

Insulin Glargine is More Suitable Than Exenatide in Preventing Muscle Loss in Non-Obese Type 2 Diabetic Patients with NAFLD



Authors

Lin Liu^{1, 2*}, Ruwen Wang^{3*}, Jian Gao^{4, 5*}, Jianhua Yan⁶, Jingtian Zhang⁴, Zhitian Zhang¹, Jiaojiao Liu¹, Huandong Lin^{1, 2}, Shengxiang Rao⁷, Xiuzhong Yao⁷, Weiyun Wu⁸, Hua Bian^{1, 2}, Xiangyu Wang⁴, Shanshan Guo^{3, 9}, Xin Gao^{1, 2}, Hongmei Yan^{1, 2, 10}

Affiliations

- 1 Department of Endocrinology and Metabolism, Zhongshan Hospital, Fudan University, Shanghai, China
- 2 Fudan Institute for Metabolic Disease, Fudan University, Shanghai, China
- 3 School of Kinesiology, Shanghai University of Sport, Shanghai, China
- 4 Department of Nutrition, Zhongshan Hospital, Fudan University
- 5 Center of Clinical Epidemiology and Evidence-based Medicine, Fudan University
- 6 Shanghai Key Laboratory of Molecular Imaging, Shanghai University of Medicine and Health Sciences, Shanghai, China
- 7 Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China
- 8 Department of Laboratory Medicine, Zhongshan Hospital, Fudan University, Shanghai, China
- 9 School of Life Sciences, Fudan University, Shanghai, China
- 10 Department of Endocrinology and Metabolism, Wusong Branch of Zhongshan Hospital, Fudan University, Shanghai, China.

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Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Hongmei Yan
Department of Endocrinology and Metabolism, Zhongshan Hospital, Fudan University, Shanghai
Fudan Institute for Metabolic Disease, Fudan University, Shanghai
Department of Endocrinology and Metabolism, Wusong Branch of Zhongshan Hospital, Fudan University
200032 Shanghai
China
yan.hongmei@zs-hospital.sh.cn

ABSTRACT

Aim This study investigated the effects of insulin glargine and exenatide on the muscle mass of patients with newly diagnosed type 2 diabetes (T2DM) and nonalcoholic fatty liver disease (NAFLD).

Methods We performed a post-hoc analysis of our previously study, a 24-week randomized controlled multicenter clinical trial (ClinicalTrials.gov, NCT02303730). Seventy-six patients were randomly assigned 1:1 to receive insulin glargine or exenatide treatment. The changes in psoas muscle area (PMA) (mm²) were obtained with the cross-sectional Dixonfat magnetic resonance images at the fourth lumbar vertebra.

* These authors contributed equally: Lin Liu, Ruwen Wang, Jian Gao

Results There were no significant differences in age, BMI, gender, and PMA in insulin glargine and exenatide groups at baseline. After treatment, PMA tended to increase by 13.13 (−215.52, 280.80) mm² in the insulin glargine group and decrease by 149.09 (322.90–56.39) mm² in the exenatide group (both $p > 0.05$). Subgroup analysis showed a 560.64 (77.88, 1043.40) (mm²) increase of PMA in the insulin group relative to the Exenatide group in patients with BMI < 28 kg/m² ($p = 0.031$)

after adjusting for gender, age, and research center. Interaction analysis showed an interaction between BMI and treatment ($p = 0.009$). However, no interaction was observed among subgroups with a BMI ≥ 28 kg/m² or with different genders and ages.

Conclusion Compared to exenatide, insulin glargine can relatively increase PMA in patients with T2DM having BMI < 28 kg/m² and NAFLD.

Introduction

Type 2 diabetes (T2DM) is one of the most widespread metabolic diseases. The current nationally representative epidemiological survey indicated that the overall prevalence of diabetes in mainland China in 2018 was 12.8%, using the American Diabetes Association (ADA) diagnostic criteria [1]. This change is mainly due to the increase in life expectancy and long-term exposure to cardiometabolic risk factors, especially obesity, skeletal muscle atrophy, and reduced levels of physical activity [2–4]. Diabetes mellitus and its complications brought enormous health risks and heavy economic burden to patients and society.

In addition to the classic chronic complications of diabetes, such as macrovascular and microvascular complications, there is another organ that is easily overlooked, the loss of muscle mass or sarcopenia [5]. Sarcopenia is a progressive and generalized skeletal muscle disease and will bring many adverse consequences, including tumble, fractures, physical disabilities, and even elevated mortality. In 2010, European consensus on the definition of sarcopenia: report of the European Working Group on Sarcopenia in Older People states that “Sarcopenia is a progressive, systemic loss of muscle mass and/or muscle strength or physiological impairment of muscle function associated with aging” [6, 7].

The overall prevalence of sarcopenia is 10% in people over 60 years old [8, 9]. Studies have shown that T2DM has a high prevalence of sarcopenia, ranging from 7% to 29.3%. The prevalence of sarcopenia in diabetic patients had a 9% increase compared with normal people. It has also been shown that the prevalence of sarcopenia was 27.6%, 21.8% and 52.6% in the groups with less than 10 years, 10 to 20 years, and more than 20 years of diabetes, respectively, when participants were classified according to the duration of diabetes [5, 10]. Although sarcopenia is more common in elderly and debilitated patients [11], it is not rare among young people, especially in diabetic patients [12].

In view of the facts that sarcopenia is associated with poor blood glucose control in diabetes, high complication rates, falls, and fractures, as well as increased social and economic burden, thereby the quality of life of the patients is affected [5, 13]. Thus, sarcopenia has been described as a new diabetic complication in the middle-aged and elderly people [14], in addition to microvascular and macrovascular complications. Therefore, it is necessary to pay more attention to the prevention and treatment of sarcopenia. At present, there is no specific drug treatment for sarcopenia. The main therapeutic method for sarcopenia is currently a high-protein diet and exercise [15, 16]. In patients with diabetes, sarcopenia can be more difficult to treat because some treatments for diabetes may worsen sarcopenia. For example, strict dietary restrictions can lead to

insufficient protein intake [17]. Some hypoglycemic drugs cause weight loss, which might further aggravate the sarcopenia. For diabetic patients with sarcopenia, using hypoglycemic drugs that could increase muscle mass is a reasonable choice [18].

Some observational cross-sectional studies reported the impact of hypoglycemic drugs on muscle mass, but prospective or intervention trials are lacking. One retrospective observational study showed that insulin treatment could attenuate the progression of sarcopenia in Japanese patients with T2DM [19]. Insulin pump therapy led to a significant increase in skeletal muscle mass in Type 1 diabetes (T1DM) patients [20]. As to GLP-1 receptor agonist (GLP-1RA), liraglutide effectively induces loss of fat and increased skeletal muscle index in elderly T2DM patients who are overweight or obese [21]. The latest human study had shown that after treatments, semaglutide showed a significant decrease in fat-free mass (FFM) or total lean mass while with a large weight loss [22, 23].

While the effects of insulin and GLP-1RA on muscle content varied in different studies, comparative studies of how the two drugs affect muscle mass in the same population have not been reported. Our previous clinical trial [ClinicalTrials.gov, NCT02303730] showed that insulin glargine and exenatide could effectively reduce blood glucose and liver fat content in diabetics, but the effect of the two drugs on muscle mass in patients was still unclear. The purpose of this study was to investigate the effects of insulin glargine and exenatide on the muscle mass of T2DM and nonalcoholic fatty liver disease (NAFLD).

Methods

Patients

Study participants were newly diagnosed T2DM and NAFLD patients, aged 18–70 years, and had a body mass index (BMI) > 24 kg/m², glycated hemoglobin A1c (HbA1c) level between 7% and 10%. Patients should have been given diet and exercise control, but not diabetes medication. Study participants and the biochemical examinations were according to previous research [24, 25]. Obesity was defined as BMI ≥ 28 kg/m².

Assessment of muscle mass

All MR imaging examinations were performed on a 1.5-T MR system (MagnetomAvanto, Siemens AG, Erlangen, Germany) with a phased-array surface coil. An axial T1 VIBE two-point Dixon gradient-echo sequence in breath-hold and reconstruction of fat-only and water-only datasets from the in- and out-of-phase acquisitions was used for the determination of skeletal muscle. More details

► **Table 1** Baseline characteristics of the population under study.

| Group | Insulin Glargine | Exenatide | P-value |
|---|-------------------------|--------------------------|---------|
| N | 36 | 35 | |
| Sex | | | 0.899 |
| Male | 19 (52.78%) | 19 (54.29%) | |
| Female | 17 (47.22%) | 16 (45.71%) | |
| Age (years) | 50.56 ± 11.78 | 47.63 ± 10.14 | 0.249 |
| <60 years old | 27 (75.00%) | 30 (85.71%) | 0.257 |
| ≥ 60 years old | 9 (25.00%) | 5 (14.29%) | |
| BMI (kg/m ²) | 27.84 ± 3.10 | 28.49 ± 3.02 | 0.370 |
| < 28 kg/m ² | 22 (61.11%) | 16 (45.71%) | 0.193 |
| ≥ 28 kg/m ² | 14 (38.89%) | 19 (54.29%) | |
| Psoas Muscle Area (mm ²) | | | |
| Before-treatment | 2306.19 ± 877.75 | 2328.93 ± 725.26 | 0.906 |
| After-treatment | 2344.01 ± 974.91 | 2187.54 ± 754.92 | 0.475 |
| Difference of after vs before treatment | 13.13 (-215.52, 280.80) | -149.09 (-322.90, 56.39) | 0.214 |

about the MR imaging parameters were as follows: repetition time (TR) 7.5 ms; echo time (TE): TE_{in-phase} = 4.76 ms, TE_{out-phase} = 2.38 ms; flip angle 13°; section thickness 5 mm; slice gap 2 mm; bandwidth 100 kHz; matrix 256 × 134; pixel spacing 0.879 mm/0.879 mm; the field of view 38 cm; and acquisition time 22 s. Participants were placed in a supine position with their arms extended. And the definition of skeletal muscle area was obtained with the cross-sectional Dixonfat images at the fourth lumbar vertebra.

Statistical Analyses

Continuous variables were shown as mean ± standard deviation (SD), while categorical variables were shown as frequency and composition ratio. Differences in baseline characteristics between groups were assessed using the unpaired Student's t-test or Mann-Whitney U test for quantitative variables, and the χ² test or Fisher's exact test for qualitative variables. Univariate and multivariate general linear models were performed to assess the associations between treatment and psoas muscle area (PMA). The interactions between treatment and the baseline factors (age, sex, BMI) were analyzed using the Wald test for the cross-product. All analyses were conducted with R software, version 3.6.1 (<http://www.r-project.org>). All significance tests were two-sided, and P < 0.05 was considered statistically significant.

Results

The baseline clinical characteristics of insulin glargine and the exenatide group

There were no significant differences in age, BMI, or gender between the two groups. Before the intervention, there was no difference in psoas muscle area (PMA) in insulin glargine and exenatide groups (2328.93 ± 725.26, 2306.19 ± 877.75; p0.906). PMA tended to increase by 13.13 (-215.52, 280.80) mm² in the insulin glargine group and decrease by 149.09 (-322.90, 56.39) mm² in the exenatide group, but both the differences were not statistically significant (► **Table 1**).

Interaction between changes in psoas muscle area and body mass index in the insulin glargine group compared with the exenatide group

As mentioned above, there was an opposite change in PMA after treatment in the insulin glargine group compared with the exenatide group, but this change was not statistically significant. We speculated that there might be other factors influencing the change of PMA in addition to the treatment. Therefore, subgroup analysis and interaction analysis were performed.

For non-obese patients (BMI < 28 kg/m²), PMA of the insulin glargine group increased by 403.04 (-17.43, 823.51) mm² compared to the exenatide group (p0.069). After adjusting for sex, age, and study center, the increase in PMA was significantly different compared to control (p0.031). The interaction between treatment and BMI was statistically significant with or without adjustment for the above factors (both the Interaction test P-value < 0.05). However, no interaction was observed among subgroups with a BMI ≥ 28 kg/m² or with different (► **Table 2**).

Discussion

In our previous study, we found that insulin glargine and exenatide can improve fatty liver while reducing blood sugar in NAFLD patients with T2DM [24]. However, it is not clear how these two drugs affect the muscle mass of the patients at that time. This post hoc study was first found that compared with exenatide, insulin glargine could relatively increase PMA content in T2DM with non-obese NAFLD patients. It could provide an evidence for the choice of treatment for diabetic patients with muscle loss or sarcopenia.

Currently, only two clinical studies have shown that insulin increases muscle mass. A retrospective observational study had shown that insulin could attenuate the progression of sarcopenia in Japanese T2DM patients [19]. In addition, insulin pump therapy led to a significant increase in skeletal muscle mass in Type 1 diabetes (T1DM) patients; meanwhile, the body weight was also significantly increased after the therapy [20]. However, the above two studies are not randomized controlled studies, so the conclusion might be underpowered. It was unclear whether the long-acting

► **Table 2** Interaction between changes in the Psoas Muscle Area (PMA) among subgroups.

| | Unadjusted | | | Adjusted * | | |
|--------------------------------|------------------------------------|---------|----------------------------------|-----------------------------------|---------|-------------------------------|
| | Changes of PMA (mm ²) | P value | Interac- tion test P value | Changes of PMA (mm ²) | P value | Interac- tion test P value |
| | β (95 %CI) | | | β (95 %CI) | | |
| Insulin Glargine vs. Exenatide | | | | | | |
| Total | 178.54 (−99.98, 457.07) | 0.214 | | 202.39 (−76.34, 481.12) | 0.16 | |
| Male | 298.92 (−214.97, 812.81) | 0.263 | 0.362 | 368.48 (−128.99, 865.95) | 0.158 | 0.189 |
| Female | 44.91 (−123.45, 213.27) | 0.605 | | 11.22 (−169.41, 191.84) | 0.904 | |
| Age < 60 y | 208.73 (−133.59, 551.06) | 0.238 | 0.758 | 185.43 (−131.85, 502.72) | 0.258 | 0.963 |
| Age ≥ 60 y | 99.04 (−164.34, 362.42) | 0.477 | | 144.83 (−114.57, 404.23) | 0.316 | |
| BMI < 28 kg/m ² | 403.04 (−17.43, 823.51) | 0.069 | 0.038 | 560.64 (77.88, 1043.40) | 0.031 | 0.009 |
| BMI ≥ 28 kg/m ² | −112.92 (−466.65, 240.80) | 0.537 | | −114.21 (−467.10, 238.68) | 0.532 | |

* adjusted for baseline PMA, age, sex and center, if appropriate; PMA: posas muscle area; BMI: body mass index.

insulin, Insulin Glargine also affected increasing muscle mass. This study showed for the first time, insulin glargine, compared with exenatide, was more suitable for increasing muscle mass in non-obese T2DM and NAFLD patients.

Some basic research explained the mechanism of insulin increases muscle mass. Insulin is a major regulator of muscle glucose metabolism, enhancing glucose uptake in the postprandial state. Insulin was also shown to control muscle protein synthesis and degradation [26]. Insulin and IGF-1 enhance muscle protein synthesis through their receptors. The IR/IGF1R signaling cascades maintain muscle mass via suppression of FoxO1/3/4-mediated autophagy and protein degradation. These data indicate that insulin and IGF-1 are critical hormonal regulators of muscle mass and proteostasis [27].

In this study, we found that insulin glargine did not increase muscle content in all T2DM and NAFLD, but in non-obese patients with BMI lower than 28 kg/m². Therefore, for T2DM patients with different BMI, selectively applied therapy is required.

GLP-1 receptor agonists have been commonly used as anti-diabetic drugs to lower blood glucose levels while reducing body weight. Most of the studies showed that GLP-1RA improves body composition by decreasing fat mass in obese diabetics (BMI > 28 kg/m²) [21, 28]. Exenatide is one of the earlier GLP-1RA to enter clinical application; many studies found that exenatide significantly decreases body weight, effectively reduced liver fat content and epicardial fat in obese patients with T2DM, and these effects were mainly weight loss dependent [28]. For the same reason, exenatide entered the Chinese market earlier, so we selected exenatide as one of the target drugs. Our previous study showed that exenatide could reduce liver fat content and fibrosis score (FIB4) [24]. Although some animal studies showed that exenatide can increase muscle mass [29], its effect on muscle content has not been reported in clinical trial before this study. In this study, we report for the first time that exenatide tended to reduce muscle mass in T2DM patients with NAFLD. Different from exenatide, other long-acting GLP-1RA, has been reported to improve the human skeletal muscle index. Twenty-four weeks of liraglutide treatment was associated with reductions in fat mass and android fat, an increase in skeletal muscle index (the sum of fat-free soft tissue mass of arms and legs), and preserved muscular tropism in overweight and obese

T2DM patients (BMI > 28 kg/m²) [21]. Dulaglutide could recover muscle mass and function in DBA/2J-mdx mice [29] but clinical evidence is lacking. The latest human study showed that after treatments, semaglutide significantly decreased fat-free mass (FFM) or total lean mass while with a large weight loss [22, 23], but the relative change in proportion of lean mass increased by 1.2% [23]. It is not clear why different types of GLP-1RA affect muscles differently; further exploration is needed. Therefore, in clinical practice, if GLP-1RA is employed in diabetic patients with sarcopenia, care should be taken to select those types that do not reduce muscle mass, such as liraglutide.

However, the study had certain limitations. First, as this is a post hoc analysis, residual confounding cannot be eliminated. The results of this study are only used as the basis for hypothesis generation, and more well-designed clinical trials with large population should be conducted to clarify this finding further. Second, the sample size is relatively small, and larger-scale clinical trials should be conducted to confirm this provocative finding. Third, we only measured the content of the psoas major muscle, without measuring the muscle strength and completely assessing muscle function, which also needed to be studied and verified in future studies.

In summary, our study suggested that in drug-naive T2DM and non-obese NAFLD patients, compared to exenatide, insulin glargine can relatively increase PMA and improved NAFLD, in addition to its classic effect of lowering blood sugar. It provided new scientific evidence for the selection of hypoglycemic drugs for similar patients. Further large sample randomized controlled interventional trials were required to verify the effects of insulin glargine on muscle mass and function in NAFLD patients with diabetes.

Author Contributions

Hongmei Yan, Jian Gao, Shanshan Guo, and Xin Gao designed the study. Lin Liu, Jian Gao, Jingtian Zhang, Shengxiang Rao, Xiuzhong Yao, and Weiyun Wu collected the data. Ruwen Wang, Jianhua Yan, Huandong Lin, and Hua Bian analyzed the data. Lin Liu, Ruwen Wang, Jianhua Yan, Jian Gao, Zhitian Zhang, and Jiaojiao Liu were responsible for drafting the article and revising it. All authors provided support for the interpretation of results, critically revised the

manuscript, and approved the final manuscript. Lin Liu, Ruwen Wang and Jianhua Yan contributed equally to this work.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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