The Relationship of Insulin Sensitivity to Abdominal Fat Accumulation, Sex Hormones, and Sex Hormone-Binding Globulin in Japanese Men with Impaired Glucose Tolerance

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The Relationship of Insulin Sensitivity to Abdominal Fat Accumulation, Sex Hormones, and Sex Hormone-Binding Globulin in Japanese Men with Impaired Glucose Tolerance

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Abstract

The goal of this study was to evaluate the levels of insulin sensitivity, sex hormones and sex hormone-binding globulin (SHBG), and the relationship of insulin sensitivity with abdominal fat accumulation, sex hormones, and SHBG in Japanese men with impaired glucose tolerance (IGT). Insulin sensitivity (glucose infusion ratio; GIR) was evaluated by the hyperinsulinemic euglycemic clamp method, abdominal fat accumulation was determined by computed tomography, sex steroid hormones and SHBG were measured in 29 men with impaired glucose tolerance who ranged in age from 31 to 75 yrs. The participants in this study included both lean and obese subjects. The distribution of sex hormones were relatively similar to the ranges observed in healthy men based on the findings of our previous report, but the SHBG levels tended to be lower than those of healthy men. Among these subjects, about 50% were within the normal ranges for GIR. In a simple correlation analysis, GIR showed a significant positive correlation with age and SHBG, and a negative association with obesity indices, especially for subcutaneous fat area (SFA). A stepwise multiple regression analysis indicated that the SFA and area under the curve of insulin (AUCIRI) are independently associated with the GIR. Moreover, it is observed that neither SHBG and free testosterone were related to insulin action after taking into account for fat levels. Based on these findings, it is suggested that abdominal subcutaneous fat accumulation and hyperinsulinemic responses to oral glucose load were independent contributors of the peripheral insulin sensitivity in Japanese men with IGT.

Key words: Japanese impaired glucose tolerance, insulin sensitivity, sex hormones, abdominal fat accumulation,
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INTRODUCTION

A significant decrease in insulin sensitivity has been reported after castration which is reversed with the administration of a small dose of testosterone in male rats[1]. Moreover, recent studies have also demonstrated that the levels of testosterone and sex hormone-binding globulin (SHBG), which is an index of hyperandrogenicity in women[2], were ignificantly lower in men with abdominal obesity and/or non-insulin

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dependent diabetes mellitus (NIDDM) than in non-diabetic healthy controls[3~10], and that they were also significantly associated with insulin sensitivity[11~13]. Marin et al.[14] documented a reduction in intra-abdominal fat depots and a significant improvement of insulin sensitivity after the long-term administration of testosterone for 6 months to men with abdominal obesity. Based on these results, it was suggested that the state of relative hypogonadism in men may thus contribute to the development of insulin resistance or NIDDM.

As mentioned previously, the levels of plasma SHBG can be used as an index of hyperandrogenicity in women[2]. It was thus demonstrated in an epidemiological study of about 1400 women in Gothenburg, Sweden that the main prospective predictors for the development of NIDDM were a low level of SHBG, abdominal obesity, and a high plasma insulin concentration[15]. On the other hand, the clinical and physiological meaning of a lower SHBG in men still remains to be clarified. In this context, Haffner et al.[16] recently reported that a decreased level of SHBG was a prospective predictor for the development of NIDDM in women, but not in men. Nevertheless, it was reported that the SHBG level was significantly and positively associated with insulin sensitivity, regardless of sex difference[12]. In men, such a relationship was also observed in healthy adults[12)13)] and patients with NIDDM[11]. However, It has not yet been reported as to whether or not such a relationship exists in men with so-called "impaired glucose tolerance (IGT)".

The purpose of the present study was to investigate the interrelationships between insulin sensitivity, adiposity and sex hormones levels in Japanese men with IGT.

SUBJECTS AND METHODS

Japanese male subjects (n=29, 53.1 ± 12.1 yrs) who all had impaired glucose tolerance (IGT) participated in this study. None took any medication which affected either their blood pressure or their lipid and glucose metabolism. None of the participating subjects engaged in any sports activity or regular exercise either before and during the period of this study. A written explanation of the experimental procedures and potential risk was presented to every subject and informed consent was obtained from all.

Body weight and height were measured in a fasting state, without shoes and clothes, and the body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Waist-hip ratio (WHR) was used as an index of body fat distribution. All measurements were performed in the upright position by one of the authors (T.G.).

To evaluate the subcutaneous (SFA) and visceral fat areas (VFA) at the umbilicus level, computed tomography (CT) scans were made using TCT- 900S (Toshiba, Japan) according to the method of Tokunaga et al.[17]. The visceral fat area was determined by drawing a line within the muscle wall surrounding the abdominal cavity using a graph pen and an attenuation range of -190 to -30 HU.

The classification of the IGT was evaluated from the fasting glucose level and/or glucose responses to 75 g oral glucose tolerance test (OGTT) according to the criteria of the Japan Diabetes Society[18]. None of the subjects were taking any medication or special diet before performing OGTT. In addition, none developed NIDDM within 1 yr after OGTT. After this observation, a hyperinsulinemic euglycemic clamp was performed to evaluate the insulin sensitivity in all subjects.

Blood samples were taken from the antecubital vein after fasting for 12 hours. Thereafter, subjects were given 75g glucose orally (Toleran GR Japan). Blood samples for the determination of plasma glucose and insulin concentrations were taken at 0, 30, 60, 90, 120 min. The plasma glucose (AUCPG) and insulin area under the curve (AUCIRI) were calculated by the trapezoidal rule using absolute values.

The following blood chemicals were analyzed; plasma glucose (PG), insulin (IRI), estradiol (E2), free testosterone (Free T), dehydroepiandrosterone - sulfate (DHEA-s), and sex hormone-binding globulin (SHBG). After centrifugation, the plasma was stored at -34 ℃ for subsequent hormone analysis. PG was analyzed by enzymatic method using

commercial kit (Kyowa Medix, Japan). The E2, Free T, and DHEA-s were measured by a specific radioimmunoassay (RIA) using commercial kits (DPC, Los Angeles, USA). IRI was measured by a radioimmunoassay technique using IRMA kit (Daiich, Japan). SHBG was measured by an immuno-radiometric assay technique using an SHBG [^{125}I] assay kit (Farmous Daiagnotisca, Oulunsalo, Finland). The inter-assay and intra-assay CV's in all of the above methods were less than 7.5%.

The hyperinsulinemic euglycemic clamp method was used to determine the whole body insulin sensitivity according to the method described by DeFronzo et al.[19]. Insulin sensitivity was evaluated as the mean glucose infusion rate (GIR;mg/kg/min) at 90 to 120 min during the clamp. The mean plasma IRI concentration during these periods was 65μU/ml.

All values were expressed as the mean ± SD. All interrelationships among the measured variables were assessed using Spearman's rank order correlation coefficient. A stepwise multiple regression analysis was calculated to detemine insulin sensitivity as well as the subcutaneous and visceral fat areas.

RESULTS

The physical characteristics, including abdominal fat accumulation, plasma glucose and insulin at fasting and at 2hr after oral glucose load, GIR, sex hormones, and SHBG of subjects are presented in Table 1. They consisted of male subjects with IGT who ranged in age from 31-75 years olds, and included both lean and obese subjects.

The mean value of the GIR is shown in Table 1. Among these subjects, about half of them were within the normal ranges for the GIR value, when compared with the data of Wasada et al.[20] who used the same methodology as that in the present study for the evaluation of insulin sensitivity.

Table 2 shows the interrelationships regarding the sex hormones, SHBG, age and several obesity indices. Age was negatively associated with, SFA ($r=-0.53$, $p<0.05$), VFA ($r=-0.41$ $p<0.05$), Free T ($r=-0.46$, $p<0.05$) and DHEA-s ($r=-0.58$, $p<0.05$) and positively with SHBG ($r=0.55$, $p<0.05$). The

Table 1. Physical characteristics of male subjects with impaired glucose tolerance (n=29).

	Mean	SD
Age (yrs.)	52.6	12.0
BMI	24.9	3.6
WHR	0.90	0.05
Visceral fat area (cm^2)	104.5	54.5
Subcutaneous fat area (cm^2)	117.4	67.9
Fasting blood glucose (mg/dl)	105.8	11.2
2hr blood glucose (mg/dl)	147.6	26.2
Fasting insulin (μU/ml)	8.5	4.1
2hr insulin (μU/ml)	42.2	24.7
GIR (mg/kg/min)	7.2	2.8
Estradiol (pg/ml)	17.8	8.6
Free testosterone (pg/ml)	17.6	5.7
DHEA-sulfate (ng/ml)	1485	814.0
SHGB (nmol/l)	33.9	15.8

GIR: Glucose infusion rate evaluated by hyper-insulinemic euglycemic clamp methods.; DHEA-sulfate : Dehydroepiandrosterone-sulfate.; SHBG: Sex hormone binding globulin.

Table 2. Correlation matrix

	Age	BMI	WHR	SFA	VFA	E2	Free T	DHEA-s	SHBG
Age	–								
BMI	-0.33	–							
WHR	-0.11	0.69*	–						
SFA	-0.53*	0.85*	0.61*	–					
VFA	-0.41*	0.79*	0.76*	0.84*	–				
E2	-0.01	-0.04	-0.42*	-0.08	-0.26	–			
Free T	-0.46*	0.20	0.08	0.29	0.05	0.07	–		
DHEA-s	-0.58*	0.31	0.24	0.34	0.42*	0.04	0.45*	–	
SHBG	0.55*	-0.32	-0.32	-0.50*	-0.47*	0.21	0.25	-0.37*	–

*p<0.05

VFA was positively associated with SFA(r=0.84, p <0.05), DHEA-s (r=0.42, p<0.05) and negatively with SHBG (r=-0.47, p<0.05). The SFA was negatively related to SHBG (r=-0.50, p<0.05).

A stepwise multiple regression analysis for sex hormones and SHBG using age and some obesity indices as the independent varables was performed. The WHR was thus found to be an independent predictor for E2 with a negative correlation. The age was the only predictor for SHBG with a positive correlation, while for the Free T and DHEA-s with a negative correlation. The levels of sex hormones as a function of age were relatively similar to the ranges observed in healthy male subjects (n=217) in our previous report[21)22)], but SHBG tended to be lower than that in healthy men (Fig.1).

The relationship of insulin sensitivity, and insulin and glucose responses to 75g oral glucose load with

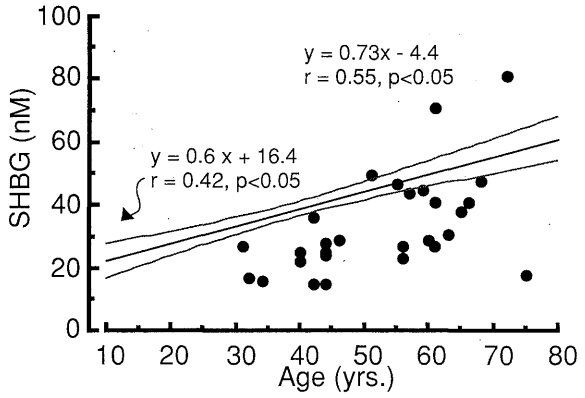

Fig. 1. The relationship between age and SHBG (n=29). Regression lines withn a 95% confidence interval were obtained from the data on helthy men (n=217).

age, obesity indices, abdominal fat accumulation, sex hormones, and SHBG were presented in Table 3. The insulin sensitivity evaluated by the GIR (ml/kg /min) was both significantly and negatively associated with IRI120' and AUCIRI , but not with fasting IRI (p=0.056), levels of glucose at fasting and after oral glucose load (Table 3). Moreover, both the VFA and SFA, respectively, were negatively associated with the GIR (Fig. 2), while they were positively associated with IRI120' and AUCIRI. The GIR was also positively associated with age and SHBG. The fasting IRI, and insulin responses to oral glucose load were significantly and positively associated with obesity indices. On the other hand, no significant relationship was observed between the glucose responses to the oral glucose load and obesity indices. The IRI120' and AUCIRI were negatively associated with Free T (p<0.05), but negatively associated with SHBG (p<0.05).

In a stepwise multiple regression analysis for insulin sensitivity (GIR) as the dependent variable (Table 4), the SFA and AUCIRI were also demonstrated to be independent predictors for the GIR.

DISCUSSION

The mean values of the GIR obtained from the present study were similar to the levels obtained in the study of Wasada et al.[20)] who used Japanese healthy males and females as their subjects and evaluated the GIR according to the DeFronzo's method[19)]. This study showed that about 50% of our subjects, even with IGT, were within the normal ranges of the GIR value reported by Wasada et al.[20)].

Table 3. Relationship of insulin sensitivity, as well as the glucoce and insulin responses to 75g OGTT to age, several obesity indices, visceral and subcutaneous fat areas, sex hormenes, and SHBG.

	Age	BMI	WHR	VFA	SFA	E2	Free T	DHEA-s	SHBG	GIR
GIR (mg/kg/min)	0.54*	-0.55*	-0.38*	-0.58*	-0.71*	0.01	-0.34	-0.36	0.40*	—
Glucose 0' (mg/dl)	-0.03	-0.10	0.07	-0.02	-0.07	-0.13	-0.12	0.49*	-0.15	-0.01
Glucose 120' (mg/dl)	0.41*	-0.27	-0.28	-0.19	-0.31	0.17	-0.39*	-0.28	0.13	0.31
AUCPG (mg/dl.hr)	0.28	-0.27	-0.35	-0.32	-0.29	0.02	-0.13	-0.18	0.09	0.29
Insulin 0' (μU/ml)	-0.29	0.43*	0.44*	0.36	0.42*	-0.08	0.23	0.22	-0.30	-0.36
Insulin 120' (μU/ml)	-0.32	0.37	0.32	0.51*	0.68*	-0.10	-0.39*	0.18	-0.42*	-0.62*
AUCIRI (μU/ml.hr)	-0.33	0.51	0.42*	0.48*	0.68*	-0.01	-0.37*	0.34	-0.37	-0.70*

*p<0.05

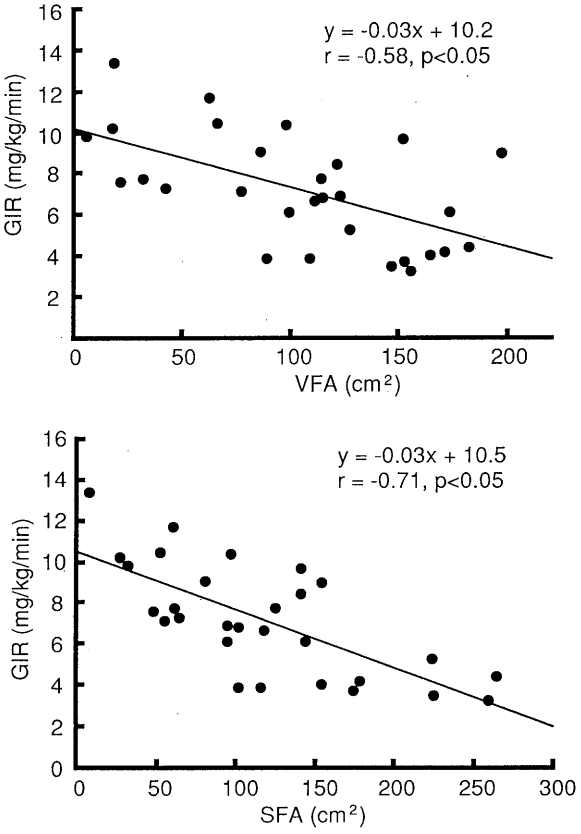

Fig. 2. The relationships of insulin sensitivity to the visceral (upper panel) and subcutaneous (lower panel) fat areas (n=29)

Tabe 4. Stepwise multiple regression analysis for insulin sensitivity as a dependent variable.

Dependent variable	1st	(β)	2nd	(β)	R^2
GIR	SFA	-0.43	AUCIRI	-0.40	0.59

Independent variables; age, BMI, WHR, VFA, SFT, SHBG, IRI120, and AUCIRI

Recently, Taniguchi[23] reported that non-obese Japanese subjects with IGT are characterized by normal insulin sensitivity, a mild impairment in pancreatic insulin secretion and decreased glucose effectiveness at zero insulin based on a minimal model analysis. The unexpected age-related increase of GIR in our subjects is thus thought to be influenced by the age-related decrease in the abdominal fat area.

It has been recently demonstrated that, in vivo, insulin is capable of stimulating testosterone production, and simultaneously, of inhibiting SHBG production in both normal weight and obese men[24] as well as in non-dieting weight-stable men[25], and that the SHBG production in vitro by the hepatoma G 2 cell line was inhibited by insulin and prolactin[26]. Therefore, hyperinsulinemia may be contributed to a reduction of the SHBG level in men with obesity, IGT, and NIDDM.

The distribution of sex hormones as a function of age in the IGT subjects showed a similar range of those in the healthy Japanese male population obtained from our previous paper[21)22)], but the SHBG levels tended to be lower than those of healthy men (Fig.1). As mentioned previously, it has been reported that both the levels of testosterone and SHBG in massively obese men[6)7)], especially visceral type[8], and patients with NIDDM[3-5] were significantly lower than those in healthy controls, and also were significantly associated with the degrees of hyperinsulinemia[5)27)], insulin sensitivity as evaluated by an euglycemic clamp[11)12)], and insulin pulse frequency[28]. We recently demonstarted[29] that both levels of the free testosterone and SHBG in men with IGT and NIDDM groups were significantly lower than that of control group ($p<0.05$) after matching for age, endurance fitness evaluated by measurement of maximal oxygen uptake and some obesity indices. In addition, significant negative correlation was observed between SHBG level and fasting blood glucose concentration ($r=-0.435$; $p<0.05$). From these results, it is suggested that relative hypogonadism within range of physiological level may be exsisted in patients with early phase of impaired glucose tolerance (so-called IGT). In this study, however, no significant differences in either levels of the sex hormones and SHBG were observed as compared with insulin sensitive and insensitive groups subdivided by the GIR.

The major finding of this study was that the SFA and the AUCIRI could predict 59% of the explained variance of the GIR in stepwise multiple linear regression analysis. It is also of great interest to note that we demonstrated a significant contribution of SFA, but not of either VFA, androgen or SHBG. In this context, many studies have reported that

subjects with the excess visceral fat accumulation[30-32] and/or relative hypogonadism[9] may thus be associated with the developments of insulin resistance and/or hyperinsulinemia. Moreover, Haffner et al.[12] demonstrated a significant positive correlation between insulin sensitivity evaluated by a minimal model and the SHBG level in men (n=8), independent of obesity. In recently, Abate et al.[33] demonstrated that the subcutaneous truncal fat mass estimated by MRI plays a major role in obesity-related insulin resistance in healthy men with a wide range of obesity, whereas the intraperitoneal and retroperitoneal fat mass play a lesser role. In addition, they reported[34] that subcutaneous truncal fat mass is the most powerful determinant of insulin sensitivity in men with NIDDM. The role of SFA as an independent predictor for the insulin response to the oral glucose load has also reported by Kawamori et al.[35] who examined Japanese male patients with coronary heart disease. They demonstrated that the SFA, as well as the VFA, as measured by CT, were significant independent predictors of ΣIRI calculated from insulin responses to 75g OGTT. On the other hand, Park et al.[32] reported that the intra-abdominal fat area, but not the subcutaneous fat area, played an important role in decreasing insulin sensitivity, even in healthy young men with a BMI ranging from 18 to 30. Moreover, Tchernof et al.[36] demonstrated that the previously reported relationship between the androgen level and plasma glucose-insulin homeostasis are mediated, to a large extent, by concomitant alterations in the levels of total body fat and visceral adipose tissue in men.

There have been a few reports[20] showing that the insulin response to the oral glucose load in Japanese subjects is one of the independent variables for insulin sensitivity. They demonstrated significant negative correlation between the GIR and AUCIRI or insulinogenic index (ΔIRI/ΔGlucose at 30 min during 75g glucose load) in Japanese males and females with borderline glucose tolerance. These results thus imply that insulin resistance plays an important role of in the pathogenesis of NIDDM in some fraction of the Japanese population.

As the background for the insulin response to oral glucose load, several and multiple factors, such as insulin secretion from pancreas and insulin degradation in the liver, were included[37]. Björntrop[38] summarized that the level of BMI was positively associated with insulin secretion, while the level of the WHR as an indirect index of abdominal type obesity was negatively associated with insulin clearance and insulin efficacy in skeletal muscle. Because the evaluation of insulin senitivity as measured by the hyperinsulinemic euglycemic clamp method mainly reflected the glucose uptake by insulin into the skeletal muscle[37] and since the AUCIRI may also be one independent predictor of insulin sensitivity in the IGT subjects in this study, the variation in the insulin response to the oral glucose load may thus explain the variation in the peripheral insulin sensitivity observed in Japanese IGT subjects.

Several studies reported that the hyperinsulinemic responses to the oral glucose load in obese men[39] and relative hypogonadism in men included obese, such as lower levels of testosterone and Free T[27], were independently associated with the VFA. Seidell et al.[27] demonstrated a significant negative association between VFA and Free T, and SHBG in obese men. Leenen et al.[40] demonstrated significant decreases in abdominal fat areas, fasting IRI, and total and free estradiol, and significant increases in SHBG, estrone, and dehydroepiandrosterone-sulfate level in obese men after their weight loss. Moreover, they did not observe any significant relationship between the changes in sex hormones or SHBG and changes in the VFA. These results did not suggest the cause and effect concerning the relationship between VFA and sex hormones and/or SHBG, found in either a previous cross-sectional study[27] or the present study.

But it must be noted that in this study the disappearance of the significant relationships between sex hormones and/or SHBG and abdominal fat (SFA, VFA) could also possibly be confounded by the negative correlation between age and the abdominal fat area.

In summary, insulin sensitivity (GIR) evaluated by hyperinsulinemic euglycemic clamp was closely

related to the SFA and area under the curve of insulin during oral glucose load, but not by either the SHBG or free testosterone levels. Therefore, our results appear to suggest that abdominal subcutaneous fat accumulation and hyperinsulinemic conditions result in insulin resistance in Japanese men with IGT.

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要　約

本研究の目的は、耐糖能境界型（IGT）男性の性ホルモン、性ホルモン結合グロブリン（SHBG）及びインスリン感受性の水準を比較検討すると共にインスリン感受性と性ホルモン及び SHBG との関連性を明らかにすることである。Hyperinsulinemic euglycemic clamp 法で評価したインスリン感受性（glucose infusion rate; GIR），CT スキャン法で評価された腹部の皮下（SFA）・内臓脂肪蓄積（VFA），性ホルモン（遊離テストステロン，エストラデイオール，dehydroepiandrosterone-sulfate）及び SHBG 水準が，やせ型から肥満者を含む31-75歳の日本人男性 IGT（n=29）を対象に測定された。性ホルモンの分布は，すでに著者らが報告した健常男性で観察された数値の範囲内にあった。しかしながら，統計処理は行っていないが，SHBG 水準は健常者よりも低い傾向にあった。GIR に関しては，IGT 男性の約50％が正常範囲内にあった。単相関分析において，GIR は年令や SHBG との間に有意な正相関を，一方肥満尺度，特に腹部の皮下脂肪面積（SFA）との間に有意な負の相関を認めた。ステップワイズ重回帰分析の結果，SFA と75ｇの経口糖負荷試験（OGTT）に伴うインスリンの曲線下面積は，GIR に関する有意な独立因子であった。さらに，SHBG や遊離テストステロンは，OGTT に伴うインスリン反応と有意な負の相関を認めたが，腹部の SFA 及び VFA の影響を考慮した偏相関分析の結果，両者の間には有意な関連性は認められなかった。これらの成績から，腹部の皮下脂肪蓄積や経口糖負荷後の高インスリン反応は，日本人 IGT 男性の末梢インスリン感受性の独立因子であることが示唆された。