# Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study

Mojca Jensterle[1] Boštjan Pirš[2], Katja Goričar[2], Vita Dolžan[2], Andrej Janež[1]

[1] Department of Endocrinology, Diabetes and Metabolic Disease, Division of Internal Medicine, University Medical Centre Ljubljana
[2]Institute of Biochemistry, Faculty of Medicine, University of Ljubljana

## OBJECTIVES

The weight lowering potential of GLP-1 receptor agonists (RAs) is inter-individually different and clinically unpredictable. The potential role of genetic variability of *GLP-1R* on body weight response to GLP-1 RAs has not yet been evaluated. We assessed the effect of common *GLP-1R* single nucleotide polymorphisms (SNPs) rs6923761 and rs10305420 on weight loss after treatment with GLP-1 RA liraglutide in obese women with PCOS.

## METHODS

57 obese women with PCOS (aged 30.7 ± 7.0, BMI 38.6 ± 5.3 kg/m$^2$) were assigned to liraglutide 1.2 mg QD sc for 12 weeks. Participants were stratified as strong responders and poor responders regarding weight loss. Strong responders were classified as subjects who lost 5 % or more of their initial body weight. They were genotyped for *GLP-1R* rs6923761 and rs10305420. Changes of measures of obesity, metabolic and hormonal parametrs were measured before and at the end of the treatment.

## RESULTS

At initiation of liraglutide administration, there were no significant differences in age, measures of obesity, metabolic or hormonal parameters between the strong and poor responders (all P-values>0.05).
After liraglutide treatment women lost on average 3.96 ± 3.24 kg (P<0.001). Twenty out of 57 subjects were strong responders and lost on average 7.38±1.74 kg, while poor responders lost 2.11±2.17 kg. BMI decreased for 2.71±0.75 kg/m$^2$ in strong responders and 0.75±0.79 kg/m$^2$ in poor responders. Waist circumference decreased for 5.38±3.68 cm in strong responders (P<0.001) and 2.19±3.97 cm in poor responders (P=0.003). In strong responders, there was also a statistically significant within-treatment reduction from baseline to last visit in visceral adiose tissue area as assessed with DXA, while fasting glucose and glucose after OGTT decreased significantly in both groups. No statistically significant differences were found in LH, FSH, total testosterone, free testosterone, SHBG and androstenedione neither over time nor when analyzing it separately by both arm. Carriers of at least one polymorphic rs10305420 allele had worse treatment response compared to carriers of two wild type alleles (OR=0.27, 95% CI=0.09-0.85, P=0.025). Carriers of at least one polymorphic rs6923761 allele tended to have better treatment response compared to carriers of two wild type alleles, but the difference was not statistically significant (OR=3.06, 95% CI=0.96-9.74, P=0.058).

**Table 1:**
Association of selected *GLP-1R* polymorphisms with response to liraglutide.

| Polymorphism | Genotype | Poor responders N (%) | Good responders N (%) | OR (95% CI) | P |
|---|---|---|---|---|---|
| rs10305420 | CC | 12 (48.0) | 13 (52.0) | | |
| | CT+TT | 24 (77.4) | 7 (22.6) | 0.27 (0.09-0.85) | 0.025 |
| rs6923761 | GG | 21 (77.8) | 6 (22.2) | | |
| | GA+AA | 16 (53.3) | 14 (46.7) | 3.06 (0.96-9.74) | 0.058 |

**Table 2:**
Association of *GLP-1R* haplotypes with response to liraglutide

| Haplotype | Non-responders (frequency) | Responders (frequency) | OR (95% CI) | P |
|---|---|---|---|---|
| CG | 0.49 | 0.42 | reference | |
| CA | 0.12 | 0.38 | 3.85 (1.24 - 11.96) | 0.020 |
| TG | 0.19 | 0.15 | 0.76 (0.14 - 4.26) | 0.757 |
| TA | 0.20 | 0.05 | 0.19 (0.02 - 1.93) | 0.160 |

## CONCLUSIONS

*GLP-1R* rs10305420 polymorphism explained some of the inter-individual differences in response to liraglutide regarding weight loss in obese PCOS women. Future studies need to determine whether such genetic variation may be clinically useful in prediction of the weight lowering potential of GLP-1 RAs in obese individuals.

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Mojca Jensterle
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