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Higher fasting glucose, triglycerides, resting pulse rate and high-sensitivity C reactive protein in adipose insulin-resistant but normal weight young Japanese women

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ABSTRACT

Introduction Adipose insulin-resistant but normal weight phenotype has not been reported and hence was characterized in young Japanese women.

Research design and methods Body composition, a broad range of cardiometabolic health and dietary intake were cross-sectionally measured in 166 normal weight young Japanese women. They were grouped into tertile of adipose tissue-insulin resistance (AT-IR) index (fasting insulin×free fatty acids) and analyzed by analysis of variance and then Bonferroni's multiple comparison procedure.

Results Body mass index averaged <21 kg/m^2 and waist <72 cm, and did not differ among three groups of women. Fasting glucose and triglycerides and homeostasis model assessment-insulin resistance were higher in the highest compared with the median and lowest AT-IR tertile. However, there was no difference in fat mass and distribution, high-density lipoprotein cholesterol and blood pressure. In addition, high-sensitivity C reactive protein (hsCRP) and resting pulse rate were higher as well. In multivariate logistic regression analyses, fasting glucose (OR: 1.10, 95% CI: 1.02 to 1.18, p=0.012), fasting triglycerides (OR: 1.04, 95% CI: 1.02 to 1.06, p<0.001), resting pulse rate (OR: 1.07, 95% CI: 1.03 to 1.11, p<0.001) and hsCRP (OR: 2.30, 95% CI: 1.01 to 5.2, p=0.04) were associated with the high AT-IR tertile.

Conclusions Adipose insulin-resistant but normal weight phenotype may be associated with increased sympathetic nervous system and low-grade systemic inflammation in addition to glucose and lipid dysmetabolism through mechanisms unrelated to adiposity in young Japanese women.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The metabolically obese but normal weight phenotype is important. However, studies evaluating adipose insulin resistance but normal weight may be missing.

WHAT THIS STUDY ADDS

⇒ Adipose insulin-resistant but normal weight young Japanese women had higher high-sensitivity C reactive protein and resting pulse rate in addition to higher fasting glucose and triglycerides in spite of comparable body fat mass and distribution.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Adipose insulin-resistant but normal weight phenotype is associated with increased cardiometabolic risk through mechanisms unrelated to adiposity in young Japanese women.

INTRODUCTION

Large studies showed that a body mass index (BMI) in the normal weight range (defined as a BMI of 18.5–24.9 kg/m^2) associates with a lower risk of cardiometabolic diseases and all-cause mortality.[1 2] However, not all normal weight subjects have this low risk. Normal weight obesity is characterized by the presence of high body fat despite having a normal BMI.[3] Normal weight obese people have a higher risk of cardiometabolic diseases than individuals with normal weight and without high body fat.[4 5]

It is also reported that metabolically unhealthy (or obese) normal weight subjects have a higher risk of all-cause mortality and/or cardiovascular events compared with people who are of normal weight and metabolically healthy (or non-obese).[6–8] Although currently, there is not a standard definition of metabolic health, a person was considered metabolically healthy when fewer than two parameters of the metabolic syndrome were present in most studies.[6] As insulin resistance is a key metabolic trait not only of obesity but also of the metabolically unhealthy (or obese) normal weight phenotype,[8] homeostasis model assessment-insulin

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resistance (HOMA-IR), in addition to the number of parameters of the metabolic syndrome, was used to distinguish metabolically obese from non-obese normal weight subjects in some studies.[9 10] HOMA-IR is calculated by the product of fasting concentrations of insulin and glucose and hence is a surrogate marker of liver insulin resistance.[11] In a manner completely analogous to HOMA-IR, the product of fasting concentrations of insulin and free fatty acid (FFA) is a validated index of the adipose tissue-insulin resistance (AT-IR).[12 13] We showed that this index may be useful in assessing adipose insulin resistance even in women without diabetes and obesity.[14] As studies are missing that characterized normal weight people with adipose insulin resistance, we investigated this issue in normal weight Japanese women, populations in which confounding factors are so scarce.[15] Because we reported that endurance training lowered fat mass and AT-IR in young women,[16] we excluded female collegiate athletes in the present study.

SUBJECTS AND METHODS

Among 210 young Japanese women whose details were reported previously,[14] we excluded 44 women who were underweight or overweight and reanalyzed cross-sectionally 166 normal weight women in the present study. They were students of the Department of Food Sciences and Nutrition, Mukogawa Women's University and were recruited as volunteers. Women with clinically diagnosed acute or chronic inflammatory diseases, endocrine, cardiovascular, hepatic and renal diseases, hormonal contraception, and unusual dietary habits were excluded from the study.

After a 12-hour overnight fast, which was slightly above the recommended Japanese guidelines of 10-hour fasting for oral glucose tolerance testing, participants underwent blood sampling, measurement of anthropometric indices, blood pressure and body composition as previously described.[14–16] Brachial blood pressure and pulse rates were measured using an automated sphygmomanometer (BP-203RV II, Colin, Tokyo, Japan) after participants were seated at least for 5 min. The measurements were repeated after 2–3 min, and the average of the measurements was used for analyses. Plasma glucose, serum aspartate aminotransferase and alanine aminotransferase (AST and ALT, respectively), insulin, triglycerides, cholesterol, high-density lipoprotein (HDL) cholesterol, FFA, high-sensitivity C reactive protein (hsCRP), and leukocytes were measured as previously reported.[14–16] Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald's formula. HOMA-IR and AT-IR were calculated as depicted in the Introduction section.

Whole-body dual-energy X-ray absorptiometry (DXA) (Hologic QDR-2000 software V.7.20D, Waltham, Massachusetts, USA) was used to measure lean tissue mass, fat mass, and bone mineral mass for arms, legs (lower body), trunk and the total body.[15] General adiposity was assessed using BMI, percentage body fat and fat mass index (FMI), the latter of which was calculated as body fat mass in kilograms divided by height in meter squared. Waist circumference and the ratio of trunk to leg fat[17] were considered as markers of abdominal fat accumulation. Muscle characteristics were evaluated by relative appendicular skeletal muscle mass (ASM) as percentage of body mass (%ASM) and absolute ASM index (ASM/height^2 in kg/m^2). %ASM is suggested to be a better predictor of insulin resistance and diabetes risk than ASM or ASM index.[18]

Dietary intake was assessed using the self-administered diet history questionnaire.[19] This has been widely used throughout Japan and its validity with respect to commonly studied nutrition factors has been confirmed.

Data were presented as mean±SD unless otherwise stated. Due to deviation from normal distribution, hsCRP was logarithmically transformed for analyses. Participants were divided by tertile of AT-IR and the highest tertile was referred to as adipose insulin-resistant group. Differences among three groups were analyzed by analysis of variance (ANOVA) and then Bonferroni's multiple comparison procedure. Stepwise multivariate logistic regression analyses were used to identify most important determinants of the high AT-IR. Independent variables included were variables, which showed significant difference among three groups. A two-tailed $p<0.05$ was considered statistically significant. All calculations were performed with SPSS system V.23.0.

RESULTS

BMI averaged 20.6 kg/m^2, waist 71.5 cm and fasting glucose 81 mg/dL, and there was no difference in BMI and waist among three groups (table 1). Their serum concentrations of triglyceride and liver enzymes were normal as well (table 2).

HOMA-IR and fasting insulin increased in a stepwise fashion from the low through the high AT-IR tertile (table 1). However, there was no difference in age, percentage body fat, FMI, trunk/leg fat ratio, ASM index, %ASM, serum adiponectin and leptin. Fasting glucose was modestly but significantly increased in the high compared with low AT-IR tertile (table 1 and figure 1). Two-hour glucose concentrations were higher in women with the median and high compared with low AT-IR tertile, but differences were not significant (ANOVA p=0.34). Post hoc power analyses yielded 0.20 in the setting of the present study, indicating a weak statistical power.

Fasting triglycerides (figure 1) and FFA were higher in the high AT-IR tertile compared with the other two groups of women, whereas serum, LDL and HDL cholesterol did not differ (table 2). Leukocyte counts and hsCRP (figure 1) were higher in the high compared with the median AT-IR tertile (table 2). Resting pulse rate was higher in the high AT-IR tertile compared with the other two groups of women, whereas AST and blood pressure did not differ. ALT was higher in the high compared with the median tertile.

Women in the high compared with the low AT-IR tertile consumed less vegetables (p=0.07), green and yellow vegetables in particular, and hence less vitamin A (table 3). However, there was no difference in daily intake of energy and macronutrients among three groups of women.

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Table 1 Anthropometric and metabolic features of young Japanese women grouped by tertile of AT-IR index

	AT-IR index			
	Low	Median	High	
Range	−1.86	1.87–3.30	3.40	*
Age (years)	20.8 ± 1.3	20.7 ± 1.2	20.7 ± 1	
BMI (kg/m^2)	20.6 ± 1.5	20.6 ± 1.6	20.5 ± 1.3	
Waist (cm)	71.6 ± 5.1	71.5 ± 4.9	71.2 ± 5	
Trunk/leg fat ratio	1.24 ± 0.18	1.25 ± 0.22	1.34 ± 0.29	
% body fat (%)	28 ± 4.7	27.1 ± 4.5	28.2 ± 4.4	
ASM index (kg/m^2)	5.9 ± 0.5	6 ± 0.4	5.8 ± 0.4	
FMI (kg/m^2)	5.7 ± 1.3	5.5 ± 1.3	5.7 ± 1.2	
%ASM (%)	28.8 ± 2.1	29.1 ± 1.9	28.5 ± 2	
Leptin (ng/mL)	7.5 ± 3.3	8.4 ± 3.5	8.9 ± 3.7	
Adiponectin (mg/L)	11.7 ± 4	11.8 ± 4.6	11.3 ± 4.2	
Fasting glucose (mg/dL)	80 ± 7	81 ± 5	83 ± 6	‡
2-hour glucose (mg/dL)	89 ± 20	96 ± 25	94 ± 25	
Fasting insulin (μU/mL)	3.5 ± 1.4	5.5 ± 1.4	9 ± 3.2	†‡§
HOMA-IR	0.6 ± 0.3	1.1 ± 0.3	1.8 ± 0.7	†‡§
AT-IR	1.4 ± 0.4	2.6 ± 0.4	6.3 ± 3.4	†‡§

Mean±SD: n=55 or 56, except for 2-hour glucose: n=40, 34 and 25 in low, median and high tertile, respectively.
*P<0.05 or less by Bonferroni's multiple comparison procedure.
†Low versus median.
‡Low versus high.
§Median versus high.
ASM, appendicular skeletal muscle mass; AT-IR, adipose tissue-insulin resistance; BMI, body mass index; % body fat, percentage body fat; FMI, fat mass index; HOMA-IR, homeostasis model assessment-insulin resistance.

In multivariate logistic regression analyses (table 4), fasting glucose, triglycerides, resting pulse rate and hsCRP were associated with the high AT-IR tertile independent of ALT and green-yellow vegetable intake.

DISCUSSION

The current study has confirmed associations of AT-IR with fasting glucose and triglycerides as previously reported by us,[14] and demonstrated that AT-IR but normal weight was associated positively with resting pulse rate and hsCRP, a marker of systemic low-grade inflammation through mechanisms unrelated to adiposity. Normal weight young Japanese women with the high AT-IR tertile were indeed in the adipose insulin-resistant state because their AT-IR (6.3±3.4, table 1) was equivalent to or even higher than AT-IR (4.3±2.4) in overweight Japanese women.[14]

Suppression of hepatic glucose production by insulin is critical for maintenance of normal glucose homeostasis, and impairment in this process plays an important role in the pathogenesis of type 2 diabetes. There is general agreement that the acute suppression of hepatic glucose production by insulin is mediated by both a direct (hepatic) and an indirect (extrahepatic) effect on the liver.[20] As reviewed by Lewis *et al*,[20] there is abundant evidence that insulin's effect on adipose tissue lipolysis is a key signal mediating insulin's extrahepatic effect to inhibit hepatic glucose production. These findings may be related to the independent association of AT-IR but normal weight with fasting glucose concentrations in the present study since hepatic glucose production has been shown to correlate with fasting glucose concentrations.[21 22]

Fat cell lipolysis results in the release of FFA to the circulation, which is used for hepatic production of very low-density lipoprotein triglycerides.[23] Consequently, high spontaneous subcutaneous fat cell lipolysis activity and resistance to the antilipolytic effect of insulin have been reported to be associated with elevated triglyceride and low HDL cholesterol concentrations.[24] As AT-IR is the product of fasting insulin and FFA, adipose tissue insulin-resistant but normal weight women had elevated FFA, suggesting that they had high spontaneous subcutaneous fat cell lipolysis activity, which may be associated with elevated triglyceride in the present study.

Facchini *et al* studied whether insulin-resistant individuals had a higher heart rate than insulin-sensitive subjects.[25] Insulin sensitivity was measured using insulin-mediated glucose disposal quantified by the insulin suppression test in apparently healthy normotensive individuals without diabetes. Heart rate was continuously monitored during sleep by an electronic device measuring RR intervals. They

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Table 2 Cardiometabolic features of young Japanese women grouped by tertile of adipose tissue-insulin resistance index

	Adipose tissue-insulin resistance index			
	Low	Median	High	*
Triglyceride (mg/dL)	47 ± 16	51 ± 18	69 ± 34	†‡
Cholesterol (mg/dL)	182 ± 30	178 ± 22	187 ± 28	
HDL cholesterol (mg/dL)	73 ± 12	75 ± 14	74 ± 12	
LDL cholesterol (mg/dL)	100 ± 27	93 ± 17	100 ± 23	
FFA (mEq/L)	0.45 ± 0.17	0.5 ± 0.13	0.71 ± 0.26	†‡
hsCRP (µg/dL)	22 ± 34	16 ± 26	50 ± 116	‡
log hsCRP	1.08 ± 0.42	0.93 ± 0.42	1.16 ± 0.58	‡
Leukocytes (x10^9/L)	5.8 ± 1.7	5.5 ± 1.4	6.4 ± 1.7	‡
AST (U/L)	17.7 ± 4	17.4 ± 4.2	18.2 ± 7.4	
ALT (U/L)	12.3 ± 4.1	12.1 ± 3.4	14.9 ± 8.5	‡
Systolic BP (mm Hg)	109 ± 10	106 ± 10	107 ± 12	
Diastolic BP (mm Hg)	64 ± 7	62 ± 7	63 ± 8	
Resting pulse rate (bpm)	63 ± 10	65 ± 8	71 ± 11	†‡

Mean±SD (n=55 or 56) AST and ALT: aspartate- and alanine-aminotransferase, FFA: free fatty acid, hsCRP: high-sensitivity C-reactive protein, HDL and LDL; high- and low-density lipoprotein.
*P<0.05 or less by Bonferroni's multiple comparison procedure.
†Low versus high.
‡Median versus high.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; bpm, beats per minute; FFA, free fatty acid; HDL, high-density lipoprotein; hsCRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein.

found that insulin-resistant individuals, with compensatory hyperinsulinemia, had a higher nocturnal heart rate, suggesting that the increased nocturnal heart rates are secondary to insulin-induced sympathetic activity.[25] These observations may be in line with the present finding that adipose tissue insulin-resistant but normal weight women had elevated resting pulse rate, which may be associated with heart rates in young healthy women.

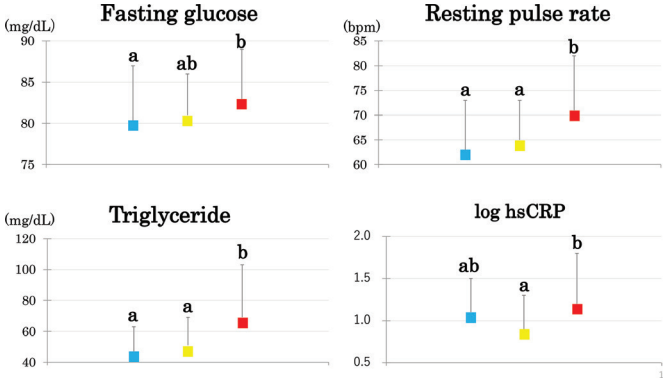

Figure 1 Fasting glucose and triglyceride, resting pulse rate and high-sensitivity C reactive protein (hsCRP) (logarithmically transformed) in normal weight young Japanese women with the low (blue squares, n=55), median (yellow squares, n=56) and high (red squares, n=55) tertile of adipose tissue-insulin resistance index. Mean±SD. Means not sharing common alphabetical letter are significantly different with each other at p<0.05 or less by Bonferroni's multiple comparison procedure. bpm, beats per minute.

CRP is a hepatic acute phase protein largely regulated by circulating levels of interleukin-6. Although the activated leukocyte is widely assumed to be the major source of circulating interleukin-6 in clinical inflammation, it was demonstrated that human subcutaneous adipose tissue secreted interleukin-6 in healthy subjects.[26] Studies including ours showed that total body fat and abdominal/central fat were associated with hsCRP,[27–32] whereas we have shown an association between abdominal/central fat and AT-IR in Japanese women.[14] Therefore, it is likely that abdominal fat may be a link of association between hsCRP and AT-IR in adipose tissue insulin-resistant but normal weight women in the present study.

Adipose tissue and the liver are major sites of storage for carotenoids, which are vital antioxidants and rich in vegetables, green-yellow vegetables in particular, and fruits.[33] Harari *et al* measured serum and adipose tissue carotenoids concentrations and tissue-specific insulin resistance in subjects without diabetes with a wide range of BMI and insulin resistance.[34] They found that serum carotenoids were correlated inversely with insulin resistance in the liver evaluated by hepatic glucose production and adipose tissue evaluated by AT-IR. Because serum carotenoids concentrations were correlated positively with consumption of green-yellow vegetables,[35] the latter finding may be in line with the present finding that women with the high AT-IR tertile had lower intake of green-yellow vegetables (87 g/day), which was lower than the recommended dose in adults (120 g/day) by the Ministry of Health, Labor and Welfare, Japan.[36]

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Table 3 Daily dietary intake of young Japanese women grouped by tertile of adipose tissue-insulin resistance index

	Adipose tissue-insulin resistance index			
	Low	Median	High	*
Energy (kcal)	2093 ± 1149	1888 ± 490	1893 ± 442	
Carbohydrate (%)	54 ± 6.2	54.3 ± 5.7	53.9 ± 5.3	
Protein (%)	13.5 ± 1.6	13.2 ± 1.6	13.5 ± 2	
Fat (%)	31.1 ± 5.3	30.7 ± 5.2	30.7 ± 4.6	
Vitamin A (µg)	671 ± 366	563 ± 327	500 ± 230	†
Vegetables (g)	265 ± 167	214 ± 143	213 ± 84	
Green-yellow vegetables (g)	124 ± 102	95 ± 72	87 ± 44	†

Mean±SD (n=55 or 56).
*P<0.05 or less by Bonferroni's multiple comparison procedure.
†Low versus high.

Studies are limited on adipose insulin resistance in normal weight people. Dumesic *et al*[37] compared 10 normal weight women with polycystic ovary syndrome and 18 control women matched for age and BMI and found that AT-IR was higher in women with polycystic ovary syndrome (4.5 vs 2.8, p=0.007) and positively correlated with serum androgen. Kim *et al* studied normal weight versus obese adolescents with and without pre-diabetes or type 2 diabetes.[38] They found that AT-IR was 2.2-fold higher in obese normal glucose tolerance, 4.3-fold higher in impaired glucose tolerance, and 4.6-fold higher in type 2 diabetes compared with normal weight adolescents (approximately 3.8, calculated by 15 µU/mL×0.25 mEq/L, figure 1), which is comparable with AT-IR (3.4) found in normal weight Japanese women.

The strength of the present study includes the accurate and reliable measures of general and central fat accumulation by DXA and the homogeneous study population with few confounding factors.[15] It is well known that socioeconomic status is associated with resting heart rate and systemic inflammatory markers.[39 40] Participants are female university students, in whom more than 95% of grade 1 students are 18 years old. This may decrease the interference of age and environmental factors, such as smoking, alcohol, educational, and socioeconomic status. Further, in almost all students, almost all school expenses for 4 years were covered by their parents, suggesting that socioeconomic status appears to be less heterogeneous even among parents. There are several limitations of this study that include the cross-sectional design, relatively small sample size, and a single measurement of biochemical variables. We did not measure daily physical activity, which may influence resting pulse rates. Statistical power and sample size were not calculated. As participants were young Japanese women, the results may not be generalized to other gender, age populations, races or ethnicities.

In conclusion, adipose insulin-resistant but normal weight young Japanese women consumed less green-yellow vegetables and had higher hsCRP and resting pulse rate in addition to higher fasting glucose and triglycerides through mechanisms unrelated to adiposity. Studies are needed to see if increased consumption of green-yellow vegetables ameliorates increased cardiometabolic risk.

Table 4 Multivariate logistic regression analysis for the high tertile of adipose tissue-insulin resistance index

Independent variables	OR	95% CI		P value
		Lower	Upper	
Fasting glucose	1.10	1.02	1.18	0.012
Triglyceride	1.05	1.02	1.07	<0.001
log hsCRP	2.30	1.01	5.23	0.046
Resting pulse rate	1.06	1.02	1.11	0.004

Other independent variables included: ALT and green-yellow vegetables.
ALT, alanine aminotransferase; hsCRP, high-sensitivity C reactive protein.

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Contributors SMI, MH, ATK and MT collected data and prepared Tables 1-4. KK, AT, MK and BW analyzed data and prepared Fig. 1. TK wrote the manuscript, and KF reviewed and edited it. All authors approved the final version of the manuscript to be published. TK supervised the study, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the manuscript.

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