Research Open

Journal of Clinical Research and Medicine
Volume 7 Issue 2

Commentary

# Sex Differences in Anti-Obesity Drugs: Is it Time to be More Proactive in Engaging Men?

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**Received:** June 26, 2024; **Accepted:** July 01, 2024; **Published:** July 03, 2024

## Introduction

The paper "Sex-differences in response to treatment with liraglutide 3.0 mg" provides a critical analysis of how responses to obesity treatments can vary by sex, with a particular focus on the efficacy of liraglutide 3.0 mg in patients with obesity (BMI ≥ 30 kg/m2), but without type 2 diabetes (T2D) [1].

The emphasis on sex-specific responses in obesity places this study within a trend of increasing recognition, among clinicians and researchers, of the critical role of sex and gender at all levels of medical research [2]. Despite this growing awareness, sexual biology is often relegated to a specialized discipline rather than being integrated as a fundamental aspect [3], underscoring the need for integration of this analysis.

The authors provide a clear picture of the increasing rates of obesity in recent decades, and of the apparent sex differences in obesity prevalence, attitudes and behaviors [4].

While it is generally accepted that the prevalence of obesity appears to be slightly higher in women than in men, it is increasing in both sexes worldwide [5]. Interestingly, the authors report that recently in Italy, obesity appears to be higher in men than in women [6,7].

This discrepancy may explain why the authors chose to emphasize that, despite the overall higher prevalence of obesity in men, women are more likely to be included in obesity clinical trials, and to seek and to be prescribed anti-obesity pharmacotherapy [8].

In addition, although previous studies have suggested a sexually dimorphic response to GLP-1RAs, with greater weight loss in women than in men, as the authors note, most of these studies were conducted in people with T2D and, in any case, sex-specific analysis remains underexplored [2].

Overall, the study highlights the importance of better understanding sex-specific responses to obesity treatments, such as liraglutide, the first GLP-1 receptor agonist approved for weight management in Italy, in a real-world setting.

## Results

The authors conducted a single-center, real-world, retrospective study at the Santa Maria Goretti Hospital in Italy, focusing on a specific cohort of patients with obesity, but without T2D. The study design includes criteria that help minimize confounding variables such as previous anti-obesity treatments or significant metabolic comorbidities or treatments, ensuring a more homogeneous sample. By including only patients who reached and maintained the maximum dose of liraglutide (3.0 mg) for at least 6 months, the study strengthens the validity of its findings regarding the effects of liraglutide on weight loss and improvements in metabolic parameters.

The results show significant sex differences in response to liraglutide. Men experienced significantly greater reductions in weight and BMI at both 3 (-10.7 vs -7.1 kg, -3.6 vs -2.6 kg/m$^2$), and 6 months (-17.9 vs -11.9 kg, -6.0 vs -4.4 kg/m2) compared with women. In addition, the authors decided to include in the analysis the assessment of percentage weight loss (%WL) and the achievement of weight loss of >5% (WL>5%) and >10% (WL>10%), which are considered meaningful for clinicians, public health, and for anti-obesity drug targets [9,10]. A higher percentage of men achieved significant WL >5% (93.7% vs. 58.0%) and %WL (-9.2% vs. -6.5%) at 3 months than women, and this trend was maintained at 6 months, with WL >10% (87.5% vs. 29.0%) and %WL (-15.2% vs. -10.5%).

The inclusion of metabolic parameters adds depth to the study and has shown that men also experienced significantly greater improvements in total (-14.0 mg/dL vs. 9.5 mg/dL) and LDL cholesterol (-19.0 mg/dL vs. 6.8 mg/dL) and the fibrosis-4 index FIB-4 (-0.25 vs. -0.003) as an indicator of liver function than women. However, no significant sex-differences were observed in glucose metabolism or renal function [1].

## Discussion

One of the key considerations in this study is the higher representation of women (65.9%) compared to men (34.0%) in the sample. This is consistent with other analyses in the literature suggesting that women are more likely than men to be enrolled in clinical trials of anti-obesity drugs [11], and may confirm that in the real world, women may also be more proactive in seeking weight management treatments in a clinical setting, possibly due to different attitudes and awareness of body weight than men [12].

In terms of results, while some previous studies have suggested superior weight loss in women with GLP-1 receptor agonists (GLP-1 RAs), this study found the opposite, confirming the complexity of sex-specific pharmacodynamics and pharmacokinetics.

The authors discuss possible explanations for these conflicting results, emphasizing that the majority of results have been obtained in people with T2D using other classes of GLP1-Ras [13-15]. Consistent with this, it has been suggested that the different molecules may have different pharmacokinetics and pharmacodynamics [13], and it is also known that diabetes is a known factor that can influence pharmacotherapy weight loss or changes in metabolic parameters in people with increased adiposity [16].

In addition, the authors noted that most studies reported different baseline body weights, and BMIs between the sex groups, describing a non-homogeneous sample. Despite in some studies researchers have hypothesized that the greater weight loss in women may be related to their greater exposure to the drug due to their lower body weight [13,15,17], while others have observed an association between women's greater weight loss and their higher baseline BMI [15,18], these hypotheses remain contradictory.

Overall, the absence of baseline differences in weight, BMI, and comparison of percent body weight loss may have helped to attenuate any differences in the authors' results, in addition to the absence of T2D and other metabolic treatments in a real-world setting, may potentially explain the different results from those reported in the literature.

Given the mean age of the cohort (50.8 years), the authors have also suggested that the contribution to the observed differences may be due to differences in body composition and hormonal changes experienced by women during the menopausal transition [19,20], which could also influence the pharmacokinetics and pharmacodynamics of the drugs [21]. Indeed, in a study conducted only in patients with obesity treated with liraglutide 3.0 mg, greater weight loss was observed in women than in men, but the mean age was 43.6 years [22], which may have influenced the results.

In line with the latter, it can be added that recent evidence suggests that central estrogen receptor (ER)α signaling is necessary for the effects of GLP-1 on food reward behavior [23,24], and that in ovariectomized animal models, lower estradiol (E2) levels were associated with hyperfagia and weight gain [25].

To date, weight loss interventions are not tailored to women's menopausal status, nor to sex differences, and studies based on sex in response to liraglutide in people with obesity only remain very limited. This context allows to highlight the significance of these findings for clinical practice implications as a major strength of this paper. Given the recent increase in the prevalence of obesity in men and their underrepresentation in weight management programs, the findings of greater efficacy of liraglutide in men are particularly significant, and underscore the need for clinicians to be more proactive in engaging men in obesity treatment programs. In addition, given the higher cardiovascular risk in men, the notable improvements in total and LDL cholesterol and liver fibrosis in men raise important questions about the cardiometabolic benefits of liraglutide.

## Conclusion

This paper makes a significant contribution to the field of obesity treatment by highlighting the importance of considering sex differences in clinical settings where, similar to lifestyle intervention trials, most pharmacological trials do not analyze weight loss separately for men and women due to the higher representation of women in pharmacological weight loss trials [11].

The potential for sex-specific tailoring of obesity treatments is in line with the need to develop more personalized treatment in the medical field, including dose adjustment where appropriate [24], with significant public health benefits.

Strengths of the study include its real-world setting, comprehensive data collection, and focus on a homogeneous cohort. However, the authors acknowledge several limitations, including the small sample size, retrospective design, and lack of data on changes in body composition, dietary habits, and physical activity levels.

Despite these limitations, the study provides valuable insights into the sex-specific effects of liraglutide and calls for further research into sex-specific responses to anti-obesity drugs to better understand the mechanisms behind these differences. In doing so, it paves the way for more effective, personalized obesity treatments that take into account the unique physiological and hormonal factors that influence treatment outcomes in men and women, and may increase men's engagement in obesity treatment programs.

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**Citation:**

Milani I, Leonetti F, Capoccia D (2024) Sex Differences in Anti-Obesity Drugs: Is it Time to be More Proactive in Engaging Men? *J Clin Res Med* Volume 7(2): 1-3.