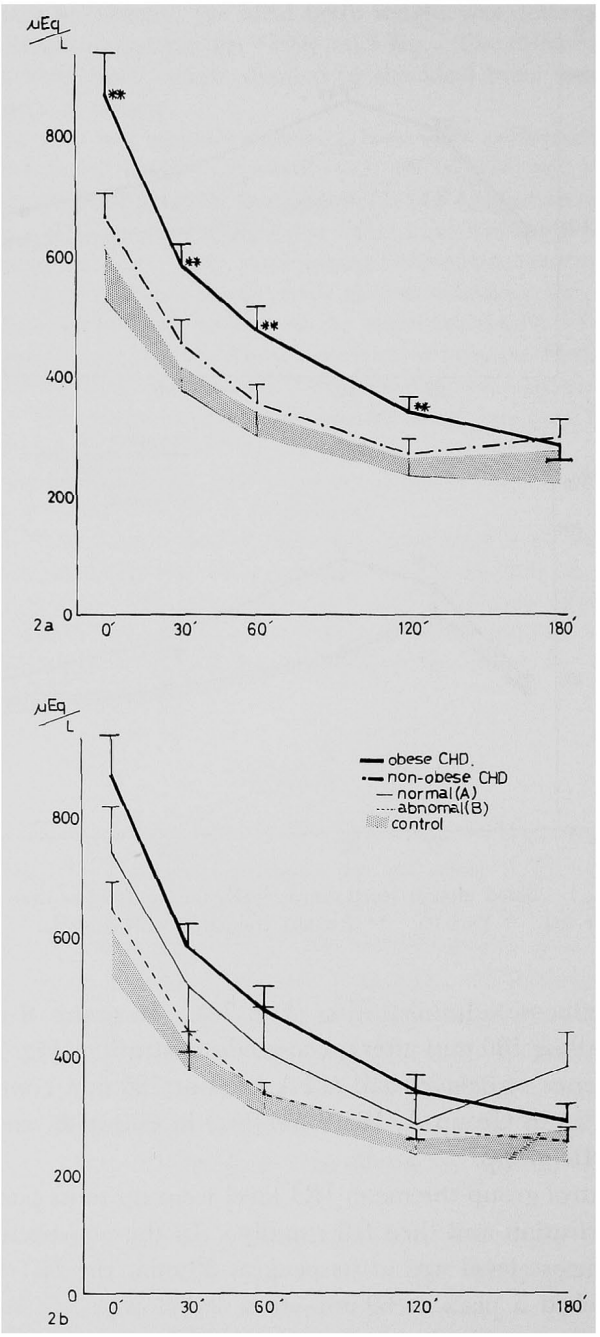

Fig. 2. Serum free fatty acid levels (mean±SE) during 100 Gm oral glucose tolerance test. ** $P<0.01$ compared with control.

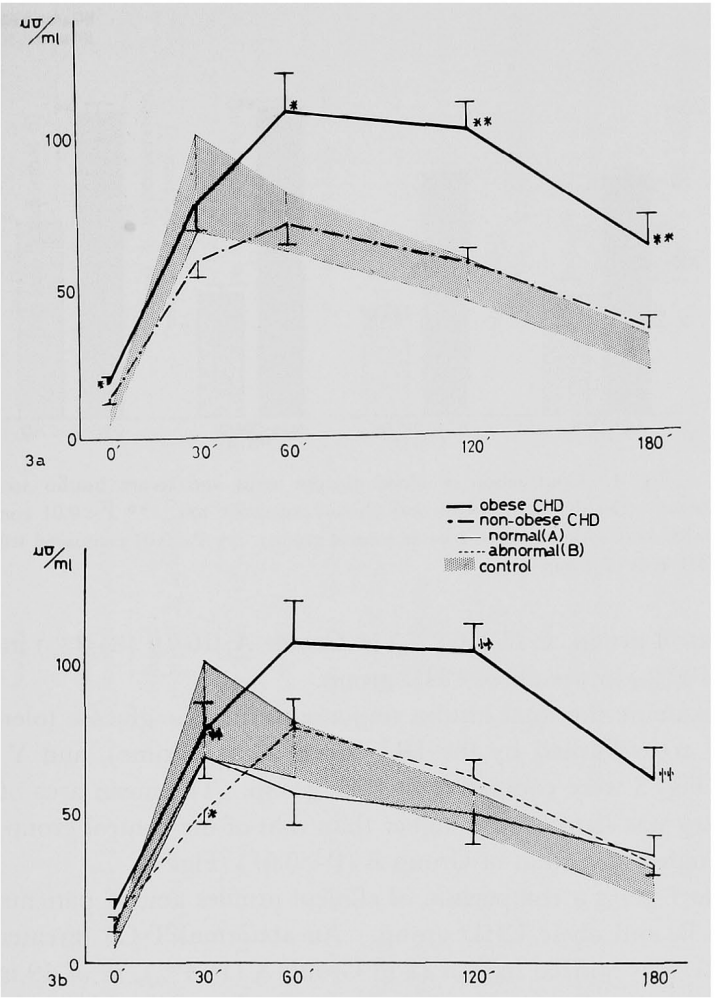

Fig. 3. Serum insulin levels (mean±SE) during 100 Gm oral glucose tolerance test. * $P<0.05$, ** $P<0.01$ compared with control; †† $P<0.01$ compared with B group.

($P<0.01$) compared with those of the control group (Fig. 3a). Furthermore, in Group A the mean IRI levels showed a time course similar to that of the control group. In Group B the IRI level was significantly lower compared with the control group at 30 min ($P<0.05$). Although the blood glucose curve of the obese CHD group was similar to that of Group B, the IRI levels of the obese CHD were significantly higher at 120($P<0.01$) and 180 min ($P<0.01$) than those of the Group B (Fig. 3b).

The incidence of a delayed peak in IRI in which the peak values were reached at 60 min or later following glucose administration was 6/12 (50.0%)

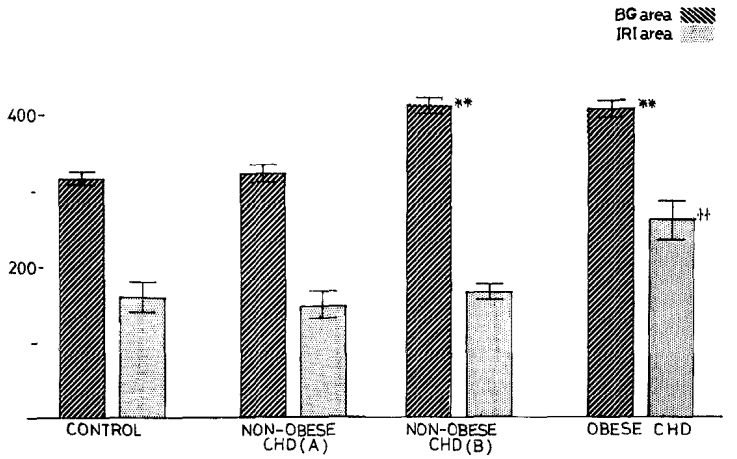

Fig. 4. Comparison of blood glucose areas and serum insulin areas (mean±SE) during 100 Gm oral glucose tolerance test. ** $P<0.01$ compared with blood glucose area of control group; †† $P<0.01$ compared with IRI area of group B.

in the control group, 6/13 (46.2%) in Group A, 16/19 (84.2%) in Group B, and 9/9 (100%) in the obese CHD group.

To examine the total insulin response during the glucose tolerance tests, the mean areas formed by the IRI curve, X axis (time), and Y axis (IRI value) in Fig. 3 were compared for each group. The mean area of the obese CHD group was significantly higher than that of the control group ($P<0.05$) and also higher than that of Group B ($P<0.01$) (Fig. 4).

Table I gives a comparison of clinical profiles among patients of Group A, Group B, and obese CHD group. An abnormal T-Ch (greater than 240 mg/100 ml) was noticed in 2 of 13 in Group A (15.4%), 12 of 19 in Group B (63.2%), and 9 of 9 in obese CHD (100%): Group A was significantly different from Group B ($P<0.05$) and the obese CHD group ($P<0.01$). The mean value of T-Ch showed also a significant difference between Group A (194.5 mg/100 ml) and Group B (250.9 mg/100 ml; $P<0.05$), and between Group A and the obese CHD group (275 mg/100 ml; $P<0.05$) respectively.

The mean value of TG showed a significant difference between Group A (149.4 mg%) and Group B (224.5 mg%; $P<0.05$), although there was no significant difference in number of patients who had abnormal TG (greater than 172 mg%) among the 3 groups.

On the basis of ECG findings the incidence of severe cases of CHD as assessed by the Minnesota code[15] (codes upper 1–2–1 or 4–1) was not different among Groups A, B, and obese CHD group. None were different in age, type of heart disease, duration of the disease, and anginal symptoms.

Table I. Differences between Non-Obese CHD Patients with Normal GTT (A) and Abnormal GTT (B), and Obese CHD Patients

	Normal GTT (A) (13)	Abnormal GTT (B) (19)	Obese CHD (9)
GTT	normal	abnormal	abnormal (normal 3 abnormal 6)
FFA reaction	normal (normal 11, delayed 2)	delayed (normal 3, delayed 15)	delayed & high (normal 1, delayed 8)
IRI reaction peak hypersecretion	normal (normal 7, delayed 6) (1)	delayed (normal 3, delayed 16) (2)	delayed & hypersecretion (normal 2, delayed 7) (5)
Age	45.7 yrs (31 yrs~54 yrs)	48.8 yrs (42 yrs~54 yrs)	48.5 yrs (43 yrs~54 yrs)
Disease	A 7, MI 6*	A 9, MI 10	A 5, MI 4
Duration from onset	2 yr 4 m (7 m~7 yr 3 m)	2 yr 8 m (6 m~6 yr 8 m)	4 yr 2 m (9 m~9 yr 3 m)
ECG severe**	7/13 53.8%	11/19 57.8%	5/9 55.6%
Angina attack present	5/13 38.5%	7/19 36.8%	5/9 55.6%
Obesity history of obesity*** over ideal body weight obesity grade	 5/13 38.5% 7/13 53.8% +1.8% (−10.4%~11.1%)	 7/16 43.7% 13/19 68.4% +3.7% (−15.0%~10.7%)	 — 9/9 100% +30.5% (+25.5%~+37.3%)
Serum total cholesterol over 240 mg/100 ml mean±SE	 2/13 15.4% 194.5±8.3 (162~260 mg/100 ml)	 12/19 63.2%† 250.9±13.0† (167~337 mg/100 ml)	 9/9 100%†† 275.0±9.2† (241~327 mg/100 ml)
Serum triglyceride over 172 mg% mean±SE	 3/10 30.0% 149.4±17.3 (84~236 mg%)	 8/13 61.5% 224.5±27.6† (84~473 mg%)	 3/8 37.5% 207.5±37.9 (97~451 mg%)

* A: Angina, MI: Myocardial infarction

** ECG severe means codes upper 1-2-1 or 4-1 in Minnesota code

*** more than 30% obese over ideal body weight within 10 years

† $P<0.05$, †† $P<0.01$ (compared with A group)

The degree of obesity in Group A and Group B was the same.

The blood glucose area (calculated in the same way as IRI area), IRI area, body weight, and ECG findings or anginal symptoms of the 16 non-obese patients who received the second oral glucose test 3 years later were compared to their original values. Among 5 patients (YS, TY, SY, KT,

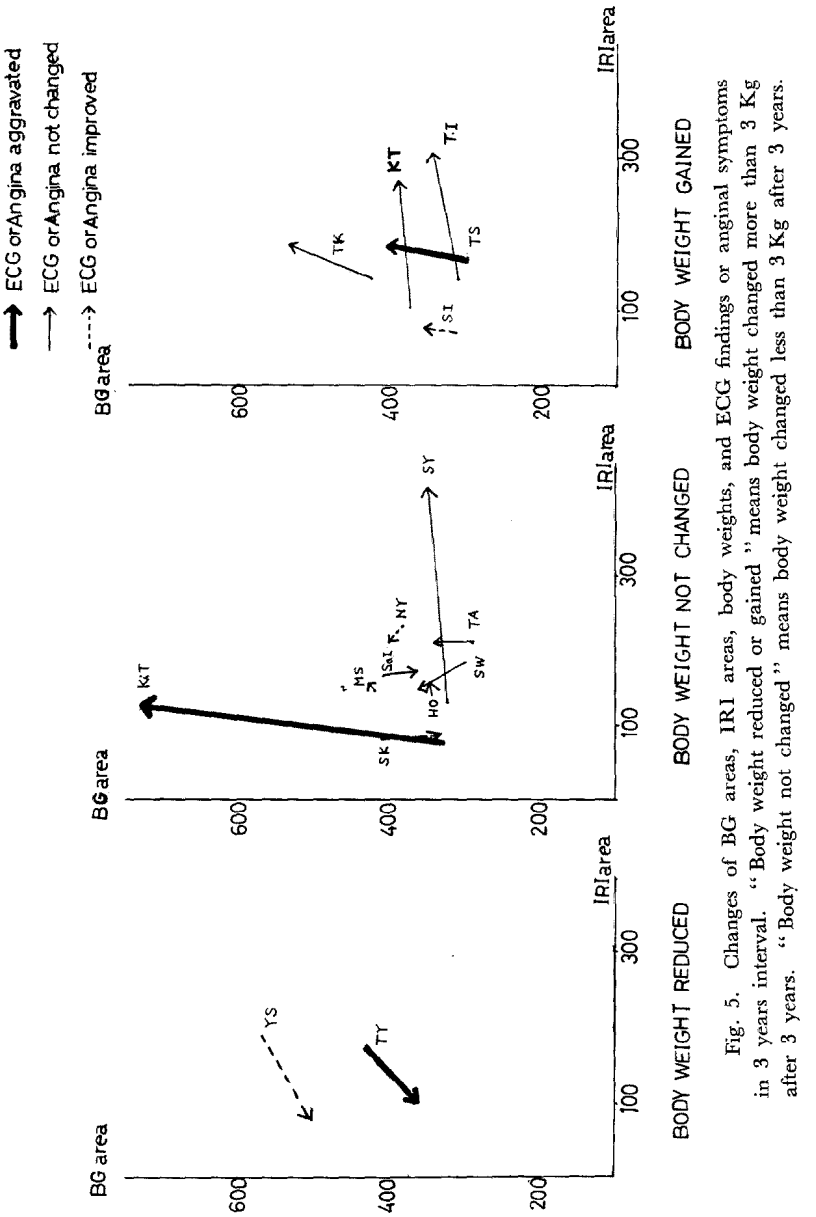

Fig. 5. Changes of BG areas, IRI areas, body weights, and ECG findings or anginal symptoms in 3 years interval. "Body weight reduced or gained" means body weight changed more than 3 Kg after 3 years. "Body weight not changed" means body weight changed less than 3 Kg after 3 years.

and TI) who showed little difference in the blood glucose area, 2 of the 3 patients with an increased IRI area showed an increase in weight, and both patients with a decreased IRI area showed a decrease in weight. These data suggested a direct relationship between body weight change and IRI area change when there was no change in glucose tolerance. There was no correlation between the change in IRI and the change in ECG findings or frequency of anginal attacks (Fig. 5).

Discussion

According to a review by Wahlberg, glucose tolerance was found to be impaired in 35 to 85% (average 61%) of patients with coronary heart disease.[16]

In studies similar to the present one Herman and Gorlin,[17] Tzagournis,[18] and Bahl[19] noticed an incidence of impaired glucose tolerance of 62, 40, and 75.5%, respectively in relatively young patients with coronary heart disease. The 59.4% figure of the non-obese CHD group in the present study is in accordance with these studies.

In the present study patients with coronary heart disease were divided into 2 groups: Group A with normal glucose tolerance and Group B with impaired glucose tolerance. Between Group A and Group B there was a significant difference in the values of serum cholesterol and serum triglyceride, and a slight delay in the fall of FFA levels in response to oral glucose. These findings might indicate abnormal lipid metabolism in Group B. There have been conflicting findings on the correlation between impaired glucose tolerance and abnormal lipid metabolism. Alblink et al,[20] Ostrander et al,[21] and Falsetti et al[22] found a strong positive correlation, while Reaven et al,[23] Sowton,[24] and Carlson et al[25] found no correlation. Ostrander put stress on the fact that elevated serum triglycerides caused impaired glucose tolerance. The present study showed a correlation between impaired glucose tolerance and hyperlipidemia and supports the hypothesis that there is a close correlation between impaired glucose tolerance and hyperlipidemia in patients with coronary heart disease.

The FFA response to oral glucose showed a rapid fall, then went up after 2 hours in Group A, but kept falling even after 3 hours in Group B. This finding is in accordance with that of Cohen et al,[26] Tzagournis et al,[18] and Christiansen et al.[27] Schalch and Kipnis[28] showed obese subjects had impaired glucose tolerance with elevated serum insulin levels and suggested elevated serum FFA might contribute to this phenomenon. The significantly elevated FFA levels in our obese CHD group accompanied by elevated IRI

levels are in agreement with this hypothesis.

There have appeared many reports on the serum insulin levels in chronic cases of coronary heart disease since Peters and Hales' in 1965.[29] However, as Epstein pointed out,[30] there are conflicting data. Peters and Hales,[27] and Nikkilia et al[31] reported elevated insulin levels in patients with coronary heart disease. Christiansen et al[27] reported elevated insulin response to intravenous glucose in patients with normal glucose tolerance, but diminished and delayed insulin response in patients with impaired glucose tolerance. Devlin[32] reported normal insulin levels. Menard et al[33] reported elevated and delayed insulin response to oral glucose in patients with abnormal glucose tolerance, but normal insulin response in patients with normal glucose tolerance. Ostrander et al[21] reported that the value of the insulin-like activity in their bioassay was not different from that of the control. An elevated insulin response or a delayed insulin response to oral or intravenous glucose in patients with coronary heart disease has also been reported in Japan by Hagura,[34] Fukushima,[35] Matsumoto et al,[36] and Shimatani et al.[37] These studies, however, were somewhat different from the present study in the clinical characteristics of the subjects. Relatively similar to the present study in the selection of subjects is Tzagournis's,[18] which indicated that there was elevated or delayed insulin response to oral glucose in 25 patients with premature coronary heart disease with mean age of 39. In the present study the serum insulin in patients with impaired glucose tolerance went up to normal levels after glucose administration, but the peak was delayed. The serum insulin levels in patients with normal glucose tolerance were similar to those of normal controls.

The present study demonstrated an elevated insulin response to oral glucose in the obese CHD group, and after 3 years an increased degree of obesity raised insulin response with little change in glucose tolerance.

This suggests that obesity is at least one of the contributing factors to the elevated serum insulin levels observed in patients with coronary heart disease.

The observation of the delayed peak in insulin response to oral glucose in patients with the impaired glucose tolerance of coronary heart disease is similar to Seltzer's findings[4] in patients with maturity onset diabetes. This observation, coupled with the delayed fall of FFA after glucose administration[38] and mild fasting hyperlipidemia,[39] is similar to the metabolic pattern found in patients with mild diabetes mellitus. Consequently, as Sowton[24] and Christiansen et al[27] pointed out, we also feel that the impaired glucose tolerance in patients with coronary heart disease is due in part to latent diabetes mellitus.

An increase in serum insulin has been proposed as a contributing factor

in the mechanism of arteriosclerosis.[40] Several animal studies that support this hypothesis have been reported.[41),42] The present study could not support this hypothesis, because elevated serum insulin levels were not directly related to the incidence and severity of coronary heart disease. Furthermore, this hypothesis is unable to explain the increased incidence of coronary heart disease in patients with diabetes mellitus who have a diminished serum insulin response.[4),43]

The significance of the abnormal metabolism (delayed insulin and FFA response to glucose, impaired glucose tolerance, and hyperlipidemia) in patients with coronary heart disease remains to be defined. When this is defined, the increased incidence of coronary heart disease in patients with diabetes mellitus may be also explained.

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