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Serum adiponectin and TNFα concentrations are closely associated with epicardial adipose tissue fatty acid profiles in patients undergoing cardiovascular surgery

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ABSTRACT

Background: Epicardial adipose tissue (EAT) releases both adiponectin and TNFα, and these two adipokines play important roles in heart diseases such as coronary arterial disease. The aim of the present study was to clarify whether fatty acid (FA) profiles in EAT are linked to the serum concentration of these adipokines. The relationships between serum adipokine levels and FA profiles in patients undergoing cardiovascular surgery were analyzed.

Methods: Patients ($n = 21$) undergoing cardiovascular surgery (11 males, 70.4 ± 9.0 years, BMI 26.0 ± 5.1 kg/m^2) were included. EAT samples were taken. We measured clinical biochemical data and FA profiles in venous blood and EAT samples using gas chromatography. Serum adiponectin and TNFα concentrations were also measured.

Results: The adiponectin and TNFα levels were not correlated with any fatty acid concentration in serum lipids. In contrast, there was a positive correlation between the serum adiponectin level and epicardial level of nervonic acid (C24:1ω9, $r = 0.525$, $P = 0.025$). In multiple regression analysis, adiponectin showed a positive association with the epicardial C24:1ω9 concentration after controlling for age and BMI, or TG, non-HDL-C, and BNP. The serum TNFα concentration was negatively correlated with the epicardial C18:3ω3, C12:0 and C18:0 content. In multiple regression analysis, the serum TNFα concentration showed a positive association with the epicardial C18:3ω3 level ($\beta = -0.575$, $P = 0.015$).

Conclusions: These results suggest that there is a close relationship between epicardial FA profiles and serum levels of adiponectin and TNFα. Dietary therapy to target FA profiles may be helpful to modulate inflammation.

1. Introduction

Fatty acids (FAs) are monovalent carboxylic acids that contain long chain hydrocarbon. They are components of lipids and important sources of fuel, and play a number of key roles in metabolism as essential components of all membranes. The FA composition of cell membranes affects cellular function including intracellular signaling [1]. Also, essential polyunsaturated FAs (PUFAs) consist of both ω6 and ω3 FAs and exert a broad range of beneficial effects on the cardiovascular system including modulation of the inflammatory response [2]. Consumption of a large amount of fish or marine mammals rich in ω3 FAs contributes to a low incidence of cardiovascular disease (CVD) among the Greenland Eskimos [3]. In addition, evidence from both epidemiologic studies and clinical trials demonstrates substantial cardioprotective effects of α-linolenic acid [4,5]. In contrast, several studies showed that an increase in circulatory linoleic acid is associated with reduced inflammation and cardiovascular risk, as well as improved outcomes [6,7]. Thus, dietary therapy that targets FA profiles may be helpful to modulate inflammation that could prevent CVD.

The relationship between the amount of PUFAs in the diet and the corresponding proportions of the same FAs in plasma lipids is strong. This is usually true for essential FAs, such as linoleic (18:2ω6) and α-linolenic acid (18:3ω3). However, most other types of FAs reflect endogenous FA metabolites and are synthesized from precursors, particularly saturated fatty acids (SFAs). SFAs can be synthesized de novo in the human body from acetyl coenzyme A and can be

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elongated or desaturated. Thus, FA profiles in serum and tissues can serve as a biomarker of the type of dietary fat intake as well as an indicator of the risk of diseases such as metabolic syndrome and CVD [8,9].

Adipose tissue is not only a lipid storage unit, but it also serves as an endocrine and paracrine organ, playing a key role in the homeostasis of body energy and the metabolism of lipids and carbohydrates [10,11]. In particular, epicardial adipose tissue (EAT), which interacts locally with the myocardium and coronary arteries, is a metabolically active organ that has a high rate of secretion of inflammatory adipokines such as TNFα [12,13]. EAT is also an important source of adiponectin, an anti-inflammatory and anti-atherosclerotic adipokine, and secretion of adiponectin from EAT can alter adiponectin levels in the systemic circulation [14,15]. Thus, adipokines released from EAT play an important role in diseases such as obesity, metabolic syndrome, and CVD including coronary arterial disease (CAD) [16]. Until now, several studies have reported the relationships between serum TNFα/adiponectin concentrations and FA profiles in serum [17,18]. Thus, it is likely that the FA composition of adipose tissue affects adipose function such as adipokine secretion, which plays an essential role in heart diseases. However, there are few reports on the relationships between serum TNFα/adiponectin concentrations and FA profiles in EAT and their underlying mechanisms.

2. Objectives

We investigated the relationships between serum adipokine levels/laboratory markers and FA profiles of EAT in patients undergoing cardiovascular surgery.

3. Materials

3.1. Participants

From October 2015 to December 2016, we evaluated 21 patients who underwent cardiovascular surgery at Dokkyo Medical Hospital. The proposal was approved by the Regional Ethics Committee of Dokkyo Medical University Hospital. The baseline characteristics of the patients are summarized in Table 1. The mean age was 70.4 ± 9.0 years, and the body mass index (BMI) was 26.0 ± 5.1 kg/m^2.

Fasting venous blood samples were obtained in tubes with and without EDTA sodium (1 mg/ml) and in polystyrene tubes without an anticoagulant. Serum and plasma were immediately separated by centrifugation at 3000 rpm at 4 °C for 10 min. Fasting blood sugar (FBS), total cholesterol (TC), hemoglobin A1c (HbA1c), brain natriuretic peptide (BNP), low-density lipoprotein (LDL)-cholesterol (LDL-C), high density lipoprotein (HDL)-cholesterol (HDL-C), non-HDL-C, triglycerides (TG), and estimated glomerular filtration rate (eGFR) were measured before the operation. The eGFR was calculated as follows.

eGFR (ml/min/1.73 m^2) = 194 × creatinine-1.094 × age − 0.287 (in men)

eGFR (ml/min/1.73 m^2) = 194 × creatinine-1.094 × age − 0.287 × 0.739 (in women)

All patients had medical treatment including statins (52.4%), β-blocking agents (42.9%), angiotensin receptor blockers (ARB)/angiotensin converting enzyme inhibitors (ACEI) (71.4%), diuretics (28.6%), and antidiabetic drugs (24%). Fasting blood glucose (FBS) and biochemical data were analyzed by routine chemical methods in the clinical laboratory of Dokkyo Medical University Hospital. Levels of the inflammatory marker, high-sensitivity C-reactive protein (hs-CRP), were measured by a latex-enhanced nephelometric immunoassay (N Latex CRP II and N Latex SAA, Dade Behring Ltd., Tokyo, Japan).

Table 1
Patient characteristics.

Number	21	Coronary artery disease, %	%
Male:Female	11:10	0-vessel disease	47.6
Age, y	70.4 ± 9.0	1-vessel disease	0
BMI, kg/m^2	26.0 ± 5.1	2-vessel disease	9.5
Risk factors, %	%	3-vessel disease	42.9
Hypertension	81.0	Cardiovascular surgery, %	%
Diabetes	33.3	CABG	52.4
Dyslipidemia	52.4	Valve replacement/repair	47.6
Smoking	4.7	Others	28.6
Hemodialysis	14.3	Drugs, %	%
NYHA class	2.3 ± 1.1	β-blockers	42.9
Laboratory blood data		Ca-blockers	47.6
HbA1c, %	6.0 ± 0.7	α-blockers	9.5
Fasting blood glucose, mg/dl	112 ± 31	ACE-I/ARB	71.4
eGFR	56 ± 27	Diuretics	28.6
Total cholesterol, mg/dl	173 ± 42	Statin	52.4
Triglycerides, mg/dl	125 ± 73	Sulfonylurea	14.3
HDL cholesterol, mg/dl	51 ± 15	α-GI	14.3
LDL cholesterol, mg/dl	98 ± 32	Biguanide	4.8
non-HDL cholesterol, mg/dl	117 ± 48	DPP4 inhibitor	9.5
hsCRP, mg/dl	0.28 ± 0.40	Insulin	4.8
BNP, pg/ml	466 ± 882		
Adiponectin, μg/ml	7.3 ± 7.3		
TNFα, pg/ml	3.2 ± 2.8		

The mean ± SD values are shown. NYHA, New York Heart Association; FBS, fasting blood sugar; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; BNP, brain natriuretic peptide; TNFα, tumor necrosis factor α; CABG, coronary artery bypass grafting; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; α-GI, α-glucosidase inhibitor.

3.2. Blood collection for measurement of adiponectin and TNFα

To measure fasting serum adiponectin and TNFα levels, peripheral venous blood was drawn into pyrogen-free tubes without EDTA in 18 of 21 patients on the morning of the cardiovascular surgery. The serum was stored in aliquots at −80 °C for ELISA and Luminex assays.

3.3. Enzyme-linked immunosorbent assay (ELISA) and Luminex

Serum adiponectin level was measured by the Human Total Adiponectin/Acrp30 Quantikine ELISA Kit (R&D Systems, USA). The detection threshold was 0.24 ng/ml. Samples, reagents, and buffers were prepared according to the manufacturer's instructions. A Luminex assay was applied to determine serum levels of TNFα. The serum concentrations of TNFα were calculated by comparing the assay readings on a Luminex200™ system (Luminex Co., Austin TX, USA). The detection threshold was 1.2 pg/ml.

3.4. Adipose tissue sampling

Adipose tissue samples were obtained before the initiation of cardiovascular surgery as previously described [19]. Epicardial adipose tissue (EAT) samples (average 0.5 to 1.0 g) were taken near the proximal right coronary artery. The specimens were stored at −80 °C for later analysis.

3.5. Determination of FA composition

3.5.1. Serum FAs

Approximately 0.2 ml of serum sample and 2 ml of chloroform-methanol (2:1) solution (1 ml water, 666 μl methanol, and 333 μl chloroform) were placed in Pyrex centrifuge tubes, homogenized with a Polytron (PCU2-110, KINEMATICA GmbH, Switzerland), and then centrifuged at 3000 rpm for 10 min. An aliquot of the chloroform-methanol extract was transferred to another Pyrex tube and dried under a stream of nitrogen gas. The dried specimens were dissolved in 100 μl 0.4 M

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