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Effectiveness of GLP1-RAs in type 2 diabetes: a gender analysis

***Alessandro Cuttone, * Annalisa Giandalia, Andrea Muscarà, Letterio Giorgianni, Carmela Morace, Giovanni Squadrito, Domenico Cucinotta, Giuseppina Russo**

Department of Clinical and Experimental Medicine, University of Messina, Italy

*These two Authors contributed to the manuscript equally.

Abstract

In type 2 diabetes (T2D), several differences have been described between men and women, concerning risk factors, clinical manifestations and chronic complications. The impact of gender on the efficacy and safety of hypoglycaemic drugs is still to be clarified. Some data suggest that GLP1-RAs may have greater efficacy on body weight in women, but comparable efficacy on glycaemic control and cardiovascular risk (CVD) in both sexes. The aim of our study was to evaluate in real-life clinical practice the possible influence of gender on the effectiveness and safety of GLP1-RAs long-acting therapy in T2D outpatients. In this single-centre observational study, we evaluated laboratory parameters, chronic complications, hypoglycaemic episodes, and any adverse events of subjects with T2D who started treatment with GLP1-RAs long-acting between 1 June 2018 and 31 May 2019, in add on to metformin or other hypoglycaemic drugs, and who practiced this therapy for at least two years. In the present analysis, 391 subjects with T2D were included (men 59.3%, women 40.7%), with a mean age of 64.1 years and mean duration of diabetes of 18.4 years. At baseline, patients were on average obese (BMI 32.8 kg/m^2) with an inadequate glycaemic control (HbA1c 7.8%). Women had higher BMI values than men; glycaemic control was similar in both genders. After two years of follow-up, therapy with GLP1-RAs long-acting determined a significant reduction of BMI and blood pressure values, HbA1c, fasting glucose and GPT levels and an improvement in lipid profile. The reduction observed in BMI values was significantly greater in T2D women than in men. At stepwise regression analysis, female gender was among the independent predictors of the effectiveness of GLP1-RAs in terms of BMI reduction, together with fasting blood glucose, but not in terms of reduction of HbA1c levels, which was significantly associated with baseline blood glucose levels and metformin use, irrespective of gender. Overall, the treatment with GLP1-RAs was well tolerated, and only mild gastro-intestinal adverse events were observed (n=22; 5.6%, 14 men and 12 women P>0.05), in both genders. In conclusion, in real-life clinical practice, the therapy with GLP1-RAs long-acting is safe and effective in both men and women, and it seems to be associated with a more beneficial effect on body weight in women than in men.

Key-Words:type 2 diabetes, GLP1-RAs, gender differences
IntroducingMember; Giuseppina Russo

Corresponding Author: Annalisa Giandalia agiandalia@yahoo.it

Introduction

According to recent estimates, diabetes mellitus affects around 6% of the Italian population, approximately 4 million individuals (1). Although metformin remains the first-line therapy for treatment of type 2 diabetes (T2D), innovative pharmacological classes entering the market in recent years, namely GLP-1 receptor agonists (GLP1-RAs) and SGLT2 inhibitors (SGLT2i), not only improve glycemic control, but have proven benefits on body weight as well as on the risk of cardiovascular (CVD) and renal complications, such that current national and international guidelines (2) place these drugs as the first treatment options in patients with high cardiovascular risk, a previous cardiovascular event or renal failure.Although biological differences

are usually referred toa s sex, while social and non-biological ones as gender, we would overall address these differences as “gender-differences”, unless specified, because especially in the field of diabetes, the interaction between sex- and gender variables is so tight that it is somehow difficult to discriminate them. T2D affects both sexes, and in recent years researchers and clinicians have explored with increasing interest the potential gender differences in diabetes phenotype, risk factors and chronic complications. The available data on gender differences in diabetes, from international and Italian studies, suggest that women with T2D have a higher burden of CVD risk factors than men, and a worse clinical control of hyperglycaemia and other major risk factors.Overall, women with T2D show greater difficulty in reaching their target values for glycated haemoglobin (HbA1c), blood pressure and low-density lipoprotein (LDL)-cholesterol, as compared to men (3).

Also, women are more often obese and less physically active, than men.T2D cardiovascular complications seem to affect the two genders differently: indeed, women with T2D have higher risk of developing coronary artery disease than men, mainly of the microvascular type, which anticipates the age of onset of myocardial infarction in diabetic women by about 20-30 years, as compared to non-diabetic ones. Women with T2D also have a higher risk of cerebrovascular pathology (risk greater than 27%) than their male counterparts and a greater susceptibility to developing heart failure, predominantly with preserved ejection fraction, due to concentric remodelling and a greater risk of left ventricular hypertrophy. Men with T2D, on the other hand, appear to be more predisposed to peripheral vascular disease, with a higher risk of lower limb amputation (3).

Genetic, hormonal (loss of oestrogen protection and lower testosterone production), anatomical (the different arrangement of visceral fat probably also caused by the composition of fat in the female body), but also socio-cultural and psychological factors underlie these sex-differences.Furthermore, this scenario is made even more heterogeneous by the gender differences observed in the field of pharmacology: the response to medications may differ in men and women, due to the influence of genetic, hormonal, and physiological factors. Among these, testosterone and oestrogen and progestogen hormones levels influence the absorption of several drugs, body weight and body composition impact the accumulation of lipophilic drugs. The two genders also differ in terms of gastric motility and acidity, with reduced gastric absorption of drugs in women, different hepatic expression of cytochromes P450 and different rates of renal and intestinal excretion of drugs. Also, environmental factors play a crucial role: women are the largest consumers of drugs, and they often take therapies for long periods of time (for example, hormonal contraception in childbearing age or hormone replacement therapy in menopause), running a greater risk of drug interactions than men. Sex and gender also influence medication adherence and persistence. Gender differences seem to affect the pharmacological response also to diabetes medications. Among these, in a study on 9108 patients with T2D from the DPV-Wiss-database, women on metformin developed higher body weight reduction than men, while men on metformin showed higher HbA1c (4).With regard to safety data, it has been shown that the negative effect of

glitazones on bone and fracture risk is more pronounced in women, mainly after the menopause (5,6). Also, women have higher risk of severe hypoglycaemia using insulin; similarly, the more common adverse events observed with SGLT-2i treatment, i.e., genital, and lower urinary tract infections, predominantly affect the female sex (5).

Aim of the study

The aim of this study was to assess, in *real-life* clinical practice, whether gender influence the effectiveness and safety of GLP1-RAs long-acting therapy in a group of subjects with type 2 diabetes who have practiced the therapy for at least two years.

Patients and methods

In this single-centre, observational retrospective study, clinical data of all adult T2D subjects referred to the outpatient clinic of Medicine of Metabolic Diseases at the University Hospital of Messina who were prescribed GLP1-RAs long acting as an add-on to the hypoglycaemic treatment, between 1 June 2018 and 31 May 2019 were analyzed; only patients who practiced the therapy for at least two years were included in the present analysis. The other inclusion criteria applied to all patients were: diagnosis of T2D according to ADA criteria, age>18 years, no previous treatment with a GLP1-RA, absence of acute or chronic diseases other than T2D and its complications.

In the examined period, 409 subjects underwent an outpatient visit to our Clinic and received a prescription for GLP1-RA; among these, 391 met the mentioned inclusion criteria and were therefore included in the study. Therefore, n=18 subjects were excluded for a shorted follow-up evaluation, and their baseline clinical characteristics (age, sex, diabetes duration, mean BMI and HbA1c levels at baseline) did not differ from those of T2D included subjects.

The following clinical and laboratory parameters available in computerized medical records were analysed, both at baseline (V1) and at follow-up (V2): weight (kg), body mass index (BMI, kg/m^2), waist circumference (cm), systolic and diastolic blood pressure (mmHg), levels of glycosylated haemoglobin (HbA1c, %), fasting blood glucose (mg/dl), total, HDL- and LDL- cholesterol, triglycerides (mg/dl), creatinine (mg/dl), estimated glomerular filtration rate (eGFR, MDRD formula), and albuminuria (mg/l).

Data on drug treatments and chronic diabetes complications (cardiovascular disease, retinopathy, nephropathy) were analysed.All T2D patients followed in our outpatient clinic undergo periodic screening for diabetes complications, as recommended by the guidelines, including a cardiological examination with ECG and an ophthalmological examination with eye fundus examination. The Diabetic Kidney Disease is diagnosed in the presence of urinary albumin excretion >30 mg/L and/or eGFR < 60 ml/min/1.73 m2 confirmed by two determinations in three months, as recommended by KDIGO clinical practice guideline.Moreover, at the V2, any adverse event due to GLP1-RAs was also recorded, including any episode of severe hypoglycaemia.

Results

A total of 391 T2D subjects were included in the present analysis (women n=159, 40.7%). As shown in table 1, at baseline the study subjects had a mean age of 64 years (64.13 ± 9.83 years) and long-standing T2D (10.84 ± 8 years); they were obese (mean BMI 32.81 ± 6.08 Kg/m^2, waist circumference 114.33±12.61 cm). Women showed significantly higher BMI values than men (BMI in women 34.31 ± 6.60 Kg/m^2*vs* men 31.78 ± 5.48 Kg/m^2, p<0.001).

Glycaemic control was inadequate (HbA1c 7.84 ± 1.02%), suggesting the need for intensification of the therapy; also, lipid profile was not on target, with higher levels of LDL-cholesterol and total cholesterol in women, as compared to men (LDL-cholesterol 95.82 ± 34.84 mg/dL in women vs 87.48 ± 30.94 mg/dL in men; p=0.016; total cholesterol ± 39.18 mg/dL in women 174.07 vs 163.97 ± 35.15 mg/dL in men). The use of statins (69.05%) and antihypertensive drugs (72.4%) was similar in the two genders (Table 1).

Tab. 1 Baseline characteristics of subjects with T2D participating to the study

	All	Men	Women	P
n (%)	391	232 (59.3)	159 (40.7)	-
Age (years)	64.13±9.83	64.73±9.61	63.26±10.11	0.151
Years of diabetes (n)	10.84±8.00	11.15±7.93	10.40±8.11	0.362
Weight (Kg)	85.87±15.39	88.67±14.60	81.71±15.63	0.058
BMI (Kg/m^2)	32.81±6.08	31.78±5.48	34.31±6.60	**<0.001**
Waist circumference (cm)	114.33±12.61	115.02±12.41	114.13±12.90	0.488
SBP (mmHg)	137.82±12.85	139.29±12.87	136.27±13.82	0.214
DPB (mmHg)	83.46±9.99	84.03±8.51	82.70±7.40	0.332
Fasting blood glucose (mg/dl)	158.20±39.06	160.73±39.78	154.52±37.81	0.119
HbA1c (%)	7.84±1.02	7.83±0.91	7.85±1.16	0.820
Subjects with HbA1c ≤7% n (%)	65 (16.6)	39 (16.8)	26 (16.35)	0.795
Subjects with HbA1c ≤6.5% n (%)	33 (8.44)	18 (7.76)	15 (9.43)	0.524
eGFR-MDRD (ml/min/1.73 m^2)	73.15±25.24	72.37±26.61	74.33±23.06	0.449
Total cholesterol (mg/dl)	168.08±37.12	163.97±35.14	174.07±39.18	**0.009**
HDL-cholesterol (mg/dl)	44.59±10.69	41.60±9.38	48.95±11.00	**<0.001**
LDL-cholesterol (mg/dl)	90.87±32.80	87.48±30.94	95.82±34.84	**0.016**
Triglycerides (mg/dl)	158.50±70.72	162.93±77.19	152.03±59.68	0.117
AST (U/L)	27.69±37.34	27.69±37.34	27.36±15.81	0.890
ALT (U/L)	31.22±23.11	31.22±23.11	33.40±20.99	0.751
GGT (U/L)	42.17±25.46	42.17±25.46	44.42±52.66	0.680
Subjects on statin therapy n (%)	270 (69.05)	155 (66.8)	115 (72.3)	0.2464
Subjects on antihypertensive drugsn (%)	269 (68.8)	158 (68.1)	111 (69.8)	0.7203

Data are n, %, mean ± standard deviation. SBP: systolicblood pressure; DPB: diastolic blood pressure

As shown in table 2, at baseline, cardiovascular disease and diabetes kidney disease (DKD) were more frequent in men. The prevalence of diabetic retinopathy was similar in the two sexes

Tab. 2 Chronic complications at baseline of subjects with T2D participating to the study

	All	Men	Women	P

n (%)	391	232 (59.3)	159 (40.7)	-
eGFR< 60 ml/min/1.73 m^2 n (%)	143 (34.6)	97 (39.9)	46 (27.0)	**0.007**
Micro/macroalbuminuria n (%)	73 (17.7)	52 (21.4)	21 (12.3)	**0.02**
Albuminuria (mg/L)	39.20 ± 111.27	57.65±145.21	16.64±29.65	**0.001**
Diabetic Kidney Disease* n (%)	174 (42.1)	118 (48.6)	56 (32.9)	**0.001**
Diabetic retinopathy n (%)	55 (13.4)	33 (13.6)	22 (12.9)	0.850
Coronary heart disease n (%)	66 (16.0)	55 (22.6)	11 (6.5)	**0.001**
Supra-aortic atherosclerosis n (%)	146 (35.3)	95 (39.1)	51 (30.0)	0.060
Peripheral atherosclerosis n (%)	68 (16.5)	55 (22.6)	13 (7.6)	**<0.001**

Data are n, %, mean ± standard deviation. Micro/macroalbuminuria: urinary albumin >30 mg/L. eGFR-MDRD, estimated glomerular filtrate (MDRD formula).*Diabetic Kidney Disease: urinary albumin excretion >30 mg/L and/or eGFR< 60 ml/min/1.73 m^2 confirmed by two determinations in three months (KDIGO clinical practice guideline. Nephrol Dial Transplant. 2014 Mar;29(3):490-6)

The follow-up period was approximately of 2 years (29.89 ± 3.44 months). The changes of the main study parameters at V2 are shown in table 3.

Tab. 3 Variation during the observation period of the main parameters under investigation, in the two genders

	All	Men	Women	P
Weight (Kg)	-3.55±6.22	-3.25±6.58	-3.99±5.63	0.268
BMI (Kg/m^2)	-1.35±2.40	-1.13±1.95	-1.67±2.91	**0.044**
Waist circumference (cm)	-6.45±8.44	-6.17±7.96	-6.85±9.04	0.647
SBP (mmHg)	-10.50±14.73	-10.37±16.24	-10.47±12.48	0.940
DBP (mmHg)	-6.88±9.18	-6.84±9.89	-6.92±8.16	0.807
Fasting blood glucose (mg/dl)	-10.97±32.82	-11.03±33.45	-10.87±31.98	0.962
HbA1c (%)	-0.78±1.09	-0.80±1.02	-0.76±1.19	0.717
Subjects con HbA1c ≤7% n (%)	+143 (36.57%)	+ 89 (38.36%)	+54 (34%)	0.507
Subjects con HbA1c ≤6.5% n (%)	+88 (22.5%)	+ 55 (23.7%)	+ 33 (20.75%)	0.490
Creatinine (mg/dl)	0.00±0.16	0.0036±0.17	-0.005±0.13	0.597
eGFR-MDRD (ml/min/1.73 m^2)	+3.76±20.52	+4.13±20.37	+3.19±20.80	0.659
Albuminuria (mg/L)	-2.39±76.52	-5.53±94.82	+2.20±35.63	0.259
Total cholesterol (mg/dl)	-13.68±37.11	-14.89±34.76	-11.91±35.64	0.412
HDL-cholesterol (mg/dl)	+0.87±9.26	+ 0.69±8.15	1.14±10.69	0.655
LDL-cholesterol (mg/dl)	-11.40±30.22	-11.56±29.69	-11.17±31.06	0.900
Triglycerides (mg/dl)	-11.15±67.98	-10.01±73.78	-12.82±58.68	0.677
AST (U/L)	+2.08±36.12	+6.81 ± 16.94	-2.65±14.35	0.059
ALT (U/L)	-5.35±19.46	-3.36 ± 19.85	-7.36±19.03	0.684
GGT (U/L)	-8.88±32.72	-7.9 ± 59.58	-10.82±41.69	0.633
Subjects on statin therapy n (%)	+13 (3.30%)	+8 (3.45%)	+5 (3.15%)	0.769
Subjects on antihypertensive drugs n (%)	+4 (1.02%)	+3 (1.29%)	+1 (0.63%)	0.778

Data are n, %, mean ± standard deviation.SBP: systolic blood pressure; DPB: diastolic blood pressure

At V2, therapy with GLP1-RAs long-acting resulted in an improvement in glycaemic control, with a mean reduction in HbA1c values -0.78±1.09% (-0.80±1.02% in men vs -0.76±1.19% in women, p=0.717) and by a 37% increase in the number of subjects with HbA1c levels < 7%. Using an even more ambitious HbA1c

target value (≤6.5%), this result was achieved by 22.5% (+88 individuals) of the patients in the study, without significant difference between men and women.

A significant reduction of BMI mean values was also observed (-1.35 ± 2.49 Kg/m^2) at V2, which was more pronounced in women than in men (women -1.67 ± 2.91 Kg/m^2*vs* men -1.13 ± 1.95 Kg/m^2, p=0.044). Furthermore, a mean reduction in waist circumference of -6.45±8.44 cm was observed, with no difference between men and women (-6.17±7.96 cm in men *vs* -6.85±9.04 cm in women, p=0.647).

At follow-up, an improvement in the lipid profile and renal function, was observed in both sexes. Also, systolic (-10.50±14.73 mmHg) and diastolic (-6.88±9.18 mmHg) blood pressure values decreased in men and women participating to the study. The use of statin (+3.3%) and antihypertensive-drugs (+1.02%) increased marginally with no differences between the two genders (table 3). Furthermore, during the observation period, a total of 3 cardiovascular (CV) events occurred, two among men and one among women.

At stepwise multiple regression analysis, female sex (B0.462, p=0.044), baseline fasting plasma glucose levels (B 0.008, p= 0.007) and the follow-up duration (B0.017, p=0.004) were the independent predictors of the effectiveness of GLP1-RAs on reducing BMI. Baseline fasting blood glucose (B 0.004, p=0.001) and cholesterol levels (B 0.003, p=0.009) were the predictors of effectiveness therapy in reducing HbA1c levels, whereas metformin therapy was a negative predictor (B-0.260, p=0.047).

From baseline to visit V2, some changes in the hypoglycemic therapy of the study subjects were observed: in detail, a reduction in the number of patients on metformin (-14, -3.6%) and on secretagogues (-20 patients, -5.1%) was observed. On the contrary, the number of patients on pioglitazone and on insulin remained almost unchanged.

During the observation period, the therapy with GLP1-RAs was well tolerated: only 6% of the patients reported mild adverse events, mostly gastrointestinal events such as nausea, vomiting, diarrhoea and constipation, without significant differences between men and women. These adverse events didn' t lead to discontinuation of the treatment. Moreover, no amylase and lipase levels and no episodes of severe hypoglycaemia were observed.

Discussion

In this study, we evaluated the effects of gender on the effectiveness and safety of GLP-1 RA long-acting therapy in real-life outpatient clinical practice, in a group of adult subjects with type 2 diabetes, observed retrospectively for two years.

In this cohort, GLP-1RA therapy resulted in benefits on glycaemic control, lipid profile and body weight in both genders, with greater weight loss in women. These data are in line with some recent observations suggesting a greater impact of this class of drugs on body weight in women (7,8).

Of note, it is known that baseline BMI values may influence body weight loss with GLP-1 RAs;

although significant differences in BMI at baseline were observed between men and women in our study population, the stepwise regression analysis confirmed that female gender, but not baseline BMI, was an independent predictor of weight loss.

Our data add to a growing body of literature exploring the impact of gender on the response to GLP1-RAs of T2D patients, up-to-date reporting discordant results. Thus, in a small population of 40 T2D patients, the treatment with high-dose liraglutide (1.8 mg/day) for a period of 5 years resulted in sustained benefits on weight and glycaemic control in both genders, but significantly more pronounced in the female gender, which emerged as a predictor of weight loss (9). At this regard, a pharmacokinetic analysis showed that liraglutide exposure was 32% higher in women than in men, being the female sex an independent predictor of weight loss (10).

In a study of more than 167,000 subjects with T2D (Marketscan-Database: 2011-2017) on metformin, the add-on of a GLP-1RA was associated with a lower risk of cardiovascular events compared to sulphonylureas, with greater advantage in women, than in men (11). In a study of 315 subjects with T2D in Italy, the therapy with exenatide was more effective on glucose control in men and on weight loss achievement in women (12). However, other Authors didn’t observe any gender difference in the clinical response to GLP1-RAs (13).

Cardiovascular and renal outcome studies (CVOTs) with GLP1-RAs didn’t show any gender differences in the reduction of cardiovascular and renal risk.

However, it should be acknowledged that any gender differences in metabolic and cardiovascular effectiveness of this class may require a long-term investigation in larger populations representative of T2D patients daily attending diabetes outpatient.

Another result of our study is that, in a real-world setting, treatment for at least two years with GLP1-RAs proved effective in both men and women, not only on glycaemic compensation, with a significant reduction in the average fasting blood glucose and HbA1c values and with almost 37% of patients whose HbA1c levels were within target, but also on other cardiovascular risk factors such as body weight, systolic and diastolic blood pressure values, lipid profile. Similarly, in a study of a population of 115 outpatients with T2D, treatment for twelve months with liraglutide was associated with an improvement in metabolic profile and in the VAI index, a sex-specific cardiometabolic risk marker, indirectly expressing visceral fat function (14).

Finally, regarding the safety of treatment with GLP-1RAs, only 6% of the study population reported adverse events, mostly gastrointestinal events; no patient discontinued therapy due to adverse events.

Some data in the literature suggest a higher incidence in women than men of gastrointestinal adverse events, such as vomiting, diarrhoea and/or constipation and nausea, which may affect adherence to therapy (6). Some Authors attribute this difference to higher exposures and higher drug plasma

concentrations. However, in our study subjects, no significant gender differences were found about these events. Notably, in our outpatient clinic we routinely provide patients with counselling to minimize the frequency and intensity of gastrointestinal side effects (appropriate dietary education, flexibility during dose escalation phase, and appropriate symptomatic treatment of complaints): this may have influenced the results.

Our study has some limitations: first, a separate analysis for the different long acting GLP-1 RAs was not performed, therefore we can't exclude that the differences observed between the two sexes also depend on the different molecules used. Furthermore, no data are available on the dosage of GLP-1 Ras, which may have an impact on weight reduction. However, as for our daily clinical practice, all subjects included in the study started GLP-1 RAs therapy at the lowest dose, in order to minimize the risk of gastrointestinal adverse events, and subsequently, reached the maximum tolerated dose, as recommend by current guidelines.

Conclusions

In conclusion, in this population of subjects with T2D, treatment with GLP1-RAs long acting for at least two years was effective in reducing body weight and improving glycaemic and lipid profile, both in men and women, but the benefit on BMI was most evident in women. The therapy was well tolerated in both sexes.

Gender differences in long-term metabolic and renal effects, pharmacokinetics and side effects of therapy with GLP1-RAs should be extensively studied in larger populations. Furthermore, the effect of other complex, cultural, socio-economic (such as family background, occupation, role of care giver, socio-economic status) and psychological (depression, anxiety, stress) variables that may influence medication adherence and persistence should be better explored.

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