Adipose Insulin Resistance and Decreased Adiponectin Are Correlated With Metabolic Abnormalities in Nonobese Men

Original Article

Adipose tissue insulin resistance and decreased adiponectin are correlated with metabolic abnormalities in non-obese men

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Abstract

Context: Adipose tissue dysfunction is characterized by decreased adiponectin (AN) levels and impaired adipose tissue insulin sensitivity (ATIS), and is associated with metabolic disorders. While Asians readily develop metabolic disease without obesity, it remains unclear how decreased AN level and impaired ATIS affect metabolic abnormalities in non-obese Asians.

Design and Setting: To investigate the relationships between decreased AN level, impaired ATIS, and metabolic abnormalities, we studied 94 Japanese men whose body mass index was less than 25 kg/m^2. We divided the subjects into four groups based on their median AN level and ATIS, the latter calculated as the degree of insulin-mediated suppression of free fatty acids during hyperinsulinemic euglycemic clamp, and compared the metabolic parameters in the four groups.

Results: The High-ATIS/High-AN group (n=29) showed similar anthropometric data to the High-ATIS/Low-AN group (n=18). In contrast, both the Low-ATIS/High-AN (n=18) and Low-ATIS/Low-AN (n=29) groups showed significantly lower muscle insulin sensitivity than the High-ATIS groups. The intrahepatic lipid level in the Low-ATIS/Low-AN group was significantly higher than that in the High-ATIS groups. In addition, the Low-ATIS/Low-AN group had a significantly higher fasting serum

triglyceride level and significantly lower high-density lipoprotein cholesterol level than the other three groups.

Conclusions: In non-obese Japanese men with high ATIS, the AN level was not associated with metabolic characteristics. On the other hand, subjects with low ATIS showed reduced muscle insulin resistance and those with a decreased AN level demonstrated multiple metabolic abnormalities, represented by fatty liver and dyslipidemia.

Keywords:

adiponectin, insulin resistance, free fatty acid, non-obese, ectopic fat, dyslipidemia

Introduction

Adipose tissue dysfunction is closely associated with insulin resistance and metabolic disorders such as diabetes and dyslipidemia [1 2 3]. Adipose tissue stores triglycerides (TGs) during feeding, and in the fasting state, the stored TGs are released into the circulation as free fatty acids (FFAs). Circulating FFA levels are elevated in obese individuals, partly due to increased FFA release from adipose tissue associated with increased adipose tissue insulin resistance and enhanced lipolysis [4, 5] and the FFA release promotes ectopic fat accumulation and insulin resistance in muscle and liver [1 2] . It has also been shown that adipose tissue secretes several adipokines, such as adiponectin (AN), and modulates glucose and lipid metabolism [6 7 8 9]. Of note, studies in rodents demonstrated that AN reduced intracellular lipids in muscle and liver by enhancing β-oxidation, and also maintained normal insulin sensitivity [6 7 10 11]. In addition, the AN level is reduced in obese subjects, and this is associated with insulin resistance and hepatic fat accumulation [1 8]. Furthermore, a prospective study showed that a low AN level was a predictor of non-alcoholic fatty liver disease (NAFLD) in middle-aged and elderly subjects [12]. Thus, it has been hypothesized that in obese individuals, both increased FFA release and decreased AN release from adipocytes promote ectopic fat accumulation in muscle and liver, thus inducing insulin resistance and the development of metabolic disorders [1 9 13 5].

Asians readily develop metabolic disease, even in the absence of obesity [body mass index (BMI) ≤ 25 kg/m^2] [14]. Specifically, East Asians show the lowest TG storage capacity in subcutaneous adipose tissue [14 15]. Intriguingly, we previously demonstrated that adipose tissue insulin sensitivity (ATIS), a marker of increased FFA release from adipose tissue is variable even in non-obese healthy Japanese men, and that impaired ATIS is associated with not only increased body fat, but muscle insulin resistance and

IHL accumulation [2 16]. Thus, it is hypothesized that increased adipose tissue could cause impaired ATIS and increased spillover of fatty acids from adipose tissue to non-adipose tissue [4 5], which subsequently induce ectopic fat accumulation, insulin resistance and metabolic abnormalities even in non-obese healthy men [1 2 5]. We also demonstrated that a low AN level was associated with hepatic fat accumulation and muscle insulin resistance in non-obese men [16 17]. However, in these subjects, ATIS was only weakly correlated with the AN level [2]. This fact led us to hypothesize that in non-obese Asians, both ATIS and AN level vary from individual to individual, and that impaired ATIS and decreased AN level independently and/or synergistically exacerbate metabolic abnormalities. However, no reports thus far have tested this hypothesis.

Based on this background, the present study was designed to clarify how impaired ATIS and decreased AN level are associated with metabolic abnormalities in non-obese Japanese subjects. For this purpose, we compared fat distribution and clinical features among four groups defined by both the median ATIS, which was calculated by two-step hyperinsulinemic euglycemic clamp, and the median level of high-molecular-weight (HMW)-AN, an active form of AN [18], in 94 non-obese (BMI $\leq$25 kg/m^2), middle-aged Japanese men without diabetes mellitus.

Research Design and Methods

Study subjects

Nondiabetic Japanese men aged between 30 and 50 years were recruited in the Sportology Center Core Study, a prospective observational study involving hypothesis-driven, hypothesis-generating research on the underlying mechanisms of metabolic abnormalities in nonobese subjects [17]. Subjects enrolled in the Sportology Center Core Study had a BMI of 21 to 27.5 kg/m^2 (≥21.0 to < 27.5 kg/m^2). Using the cohort, we previously investigated the role of reduced ATIS in non-obese men (≥21.0 to <25.0 kg/m^2) without cardiometabolic risk factors (n=52) [2]. In the present study, we analyzed all of non-obese men with (n=42) and without (n=52) cardiometabolic risk factors in the cohort. Thus, 52 in 94 subjects in the present study were also included in the previous study [2]. In addition, the previous study only compared apparently healthy non-obese men with low ATIS and high ATIS in apparently healthy non-obese men [2]; however, the present study firstly evaluated how the various combinations of high and low AN levels and ATIS values are associated with metabolic abnormalities in non-obese Japanese men. All participants provided written informed consent, which was approved by the ethics committee of Juntendo University (No. 2011042). This study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Study design

The design of the Sportology Center Core Study has been previously reported in detail [17]. Briefly, after the screening session, all participants visited our institute three times for a baseline evaluation. At the first or second visit, each participant underwent an oral glucose

tolerance test (OGTT) or peak oxygen uptake test [17]. In the OGTT, blood samples were obtained before and 30, 60, 90, 120 and 180 min after 75g glucose ingestion to determine plasma glucose and insulin levels. Regular exercise was prohibited for 10 days before the third visit, and the mean daily physical activity level was evaluated for 7 days using an accelerometer (Lifecorder; Suzuken, Nagoya, Japan). Next, each participant was asked to maintain the same mean daily physical activity level (±10%) at that of the previous 3 days, which was monitored with an accelerometer. On the day of the experiment, we measured intramyocellular lipid (IMCL) and intrahepatic lipid (IHL) by ^{1}H-magnetic resonance spectroscopy (MRS) after an overnight fast [19]. Total body fat content and fat-free mass (FFM) were measured by the bioimpedance method (InBody; Biospace, Tokyo) [20]. Furthermore, visceral fat area (VFA) and subcutaneous fat area (SFA) were measured by magnetic resonance imaging (MRI). Lastly, hyperinsulinemic euglycemic clamp was performed to measure insulin sensitivity in muscle, liver, and adipose tissue.

Hyperinsulinemic euglycemic clamp

Subjects were instructed to consume a standard weight-maintenance diet during the 3 days immediately before the clamp test. A two-step hyperinsulinemic euglycemic clamp study was performed with an artificial endocrine pancreas (STG-22; Nikkiso, Shizuoka, Japan) after an overnight fast [17]. Briefly, after an intravenous cannula was secured in the forearm, primed (200 mg/m^2 body surface area [BSA]) [6,6-$^{2}H_2$]glucose (Cambridge Isotope Laboratories) was given intravenously, followed by a constant infusion of 2 mg/m^2 BSA/min for 3 h (range, -180 to 0 min) to measure fasting endogenous glucose production (EGP) [21]. This was followed by a primed insulin infusion (40 mU/m^2/min, followed by 20 mU/m^2/min, each lasting 5 min) and a continuous insulin infusion at 10

mU/m^2/min for 3 h (first step; range, 0 to 180 min). In the second step of the clamp, after a primed insulin infusion (80 mU/m^2 /min, followed by 40 mU/m^2/min, each lasting 5 min), insulin was continuously infused at 20 mU/m^2/min for 3 h (range, 180 to 360 min). A warming blanket was used for arterialization of the hand vein. The plasma glucose level in the arterialized blood was maintained at approximately 95 mg/dL by a variable-rate infusion of 20% glucose containing approximately 2.5% [6,6-$^2H_2$]glucose. Blood samples were obtained for biochemical analysis at 10-min intervals during the last 30 min of the steady-state period of the first and second steps of the clamp. We also performed blood sampling every 60 min. Enrichment of [6,6-$^2H_2$]glucose in plasma was measured using high-performance liquid chromatography (LTQ-XLOrbitrap mass spectrometer; Thermo Scientific, Waltham, MA) [17].

Calculations

A steady-state equation was used to calculate the rates of endogenous glucose production (EGP) and glucose disappearance (Rd) at each step [17]. The EGP and Rd were normalized by the body weight and fat-free mass, respectively. Since EGP suppression is known to be positively correlated with insulin concentration at low insulin levels (~20 μU/mL) [22], we divided the percent reduction of EGP at the first step by the steady-state serum insulin (SS_{SI}) level during the glucose clamp and used the result as an index of hepatic insulin sensitivity [23]. The Rd is also known to be enhanced in parallel with the serum insulin concentration [22]; we therefore evaluated muscle insulin sensitivity by dividing the Rd at the second step by the SS_{SI}. ATIS was evaluated according to the degree of insulin-mediated suppression of circulating FFAs [23 24]. In brief, the percent reduction of FFAs at the first step was calculated using the basal and nadir FFA concentrations during the last

1 h of the glucose clamp at the first step and was then adjusted by the insulin concentration and used as an index of ATIS [23 24]. Since using tracer to measure the rate of appearance (Ra) of FFA or glycerol suppression during glucose clamp has been recognized as the gold standard to evaluate ATIS, a recent study suggested that %FFA suppression during glucose clamp is highly correlated (r = 0.899) with tracer-determined suppression of Ra-glycerol by insulin [24]. The metabolic clearance rate of serum insulin during the glucose clamp at the second step was calculated as described previously [16].

Biochemical tests

Serum lipids, specifically FFAs, total cholesterol, high- and low-density lipoprotein cholesterol, and TGs, and liver function tests, namely aspartate aminotransferase, alanine aminotransferase, and gammaglutamyl transferase, were measured using enzymatic methods and ultraviolet methods, respectively (SRL Inc., Tokyo, Japan). Serum HMW-AN concentrations were measured using a 30 enzyme-linked immunosorbent assay (Daiichi Pure Chemicals, Tokyo, Japan).

Statistical analysis

Data are presented as mean ± SD. Data were compared by one-way ANOVA or Kruskal-Wallis analysis for continuous variables as appropriate, and groups were compared using the Tukey-Kramer or Games-Howell post hoc tests. The correlation between parameters was assessed by Pearson or Spearman correlation coefficient, as appropriate. Multiple regression analysis was performed to determine the independent contribution of HMW-AN and ATIS on metabolic parameters. To approximate normal distribution, log-transformed values were used in the analysis, as appropriate.

Results

Correlation analysis of AN and ATIS

The anthropometric data of the total study subjects are shown in Table 2. The mean age of the subjects was 42 years old and the mean values of BMI, IHL, and abdominal visceral fat area were within the normal ranges. Using this data, we first investigated the association of ATIS, median AN level, and body fat composition. As shown in Fig. 1, ATIS was significantly but very modestly correlated with AN level ($r = 0.25$, $P = 0.016$) (Fig. 1). The correlations between ATIS or AN level and body fat composition are shown in Table 1. ATIS was moderately correlated with percent body fat and SFA, while the correlations of AN level with these two body composition indicators were relatively weak. On the other hand, both AN level and ATIS were only weakly correlated with VFA.

Anthropometric characteristics and body compositions of groups defined based on ATIS and AN level

To investigate the association of ATIS and AN level with metabolic abnormalities, we divided the subjects into the following four groups based on the median values of ATIS ($4.05\%/\mu U \cdot mL^{-1}$) and HMW-AN (1.245 μg/mL): High-ATIS/High-AN group (n = 29), High-ATIS/Low-AN group (n = 18), Low-ATIS/High-AN group (n = 18), Low-ATIS/Low-AN group (n = 29).

The anthropometric data in each group are shown in Table 2. All values in the High-ATIS/High-AN group were similar to those in the High-ATIS/Low-AN group. On the other hand, percent body fat and BMI were significantly higher in the Low-ATIS/Low-AN group than in the High-ATIS/High-AN group. In terms of local fat

deposition, while SFA, VFA, and IMCL were comparable among the four groups, IHL was significantly higher in the Low-ATIS/Low-AN group than in the High ATIS/High-AN and High-ATIS/Low-AN groups. In addition, the IHL level in the Low-ATIS/High-AN group was numerically intermediate between that of the two High-ATIS groups and that of the Low-ATIS/Low-AN group (Figure 2). Also, liver function tests including aspartate aminotransferase and alanine aminotransferase were higher in the Low-ATIS/Low-AN group than in the two High-ATIS groups. Furthermore, the TG level in the Low-ATIS/Low-AN group was significantly higher than those in the other three groups, and the TG level in the Low-ATIS/High-AN group was significantly higher than that in the High-ATIS/High-AN group (Figure 2). Conversely, the high-density lipoprotein cholesterol (HDL-C) level in the Low-ATIS/Low-AN group was significantly lower than those in the other three groups (Figure 2).

Regarding glucose metabolism parameters, fasting glucose levels were similar among all four groups; however, compared with the High-ATIS groups, the Low-ATIS groups showed a significantly higher area under the curve (AUC) for insulin during OGTT. In addition, the Low-ATIS/Low-AN group had a significantly higher AUC for glucose during OGTT than the High-AN groups, and the HbA1c level in the Low-ATIS/Low-AN group was significantly higher than that in the High-ATIS/High-AN group. VO_2peak was lower in the Low-ATIS/Low-AN group than in the two High-ATIS groups.

Insulin sensitivity in muscle and liver as evaluated by glucose clamp

We evaluated insulin sensitivity in muscle and liver by the gold standard method: two-step hyperinsulinemic euglycemic clamp (Table 3). Both parameters were similar in the High-ATIS/High-AN group and the High-ATIS/Low-AN group. However, muscle

insulin sensitivity, defined as Rd/SS_{SI} at the second step, was significantly lower in the Low-ATIS groups than in the High-ATIS groups. The metabolic clearance rate of serum insulin also showed a similar tendency. On the other hand, hepatic insulin sensitivity, defined as %reduction of EGP/SS_{SI} at the first step, was lower in the Low-AN/Low-ATIS group than in the High-AN/High-ATIS group.

Single and multiple regression analyses

To further evaluate the independent contribution of HMW-AN and ATIS on IHL, TG and HDL-C, we performed single and multiple regression analyses using potential confounders including BMI, percent body fat and VO_2peak, which are known to be associated with not only TG, HDL-C and IHL [13, 25-27], but AN and ATIS [2, 28, 29]. As shown in Table 4, single correlation analysis revealed that both ATIS and HMW-AN were significantly correlated to IHL, TG and HDL-C, respectively. Both percent body fat and VO_2peak significantly correlated to IHL and TG, but not to HDL-C, while BMI did not significantly correlate to any of those parameters. As shown in Table 5, multiple regression analysis revealed that ATIS was a significant independent variable for IHL, TG and HDL-C. HMW-AN was a significant independent variable for both TG and HDL-C, while it was tended to be independently associated with IHL ($\beta = -0.198$, $p = 0.061$). Other variables, including BMI, percent body fat and VO_2peak, were not significant independent variable for IHL, TG or HDL-C.

Discussion

Although decreased AN level and impaired ATIS are associated with metabolic abnormalities, it has been unclear how the various combinations of high and low AN levels and ATIS values are associated with metabolic abnormalities in non-obese Japanese men. The present study showed that the High-ATIS/High-AN group had similar metabolic characteristics as the High-ATIS/Low-AN group. On the other hand, lower muscle insulin sensitivity was observed in the Low-ATIS groups than in the High-ATIS groups, while hepatic insulin sensitivity was reduced in the Low-ATIS/Low-AN group compared with the High-ATIS/High-AN group. Furthermore, the IHL level in the Low-ATIS/Low-AN group was higher than those in the High-ATIS groups, while that in the Low-ATIS/High-AN group was numerically intermediate between those in the Low-ATIS/Low-AN group and High-ATIS groups. In addition, the Low-ATIS/Low-AN group demonstrated a significantly higher fasting serum TG level and a significantly lower HDL-C level than the other 3 groups. These data suggest that AN level was not associated with metabolic characteristics in non-obese Japanese men with high ATIS. On the other hand, the subjects with low ATIS showed reduced muscle insulin resistance, and the coexistence of low ATIS and low AN level was associated with hepatic insulin resistance and multiple metabolic abnormalities as represented by fatty liver and dyslipidemia.

The present study showed a very modest correlation between ATIS and AN level (Figure 1). In addition, impaired ATIS was correlated with increased body fat, which is consistent with the hypothesis that increased adipocyte TG stores cause adipose tissue insulin resistance [1 4 5]. On the other hand, AN level was also correlated with body fat; however, the correlation coefficient was relatively low compared with that of ATIS (Table 1). Like impaired ATIS, decreased circulating AN levels are caused by adipocyte

hypertrophy [9] [30], and thus serum AN levels are generally lower in obese individuals; however, there is a large variation in serum AN levels even in this population. In fact, a previous study in a mixed population of obese and non-obese subjects showed that the serum AN level was only weakly correlated with body fat ($r = -0.27$, $P = 0.02$) [23]. That study suggested that genetic polymorphisms in the AN gene may be an obesity-independent determinant of the serum AN level. Hara et al. identified SNP276 (TT, GT, and GG genotypes) in intron 2 of the AN gene, and 65% of Japanese are known to have the GG genotype [31]. Interestingly, subjects with the GG genotype had significantly lower serum AN levels and insulin sensitivity than those with the TT genotype [31]. Thus, in non-obese Japanese, AN levels are affected by genetic polymorphisms in the AN gene as well as by body fat composition, which may partly explain why AN was only modestly correlated with body fat.

We found that the IHL level in the Low-AN/Low-ATIS group was higher than those in the High-ATIS groups, while that in the Low-ATIS/High-AN group was numerically intermediate between those in the Low-ATIS/Low-AN group and High-ATIS groups. In addition, the TG level in the Low-ATIS/Low-AN group was significantly higher than those in the other 3 groups, and that in the Low-ATIS/High-AN group was significantly higher than that in the High-ATIS/High-AN group (Figure 2). In this regard, it was shown that ATIS was negatively correlated with IHL in non-obese non-diabetic subjects [23], which is consistent with the fact that circulating FFAs are the main source of accumulated TGs in the liver [32]. On the other hand, in obese mice, AN reduced ectopic lipid accumulation in muscle and liver by enhancing fat oxidation [6] [7] [8] [10] [11]. Meta-analysis revealed that NAFLD patients have lower AN compared with controls [33] and large cohort study showed that low AN level was an independent predictor of NAFLD incidence in

316 Chinese [12]. In the present study, multiple regression analysis showed non-significant
317 (p=0.061) association between AN and IHL (Table 5) after adjustment for potential
318 confounders including BMI, percent body fat and VO_2peak; however, we cannot deny the
319 possibility that this is due to type II error because of small number of subjects. In addition,
320 TG release from the liver was enhanced in parallel with IHL accumulation [34]. These
321 studies suggest that impaired ATIS and decreased AN levels induce IHL accumulation
322 and TG elevation through different mechanisms, and thus the coexistence of low ATIS
323 and a low AN level was associated with a significant increase in IHL and TGs.

324 In the present study, the Low-ATIS groups demonstrated greater impairment in
325 muscle insulin sensitivity and higher insulin levels during OGTT than the High-ATIS
326 groups. On the other hand, AUC-glucose during OGTT was higher in the Low-
327 ATIS/Low-AN group than in the Low-ATIS/High-AN group. These differences might
328 contribute to the finding that the Low-ATIS/Low-AN group, but not the Low-ATIS/High-
329 AN group, had a higher IHL level than the High-ATIS groups and a higher TG level than
330 the other 3 groups. Accordingly, *de novo* lipogenesis (DNL) is thought to account for
331 ~20–40% of liver fat accumulation [32 35], and increased hepatic DNL is therefore a major
332 mechanism of IHL accumulation [32 36]. It has also been suggested that muscle insulin
333 resistance enhances DNL by increasing glucose flow to the liver [35]. In this regard, hepatic
334 DNL may be enhanced by glucose and insulin through the activation of carbohydrate
335 response element–binding protein and sterol regulatory element–binding protein 1c,
336 respectively [37]. In fact, recent research demonstrated that 24-h glucose and insulin levels
337 were correlated with DNL [35]. Thus, characteristics of the Low-ATIS groups, including
338 muscle insulin resistance and higher insulin levels, are likely to promote DNL. In addition,
339 the higher glucose level in the Low-AN/Low-ATIS group might further enhance DNL,

resulting in higher levels of IHL and TG in the group.

Previous studies demonstrated that AN level is positively associated with HDL-C level [38]. For example, in non-obese healthy Koreans, the AN level was significantly correlated with the HDL-C level independent of various parameters such as BMI and the index of insulin sensitivity [39]. In addition, many studies have suggested that insulin resistance is closely associated with low HDL-C [25 40], probably thorough several mechanisms such as decreased lipoprotein lipase activity and enhanced HDL-C clearance [41]. We also previously showed that in non-obese, non-diabetic Japanese men, low HDL-C was associated with impaired insulin sensitivity in muscle and adipose tissue but not in liver [2 17]. These associations between AN level or insulin resistance and HDL-C may explain our finding that the HDL-C level was significantly lower in the Low-ATIS/Low-AN group than in the other three groups; however, it remains unclear why the combined effect of low ATIS and low AN level synergistically decreased the HDL-C level.

The present study showed that only ATIS and AN were significant independent variables for several metabolic abnormalities when we performed multiple regression analysis with BMI, percent body fat and VO_2peak, which are known to be associated with those metabolic abnormalities [13, 25-27]. These results suggested that not increased body fat mass, but adipose tissue dysfunction represented by impaired ATIS and decreased AN level may be more essential causes of metabolic abnormalities in non-obese Japanese men. However, mechanisms of impaired ATIS and decreased AN level in non-obese Asians remain unclear. Further studies are required to elucidate the mechanisms of adipose tissue dysfunction in non-obese Asians.

In the present study, insulin sensitivity in muscle was more impaired in the Low-ATIS groups than in the High-ATIS groups, and AN level was not associated with muscle

insulin sensitivity in the Low-ATIS or High-ATIS groups. These data suggest that impaired ATIS, but not lower AN level, is associated with muscle insulin resistance. Previous studies suggested that AN level was not correlated with insulin sensitivity in either lean subjects [42] or apparently healthy Japanese men [43]. In the present study, we enrolled non-obese Japanese men, and in this limited population AN level was not associated with insulin sensitivity.

The present study has several limitations. First, we did not directly measure FFA kinetics by tracer. The Ra-FFA or Ra-glycerol suppression during glucose clamp has been recognized as the gold standard to evaluate ATIS. Although %FFA suppression during glucose clamp was highly correlated with tracer-determined suppression of Ra-glycerol by insulin (r=0.899) [24], the correlation was not perfect probably because %FFA suppression during glucose clamp reflects both suppressed Ra-FFA and increased Rd-FFA. Secondly, we recruited only non-obese Japanese men. Fat distribution [15] and the frequency of SNP276 mutant alleles of AN differ among races [44]. In addition, fat distribution and metabolism are different in men and women. Thus, our results may not be applicable to women or other ethnic groups.

In conclusion, in non-obese Japanese men with high ATIS, AN level was not associated with metabolic characteristics. On the other hand, subjects with low ATIS showed reduced muscle insulin resistance, and those who also demonstrated decreased AN levels had multiple metabolic abnormalities, represented by fatty liver and dyslipidemia.

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Competing interests statement

The authors have nothing to disclose.

Author contributions

M.K., Y.S., H.K., K.T., and Y.T. researched the data and contributed to study design, data collection, interpretation of results. They also wrote and edited the manuscript. Sao.K., T.F., Y.F., R.S., D.S., Sat.K., M.S., N.Y., M.N-Y., and K.S. participated in data collection and data analysis and contributed to the discussion. H.D., S.A., H.S., and R.K. contributed to the discussion. H.W. contributed to study design and edited the manuscript.

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550 Table 1. Single-correlation analysis of adiponectin and ATIS

	HMW adiponectin		ATIS	
	r	P value	r	P value
Percent body fat	-0.22	0.033	-0.37	< 0.001
Abdominal subcutaneous fat area	-0.21	0.043	-0.37	< 0.001
Abdominal visceral fat area	-0.27	0.009	-0.21	0.044

551 Abbreviations: HMW adiponectin, high-molecular-weight adiponectin; ATIS, adipose tissue insulin sensitivity

552

553 Table 2. Clinical characteristics of the study subjects

	Total	High-ATIS/ High-AN	High-ATIS/ Low-AN	Low-ATIS/ High-AN	Low-ATIS/ Low-AN	P value
Number of subjects	94	29	18	18	29	
Age (years)	41.9±5	42.2±4.4	42.4±5.1	40.1±6	42.6±4.9	.360
BMI (kg/m^2)	23.5±1.0	23.3±0.9	23.3±1.1	23.4±1.1	23.9±0.6†	.026
Percent body fat (%)	21.3±4.4	19.6±4.9	20.4±4	22.5±4.8	22.7±3.2†	.023
Abdominal subcutaneous fat area (cm^2)	118.3±39.1	109.9±42.7	103.9±44.4	123.7±33.4	131.7±31.5	.059
Abdominal visceral fat area (cm^2)	86.4±32.9	74.8±28.7	96±41.7	86.8±29.4	92.2±31.4	.151
Intrahepatic lipid (%)	3.2±4.3	1.2±1.3	1.6±2.8	2.8±4.1	6.1±5.4†‡	<.001
IMCL in TA (S-fat/Cre)	2.9±1.7	2.6±1.8	3.1±2.0	3.1±1.5	3.1±1.6	.518
IMCL in SOL (S-fat/Cre)	13.0±6.8	13.8±8.1	12.7±6.4	10.9±5.7	13.7±6.4	.508
Fasting plasma glucose (mg/dL)	95.7±7.4	94.9±6.4	94.9±7.2	93.6±8.0	98.5±7.7	.110
Fasting serum insulin (μU/mL)	5.7±2.5	4.3±1.3	4.4±2.0	6.1±1.9†	7.5±2.7†‡	<.001
HbA_{1C} (%)	4.9±0.2	4.8±0.3	4.9±0.2	4.9±0.2	5.0±0.2†	.039
Triglycerides (mg/dL)	138.0±76.3	93.7±35.6	104.1±37.7	140.6±55.0†	201.6±91.6†‡§	<.001
Low-density lipoprotein cholesterol (mg/dL)	120.8±27.7	115.0±33.1	117.4±23.5	128.4±24.0	124.1±26.0	.355
High-density lipoprotein cholesterol (mg/dL)	55.4±13.3	59.8±12.0	61.2±16.0	57.1±13.7	46.3±6.4†‡§	<.001
Free fatty acids (μEq/L)	372.1±108.5	330.8±102.8	355.7±115.3	380.3±112.9	420.0±91.0†	.015
High-molecular-weight adiponectin (μg/mL)	1.5±1.2	2.4±1.3	0.7±0.3†	2.1±0.6‡	0.6±0.4†§	<.001
Aspartate aminotransferase (IU/L)	22.1±6.7	20.9±5.1	20.7±6	20.2±6.8	25.3±7.6†‡	.016

Alanine aminotransferase (IU/L)	25.3±14.9	21.1±7.6	19.4±6.9	23.8±11.3	34.1±21.3†‡	.012
γ-glutamyl transferase (IU/L)	44.1±39.7	30.3±17	42.3±39.8	40.3±25.5	61.4±55.5†	.023
AUC-glucose during OGTT (mg·min/dL·10^3)	22219.1±3154.6	20540.7±2830.5	22269.2±2392.0	21820.0±2992.0	24114.3±3064.3†§	<.001
AUC-insulin during OGTT (μU·min/mL·10^3)	7292.9±3806.4	5057.6±2322.6	5297.5±2149.9	7946.7±3449.1†‡	10361.1±3865.3†‡	<.001
C-reactive protein (mg/dL)	606.2±1261.1	658.9±1527	232.1±180.7	747.7±1923.1	672.1±688.2	.053
Physical activity (METs·h/day)	4.7±1.8	5.3±2.0	4.9±2.5	4.1±1.0	4.3±1.4	.062
VO_{2peak} (ml/kg per min)	33.0±7.3	34.0±6.8	36.6±7.9	32.8±9.5	29.9±4.3†‡	<.001

554 Data are expressed as mean±SD.

555 Abbreviations: AN, adiponectin; ATIS, adipose tissue insulin sensitivity; IMCL, intramyocellular lipid; TA, tibialis anterior muscle; SOL, soleus muscle; S-fat,

556 methylene signal intensity; HbA1c, glycosylated hemoglobin; HOMA-IR, the homeostasis model assessment of insulin resistance; AUC, area under the curve;

557 VO_{2peak}, peak oxygen consumption.

558 P value: one-way analysis of variance or Kruskal-Wallis analysis.

559 $P<0.05$: †vs High-ATIS/High-AN, ‡vs High-ATIS/Low-AN, §vs Low-ATIS/High-AN for Tukey-Kramer or Games-Howell post hoc test.

560

Table 3. Hyperinsulinemic euglycemic clamp data

	High-ATIS / High-AN/	High-ATIS / Low-AN/	Low-ATIS / High-AN/	Low-ATIS / Low-AN/	P value
SS_{SI} at first step (μU/mL)	17.7±2.4	17.6±2.7	21.6±3.4†‡	21.9±3.9†‡	<.001
SS_{SI} at second step (μU/mL)	35±5.8	35±5.1	38.7±4.3	42±5.0†‡	<.001
Basal EGP (mg/kg·min^{-1})	2.1±0.2	2.1±0.2	2.1±0.2	2.1±0.2	.432
%reduction of EGP at first step (%)	68.5±19.3	66.9±25.1	67.4±21.4	64.3±14.5	.875
%reduction of EGP/SS_{SI} at first step (%/μU·mL^{-1})	3.9±1.1	3.8±1.3	3.2±1	3.0±0.7†	<.001
Rd at second step (mg/kg FFM·min^{-1})	9.3±1.7	8.8±1.7	7.3±2.2†	6.0±1.9†‡	<.001
Rd/SS_{SI} at second step (mg/kg FFM·min^{-1}/μU·mL^{-1})	0.27±0.05	0.26±0.08	0.19±0.06†‡	0.15±0.05†‡	<.001
%FFA suppression at first step (%)	85.8±7.9	84.6±5.7	72.6±17.2†‡	69.2±11.9†‡	<.001
%FFA suppression/insulin at first step (%/μU·mL^{-1})	5.0±0.8	5.2±1.3	3.2±0.7†‡	3.1±0.6†‡	<.001
MCRI at first step (mL/min per m^2)	576.4±84.1	581.9±101.1	474.1±74.1†‡	472±103.3†‡	<.001
MCRI at second step (mL/min per m^2)	588.1±107.7	584.6±93.7	521.3±55.2†	483.7±55.7†‡	<.001

Data are expressed as mean±SD.

Abbreviations: AN, high-molecular-weight adiponectin; ATIS, adipose tissue insulin sensitivity; SS_{SI}, steady-state serum insulin; EGP, endogenous glucose production; Rd, rate of disappearance; MCRI, metabolic clearance rate for serum insulin.

P value: one-way analysis of variance or Kruskal-Wallis analysis.

P<0.05: †vs High-ATIS/High-AN, ‡vs High-ATIS/Low-AN for Tukey-Kramer or Games-Howell post hoc test.

567 Table 4. Single-correlation analysis of intrahepatic lipid, triglyceride and HDL-C

	Intrahepatic lipid		Triglyceride		HDL-C	
	r	P value	r	P value	r	P value
BMI (kg/m^2)	0.156	0.149	0.194	0.061	-0.165	0.111
Percent body fat (%)	0.224	0.037	0.257	0.012	-0.195	0.060
VO_{2peak} (mL/kg per min)	-0.221	0.044	-0.319	0.002	0.141	0.186
ATIS	-0.504	<0.001	-0.454	<0.001	0.326	0.001
HMW adiponectin	-0.335	0.001	-0.424	<0.001	0.302	0.003

568 Abbreviations: HDL-C, High-density lipoprotein cholesterol; VO_{2peak}, peak oxygen consumption; HMW adiponectin, high-molecular-weight adiponectin; ATIS, adipose

569 tissue insulin sensitivity

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571

572 Table 5. Multiple linear regression analysis of intrahepatic lipid, triglyceride and HDL-C

Dependent variable	Independent variable	B	SE	β	P value
Intrahepatic lipid (r^2 = 0.244)	Intercept	-0.783	2.021		0.700
	BMI (kg/m^2)	0.073	0.089	0.100	0.414
	Percent body fat (%)	0.000	0.022	-0.001	0.992
	VO_{2peak} (mL/kg per min)	0.002	0.012	0.018	0.871
	ATIS	-0.232	0.068	-0.376	0.001
	HMW adiponectin	-0.340	0.179	-0.198	0.061
Triglyceride (r^2 = 0.319)	Intercept	2.262	0.562		<0.001
	BMI (kg/m^2)	0.006	0.025	0.027	0.800
	Percent body fat (%)	0.001	0.006	0.016	0.888
	VO_{2peak} (mL/kg per min)	-0.004	0.003	-0.125	0.239
	ATIS	-0.053	0.018	-0.315	0.004
	HMW adiponectin	-0.169	0.051	-0.313	0.001
HDL-C (r^2 = 0.174)	Intercept	81.457	37.347		0.032
	BMI (kg/m^2)	-1.485	1.648	-0.106	0.370
	Percent body fat (%)	-0.007	0.383	-0.002	0.985
	VO_{2peak} (mL/kg per min)	-0.079	0.215	-0.043	0.713
	ATIS	2.828	1.175	0.279	0.018
	HMW adiponectin	7.537	3.386	0.231	0.029

573 Abbreviations: HDL-C, High-density lipoprotein cholesterol; VO_{2peak}, peak oxygen consumption; HMW adiponectin, high-molecular-weight adiponectin; ATIS, adipose

574 tissue insulin sensitivity; B, the unstandardized β; β, standardized β

Figure Legends

Figure 1.

Relation between high-molecular-weight (HMW) adiponectin level and adipose tissue insulin sensitivity (ATIS) in all subjects.

Figure 2.

Intrahepatic lipid levels in groups defined by the median adipose tissue insulin sensitivity (ATIS) and median high-molecular-weight adiponectin (AN) level

$p<0.05$: †vs High-ATIS/High-AN, ‡vs High-ATIS/Low-AN, §vs Low-ATIS/High-AN for Games-Howell post hoc test.

Figure 1

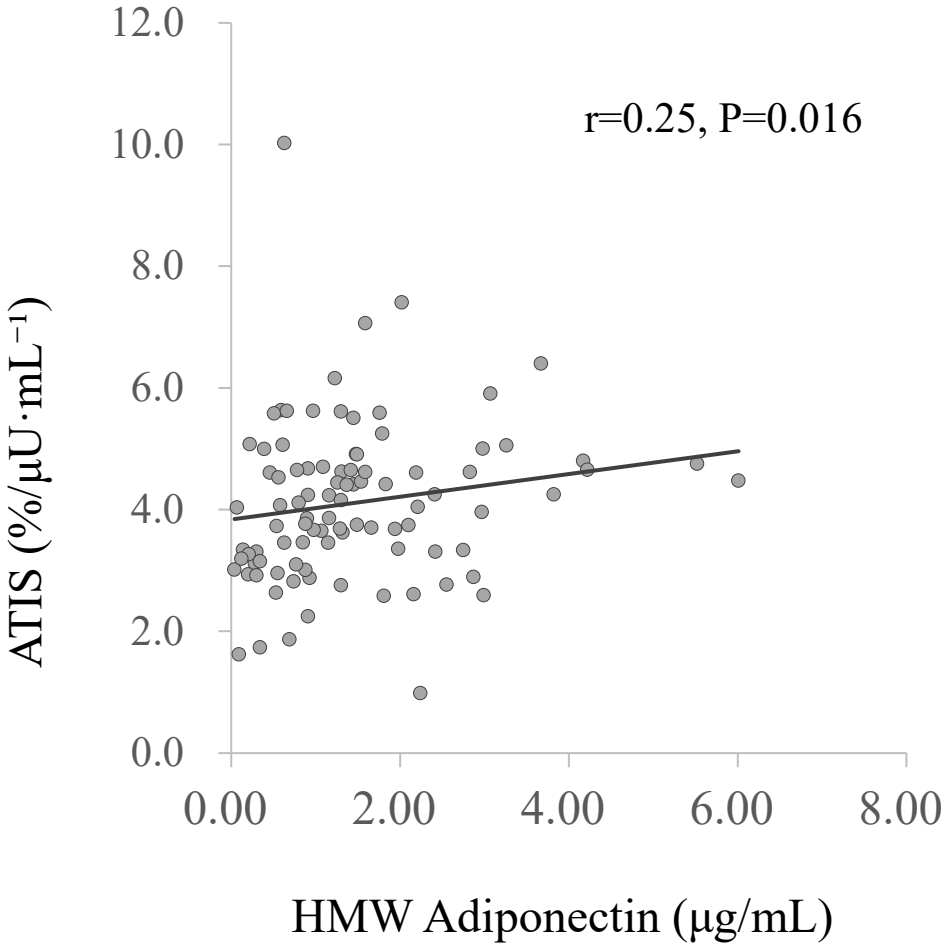
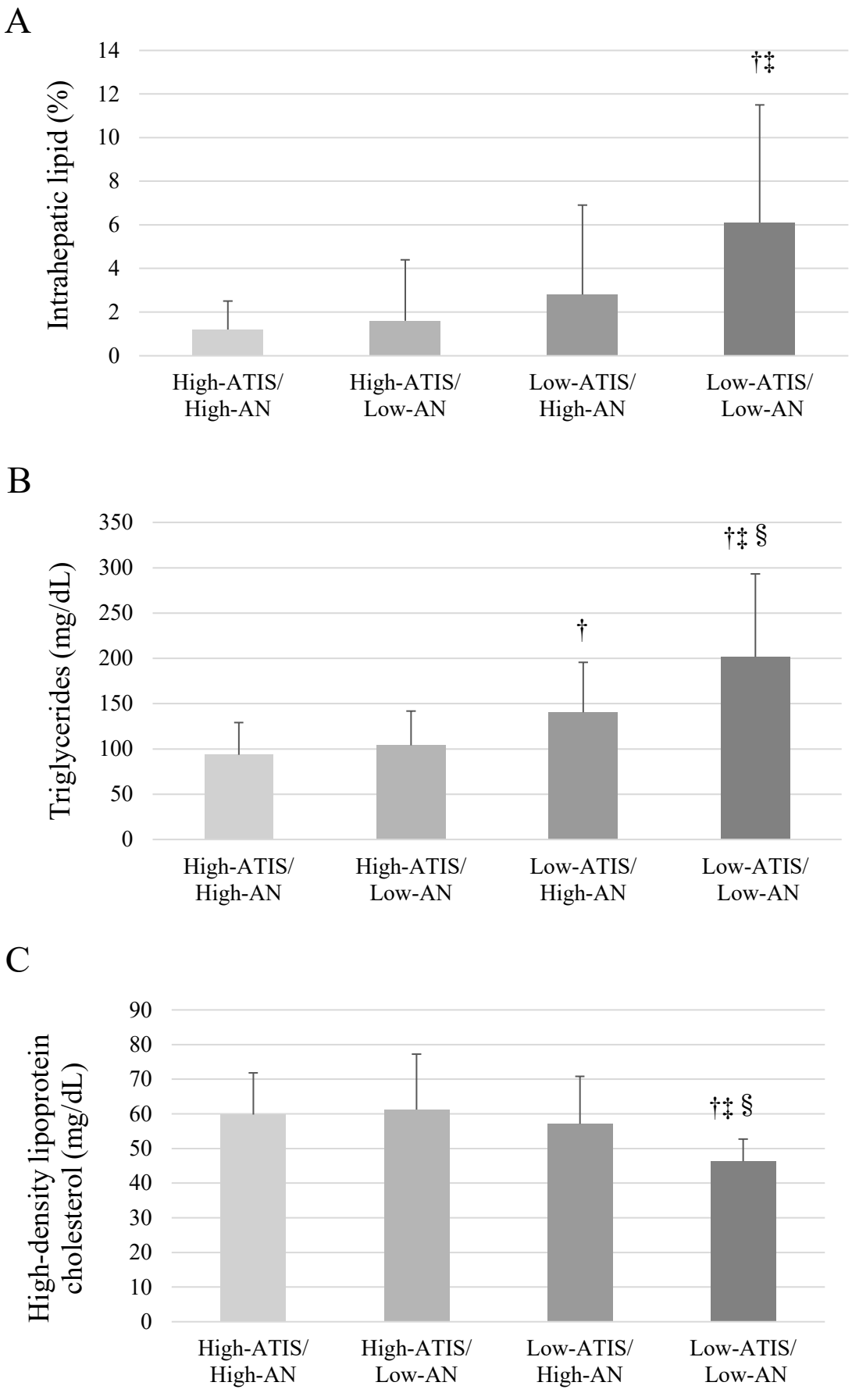

12.0
10.0
8.0
6.0
4.0
2.0
0.0
ATIS (%/μU·mL⁻¹)
r=0.25, P=0.016
0.00
2.00
4.00
6.00
8.00
HMW Adiponectin (μg/mL)

Figure 2


A
Intrahepatic lipid (%)
14
12
10
8
6
4
2
0
†‡
High-ATIS/ High-AN
High-ATIS/ Low-AN
Low-ATIS/ High-AN
Low-ATIS/ Low-AN
B
Triglycerides (mg/dL)
350
300
250
200
150
100
50
0
†‡ §
†
High-ATIS/ High-AN
High-ATIS/ Low-AN
Low-ATIS/ High-AN
Low-ATIS/ Low-AN
C
High-density lipoprotein cholesterol (mg/dL)
90
80
70
60
50
40
30
20
10
0
†‡ §
High-ATIS/ High-AN
High-ATIS/ Low-AN
Low-ATIS/ High-AN
Low-ATIS/ Low-AN