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Decreased serum fatty acid binding protein 4 concentrations are associated with sarcopenia in chronic hemodialysis patients

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ABSTRACT

Background: Fatty acid binding protein 4 (FABP4) is found to play a role in skeletal muscle homeostasis. Since the dysregulation of FABP4 and sarcopenia are both highly prevalent in patients on chronic hemodialysis (HD), the correlation between them remains unknown. We aimed to examine this relationship in a cross-sectional study.

Methods: A total of 120 chronic HD patients were recruited, and whose skeletal muscle mass, handgrip strength, and gait speed were assessed and blood samples were obtained. We grouped these participants into sarcopenia (n = 20) and non-sarcopenia groups according to European Working Group on Sarcopenia in Older People criteria.

Results: The sarcopenia group exhibited lower weight ($P < 0.001$), height ($P = 0.019$), waist circumference ($P < 0.001$), body mass index ($P < 0.001$), body fat mass ($P = 0.004$), and lower serum triglycerides ($P = 0.009$), creatinine ($P < 0.001$), phosphorus ($P = 0.013$), intact parathyroid hormone ($P = 0.012$), and FABP4 concentrations ($P = 0.005$), and higher malnutrition–inflammation scores (MIS) ($P = 0.031$), urea reduction rates ($P < 0.001$), and fractional clearance index for urea (Kt/V) values ($P < 0.001$). Serum FABP4 concentrations (odds ratio (OR): 0.98, 95% confidence interval (CI): 0.96–0.99, $P = 0.043$), body fat mass (OR: 0.86, 95% CI: 0.77–0.97, $P = 0.013$), MIS (OR: 6.90, 95% CI: 1.31–36.36, $P = 0.023$), and Kt/V (each increase of 0.1, OR: 2.15, 95% CI: 1.29–3.57, $P = 0.003$) were independent predictors of sarcopenia in chronic HD patients.

Conclusions: We delineated the association between serum FABP4 concentrations and sarcopenia in chronic HD patients.

1. Introduction

Sarcopenia, characterized by a gradual decline in both muscle quantity and strength, is a geriatric syndrome that usually leads to impaired activities, poor quality of life, falls and fractures, disabilities, and even death [1–3]. Reduced protein intake, physical inactivity, vitamin D abnormalities, decline in satellite cells, and hormone derangements are usually clamed to contribute to development of geriatric sarcopenia. Not only in patients with advanced organ failure, inflammatory disease, malignancy, and endocrine diseases [4], but also in patients with chronic kidney disease (CKD) are observed to have higher prevalence of sarcopenia [5, 6]. Metabolic acidosis, myostatin over-expression, excess angiotensin II activity, protein energy wasting, and chronic inflammatory status that usually co-exist in CKD were also learned as the contributing factors for this syndrome [7]. Therefore, the pathogenesis of sarcopenia in CKD patients is more complicated than that in non-CKD patients.

Through secreting adipokines, adipose tissue is known to have an endocrine function in lipid metabolism, vascular function, inflammation, and insulin resistance [8]. When skeletal muscle mass decrease, intramuscular adipose tissue infiltration and visceral adipose tissue mass will increase, this indicates a possible role of adipokines in skeletal

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muscle homeostasis [9–13]. Fatty acid binding protein 4 (FABP4), a novel adipokine primarily synthesized by adipocytes or macrophages, is expressed within human skeletal muscle fibers and found to be positively correlated with weight, body mass index (BMI), adipocyte counts and sarcopenic obesity in general population [14, 15]. However, in chronic hemodialysis (HD) patients, whether serum FABP4 concentrations that at least 10 times higher than those in general population can modulate skeletal muscle homeostasis remains unknown [16].

2. Materials and methods

2.1. Patients

We performed a cross-sectional study to recruit a total of 160 patients who were > 20 y were maintained on HD for at least 3 months at a medical center from January 2015 to December 2015. Patients who refused to participate or who had amputated limbs, acute infection, active malignancy, or bed-ridden status were excluded from this study. Finally, 120 patients (63 males and 57 females) were recruited and their ages ranged from 27 to 92 y. The data of basic characteristics, medical history, and drug usage were collected. Diabetes mellitus (DM) was defined by history or current use of anti-diabetic drugs, and hypertension was defined as blood pressure > 140/90 mmHg or current treatment with anti-hypertensive agents. All participants signed an informed consent that had been approved by the Institutional Review Board of Tzu-Chi Hospital.

2.2. Anthropometric analysis

Body weight was measured in light clothing and without shoes to the nearest half-kilogram before and after HD session, while height was to the nearest half-centimeter. Waist circumference was measured at the shortest point below the lower rib margin and the iliac crest.

2.3. Sarcopenia definition

The consensus from European Working Group on Sarcopenia in Older People (EWGSOP) was adopted to define sarcopenia as having low muscle mass combined with low handgrip strength (HGS) or slow gait speed in this study [4]. We used a portable whole-body bioelectrical impedance device (Tinita 706 BCE dB, Tanita Corp.) to assess skeletal muscle mass and body fat with the patient in standing position. This measurement using the leg-to-leg bioimpedance analysis, 2 footpad electrodes are incorporated into the platform of a precision electronic scale, is noninvasive and highly reproducible. Skeletal muscle index (SMI) was defined as skeletal muscle mass/height^2 (Kg/m^2). Low muscle mass were defined as < 10.76 and < 6.76 kg/m^2 in men and women, respectively. HGS was measured at the arm without vascular access, using a Jamar Plus Digital Hand Dynamometer (SI Instruments Pty Ltd.). The patients held the dynamometer in the hand to be tested, with the arm at right angles and elbow at the side of the body. The measurements of HGS were repeated trice before HD and the average value was recorded. Low handgrip strength was classified as HGS < 30 kg for men and < 20 kg for women. Gait speed was measured by walking for 5 m at usual speed. Slow gait speed was defined as gait speed < 1.0 m/s, both in men and women. All the measurements of muscle mass, HGS, and gait speed were carried out by the same trained operator.

2.4. Biochemical investigations

Approximately 5 ml of blood were obtained from each participant and the blood sample was immediately centrifuged at 3000 × *g* for 10 min for biochemical analyses within 1 h after collection. Serum concentrations of blood urea nitrogen, creatinine (Cre), glucose, total cholesterol (TCH), triglyceride (TG), total calcium, phosphorus, and C-reactive protein (CRP) were measured using an chemistry analyzer (Siemens Advia 1800). The fractional clearance index for urea (Kt/V) and urea reduction ratio (URR) were calculated before and immediately after dialysis, using single-compartment urea kinetic model. Serum intact parathyroid hormone (iPTH) concentrations were measured by using enzyme-linked immunosorbent assays (ELISA; Diagnostic Systems Laboratories), and serum FABP4 concentrations by a commercially available enzyme immunoassay (SPI-BIO, Montigny le Bretonneux, France) before HD.

2.5. Assessment of nutritional status and daily protein intake

The nutritional status was evaluated based on the Malnutrition–Inflammation Score (MIS), which includes 4 sections (medical and nutritional history, physical examination of fat and muscle stores, assessment of BMI, and biochemical assessment) and 10 components [17]. Each component has 4 severity levels ranging from 0 (normal) to 3 (very severe). A final score of 0–30 was assigned to each patient. A higher total score reflects a more severe degree of malnutrition. Scores of ≥7 points were defined as malnutrition in our study [18, 19]. Normalized protein nitrogen appearance rate (nPNA) was used to estimate the daily protein intake, through the 3-point method. PNA (G) = (Kr + a) × [C0 − Ct (Vt + a(theta))/Vt] − (Kr + a), where Vt is the post-dialysis volume, G is the interdialytic urea generation rate, Kr is the renal urea clearance, Ct and C0 are the blood urea nitrogen concentrations at the end and beginning of dialysis, and a is the rate of inter-dialytic volume expansion, which is calculated as the total inter-dialysis weight gain divided by the length of the inter-dialytic period (theta) [20].

2.6. Statistical analysis

Continuous variables are expressed as mean ± SD or as median and interquartile range. These variables were analyzed either by the Student's independent *t*-test or the Mann–Whitney U test, according to the result of data distribution examined by using the Kolmogorov–Smirnov test. Categorical variables are expressed as absolute (n) and relative frequency (%) and were analyzed using the chi-square test or Fisher's exact test. Clinical variables that correlated with FABP4 in chronic HD patients were evaluated through univariate linear analysis. Variables that were significantly associated with FABP4 in chronic HD patients were tested for independence through multivariate forward stepwise regression analysis. The factors associated with sarcopenia in chronic HD patients were analyzed through univariate and multivariate logistic regression. Statistical analysis was performed using SPSS software (ver 19.0). A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Population characteristics

The clinical and laboratory characteristics of 120 chronic HD patients with or without sarcopenia are presented in Table 1. The mean age of the total participants was 63.33 ± 13.18 y, and 20 (16.7%) of them had sarcopenia. Compared with the non-sarcopenia group, patients in the sarcopenia group weighed less and had lower height ($P = 0.019$), waist circumference ($P < 0.001$), BMI ($P < 0.001$), body fat mass ($P = 0.004$); and lower serum TG ($P = 0.009$), Cre ($P < 0.001$), phosphorus ($P = 0.013$), iPTH ($P = 0.012$), and FABP4 ($P = 0.005$) concentrations; whereas had higher MIS ($P = 0.041$), URR ($P < 0.001$), and Kt/V ($P < 0.001$) value. Moreover, we assessed muscle mass after HD session in 74 patients to evaluate the impact of hydration status. Among these patients, the mean ultrafiltration amount was 2.29 ± 1.09 Kg. The mean SMI was 12.09 ± 4.68 Kg/m^2 before and 11.28 ± 4.24 Kg/m^2 after HD session (mean difference 0.81 Kg/