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U-shaped association between plasma C-peptide and sarcopenia: A cross-sectional study of elderly Chinese patients with diabetes mellitus

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Abstract

Limited research exists regarding the relationship between fasting plasma C-peptide levels and sarcopenia. As a result, our study aimed to examine this association in elderly Chinese diabetic patients. This cross-sectional study included 288 elderly patients with diabetes mellitus from the Fourth People's Hospital in Guiyang who were enrolled prospectively between March 2020 and February 2023. The independent variable of interest was fasting plasma C-peptide, while the dependent variable was sarcopenia. Data on several covariates, including demographic factors, lifestyle habits, co-morbidities, anthropometric indicators, and laboratory indicators, were also collected. Of the 288 participants, 27.43% (79/288) had sarcopenia. After adjusting for potential confounding variables, we found a U-shaped association between fasting plasma C-peptide levels and sarcopenia, with inflection points identified at approximately 774 pmol/L and 939 mmol/L. Within the range of 50–744 pmol/L, each 100 pmol/L increase in CysC was associated with a 37% decrease in the odds of sarcopenia (odds ratio [OR], 0.63; 95% confidence interval [CI], 0.49 to 0.83; P < 0.001). Additionally, within the range of 939–1694 pmol/L, each 100 pmol/L increase in fasting plasma C-peptide was associated with a 76% increase in the odds of sarcopenia (odds ratio [OR], 1.76; 95% confidence interval [CI], 1.11 to 2.81; P = 0.017). Our study revealed a U-shaped association between fasting plasma C-peptide levels and the likelihood of sarcopenia, with lower risk in the range of 774–939 pmol/L. These findings may assist in the development of more effective prevention and treatment strategies for sarcopenia in elderly diabetic patients.

Introduction

Sarcopenia is a condition where there is progressive loss of skeletal muscle mass and function with age, caused by a decrease in the number of muscle fibers and impaired muscle remodeling due to reduced satellite cell activation and proliferation capacity [1, 2]. The prevalence of sarcopenia is rising, affecting around 25% of people under 70 years old and 40% of those aged 80 years or older [3]. In China, the prevalence of sarcopenia among adults above 65 years old is 15% [4]. As the aging population continues to grow, this number is expected to increase in the future [5]. Sarcopenia poses significant health risks for older adults, including reduced physical

activity and increased incidence of falls and fractures [6]. Effective pharmacological treatments for sarcopenia are currently lacking, making it a major public health concern [7].

Insulinogenic ligand peptide, also known as C-peptide, was initially considered a biologically insignificant byproduct but later found to affect various physiological complications associated with diabetes such as neuropathy, nephropathy, and encephalopathy [8, 9]. A recent animal study also showed that c-peptide administration modulates body composition and protects skeletal muscle mass from type 1 diabetes-induced atrophy [10].

However, there is limited evidence on the association between C-peptide and sarcopenia. Since C-peptide is associated with insulin, which plays an important role in maintaining metabolic homeostasis in the body, including metabolic regulation of muscle tissue [11], and the prevalence of skeletal sarcopenia was significantly higher in elderly diabetic patients than in non-elderly diabetic patients [12], we hypothesized that there might be an association between C-peptide and skeletal sarcopenia in elderly diabetic patients. Thus, we propose a single-center cross-sectional study to observe the association between fasting C-peptide and skeletal sarcopenia in elderly diabetic patients above 65 years old.

## Participants and methods

Study design

This is a cross-sectional study conducted by the Endocrine Care Center of the Fourth People's Hospital in Guiyang, China. In 2021, a health management program was launched for elderly patients with diabetes. The aim of this program is to evaluate the health condition of elderly diabetic patients through a series of physical examinations and health monitoring, thereby preventing the development of chronic complications such as diabetic nephropathy, diabetic foot, and diabetic retinopathy. Additionally, the program includes monitoring for sarcopenia.

Study population

This study prospectively enrolled patients who participated in a health management program for older patients with diabetes at our endocrine care center from May 2021 to February 2023. The patient inclusion process was non-selective and consecutive. The diagnosis of type-2 diabetes mellitus was based mainly on the Chinese Diabetes Control Guidelines 2020 Edition published by the Chinese Diabetes Association. The inclusion criteria were: (1) age greater than or equal to 65 years, (2) clear history or diagnosis of type 2 diabetes. Exclusion criteria were: (1) age younger than 65 years, (2) liver or renal insufficiency, (3) various types of acute infections in combination, (4) tumors, (5) thyroid disease, (6) autoimmune diseases, (7) combined connective tissue diseases, (8) acute myocardial infarction, (9) acute cerebral infarction and cerebral hemorrhage, (10) type 1 diabetes, diabetic nephropathy or hyperosmolar coma, (11) long-term bed rest, local braking or hemiplegia. This study was approved by the Ethics Committee of the Fourth People's Hospital (approval number: [2021]No 005). All patients and their blood relatives were informed in detail about the health management program for elderly diabetic patients, signed informed consent forms, and agreed to use their clinical information and measurement data for data analysis under the premise of anonymisation of personal privacy. Initially, 318 elderly diabetic patients were enrolled, and based on a series of nadir criteria, 288 remained for final data analysis. The specific screening process is detailed in Fig 1.

Variable

Outcome variable. The outcome variable in this study was the presence or absence of sarcopenia, which was recorded as a dichotomous variable (yes/no) in the database. The diagnosis
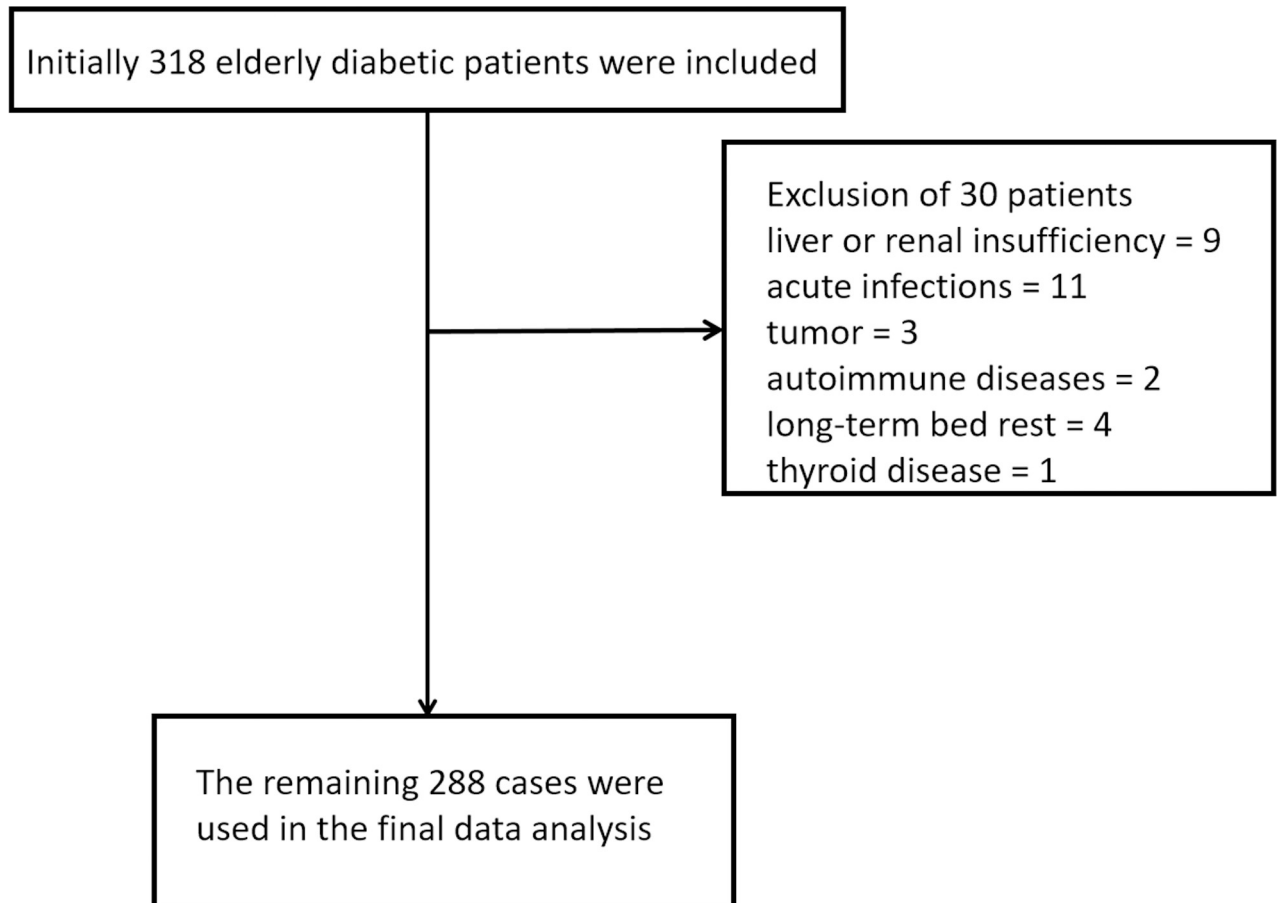
Fig 1. The process of enrolling patients involved in this study.

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of sarcopenia was based on the criteria defined by the Asian Working Group on Sarcopenia Consensus 2019 (AWGS2019) [13], which describes sarcopenia as a condition characterized by low skeletal muscle mass accompanied by low hand grip strength, decreased gait speed, or both. We mainly referred to the cut-off values provided by AWGS2019 for the diagnosis of sarcopenia. Specifically, we used the diagnostic cut-off values of <7.0 kg/m2 for males and <5.4 kg/m2 for females for low skeletal muscle mass, as defined by skeletal muscle index (SMI). For low muscle strength, we used handgrip strength values of <28.0 kg for males and <18.0 kg for females. Additionally, a decrease in gait speed to <1.0 m/s was defined as decreased gait speed. Skeletal muscle mass, muscle strength, and somatic function were measured according to the details provided in S1 Table in S1 File.

Independent variable of interest. The independent variable of interest in this study was fasting C-peptide, which was recorded as a continuous variable in the database. All patients fasted for 8 hours, and venous blood was drawn from the elbow at 8:00am and sent to the central laboratory of the Fourth People's Hospital in Guiyang for testing (Roche Automated Chemistry Analyzer (machine model: E601, Manufacturer: Roche). The testers were blinded to the subjects' sarcopenia status at the time of the test.

Covariates. The selection of covariates was mainly based on previous literature that studied the risk factors for sarcopenia and the clinical experience of the investigators. The covariates used in this study included: (1) socio-demographic variables such as gender (male/

female), age (continuous variable in years), literacy (illiterate + primary/junior high/high school and above), and marital status (married/other (divorced, widowed)); (2) anthropometric indicators such as body mass index (BMI) [14] and fat mass [15]; (3) Barthel Index score [16, 17]; (4) lifestyle habits such as smoking (current smoker/non-smoker/ex-smoker) and drinking status (current drinker/non-drinker/ex-drinker); (5) co-morbid history including hypertension, hyperlipidemia, cardiovascular disease, osteoporosis, and chronic obstructive pulmonary disease (COPD); and (6) other indicators such as hemoglobin [18], glycated hemoglobin, and globulin [19].

Missing data addressing

Because the percentage of missing data in this study was less than 5%, no multiple imputation was employed (S2 Table in S1 File).

Statistical analysis

We summarized continuous variables using means and standard deviations, and categorical variables using numbers and proportions. Additionally, we categorized participants into three groups based on their fasting c-peptide tertiles and used chi-square tests for categorical variables and one-way ANOVA for continuous variables to analyze differences between the three groups. Multivariable logistic regression was used to investigate the relationship between fasting c-peptide and sarcopenia. We displayed model 1 with no adjusted covariates, model 2 which was only adjusted for age, sex, education level and marital status, and model 3 which was adjusted for all covariates presented in Table 1 simultaneously. We divided the fasting C-peptide by 100 to facilitate observation of changes in OR. Therefore, the results should be interpreted per 100 unit change.

As logistic regression is not well-suited for analyzing non-linear associations, we utilized a generalized additive model (GAM) to investigate the relationship between fasting C-peptide and sarcopenia. Initially, we smoothed the curve to observe the true association between fasting C-peptide and sarcopenia, and then determined the inflection point values using a recursive algorithm. Finally, effect values (Odds ratio) and 95% confidence intervals for fasting C-peptide and sarcopenia were calculated using a two-piecewise linear model on both sides of the inflection point. To ensure the robustness of our findings, we conducted a series of sensitivity analyses: (1) Fasting C-peptide was divided into three categories and P for trend was calculated to observe the robustness of the association between fasting C-peptide as a continuous variable and as a categorical variable with sarcopenia. (2) We used a log-likelihood ratio test to determine whether a two-piecewise linear model or a logistic regression model more accurately fit the association between fasting C-peptide and sarcopenia. All analyses were performed using the statistical packages R Foundation (http://www.R-project.org) and EmpowerStats (http://www.empowerstats.com,X&Y Solutions, Inc., Boston, MA). Statistical significance was defined as a two-sided p-value less than 0.05.

Results and discussion

The baseline characteristics of Chinese HF patients

We analyzed and compared the distribution of patient characteristics between the sarcopenic and non-sarcopenic groups. The results are presented in Table 1. Our study included elderly diabetic patients, with a mean age of 69.74 ± 6.28 years, and a male-to-female ratio of 1:1.6, with males accounting for 37.5% (108/288) of the total patients. Of the patients, 27.43% (79/288) were found to have sarcopenia. Compared to non-sarcopenic patients, those in the

Table 1. Baseline characteristics of elder patients with diabetes categorized by fasting C-peptide (tertile).

	Non-myasthenia gravis	Sarcopenia	P-value
N	209	78	
BMI, mean±sd, (kg/m2)	24.30 ± 3.06	23.10 ± 2.72	0.003
Fat mass, mean±sd	18.36 ± 7.22	20.46 ± 6.63	0.026
Diabetes duration time, mean±sd, year	9.77 ± 7.44	11.64 ± 5.64	0.045
Glycated hemoglobin, mean±sd, %	8.82 ± 2.62	9.14 ± 2.54	0.354
Hemoglobin, mean±sd, g/L	141.44 ± 17.72	136.06 ± 16.60	0.021
Globulin, mean±sd, g/L	30.07 ± 4.92	30.86 ± 5.77	0.250
Fasting C-peptide, mean±sd, pmol/L	766.09 ± 316.90	714.18 ± 435.50	0.269
Age, mean±sd, year	69.25 ± 6.06	71.12 ± 6.75	0.025
Bartel Index, mean±sd	96.62 ± 6.70	90.75 ± 10.91	<0.001
Sex, No (%)			0.233
Male	83 (39.71%)	25 (32.05%)	
Fmale	126 (60.29%)	53 (67.95%)	
Education level, No (%)			0.710
Primary + illiterate	34 (17.62%)	13 (18.31%)	
junior high school	84 (43.52%)	27 (38.03%)	
High school and above	75 (38.86%)	31 (43.66%)	
Marital status, No (%)			0.843
Married	152 (74.51%)	56 (75.68%)	
Living alone (divorced, widowed)	52 (25.49%)	18 (24.32%)	
Hypertension history, No (%)			0.028
No	144 (70.24%)	44 (56.41%)	
Yes	61 (29.76%)	34 (43.59%)	
Hyperlipidemia, No (%)			0.937
No	53 (25.85%)	20 (26.32%)	
Yes	152 (74.15%)	56 (73.68%)	
History of osteoporosis, No (%)			0.035
No	148 (70.81%)	45 (57.69%)	
Yes	61 (29.19%)	33 (42.31%)	
COPD history, No (%)			0.247
No	92 (44.88%)	41 (52.56%)	
Yes	113 (55.12%)	37 (47.44%)	
Smoking status, No (%)			0.019
Non-smoker	128 (65.31%)	36 (46.75%)	
Current smoker	54 (27.55%)	32 (41.56%)	
Smoking cessation	14 (7.14%)	9 (11.69%)	
Alcohol consumption status, No (%)			<0.001
Never drank alcohol	160 (80.81%)	43 (55.13%)	
Drinking alcohol	13 (6.57%)	19 (24.36%)	
Quit drinking	25 (12.63%)	16 (20.51%)	
Cardiovascular disease, No (%)			0.098
No	106 (50.72%)	31 (39.74%)	
Yes	103 (49.28%)	47 (60.26%)	

Note: The difference between the sample sum of each column and the total number shown in Table 1 is due to missing data

Abbreviation:

BMI: body mass index

SD: Standard deviation

COPD: Chronic Obstructive Pulmonary Disease

sarcopenic group had a lower body mass index, fasting plasma C-peptide levels, hemoglobin levels, and Bartel Index (indicating poorer physical function). In contrast, elderly diabetic patients in the sarcopenic group had higher fat mass, duration of diabetic load, combined cardiovascular disease, hypertension, diabetes mellitus, osteoporosis, smoking and alcohol consumption compared to the non-sarcopenic group. higher. There were no statistically significant differences in HbA1C levels, globulin, education, gender, marital status, hyperlipidemia, and COPD between the two groups.

The association between fasting C-peptide and sarcopenia obtained from logistic regression model, both univariate and multivariable

We investigated the association between fasting C-peptide and sarcopenia using different covariate adjustment strategies (Table 2). In model 1 (the unadjusted model), the results indicated that there was no significant correlation between fasting C-peptide and the prevalence of sarcopenia (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.85 to 1.00; P = 0.065). The same results were obtained from model 2. Even after adjusting for sex, age, education level, and marital status, we still did not observe a substantial association between fasting C-peptide (per 100 pmol/L) and sarcopenia (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.84 to 1.01; P = 0.085). When we adjusted for all the covariates listed in Table 1 (model 3, fully-adjusted model), we found a 4% decrease in the probability of sarcopenia for each 100 pmol/L increase in fasting C-peptide. Nevertheless, due to the wider distribution of confidence intervals, we could not reject the null hypothesis (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.85 to 1.07; P = 0.442).

To conduct a sensitivity analysis, we transformed fasting C-peptide into a categorical variable based on tertile and assessed whether the outcomes remained consistent when fasting C-peptide was used as either a categorical or continuous variable (Table 2). The p-values of the trend test for the three models were 0.056 (model 1), 0.093 (model 2), and 0.418 (model 3), respectively. These outcomes were consistent with the findings when fasting C-peptide was applied as a continuous variable.

The nonlinearity addressing

To investigate the potential nonlinear relationship between fasting C-peptide and sarcopenia, we utilized a GAM model and smoothed curve fitting to reveal a U-shaped correlation between

Table 2. Associations between fasting C-peptide and sarcopenia using logistic regression models.

|	model 1 OR, 95%CI, P value	model 2 OR, 95%CI, P value	model 3 OR, 95%CI, P value
Sarcopenia (Yes/No)			
Fasting C-peptide (continuous variable)	0.92 (0.85, 1.00) 0.065	0.92 (0.84, 1.01) 0.085	0.96 (0.85, 1.07) 0.442
Fasting C-peptide (grouped by tertile)			
Low	Reference	Reference	Reference
Middle	0.44 (0.23, 0.84) 0.012	0.37 (0.18, 0.75) 0.006	0.38 (0.16, 0.93) 0.035
High	0.54 (0.29, 1.02) 0.057	0.58 (0.29, 1.13) 0.107	0.71 (0.29, 1.72) 0.443
P for trend	0.056	0.093	0.418

Abbreviation:

OR: odds ratio

CI: Confidence interval

model 1: No covariates were adjusted for

model 2: Adjusted for age, sex, education level and marital status

model 3: Adjusted for all covariates presented in Table 1.
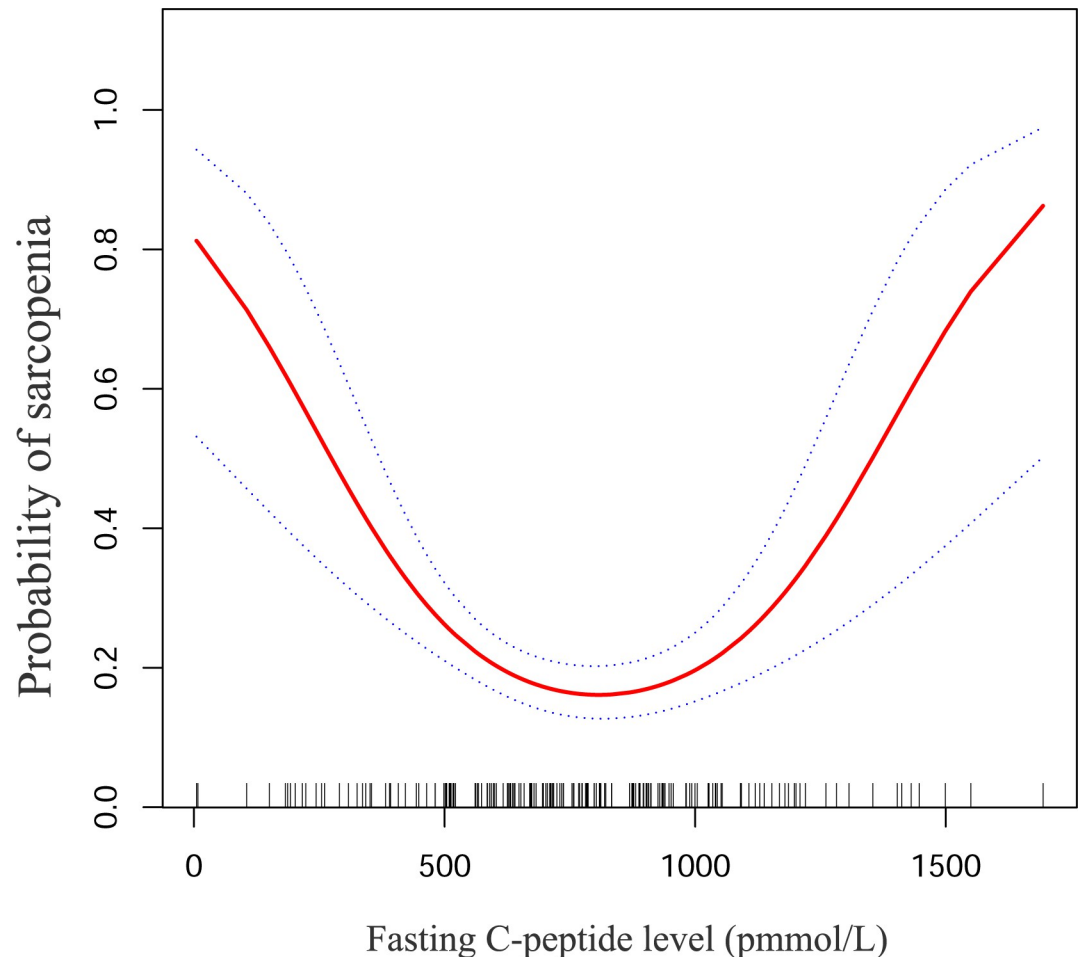
Fig 2. A non-linear relationship between fasting C-peptide and sarcopenia. The level of fasting C-peptide is plotted on the horizontal axis, while the probability of sarcopenia is plotted on the vertical axis. The middle line reflects the trend in the association between C-peptide and sarcopenia, while the upper and lower lines indicate the corresponding 95% confidence intervals.

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these two variables (Fig 2). To better explicate this U-shaped curve, we applied a recursive algorithm to calculate the inflection points of fasting C-peptide, which were determined to be 744 and 939 pmol/L. Thereafter, we deployed a two-piece linear model to estimate the effect values and confidence intervals on both sides of the inflection points (Table 3). Our results showed that for every 100 pmol/L increase in fasting C-peptide within the range of 50–744 pmol/L, there was a tendency for the probability of sarcopenia to decrease by 37% (odds ratio [OR] 0.63; 95% confidence interval [CI] 0.49 to 0.83; $P < 0.001$). On the contrary, we did not observe a substantial association between fasting c-peptide and the probability of sarcopenia when fasting c-peptide was within the 744–939 pmol/L interval (odds ratio [OR] 1.27; 95% confidence interval [CI] 0.34 to 4.59; $P = 0.720$). However, when fasting C-peptide was in the 939–1694 range, each 100 pmol/L increase in fasting C-peptide was associated with a 76% increase in the probability of sarcopenia (odds ratio [OR] 1.76; 95% confidence interval [CI] 1.11 to 2.81; $P = 0.017$)). Additionally, upon comparing the logistic regression model fit with the two-piece linear model fit, the log likelihood ratio yielded a P value of less than 0.001, indicating that the two-piece linear model provided a better fit for the association between fasting C-peptide and sarcopenia.

Table 3. Exploration of nonlinear association between fasting C-peptide and sarcopenia using two-piecewise linear model.

	Probability of sarcopenia OR, 95% CI, P value
Fitting model by standard binary logistic regression model (per 100 change of fasting C-peptide)	0.96 (0.85, 1.07) 0.442
Fitting model by two-piecewise linear model (per 100 change of fasting C-peptide)	
Inflection point (Actual value of fasting C-peptide / 100)	7.74 and 9.39
≤ 7.74	0.63 (0.49, 0.83) 0.0007
>7.74 and ≤ 9.39	1.27 (0.35, 4.59) 0.7203
> 9.39	1.76 (1.11, 2.81) 0.0173
P for log likely ratio test	<0.001

We conducted a single-centre cross-sectional study in an elderly Chinese diabetic population to investigate the association between fasting plasma C-peptide and sarcopenia. The results showed that both low and high fasting C-peptide levels were associated with a higher probability of sarcopenia, indicating a U-shaped association between C-peptide and sarcopenia. We observed that fasting C-peptide was associated with a lower probability of sarcopenia within the range of 774 to 939 pmol/L.

Previous evidence on the association of fasting C-peptide with sarcopenia is insufficient. Lu YX et al [20]. found a negative association between fasting C-peptide and the risk of sarcopenia in 41 diabetic patients and 205 non-diabetic patients, but their study only included 41 diabetic patients and diabetes status was only adjusted as a covariate. In addition, they only adjusted for sex, age, diabetes status, and total body fat mass. Our study explored possible non-linear associations and found negative associations between fasting C-peptide and sarcopenia in the 50–774 pmol/L range, which is partially consistent with the results of Hitomi Miyake et al [21]. and Tanaka K et al [22]. Hitomi Miyake et al. found that fasting C-peptide values were significantly higher in patients in the high skeletal muscle content group than in the low skeletal muscle content group in a study on the association between low skeletal muscle content and all-cause mortality in a diabetic population. Tanaka K et al. similarly found a negative association between C-peptide and sarcopenia in 191 men with type 2 diabetes but did not explore non-linear associations.

In contrast to earlier findings, our study discovered a link between high fasting C-peptide levels (939 pmol/L–1700 pmol/L) and sarcopenia in elderly diabetes patients, which we believe is the first of its kind. We propose many explanations for this unusual U-shaped association trend: First, C-peptide is an insulin precursor that, unlike insulin, is filtered by the kidneys and eliminated in the urine rather than being metabolized by the liver. As a result, monitoring C-peptide levels can reflect islet cell function without being influenced by external influences such as food [23]. Low fasting C-peptide levels may indicate insulin production and release inhibition, resulting in metabolic inefficiency, decreased muscle mass, and an increased risk of sarcopenia [24]. Previous research has shown that insulin is a key regulator of glucose absorption and use in peripheral tissues, including muscle [25]. Inadequate insulin secretion and release caused by low C-peptide levels can result in diminished insulin signaling and impaired glucose metabolism, resulting in decreased amino acid absorption and protein synthesis in muscle, resulting in decreased muscle mass and an increased risk of sarcopenia [25, 26]. Furthermore, low insulin levels stimulate glucagon secretion, which causes muscle proteolysis and amino acid release into the circulation, increasing the risk of sarcopenia [27]. High fasting C-peptide levels, on the other hand, may indicate insulin resistance [28, 29]. As a result, increased

insulin signaling, particularly in peripheral tissues, might result in decreased muscle mass. Sarcopenia is caused by three mechanisms: (1) increased proteolytic metabolism and decreased protein synthesis in skeletal muscle; (2) increased expression of the FoxO family, which either directly or indirectly attenuates skeletal muscle; and (3) autophagy in skeletal muscle cells [29]. Furthermore, Sara Manrique-Arija et al [30]. discovered that insulin resistance was associated with higher levels of CRP and interleukin-1 in a cross-sectional study of arthritis patients, whereas previous literature confirmed that muscle atrophy is a major determinant of vulnerability in old age and is associated with high levels of inflammation [31]. Thus, despite the fact that this study was merely cross-sectional in nature, the association between high C-peptide, insulin resistance, inflammation, and muscle atrophy may be the cause of the positive correlation between these variables. To establish definitive evidence, additional high-level investigations, including cohort studies and randomized controlled clinical trials, are required. Second, high levels of C-peptide point to poorly controlled diabetes. On the other hand, prior clinical research indicates that vulnerability in older people is frequently linked to inadequate chronic disease management [32]. As a result, this may also be one of the possible causes of the positive association between high C-peptide levels and muscle atrophy. Lastly, 25-hydroxyvitamin D3 in elderly people is frequently linked to muscular atrophy [33]. We used the cut points of 7.74 and 9.39 to divide the population into three categories. The levels of 25-hydroxyvitamin D3 were substantially greater in the two low C-peptide groups (7.74 and 7.74–9.39) than in the high C-peptide group (>9.39), according to our research (S1 Fig in S1 File). Therefore, the considerable drop in 25-hydroxyvitamin D3 levels may potentially be linked to the positive connection between a high C-peptide group and muscle atrophy.

Our study reports a U-shaped association between fasting C-peptide levels and the risk of sarcopenia, which, to our knowledge, has not been previously reported in the literature. Our findings suggest that in elderly diabetic patients, maintaining appropriate C-peptide levels is crucial for normal metabolism and muscle mass and may prevent the development of sarcopenia. While our study provides relevant clinical data for future research on this topic, we acknowledge that cross-sectional evidence is relatively weak and further studies, such as prospective cohort studies, are required for validation. We continue to follow up with elderly people with diabetes mellitus but without concomitant sarcopenia in our center, and as such, our findings have important implications for future research on this topic. By utilizing easily accessible, simple, and inexpensive assessments such as fasting C-peptide levels, healthcare professionals can identify patients at risk of sarcopenia early on and take preventive measures accordingly. In summary, our study supports the notion that monitoring C-peptide levels in elderly diabetic patients is important for maintaining normal metabolism and muscle mass, thus avoiding the development of sarcopenia. We hope that our findings will promote further research in this area and eventually lead to the adoption of more effective prevention and treatment strategies for sarcopenia.

Our study has several strengths that contribute to its validity. Firstly, we utilized advanced algorithms (GAM model and two-piece linear model) which allowed us to effectively detect a true association between fasting C-peptide levels and the risk of sarcopenia in elderly Chinese diabetics. Secondly, we conducted a series of sensitivity analyses and utilized different variable tuning strategies, reducing the possibility that our findings were merely incidental and increasing the robustness of our results. Thirdly, our study's prospective, continuous, and non-selective inclusion of patients, combined with the application of blinding to reduce possible distortion of results due to selection bias and observation bias.

However, our study does have some limitations that must be taken into account when interpreting our findings. Firstly, the study population was limited to Chinese diabetics and caution should be taken when extrapolating our findings to other races. Secondly, our results are only

applicable to diabetic patients over 65 years of age and cannot be generalized to other populations (e.g., type 1 diabetes, hepatic and renal insufficiency, tumor patients, autoimmune system diseases, etc.). Thirdly, as an observational cross-sectional study, our findings are subject to confounding, although we have rigorously adjusted for confounders and assessed the robustness of our results through sensitivity analysis. Fourthly, the nature of the cross-sectional study design limits our ability to assess causality; we can only observe associations. Finally, we can only adjust for measurable confounders, making it impossible to adjust for unmeasurable confounding factors. Therefore, future clinical studies with higher levels of evidence in larger populations are warranted to validate our findings.

Conclusion

In conclusion, our study found that the association between fasting plasma C-peptide levels and the risk of sarcopenia is U-shaped. Specifically, fasting plasma C-peptide was associated with a lower risk of sarcopenia when in the range of 774–939 pmol/L. We hope that our findings will contribute to the development of more effective prevention and treatment strategies for sarcopenia in elderly diabetic patients.

Supporting information

S1 Checklist. STROBE statement—checklist of items that should be included in reports of observational studies.
(DOCX)

S1 File. The "Supporting information" as a whole file contains two tables and one figure.
They are listed separately as follows: S1 Fig. The distribution of 25-hydroxyvitamin D3 in different Group of C-peptide. The y-axis represents the levels of 25-hydroxyvitamin D3. The different modes of bars represent different C-peptide groups. The error bars represent the standard deviation. S1 Table: The measurement of Skeletal muscle mass, muscle strength, and somatic function. The first column of the table lists the names of the test indicators, and the second column lists the corresponding test methods and procedures. S2 Table: The description of missing data. The first column represents variable names, the second and third columns represent the number of missing and non-missing samples, respectively, and the fourth column represents the proportion of missing values.
(DOCX)

S2 File.
(PDF)

S3 File.
(PDF)

S1 Data.
(XLS)

Author Contributions

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References

1. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011; 12(4): 249–56. https://doi.org/10.1016/j.jamda.2011.01.003 PMID: 21527165

2. Jones G, Trajanoska K, Santanasto AJ, Stringa N, Kuo CL, Atkins JL, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. Nat Commun. 2021; 12(1): 654. https://doi.org/10.1038/s41467-021-20918-w PMID: 33510174

3. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998; 147(8): 755–63. https://doi.org/10.1093/oxfordjournals.aje.a009520 PMID: 9554417

4. Tyrovolas S, Koyanagi A, Olaya B, Ayuso-Mateos JL, Miret M, Chatterji S, et al. Factors associated with skeletal muscle mass, sarcopenia, and sarcopenic obesity in older adults: a multi-continent study. J Cachexia Sarcopenia Muscle. 2016; 7(3): 312–21. https://doi.org/10.1002/jcsm.12076 PMID: 27239412

5. Wu M, Wei Y, Lv J, Guo Y, Pei P, Li JC, et al. Associations of muscle mass, strength, and quality with all-cause mortality in China: a population-based cohort study. Chin Med J (Engl). 2022; 135(11): 1358–1368. https://doi.org/10.1097/CM9.0000000000002193 PMID: 35838536

6. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019; 48(4): 601.

7. Jang YC, Liu Y, Hayworth CR, Bhattacharya A, Lustgarten M, Muller FL, et al. Dietary restriction attenuates age-associated muscle atrophy by lowering oxidative stress in mice even in complete absence of CuZnSOD. Aging Cell. 2012; 11(5): 770–82. https://doi.org/10.1111/j.1474-9726.2012.00843.x PMID: 22672615

8. Bonser AM, Garcia-Webb P. C-peptide measurement: methods and clinical utility. Crit Rev Clin Lab Sci. 1984; 19(4): 297–352. https://doi.org/10.3109/10408368409165766 PMID: 6373142

9. Lachin JM, McGee P, Palmer JP. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes. 2014; 63(2): 739–48. https://doi.org/10.2337/db13-0881 PMID: 24089509

10. Maurotti S, Pujia R, Galluccio A, Nucera S, Musolino V, Mare R, et al. Preventing muscle wasting: proinsulin C-peptide prevents loss in muscle mass in streptozotocin-diabetic rats. J Cachexia Sarcopenia Muscle. 2023; 14(2): 1117–1129. https://doi.org/10.1002/jcsm.13210 PMID: 36878894

11. Feraco A, Gorini S, Armani A, Camajani E, Rizzo M, Caprio M. Exploring the Role of Skeletal Muscle in Insulin Resistance: Lessons from Cultured Cells to Animal Models. Int J Mol Sci. 2021. 22(17). https://doi.org/10.3390/ijms22179327 PMID: 34502235

12. Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, et al. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care. 2010; 33(7): 1497–9. https://doi.org/10.2337/dc09-2310 PMID: 20413515

13. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc; 2020. 21(3): 300–307.e2. https://doi.org/10.1016/j.jamda.2019.12.012 PMID: 32033882

14. Chung JY, Kang HT, Lee DC, Lee HR, Lee YJ. Body composition and its association with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity. Arch Gerontol Geriatr. 2013. 56(1): 270–8. https://doi.org/10.1016/j.archger.2012.09.007 PMID: 23079031

15. Merchant RA, Seetharaman S, Au L, Wong MWK, Wong BLL, Tan LF, et al. Relationship of Fat Mass Index and Fat Free Mass Index With Body Mass Index and Association With Function, Cognition and Sarcopenia in Pre-Frail Older Adults. Front Endocrinol (Lausanne). 2021. 12: 765415. https://doi.org/10.3389/fendo.2021.765415 PMID: 35002957

16. Sakai K, Nakayama E, Yoneoka D, Sakata N, Iijima K, Tanaka T, et al. Association of Oral Function and Dysphagia with Frailty and Sarcopenia in Community-Dwelling Older Adults: A Systematic Review and Meta-Analysis. Cells. 2022; 11(14):2199. https://doi.org/10.3390/cells11142199 PMID: 35883642

17. Zhao WT, Yang M, Wu HM, Yang L, Zhang XM, Huang Y. Systematic Review and Meta-Analysis of the Association between Sarcopenia and Dysphagia. J Nutr Health Aging. 2018. 22(8): 1003–1009. https://doi.org/10.1007/s12603-018-1055-z PMID: 30272106

18. Liu Q, You J, Zhong M, Wu Z, Geng Y, Huang C. Hemoglobin level is negatively associated with sarcopenia and its components in Chinese aged 60 and above. Front Public Health. 2023. 11: 1081843. https://doi.org/10.3389/fpubh.2023.1081843 PMID: 36992883

19. Yuan S, Larsson SC. Epidemiology of sarcopenia: Prevalence, risk factors, and consequences. Metabolism. 2023: 155533. https://doi.org/10.1016/j.metabol.2023.155533 PMID: 36907247

20. Lu Y, Lim WS, Jin X, Nyunt MSZ, Fulop T, Gao Q, et al. Lower insulin level is associated with sarcopenia in community-dwelling frail and non-frail older adults. Front Med (Lausanne). 2022; 9: 971622. https://doi.org/10.3389/fmed.2022.971622 PMID: 36482911

21. Miyake H, Kanazawa I, Tanaka KI, Sugimoto T. Low skeletal muscle mass is associated with the risk of all-cause mortality in patients with type 2 diabetes mellitus. Ther Adv Endocrinol Metab. 2019. 10: 2042018819842971. https://doi.org/10.1177/2042018819842971 PMID: 31040938

22. Tanaka K, Kanazawa I, Sugimoto T. Reduction in Endogenous Insulin Secretion is a Risk Factor of Sarcopenia in Men with Type 2 Diabetes Mellitus. Calcif Tissue Int. 2015. 97(4): 385–90. https://doi.org/10.1007/s00223-015-9990-8 PMID: 25850525

23. Kjems LL, Vølund A, Madsbad S. Quantification of beta-cell function during IVGTT in Type II and non-diabetic subjects: assessment of insulin secretion by mathematical methods. Diabetologia. 2001. 44 (10): 1339–48. https://doi.org/10.1007/s001250100639 PMID: 11692185

24. Liu ZJ, Zhu CF. Causal relationship between insulin resistance and sarcopenia. Diabetol Metab Syndr. 2023. 15(1): 46. https://doi.org/10.1186/s13098-023-01022-z PMID: 36918975

25. Armandi A, Rosso C, Caviglia GP, Ribaldone DG, Bugianesi E. The Impact of Dysmetabolic Sarcopenia Among Insulin Sensitive Tissues: A Narrative Review. Front Endocrinol (Lausanne). 2021. 12: 716533. https://doi.org/10.3389/fendo.2021.716533 PMID: 34858322

26. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001. 414(6865): 799–806. https://doi.org/10.1038/414799a PMID: 11742412

27. Pinheiro-Dardis CM, Gutierres VO, Assis RP, Peviani SM, Delfino GB, Durigan JLQ, et al. Insulin treatment reverses the increase in atrogin-1 expression in atrophied skeletal muscles of diabetic rats with acute joint inflammation. Ther Clin Risk Manag. 2018; 14: 275–286. https://doi.org/10.2147/TCRM.S142948 PMID: 29497304

28. Kaga H, Tamura Y, Takeno K, Kakehi S, Someya Y, Funayama T, et al. Higher C-Peptide Level During Glucose Clamp Is Associated With Muscle Insulin Resistance in Nonobese Japanese Men. J Endocr Soc. 2019; 3(10): 1847–1857. https://doi.org/10.1210/js.2019-00167 PMID: 31555755

29. Wang Y, Zou X, Cai X, Liu W, Chen L, Zhang R, et al. Urinary C-peptide/creatinine ratio: A useful biomarker of insulin resistance and refined classification of type 2 diabetes mellitus. J Diabetes. 2021; 13 (11): 893–904. https://doi.org/10.1111/1753-0407.13203 PMID: 34051046

30. Manrique S, Mena M, Ureña I, Rioja J, Valdivielso P, Ginel-Mendoza L, Cumulative inflammatory burden and obesity as determinants of insulin resistance in patients with established rheumatoid arthritis: cross-sectional study. BMJ Open. 2021; 11(2):e044749. https://doi.org/10.1136/bmjopen-2020-044749 PMID: 33563625

31. Bilgin S, Aktas G, Kahveci G, Atak BM, Kurtkulagi O, Duman TT. Does mean platelet volume/lymphocyte count ratio associate with frailty in type 2 diabetes mellitus? Bratisl Lek Listy. 2021; 122(2):116–119. https://doi.org/10.4149/BLL_2021_017 PMID: 33502879

32. Akan S, Aktas G, Relationship between frailty, according to three frail scores, and clinical and laboratory parameters of the geriatric patients with type 2 Diabetes Mellitus. Rev Assoc Med Bras (1992). 2022; 68(8):1073–1077. https://doi.org/10.1590/1806-9282.20220271 PMID: 36000603

33. Kocak MZ, Aktas G, Atak B, Bilgin S, Kurtkulagi O, Duman TT, et al. THE ASSOCIATION BETWEEN VITAMIN D LEVELS AND HANDGRIP STRENGTH IN ELDERLY MEN. Acta Endocrinol (Buchar). 2020; 16(2):263–266. https://doi.org/10.4183/aeb.2020.263 PMID: 33029248