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The association between glucose fluctuation with sarcopenia in elderly patients with type 2 diabetes mellitus

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Abstract. – OBJECTIVE: Growing evidence shows that sarcopenia is more prevalent in patients with type 2 diabetes mellitus (T2DM) than in the normal population. However, currently, data on the relationship between blood glucose fluctuation and sarcopenia in elderly patients with T2DM are still limited.

PATIENTS AND METHODS: In this study, 280 patients ≥ 60 years with T2DM were divided into sarcopenic group and non-sarcopenic group, according to the diagnostic criteria of 2019 Asian Working Group for Sarcopenia. They wore MeiQi to acquire the indexes including time in range (TIR), time above range (TAR), time below range (TBR), mean amplitude of glycemic excursion (MAGE), coefficient of Variation (CV), blood glucose standard deviation (SD), largest amplitude of glycemic excursions (LAGE) and mean glucose (MG). The prevalence rate of sarcopenia was statistically analyzed and the different indicators of glucose fluctuation between the two groups were compared. We analyzed the indexes of glucose fluctuation and appendicular skeletal muscle mass index (ASMI), handgrip strength, the time of five times sit to stand test (FTSST) with Spearman's correlation analysis. Logistic regression was used to analyze the influence factors for sarcopenia.

RESULTS: The prevalence of sarcopenia was 15.36%. TIR, MG and TAR were correlated with ASMI, handgrip strength, the time of FTSST. MG and TAR were risk factors for sarcopenia, while TIR was the protective factor of sarcopenia. After adjusting mixing factors, logistic regression analysis showed that TIR was an independent protective factor. The result of the Chi-square test showed that the incidence of sarcopenia in different TIR ranges was different: the proportion of patients with sarcopenia was 40.48% (TIR ≤50%), 20.41% (50%<TIR≤70%) and 8.47% (TIR >70%).

CONCLUSIONS: TIR is associated with sarcopenia in elderly T2DM patients. Furtherly, the incidence rate of sarcopenia decreases with the increase of TIR.

Key Words:
Sarcopenia, Blood glucose fluctuation, Time in range.

Introduction

Sarcopenia is a syndrome of reduced muscle mass, decreased muscle strength and decreased function that occurs with increasing age[1]. With the aging of the Chinese population, the incidence of sarcopenia is gradually increasing. In recent years, a number of domestic and foreign studies[2] have found a higher incidence of sarcopenia in T2DM patients than in the normal population. Thus, sarcopenia is considered one of the chronic complications in patients with T2DM[3]. Previous studies[4,5] have found that glucose fluctuation is associated with chronic complications such as diabetic peripheral neuropathy, diabetic retinopathy, and diabetes nephropathy. However, the studies on glucose fluctuation and sarcopenia were few. The purpose of this study was to explore the correlation between blood glucose fluctuation and sarcopenia in elderly patients with T2DM diabetes. This will provide the most appropriate blood glucose range for patients with sarcopenia in elderly T2DM.

Patients and Methods

Subjects

280 patients with T2DM were hospitalized in the Department of Endocrinology, Hefei Second People's Hospital from December 2020 to June 2022. Patients who were 60 years old and over, diagnosed with T2DM, without acute complications of diabetes and whose hypoglycemic regimen remained unchanged in the last 3 months were included in the study. The exclusion criteria were: (1) patients with serious systemic diseases [e.g., severe renal diseases including with estimated glomerular filtration rate (GFR) <15 mL/min/1.73 m^2 or under-

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going renal replacement therapy, liver failure, heart failure with New York Heart Association (NYHA) class II or III, respiratory failure, acute infectious, malignant diseases, etc.]; (2) patients with primary hyperparathyroidism and diseases related to bone metabolism; (3) patients receiving glucocorticoid therapy; (4) patients with chronic gastrointestinal diseases; (5) patients taking vitamin D and other drugs that affect bone metabolism in the last 3 months. All patients were informed and signed the informed consent, and the Ethics Committee of the hospital approved the study.

Demographic Characteristics and Biochemical Data

We collected the data of recruited patients including age, gender, duration of diabetes, height, weight and body mass index (BMI). All recruited patients had venous blood samples in the morning after 10 hours of overnight fasting to test fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), glycated hemoglobin (HbA1c), fasting C-peptide (F-CP), fasting insulin, blood calcium, blood phosphorus, parathyroid hormone (PTH) and 25-hydroxyvitamin D. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated using: [fasting insulin (uU/mL) × fasting glucose (mmol/l)/22.5][6]. The morning urine was collected to measure urinary albumin/creatinine ratio (UACR). According to the diagnostic criteria of diabetic complications in the Chinese guidelines for the prevention and treatment of type 2 diabetes[7], lower limb arterial vascular ultrasound, electro neurophysiology examination and fundus photography were improved to screen for diabetic peripheral angiopathy (PAD), diabetic peripheral neuropathy (DPN), diabetes retinopathy (DR) and diabetes nephropathy (DN).

Continuous Blood Glucose Monitoring

On the first day of hospitalization, all enrolled patients wore MeiQi (Model RGMS-II), a continuous blood glucose monitoring system, for the next 3 days, to obtain the following parameters: time in range (TIR), time above range (TAR), time below range (TBR), mean amplitude of glycemic excursion (MAGE), coefficient of Variation (CV), MG, blood glucose standard deviation (SD), largest amplitude of glycemic excursions (LAGE). When MeiQi's was used, the patients keep their diet, exercise routines and hypoglycemic regimen as usual.

Diagnosis and Grouping of Sarcopenia

The 2019 Asian Consensus on sarcopenia[1] indicates these conditions as: (1) Reduced muscle mass defined as appendicular skeletal muscle mass index (ASMI) <7.0 Kg/m^2 in men and ASMI <5.4 Kg/m^2 in women; (2) Reduced muscle strength defined as handgrip strength <28 Kg in men and handgrip strength <18 Kg in women; (3) Reduced muscle function defined as the time of five times sit to stand test (FTSST) >12 seconds. The condition 1 and 2 or 3 were met for the diagnosis of sarcopenia. The skeletal muscle mass of the patient's extremities was measured using dual-energy X-ray absorptiometry (DXA) and the skeletal muscle mass index of the limbs (ASMI) was calculated using: [skeletal muscle mass of the extremities (Kg)/height (m^2)]. Patients' dominant handgrip strength was measured three times using an electronic grip strength meter (Xiangshan EH101) with a one-minute interval between each measurement and the maximum value was recorded.

The patient sat on forty-three centimeters highchair without armrests, with feet on the ground, back not against the back of the chair, arms crossed in front of the chest and completed five rising and sitting movements as fast as possible after hearing the command to start the test. The time in seconds for the subject to complete the five movements was recorded. The test was performed three times with one minute of rest between each test, and the average time of the three tests was used as the test result. Those who met the diagnostic criteria of sarcopenia were considered as sarcopenic group, otherwise they were considered as non-sarcopenic group.

Exercise Volume Assessment

The Chinese version of the International Physical Activity Questionnaire[7] (IPAQ-C) with a total of 27 entries was used to investigate the exercise volume of the enrolled patients, then they were divided into high intensity, medium intensity and low intensity.

Statistical Analysis

Data analysis was conducted by SPSS v. 26.0 (IBM Corp., Armonk, NY, USA). The distributions of data were assessed for normality using the Shapiro-Wilk's test. Differences in demographics and glucose fluctuation levels with and without sarcopenia were examined by student's *t*-tests (for parametric variables) or the Mann-Whitney U test (for non-parametric variables). Categorical variables were analyzed by the Fisher's exact test. To

identify the factors associated with sarcopenia, we performed logistic regression analysis. Statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

The 15.36% patients were diagnosed as sarcopenia in all recruited patients. Age, male prevalence, UACR and the time of FTSST were higher in the sarcopenic group than in the non-sarcopenic group. While handgrip strength, BMI, F-CP, HOMA-IR, 25-hydroxyvitamin D and ASMI were lower in the sarcopenic group than in the non-sarcopenic group (Table I) ($p < 0.05$).

Glucose Fluctuation Indexes

TIR was lower in the sarcopenic group than non-sarcopenic group. While SD, TAR and MG were higher in the non-sarcopenic group (Table II) ($p < 0.05$).

The Correlation Between ASMI, Handgrip Strength, Time of FTSST and Glucose Fluctuation Indexes

Spearman's correlation analysis was used to analyze the relationship between ASMI, hand-

Table I. Characteristics of patient in two groups.

	Non-sarcopenic group n=237	Sarcopenic group n=43	*p*-value
Age (years)	63.00 (60.00, 67.00)	71.00 (62.75, 73.00)	<0.001
Handgrip strength (Kg)	26.20 (20.20, 31.00)	17.80 (14.18, 24.73)	<0.001
Male n (%)	84.00 (35.40%)	27.00 (62.80%)	0.001
Duration of diabetes (years)	7.00 (4.00, 12.00)	12.00 (8.00, 16.75)	0.499
Height (meter)	1.62±0.08	1.61±0.09	0.784
BMI (Kg/m^2)	24.22 (22.03, 26.13)	23.55 (21.90, 24.92)	0.037
FPG (mmol/l)	7.33 (5.90, 9.13)	6.75 (5.86, 10.34)	0.357
Blood calcium (mmol/l)	2.31 (2.25, 2.41)	2.35 (2.26, 2.39)	0.261
Blood phosphorus (mmol/l)	1.21 (1.09, 1.34)	1.14 (1.03, 1.24)	0.071
PTH (pg/ml)	47.85 (40.33, 55.60)	48.10 (34.30, 87.30)	0.482
TG (mmol/l)	1.36 (0.90, 1.96)	1.43 (1.58, 2.01)	0.316
TC (mmol/l)	4.41 (3.86, 5.18)	4.65 (3.32, 5.29)	0.369
HDL (mmol/l)	1.20 (1.04, 1.36)	1.25 (0.93, 1.38)	0.376
LDL (mmol/l)	2.81 (2.37, 3.33)	2.47 (1.61, 3.10)	0.106
HbA1c (%)	7.90 (6.70, 9.50)	7.85 (6.75, 10.03)	0.175
F-CP (ng/ml)	1.84 (1.11, 2.56)	1.41 (0.81, 2.00)	0.016
HOMA-IR	0.49 (0.30, 1.04)	0.22 (0.12, 0.58)	0.001
UACR (mg/g.cr)	10.00 (6.50, 19.80)	24.95 (15.23, 77.83)	<0.001
25-hydroxyvitamin D (ng/ml)	30.00 (26.00, 40.00)	29.50 (21.96, 41.25)	0.002
ASMI (Kg/m^2)	6.64 (6.00, 7.34)	5.46 (5.16, 6.23)	<0.001
FTSST (seconds)	7.43 (6.24, 8.71)	11.24 (8.89, 13.09)	<0.001
Physical activity			
High intensity	51.00 (21.50%)	8.00 (18.60%)	0.447
Medium intensity	154.00 (65.00%)	26.00 (60.47%)	0.471
Low intensity	32.00 (13.50%)	14.00 (32.60%)	0.143
DPN	144.00 (60.80%)	30.00 (69.80%)	0.263
PAD	175.00 (73.80%)	35.00 (81.40%)	0.292
DR	26.00 (11.00%)	8.00 (18.60%)	0.159
DN	65.00 (27.09%)	16.00 (37.20%)	0.218

BMI: Body mass index, FPG: fasting plasma glucose, PTH: parathyroid hormone, TG: triglycerides, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HbA1c: glycated hemoglobin, F-CP: fasting C-peptide, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, UACR: urinary albumin/creatinine ratio, ASMI: appendicular skeletal muscle mass index, FTSST: five times sit to stand test, DPN: diabetic peripheral neuropathy, PAD: diabetic peripheral angiopathy, DR: diabetes retinopathy, DN: diabetes nephropathy.

Table II. Glucose fluctuation indexes in two groups.

	Non-sarcopenic group n=237	Sarcopenic group n=43	*p*-value
TIR (%)	82.60 (67.85, 93.44)	57.08 (38.33, 81.46)	<0.001
CV	20.93 (18.01, 25.82)	20.61 (18.00, 25.78)	0.872
MAGE (mmol/l)	3.61 (2.83, 5.91)	3.63 (2.86, 5.39)	0.366
SD	1.76 (1.40, 2.20)	1.92 (1.63, 2.62)	0.028
TBR (%)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.624
TAR (%)	17.01 (6.25, 32.01)	39.48 (18.54, 56.53)	<0.001
MG (mmol/l)	8.09 (7.29, 10.12)	9.28 (8.20, 10.57)	<0.001
LAGE (mmol/l)	9.42 (7.62, 11.86)	9.75 (8.22, 11.31)	0.359

TIR: time in range, CV: coefficient of Varia-tion, MAGE: mean amplitude of glycemic excur-sion, SD: blood glucose standard deviation, TBR: time below range, TAR: time above range, MG:mean glucose,LAGE: largest amplitude of glycemic excursions.

grip strength, time of FTSST and glucose fluctuation indexes. The results showed that TIR was positively correlated with ASMI and handgrip strength, while it was negatively correlated with time of FTSST. TAR and MG were negatively correlated with ASMI and handgrip strength, while they were positively correlated with time of FTSST (Figure 1). Meanwhile CV (r=-0.152, p=0.038), SD (r=-0.178, p=0.003) and LAGE (r=-0.168, p=0.005) were negatively correlated with ASMI. LAGE (r=-0.140, p=0.019) was negatively correlated with handgrip strength.

Logistic Univariate Regression Analysis of Sarcopenia

In summary, age, gender, TAR and MG were the risk factors for sarcopenia. BMI, 25-hydroxyvitamin D and TIR were the protective factors for sarcopenia (Table III).

Logistic Multivariate Regression Analysis of Sarcopenia

Using the presence of sarcopenia as the dependent variable (no=0, yes=1) and including the variables in Table III (removing interacting factors) in a multivariate regression analysis, age (OR=1.167, 95% CI: 1.069-1.273), male (OR=3.451, 95% CI: 1.338-8.900), TIR (OR=0.967, 95% CI: 0.941-0.995) were found to be independent influencing factors of sarcopenia. Only TIR was a protective factor for sarcopenia and the prevalence of sarcopenia decreased significantly with higher TIR values (Table IV).

Comparison of the Incidence of Sarcopenia in Different TIR

According to the guideline recommendation[8], TIR control goal should be >70%. If there are high-risk factors and elderly patients, TIR should be >50%, so we divided it into three groups: TIR≤50%, 50<TIR≤70% and TIR>70%. The result of Chi-square test showed that the incidence of sarcopenia in different TIR ranges was different: the proportion of patients with sarcopenia was 40.48% (TIR ≤50%), 20.41% (50%<TIR≤70%) and 8.47% (TIR>70%) (Figure 2). The differences between all groups were statistically significant (p<0.05).

Discussion

Sarcopenia severely affects the quality of life of patients with T2DM, leading to an increased incidence of clinical adverse events such as falls, rehospitalization and death[9]. In recent years, epidemiological surveys[10] of sarcopenia in the Chinese population have shown that the prevalence of sarcopenia in elderly people in the community ranges from 8.9% to 38.8% with a higher prevalence in men than in women, which is similar to the prevalence of sarcopenia in this study with a result of 15.36%. In this study, the comparison of patient characteristics between the two groups revealed that gender, age, PTH, HOMA-IR and 25-hydroxyvitamin D were the influencing factors of sarcopenia. These are consistent with domestic and international studies[11-13]. In addition, one study[14] found an increased risk of sarcopenia in diabetic patients with elevated HbA1c. It has also been proposed[15] that leg muscle mass is significantly reduced in T2DM patients with HbA1c ≥ 8.5%. Interestingly, this paper did not find a difference in HbA1c between the two groups. The reasons may be related to the small sample size included and the fact that the mean HbA1c value of the recruited patients was below 8.5%.

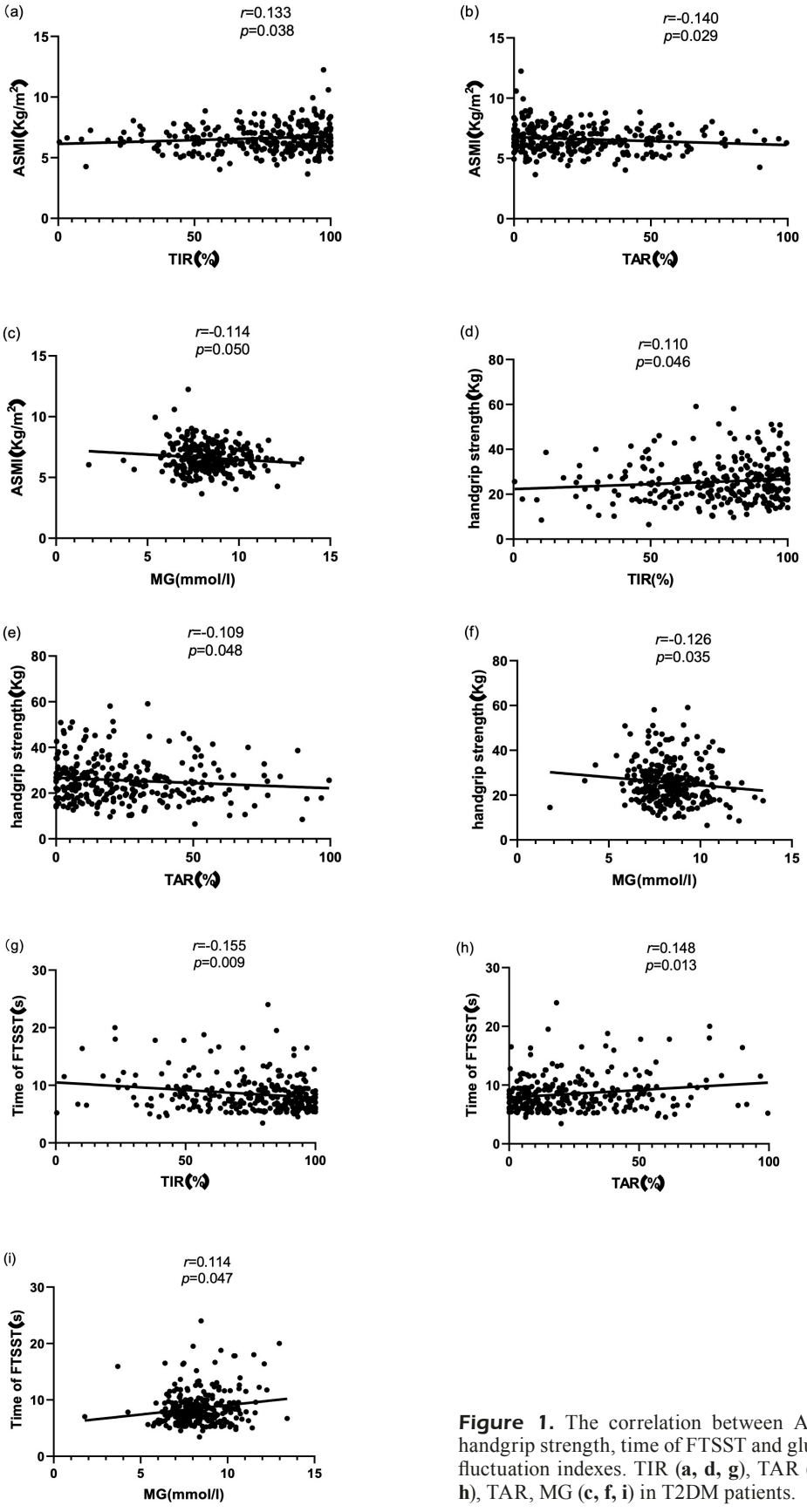

Figure 1. The correlation between ASMI, handgrip strength, time of FTSST and glucose fluctuation indexes. TIR (**a, d, g**), TAR (**b, e, h**), TAR, MG (**c, f, i**) in T2DM patients.

Table III. The logistic univariate regression analysis of sarcopenia.

	B	SE	Walds	*p*-value	Exp (B)	CI	
Age	0.141	0.030	22.468	0.001	1.152	1.068	1.221
Male	1.123	0.343	10.687	0.001	3.074	1.568	6.026
BMI	-0.118	0.057	4.279	0.039	0.889	0.795	0.994
25-hydroxyvitamin D	-0.037	0.014	7.107	0.008	0.964	0.938	0.990
TIR	-0.037	0.007	25.386	<0.001	0.963	0.950	0.977
TAR	0.035	0.007	22.769	<0.001	1.036	1.021	1.051
MG	0.468	0.117	15.898	<0.001	1.597	1.269	2.009

BMI: Body mass index, TIR: time in range, TAR: time above range, MG: mean glucose, CI: confidence intervals.

Table IV. Logistic multivariate regression analysis of sarcopenia.

	B	SE	Walds	*p*-value	Exp (B)	CI	
Age	0.154	0.045	11.990	0.001	1.167	1.069	1.273
Male	1.239	0.483	6.569	0.010	3.451	1.338	8.900
TIR	-0.033	0.014	5.461	0.019	0.967	0.941	0.995

TIR: time in range, CI: confidence intervals.

Glucose fluctuation refers to the unstable state of fluctuating blood glucose between peaks and troughs in the body. Some studies[16] have shown that fluctuating hyperglycemia is more harmful to chronic complications of diabetes than persistent hyperglycemia. The key indicator for assessing glucose fluctuation is TIR (the percentage of time that blood glucose is within the target range of usually 3.9 to 10.0 mmol/L in 24 h). It can describe short-term and long-term glycemic control, sensitive and accurate capture of hyperglycemia and hypoglycemia[17-18]. Many studies[19] have confirmed that TIR is an important indicator for the evaluation of clinical trials in diabetes and is closely associated with diabetic complications. TAR (the percentage of time that blood glucose above 10 mmol/l in 24 h) and TBR (the percentage of time that blood glucose is below 3.9 mmol/l in 24 h) are also important indicators of glycemic control and mainly respond to hyperglycemic and hypoglycemic levels[20]. Besides, the commonly used indicators to evaluate glucose fluctuations include MAGE, LAGE, and SD, which are used to assess intra-day glucose fluctuations. Simultaneously,

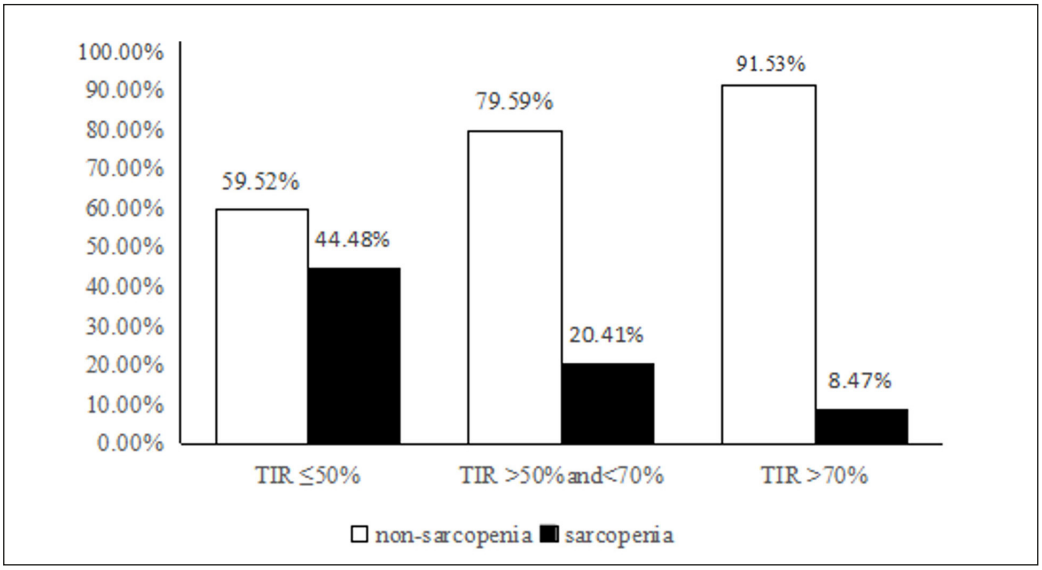

Figure 2. Comparison of the incidence of sarcopenia in different TIR.

CV assesses inter-day glucose fluctuations. MG indicates the overall glucose level.

In these indexes for assessing blood glucose fluctuation, this study found that TIR was lower in the sarcopenia group than in the non-sarcopenia group. However, TAR, SD and MG were higher in the sarcopenia group than in the non-sarcopenia group. These suggesting that glucose fluctuation was more significant in the sarcopenia group than in the non-sarcopenia group. Correlation analysis showed that TIR, TAR and MG were correlated with ASMI, handgrip strength and the time of FTSST. Univariate logistic regression analysis showed that TIR was a protective factor for sarcopenia. While TAR and MG were risk factors for sarcopenia. After further multivariate regression analysis, TIR still had a good correlation with ASMI. When the TIR rose, the prevalence of sarcopenia was lower. It indicates that the longer the duration of glycemic control within the target range, the lower the prevalence of sarcopenia. Conversely, if the TIR was lower and TAR and MG were higher, the risk of sarcopenia increased significantly.

Nevertheless, there was no significant difference in TBR between the two groups. The probable cause is the lower incidence of hypoglycemia in the included data. In the meantime, the correlation analysis of this study suggested that LAGE and CV were correlated with ASMI and handgrip strength. SD and ASMI were correlated. SD was statistically different between the two groups. Yet logistic regression analysis showed that SD, CV and LAGE were not statistically significant. It may be related to the relatively small sample and short monitoring time of blood glucose in this study. We will expand the sample size to explore its correlation in the future. Previous consensus[21] points out that MAGE is the gold standard for assessing blood glucose fluctuations. Many domestic and international studies[22-26] have found that MAGE is associated with diabetic vasculopathy, peripheral neuropathy, retinopathy, cardiovascular autonomic neuropathy and osteoporosis in T2DM patients. Nevertheless, the correlation between MAGE and sarcopenia was not found in our study which suggesting that TIR, TAR and MG are more relevant than MAGE in the assessment of sarcopenia.

Current studies[14,27,28] suggest that the possible mechanisms of glucose fluctuations leading to sarcopenia are as follows: (1) Glucose fluctuations can damage endothelial cell function and exacerbate the chronic inflammatory state by activating oxidative stress pathways, which in turn inhibit muscle growth and accelerates muscle protein degradation[27]. Moreover, the trigger effect of poorly controlled glucose fluctuations on oxidative stress is more specific than that of chronic persistent hyperglycemia[14]. (2) Glucose fluctuations can activate advanced glycation end products (AGEs). The accumulated AGEs can induce the cross-linking and decomposition of muscle proteins, increase muscle stiffness, reduce muscle contractility and aggravate muscle injury[28]. Then it affects handgrip strength and speed in older patients. (3) Fluctuating hyperglycemia can aggravate the damage and apoptosis of pancreatic islet β-cells, which are difficult to repair and regenerate after apoptosis. So, it is resulting in reduced secretion of insulin and insulin growth-like factor-1 which aggravates the development of sarcopenia. (4) Increased tumor necrosis factor-α and inflammatory factors in muscle tissue can induce apoptosis and lead to the destruction of muscle structure in diabetic patients with poor glycemic control[14].

Limitations

There are still some limitations in this paper: firstly, it is difficult to confirm the causal relationship between TIR and T2DM patient with sarcopenia due to the limitations of cross-sectional study. Secondly, due to the small number of sarcopenia patients included in the study, it is still necessary to expand the sample size for further study and validation. Thirdly, the possible effects of diet and lifestyle on sarcopenia were not analyzed[29]. Fourthly, the dynamic glucose monitoring time is relatively short which may not completely reflect the long-term glucose fluctuations of the patients.

Conclusions

Our study demonstrates that TIR had a strong correlation with sarcopenia. Furtherly, the incidence rate of sarcopenia decreases with the increase of TIR. TIR was a protective factor for sarcopenia. MG and TAR were the risk factors for sarcopenia. Therefore, it is emphasized that dynamic blood glucose monitoring should be actively used in the diagnosis and treatment of T2DM in elderly people. Clinically, the risk of sarcopenia can be reduced by increasing the TIR level.

Informed Consent

An informed consent form was obtained from the patients before participating in the study.

Authors' Contribution

Guocui Ma and Lingling Zou designed the study, Guocui Ma and Zhenzhen Wang collected the data, Guocui Ma analyzed the data and wrote the manuscript. Wu Dai and Yonghong Cao contributed to modify the manuscript. All authors read and approved the final manuscript.

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Ethics Approval

Ethics Committee approval was released from Hefei Second People's Hospital. Date 25.10.2019 and number 2019-research-084.

Conflict of interests

The Authors declare that they have no conflict of interests.

References

1) Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, Jang HC, Kang L, Kim M, Kim S, Kojima T, Kuzuya M, Lee JSW, Lee SY, Lee WJ, Lee Y, Liang CK, Lim JY, Lim WS, Peng LN, Sugimoto K, Tanaka T, Won CW, Yamada M, Zhang T, Akishita M, Arai H. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc 2020; 21: 300-307.e2.
2) Yang Q, Zhang Y, Zeng Q, Yang C, Shi J, Zhang C, Ni X, Du Z, Tang Z, Hu J, Li X, Cai J, Li Q, Cheng Q. Correlation Between Diabetic Peripheral Neuropathy and Sarcopenia in Patients with Type 2 Diabetes Mellitus and Diabetic Foot Disease: A Cross-Sectional Study. Diabetes Metab Syndr Obes 2020; 13: 377-386.
3) Sinclair AJ, Abdelhafiz AH, Rodríguez-Mañas L. Frailty and sarcopenia - newly emerging and high impact complications of diabetes. J Diabetes Complications 2017; 31: 1465-1473.
4) Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring. J Clin Endocrinol Metab 2022; 107: e2221-e2236.
5) Zhou JJ, Coleman R, Holman RR, Reaven P. Long-term glucose variability and risk of nephropathy complication in UKPDS, ACCORD and VADT trials. Diabetologia 2020; 63: 2482-2485.
6) Singh B, Saxena A. Surrogate markers of insulin resistance: a review. World J Diabetes 2010; 1: 36-47.
7) Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group; Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Society; Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Health Care Society; Geriatric Professional Committee of Beijing Medical Award Foundation; National Clinical Medical Research Center for Geriatric Diseases (PLA General Hospital). Clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition). Zhonghua Nei Ke Za Zhi 2022; 61: 12-50.
8) Fan M, Lyu J, He P. Chinese guidelines for data processing and analysis concerning the International Physical Activity Questionnaire. Zhonghua Liu Xing Bing Xue Za Zhi 2014; 35: 961-964.
9) Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48: 601.
10) Chen Z, Ho M, Chau PH. Prevalence, Incidence, and Associated Factors of Possible Sarcopenia in Community-Dwelling Chinese Older Adults: A Population-Based Longitudinal Study. Front Med (Lausanne) 2022; 8: 769708.
11) He X, Song Y, Ma L, Ainsworth BE, Liu Y, Chen N. Prevalence and Factors Influencing Sarcopenia Among Community-Dwelling Older Adults Using the Asian Working Group for Sarcopenia Definition. Clin Interv Aging 2022; 17: 1707-1727.
12) Fung FY, Koh YLE, Malhotra R, Ostbye T, Lee PY, Ghazali SS, Tan NC. Prevalence of and factors associated with sarcopenia among multi-ethnic ambulatory older Asians with type 2 diabetes mellitus in a primary care setting. BMC Geriatr 2019; 19: 122.
13) Oh TJ, Kang S, Lee JE, Moon JH, Choi SH, Lim S, Jang HC. Association between deterioration in muscle strength and peripheral neuropathy in people with diabetes.J Diabetes Complications 2019, 33: 598-601.
14) Lin Y, Zhang Y, Shen X, Huang L, Yan S. Influence of glucose, insulin fluctuation, and glycosylated hemoglobin on the outcome of sarcopenia in patients with type 2 diabetes mellitus. J Diabetes Complications 2021; 25: 107926.
15) Yoon JW, Ha YC, Kim KM, Moon JH, Choi SH, Lim S, Park YJ, Lim JY, Kim KW, Park KS, Jang HC. Hyperglycemia is associated with impaired muscle quality in older men with diabetes: the Korean longitudinal study on health and aging. Diabetes Metab J 2016; 40: 140-146.

16) Nusca A, Tuccinardi D, Albano M, Cavallaro C, Ricottini E, Manfrini S, Pozzilli P, Di Sciascio G. Glycemic variability in the development of cardiovascular complications in diabetes. Diabetes Metab Res Rev 2018; 34: e3047.

17) Rodbard D. Glucose Time In Range, Time Above Range, and Time Below Range Depend on Mean or Median Glucose or HbA1c, Glucose Coefficient of Variation, and Shape of the Glucose Distribution. Diabetes Technol Ther 2020; 22: 492-500.

18) Saboo B, Kesavadev J, Shankar A, Krishna MB, Sheth S, Patel V, Krishnan G. Time-in-range as a target in type 2 diabetes: An urgent need. Heliyon 2021; 7: e05967.

19) Beck RW, Bengenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, Close K. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trial. Diabetes Care 2019; 42: 400-405.

20) Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care 2019; 42: 1593-1603.

21) Monnier L, Colette C, Boengner C, Pham TC, Lapinski H, Boniface H. Continuous glucose monitoring in patients with type 2 diabetes: Why? When? Whom? Diabetes Metab 2007; 33: 247-252.

22) Liu M, Ao L, Hu X, Ma J, Bao K, Gu Y, Zhao J, Huang W. Influence of blood glucose fluctuation, C-peptide level and conventional risk factors on carotid artery intima-media thickness in Chinese Han patients with type 2 diabetes mellitus. Eur J Med Res 2019; 24: 13.

23) Yapanis M, James S, Craig ME, Neal D, Ekinci EI. Complications of Diabetes and Metrics of Glycemic Management Derived from Continuous Glucose Monitoring. J Clin Endocrinol Metab 2022; 107: e2221-e2236.

24) Sonoda S, Okada Y, Mori H, Uemura F, Sugai K, Hajime M, Tanaka K, Kurozumi A, Narisawa M, Torimoto K, Tanaka Y. Association Between Diabetic Microangiopathies and Glycemic Variability Assessed by Continuous Glucose Monitoring. J UOEH 2018; 40: 11-18.

25) Xu W, Zhu Y, Yang X, Deng H, Yan J, Lin S, Yang H, Chen H, Weng J. Glycemic variability is an important risk factor for cardiovascular autonomic neuropathy in newly diagnosed type 2 diabetic patients. Int J Cardiol 2016; 215: 263-268.

25) Huang R, Wang H, Shen Z, Cai T, Zhou Y, Wang Y, Xia W, Ding B, Yan R, Li H, Wu J, Ma J. Increased Glycemic Variability Evaluated by Continuous Glucose Monitoring is Associated with Osteoporosis in Type 2 Diabetic Patients. Front Endocrinol (Lausanne) 2022; 13: 861131.

27) Škrha J, Šoupal J, Škrha J Jr, Prázný M. Glucose variability, HbA1c and microvascular complications. Rev Endocr Metab Disord 2016; 17: 103 110.

28) Mori H, Kuroda A, Ishizu M, Ohishi M,Takashi Y, Ostuka Y, Tangiguchi S, Tamaki M, Kurahashi K,Yoshida I,Endo I,Aihara K,Funaki M,Akehi Y,Matsuhisa M. Association of accumulated advanced glycation end-products with a high prevalence of sarcopenia and dynapenia in patients with type 2 diabetes. J Diabetes Investig 2019; 10: 1332-1340.

29) Lombardo M, Boaria A, Aulisa G, Padua E, Annino G, Pratesi A, Caprio M, Iellamo F, Bellia A. Sarcopenic obesity: etiology and lifestyle therapy. Eur Rev Med Pharmacol Sci 2019; 23: 7152-7162.