Original

CHARACTERISTICS OF INSULIN RESISTANCE IN JAPANESE OLDER MALES 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 645 Japanese older men working abroad. All older adults working abroad were divided to three groups according to BMI; 180 subjects in the lean group (BMI ≦ 22.0 kg/m^2), 290 subjects in the normal weight group (22 < BMI < 25 kg/m^2) and 175 subjects in the obese group (25 ≧ BMI kg/m^2), respectively. A significantly positive correlation was observed between BMI and HOMA-IR values in the obese group (r=0.42; $p < 0.0001$), but not in the lean group (r=0.14; p=0.06) and the normal weight (r=0.08; p=0.16). There was a significantly positive correlation between fasting plasma glucose (FPG), fasting plasma insulin (FIRI), HbAlc, pancreas β cell function (HOMA-β) values and HOMA-IR in three groups (lean group: FPG: r=0.21, p=0.004, HbAlc: r=0.25, p=0.002, FIRI: r=0.99, $p < 0.0001$, HOMA-β: r=0.81, $p < 0.0001$, normal weight group: FPG: r=0.32, $p < 0.0001$, HbAlc: r=0.23, p=0.002, FIRI: r=0.94, $p < 0.0001$, HOMA-β: r=0.64, $p < 0.0001$, obese group: FPG: r=0.24, p=0.002, HbAlc: r=0.20, p=0.005, FIRI: r=0.96, $p < 0.0001$, HOMA-β: r=0.68, $p < 0.0001$). Plasma TG value was significantly lower in the non-obese group than those in other groups; 113, 135, 154 mg/dl, respectively. Plasma HDL-ch value was significantly higher in the non-obese group than those in other groups; 61, 52, 49 mg/dl, respectively. There was a significantly positive correlation between HOMA-IR and plasma TG value and significantly a negative correlation between HOMA-IR and plasma HDL-ch in three groups (TG: lean group: r=0.16, p=0.03, normal weight group: r=0.19, p=0.001, obese group: r=0.42, $p < 0.0001$, HDL-ch: lean group: r=–0.22, p=0.003, normal weight group: r=–0.22, p=0.0002, obese group: r=–0.24, p=0.002), but other lipid and liver function values were not correlated with HOMA-IR in three groups. These data indicated that insulin resistance was present in almost all older men working abroad with impaired glucose tolerance, hypertriglyceridemia and low HDL-ch concentrations, and insulin resistance was never associated with obesity, fatty liver in the non-obese older men, and the mechanism for underlying insulin resistance in the non-obese older men might be different from that in the younger men or the obese older men working abroad.

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—Key words—

Insulin Resistance, Hypertriglyceridemia and low HDL-ch concentrations, Japanese non-obese older men working abroad

Introduction

As the Japanese technological or economical power becomes more expanded on global scale, more and more Japanese work overseas. Older adults, especially who have many special technologies, are increasing for overseas workers. 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 older 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 es-

tablished 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)].

Table 1 Clinical and metabolic characteristics of older adults

	BMI ≦ 22.0kg/m² (Lean type)	22.0 < BMI < 25.0kg/m² (Normal weight type)	25.0kg/m² ≦ BMI (Obese type)
N =	180	290	175
Age (yrs)	65.9 ± 5.4	64.9 ± 4.5	64.3 ± 4.0
Height (cm)	165.4 ± 6.2	165.9 ± 5.9	165.4 ± 5.6
Body weight (kg)	55.5 ± 4.3 ⋯	64.8 ± 6.0 ***	73.2 ± 6.6
BMI (kg/m²)	20.2 ± 1.5 ⋯	23.5 ± 0.8 ***	26.8 ± 1.6
S-BP (mmHg)	121.9 ± 14.4 ¨	130.5 ± 19.0 *	136.1 ± 19.8
D-BP (mmHg)	74.5 ± 11.2 ¨	78.9 ± 11.0 *	82.3 ± 12.4
HbA1c (%)	5.4 ± 1.4	5.5 ± 0.8	5.5 ± 0.6
FPG (mg/dl)	102.8 ± 19.0 ·	107.0 ± 21.3 *	110.9 ± 19.1
FIRI (μU/ml)	5.0 ± 3.8 ⋯	7.2 ± 3.8 ***	9.7 ± 5.2
HOMA index	1.25 ± 1.05 ⋯	1.90 ± 1.08 ***	2.67 ± 1.52
HOMA β index	50.3 ± 34.4 ⋯	65.8 ± 39.1 ***	79.0 ± 46.7
T-chol. (mh/dl)	202.7 ± 30.5	202.9 ± 31.9 *	207.2 ± 34.2
LDL-chol. (mg/dl)	119.3 ± 31.9 ·	124.0 ± 30.0 *	127.7 ± 31.4
TG. (mg/dl)	113.1 ± 86.5 ⋯	134.6 ± 79.6 ***	153.8 ± 87.6
HDL-chol. (mg/dl)	60.6 ± 13.2 ⋯	52.1 ± 12.7 ***	48.8 ± 9.2
AST (IU/l)	25.1 ± 12.7	24.4 ± 9.3 *	27.2 ± 12.0
ALT (IU/l)	21.4 ± 10.2 ¨	24.7 ± 13.1 **	31.5 ± 17.8
γ-GTP (IU/l)	47.6 ± 74.7 ¨	52.8 ± 62.6 **	64.1 ± 63.4
Ch-E (IU/l)	278.2 ± 66.7 ¨	310.3 ± 55.2 *	319.1 ± 56.8
Amylase (IU/l)	87.2 ± 32.3	74.7 ± 26.2	70.9 ± 22.5

· 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.

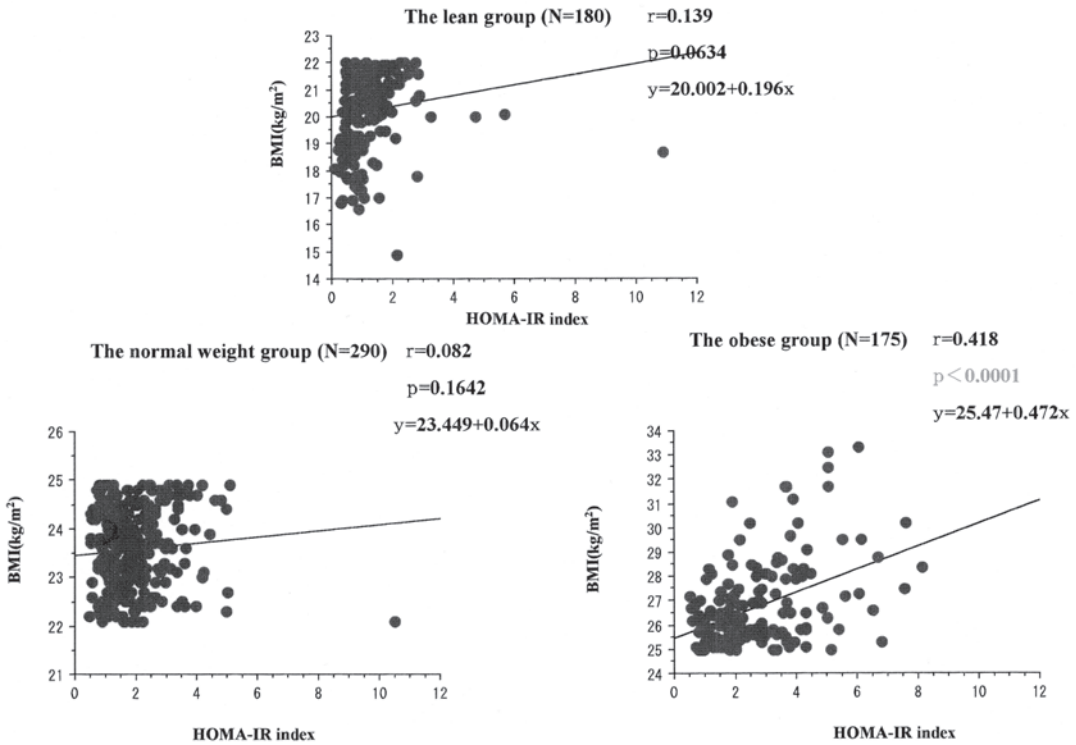

Figure 1. Relationship between BMI and HOMA-IR value in the lean group, the normal weight group and the obese group.

Obesity and hyperlipidemia play an important role of diminished insulin action, which may be a main etiologic cause of life style related diseases and atherogenic diseases. Futhermore, 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 no clinical significance. However, the mechanism of insulin resistance and/or hyperinsulinemia in the non-obese and normo-lipidemic older adults 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 non-obese older (≧60 years) males working abroad.

Materials and Methods

Six hundred forty five Japanese older adults working abroad, who were from 60 yrs old to 85 yrs old; mean age 65.0 yrs old and 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. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. All older adults working abroad were divided to three groups according to BMI; 180 subjects in the lean group (mean Age; 65.9 yrs, BMI ≦ 22.0 kg/m^2: mean BMI; 20.2··· kg/m^2) and 290 subjects in the normal weight group (mean Age; 64.9 yrs, 22 < BMI < 25 kg/m^2; mean BMI; 23.5*** kg/m^2) and 175 subjects in the obese group (mean Age; 63.3 yrs, 25 ≧ BMI kg/m^2; mean BMI; 26.8 kg/m^2), respectively. (···p < 0.0001 vs normal weight group, ***p < 0.0001 vs obese group).

Blood samples were drawn from an antecubital vein after a 12-hour fast to determine the fasting plasma glucose (FPG), fasting plasma insulin (FIRI) and fasting plasma 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:

HOMA-IR=FIRI (U/ml) × FPG (mmol/ml)/22.5, and HOMA-β =20 × FIRI (U/ml)/(FPG (mmol/ml)–3.5).

Results were expressed as the mean ± 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.

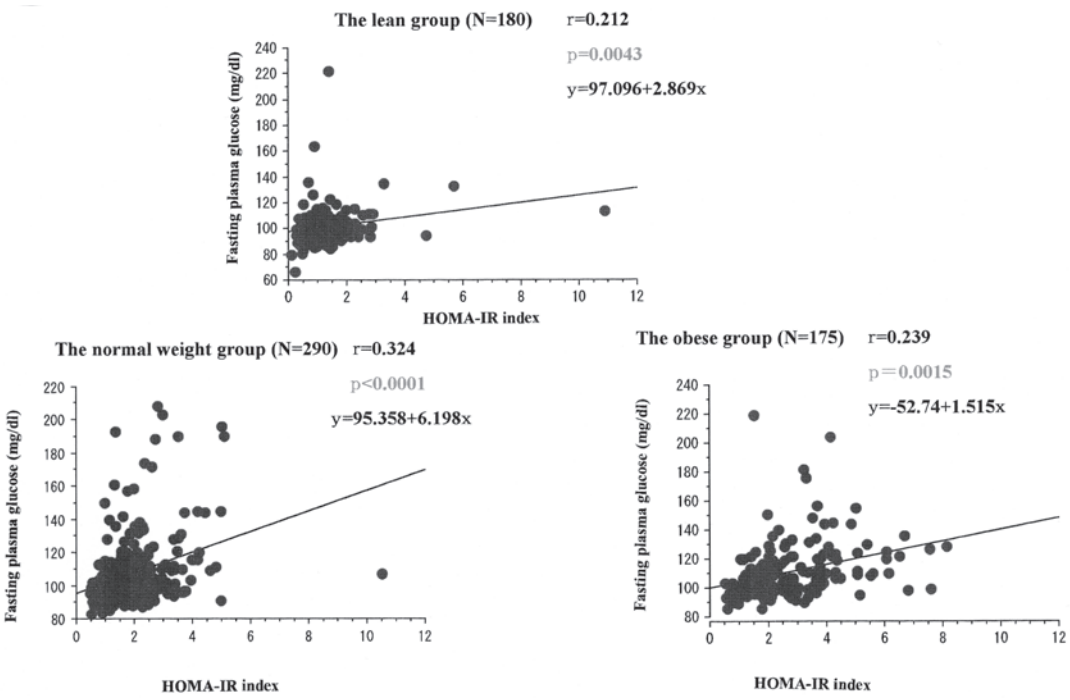

Figure 2. Relationship between fasting plasma glucose values and HOMA-IR values in the lean group, the normal weight group and the obese group.

Table 2 Relationship between HOMA-IR and Age, BMI, blood pressure, HbA1c, FPG, FIRI, HOMA- β index, plasma lipids and liver function in older males

	BMI ≦ 22.0kg/m² (Lean type) HOMA index	22.0 < BMI < 25.0kg/m² (Normal weight type) HOMA index	25.0kg/m² ≦ BMI (Obese type) HOMA index
N =	180	290	175
Age	0.142	0.105	0.106
BMI	0.144	0.083	0.418 ***
S-BP	0.114	0.099	0.125
D-BP	0.013	0.170	0.108
HbAlc	0.246 **	0.234 **	0.204 *
FPG	0.212 **	0.324 ***	0.314 ***
FIRI	0.986 ***	0.939 ***	0.959 ***
HOMA β index	0.810 ***	0.639 ***	0.679 ***
T-chol.	0.017	0.056	0.129
LDL-chol.	0.058	0.055	0.027
TG.	0.162 *	0.192 **	0.327 ***
HDL-chol.	− 0.223 **	− 0.217 **	− 0.239 **
AST	0.032	0.114	0.333 ***
ALT	0.001	0.195 **	0.419 ***
γ-GTP	0.031	0.098	0.112
Ch-E	0.004	0.044	0.214 *
Amylase	0.141	0.007	0.072

Note : Correlation coefficients; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

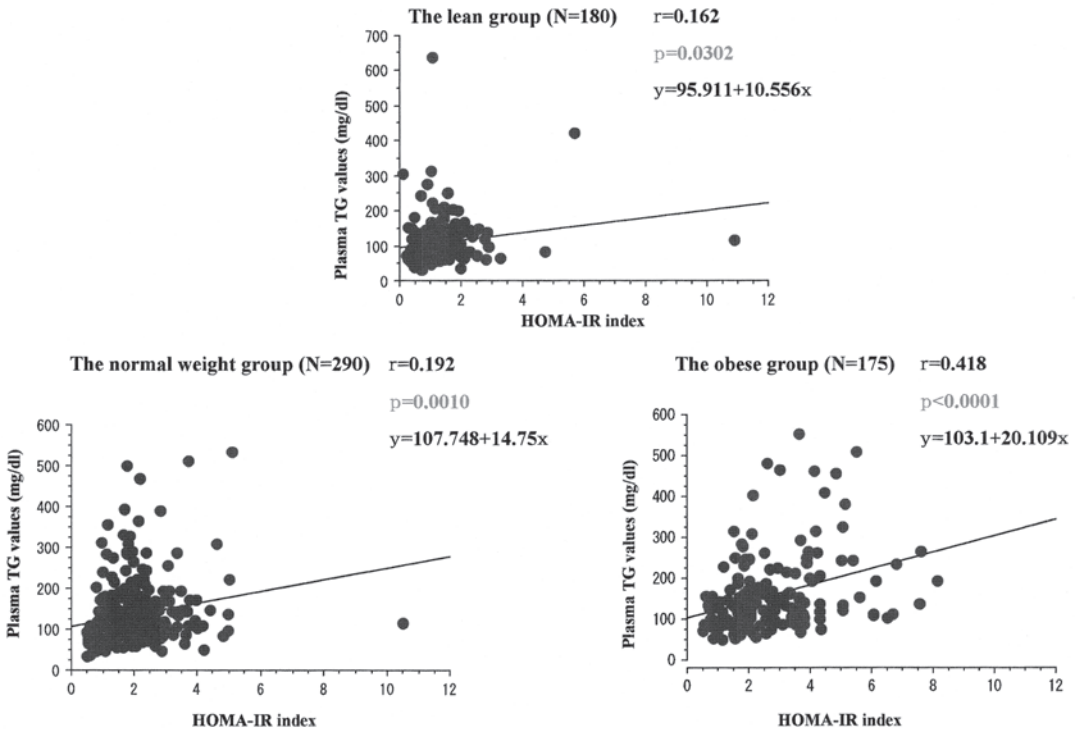

Figure 3. Relationship between plasma TG values and HOMA-IR values in the lean group, the normal weight group and the obese group.

Results

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

Subject characteristics are listed in Table 1. The mean age and HbAlc values were not different among three groups; age 65.9: 64.9: 64.3 yrs, HbAlc 5.4, 5.5, 5.5%, respectively, but the mean levels of FPG, FIRI, systolic and diastolic BP were significantly higher in the obese group than those in the lean and the normal weight groups; FPG: 103* mg/dl (the lean group), 107* mg/dl (the normal weight group), 111 mg/dl (the obese group); FIRI: 5.0***

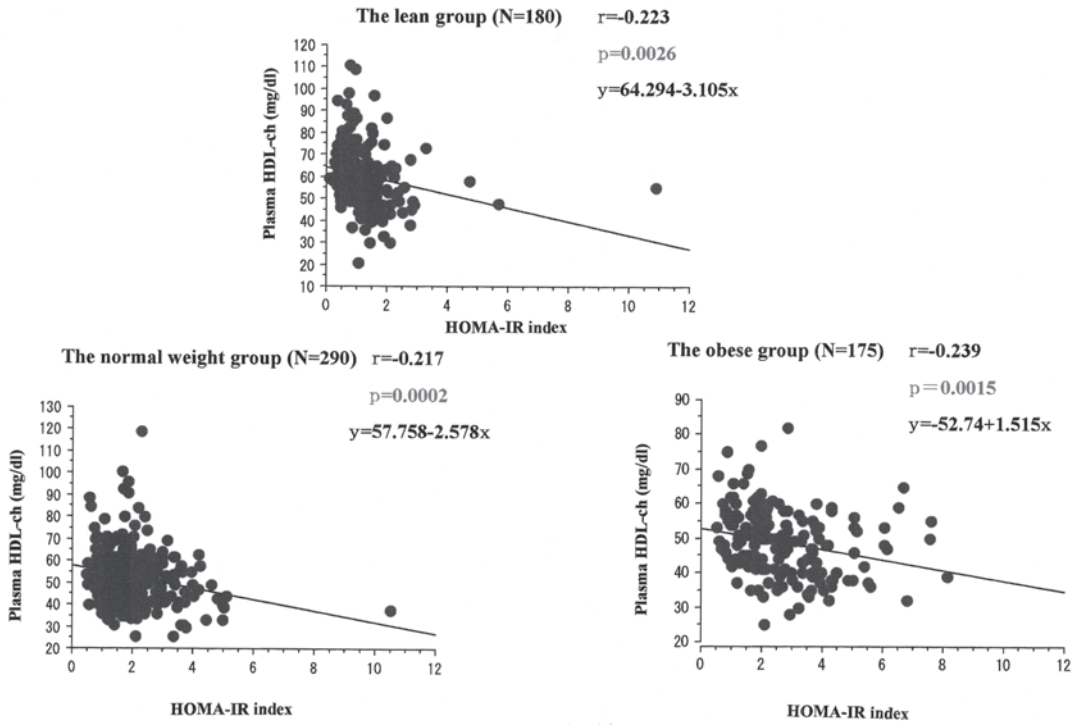

Figure 4. Relationship between plasma HDL-ch values and HOMA-IR values in the lean group, the normal weight group and the obese group.

μU/ml, 7.2*** μU/ml, 9.7 μU/ml, systolic BP: 122** mmHg, 131* mmHg, 136 mmHg; diastolic BP: 75** mmHg, 79* mmHg, 82 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: 1.25***, 1.90***, 2.67; HOMA-β index: 50.3***, 65.8***, 79.0, 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; 25.1 IU/l, 24.4*, 27.2 IU/l, respectively. Plasma r-glutamyl transpeptidase (γ-GTP) and cholinesterase (Ch-E) values were significantly lower in the lean group than those in other groups; ALT: 21.4**, 24.7**, 31.5 IU/l; γ-GTP: 47.6**, 52.8**, 64 IU/l, CH-E: 278***, 310*** 319 IU/l, respectively.

Plasma total cholesterol (T-ch) was significantly higher in the obese group than that in other two groups; T-ch: 203 mg/dl, 203* mg/dl, 207 mg/dl, respectively. Plasma LDL-cholesterol (LDL-ch) and TG values were significantly lower in the lean group than those in the normal weight and the obese groups; LDL-ch: 119* mg/dl, 124* mg/dl, 128 mg/dl; TG: 113*** mg/dl, 135*** mg/dl, 154 mg/dl, respectively, however, plasma HDL-ch values were significantly higher in the lean group than those in other two groups; 61*** mg/dl, 52*** mg/dl, 49 mg/dl, respectively.

(*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$ vs normal weight group, *$p < 0.05$, **$p < 0.01$, *** $p < 0.0001$ vs obese group)

2) Relationship between HOMA-IR index and characteristics in the older subjects in three groups.

①BMI and HOMA-IR index

As shown in Figure 1, a significantly positive correlation was observed between BMI and HOMA-IR values in the obese group (r=0.42; $p < 0.0001$), but not in the normal weight (r=0.08; p=0.16) and the lean group (r=0.14; p=0.06).

②FPG and HOMA-IR index

As shown in Figure 2, there was significantly a positive correlation between HOMA-IR and FPG in three groups (Figure 2: the lean group: r=0.21; p=0.004, the normal weight group: r=0.32; $p < 0.0001$, the obese group: r=0.24; p=0.002). Furthermore, as shown Table 2, HbAlc, FIRI and HOMA-β index values were significantly and positively correlated with HOMA-IR in three groups; HbAlc: the lean group: r=0.25; $p < 0.01$, the normal weight group:

r=0.23; $p < 0.01$, the obese group: r=0.20; $p < 0.05$, FIRI: the lean group: r=0.99; $p < 0.0001$, the normal weight group: r=0.94; $p < 0.0001$, the obese group: r=0.96; $p < 0.0001$, HOMA-β index: the lean group: r=0.81; $p < 0.0001$.

③Plasma lipids and HOMA-IR index

As shown in Figure 3, a significantly positive correlation was observed between TG and HOMA-IR values in three group (Figure 3: the lean group: r=0.16; p=0.03, the normal weight group: r=0.19; p=0.001, the obese group: r=0.42; $p < 0.0001$). As shown in Figure 4, a significantly negative correlation was observed between HDL-ch and HOMA-IR values in three group (Figure 4: the lean group: r=–0.22; p=0.003, the normal weight group: r=–0.22; p=0.0002, the obese group: r=–0.24; p=0.002). However, T-ch and LDL-ch values were not correlated with HOMA-IR in three groups.

Discussion

We have reported that insulin resistance was present in almost all young men working abroad with fatty liver, and insulin resistance was never correlated with BMI 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[12]. The present study showed that in the older adults working abroad, insulin resistance was significantly and positively correlated with fasting plasma glucose, HbAlc, FIRI levels and plasma TG levels and was significantly and negatively correlated with plasma HDL-ch, however, there was no difference between insulin resistance and hypertension, fatty liver or BMI in the non-obese older adults. The mechanism of insulin resistance in the non-obese older adults is different from that in those younger adults. In the obese older adults, insulin resistance is significantly and positively correlated with BMI; abdominal visceral fat, obesity and fatty liver. Several studies have reported an association between abdominal obesity and insulin resistance[4)5)]. Abdominal visceral fat generally increased with age in both men and women. And this incerase was present in normal weight as well as in overweight and obese individuals[12].

The genesis of insulin resistance in the older adults working abroad was different from that in the younger adults working abroad. The younger adults working abroad often received the psychical stress of living in different climates, cultures, medical situations and environments. The younger adults working abroad drank alcohol more than the older adults, when the psychical stress was received. Generally, as the younger adults working abroad did exercise more, the amount of alcohol increased more[12]. However, the amount of alcohol didn't increase even if the older adults working abroad did exercise or received the psychical stress more. The difference between the younger and the older adults resulted from the relationship between the exercise or the psychical stress and the amount of alcohol, which influenced various factors of insulin resistance greatly.

However, the non-obese older males with insulin resistance had impaired glucose tolerance and dyslipidemia; higher levels of plasma TG and lower levels of plasma HDL-ch, as well as those in the normal weight and obese older men. Many studies reported that insulin resistance and/or hyperinsulinemia were conditions known to be associated with impaired glucose tolerance, hypertriglyceridemia and low HDL-ch concenrations[13)14)]. Recently, two expert groups; the World Health Organization (WHO) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) have proposed criteria defining what they called the metabolic syndrome based on insulin resistance[15)16)]. According to these criteria, the metabolic syndrome is common in older men and will increase in prevalence as age and become more obese. This study showed that the obese subjects had higher TG, ALT, GTP and CH-E levels and lower HDL-ch levels than the non-obese subjects. Insulin resistant subjects may have much greater overall adiposity and significantly more adverse body fat distribution than insulin sensitive subjects[13)14)]. Interestingly, this study showed that the non-obese older subjects with insulin resistance had much more metabolic risk factors based on insulin resistance than those older subjects without insulin resistance as well as the obese older subjects. Overall, identification of the insulin resistant syndrome warrants interventions known to prevent type 2 diabetes and cardiovascular disease, including weight reduction, increased physical activity and control of impaired glucose tolerance and dyslipidemia.

The mechanism for underlying link between dyslipidemia and insulin resistance has been demonstrated in several studies[13)14)]. Generally, overweight patients in whom there was a large amount of visceral adipose tissue were characterized by a cluster of metabolic disturbances that included glucose intolerance, insulin resistance, hyper-

triglyceridemia and abnormally low HDL-ch concentrations. However, this study demonstrated that in all older men without diabetes, the higher levels of FPG, HbAlc, FIRI and plasma TG and the lower level of plasma HDL-ch might be a marker for a cluster of metabolic abnormalities based on insulin resistance. It might be speculated that the mechanism of insulin resistance in older men was entirely different from that in younger men[12]. Recently, many clinical reports and genetic studies demonstrated decreased circulating levels of adipokines in metabolic dysfunction, such as obesity and insulin resistance, in both humans and animal models[15)~17)]. In the non-obese older subjects working abroad, the mechanism of dyslipidemia inducing insulin resistance might be due to decreased circulating levels of adiponectin and leptin in adipose tissue, which were usually present in human obesity and correlated with BMI[15)~17)]. Thus, hypoadiponectinemia may be an important component of the association between insulin resistance and dyslipidemia. However, reseach on the pathophysiological genesis of these adipokines, such as adiponectin and leptin has not still done in this study.

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

In conclusion, our results indicated that (1) insulin resistance was not correlated with abdominal obesity and fatty liver in the non-obese men, and (2) insulin resistance was significantly correlated with impaired glucose tolerance and dyslipidemia; high TG and low HDL-ch concentrations in the all older men, and (3) the mechanism for underlying insulin resistance in the non-obese older men might be different from that in the obese older men working abroad.

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海外勤務高齢者男性例における インスリン抵抗性の特徴

飯塚 孝

海外勤務健康管理センター

—キーワード—
インスリン抵抗性，脂質代謝異常，高齢男性海外勤務者

海外勤務者は年々増加し，特に，高い技術力を持つ高齢者の海外勤務も増加して来ている．今回，60歳以上（平均年齢65.0歳）の日本人海外勤務男性645例で，インスリン抵抗性（HOMA-IR）と臨床像・血液生化学検査との関係を肥満の有無で検討した．全例をBMIで痩せ群（BMI≦22.0kg/m^2：180例），正常群（22.0＜BMI＜25.0kg/m^2：290例），肥満群（BMI≧25.0 kg/m^2：175例）に分類した．BMIとHOMA-IRは，肥満群で正の相関（r = 0.418，p＜0.0001）をしたが，正常群（r = 0.08，p = 0.16）と痩せ群（r = 0.14，p = 0.06）では相関はしなかった．HOMA-IR値は，3群で，空腹時血糖（痩せ群r = 0.21，p = 0.004，正常群r = 0.32，p＜0.0001），肥満群r = 0.24，p = 0.002），HbAlc（r = 0.25；p＜0.01, r = 0.23；p＜0.01, r = 0.20；p＜0.05），空腹時インスリン（r = 0.99；p＜0.0001，r = 0.94；p＜0.0001，r = 0.96；p＜0.0001）HOMA-β指数（r = 0.81；p＜0.0001，r = 0.64；p＜0.0001，r = 0.68；p＜0.0001），中性脂肪（r = 0.16，p = 0.03，r = 0.19，p = 0.001，r = 0.42，p＜0.0001）と正の相関をし，HDL-ch（r = −0.22, p = 0.003, r = −0.22, p = 0.0002, r = −0.24, p = 0.002）と負の相関をしたが，他の脂質や肝機能とは相関しなかった．以上，60歳以上の非肥満の海外勤務男性では，インスリン抵抗性は，肥満や脂肪肝で起こるのではなく，耐糖能異常や血清中性脂肪高値及びHDL-ch低値と相関して出現し，肥満男性や若年男性とは作用機序が違うことが判明した．