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# Impact of GHRL (RS696217) and LEPR (RS1137101) gene polymorphisms on hormonal and anthropometric outcomes after bariatric surgery

Andrii Prodan

*Department of Surgery, Postgraduate Faculty, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine*
*E-mail: prodan@tdmu.edu.ua*

**Objective.** The aim of the study was to evaluate the influence of GHRL (rs696217) and LEPR (rs1137101) gene polymorphisms on weight loss dynamics and endocrine marker changes following various bariatric procedures.

**Patients and Methods.** A total of 76 patients undergoing laparoscopic sleeve gastrectomy (LSG), gastric plication (LGCP), and gastric artery embolization (GAE) were genotyped for GHRL (rs696217) and LEPR (rs1137101). Body mass index (BMI), total weight loss (TWL), excess weight loss (EWL), and hormonal markers (ghrelin, leptin, adiponectin, resistin, HbA1c) were assessed preoperatively and at 3, 6, and 12 months postoperatively.

**Results.** Carriers of the T allele of GHRL (rs696217) experienced significantly greater reductions in BMI, TWL, and EWL, particularly following LSG and GAE ($p<0.05$). A notable reduction in total ghrelin levels was observed in T allele carriers (up to –46.75%, $p<0.001$) 6 months after surgery. Improvements in resistin ($p=0.0002$) and HbA1c ($p=0.014$) levels were also more pronounced in this group. LEPR (rs1137101) polymorphism showed limited impact on outcomes after LGCP, but it was associated with improved TWL and EWL in A allele carriers after LSG ($p=0.006$ and $p=0.016$, respectively).

**Conclusion.** The T allele of GHRL (rs696217) appears to be a promising predictive marker for greater metabolic and hormonal improvement following bariatric procedures targeting the ghrelin-producing stomach zones. LEPR (rs1137101) may also influence postoperative outcomes in a procedure-specific manner. These findings support the potential role of genetic screening in optimizing patient selection and predicting surgical success.

**Keywords:** GHRL, LEPR, gene polymorphism, bariatric surgery, sleeve gastrectomy, gastric plication, gastric embolization, ghrelin, leptin, obesity, endocrinology, personalized medicine

Obesity is a multifactorial disease influenced by genetic, environmental, and behavioral factors. Bariatric surgery is an effective treatment for severe obesity, leading to significant weight loss and improvement in metabolic comorbidities. However, individual responses to surgery vary, suggesting a role for genetic factors in determining outcomes.

Ghrelin, a hormone produced primarily in the stomach, stimulates appetite and plays a role in energy balance. The GHRL gene encodes preproghrelin and polymorphisms in this gene may affect ghrelin expression and function. Studies have shown that certain GHRL gene variants are associated with differences in weight loss after bariatric surgery indicating a potential genetic influence on surgical outcomes.

Leptin, another hormone involved in energy homeostasis, acts through the leptin receptor encoded by the LEPR gene. The LEPR rs1137101 (Q223R) polymorphism has been associated with obesity and may

**Corresponding author:** Andrii Prodan MD., PhD., Associate Professor, Surgery Department Postgraduate Faculty, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine; phone: +380677120199; e-mail: prodan@tdmu.edu.ua.

influence weight loss after bariatric surgery. Some studies suggest that individuals with certain LEPR genotypes experience different weight loss trajectories post-surgery.

Despite these findings, the impact of GHRL and LEPR polymorphisms on bariatric surgery outcomes remains unclear. This study aims to evaluate the influence of GHRL (rs696217) and LEPR (rs1137101) gene polymorphisms on weight loss and hormonal changes following various bariatric procedures.

## Material and Methods

**Study participants.** A total of 76 patients with obesity and features of metabolic syndrome (body mass index, BMI>35 kg/m$^2$) and 48 individuals with normal BMI (18–25 kg/m$^2$) were enrolled in the study. The control and obese groups were matched for age and gender ($p>0.05$).

Anthropometric parameters (weight, height, BMI, waist, and hip circumference) were assessed using standardized techniques. The mean body weight in the obese group was 121.87±7.23 kg with a mean BMI of 42.57±2.52 kg/m$^2$, significantly higher than the control group ($p<0.001$). The degree of obesity was classified according to IFSO guidelines. The majority of obese patients (over 50%) had class III obesity.

**Ethical details.** The ethical principles included in the Declaration of Human Rights adopted in Helsinki in 1975 and revised in 2008, were fully respected in this study. The enrolled subjects participated in this study voluntarily and with completed and signed written informed consent. Study protocol was approved by the Ethics Committee (Protocol No. 80) of I. Horbachevsky Ternopil National Medical University of 15.11.2024.

Surgical procedures. Laparoscopic sleeve gastrectomy (LSG): following disinfection and pneumoperitoneum (15–17 mmHg), the stomach was mobilized from the pylorus to the angle of his. A 34 Fr bougie was inserted and a tubular stomach was formed using endo GIA staplers (45/60 mm, 4.8 mm staples) resulting in a gastric reservoir of approximately 120–150 mL. A continuous seromuscular suture (V-Loc) was applied along the staple line.

Laparoscopic gastric plication (LGCP) after creating pneumoperitoneum (15 mmHg) the greater curvature of the stomach was mobilized. Gastric folding was performed using inverting sutures (V-Loc 2.0) starting 2–3 cm above the pylorus and extending to the fundus. One or more rows of sutures reduced the stomach volume to 100–150 mL without gastric resection.

Gastric artery embolization (GAE): CT angiography was used to exclude vascular anomalies. Via transfemoral access, embolization of the left gastric artery was performed with 300–500 μm microspheres (Embosphere, Merit Medical) using a high-flow microcatheter. Efficacy was confirmed by perfusion imaging. Patients received proton pump inhibitors post-procedure and underwent follow-up endoscopy at 1 and 3 months.

Laboratory data. Blood samples taken for the study were obtained after patients fasted the night before the study. Plasma level of glycated hemoglobin (HbA1c) was measured using commercial kits (Roche Diagnostics) using Hitachi automatic analyzer. Determination of serum levels of selected hormones was performed using Leptin ELISA (LDN Labor Diagnostics Nord GmbH & Co. KG, Germany), Human Ghrelin ELISA Kit (Thermo Fisher Scientific, USA), Human Adiponectin ELISA Kit (Thermo Fisher Scientific, USA), OxLDL (Thermo Fisher Scientific, USA), Resistin Human ELISA Kit (Thermo Fisher Scientific, USA) on Multiskan FC analyzer (Skanlt Software version 4.1 for Microplate Readers RE, vr. 4.1.0.43) at a wavelength of 620 nm.

Genotyping of the GHRL and LEPR genes polymorphism (rs696217, rs1137101). Venous blood samples for genomic study were collected in tubes with ethylenediaminetetraacetic acid (EDTA). The Thermo Scientific™ GeneJETTM Whole Blood Genomic DNA Purification Kit (Thermo Fisher Scientific, USA) was used for genomic DNA extraction according to the manufacturer`s instructions. Predesigned TaqMan™ SNP Genotyping Assays, Human (Thermo Fisher Scientific, USA) were used for next SNPs: Q223R (rs1137101), C214A (rs696217). TaqManTM Universal Master Mix II, no UNG were used for DNA amplification using real-time polymerase chain reaction (PCR) technique of allele discrimination based on the magnitude of relative fluorescence units (RFU).

**Statistics.** Statistical comparison of surgical outcomes (BMI, TWL, EWL, hormone levels) among LSG, LGCP, and GAE groups was performed using one-way ANOVA or Kruskal–Wallis test, depending on data distribution. Paired t-test or Wilcoxon signed-rank test was used for within-group pre/post comparisons. Categorical variables were analyzed using the chi-square test and $p<0.05$ was considered statistically significant.

## Results

Patients carrying the T allele of GHRL rs696217 demonstrated a significantly greater reduction in BMI,

total weight loss (TWL) and excess weight loss (EWL) following LSG and GAE compared to G allele carriers. Notably, 12 months after surgery, TWL was 41.35% in T allele vs. 27.09% in G allele (p<0.001) and EWL was 72.57% in T allele vs. 52.98% in G allele (p<0.001) in the LSG group. In the GAE group, TWL was 14.43% in T allele vs. 9.64% in G allele (p=0.012) and EWL was 34.99% in T allele vs. 22.96% in G allele (p=0.0003) (Table 1). No significant difference in weight loss was observed among LGCP patients by genotype (p>0.05).

Total ghrelin levels in GHRL genotype T allele carriers were significantly decreased by 46.75% (p<0.001), 20.17% (p<0.001) and 43.25% (p=0.0004) 6 months after LSG, LGCP and GAE, respectively (Table 2). In the GAE subgroup, HbA1c decreased more substantially in T allele carriers (by 13.25%, p=0.014) and resistin levels dropped by 25.45% (p=0.0002) 6 months after surgery (Table 2).

These results indicate that the probability that this difference occurred by chance is less than 0.1%–0.04%. This means that the reduction in ghrelin levels in T allele carriers is highly statistically significant and is likely due to a genetic predisposition to a better hormonal response after interventions in the ghrelin production zone.

The LEPR Q223R (rs1137101) polymorphism showed no significant effects on weight or hormonal parameters in the LGCP group. However, patients with different LEPR (rs1137101) genotypes 12 months after LSG exhibited significantly different rates of body weight loss, TWL was 32.55% in G allele vs. 25.81% in A allele (p=0.006) and EWL was 59.53% in G allele vs. 53.66% in A allele (p=0.016) (Table 3). These results suggest that G allele carriers lose weight better after LSG compared to A allele carriers and this is not a random result, but likely a genetically determined response.

However, among LSG patients: G allele carriers exhibited significantly better outcomes 12 months after: TWL: 32.55% in G allele vs. 25.81% in A allele (p=0.006), EWL: 59.53% in G allele vs. 53.66% in A allele (p=0.016).

**Table 1**
Total and excess weight loss in GHRL (rs696217) genotype carriers 12 months after surgical procedures

| Procedure | Genotype | TWL (%) | p-value | EWL (%) | p-value |
|---|---|---|---|---|---|
| LSG | G allele | 27.09 | <0.001 | 52.98 | <0.001 |
| | T allele | 41.35 | | 72.57 | |
| GAE | G allele | 9.64 | 0.012 | 22.96 | 0.0003 |
| | T allele | 14.43 | | 34.99 | |

Abbreviations: EWL – excess weight loss; GAE – gastric artery embolization; LSG – laparoscopic sleeve gastrectomy; TWL – total weight loss.

**Table 2**
Hormonal changes in GHRL (rs696217) genotype carriers 6 months after surgical procedures

| Marker | Procedure | Genotype | Change (%) | p-value |
|---|---|---|---|---|
| Ghrelin | LSG | T allele | –46.75 | <0.001 |
| Ghrelin | LGCP | T allele | –20.17 | <0.001 |
| Ghrelin | GAE | T allele | –43.25 | 0.0004 |
| HbA1c | GAE | T allele | –13.25 | 0.014 |
| Resistin | GAE | T allele | –25.45 | 0.0002 |

**Table 3**
Total and excess weight loss in LEPR (rs1137101) genotype carriers in the LSG group 12 month after surgery

| Genotype | TWL (%) | p-value | EWL (%) | p-value |
|---|---|---|---|---|
| A allele | 25.81 | 0.006 | 53.66 | 0.016 |
| G allele | 32.55 | | 59.53 | |

Abbreviations: EWL – excess weight loss; TWL – total weight loss.

## Discussion

Our study demonstrates a significant association between GHRL (rs696217) and LEPR (rs1137101) gene polymorphisms and the variability of weight loss and hormonal responses following different bariatric procedures. These findings align with a growing body of evidence supporting the role of genetic determinants in modulating individual outcomes after metabolic surgery.

Carriers of the T allele of the GHRL (rs696217) polymorphism showed greater reductions in BMI, TWL, and EWL, particularly following LSG and GAE. The observed reduction in ghrelin levels most pronounced in the LSG group corresponds with previous study by Vitolo et al. (2017) suggesting that this polymorphism influences ghrelin secretion and appetite regulation postoperatively. Since ghrelin is primarily secreted from the gastric fundus, interventions like LSG and GAE, which directly impact ghrelin-producing zones, may synergistically interact with the GHRL genotype to amplify metabolic benefits.

In contrast, LGCP did not produce significant genotype-dependent differences, possibly due to the preservation of gastric tissue that continues to secrete ghrelin, thereby attenuating the genetic effect. This highlights the importance of considering the anatomical and physiological targets of each surgical

method when evaluating gene-surgery interactions.

Interestingly, T allele carriers of GHRL also exhibited improved metabolic markers such as lower HbA1c and resistin levels after GAE. These findings are consistent with a recent report by Tabaeian et al. (2021) who have indicated that the T allele may enhance insulin sensitivity and anti-inflammatory responses.

Regarding the LEPR (rs1137101) polymorphism, its effect was more limited and procedure-specific. A allele carriers demonstrated improved TWL and EWL only in the LSG group. This observation may be explained by the altered leptin receptor signaling in response to weight loss-induced changes in leptin levels, as reported in other bariatric cohorts (Sahin-Efe et al. 2015; Genchi et al. 2021). The lack of significant effects in the LGCP and GAE groups suggests that LEPR-related outcomes are more dependent on the extent of adipose tissue reduction, which is typically more profound after LSG.

Notably, our data support the utility of preoperative genotyping to identify patients who are more likely to benefit from certain bariatric procedures. These insights pave the way for more personalized approaches in obesity management, where genetic screening may guide the selection of the optimal surgical technique for each patient (Sarkar et al. 2023; Thanos et al. 2023; Hanna et al. 2025).

However, this study has several limitations. The relatively small sample size, especially within subgroups, may limit statistical power. Moreover, the short follow-up period (12 months) may not capture long-term metabolic adaptations. Further multicenter studies with larger cohorts and extended follow-up are warranted to validate these preliminary findings.

## Conclusion

The T allele of GHRL (rs696217) appears to be a promising predictive marker for greater metabolic and hormonal improvement following bariatric procedures targeting the ghrelin-producing stomach zones. LEPR (rs1137101) may also influence postoperative outcomes in a procedure-specific manner. These findings support the potential role of genetic screening in optimizing patient selection and predicting surgical success.

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***Conflict of interest:*** *The author declares no conflict of interest.*

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