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Original Research Article

25-Hydroxyvitamin D: A potential marker of the incidence of osteoporosis and sarcopenia in diabetic mellitus patients

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Abstract

Purpose: *To investigate the feasibility of using the 25-hydroxyvitamin D (25(OH)D) levels in assessing osteoporosis (OP) and sarcopenia in elderly patients with diabetes mellitus (DM).*
Methods: *One hundred and forty elderly patients with DM were allocated to DM (n = 40), OP (n = 50), and DM + OP (n = 50) groups. Their clinical data were collected, and muscle function assessed. The levels of fasting insulin, glycated hemoglobin (HbAlc), t-P1NP, and 25(OH)D were determined by chemiluminescent microparticle immunoassay, high-pressure liquid chromatography, electrochemical immunoassay, and liquid chromatography-tandem mass spectrometry, respectively.*
Results: *The 25(OH)D levels were lowest in DM + OP group, followed by the OP group, and highest in the DM group ($p < 0.05$). The DM + OP group showed significantly lower gait speed and grip strength than the OP and DM groups ($p < 0.05$). The diagnostic AUC of 25(OH)D for OP and sarcopenia were 0.9733 (95 % CI: 0.9274 - 1.000, $p < 0.001$) and 0.9866 (95 % CI: 0.9632 - 1.000, $p < 0.001$). Patients with sarcopenia had significantly lower 25(OH)D and t-PINP levels than patients without sarcopenia ($p < 0.05$). Logistic regression analysis revealed that the 25(OH)D level, duration of DM, and age were independent risk factors for sarcopenia ($p < 0.05$).*
Conclusion: *Patients with DM and OP exhibit increase in the incidence of sarcopenia. Serum 25(OH)D may be used as a potential marker for the incidence of OP and sarcopenia in DM patients.*

Keywords: *25(OH)D, Elderly, Diabetic patients, Osteoporosis, Sarcopenia, Feasibility analysis*

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INTRODUCTION

The morbidity of diabetes mellitus (DM) has increased significantly with changes in people's dietary habits and the improvement of living standards [1]. Diabetes mellitus causes chronic lesions in multiple organs of the body over time, seriously threatening the life and health of patients. According to the guidelines for the prevention and treatment of type 2 diabetes mellitus (T2DM) in China [2], the prevalence of T2DM in adults over the age of 18 grew up to 10.4 % in China, and 20 % in those aged ≥ 60 years. Diabetes mellitus is a metabolic disorder that is associated with insulin levels in the blood. Normal levels of insulin have an inhibitory effect on protein catabolism in skeletal muscle. Clinical practice shows that most elderly patients with

DM are in a state of skeletal muscle dystrophy, which may be related to abnormally elevated blood glucose levels, declining muscle strength, muscle mass, and muscle function [3]. The incidence of sarcopenia in DM patients over 60 years old is about 3 times as high as that in non-DM patients, suggesting a close relationship between DM and the development of sarcopenia [4].

Osteoporosis (OP) is a group of conditions with features of decreases in bone density and bone mass, and patients tend to experience altered bone microarchitecture and increased bone fragility, resulting in a significantly higher incidence of systemic bone disease [5]. It has been revealed that bone and muscle share a common paracrine and endocrine regulatory mechanism, and that when individuals experience bone loss due to aging or chronic disease, muscle atrophy often occurs at the same time [6]. Evidence has revealed that an increase in muscle mass in the extremities of older individuals with T2DM can significantly decrease the risks of bone loss or OP, and the risk of OP is about 1.8 times higher in those with reduced muscle mass [7].

The 25(OH)D is a major circulating form of vitamin D, and as a fat-soluble vitamin, vitamin D not only affects phosphorus metabolism and calcium, but is also extensively involved in several physiological processes, and is essential for the maintenance of individual health as well as cell growth and development [8]. It has been found that 25(OH)D deficiency causes reduced bone conversion, inhibition of bone resorption and ultimately induces the occurrence of OP [9]. However, investigations have rarely studied the relationship between 25(OH)D and sarcopenia. The objective of this research is to investigate the feasibility of 25(OH)D in assessing OP and sarcopenia in elderly DM patients, and to provide some clinical reference for reducing the incidence of OP and sarcopenia in elderly DM patients.

METHODS

General patient data

A total of 140 elderly DM patients who received treatment in the Lushan Branch, Medical Community of the First People's Hospital, Fuyang District, Hangzhou, between January 2018 and January 2020 were enrolled. The sample size of the enrolled subjects was estimated using Epi info software. Subjects were allocated to DM (n = 40), OP (n = 50), and DM + OP (n = 50) groups according to conditions. The research followed the ethical principles of Declaration of Helsinki for medical research involving human subjects [10], and was submitted to the hospital's Ethics Committee for approval (approval no. NCT02125635). Each subject submitted a written informed consent.

Inclusion criteria

The subjects who had a clear clinical diagnosis [11] and typical clinical symptoms, who were aged between 60-80 years, who were conscious and able to cooperate with the study, and who had complete demographic data were included.

Exclusion criteria

Patients who had co-morbidities with consciousness disorders or psychiatric disorders, who took glucocorticoid interventions within the last 3 months, who had co-morbidity with autoimmune system disorders, acute complications or chronic complications of DM, chronic malnutrition, fractures, infections or bone and joint disorders, as well aa impaired cognitive function, were excluded from the study.

Evaluation of parameters/outcomes

Laboratory tests

Fasting plasma glucose (FPG): blood samples were collected from three groups of patients after fasting for 8-12 hours, and FPG was determined using oxidase method.

Fasting insulin level: Blood samples were collected after fasting for 8-12 hours, centrifuged, and the remaining serum was detected by chemiluminescent microparticle immunoassay.

Glycosylated hemoglobin (HbAlc): Blood samples were collected, and HbAlc level was measured by high pressure liquid chromatography.

Type I procollagen amino acid prolonging peptide (t-P1NP): Blood samples were collected, and the t-P1NP level was determined by electrochemical immunoassay.

25 (OH) D: Blood samples were collected, and 25 (OH) D level was detected by liquid chromatography-tandem mass spectrometry.

Muscle function test

The muscle function tests were performed using 6 m walking speed, as well as grip strength tests: the subjects walked a distance of 6 m in a

straight line at their usual pace, the time taken was recorded twice consecutively, and the mean gait speed was calculated. The grip strength was tested using a grip meter, which needed to be tested three times consecutively, and the mean value was taken as the final result.

Diagnostic criteria for sarcopenia

Sarcopenia is defined as a slow walking speed and a decrease in muscle mass of two standard deviations or more below the normal means of relevant people, designated as the presence of reduced muscle mass and either low physical performance or reduced muscle strength.

Statistical analysis

Data analysis was implemented using Statistical Package for the Social Sciences (SPSS) 22.0 (IBM, Armonk, USA). The normal distribution was tested for the validity of the collected data. Counting data meeting the normal distribution were described by [n (%)], and was analyzed using the chi-square test for between-group comparison. Measurement data was described by mean ± SD, and was analyzed using t-test. Multi-factor ANOVA was implemented for comparisons between multiple groups, t-test was used for the comparison of the differences in quantitative indicators between patients with and without sarcopenia, followed by multiple logistic regression analyses. $P < 0.05$ denotes statistically significant differences.

RESULTS

Patient's baseline data

The three groups showed no marked differences in baseline data, including gender, mean age, mean body weight, mean BMI, 25 (OH)D, t-PINP, FPG, fasting plasma glucose, HbAlc, and duration of DM ($p > 0.05$, Table 1).

25(OH)D levels and incidence of sarcopenia

Patients in the DM + OP group showed significantly lower appendicular lean mass index (ALMI) and 25(OH)D levels than those in the DM and OP groups ($p < 0.05$), and the incidence of sarcopenia was 70.00 % in the DM + OP group, 40.00 % in the OP group, and 30.00 % in the DM group, indicating that the DM + OP group had significantly higher incidence of sarcopenia than the DM and OP groups ($p < 0.05$, Figure 1).

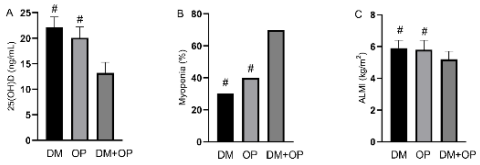

Figure 1: Comparison of 25(OH)D levels and incidence of sarcopenia. A: 25(OH)D, B: incidence of sarcopenia, C: ALMI. $^{\#}p < 0.05$ *vs.* DM + OP group

Gait speed and grip strength

Patients in the DM + OP group had lower grip strength and gait speed than the DM and OP groups ($p < 0.05$). The DM group exhibited higher gait speed and grip strength than the OP group ($p < 0.05$; Figure 2).

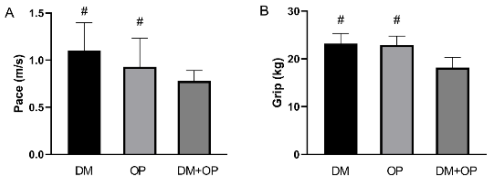

Figure 2: Comparison of gait speed and grip strength. A: gait speed, B: grip strength. $^{\#}p < 0.05$ *vs.* DM + OP group

Table 1: Comparison of patient's general data {mean ± SD; n (%)}

Parameter		DM (n=40)	OP (n=50)	DM+OP (n=50)	F	*P*-value
Gender	M	14	18	17	0.454	0.554
	F	26	32	33		
Mean age (years)		71.31±2.11	71.08±2.10	71.21±1.98	0.141	0.869
Mean body weight (kg)		64.29±3.91	64.34±3.89	64.32±3.33	0.002	0.998
Mean BMI (kg/㎡)		23.19±2.31	23.21±2.29	23.28±2.19	0.02	0.98
25 (OH)D (ng/mL)		22.10±2.10	20.10±2.10	13.20±1.98	240.726	<0.001
t-PINP (ng/mL)		48.98±3.22	49.77±2.98	50.21±3.01	1.814	0.167
FPG (mmol/L)		7.08±0.32	6.29±0.32	7.23±0.41	99.349	<0.001
Fasting plasma glucose (uU/mL)		7.21±0.12	6.78±0.98	7.41±0.21	14.173	<0.001
HbAlc (%)		6.41±0.23	5.98±0.31	6.98±0.32	146.069	<0.001
Duration of DM (years)		5.66±2.19	5.72±2.21	5.69±2.28	0.008	0.992

Effect of sarcopenia on glucose indicators and bone metabolism indicators

The enrolled subjects were allocated to 62 cases in sarcopenic group and 38 cases in non-sarcopenic group, and glycemic indices (FPG, fasting insulin, HbAlc) and bone metabolic indices {25(OH)D, t-PINP} were determined. Patients in the sarcopenic group exhibited significantly lower 25(OH)D levels than those in the non-sarcopenic group ($p < 0.05$). However, both groups exhibited no noticeable differences in t-PINP levels ($p > 0.05$, Figure 3).

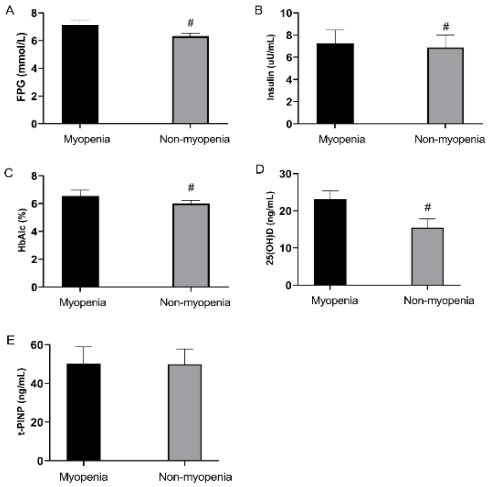

Figure 3: Effects of sarcopenia on glycemic and bone metabolic indices. A: FPG, B: fasting insulin, C: HbAlc, D: 25(OH)D, E: t-PINP. $^{\#}p < 0.05$ *vs* sarcopenic group

Diagnostic potential of 25(OH)D for OP and sarcopenia

The diagnostic AUC of 25(OH)D for OP and sarcopenia was 0.9733 (95 % CI 0.9274-1.000, $p < 0.001$) and 0.9866 (95 % CI 0.9632-1.000, $p < 0.001$), respectively in DM patients, suggesting that 25(OH)D has good diagnostic potential for OP and sarcopenia in DM patients (Figure 4).

Logistic regression analysis

The presence of sarcopenia was taken as the dependent variable, and the underlying disease, age, body mass index, 25(OH)D level, and duration of DM were taken as indicators in the regression analysis, so as to evaluate the risk factors that affect the incidence of sarcopenia in DM patients. The results showed that patients with sarcopenia exhibited significantly lower 25(OH)D levels and longer duration of DM disease than non-sarcopenic patients, and the age of sarcopenic patients was older than that of non-sarcopenic patients ($p < 0.05$, Table 2).

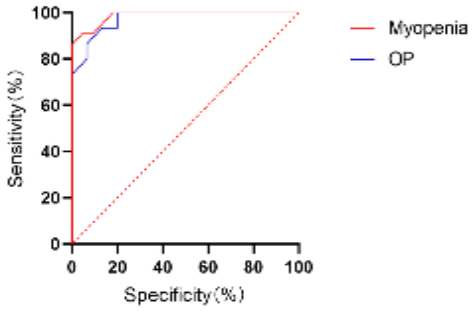

Figure 4: ROC curve of 25(OH)D for diagnostic potential of OP and sarcopenia in DM patients

DISCUSSION

Diabetes mellitus, OP, and sarcopenia are all common diseases associated with aging. Evidence has shown that there is a significant correlation between DM and the occurrence of OP [12]. A retrospective analysis of 220 patients with DM showed that the bone density of DM patients is closely related to their blood glucose level [13]. The higher the patient's FPG, HbAlc and other indicators, the higher the risk of OP. The reason may be that long-term glucose metabolism disorders will hinder the bone matrix maturation and conversion, leading to calcium loss. It has also been pointed out that the presence of microcirculatory disorders exacerbates the risk of disorders of bone metabolism, and that the incidence of OP rises with increasing duration and age [14].

Sarcopenia is defined by the International Working Group as an age-related progressive decrease in muscle mass, decreased muscle strength, or impaired muscle physiology [15]. It has been indicated that the incidence of sarcopenia is approximately 10 - 30 % in people aged 60 to 70 years and it has exceeded 50 % in people over 80 years [16].

Table 2: Logistic regression analysis of sarcopenia in patients with DM

Risk factor	B	Wald	*P*-value	OR	95% CI
Underlying disease	0.843	2.298	0.123	1.287	0.781-0.887
Age	0.078	2.221	0.021	1.313	0.871-0.991
BMI	0.671	1.112	0.431	0.989	0.872-0.918
25(OH)D	0.098	8.298	<0.001	1.098	1.032-1.231
Duration of DM disease	0.081	9.981	<0.001	1.221	1.043-1.115

Sarcopenia is now an important marker of diminished function of various organs. For patients with sarcopenia in advanced age, the loss of body function is associated with the loss of muscle mass, resulting in a significantly higher incidence of events such as falls and fractures, causing a significant reduction in their ability to perform daily living activities [16]. A previous research has shown correlations among sarcopenia, DM, and OP, and also indicated that there may be an indicator that could be used for the assessment of the patient's condition [17]. In this study, the feasibility of the use of 25(OH)D in assessing OP and sarcopenia in elderly DM patients was investigated by setting up different subgroups, and the findings revealed that the DM + OP group exhibited significantly lower ALMI and 25(OH)D levels and higher incidence of sarcopenia than the DM and OP groups. This indicates that the presence of OP raises the incidence of sarcopenia. The incidence of sarcopenia in patients with DM alone was 18.98 % [18], which was lower than the 30 % in this current study, which may have been caused by the higher average age of the patients enrolled in this research. The authors of the current research believe that the pathogenesis of sarcopenia and OP is complex, including changes in muscle contractility and endocrine regulation between muscles and bones. The current research suggests that skeletal muscle contraction can provide mechanical stimulation to the bones, which can promote bone metabolism and production. However, due to muscle atrophy, the bone mass loss of sarcopenia patients will be significantly increased, resulting in a weakened body balance [19]. This was evidenced by the differences in grip strength and gait speed among the three groups, with the DM + OP group exhibiting the lowest grip strength and gait speed, followed by the OP group, and the DM group exhibiting the highest grip strength and gait speed. Further comparisons were made regarding the effect of sarcopenia on indices of glucose and bone metabolism in DM patients. The results showed that the sarcopenic group had significantly higher FPG, fasting insulin, and HbAlc, and had significantly lower 25(OH)D levels than the non-sarcopenic group. This further confirmed the effect of sarcopenia on individual metabolism. Insulin resistance is prevalent in patients with DM. Insulin plays a role in promoting muscle protein synthesis, and that insulin resistance leads to decreased production of muscle protein, which leads to reduced muscle mass. It was found that DM leads to diabetic neuropathy, with reduced muscle function [20], and this may be an important mechanism leading to sarcopenia. The authors of this study found that the correlation between DM and sarcopenia may be related to the fact that glucose affects the intensity of inflammatory responses. A long-term hyperglycemic state elevates the indicators such as IL-6 and TNG-α and reduces individual muscle mass, strength and function. In this research, 25(OH)D levels were found to have a good diagnostic value for OP and sarcopenia in DM patients, which indicates the role of serum levels of 25(OH)D in bone metabolism. Finally, this research also preliminarily investigated the risk factors for sarcopenia in DM patients. The results suggested that age, 25(OH)D levels, and the duration of DM significantly affect the incidence of sarcopenia. This may be related to the fact that a chronic microinflammatory state was present in patients with advanced age, and low serum levels of 25(OH)D accelerates bone loss. Furthermore, the progression of DM raises the risks of chronic kidney disease and OP.

Limitations of this study

The limitations of this research are that only patients aged 60 - 80 years were included and the subjects' diet, lifestyle and exercise were not investigated, which may lead to some bias in the conclusions.

CONCLUSION

The incidence of sarcopenia is significantly elevated in DM patients with concomitant OP, and 25(OH)D is feasible for the prediction of OP and sarcopenia conditions in DM patients. Sarcopenia monitoring should be performed in aged diabetic patients with longer duration of DM and lower 25(OH)D levels.

DECLARATIONS

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None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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