Yamada et al., J Metabolic Synd 2016, 5:4
DOI: 10.4172/2167-0943.1000215

Journal of Metabolic Syndrome
ISSN: 2167-0943

Short Communication OMICS International

Close Association of Hypoadiponectinemia and Increased Insulin Resistance in Non-Obese Japanese Type 2 Diabetes with Visceral Adiposity

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Abstract

Objective: Visceral fat accumulation because of obesity plays a central role in metabolic syndrome and causes cardiovascular disease (CVD).

Methods: The aims of this study were to investigate associations between visceral fat accumulation and adipokines in non-obese type 2 diabetic patients.

Results: In total, 138 type 2 diabetic patients were enrolled, with a mean age of 64 years. Among the participants, 69 were males. We found that serum high-molecular-weight adiponectin level was decreased, C-reactive protein increased, and using homeostatic model assessment of insulin resistance was also increased in non-obese patients with visceral adiposity (body mass index: BMI, <25 kg/m^2; visceral fat area: VFA, ≥ 100 cm^2) compared with those without visceral adiposity (BMI, <25 kg/m^2, VFA, <100 cm^2). VFA in non-alcoholic fatty liver disease (NAFLD) was higher than in those with no NAFLD.

Conclusion: We demonstrated that visceral fat accumulation is a risk for CVD in non-obese diabetic patients with visceral adiposity.

Keywords: Adipokine; Insulin resistance; Diabetes; Non-alcoholic fatty liver disease; Visceral fat; Metabolic syndrome

Introduction

Visceral fat accumulation is a central pathophysiologic characteristic of metabolic syndrome [1]. It is well known that visceral adiposity increases pro-inflammatory adipokines, such as interleukin-6 and release of plasminogen activator inhibitor type 1 from adipocytes. It also decreases adiponectin, which is a protective protein for atherosclerosis and insulin resistance [1]. In Japan, obesity is defined as a body mass index (BMI) of ≥ 25 kg/m^2; however, Okauchi et al. reported that non-obese people with visceral adiposity (visceral fat area, VFA, ≥ 100 cm^2 and BMI, <25 kg/m^2) showed significantly more metabolic risk factors than obese individuals without visceral adiposity (VFA, <100 cm^2 and BMI, ≥ 25 kg/m^2) [2]. Furthermore, in Japanese patients with non-obese type 2 diabetes, adiposity was a strong predictor of non-alcoholic fatty liver disease (NAFLD) [3]. Indeed, a meta-analysis revealed that Japanese people accumulate visceral fat more easily compared with Caucasian populations [4]. Therefore, even if BMI is <25 kg/m^2, visceral adipose accumulation could cause systemic inflammatory changes and cardiovascular risk in Japanese populations. However, evaluation of adipokine levels and insulin resistance is not enough. The aims of this study were to elucidate (i) the degree of inflammation and insulin resistance in non-obese Japanese type 2 diabetic patients with visceral adiposity and (ii) the relationship between fatty liver and VFA.

Materials and Methods

Participants

The study enrolled Japanese type 2 diabetic patients who had been hospitalized to control their diabetes at the Jichi Medical University Saitama Medical Center. We excluded patients receiving hemodialysis and those with infectious diseases (including hepatitis B and C), malignancies, and pregnancy. The occurrence of diabetic retinopathy was confirmed by an ophthalmologist.

Measurements

We collected blood samples after overnight fasting into tubes, which were centrifuged at 3,000 rpm at 4°C for 15 min. The supernatants were stored at -80°C. We measured serum retinol-binding protein 4 (RBP4), serum high-molecular-weight (HMW) adiponectin, and serum interleukin-18 (IL-18) by ELISA using Human RBP4 (AdipoGen, Seoul, Korea); Human HMW adiponectin (Fuji Rebio, Tokyo, Japan); and Human IL-18 (MBL, Nagoya, Japan) ELISA kits. In addition, we measured aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GPT) and the following lipid parameters, total cholesterol (TC), high-density lipoprotein (HDL-C) and triglyceride (TG) in the central laboratory section of the Jichi Medical University Saitama Medical Center using standard techniques. We measured visceral and subcutaneous fat area (SFA) by abdominal CT scan using a horizontal view at the level of the navel. To detect fatty liver, we performed abdominal ultrasonography. If fatty liver was present, NAFLD was defined if daily alcohol consumption was <30 g/day for men and <20 g/day for women. We divided participants into four groups: (A) BMI, <25 kg/m^2 and VFA, <100 cm^2; (B) BMI, <25 kg/m^2 and VFA, ≥ 100 cm^2; (C) BMI, ≥ 25 kg/m^2 and VFA, ≥ 100 cm^2; and (D) BMI, ≥ 25 kg/m^2 and VFA, <100 cm^2. The study was approved by

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Received September 26, 2016; **Accepted** October 07, 2016; **Published** October 14, 2016

Citation: Yamada H, Suzuki D, Kakei M, Kusaka I, Ishikawa S (2016) Close Association of Hypoadiponectinemia and Increased Insulin Resistance in Non-Obese Japanese Type 2 Diabetes with Visceral Adiposity. J Metabolic Synd 5: 215. doi: 10.4172/2167-0943.1000215

the Ethics Committee at the Jichi Medical University Saitama Medical Center (No. 13-95) and performed in compliance with the Declaration of Helsinki. We obtained written consent from participants.

Statistical analysis

Data are expressed as means ± SD, and skewed variables are described as medians with an interquartile range. We compared three groups using one-way ANOVA or a Kruskal–Wallis test and categorical variables using Fisher's exact test. The *post-hoc* analysis was performed as needed (Holm test). All analyses were performed using EZR (Jichi Medical University Saitama Medical Center), a graphical user interface for R (The R Foundation for Statistical Computing, ver. 2.13.0) and a modified version of the R commander (ver. 1.6-3) that was designed to add statistical functions frequently used in biostatistics [5]. A value of $p<0.05$ was considered significant.

Results

The study enrolled 138 participants with type 2 diabetes. Their characteristics are described in Table 1. There were 40 patients in group (A), 45 in group (B), 50 in group (C), and three in group (D). BMI showed positive correlation with VFA (Figure 1a). There are significant differences in the homeostatic model assessment of insulin resistance (HOMA-IR), serum C-reactive protein (CRP), and HMW adiponectin. HOMA-IR and serum CRP were significantly elevated in groups (B) and (C), whereas serum HMW adiponectin level was lower in group (B) (Figures 1b–1d). Alcohol consumption and abdominal ultrasonography identified 64 patients without fatty liver, 41 patients with NAFLD, and 33 patients with alcoholic fatty liver. Patients with NAFLD had higher VFA but lower plasma HMW adiponectin compared with those with no NAFLD (Table 2).

Discussion

We showed that visceral adiposity without obesity was related to high insulin resistance, high CRP levels, and hypoadiponectinemia in type 2 diabetes. Diabetes is a major risk factor for cardiovascular disease (CVD). This study revealed that diabetic patients with visceral adipose accumulation might be in a higher risk state for CVD than those without visceral adiposity. Fukuda et al. reported the visceral fat accumulation related to progression of systemic arteriosclerosis and hypoadiponectinemia in Japanese type 2 diabetic populations [6]. There was no significant difference in prevalence of CVD between non-obese participants with abdominal obesity (defined by waist circumference) and obese participants with obesity [7]. It is well known that the Japanese capacity for insulin secretion is low compared with Caucasian populations, and absence of obesity is a typical clinical feature of Japanese diabetics. Recent increases in obesity are associated with a prevalence of diabetic patients in Asia, even in mild weight gain [8]. In Japanese Americans, changes in diet and physical activity have resulted in visceral fat accumulation and overt diabetes [8]. The American Diabetes Association recommends the use of BMI ≥ 23 kg/m^2 to test for diabetes in Asian American adults [9]. Taken together with these other findings, our study suggests that non-obese Japanese people with visceral adiposity are at risk of diabetes. We believe that visceral fat accumulation led to high CRP, high HOMA-IR, and hypoadiponectinemia in our study population.

Furthermore, VFA was higher in the NAFLD group than in the non-NAFLD group. Some previous studies suggested that visceral adiposity was correlated with liver attenuation, a marker of steatosis in non-obese type 2 diabetic patients [3] and significantly increased in NAFLD [10], although serum adiponectin levels were decreased [11]. Our findings on serum adiponectin level in NAFLD were not inconsistent with these previous studies. Adiponectin prevents hepatic

Groups	All subjects	(A)	(B)	(C)	(D)	p value
Age (years)	64 ± 12	65 ± 11	64 ± 10	63 ± 13	43 ± 17	0.100
Sex (male), n (%)	69 (50)	22 (55)	28 (62)	17 (34)	2 (67)	0.020
BMI (kg/m²)	24 ± 4.1	21 ± 2.5	23 ± 1.1	29 ± 2.7	30 ± 4.7	<0.001
Durations of Diabetes (years)	11.7 ± 8.5	12 ± 8.6	12 ± 9.3	11 ± 11.9	6.3 ± 1.1	0.628
Current smoker, n (%)	20 (14)	7 (18)	5 (11)	7 (14)	1 (33)	0.124
Fatty liver, n (%)	74 (54)	7 (18)	27 (60)	37 (74)	3 (100)	<0.001
SBP (mmHg)	135 ± 18	132 ± 17	137 ± 20	135 ± 18	121 ± 17	0.396
DBP (mmHg)	75 ± 11	73 ± 11	74 ± 11	77 ± 10	85 ± 5	0.124
eGFR (mL/min/1.73 m² 3	77 ± 25	79 ± 27	75 ± 25	77 ± 24	95 ± 30	0.532
HbA1c (%)	8.6 (7.8-9.7)	8.8(7.8-10.1)	8.4 (7.7-9.6)	8.6 (7.9-9.5)	8.4 (8.4-9.9)	0.864
Diabetic Retinopathy, n (%)	66 (48)	21 (53)	24 (53)	21 (42)	0 (0)	0.226
VFA (cm²)	128 ± 59	62 ± 25	133 ± 26	180 ± 47	82 ± 3	<0.001
SFA (cm²)	170 ± 85	100 ± 58	149 ± 43	240 ± 71	233 ± 174	<0.001
AST (IU/L)	22 (17-31)	19 (17-23)	21 (17-30)	26 (20-32)	19 (17-22)	0.004
ALT (IU/L)	23 (17-35)	18 (12-28)	23 (16-32)	30 (19-40)	34 (24-37)	0.007
γ-GTP (IU/L)	27 (17-53)	20 (14-31)	30 (17-62)	34 (23-57)	60 (34-61)	0.022
TC (mg/dL)	197 (170-231)	194 (161-219)	195 (170-243)	176 (127-240	174 (161-201)	0.275
HDL-C (mg/dL)	47 ± 13	53 ± 14	44 ± 11	46 ± 13	37 ± 2	0.006
TG (mg/dL)	129 (97-186)	99 (79-121)	145 (106-211)	163 (114-210)	127 (114-232)	<0.001
RBP-4 (μg/mL)	65 (47-82)	67 (44-82)	61 (49-81)	68 (48-83)	42 (36-71)	0.870
IL-18 (pg/mL)	230 (177-339)	195 (171-274)	259 (185-354)	246 (188-366)	195 (163-199)	0.071

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1c: Glycated Hemoglobin; VFA: Visceral Fat Area; SFA: Subcutaneous Fat Area; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; γ-GPT: γ-Glutamyl Transpeptidase; TC: Total Cholesterol; HDL-C: High-Density Lipoprotein; TG: Triglyceride; RBP-4: Retinol-Binding Protein 4; IL-18: Interleukin-18

Table 1: Characteristics of all subjects and each group of (A) to (D).

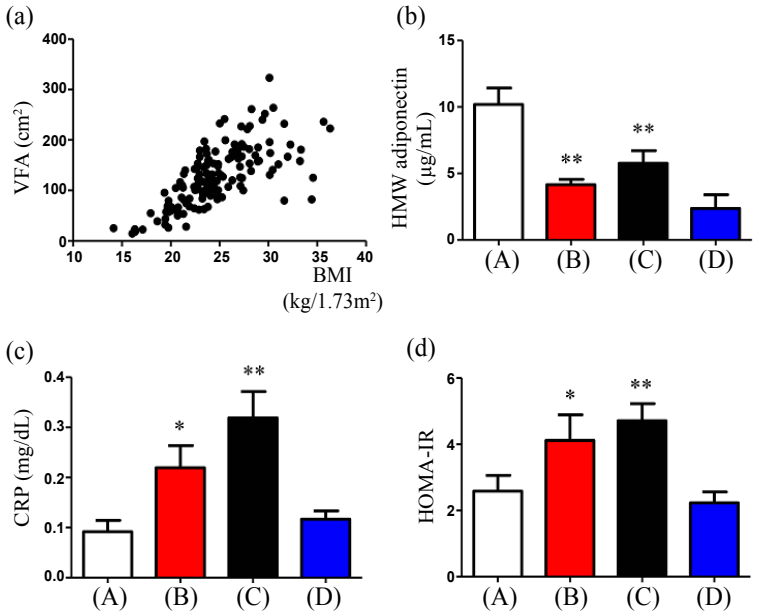

Figure 1: (a) Positive correlation between (body mass index) BMI and VFA (visceral fat area) (r=0.725, p<0.001), and (b–d) serum HMW (high-molecular-weight) adiponectin, CRP (C-reactive protein), and HOMA-IR (increased, and using homeostatic model assessment insulin resistance) in four divided categories from (A) to (D). *p<0.05 *vs.* (A), **p<0.01 *vs.* (A) by *post-hoc* analysis (Holm test) after Kruskal–Wallis test (p<0.05).

	Non-NAFLD	NAFLD	p value
Age (years)	67 ± 10	63 ± 14	0.293
Sex (male) n, (%)	32 (50)	14 (34)	0.104
BMI (kg/m²)	22.6 ± 3.8	26.3 ± 3.5	<0.001
HbA1c (%)	8.5 (7.5-9.4)	8.5 (7.9-9.8)	0.325
HOMA-IR	2.1 (1.2-3.2)	3.4 (2.2-5.2)	<0.001
VFA (cm²)	101 ± 58	151 ± 50	<0.001
SFA (cm²)	133 ± 75	201 ± 81	<0.001
AST (IU/L)	19 (16-23)	26 (19-31)	<0.001
ALT (IU/L)	17 (13-22)	30 (19-40)	<0.001
γ-GT (IU/L)	19 (15-29)	31 (20-57)	0.004
TC (mg/dL)	192 (159-221)	191 (170-228)	0.506
HDL-C (mg/dL)	50 ± 15	45 ± 12	0.060
TG (mg/dL)	98 (80-122)	162 (127-202)	<0.001
CRP (mg/mL)	0.05 (0.03-0.21)	0.27 ± 0.34	0.015
RBP-4 (μg/mL)	67 (45-81)	63 (43-83)	0.964
IL-18 (μg/mL)	193 (167-316)	257 (205-367)	0.003
HMW adiponectin (μg/mL)	5.6 (3.3-12.3)	3.0 (1.8-6.0)	0.002

BMI: Body Mass Index; HbA1c: Glycated Hemoglobin; HOMA-IR: Homeostasis Model Assessment of Insulin Resistant; VFA: Visceral Fat Area; SFA: Subcutaneous Fat Area; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; γ-GPT: γ-Glutamyl Transpeptidase; TC: Total Cholesterol; HDL-C: High-Density Lipoprotein; TG: Triglyceride; CRP: C-Reactive Protein; RBP-4: Retinol-Binding Protein 4; IL-18: Interleukin-18; HMW: High-Molecular-Weight

Table 2: Differences of characteristics and clinical metabolic parameters in non-NAFLD and NAFLD group.

inflammation and fibrosis [12], so hypoadiponectinemia induced by visceral fat accumulation may not decelerate liver fibrosis in patients with NAFLD [13].

There are some limitations in this study. First, this study had a small number of patients and is a retrospective observational study. We could not analyze differences between male and female participants because of the small sample size. Second, we did not perform liver biopsies to determine NAFLD histologically. Third, the enrolled participants were uncontrolled type 2 diabetic patients who need admission for control of their diabetes. To avoid the resulting biases, further study will be needed.

In conclusion, we demonstrated that visceral fat accumulation is associated with high insulin resistance and hypoadiponectinemia in non-obese Japanese type 2 diabetic patients. We need to be aware that visceral adiposity is a high risk state for CVD, even if the BMI in Japanese individuals is <25 kg/m².

Acknowledgment

The authors thank Taeko Otani for the assistance with the ELISA technique. The authors would like to thank Enago for the English language review.

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