Characteristics of Insulin Resistance in Japanese Men Working Abroad

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ABSTRACT

The aim of the present study was to investigate the relationship among the clinical and laboratory signs in response to insulin resistance evaluated by a homeostasis model (HOMA-IR) in Japanese non-obese men working abroad. A significantly positive correlation was observed between body mass index (BMI) and HOMA-IR values in the normal weight ($r=0.34$; $p<0.0001$) and the obese group ($r=0.52$; $p<0.0001$), but not in the lean group ($r=0.16$; $p=0.28$). There was a significantly positive correlation between fasting plasma glucose values and HOMA-IR in three groups. Plasma alanine transferase (ALT), γ -glutamyltranspeptidase (γ -GPT) and Cholinesterase (Ch-E) values were significantly lower in the lean group than those in other groups; ALT: 18.7, 24.2, 42.3 IU/l; γ -GTP: 36.0, 51.0, 74.3 IU/l; Ch-E: 268, 310, 353 IU/l, respectively. There was a significantly positive correlation between HOMA-IR and plasma ALT or Ch-E values in three groups, but other liver functions values were not correlated with HOMA-IR in three groups. These data indicated that insulin resistance was present in almost all men with fatty liver, and insulin resistance was never associated with obesity, hyperdyslipemia in the non-obese men, and the mechanism for underlying insulin resistance in the non-obese men might be different from that in the obese men.

Key Words Men Working Abroad; Insulin Resistance; Fatty Liver Disease

INTRODUCTION

As the Japanese technological or economical power becomes more expanded on global scale, more and more Japanese work overseas. This gives rise to growing concern over the health care of those working abroad and their accompanying families living in different climates, cultures, medical situations and environments. They must undergo medical health examination once at least a year according to the law. Some workers suffered from any diseases such as life style related diseases. However, it is difficult for overseas workers to receive medical health examination in foreign countries, we must do great support to all men working abroad at medical health examination.

On the other hand, it is well known that insulin resistance or hyperinsulinemia is closely associated with established risk factors for life style related diseases and cardio- or cerebrovascular diseases.^{[1]-[3]} Obese subjects, especially those with visceral fat obesity, and patients with type 2 diabetes mellitus frequently demonstrate insulin resistance.^{[4], [5]} Whole-body insulin resistance is often accompanied by elevated plasma triglyceride (TG), decreased plasma high density lipoprotein (HDL) and a preponderance of small, dense low-density lipoprotein (LDL).^{[6]-[9]} Obesity and hyperlipidemia play an important role of diminished

insulin action, which may be a main etiologic cause of life-styled diseases and atherogenic diseases. Furthermore, the presence of fatty liver in patients with type 2 diabetes and obesity has long been reported.^[10] It is usually considered an incidental pathologic finding, with scarce no clinical significance. However, the mechanism of insulin resistance and/or hyperinsulinemia in the non-obese and normo-lipidemic populations with negligible alcohol intake has not been fully understood. Therefore, we investigated the relationship between insulin resistance and various factors including serum lipids and life style in order to clarify the characteristics of insulin resistance in healthy lean men working abroad.

MATERIALS AND METHODS

Five hundred five Japanese males working abroad, who underwent medical examinations before going abroad in our center, were subjected to the present study. They all had no history of diabetes mellitus and had not received any medications affecting blood glucose and serum lipids. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. All subjects working abroad were divided to three groups according to BMI; 47 subjects in the lean group (mean Age; 45.0 yrs, $BMI \leq 19.5$ kg/m²; mean BMI; 18.5 kg/m²) and 323 subjects in the normal weight group (mean Age; 46.7 yrs, $19.5 < BMI < 25$ kg/m²; 22.6 kg/m²) and 135 subjects in the obese group (mean Age; 46.9 yrs, $25 \leq BMI$ kg/m²; 27.4 kg/m²), respectively.

Blood samples were drawn from an antecubital vein after a 12-hour fast to determine the fasting plasma glucose (FPG), fasting insulin (FIRI) and fasting serum lipids and other laboratory data. Plasma glucose and insulin were measured by an enzymatic method and by enzyme immunoassay using IRI Kit (Dainabot Co. LTD., Japan), respectively. Insulin resistance (HOMA-IR)^[11] and pancreas β -cell function (HOMA- β)^[11] were calculated using a homeostasis model based on the following formula:

$$\cdot \text{HOMA-IR} = \text{FIRI (U/ml)} \times \text{FPG (mmol/ml)} / 22.5,$$

$$\cdot \text{HOMA-}\beta = 20 \times \text{FIRI (U/ml)} / (\text{FPG (mmol/ml)} - 3.5).$$

Results were expressed as the mean $\pm$ SD. Linear correlation coefficient and unpaired *t*-test were used for statistical analysis using the StatView: 5 software package. A probability value of less than 0.05 was considered to indicate statistical significance.

RESULTS

1) Clinical and metabolic characteristics of the subjects in three groups

Subject characteristics are listed in Table 1. The mean age was not different among three groups; 44.9 : 46.7 : 46.9 yrs, but the levels of FPG, HbA1c, systolic and diastolic blood pressure were significantly higher in the obese group than those in the lean and

Received: May 24, 2003.

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Table 1 Clinical and metabolic characteristics of all subjects.

	BMI≤19.5 kg/m ² (Lean group)	19.5<BMI<25.0 kg/m ² (Normal weight group)	25.0 kg/m ² ≤BMI (Obese group)
N=	47	323	135
Age (yrs)	44.9±11.0	46.7±10.0	46.9±9.9
Height (cm)	170.3±5.9	169.8±6.0	170.0±6.4
Body weight (kg)	53.6±4.3 ^{†††}	62.2±6.0 ^{***}	79.3±8.5
BMI (kg/m ²)	18.5±0.7 ^{†††}	22.6±1.4 ^{***}	27.4±2.2
S-BP (mmHg)	107.7±14.4 ^{††}	120.4±16.2*	127.9±20.5
D-BP (mmHg)	66.3±8.8 ^{††}	73.2±10.6*	78.9±12.7
HbA1c (%)	5.1±0.4	5.1±0.5*	5.5±0.7
FBG (mg/dl)	95.9±8.8 [†]	102.0±13.5 ^{***}	110.4±24.6
FIRI (μU/ml)	3.5±1.5 ^{†††}	6.1±3.4 ^{***}	11.4±10.2
HOMA index	0.84±0.40 ^{†††}	1.56±0.95 ^{***}	2.97±1.92
HOMA-β index	39.7±17.0 ^{†††}	58.2±30.9 ^{***}	81.8±83.6
T-chol. (mg/dl)	182.2±24.7 [†]	199.4±30.9*	208.8±34.8
LDL-chol. (mg/dl)	100.2±23.5 [†]	118.9±30.4*	124.4±30.2
TG. (mg/dl)	89.8±52.5 ^{†††}	127.2±119.7 ^{***}	179.6±94.9
HDL-chol. (mg/dl)	64.2±13.2 ^{†††}	55.2±12.8 ^{***}	48.6±10.1
AST (IU/l)	21.6±7.4	22.3±6.5*	29.0±11.6
ALT (IU/l)	18.7±9.0 ^{††}	24.2±12.6 ^{**}	42.3±30.1
γ-GTP (IU/l)	36.0±35.6 ^{†††}	51.0±50.9 ^{***}	74.3±58.0
Ch-E (IU/l)	268.4±60.5 ^{††}	309.7±56.9 ^{**}	353.1±62.6
Amylase (IU/l)	70.2±23.0	69.3±20.6	59.7±20.3

[†]*p*<0.05, ^{††}*p*<0.01, ^{†††}*p*<0.001 vs Normal weight group

p*<0.05, *p*<0.01, ****p*<0.001 vs Obese group

Mean ± S.D.

the normal weight groups; 96 (the lean group; *p*<0.05), 102 (the normal weight group; *p*<0.0001), 110 mg/dl (the obese group); 5.1, 5.1 (*p*<0.05), 5.5%; 108 (*p*<0.01), 120 (*p*<0.05), 128 mmHg; 66 (*p*<0.01), 73 (*p*<0.05), 79 mmHg, respectively. HOMA-IR index and HOMA-β index are significantly lower in the lean group than that in the normal weight and the obese group; HOMA-IR index: 0.84 (*p*<0.0001), 1.56 (*p*<0.0001), 2.97; HOMA-β index: 39.7 (*p*<0.0001), 58.2 (*p*<0.0001), 81.8, respectively. As to transaminase levels, plasma aspartate transaminase (AST) values were significantly higher in the obese group than those in the lean and normal weight groups; 21.6, 22.3 (*p*<0.05), 29.0 IU/l, respectively. Plasma alanine transferase (ALT) and γ-glutamyltranspeptidase (γ-GPT) values were significantly lower in the lean group than those in other groups; ALT: 18.7 (*p*<0.05), 24.2 (*p*<0.01), 42.3 IU/l; γ-GTP: 36.0 (*p*<0.0001), 51.0 (*p*<0.0001), 74.3 IU/l, respectively. Furthermore, Plasma Cholinesterase (Ch-E) values were significantly lower in the lean group than those in other groups; CH-E: 268 (*p*<0.0001), 310 (*p*<0.0001), 353 IU/l, respectively. Plasma total cholesterol, LDL-cholesterol and TG values were significantly lower in the lean group than those in the normal weight and the obese groups, however, plasma HDL-cholesterol values were significantly higher in the lean group than those in other two groups.

2) Relationship between HOMA-IR and characteristic variables in the subjects in three groups

① BMI and HOMA-IR

As shown in Fig. 1, a significantly positive correlation was observed between BMI and HOMA-IR values in the normal weight (*r*=0.34; *p*<0.0001) and the obese group (*r*=0.52; *p*<0.0001), but not in the lean group (*r*=0.16; *p*=0.28).

② Plasma lipids and HOMA-IR

A significantly positive correlation between HOMA-IR and plasma total cholesterol or LDL-cholesterol values was observed in the normal weight and the obese groups, however, not in the lean group. A significantly negative correlation between HOMA-IR and HDL-cholesterol levels was also observed only in the normal weight group. HOMA-IR was significantly and positively correlated with plasma TG levels only in the normal weight group.

③ Liver functions and HOMA-IR

As shown in Figs. 2 and 3, there was significantly a positive correlation between HOMA-IR and plasma ALT (Fig. 2: the lean group: *r*=0.33; *p*=0.02, the normal weight group: *r*=0.30; *p*<0.0001, the obese group: *r*=0.27; *p*=0.002) or Ch-E (Fig. 3: the lean group: *r*=0.42; *p*=0.001, the normal weight group: *r*=0.26; *p*<0.0001, the obese group: *r*=0.29; *p*=0.004) values in three groups, but other liver functions values were not correlated with HOMA-IR in three groups.

DISCUSSION

The present study showed that in the non-obese subjects working abroad, insulin resistance was significantly and positively correlated with fasting blood glucose levels and plasma ALT and Ch-E levels, however, there was no difference between insulin resistance and BMI. The mechanism of insulin resistance in the non-obese subjects is different from that in the normal weight or the obese subjects. In normal weight subjects and the obese subjects, insulin resistance is significantly and positively correlated with BMI; visceral fat obesity and serum dyslipidemia. Several studies have reported an association between abdominal obesity and insulin resistance.^{[4], [5]}

Fig. 1 Relationship between BMI and HOMA-IR values in the lean group, the normal weight group and the obese group.

Fig. 2 Relationship between ALT values and HOMA-IR values in the lean group, the normal weight group and the obese group.

In recent years, the association of obesity, diabetes mellitus, hypertriglyceridemia, and hypertension with insulin resistance has been well recognized.^{[4], [5]} It has also been reported that the patients with fatty liver was associated with insulin resistance and obesity.^{[10], [12]} This study showed that elevations in plasma ALT and Ch-E levels could represent fatty liver, so that fatty liver played an important role of insulin sensitivity in the lean men as

well as in the normal weight or the obese men. The presence of fatty liver in patients with type 2 diabetes and obesity has long been reported.^{[9], [10], [12]-[17]}

Ludwig *et al.*^[17] identified a syndrome characterized by the association of fatty liver and lobular hepatitis and chronically elevated plasma ALT levels in patients with negligible alcohol intake. The syndrome is mainly associated with obesity, diabetes and

Fig. 3 Relationship between Ch-E values and HOMA-IR values in the lean group, the normal weight group and the obese group.

hyperdyslipemia, but a few patients are lean, have normal fasting plasma glucose levels.^[11] Fatty liver disease, which could range from fatty liver alone to nonalcoholic steatohepatitis and cirrhosis, was related to insulin resistance. Interestingly, the present study shows that the lean men with insulin resistance have nonalcoholic fatty liver disease (NAFLD). The mechanism for underlying link between fatty liver disease and insulin resistance has been demonstrated in several studies.^{[9], [10], [12]-[17]} It was well known that increased free fatty acid flux to the liver from visceral adipose tissue might account for hepatic insulin resistance in the moderately obese state.^[13] The other mechanism of NAFLD inducing insulin resistance may be increased tumor necrosis factor alpha (TNF- α) and TNF- α polymorphisms in adipose tissue, which are present in human obesity and correlated with BMI.^[16] However, research on the pathogenesis of NAFLD has not still done in this study.

Marchesini *et al.*^[12] reported that in the presence of normoglycemia and normal or moderately increased body weight, insulin resistance was characterized by clinical and laboratory data similar to that found in diabetes and obesity, therefore, fatty liver disease might be considered an additional feature of the metabolic syndrome, with specific hepatic insulin resistance. This present study showed that relationship between HOMA-IR and fatty liver data in the lean group was similar to that found in the normal weight and the obese groups.

Although much work needs to be done, the current studies begin to focus attention on the role of insulin resistance in the non-obese men working abroad.

In conclusion, our results indicated that (1) insulin resistance was present in almost all men with fatty liver, and (2) insulin resistance was never associated with obesity, hyperdyslipemia in the non-obese men, and (3) the mechanism for underlying insulin resistance in the non-obese men might be different from that in the obese men.

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