Serum Low C-Peptide Levels Correlate With Low Muscle Mass in Patients With Type 2 Diabetes Mellitus

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The interplay of diabetes and sarcopenia is increasingly recognized. Currently, sarcopenia has been characterized as a new complication of diabetes that seriously harms the physical activity and health of patients with diabetes and leads to increased clinical adverse events, such as falls, fractures, hospitalizations, and even death (1). Early diagnosis and treatment of sarcopenia are of great importance to reduce morbidity and mortality and improve quality of life. C-peptide is a bioactive peptide that can act independently of insulin by targeting multiple tissues and exerting diverse biological functions (2). A small-sample-size study revealed the association between fasting C-peptide levels and skeletal muscle index in community-dwelling older adults (3). Furthermore, a preclinical study demonstrated that C-peptide administration could prevent muscle mass loss in streptozotocin-induced diabetic rats (4). However, the association between C-peptide and low muscle mass in type 2 diabetes mellitus (T2DM) remains unknown. Therefore, we aimed to investigate the relationship between C-peptide levels and low muscle mass and the potential of C-peptide as a biomarker for identifying the presence of low muscle mass in T2DM.

We performed this cross-sectional study based on the medical records of patients with T2DM hospitalized for hyperglycemia in the Department of Endocrinology and Diabetes, the First Affiliated Hospital of Xiamen University, from 2017 to 2021. The study was approved by the ethics committee of the First Affiliated Hospital of Xiamen University. The extracted information included demographics, comorbidities, diagnoses, medications, and laboratory parameters. Fasting serum C-peptide was measured. Body composition was determined by dual-energy X-ray absorptiometry. The appendicular skeletal muscle mass index was calculated as appendicular skeletal muscle mass divided by height squared (kg/m^2). Low muscle mass was defined as appendicular skeletal muscle mass index of <7.0 and <5.4 kg/m^2 for men and women, respectively (5).

Participants with incomplete information on C-peptide ($n = 47$) were excluded. A total of 2,118 patients (819 women and 1,299 men), with an average age of 53 years, were included. The median serum concentration of C-peptide was 1.48 ng/mL (interquartile range, 0.95–2.21 ng/mL). The prevalence of low muscle mass was 29.8% in total and 41.9%, 28.0%, and 19.1% in the increasing tertiles of serum C-peptide levels. In the multivariable logistic regression analysis, serum C-peptide levels (estimated β coefficient [SE] = 1.17 [0.19]), increased age (estimated β coefficient [SE] = 0.04 [0.01]), male sex (estimated β coefficient [SE] = 1.28 [0.19]), and low systolic blood pressure (BP) (estimated β coefficient [SE] = −0.03 [0.004]) were identified as risk factors associated with low muscle mass. Compared with the patients with serum C-peptide levels in the highest tertile, the odds ratio (95% CIs) of low muscle mass for those with serum C-peptide in the lowest tertile was 3.21 (95% CI, 2.19–4.70) after adjustment for potential confounders, including current smoking, alcohol consumption, dyslipidemia, HbA_{1c}, systolic BP, diabetes duration, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, cardiovascular disease, antidiabetic drugs, sex, and age (Fig. 1*A*). A multiply adjusted spline regression model showed a linear dose-response association between serum C-peptide levels and low muscle mass (*P* for nonlinearity, 0.090; *P* for linearity, <0.001) (Fig. 1*B*). A receiver operating characteristic analysis demonstrated that a C-peptide level of 1.15 ng/mL was the optimal cutoff using the Youden index to potentially identify individuals with low muscle mass, with a sensitivity of 50.5%, specificity of 71.3%, positive predictive value of 42.3%, negative predictive value of 76.9%, and area under the receiver operating characteristic curve of 0.646 (95% CI, 0.620–0.672, $P < 0.001$).

To the best of our knowledge, our study is the first investigation of the association of serum C-peptide levels with low muscle mass in patients with T2DM. We demonstrated a dose-response association between lower C-peptide levels and higher prevalence of low muscle mass. The suggested cutoff of the C-peptide

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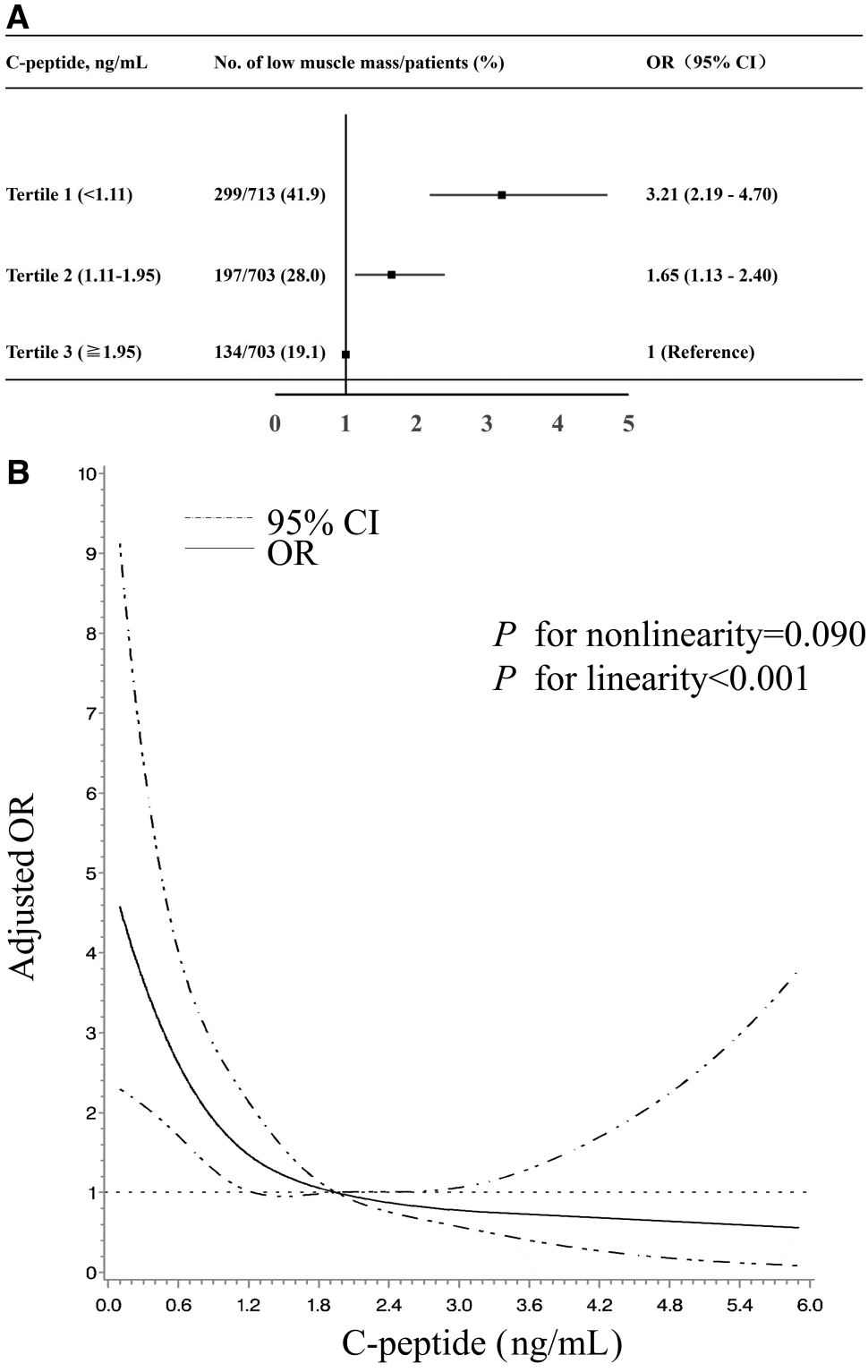

Figure 1—Association of serum C-peptide levels with low muscle mass. *A*: Odds ratios (OR) (95% CIs) of low muscle mass according to the tertiles of serum C-peptide levels. *B*: Restricted cubic spline of the association between serum C-peptide levels and low muscle mass. A reference point is the highest quartile of serum C-peptide (1.95 ng/mL). OR were adjusted for current smoking, alcohol consumption, dyslipidemia, HbA_{1c}, systolic BP, diabetes duration, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, cardiovascular disease, antidiabetic drugs, sex, and age. Antidiabetic drugs included insulin, metformin, sulfonylureas, sodium–glucose cotransporter inhibitors, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, and acarbose.

level for identifying low muscle mass of 1.15 ng/mL needs to be further assessed across diabetes types and in populations with a lower prevalence of low muscle mass and a wider spectrum of diabetes duration, as our findings have restricted generalizability. The potential limitation was missing information on physical activity and nutrition and precluding causal

inference due to the study's observational nature.

In summary, we provide new evidence to support a dose-response association between low C-peptide levels and higher presence of low muscle mass, which suggest that C-peptide is a potential biomarker of low muscle mass in patients with T2DM.

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