Diabetology International (2019) 10:219–224
https://doi.org/10.1007/s13340-018-0384-9

ORIGINAL ARTICLE

Low muscle mass and inflammation among patients with type 2 diabetes mellitus in Indonesia

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Received: 1 September 2018 / Accepted: 11 November 2018 / Published online: 19 November 2018

Abstract

Introduction Chronic inflammation, as observed in type 2 diabetes mellitus (T2DM), is associated with complications. How chronic inflammation influences body composition in patients with T2DM remains to be investigated. Our study aimed to evaluate the difference of skeletal muscle mass between patients with and without inflammation indicated by plasma high sensitivity C-reactive protein (hs-CRP).

Methods Patients with T2DM were recruited from primary health care in Sleman district, Indonesia. Measurements were performed to obtain information on body weight, body mass index, waist circumference, waist-to-height ratio, total body fat, subcutaneous fat, visceral fat, mid-upper arm circumference, and muscle mass. Spearman's rank correlation was performed to test the correlation between hs-CRP level and several components of body composition. To test the difference of percent skeletal muscle mass between subjects with and without inflammation (hs-CRP ≥ 3 or < 3 mg/dL), general linear model was utilized with adjustment for several variables. Analysis with p value of less than 0.05 is considered statistically significant.

Result In all subjects, hs-CRP is correlated with skeletal muscle mass (r: −0.343; $p = 0.04$), total body fat (r: 0.353; $p = 0.04$), and subcutaneous fat (r: 0.369; $p = 0.02$) but not visceral fat (p: −0.065; $p =$ ns). Significant difference of skeletal muscle mass between subjects with and without inflammation was found in all and female subjects after adjustment for covariates.

Conclusion There was a negative correlation between skeletal muscle mass percentage and inflammation indicated by hs-CRP in type 2 diabetes patients.

Keywords Diabetes · Anthropometry · Body composition · Inflammation · hs-CRP

Introduction

Diabetes mellitus is an inflammatory disease with a worldwide prevalence of 8.5% in adult population [1]. Evidence showed that inflammation, as indicated by elevated CRP levels, is significantly associated with increased risk of T2DM (RR 1.26; 95% CI 1.16–1.37) [2]. Moreover, inflammation may play a role in the development of diabetic complications. In type 1 and type 2 diabetes, elevated levels of inflammatory markers including IL-6, CRP, and TNFα are associated with cardiovascular disease, retinopathy, and nephropathy [3].

Patients with inflammatory diseases are commonly characterized by alteration of nutritional status. Cardiac and cancer cachexia, for example, are manifestation of chronic inflammation which are indicated by muscle protein depletion. Increased inflammatory biomarkers, such as TNF-α, IL-1, and IL-6, were observed in chronic heart and renal failure patients as well as being associated with disease severity and mortality in sepsis [4–6]. In aging, sarcopenia and loss of muscle quality were associated with high level of proinflammatory cytokines [7].

Reduced muscle mass is observed in type 2 diabetes patients [8]. This condition may result from a functional impairment in skeletal muscle mitochondria respiration [9]. Mitochondrial dysfunction is known to promote the activation of muscular atrophy [8]. Muscle facilitates glucose disposal from the circulation and converts it into physical force and, therefore, muscle quality and quantity are important in glycemic control. Skeletal muscle insulin resistance, as seen in T2DM [10], may contribute to reduced uptake of glucose.

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Moreover, sarcopenia may lead to decreased surface area for insulin-mediated glucose uptake [11].

Based on those findings, this study aimed to examine the association between inflammation and muscle mass in patients with diabetes. High-sensitivity C-reactive protein (hs-CRP) was used as an inflammatory marker in this study.

Methods

Patients

Adult patients (30 years old and older) diagnosed with type 2 diabetes mellitus were recruited from three primary health cares in Sleman district, Yogyakarta province, Indonesia. Informed consents were obtained from all participants. Eligible patients were then invited to research facility in the Department of Nutrition and Health, Universitas Gadjah Mada for further research processes.

Patients were required to wear light clothing and instructed to empty their pockets, remove hair accessory and foot wear prior to the measurements. Body weight measurements were performed on validated digital scale with 0.1 kg precision. Height measurements were performed using roll-up height measuring tape attached to the wall with 0.1 cm precision. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2) and subjects were categorized according to WHO international BMI cutoffs [12]. Waist circumference was measured using non-stretch measuring tape with precision of 0.1 cm. Ratio of waist to height was calculated and value of 0.5 or higher is considered abdominal obesity [13]. Mid-upper arm circumference (MUAC) measurements were performed with precision of 0.1 cm. Body composition measurements including total body fat, subcutaneous fat, visceral fat, and muscle mass were obtained using bioelectrical impedance analyzer (Omron, HBF-375). Measurement was carried out with the subjects positioned their feet on the footpad and grasping the handle precisely so that the four-metal electrode were touched. Blood pressure was measured using electronic blood pressure monitors (Omron, HEM 6200).

Laboratory method

Venous blood was drawn from all subjects after overnight fasting and stored in vacuum tubes contained EDTA. Tubes were frozen prior to the analysis. Blood glucose was measured using colorimetric method according to the manual (Dyasis). Measurement of plasma hs-CRP was performed using enzyme-linked immunosorbent assay (ELISA) method (Calbiotech, USA). The analysis was carried out according to the manufacturer's instruction. The reference range for normal hs-CRP level was < 3 mg/L. Hs-CRP level of 3 mg/L or above was considered high and indicated inflammation.

Statistical analysis

Spearman's rank correlation was performed to test the correlation between hs-CRP level and several components of body composition. To test the difference of percent skeletal muscle mass between subjects with and without inflammation (hs-CRP ≥ 3 or < 3 mg/dL), general linear model was utilized with adjustment for several variables. Analysis with p value of less than 0.05 is considered statistically significant.

Result

Subjects' characteristics of this study can be observed in Table 1. The average age of the subjects was 62.2 ± 9.1 years and half of them were males. Over half (52%) of the subjects had normal body mass index, while overweight and obesity was found in 14 (38.9%) and 2 (5.6%) subjects, respectively. According to waist-to-height ratio, almost all (34; 94.4%) of the patients had abdominal obesity. Half (18; 50.0%) of the

Table 1 Characteristics of subjects

Characteristic	Mean ± SD	*n* (%)
Age (years)	62.2 ± 9.1	
Sex (%male)		18 (50%)
Weight (kg)	59.7 ± 10.7	
Height (cm)	154.5 ± 9.2	
Body mass index (kg/m^2)	24.8 ± 3.0	
Underweight (< 18.5)		1 (2.8%)
Normal (18.5–24.9)		19 (52.8%)
Overweight (25–29.9)		14 (38.9%)
Obesity (≥ 30)		2 (5.6%)
Waist circumference (cm)	90.13 ± 9.66	
Waist-to-height ratio	0.58 ± 0.06	
Normal (< 0.5)		2 (5.6%)
High (≥ 0.5)		34 (94.4%)
Systolic blood pressure (mmHg)	126.7 ± 25.5	
Diastolic blood pressure (mmHg)	81.9 ± 11.6	
Blood pressure categories		
Normal		6 (16.7%)
Pre-hypertension		18 (50.0%)
Hypertension		12 (33.3%)
Fasting blood glucose (mg/dL)	159.6 ± 93.9	
hs-CRP level (mg/L)	5.5 ± 6.3	
hs-CRP category		
Normal (< 3 mg/L)		19 (52.8%)
High (≥ 3 mg/L)		17 (47.2%)

subjects were pre-hypertensive and one-third (12; 33.3%) fell into hypertension category. Mean fasting blood glucose was 159.6 ± 93.9 mg/dL.

Spearman's rank correlation coefficient between hs-CRP level and several components of body composition can be observed in Table 2. In all subjects, hs-CRP is correlated with skeletal muscle mass (r: −0.343; p = 0.04), total body fat (r: 0.353; p = 0.035), and subcutaneous fat (r: 0.369; p = 0.024) but not visceral fat (p: −0.065; p = ns). Analysis was also performed on separate gender. Both in male and female subjects, no significant correlation was found between hs-CRP and body composition.

Further analysis was conducted to see the difference of skeletal muscle mass between patients with and without inflammation (Table 3). Analysis was performed in all subjects and also in each gender separately. In all subjects, difference of muscle mass was observed between patients with inflammatory and non-inflammatory state after adjustment of several variables (glucose, BMI and waist circumference). In female patients, we found difference in percent skeletal muscle mass with adjustment in model 3 (adj. for fasting glucose, % total body fat and body weight) and model 4 (adj. for fasting glucose, age, % total body fat and body weight).

Table 2 Correlation between hs-CRP levels with body composition

Component of body composition	r	p value
Body weight		
All	−0.117	ns
Male	−0.017	ns
Female	0.051	ns
BMI		
All	0.063	ns
Male	0.030	ns
Female	0.165	ns
Waist circumference		
All	−0.014	ns
Male	0.260	ns
Female	−0.310	ns
Waist-to-height ratio		
All	0.150	ns
Male	0.284	ns
Female	−0.278	ns
Mid-upper arm circumference		
All	0.024	ns
Male	0.129	ns
Female	0.174	ns
% skeletal muscle mass		
All	−0.343	0.04*
Male	−0.267	ns
Female	0.020	ns
% total body fat		
All	0.353	0.04*
Male	0.265	ns
Female	0.067	ns
% subcutaneous fat		
All	0.369	0.02*
Male	0.304	ns
Female	0.098	ns
% visceral fat		
All	−0.065	ns
Male	0.116	ns
Female	0.010	ns

ns not significant

*Statistically significant, $p < 0.05$

Discussion

In general population, previous study showed that inflammation was associated with adiposity [14]. However, it is important to note that the correlations among several inflammatory markers for instance IL-6, IL-8, TNFα, IL-18, and MCP-1 were either weak or not exist [14], indicating that inflammation determined by different inflammatory markers may not in agreement. Moreover, it was reported that general and central obesity exhibited different cytokine profiles [15]. Variation in cytokine profiles in this condition should alert the investigators to carefully select the relevant cytokine in their studies. Highest vs. lowest baseline CRP was associated with increased 15-fold risk of developing T2DM in women after 4-year follow-up (RR 15.7; 95% CI 6.5–37.9) [16]. In the context of coronary heart disease (CHD), top vs. bottom third of CRP is associated with more than double the risk of this disease after adjustment for age, sex, and country (OR 2.21; 95% CI 1.76–2.78). The risk remains among statin and aspirin non-user (OR 1.96; 95% CI 1.29–2.98 and OR 1.92; 95% CI 1.19–3.10) but not in all subjects [17]. In a large study involving 1301 participants with T2DM, each SD increment in baseline hs-CRP was significantly associated with increased risk of CHD (HR 1.028; 95% CI 1.024–1.032), diabetic neuropathy (HR 1.025; 95% CI 1.021–1.029), diabetic retinopathy (HR 1.037; 95% CI 1.030–1.043), and diabetic kidney disease (HR 1.035; 95% CI 1.027–1.043) [18]. These findings suggest that the use of CRP is relevant as inflammatory marker which predict development of diabetes and diabetes complication.

In our study, besides its correlation with body fat percentage, hs-CRP was negatively correlated with skeletal muscle mass percentage in T2DM patients (r: −0.343; p = 0.04). Furthermore, patients with inflammatory state (hs-CRP ≥ 3 mg/L) exhibited lower muscle mass compared to those with non-inflammatory state (hs-CRP < 3 mg/L) after being adjusted for fasting blood glucose levels, BMI, and waist circumference (p = 0.04). Our result was in line

Table 3 Percent skeletal muscle mass in subjects with and without inflammation

	hs-CRP < 3	hs-CRP ≥ 3	*p* value				
			Model 1	Model 2	Model 3	Model 4	Model 5
All sample	27.41 ± 7.69[a]	23.43 ± 3.12[a]	0.06	0.06	0.29	0.30	0.04*
Male	30.50 ± 8.19[a]	26.55 ± 1.79[a]	0.27	0.39	0.43	0.43	0.49
Female	22.11 ± 1.68[a]	21.73 ± 2.24[a]	0.71	0.90	0.02*	0.04*	0.99

Model 1: unadjusted

Model 2: adj. for fasting glucose

Model 3: adj. for fasting glucose, % total body fat and body weight

Model 4: adj. for fasting glucose, age, % total body fat and body weight

Model 5: adj. for glucose, BMI and waist circumference

*Statistically significant, $p < 0.05$

[a]Unadjusted mean

with other studies involving elderly participants [19, 20] and with a meta-analysis which showed that the levels of CRP were significantly higher in sarcopenic patients than in controls [21]. Moreover, a cohort study reported an association between higher CRP and lower muscle strength [22].

A possible mechanism underlying the relationship between inflammation and the decline in muscle mass was explained by Wåhlin-Larsson et al. [23]. Their in vitro study reported that myotubes that were exposed to CRP showed altered phosphorylation on several proteins responsible for muscle growth and muscle protein synthesis, such as phosphorylated ribosomal protein S6 (rpS6) and AMP-activated protein kinase (AMPK), resulting in reduced muscle size compared to controls [23].

More than 90% of the subjects had abdominal obesity and almost half of the subjects (47.2%) fell into high hs-CRP category. The mechanism of obesity-induced muscular atrophy was investigated by Pellegrinelli et al. [24]. It was shown that secretome of obese adipocytes decreased the expression of contractile proteins in muscle, which indicated development of atrophy. Moreover, the role of adipocyte was site specific in which visceral were more potent than subcutaneous adipocytes in inducing this condition [24].

In this study, female subjects had higher level of hs-CRP compared to their male counterparts, even though it was not statistically significant (6.43 ± 4.98 vs 5.04 ± 7.00, $p = 0.07$). The skeletal muscle mass percentage was higher in male, while subcutaneous fat and total body fat percentages were higher in female ($p < 0.001$). Our female subjects age ranged from 51 to 70 years. It means that most if not all female participants were in menopause. Post-menopausal women are more susceptible to metabolic diseases and low estrogen level leads to increased adiposity [25]. After being adjusted for fasting blood glucose, total body fat percentage, and body weight, only female subjects showed difference in skeletal muscle mass between those with high and normal hs-CRP levels ($p = 0.02$).

The average age of subjects was 62.2 ± 9.1, showing that high proportion of them were either elderly or elder adults. It was known that elderly people are at risk of sarcopenia [26]. Anabolic hormones such as testosterone play a role in this process. In males, testosterone decreased 1% per year from the age 30, while in women, rapid drop was observed from 20 to 45 years of age [27]. Furthermore, aging is associated with a chronic inflammatory state with slight increase in plasma levels of pro-inflammatory mediators, such as CRP [28]. In our subjects, small increase of hs-CRP (> 3 mg/L) indicates low-grade inflammation as seen in chronic inflammation. However, if the value of hs-CRP is much higher than this threshold, higher degree of inflammation may occur which is usually observed during infection [29].

Both FBG and HbA1c are used to diagnose diabetes. HbA1C represents blood glucose level for a time of 2–3 months and produces more constant and reliable value in multiple testing. Conversely, FBG reading can be easily affected by exercise, recent food ingestion, and sample handling [30]. Despite this, several studies showed that fasting blood glucose was comparable to HbA1C and was significantly correlated with hs-CRP value in type 2 diabetes patients with and without complications and in healthy middle-aged subjects [31, 32]. In our study, adjustment for blood glucose alone did not exhibit significant difference in percent muscle mass between those with normal and high hs-CRP ($p = 0.06$).

Disruption of protein turnover in T2DM patients may be attributed to insulin dysfunction which results in dysregulation of anabolic process. Chronic inflammation affects the body with multiple impairments such as insulin resistance and hormonal alterations [33]. Our study did not measure the fasting insulin of patients. Thus, we cannot assess the level of insulin resistance among subjects. However, a cross-sectional study showed that log CRP was significantly associated with fasting blood glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) in type 2 diabetes patients [34]. It was also reported that HOMA-IR

was inversely associated with appendicular skeletal muscle mass in older adults [35].

There were a number of limitations to this study including the lack of data on diabetes-related measurements such as HbA1c and HOMA-IR to further elaborate our findings. Furthermore, we did not assess data of diabetes duration and oral drugs taken by patients. This study used BIA to measure body composition which is less accurate than the standard methods dual-energy X-ray absorptiometry (DXA) scan or magnetic resonance imaging (MRI), considering the small number of subjects. However, previous study reported that the deviations of measurements using Omron BIA from MRI for all subjects regardless of gender were minimal for skeletal muscle mass percentage (+1.8%; 95% CI +0.6 to +3.0; $p=0.005$) [36].

Despite the small number of samples, our findings provided insight into the possible link between chronic inflammation and lower muscle mass in type 2 diabetes patients in Indonesia. Nevertheless, a population-based study involving T2DM patients on a larger scope is required to further confirm the findings of this present study.

Conclusion

There was a negative correlation between skeletal muscle mass percentage and inflammation indicated by hs-CRP in type 2 diabetes patients. Patients with hs-CRP level of ≥ 3 mg/L exhibited lower muscle mass after adjustment for fasting blood glucose levels, BMI, and waist circumference.

Acknowledgements This work was funded by Young Investigator Grant from Universitas Gadjah Mada.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval for this study was obtained from Ethical committee of Faculty of Medicine, Universitas Gadjah Mada (KE/FK/833/EC/2016) on July 25th 2016.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from Ethical Committee of Faculty of Medicine, Universitas Gadjah Mada (KE/FK/833/EC/2016) on July 25th 2016.

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