Glucagon-Like Peptide 1 Receptor Agonists: Sex Differences

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Contributor: Stavroula Pegiou , Theocharis Koufakis , Elpiniki Rentzeperi , Maria Grammatiki , Kalliopi Kotsa

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are a relatively new class of anti-diabetic medications that have exhibited very promising results in the treatment of type 2 diabetes mellitus (T2DM). According to the 2021 American Diabetes Association guidelines, they constitute one of the preferred add-on agents when metformin monotherapy and lifestyle modifications have failed to achieve adequate glycemic control.

GLP-1 receptor agonists | sex/gender differences | diabetes | weight loss

1. Introduction

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are a relatively new class of anti-diabetic medications that have exhibited very promising results in the treatment of type 2 diabetes mellitus (T2DM) [1]. According to the 2021 American Diabetes Association guidelines, they constitute one of the preferred add-on agents when metformin monotherapy and lifestyle modifications have failed to achieve adequate glycemic control [2]. GLP-1 RAs might be useful for the treatment of people with T2DM and overweight/obesity, since they have been shown to be beneficial in achieving weight loss targets, an essential component of the therapeutic strategy of T2DM [3]. Moreover, liraglutide and semaglutide have been licensed for the management of overweight and obesity regardless of diabetes status at a dose higher than that used to treat hyperglycemia. They are also strongly recommended for the treatment of individuals with T2DM and established atherosclerotic disease or multiple cardiovascular disease (CVD) risk factors [4], due to their ability to effectively lower the risk of CVD, through various mechanisms, including antiatherogenic properties and optimal effects on blood pressure and lipid profile [5][6]. As reported by the results of a recent meta-analysis certain GLP-1 RAs, namely liraglutide and exenatide, are also considered safe and effective for the treatment of pediatric T2DM. In this study, it was mentioned that the administration of these drugs in children with confirmed insulin resistance resulted in reduction in body weight and HbA1c values. Cardiometabolic parameters did not show any significant improvement, with the exception of a slight decrease in systolic blood pressure. The main adverse effect reported after administration of the aforementioned GLP-1 RAs in the pediatric population was nausea (risk ratio 2.11) [7]. GLP-1 RAs have also been used in the treatment of children with prediabetes and/or obesity. According to another systematic review and meta-analysis, GLP-1 RAs were more effective in lowering the glycated hemoglobin (HbA1c) values in children with diabetes and prediabetes compared with children with obesity (−0.72% in children with (pre-)diabetes versus −0.08% in children with obesity). The exact opposite was demonstrated regarding the effectiveness in weight loss (−2.74 kg in children with obesity versus −0.97 kg in children with (pre-)diabetes) [8]. In accordance with the above, it appears that GLP-1

RAs act via influencing several key pathophysiologic aspects of T2DM, such as increased insulin resistance and adiposity [6]. Interestingly, both entities seem to be strongly influenced by sex hormones [9][10]. Besides, T2DM is characterized to a great extent by sexual dimorphism, which affects the presentation, diagnosis, and progression of the disease, as well as influences its potential complications. For instance, it has been shown that men with diabetes are diagnosed at an earlier age and at a lower body mass index (BMI) compared to women. On the other hand, females with diabetes present with greater levels of obesity than men with diabetes, even though males in the general population account for the majority of individuals with overweight/obesity [11]. However, differences in adipose tissue distribution should also be taken into consideration. More specifically, 70% of women with T2D present with abdominal obesity, whereas the corresponding percentage for men with T2D is approximately 40% [12]. Hence, a very strong association is indicated between T2DM and obesity in women, especially regarding the abdominal type of obesity. Similar to the above, the expected male predominance regarding CVD risk is inverted in people with diabetes, with females exhibiting higher CVD risk, possibly due to a hyperglycemia-induced loss of estrogen's protective effect [11]. Women with T2DM present with a three- to sixfold increase in the risk of CVD compared to women without diabetes. In comparison, as far as men with diabetes are concerned, a two- to fourfold increase has been noted. The proposed risk factors for CVD may also differ between sexes. It has been recognized that increased total cholesterol and LDL levels act as significant risk factors for CVD in males, whereas in females hypertriglyceridemia and low HDL levels may constitute stronger risk factors [13]. Additional differences between sexes exist with regard to T2DM laboratory findings. It has been shown that fasting plasma glucose is more sensitive in diagnosing T2DM in males, while females exhibit a greater impairment in glucose tolerance [14]. This specific dissimilarity between sexes is extremely important since it may impact the diagnostic process of the disease. Furthermore, the prognosis of T2DM is also affected by sex. Cumulative evidence suggests that females with T2DM exhibit inferior glycemic control and are less likely to achieve their HbA1c targets [15]. They also face a higher all-cause mortality and a higher CVD-related morbidity and mortality [16].

The pathophysiology of these sex-specific differences is to a great extent hormonally regulated, with estrogen playing a key role in the disease process in females [13]. Estrogen seems to exert a protective effect on glucose metabolism in pre-menopausal women, provided that its concentration ranges within a physiological window [17]. Consequently, the post-menopausal lack of estrogen contributes to the pathogenesis of insulin resistance and T2DM. Interestingly, a hyperestrogenic environment may also lead to insulin resistance [18]. Gestational diabetes for instance serves as a great example of insulin resistance induced by the hormonal changes of pregnancy, such as elevated estrogen levels, as well as other placenta-derived hormones. In a normal pregnancy, the pancreatic β-cells undergo hypertrophy and hyperplasia. However, in an individual with pre-existing β-cell dysfunction this process of adaptation is not possible and therefore a hyperglycemic state occurs [19]. Insulin resistance associated with gestational diabetes is either transient and disappears after delivery, when hormonal levels are back to their pre-gestational state or remains impaired and leads to increased risk of T2DM in the future [20]. Apart from estrogen, testosterone levels also affect the two genders differently with regard to glucose metabolism and incidence of dysglycemia. More specifically, it has been argued that testosterone deficiency may be responsible for insulin resistance in males, whereas in females the latter can occur as a result of a hyperandrogenic state [14]. Thus, taking into consideration that T2DM is a highly sexual-dimorphic entity and that GLP-1 RAs exhibit their

actions via modulating processes that are characterized by hormonal regulation, the question of whether biological sex could differentiate the response to GLP-1RAs treatment is raised. Due to the relatively recent authorization for clinical use for the treatment of T2DM, the sex-specific properties of these agents have not been adequately investigated [21][22].

2. GLP-1 RAs: An Overview of the Class

GLP-1 is a peptide hormone that is mostly secreted by the endocrine cells of the small intestine in response to nutrient load. Its main functions are to stimulate insulin and inhibit glucagon secretion. It also induces satiety by delaying the rate of gastric emptying and decreasing gastrointestinal (GI) motility. In addition, it has been shown that GLP-1 may play a role in the modification of gastric volume in expectation of or in response to a meal [23]. The currently available GLP-1 RAs, which act by mimicking the actions of endogenous GLP-1, are exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide, and semaglutide. With the exception of oral semaglutide, all of the above agents are administered by subcutaneous injection. Due to their glucose-dependent mechanism of action, meaning that their effects are elicited only when glucose levels are elevated, GLP-1 RA therapy involves a low risk of hypoglycemia [24]. Nevertheless, possible side effects do exist, and are mainly manifested throughout the GI system consisting of, but not restricted to, nausea, vomiting and diarrhea [25]. **Table 1** summarizes the characteristics of the drugs mentioned above.

Table 1. Characteristics of GLP-1 RAs.

	Exenatide	Liraglutide	Albiglutide	Lixisenatide	Dulaglutide	Semaglutide
Molecular weight (Dalton)	4187 [26]	3751 [27]	3283.6 [28]	4858 [29]	59,669 [30]	4114 [31]
Molecular formation	$C_{184}H_{282}N_{50}O_{60}S$ [26]	$C_{172}H_{265}N_{43}O_{51}$ [27]	$C_{148}H_{224}N_{40}O_{45}$ [28]	$C_{215}H_{347}N_{61}O_{65}S$ [29]	$C_{2646}H_{4044}N_{704}O_{836}S_{18}$ [32]	$C_{187}H_{291}N_{45}O_{59}$ [31]
Structure	Natural peptide (exendin-4) from the saliva of the lizard Heloderma suspectum (53% homology) [33]	Slightly modified GLP-1 (97% homology) with free fatty acid side chain attached [33]	Two modified GLP-1 molecules amino-terminally attached to the linear structure of albumin [33]	Exenatide plus poly-lysine tail [33]	Two modified GLP-1 molecules attached to an immunoglobulin (Fc) fragment [33]	Slightly modified GLP-1 (94% homology) with free fatty acid side chain attached [33]
Time to peak (h/days)	2.1–2.2 h [34]	11.0–13.75 h [35]	3–5 days [36]	≈2 h [37]	48 h [38]	24 h (subcutaneous injection) [39]
Elimination half-life (t 1/2)	3.3–4 h [34]	12.6–14.3 h [35]	5.7–6.8 days [36]	2.6 h [37]	4.7–5.5 days (0.75 mg); 4.7 days (1.5 mg) [40]	7.6 days [39]

	Exenatide	Liraglutide	Albiglutide	Lixisenatide	Dulaglutide	Semaglutide
Drug-drug interactions	Drug-drug interactions with digoxin, lovastatin, lisinopril, and acetaminophen [41]	Very low potential for pharmacokinetic drug–drug interactions related to cytochrome P450. No clinically relevant interactions between steady-state liraglutide and insulin detemir, atorvastatin, griseofulvin, paracetamol, digoxin, lisinopril or oral contraceptives [42]	Coadministration with chloroquine, hydroxychloroquine, lanreotide, octreotide, pasireotide, thioctic acid is not recommended [43]	Delays gastric emptying and can reduce the rate of absorption of oral medications such as acetaminophen, ethinyl estradiol, and warfarin. Does not affect the activity of cytochrome P450 isoenzymes [44]	Delays gastric emptying and can reduce the rate of absorption of oral medications. Concomitant use with an insulin secretagogue (e.g., sulfonylurea) or with insulin may increase the risk of hypoglycemia [38]	Minor delay of gastric emptying. No clinically relevant effect on the exposure of metformin, warfarin, atorvastatin or digoxin [45]
Adverse effects	Nausea, vomiting, diarrhea, dyspepsia, dizziness, headache [41]	Nausea, vomiting, diarrhea, dyspepsia, constipation, injection site reactions, low incidence of hypoglycemia [42]	Nausea, vomiting, diarrhea, constipation, gastroesophageal reflux disease, abdominal pain [46]	Nausea, vomiting, diarrhea. Concomitant use with an additional medication known to cause hypoglycemia can increase the risk of the latter [44]	Nausea, vomiting, diarrhea, abdominal pain, decreased appetite, hypoglycemia [47]	Nausea, vomiting and diarrhea, increased risk of cholelithiasis [48]

w years. However, achieving optimal glycemic control remains the primary goal of the treatment of T2DM, as HbA1c levels < 7% (<53 mmol/mol) are associated with a lower risk of long-term disease complications [49].

According to a large-scale retrospective pool analysis of patients receiving exenatide twice daily, the reduction in HbA1c appeared to be irrespective of sex, but highly dependent on baseline HbA1c values [21]. Similar results have been demonstrated in another pooled analysis of clinical trials that examined the use of dulaglutide in people with diabetes, in which sex did not influence the dulaglutide-mediated reduction in HbA1c level (for reference, the observed reduction in HbA1c was −1.26% in men vs. −1.33% in women) [50]. This is in agreement with a post hoc analysis of 855 patients undergoing dulaglutide treatment, in which the reduction in HbA1c was once again shown to be unaffected by sex [51].

On the contrary, several studies demonstrate a sex-specific response to GLP-1 RA with regard to HbA1c levels. A very interesting example is a study conducted in newly diagnosed T2DM individuals who were overweight or obese, without prescription of weight loss medication in the last three months and without concomitant use of oral glucose lowering agents. The results showed that women exhibited a greater decrease in HbA1c levels compared to men after the administration of combination therapy consisting of exenatide plus metformin (HbA1c levels after treatment reduced from 8.8% (73 mmol/mol) to 6.8% (51mmol/mol) in females and from 8.9% (74 mmol/mol) to 7.5% (58 mmol/mol) in males, respectively, $p < 0.05$) [6]. Additional benefits of combined treatment, with respect to adiponectin levels (which serves as an index of insulin sensitivity) [52], β-cell function and inflammation were also more pronounced in women, further supporting the concept of sexual dimorphism in response to the exenatide-metformin regimen [6]. Furthermore, a retrospective study focusing on the long-term effectiveness of exenatide indicated male sex as a predictor of treatment failure (defined as “insufficient improvement or deterioration of glycemic balance”, which corresponds to “HbA1c values > 7.5% (>58 mmol/mol) or a decrease less than 1% after one year of treatment”) with a calculated odds ratio (OR) of 2.55 [53]. Similar conclusions were drawn when

examining the effects of metformin and liraglutide combination therapy. In a subgroup analysis comparing sexes, a significantly stronger reduction in HbA1c levels was noted in females compared to males (−1.5 vs. −0.75), indicating that female gender is a predictor of a better glycemic response (p = 0.028). However, it may be important to note that the population of this study was reported by the authors to be lacking genetic diversity, which could potentially affect the generalizability of its conclusions [5]. In another analysis investigating the efficacy of liraglutide in reducing Hb1Ac, females were more likely to achieve good glycemic control at follow-up in comparison to males (OR 1.75). Specifically, when stratified by age, female superiority was identified in the 18–64 age group, while in the over 65 age group, male predominance was observed [54]. It is plausible that these differences could be attributed to age-dependent hormonal alterations, manifested primarily as lower estrogen levels in women after menopause [55].

Other studies, however, are suggestive of a better response of men to GLP-1 RA treatment. A cohort study used exenatide twice daily as an additional agent in patients who experienced failure in metformin treatment. After 12 months of treatment, a higher percentage of male subjects achieved HbA1c target (≤7% or 53 mmol/mL) compared to females (38% vs. 27%, p = 0.03). Another interesting finding of this study was that the predictors of the achievement of the annual glycemic targets differed between the sexes. For males, lower baseline HbA1c levels were associated with increased likelihood of accomplishing glycemic control, whereas for females, history of previous management exclusively with metformin monotherapy was linked with lower probability of treatment failure (OR 0.321) [22].

3.2. Weight Loss

As mentioned above, weight loss is one of the main collateral benefits of GLP-1 RA treatment [23]. Cumulative evidence suggests that weight reduction due to GLP-1 RAs is more pronounced in females. This disproportionate response of women was evident in a retrospective study in which women exhibited on average greater weight loss compared to men (−7.0 kg vs. −3.3 kg, p < 0.06) [56]. Similar results were presented in another cohort study in which after a 12-month period of exenatide treatment, 33% of women achieved weight loss targets compared to 17% of men [22]. An additional study showed that the same pattern applied to BMI values, with females exhibiting greater BMI reduction at the end of the treatment period (BMI reduction: 4.8 kg/m^2 in females vs. 2.6 kg/m^2 in males, p < 0.05) [6]. Studies that used different representatives of the class, such as dulaglutide and liraglutide, have generated similar findings [50][57]. Nevertheless, the different GLP-1 RAs do not possess identical degrees of efficacy as far as weight reduction is concerned. In more detail, in a comparative study of dulaglutide versus liraglutide, the former seemed to provoke a more prominent weight loss effect. Still, in all groups examined, females consistently benefited from greater weight loss when compared with males [−1.32 kg in females (p = 0.001) vs. + 0.09 kg in males for dulaglutide (p < 0.001) and −0.51kg (p = 0.413) vs.−0.03 kg (p= 0.014) for liraglutide, respectively)] [57].

The mechanism behind the better female response to weight reduction remains unclear, but it could potentially be associated with increased drug exposure observed in women, possibly due to their lower average body weight [57]. Interestingly enough, another study with liraglutide produced opposing results, as it concluded that in this case, in

addition to female sex, a higher baseline BMI was also associated with greater weight loss. It should be noted that in this particular case, the female participants were slightly heavier than the males at the beginning of the study [58]. To these conflicting results, an explanation could be potentially provided by examining the findings of a pharmacokinetic analysis on liraglutide. This analysis showed that liraglutide exposure was 32% higher in women than in men of comparable weight, thus identifying the female sex as an independent predictor of weight loss achievement [59].

3.3. Cardiovascular Risk and Major Adverse Cardiovascular Events (MACE)

Aside from their previously mentioned benefits, GLP-1 RAs exert several other favorable effects such as the decrease of waist circumference (WC) [60] and blood pressure (BP) [61], as well as the modification of various elements of the lipid profile, thus resulting in reduced CVD risk [62]. This is of utmost importance, since it is well established that patients with T2DM are characterized by a high risk of CVD, which is the main cause of morbidity and mortality in this population. In this concept, it is essential to examine whether the effects of GLP-1 RAs on certain variables that serve as recognized modifiable regulators of CVD risk exhibit sexual dimorphic patterns [63].

With respect to the above, a study of 179 patients receiving liraglutide treatment concluded that even though the reduction in HbA1C was more evident in women, WC and BP decreased significantly in both sexes to a similar extent [5]. The absence of sex-related differences in the control of BP levels was also supported by a pool analysis of exenatide twice daily [21]. However, according to this analysis, low-density lipoprotein cholesterol (LDL-C) did not decrease in women, indicating the presence of a specific sex effect of exenatide on lipid profiles [21]. However, even though several studies have explored the link between GLP-1 RAs and parameters that influence CVD risk, only a small number of them have stratified their data by sex.

Approaching this matter from a different perspective, the sex specificity of GLP-1 RAs on CVD risk could also be examined by measuring the incidence rates of MACE. Although the definition of MACE might vary between different trials, it generally encompasses the major complications of CVD that correspond to nonfatal myocardial infarction, nonfatal stroke, and cardiac death, among others [64].

Only a few studies examined the potential sex-specific protective effect of GLP-1 RAs on MACE, occurring as a diabetic complication [65]. This is of great interest because the population of patients with diabetes manifests a distinct epidemiological composition; as already mentioned above, in contrast to the male predominance observed in the general population as far as cardiovascular events are concerned, in diabetic individuals this risk appears to be higher in females [66].

Studies that examined the efficacy of GLP-1 RA with respect to cardiovascular outcomes noted a remarkable reduction in MACE in both sexes [67][68], although without apparent sex-related divergence (hazard ratio of MACE occurrence 0.88 in both sexes) [68]. This was further supported by a meta-analysis that concluded that the effect of GLP-1 RAs on MACE was similar between men and women (p = 0.375) [69]. A conflicting conclusion was drawn by another study which demonstrated that the use of GLP-1 RAs was linked to a lower frequency of MACE in women

than in men (incidence rate: 6.6 per 1000 person-year [PY] for females versus 11.9 per 1000 PY for males, $p < 0.001$). Furthermore, when comparing sulfonylureas with GLP-1 RAs, the risk of MACE was found to be lower in those treated with the latter. An important aspect of this comparative study is that the reduction in risk associated with GLP-1 RA treatment was even higher in women than in men (adjusted hazard ratio in patients treated with GLP-1 RA vs. patients treated with sulfonylurea was 0.57 in females vs. 0.82 in males, $p = 0.001$), further suggesting a two-way drug-by-sex interaction [70].

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