Insulin Glargine is more suitable than Exenatide to prevent muscle loss in non-obese type 2 diabetic patients with NAFLD


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DOI: 10.1055/a-2145-1004

Please cite this article as: Liu L, Gao J, Wang R et al. Insulin Glargine is more suitable than Exenatide to prevent muscle loss in non-obese type 2 diabetic patients with NAFLD. Experimental and Clinical Endocrinology & Diabetes 2023. doi: 10.1055/a-2145-1004

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by Medical Guidance Project of Shanghai Science and Technology Commission, 19401931100 to Wang XY, Science and Technology Commission of Shanghai Municipality (http://dx.doi.org/10.13039/501100003399), 21ZR1413200 to HM Yan, Scientific Research and Development Foundation of Zhongshan Hospital, Fudan University, 2019ZSFZ110 to HD LIN

Trial registration: 21ZR1413200 to HM Yan; 2019ZSFZ10 to HD LIN; 19401931100 to Wang XY, Chinese Clinical Trial Registry (http://www.chictr.org/), Multi-Center Study

Abstract:

Aim: The aim of this study was to investigate 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) was obtained with the cross-sectional Dixonfat magnetic resonance images at the fourth lumber vertebra.

Results: There were no significant differences in age, BMI, gender, and PMA in Insulin Glargine and Exenatide group at baseline. After treatment, PMA tended to increase by 13.13 (-215.52, 280.80) mm² in Insulin Glargine group and decrease by 149.09 (322.90,-56.39) mm² in Exenatide group (both p >0.05). Subgroup analysis showed a 560.64 (77.88, 1043.40) (mm²) increase of PMA in Insulin group relative to Exenatide group in patients with BMI < 28kg/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 ≥ 28kg/m² or with different genders and ages.

Conclusion: Compared to the Exenatide, Insulin Glargine can relativity increase PMA in T2DM patients with BMI< 28 kg/m² and NAFLD.

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Insulin Glargine is more suitable than Exenatide to prevent muscle loss in non-obese type 2 diabetic patients with NAFLD

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Abstract

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**Conclusion:** Compared to the Exenatide, Insulin Glargine can relatively increase PMA in T2DM patients with BMI < 28 kg/m² and NAFLD.

**Keywords**
body composition; basal insulin; exenatide; fatty liver disease; type 2 Diabetes; clinical trial

**Introduction**
Type 2 diabetes (T2DM) is one of the most widespread metabolic diseases. This 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, even elevated mortality. In 2010, European consensus on definition of sarcopenia: report of the European Working Group on Sarcopenia in Older People states “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 have a high prevalence of sarcopenia, which ranging from 7% to 29.3%. Prevalence of sarcopenia in diabetic patients had a 9% increased compared with ordinary 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 poorly blood glucose control in diabetes, high complication rates, falls and fractures, as well as increase the social and economic burden, thereby affecting their life quality[5, 13]. Thereby, 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, more attention for the prevention and treatment of sarcopenia is necessary. At present, there is no specific drug treatment for sarcopenia. The main therapeutic method for sarcopenia is currently 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 hypoglycemics cause weight loss, it might further aggravate the sarcopenia. For diabetic patients with sarcopenia, using hypoglycemics 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 the prospective or intervention trials are lacking. A retrospective observational study had shown that insulin treatment could attenuate the progression of sarcopenia in Japanese patients with T2DM[19]. Insulin pump therapy led to a significant increase of 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 insulin and GLP-1RA had different effects on muscle content in different studies, but 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 NAFLD.

**Methods**

**2.1 Patients**

Study participants were newly diagnosed T2DM and NAFLD patients, aged 18−70 yeas, 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 referred to previous research[24, 25]. Obesity was defined as BMI ≥ 28kg/m².

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

2.3 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 \(\chi^2\) 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.rproject.org). All significance tests were two-sided and \(P<0.05\) was considered statistically significant.

Results
The baseline clinical characteristics of Insulin Glargine and Exenatide group
There were no significant differences in age, BMI, gender between the two groups. Before the intervention, there was no difference of psoas muscle area (PMA) in Insulin Glargine and Exenatide group (2328.93 ± 725.26, 2306.19 ± 877.75; \(p=0.906\)). PMA tended to increase by 13.13 (-215.52, 280.80) mm\(^2\) in Insulin Glargine group and decrease by 149.09 (-322.90, 56.39) mm\(^2\) in Exenatide group, but both the differences were not statistically significant. (Table 1)

Interaction between changes of Psoas Muscle Area and BMI 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<28kg/m\(^2\)), PMA of Insulin Glargine group increased by 403.04 (-17.43, 823.51) mm\(^2\) compared to the Exenatide group (p=0.069). After adjusting for sex, age, and study center, the increase in PMA was significantly different compared to control (p=0.031). 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 ≥ 28kg/m\(^2\) or with different. (Table 2)

**Discussion**

Our previous study 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 muscle mass of the patients at that time. This post hoc study was first found that Insulin Glargine could relatively increase PMA content in T2DM with non-obese NAFLD patients compared with Exenatide. It could provide an evidence for the choice of treatment for diabetic patients with muscle loss or sarcopenia. Currently, there were 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 leaded to a significant increase of skeletal muscle mass in Type 1 diabetes (T1DM) patients, meanwhile, the body weight was also significantly increased after the therapy[20]. But the above two studies are not randomized controlled studies, so the conclusion might be underpowered. And it was unclear whether the long-acting insulin Insulin Glargine also had the effects on increasing muscle mass. This study showed for the first time that 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 was a major regulator of muscle glucose metabolism, enhancing glucose uptake in the postprandial state. Insulin had also been shown to control muscle protein synthesis and degradation[26]. Insulin and IGF-1 enhance muscle protein synthesis through their receptors. IR/IGF1R signaling cascades maintained 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/m\(^2\). Therefore, for T2DM patients with different BMI, selectively applied therapy is required. GLP-1 receptor agonist had been commonly used as anti-diabetic drugs to lower blood
glucose levels while reducing body weight. Most of the studies showed that GLP-1RA improved body composition by decreasing fat mass in obese diabetics (BMI > 28kg/m²)[21, 28]. Exenatide is one of the earlier GLP-1RA to enter clinical application, many studies has shown that Exenatide significantly decreased body weight, effectively reduced liver fat content and epicardial fat in obese patients with T2DM, and these effects were mainly weight loss dependent[28]. And for the same reason, Exenatide entered the Chinese market earlier, so we chose 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], the effect of Exenatide 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 had been reported in improving human skeletal muscle index. Twenty-four weeks of liraglutide treatment was associated with reductions in fat mass and android fat, increased in skeletal muscle index (the sum of fat free soft tissue mass of arms and legs), and preserved the muscular tropism in overweight and obese T2DM patients (BMI>28kg/m²)[21]. Dulaglutide could recover muscle mass and function in DBA/2J-mdx mice[29] but clinical evidence is lacking. 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], but the relative change 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 applied 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. Firstly, 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. Secondly, the sample size is relatively small, and larger-scale clinical trials should be conducted to confirm this provocative finding. Thirdly, we only measured the content of psoas major muscle, without measuring the muscle strength and completely assessing of muscle function, which also needed to be studied and verified in future studies.

In summary, compared with Exenatide, our study suggested that in drug-naive T2DM and non-obese NAFLD patients, Insulin Glargine can relatively increased PMA and improved NAFLD, in addition to its classic effect of lowering blood sugar. It provided a 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.

**Data Availability Statement**
Data was not available.

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 interpretation of results, critically revised the manuscript, and approved the final manuscript. Lin Liu, Ruwen Wang and Jianhua Yan contributed equally to this work.

Acknowledgement:
This study was supported by Shanghai Municipal Science and Technology Commission (21ZR1413200 to HM Yan) and Scientific Research and Development Foundation of Zhongshan Hospital, Fudan University (2019ZSFZ10 to HD LIN) and Medical Guidance Project of Shanghai Science and Technology Commission [19401931100 to Wang XY].

References


Table 1: Baseline characteristics of the population

<table>
<thead>
<tr>
<th>Group</th>
<th>Insulin Glargine</th>
<th>Exenatide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>36</td>
<td>35</td>
<td>0.899</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (52.78%)</td>
<td>19 (54.29%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (47.22%)</td>
<td>16 (45.71%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years old</td>
<td>27 (75.00%)</td>
<td>30 (85.71%)</td>
<td>0.257</td>
</tr>
<tr>
<td>≥60 years old</td>
<td>9 (25.00%)</td>
<td>5 (14.29%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28 kg/m²</td>
<td>22 (61.11%)</td>
<td>16 (45.71%)</td>
<td>0.193</td>
</tr>
<tr>
<td>≥28 kg/m²</td>
<td>14 (38.89%)</td>
<td>19 (54.29%)</td>
<td></td>
</tr>
</tbody>
</table>

Psoas Muscle Area (mm²)

| 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 | 13.13 (-215.52, 280.80) | -149.09 (-322.90, 56.39) | 0.214   |

Table 2: Interaction between changes of Psoas Muscle Area among subgroups

<table>
<thead>
<tr>
<th></th>
<th>Changes of PMA (mm²)</th>
<th>P-value</th>
<th>Interaction test P-value</th>
<th>Changes of PMA (mm²)</th>
<th>P-value</th>
<th>Interaction test P-value</th>
</tr>
</thead>
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<tr>
<td></td>
<td>β (95%CI)</td>
<td></td>
<td></td>
<td>β (95%CI)</td>
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<tr>
<td>Insulin Glargine vs. Exenatide</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>178.54 (-99.98, 457.07)</td>
<td>0.214</td>
<td></td>
<td>202.39 (-76.34, 481.12)</td>
<td>0.16</td>
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</tr>
<tr>
<td>Male</td>
<td>298.92 (-214.97, 812.81)</td>
<td>0.263</td>
<td></td>
<td>368.48 (-128.99, 865.95)</td>
<td>0.158</td>
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<tr>
<td>Female</td>
<td>44.91 (-123.45, 213.27)</td>
<td>0.605</td>
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<td>11.22 (-169.41, 191.84)</td>
<td>0.904</td>
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<tr>
<td>Age &lt;60 y</td>
<td>208.73 (-133.59, 551.06)</td>
<td>0.238</td>
<td>0.362</td>
<td>185.43 (-131.85, 502.72)</td>
<td>0.258</td>
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<tr>
<td>Age ≥60 y</td>
<td>99.04 (-164.34, 362.42)</td>
<td>0.477</td>
<td>0.758</td>
<td>144.83 (-114.57, 404.23)</td>
<td>0.316</td>
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<tr>
<td>BMI &lt;28 kg/m²</td>
<td>403.04 (-17.43, 823.51)</td>
<td>0.069</td>
<td></td>
<td>560.64 (77.88, 1043.40)</td>
<td>0.031</td>
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</tr>
<tr>
<td>BMI ≥28 kg/m²</td>
<td>-112.92 (-466.65, -61.70)</td>
<td>0.038</td>
<td></td>
<td>-114.21 (-467.10, -88.68)</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

* adjusted for baseline PMA, age, sex and center, if appropriate