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Original research

Effects of microvascular complications on structural changes in visceral and subcutaneous adiposity among type 2 diabetes patients

Shuhei Nakanishi [a,*], Rui Kishimoto [a], Aya Hamaoka [a], Chihiro Nagano [a], Mitsue Miyahara [a], Fumio Sawano [b]

[a] *Endocrinology and Metabolism, Department of Internal Medicine, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Japan*
[b] *Sawano Thyroid and Diabetes Specialized Clinic, Japan*

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ABSTRACT

Purpose: The aim of this study was to clarify the effects of diabetic microvascular complications on changes in visceral-fat-area-(VFA)-to-subcutaneous-fat-area (SFA) ratio (V/S ratio) during hospitalization among type 2 diabetes patients.
Procedures: The study participants totaled 72 men and 82 women who were hospitalized for treatment of type 2 diabetes. Analysis was made of associations between retinopathy categorized by ophthalmologists, nephropathy diagnosed by albuminuria (mg/gCr), and neuropathy diagnosed by coefficient of R–R interval variation in ECG (CVRR) (%), as well as changes in V/S ratio during hospitalization, measured with computed tomography.
Main findings: Mean age of the study participants was 61.7 ± 13.6 years. Mean HbA1c was 9.77 ± 2.14%. Stages of retinopathy, urinary albumin dose, and CVRR showed a significant association with reduction in V/S ratio in Cox proportional hazards models after adjustment for age, sex, initial HbA1c, and BMI, with the hazards ratios for the conditions being 0.708 (95% CI 0.529–0.947), 0.864 (0.762–0.980), and 1.450 (1.019–2.062), respectively.
Principal conclusions: These results suggest the possibility that subjects with diabetes microvascular complications may be resistant to decreased visceral fat compared with subcutaneous fat. Microvascular complications themselves may thus play an important role in visceral fat accumulation.

1. Introduction

Obesity is known to induce low-grade inflammation and insulin resistance (Hirosumi et al., 2002; Pou et al., 2007), conditions that make difficult the treatment of type 2 diabetes. In particular, the accumulation of visceral fat plays a central role in diseases relating to obesity, such as glucose intolerance, lipid abnormality, atherosclerosis (Kishida et al., 2012), and so on. Visceral-to-subcutaneous ratio (V/S ratio), in addition to visceral fat area (VFA) itself, is the index generally used to describe abdominal fat distribution, and carefully monitoring these indices can help control blood glucose level in type 2 diabetes. Fujioka et al. (1987) reported that V/S ratio is significantly correlated with plasma glucose, insulin, triglyceride, and total cholesterol levels. Furthermore, a recent study reported that the ratio between these two abdominal fat deposits is crucial in predicting the development of an unfavorable metabolic profile (Taksali et al., 2008), suggesting that individuals with a high proportion of visceral fat relative to abdominal subcutaneous fat have more adverse metabolic profiles compared to those with the opposite phenotype (Taksali et al., 2008).

Diabetic retinopathy, nephropathy, and neuropathy are generally common microvascular complications of type 2 diabetes. In addition, with the worldwide increase in prevalence of diabetes in recent years, such complications are becoming serious problems that can harm and create downstream effects in terms of both quality of life and obesity in patients with type 2 diabetes mellitus. Diabetic retinopathy is a serious cause of blindness in industrialized countries (Congdon et al., 2003). Moreover, retinopathy is reported to be associated with blood pressure, lipid concentrations, and BMI (van Leiden et al., 2002). Diabetic nephropathy is the leading cause of end-stage renal disease (Ahmad, 2015). In addition, large epidemiological studies have revealed an association between BMI

* Corresponding author. Postal address; Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, 1-9-6, Senda-machi, Naka-ku, Hiroshima 730-8619, Japan. Tel.: +81 82 241 3111; fax: +81 82 246 0676.
E-mail address: n-shuhei@umin.net (S. Nakanishi).

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and kidney disease as well as hypertension and other cardiovascular disease risk factors (Bayliss et al., 2012). The constellation of symptoms surrounding diabetic neuropathy affects patient quality of life, both physically and psychologically (Callaghan et al., 2012). In addition, obesity is a significant factor in increased risk of peripheral neuropathy, independent of glucose control (Smith and Singleton, 2013).

Accordingly, preventing visceral fat accumulation through diet and exercise is important for controlling glucose level, leading to the prevention of these complications and maintenance of the quality of life among subjects with type 2 diabetes. In brief, weight loss has been suggested to delay the onset of diabetic complications in obese subjects. Conversely, such diabetic complications might affect the accumulation of visceral fat. Nevertheless, losing body weight can be challenging for type 2 diabetes patients (Pi-Sunyer, 2005). In addition, the effects of these microvascular complications on altering visceral or subcutaneous fat accumulation are unclear.

2. Theory/calculation

The aim of this study was to clarify during hospitalization of type 2 diabetes patients the effects of diabetic microvascular complications on changes in VFA and SFA, using as a measure changes in V/S ratio, hypothesizing that microvascular complications make a decreased V/S ratio difficult to achieve because they could impede the loss of visceral fat compared with subcutaneous fat.

3. Material and methods

3.1. Study population

Study participants numbered 72 men and 82 women diagnosed with type 2 diabetes who had been hospitalized for improvement of blood glucose control at the Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital at some point in time between April 2012 and December 2014. Their VFA and SFA were monitored at the beginning of hospitalization and before discharge by CT scan. Subjects with serum creatinine level of more than 3 mg/dl or under artificial dialysis were excluded at the outset of the study. All subjects were free of infectious symptoms, autoimmune diseases, or any other acute condition, as assessed by medical interview and examinations.

During hospitalization, the study subjects were placed on a diet designed by registered dietitians and based on criteria of the Japan Diabetes Society that restricted daily caloric intake to around 20–25 kcal multiplied by ideal body weight. The subjects were also urged to exercise, underwent consultation and education about diabetes, and if necessary were prescribed anti-diabetic drugs including insulin to control blood glucose level based on the determination of the physician in charge. Written informed consent for hospitalization and examinations was obtained from all participants. This study was approved by the ethics committee of the Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital.

3.2. Measurements and evaluation of microvascular complications

At the beginning of patient hospitalization, we measured certain anthropometric variables: height, weight, and waist circumference in the standing position, as well as blood pressure. Body mass index (BMI) was calculated as body weight (kg) divided by the square of standing height (m). All participants provided blood and urine samples after an overnight fast. Glycated haemoglobin (HbA1c) was measured in derived NGSP units (%; to one decimal point).

All participants underwent fundoscopic examination after pupillary dilation, and diagnosis regarding diabetic retinopathy was made by an ophthalmologist using retinal photography, with fluorescein angiography when necessary. The patients were categorized into three groups: patients with no diabetic retinopathy (NDR), those with simple retinopathy (SDR), and patients with preproliferative or proliferative diabetic retinopathy (PDR) (Davis, 1965). Albuminuria was determined by validated measurements of morning spot urine samples, defined as urinary albumin-to-creatinine ratio (ACR), with albumin measured in milligrams using the latex agglutination method and normalized by urinary creatinine as a surrogate marker for nephropathy. Neuropathy was assessed using coefficient of R–R interval variation (CVRR) as a surrogate marker. After a few minutes rest, an electrocardiogram was conducted with the patient in the supine position, with 100 consecutive R–R intervals being analyzed. During rest breathing, the patients were instructed to breathe naturally. Mean value of one R–R interval and standard deviation (SDRR) were analyzed, and coefficients of variation of R–R intervals (CVRR = SDRR/mean R–R $\times$ 100) were calculated for the same periods. Higher values of this variable indicated greater levels of parasympathetic activation at the level of the heart.

CT (SYMBIA T6; Siemens, Germany) was performed with subjects in a supine position (130 kV, 100 mA, section thickness of 5 mm, scanning time of 3 s, field of view of 250 mm, gantry rotation time of 600 ms) on two occasions: at the beginning of hospitalization and before discharge. Total fat area (TFA), SFA, and VFA were measured using a high-quality two-dimensional computed tomography image analysis system (Synapse Vincent, Fuji Film Co., Ltd., Tokyo, Japan) (Yamaji et al., 2009). Using these data, V/S ratio was calculated for each subject, and that value was compared with change in V/S ratio during the period of hospitalization.

3.3. Statistical analysis

Results were expressed as means $\pm$ standard error or median and interquartile range. Since ACR, CVRR, BMI, SFA and VFA data did not show normal distributions, the data were analyzed after logarithmic transformation. All patients were categorized into two groups: a group with mainly reduced visceral fat (characterized by decreased V/S ratio during hospitalization) and a group with mainly reduced subcutaneous fat (characterized by increased V/S ratio during hospitalization). To test the significance of each microvascular complication as a predictor of body compositional change determined by increased or decreased V/S ratio, Cox proportional hazards model was used to consider variation in duration of hospitalization.

To express their impact, microvascular complications were calculated as both numeric values and categorical data. Retinopathy was divided into three variables (NDR, SDR, and PDR). For ACR, row data were used, and categorical data based on population value (<4.5, 4.5–15.0, and >15.0 mg/g Cr, N = 51, 52, and 51, respectively) were calculated in addition to the row data. CVRR was divided into three categories based on population values (<1.38, 1.38–2.40, and >2.40%, N = 50, 53, and 51, respectively). With respect to potential confounders, adjustment was made for continuous age, HbA1c, and BMI, as well as for categorical sex.

Hazard ratios for row data of microvascular complications were estimated after adjustment by two sets of potential confounders in addition to crude data: the first set comprised age and sex only, and the second comprised age, sex, BMI, and HbA1c. Hazard ratios for categories of microvascular diseases were estimated after adjustment for the second set. The proportional hazards assumption was