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ORIGINAL RESEARCH

Assessment of Changes in Body Composition After 3 Months of Dulaglutide Treatment

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Background: Changes in body composition accompanied by glucagon-like peptide 1 receptor agonist (GLP-1RA) induced weight loss have drawn much attention. However, fewer studies have reported body composition changes in patients receiving dulaglutide therapy in Chinese population.

Methods: A total of 70 overweight/obese type 2 diabetes mellitus (T2DM) patients who received dulaglutide therapy were included. Clinical data were collected. Visceral fat area (VFA) and body composition were also measured. Changes in clinical indicators and body composition of patients before and after intervention were also analyzed. Correlation analysis and multiple linear regression model were used to evaluate the association between hemoglobin A1C (HbA1c) and body composition.

Results: The results showed that body weight (BW), VFA, body fat (BF), lean body mass (LBM), skeletal muscle mass (SMM) and water content were reduced after 3 months dulaglutide intervention. The lean body mass percentage (LBMP) and skeletal muscle mass percentage (SMMP) significantly increased. Moreover, there was no significant difference in bone mineral quality (BMQ) after the intervention. The multiple linear regression model revealed that the % change in BF was independently associated with % change in HbA1c ($\beta = 0.449$, $t = 3.148$, $p=0.002$).

Conclusion: These results indicate that dulaglutide intervention does not cause muscle and bone mass loss while inducing weight loss, and % change in BF was independently associated with improved glucose control during dulaglutide therapy. This study offers some positive results to support the clinical application of dulaglutide.

Keywords: dulaglutide, obesity, diabetes, body fat mass, visceral fat

Introduction

T2DM is a chronic metabolic disease that causes significant economic and social burdens worldwide.[1] Traditional hypoglycemic agents, such as sulfonylureas and insulin, cannot play effective hypoglycemic roles when used in patients with severe insulin resistance, and can cause side effects, as patients may gain weight after therapy. Increasing the drug dosage to enhance hypoglycemic effects may increase the risk of hypoglycemia. Therefore, identifying new drug targets and more effective and safer therapies are urgently needed.

Glucagon-like peptide-1 (GLP-1), which is secreted by intestinal enteroendocrine L cells, exerts antidiabetic effects by activating GLP-1 receptors. During food intake, GLP-1 stimulates insulin secretion and inhibits glucagon secretion to lower serum glucose levels.[2] In addition, GLP-1 can improve pancreatic β-cell function and inhibit β-cell apoptosis, which can prevent or slow the progression of β cell failure in T2DM.[3,4] When glucose levels are normal, the insulinotropic effect of GLP-1 is minimal and the risk of hypoglycemia is relatively low.[5] GLP-1 can also delay the

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emptying of the gastrointestinal tract, increase satiety, and reduce food intake, all of which contribute to weight loss.[6–8] Because of their potent antidiabetic effects, GLP-1RAs have emerged as novel hypoglycemic agents with excellent weight loss effects and a low risk of hypoglycemia.

Dulaglutide, a typical long-acting GLP-1 RA, can significantly prolong the effect time by changing its molecular structure without effecting its physiological effects.[9] It has been widely used to treat T2DM in China, especially in patients who are overweight or obese.[10] Although the subgroup analysis of the AWARD studies showed that dulaglutide significantly improved glycemic control, reduced the risk of weight gain and had acceptable gastrointestinal side effects in the Chinese population,[11,12] research data on dulaglutide in the Chinese population are limited. The obesity profile and fat distribution of the Chinese population are different from those of the European and American populations considering ethnic and dietary characteristics. Evidence on the clinical efficacy of dulaglutide in the Chinese population needs to be explored. Fat, muscle, bone, blood, and tissue fluid are the main components of the body. Dulaglutide treatment can reduce body weight, but what is the effect on body composition? And the question of whether weight loss caused by dulaglutide treatment brings about the loss in muscle and bone mineral has not been reported in the literature. It was reported that dulaglutide may have similar hypoglycemic effects on diabetic patients with different baseline BMIs.[13] However, BMI is not an ideal indicator and its limitations have been gradually recognized and emphasized by scientists in recent years. Factors such as age, sex, body mass index (BMI), and duration of diabetes may influence the therapeutic efficacy of the drug. Currently, differences in the therapeutic effectiveness of GLP-1RA have been reported.[14] However, the effect of different body composition, including fat mass, on the therapeutic efficacy of dulaglutide has not been reported.

To answer these questions, we analyzed the changes in various body composition and visceral fat indices and further analyzed the associations between glucose control indicators and changes in body fat indices after dulaglutide therapy in overweight/obese T2DM patients. To the best of our knowledge, our work is the first study to investigate the changes in body composition in the Chinese population caused by dulaglutide treatment. This study provides additional positive clinical evidence for future applications of dulaglutide.

Methods

Data Source and Study Population

This was a retrospective cohort study. A total of 70 overweight/obese patients with T2DM who visited the National Metabolic Management Center (MMC) in Ningbo from December 2020 to December 2021 were included in the study. The inclusion criteria were as follows: (1) the patient met the diagnostic criteria for T2DM; (2) the patient was aged 18–70 years; (3) the patient has a BMI≥24kg/m^2 (Obesity is defined by the Chinese criteria. BMI cutoffs of 24 kg/m² for overweight and 28 kg/m² for obesity). Exclusion criteria were as follows: (1) patients with type 1 diabetes or other specific types of diabetes; (2) patients with acute complications of diabetes mellitus; (3) patients with a history of pancreatic disease such as acute and chronic pancreatitis, pancreatic tumors, etc. (4) patients with severe liver and kidney insufficiency; (5) patients with a history of malignancy; (6) patients who is pregnant or planned to get pregnant; (7) patients in the active phase of infectious diseases; (8) patients with uncontrolled thyroid disease.

Patients were treated with a subcutaneous injection of 1.5 mg dulaglutide once a week, along with a diabetes diet, exercise intervention and education.

Clinical Data Collection

Age, sex, height, weight, body mass index, diabetes history, baseline drug treatment regimen, glycated hemoglobin (HbA1c), fasting blood glucose (FBG) and fasting insulin (FIN) were extracted from the database of the patients (measured at the first visit to the MMC in Ningbo).

Anthropometric, VFA and Body Composition Measurements

Height without shoes and body weight (BW) in the lightest clothing were measured with an electronic device (OMRON, HNH-318). BMI was calculated by dividing weight by the square of height.

Bioelectrical impedance analysis (OMRON, DUALSCAN HDS-2000) was used to measure the VFA. The patient was positioned flat on the bed. The abdominal electrode belt was applied, and the hand and foot electrode clips were attached. The patient was asked to breathe calmly and to hold their breath at the end of exhalation. The instrument subsequently measured the abdominal VFA.

Bioelectrical impedance analysis is widely used for estimating body composition and health-related parameters.[15] In this study, the body composition of the patients was measured via bioelectrical impedance device (InBody770). Patients were instructed to stand on the instrument in an upright position with their feet centered on the electrodes. Patients then grasped the hand electrodes with their arms held wide. Patients were required to maintain this position for approximately 60 seconds during the analysis. Bioelectrical impedance analysis can provide a wide range of indicators, including body fat (BF), body fat percentage (BFP), skeletal muscle mass (SMM), skeletal muscle mass percentage (SMMP), lean body mass (LBM), lean body mass percentage (LBMP), bone mineral quality (BMQ) and water content.

HbA1c, FBG and FIN Measurements

Blood samples (collected after patients had fasted for at least 8 hours overnight) were measured in the clinical laboratory of the hospital. HbA1c was estimated by high-performance liquid chromatography (D-10 Hemoglobin Analyzer, Bio-Rad, USA). FBG was estimated by the glucose oxidase method. FIN was estimated by an electrochemical luminescence immunoassay.

Calculation of Insulin Sensitivity, β-Cell Function and % Change of Clinical Parameters

The degree of insulin resistance was determined by the Homeostasis Model Assessment of Insulin Resistance Index (HOMA-IR): [fasting glucose (mmol/L) × fasting insulin (mIU/L)] / 22.5. β-cell function was determined by the Homeostasis Model Assessment of β-cell Function Index (HOMA-β): [20 × fasting insulin (mIU/L)] / [fasting glucose (mmol/L) – 3.5]. The % change in clinical parameters was calculated by the following formula: % change in indicators = (indicator value after intervention – indicator value before intervention) / indicator value before intervention × 100%.

Statistical Analysis

IBM SPSS Statistics version 23.0 for Windows was used for statistical analysis. Before proceeding with the statistical analysis, all the parameters were tested for a normal distribution. Normal-distribution variables were expressed as mean and standard deviation (mean ± SD). Paired sample *t*-test were used for comparisons before and after the interventions. Nonnormally distributed variables were expressed as medians (interquartile range). Wilcoxon rank sum test was used for the comparisons before and after the interventions. Associations were assessed using Spearman correlation coefficient. Multiple linear regression analysis was used to assess the independent associations. A Two-tailed P value < 0.05 indicated a statistically significant difference.

Ethics

This study was performed in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the First Affiliated Hospital of Ningbo University. Informed consent was acquired when patients were enrolled in the MMC in Ningbo.

Results

Changes in Clinical Indicators Before and After Intervention

There were 70 participants received dulaglutide treatment, with a mean age of 44.19 ± 10.57 years old, including 57 males and 13 females (Table 1). HbA1c, fasting glucose, fasting insulin, HOMA-IR, body weight, and BMI were

Table 1 Comparison of Clinical Indictors Before and After Intervention

Characteristic	Before Intervention	After Intervention	p
General information			
Age (years)	44.19±10.57	–	–
Gender (male/female)	57/13	–	–
Course of disease (months)	36.00 (15.8, 67.0)	–	–
Blood glucose indicators			
HbA1c (%)	6.80 (5.88, 8.15)	5.90 (5.30, 6.40)	<0.001
FBG (mmol/L)	7.04 (5.91, 9.39)	5.86 (5.30, 6.67)	<0.001
FI (pmol/L)	88.70 (67.37, 120.48)	72.66 (44.92, 118.85)	0.001
HOMA-IR	4.32 (2.74, 6.80)	2.72 (1.79, 4.67)	<0.001
HOMA-β	71.30 (44.15, 117.42)	85.71 (51.29, 155.62)	0.002
Weight indicators			
BW (kg)	79.05 (73.75, 88.95)	75.70 (70.33, 82.70)	<0.001
BMI (kg/m2)	27.20 (25.80, 29.85)	26.00 (24.38, 27.95)	<0.001

Abbreviations: FBG, fasting blood glucose; FI, fasting insulin; BW, body weight; BMI, body mass index;

significantly lower after the intervention (Table 1). HOMA-β was significantly increased (p<0.05).These results indicated improved glucose control, insulin sensitivity and significant weight loss.

Changes in Body Composition of Patients Before and After the Intervention

We further analyzed the changes in body composition (Table 2). Patients significantly lost body weight (BW), visceral fat area (VFA), body fat (BF), body fat percentage (BFP), lean body mass (LBM), skeletal muscle mass (SMM) and water content after intervention ($P < 0.05$).

Although the LBM and SMM decreased after intervention ($P < 0.05$), the lean body mass percentage (LBMP) and skeletal muscle mass percentage (SMMP) significantly increased ($P < 0.05$). There was no significant difference in bone mineral quality (BMQ) before or after intervention (Table 2).

Since differences in patient baseline data may affect pre and post intervention comparisons, we calculated the % change in body composition parameters (Table S1). VFA decreased by approximately 25.65 cm^2, representing 21.64% of the baseline visceral fat area. BF decreased by 3.10 kg, approximately 14.20% from baseline. LBM decreased by 0.6 kg, or 1.19% of the baseline level. SMM decreased by approximately 0.41 kg, a decrease of 1.25% from baseline, and body water content showed a slight decrease of approximately 1.17%. The proportions of lean body mass and skeletal muscle mass increased by 2.52% and 1.40%, respectively.

Table 2 Comparison of Body Composition Analysis Before and After Intervention in People Received Dulaglutide Treatment

Body Composition	Before Intervention	After Intervention	p
BW (kg)	79.05 (73.75, 88.95)	75.70 (70.33, 82.70)	<0.001
VFA (cm^2)	111.55 (89.98, 137.00)	83.25 (71.30, 102.63)	<0.001
BF (kg)	22.10 (19.80, 28.20)	19.25 (16.80, 25.03)	<0.001
BFP (%)	27.65 (25.40, 33.10)	25.70 (22.13, 30.45)	<0.001
LBM (kg)	57.63±9.06	56.94±9.00	0.001
LBMP (%)	72.34 (66.92, 74.49)	74.38 (69.57, 77.87)	<0.001
SMM (kg)	32.20±5.46	31.80±5.42	<0.001
SMMP (%)	40.25 (36.60, 41.80)	41.60 (38.35, 43.90)	<0.001
BMQ (kg)	3.27±0.57	3.26±0.57	0.299
Water (L)	42.30±6.58	41.80±6.55	0.001

Abbreviations: BF, body fat; BFP, body fat percentage; LBM, lean body mass; LBMP, lean body mass percentage; SMM, skeletal muscle mass; SMMP, skeletal muscle mass percentage; BMQ, bone mineral quality.

Correlation Analysis Between % Change in HbA1c and % Change in Body Composition

Spearman correlation analysis was performed between the % change in HbA1c and the % change in body composition (Table 3). The results showed that the % change in HbA1c was positively correlated with the % change in VFA ($r = 0.468$, $p < 0.05$) and the % change in BF ($r = 0.457$, $p < 0.05$). Furthermore, a multiple linear regression model was used to evaluate the relationship between the improvement in HbA1c and change in body composition. The multivariate model consisted of % change in HbA1c as the dependent variable and the % change in VFA and % change in BF which were significantly related to the % change in HbA1c according to Spearman correlation analysis as independent variables. The results revealed that the % change in BF ($\beta = 0.449$, $t = 3.148$, $p=0.002$) was independently associated with % change in HbA1c (Table 4).

Discussion

In this retrospective study, we analyzed body composition changes in overweight and obese T2DM patients receiving dulaglutide therapy. Dulaglutide treatment significantly improved glycemic control, increased insulin sensitivity, and induced weight loss. The lean body mass percentage (LBMP) and skeletal muscle mass percentage (SMMP) were significantly increased. And bone mineral quality (BMQ) did not decrease after treatment with dulaglutide. The correlation and regression analyses indicated that the % change in BF was independently associated with improvement in HbA1c. This is the first study to investigate the changes in body composition in the Chinese population caused by dulaglutide treatment. Our work also found that dulaglutide did not cause loss of muscle mass and bone mineral, which provides a rationale for the safe use of dulaglutide in clinical practice.

Sarcopenia is considered a new type of diabetic complication in elderly patients with diabetes and needs to be considered in the management of type 2 diabetes.[16] Insulin resistance, inflammation, oxidative stress, and many other factors lead to protein metabolic disorders, mitochondrial dysfunction, and muscle cell death, ultimately leading to adverse effects on muscle quality and strength, and resulting in the development of sarcopenia. Sarcopenia may also cause altered glucose distribution and local inflammatory responses that promote the progression of diabetes.[17] Muscle loss is not the desired outcome of weight loss therapy for diabetes. Therefore, it is necessary to pay attention to the changes in muscle mass during dulaglutide therapy. Our study demonstrated that, after intervention, the LBMP and

Table 3 Spearman Correlation Analysis of % Change of HbA1c with % Change of Body Composition in People Received Dulaglutide Treatment

% Change of Body Composition	r	p
% change of VFA	0.468	<0.001
% change of BF	0.457	<0.001
% change of LBM	−0.016	0.895
% change of SMM	0.016	0.894
% change of Water	0.024	0.844

Table 4 Multiple Linear Regression Analysis of HbA1c Improvement Rate in People Received Dulaglutide Treatment

	β (95% CI)	t	p
% change of BF	0.449 (0.165~0.734)	3.148	0.002
% change of VFA	–	1.363	0.177

SMMP significantly increased, indicating that the weight reduction does not cause concomitant loss of muscle mass after dulaglutide treatment, and our results were consistent with previous animal studies.[18]

Recent scientific evidence has shown an increased risk of fractures in patients with obesity, which contradicts the old paradigm that obese patients are more protected than those with a normal weight.[19] The correlation between BMI and frailty has been shown to be U-shaped in older subjects.[20] Meta-analysis revealed that GLP-1 RAs are associated with a decreased risk of bone fracture compared with the risk associated with the use of a placebo or other antihyperglycemic drugs in T2DM patients.[21,22] Specifically, compared with a placebo, dulaglutide was reported to increase bone mineral density at multiple sites in the body.[23] In our study, the amount of BMQ did not change significantly after dulaglutide treatment. Our work and those of others suggest that dulaglutide does not exacerbate the risk of bone fracture.

VFA, as a criterion for the diagnosis of abdominal obesity, can visually reflect visceral fat accumulation, and accurate detection methods include abdominal CT and MRI. However, the cost is expensive, which limits the clinical promotion. The dual X-ray absorptiometry (DXA) scan is currently the gold standard measure of body composition; however, DXA scan is costly, may only be available in limited settings, is time-consuming, and involves exposure to ionizing radiation. Bioelectrical impedance analysis (BIA) is a noninvasive, low cost, and reliable method for body composition assessment. Validation studies have revealed that there is good agreement between DXA and BIA in body composition analysis.[24,25] Bioelectrical impedance device (InBody 770) was used to measure the body composition of the patients in our study. Compared with traditional DXA, this method has relatively reliable accuracy for the measurement of body fat mass.[26] However, the results of measuring the visceral fat area using this method are quite different from those obtained via Computed Tomography (CT). Therefore, in addition, this study used the other bioelectrical impedance device (OMRON, DUALSCAN HDS-2000) which has high accuracy to measure VFA.[27]

Previous studies have clearly pointed to a clear correlation between visceral fat and insulin resistance. Visceral fat can secrete tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1 and other proinflammatory factors to promote the onset and development of insulin resistance.[28] However, the VFA does not reflect fat accumulation in the liver, skeletal muscle,[29] submucosa of the intestinal wall,[30] or even astrocytes.[31] This ectopic fat accumulation can also lead to the development of insulin resistance and affect blood glucose metabolism. Therefore, compared to changes in VFA, changes in BF may better reflect the overall metabolic benefits of weight loss in the body. This may partly explain why the % change in BF rather than VFA was independently associated with the improvement in HbA1c (Table 4) in our study. However, at present, this study did not further explore whether the reduction in BF is related to the reduction in these ectopic fat distributions, and further related studies are needed. The decrease in appetite caused by dulaglutide treatment is also responsible for the improvement in HbA1c.

This study has several limitations. Firstly, the follow-up time in this study was relatively short. Data from previous studies showed that the fastest period of weight change after the use of 1.5 mg dulaglutide was the first 3 months (12 weeks), after which weight change entered a slow period.[32] The aim of our study was to find out whether the weight change was accompanied by bone and muscle loss. Taking all factors into account, 3 months was chosen as the follow-up period for this study. In the follow-up, we will continue to focus on the effect of longer dulaglutide treatment on the patients' body composition changes. Secondly, the inclusion criterion of this study did not limit the use of basic drug treatment plans, so the included population lacked a treatment washout period, and the basic treatment plan may bias the results of this study. The use of antidiabetic medications for all patients before dulaglutide therapy is shown in Table S2. SGLT2 inhibitors, and other medications that can lead to weight loss (eg, glucosidase inhibitors) are drug regimens that patients have used in the past. Our study protocol was to add dulaglutide to the original glucose-lowering drug regimen without changing the previous regimen. Based on the long-term use of this glucose-lowering regimen, we believe that the short-term (3-month) weight changes were mainly caused by the addition of dulaglutide. We compared the two groups of patients using SGLT2 inhibitors and those not using SGLT2 inhibitors and found that the use or non-use of SGLT2 inhibitors had no significant effect on the % change of BF, LBM and SMM (Table S3). We believe that this confounding factor does not significantly affect the conclusions of this study. Thirdly, VFA and skeletal muscle mass were not measured with golden standard and consistency test was not performed, although there was good agreement between these detection methods. In addition, this study did not

further explore the ability of dulaglutide to improve islet function or its effect on body fat distribution. A Further prospective design is necessary with the help of imaging or pathologic data.

Conclusion

Our work provides research data about the effect of dulaglutide on body composition in the Chinese population. The results showed that dulaglutide treatment can reduce body weight, and indicators of muscle mass (LBMP, SMMP) increased and the indicator of bone mass (BMQ) did not decrease. suggesting that weight reduction does not cause concomitant loss of bone mass or muscle mass. Further correlation and regression analysis indicated that % change in BF was independently associated with improvement in HbA1c with dulaglutide therapy. Our work provides a rationale for the safe use of dulaglutide in clinical practice.

Data Sharing Statement

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

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Sun H, Saeedi P, Karuranga S, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabet Res Clin Pract*. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
2. De Marinis YZ, Salehi A, Ward CE, et al. GLP-1 inhibits and Adrenaline stimulates glucagon release by differential modulation of N- and L-type Ca2+ channel-dependent exocytosis. *Cell Metab*. 2010;11(6):543–553. doi:10.1016/j.cmet.2010.04.007
3. Li Y, Hansotia T, Yusta B, Ris F, Halban PA, Drucker DJ. Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. *J Biol Chem*. 2003;278(1):471–478. doi:10.1074/jbc.M209423200
4. Yusta B, Baggio LL, Estall JL, et al. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. *Cell Metab*. 2006;4(5):391–406. doi:10.1016/j.cmet.2006.10.001
5. Meloni AR, DeYoung MB, Lowe C, Parkes DG. GLP-1 receptor activated insulin secretion from pancreatic β-cells: mechanism and glucose dependence. *Diabetes Obes Metab*. 2013;15(1):15–27. doi:10.1111/j.1463-1326.2012.01663.x
6. Flint A, Raben A, Ersbøll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. *Int J Obes Relat Metab Disord*. 2001;25(6):781–792. doi:10.1038/sj.ijo.0801627
7. Wishart JM, Horowitz M, Morris HA, Jones KL, Nauck MA. Relation between gastric emptying of glucose and plasma concentrations of glucagon-like peptide-1. *Peptides*. 1998;19(6):1049–1053. doi:10.1016/S0196-9781(98)00052-7
8. Turton MD, O'Shea D, Gunn I, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature*. 1996;379(6560):69–72. doi:10.1038/379069a0
9. Yu M, Benjamin MM, Srinivasan S, et al. Battle of GLP-1 delivery technologies. *Adv Drug Deliv Rev*. 2018;130:113–130. doi:10.1016/j.addr.2018.07.009
10. Hu S, Wang S, Qi C, et al. Cost-utility analysis of once-weekly semaglutide, dulaglutide, and exenatide for type 2 diabetes patients receiving metformin-based background therapy in China. *Front Pharmacol*. 2022;13:831364. doi:10.3389/fphar.2022.831364

11. Shi LX, Liu XM, Shi YQ, et al. Efficacy and safety of dulaglutide monotherapy compared with glimepiride in Chinese patients with type 2 diabetes: post-hoc analyses of a randomized, double-blind, Phase III study. *J Diabetes Investig*. 2020;11(1):142–150. doi:10.1111/jdi.13075
12. Li Y, Li L, De Peng Y, et al. Efficacy and safety of dulaglutide versus insulin glargine in Chinese T2DM patients: a subgroup analysis of a randomized trial (AWARD-CHN2). *Diabetes Ther*. 2019;10(4):1435–1452. doi:10.1007/s13300-019-0646-y
13. Gentilella R, Sesti G, Vazquez L, et al. Dulaglutide is an effective treatment for lowering HbA1c in patients with type 2 diabetes regardless of body mass index. *Diabetes Obes Metab*. 2019;21(12):2660–2666. doi:10.1111/dom.13853
14. Monami M, Dicembrini I, Nreu B, Andreozzi F, Sesti G, Mannucci E. Predictors of response to glucagon-like peptide-1 receptor agonists: a meta-analysis and systematic review of randomized controlled trials. *Acta Diabetol*. 2017;54(12):1101–1114. doi:10.1007/s00592-017-1054-2
15. Brunani A, Perna S, Soranna D, et al. Body composition assessment using bioelectrical impedance analysis (BIA) in a wide cohort of patients affected with mild to severe obesity. *Clin Nutr*. 2021;40(6):3973–3981. doi:10.1016/j.clnu.2021.04.033
16. Izzo A, Massimino E, Riccardi G, Della Pepa G. A narrative review on sarcopenia in type 2 diabetes mellitus: prevalence and associated factors. *Nutrients*. 2021;13(1):183. doi:10.3390/nu13010183
17. Mesinovic J, Zengin A, De Courten B, Ebeling PR, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. *Diabetes Metab Syndr Obes*. 2019;12:1057–1072. doi:10.2147/DMSO.S186600
18. Khin PP, Hong Y, Yeon M, Lee DH, Lee JH, Jun HS. Dulaglutide improves muscle function by attenuating inflammation through OPA-1-TLR-9 signaling in aged mice. *Aging*. 2021;13(18):21962–21974. doi:10.18632/aging.203546
19. Piñar-Gutierrez A, García-Fontana C, García-Fontana B, Muñoz-Torres M. Obesity and bone health: a complex relationship. *Int J Mol Sci*. 2022;23(15):8303. doi:10.3390/ijms23158303
20. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women. *Obes Res*. 2004;12(6):913–920. doi:10.1038/oby.2004.111
21. Zhang YS, Weng WY, Xie BC, et al. Glucagon-like peptide-1 receptor agonists and fracture risk: a network meta-analysis of randomized clinical trials. *Osteoporos Int*. 2018;29(12):2639–2644. doi:10.1007/s00198-018-4649-8
22. Cheng L, Hu Y, Li YY, et al. Glucagon-like peptide-1 receptor agonists and risk of bone fracture in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Metab Res Rev*. 2019;35(7):e3168. doi:10.1002/dmrr.3168
23. Cai TT, Li HQ, Jiang LL, et al. Effects of GLP-1 receptor agonists on bone mineral density in patients with type 2 diabetes mellitus: a 52-week clinical study. *Biomed Res Int*. 2021;2021:3361309. doi:10.1155/2021/3361309
24. Plank LD. Dual-energy X-ray absorptiometry and body composition. *Curr Opin Clin Nutr Metab Care*. 2005;8(3):305–309. doi:10.1097/01.mco.0000165010.31826.3d
25. Ward LC. Segmental bioelectrical impedance analysis: an update. *Curr Opin Clin Nutr Metab Care*. 2012;15(5):424–429. doi:10.1097/MCO.0b013e328356b944
26. Lee LC, Hsu PS, Hsieh KC, et al. Standing 8-electrode bioelectrical impedance analysis as an alternative method to estimate visceral fat area and body fat mass in athletes. *Int J Gen Med*. 2021;14:539–548. doi:10.2147/IJGM.S281418
27. Enomoto M, Adachi H, Fukami A, et al. A useful tool as a medical checkup in a general population-bioelectrical impedance analysis. *Front Cardiovasc Med*. 2017;4:3. doi:10.3389/fcvm.2017.00003
28. Gómez-Hernández A, Beneit N, Díaz-Castroverde S, Escribano Ó. Differential role of adipose tissues in obesity and related metabolic and vascular complications. *Int J Endocrinol*. 2016;2016:1216783. doi:10.1155/2016/1216783
29. Umek N, Horvat S, Cvetko E. Skeletal muscle and fiber type-specific intramyocellular lipid accumulation in obese mice. *Bosn J Basic Med Sci*. 2021;21(6):730–738. doi:10.17305/bjbms.2021.5876
30. Wada S, Yasunaga Y, Oka K, et al. Submucosal fat accumulation in human colorectal tissue and its association with abdominal obesity and insulin resistance. *United Eur Gastroenterol J*. 2018;6(7):1065–1073. doi:10.1177/2050640618766926
31. Heni M, Eckstein SS, Schittenhelm J, et al. Ectopic fat accumulation in human astrocytes impairs insulin action. *R Soc Open Sci*. 2020;7(9):200701. doi:10.1098/rsos.200701
32. Frias JP, Bonora E, Nevarez Ruiz L, et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). *Diabetes Care*. 2021;44(3):765–773. doi:10.2337/dc20-1473