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COMMENTARY

Semaglutide in Obesity: Unmet Needs in Men

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Key Summary Points

Men were understudied in the STEP Phase 3a clinical program.

A number of gender-specific differences in efficacy of semaglutide between men and women were identified in subgroup analysis overviews of the STEP program.

Gender-specific issues in weight management with semaglutide need to be addressed to maximize the benefits of this agent to patients.

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Global average data suggest that the prevalence of male obesity is increasing and that its prevalence in some regions of Western Europe, Japan, China, Korea and USA is higher than that of female obesity [1]. However, men appear reluctant to engage in weight loss intervention programs despite verified established links between obesity and health-related diseases [2]. This reticence may reflect a general failure to recognize gender issues in weight management.

A novel second-generation anti-obesity pharmacotherapy strategy against obesity represents a considerable advance in the efficacy of obesity management programs, as well as a significant change in the treatment of obesity [3]. The Semaglutide Treatment Effect in People with Obesity (STEP) Phase 3a clinical development program evaluated the safety and efficacy of the first second-generation medication, namely semaglutide, administered subcutaneously once weekly, for weight management in adults with obesity or overweight with at least one weight-related comorbidity [4–7]. STEP 2 enrolled patients with overweight or obesity with type 2 diabetes (T2D), while the other STEP studies (STEP 1, 3 and 4) enrolled patients with overweight or obesity, without T2D [4–7]. In STEP 4, patients who reached and tolerated a maintenance dose of semaglutide 2.4 mg during a 20-week run-in period were randomized at week 20 to continue semaglutide or switch to placebo [7].

An overview of the demographics of randomized patients in the STEP 1–4 trials demonstrated that there were significantly more women than men in STEP 1, 3 and 4 [4–8]. Specifically, men represented only 26.9% of the included study population randomized to semaglutide in STEP 1, 22.6% in STEP 3 and 19.8% in STEP 4. In STEP 2, the distribution between women and men was more even (55.2 vs. 44.8%, respectively) [4–8]. Similar to the demographics in the STEP trials, the study population of the recently published STEP TEENS phase 3a trial comprised 62% girls (of 201 adolescents) with a mean age of 15.4 years and body mass index (BMI) in the 95th percentile or higher according to sex- and age-specific growth charts, or a BMI in the 85th percentile or higher with at least one weight-related coexisting condition [9]. The mean change in BMI in this population from baseline to week 68 was − 16.1% with semaglutide and 0.6% with placebo [9].

Subgroup analyses of trials on adults conducted to evaluate the change in efficacy response of semaglutide by sex found a greater mean weight reduction in women than in men in STEP 1, 2 and 4. The estimated treatment difference in weight reduction in the semaglutide group compared to the group receiving placebo was − 14.0% in women versus − 8.0% in men in STEP 1, 7.5% (women) versus 4.6% (men) in STEP 2 and 16.2% (women) versus 9.3% (men) in STEP 4 [4–8].

A number of explanations have been proposed for this difference between the sexes. One factor is presumably related to exposure difference due to women having a lower average body weight. A number of studies have shown the weight loss increased with greater exposure to glucagon-like peptide 1 receptor agonist (GLP-1 RA) and appeared to level off at the highest exposure in most women [10, 11]. By contrast, drug concentration did not fully plateau in men at the doses approved for weight management [12].

Secondly, recent evidence suggests that women and men may regulate feeding behavior differently due to the impact of sex hormones [13, 14]. In preclinical models, conjugated GLP-1 RA and estrogen reduced body weight, food intake and food reward more than either of these agents applied separately [15]. It has been also reported that gender is significantly associated with the rate of gastric emptying (GE) [16, 17]. GE of solids in pre-menopausal women has been found to be slower than that in men, irrespective of the phase of the menstrual cycle [18, 19]. Whether GLP-1 RA has a different impact on GE in women and men has not been evaluated by scintigraphy, the reference method for this purpose.

There are also a number of minor differences between men and women in terms of adverse event profiles that might also lead to some differences in the efficacy of semaglutide [8]. Knowing the positive correlation between frequency and severity of gastro-intestinal adverse events (GI-AEs) and weight reduction, sex-related differences in the occurrence of GI-AEs may also be associated with observed increased GLP-1 RA efficacy among women [20]. A phase 3a pool subgroup analysis demonstrated that 90.5% of women versus 83.4% of men had AEs, 9.5% of women versus 9.1% of men had serious AEs and 6.1% of women versus 4.6% of men had AEs leading to permanent treatment discontinuation [4–8]. This higher frequency of GI-AEs in women could be partially attributed to higher drug exposures, yet the findings of an exposure– response analysis of semaglutide demonstrated that GI-AEs were more frequent in women also across different levels of exposure and that they were not exclusively related to drug concentrations [9, 10].

Finding the optimal dose titration scheme helps to reduce AEs, and improve tolerability and adherence. A phase 2 dose-finding study for semaglutide in which 65% of the study population were men reported that slow dose escalation of semaglutide using 4-week dose escalation steps starting from an initial dose of 0.25 mg/week ameliorated AEs without compromising efficacy [21]. A trial that included only a male population, which had the aim to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single escalating doses of semaglutide, identified the maximum tolerated single dose (MTSD) to be 15 μg/kg body weight, which was worked out to be 1.2 mg in a male subject weighing 80 kg.

There were no serious AEs and no subjects were withdrawn due to AEs [22].

Based on differences in exposure-response analysis between men and women, established MTSD and our clinical experience, we propose that a higher initial dose of semaglutide of 0.5 mg/week should be considered for men, especially those with BMI > 35 kg/m^2. In the event of good tolerability, a rapid titration scheme in general may then be used in men. Since the response on weight reduction in men seems to be delayed in comparison to that in women, we also advise to delay the efficacy assessment in men to later than 3 months after treatment initiation. It would be of specific clinical interest to design randomized controlled trails to address these issues.

There is another largely issue related to male obesity that remains unaddressed. Obesity contributes significantly to male hypogonadism and infertility. The underlying mechanisms include obesity-related abnormalities in the hypothalamic-pituitary–gonadal axis and abnormal hormone levels due to increased release of adipose-derived hormones and adipokines, increased aromatization of testosterone in adipose tissue, sleep apnea, obesity-related psycho-social challenges, increased scrotal temperatures causing DNA damage in sperm and the trans-generation impact of paternal obesity in offspring phenotypes by reprogramming of spermatogonial stem cells [23]. The potential benefit of weight loss induced by GLP-1 RA on male sexual function and fertility remains significantly understudied, and the impact of GLP-1 RA on the gonadal axis and on obesity-related hypogonadism in men has been evaluated only in one study [24]. This study demonstrated that treatment with GLP-1 RA had a modest effect on testosterone levels and a significant potential to improve sexual symptoms irrespective of modest increase in total testosterone [24]. The authors hypothesized that mechanisms other than increased levels of testosterone, including psychosocial factors related to improved body image due to significant weight reduction, might play a role in clinically improved sexual symptoms [24].

It is of great importance to translate results from trials with GLP-1 RA into clinical practice [25]. In our opinion, the male population was understudied in the STEP Phase 3a clinical program. Since some sex-specific differences in efficacy and safety of semaglutide between men and women were identified in the subgroup analysis overviews of the program, it would appear that the male population in adults and adolescents needs to be separately addressed in future research in order to maximize the benefits to the patients. Men often benefit from weight management interventions in different ways from women.

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