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Sleeve gastrectomy to treat concomitant polycystic ovary syndrome, insulin and leptin resistance in a 27-years morbidly obese woman unresponsive to insulin-sensitizing drugs: A 3-year follow-up

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ABSTRACT

INTRODUCTION: Insulin resistance (IR), leptin resistance (LR), and polycystic ovary syndrome (PCOS) commonly coexists with obesity. IR and PCOS are often successfully treated with the use of insulin-sensitizing drugs (ISDs). However, some women are poorly responsive or intolerant to them. If we additionally consider that currently no medical treatment for LR exists, it is crucial for the physician to find different therapeutic ways to treat patients with such multifactorial endocrinopathy.

PRESENTATION OF CASE: We present a case where sleeve gastrectomy (SG) was applied to a 27-year-old obese woman affected by concomitant IR, LR and PCOS, and unresponsive to ISDs. At three years from surgery the patient is now 71.6 kg. More importantly, her levels of insulin and leptin started to improve at postoperative month 6 and became normal at postoperative month 24. Patient's ovaries that at baseline had characteristic aspects related to PCOS, at postoperative month 36 were normal.

DISCUSSION: SG is one of the most commonly performed bariatric procedures. The literature has moved away from labeling SG as a purely restrictive procedure, as its interactions with several hormones (ghrelin, leptin, insulin, etc.) are now recognized.

CONCLUSION: In the present report, SG was applied to resolve an intricate endocrinological framework confirming its therapeutic value not only in determining weight loss but also as endocrine/metabolic surgery able to treat multifactorial endocrinopathy. The underlying molecular mechanisms contributing to these benefits remain largely undetermined, despite offering tremendous potential to reveal new targets for therapeutic intervention, mostly in those patients unresponsive to classical pharmacotherapy.

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1. Introduction

Obesity is a complex disease for which no single cause exists. Although eating habits, lifestyle, genetics and emotional concerns are main factors involved in obesity etiopathogenesis, some medical conditions may also cause weight gain. Insulin resistance (IR), leptin resistance (LR) and polycystic ovary syndrome (PCOS) commonly coexist with obesity [1]. PCOS is a common endocrine disorder affecting 6–21% of women of reproductive age [2], and about 50% of PCOS patients are obese [3]. In most cases, PCOS also involves metabolic alterations such as IR, hyperinsulinemia, and dyslipidemia. PCOS can thus lead to increased risk of developing type 2 diabetes mellitus and cardiovascular disease in patients [4]. Obesity is defined by abnormal or excessive lipid storage in the

adipose tissue cells. Adipose tissue is not only considered the main energy reservoir but also a pivotal endocrine organ involved in the regulation of many physiological processes, by secreting a variety of bioactive cytokines, such as leptin [5]. Leptin is involved in the regulation of food intake, energy balance, and body weight [5].

Obesity and IR are crucial parameters of PCOS. As leptin is primarily secreted by adipose tissue and also has activity at an ovarian level, it is interesting to know whether serum leptin levels are correlated with IR in PCOS. However, this correlation is still a matter of debate and further research is required to clarify the relationship between leptin, IR in PCOS.

While there is currently no medical treatment for LR, IR and PCOS are often successfully treated with the use of insulin-lowering agents (ISDs) [6–7]. However, some women are unresponsive to this type of pharmacotherapy [8].

The case of a 27-year-old morbidly obese woman suffering from concomitant IR, LR, PCOS, and unresponsive to ISDs, treated with SG is here reported.

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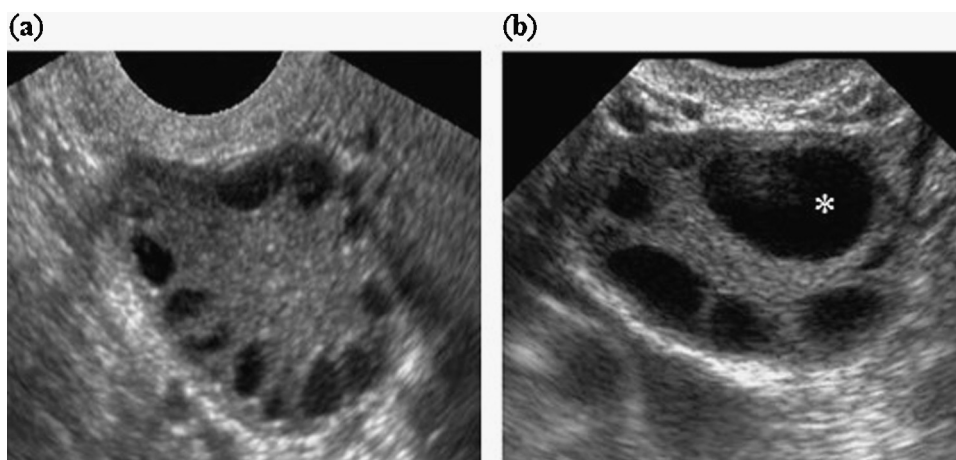


Fig. 1. Ovary ultrasound image (a) Baseline. The ovary has many small cysts (2–7 mm diameter), giving the ovary a characteristic “polycystic” appearance. (b) Postoperative month 36. The ovary appears normal with a dominant (asterisk) follicle present.

2. Case presentation

In 2011, a 27-year-old Italian female with a body mass index (BMI) of 49.9 kg/m² (weight = 141 kg; height = 168 cm) was referred for bariatric surgery intervention for obesity. The patient had known concomitant IR and LR associated to PCOS since puberty. Patient clinical history was also characterized by unresponsiveness to ISDs (metformin, and thiazolidinedione) even at maximum dose. The patient also reported that she stopped high doses of prescribed pharmacotherapy on several occasions due to side effects (abdominal discomfort, cramping, diarrhoea and nausea).

Despite strict adherence to several exercise-associated diet programs, extremely aggressive diets, such as ketogenic enteral nutrition, and drugs for obesity treatment, the patient had continued to gain weight. Over the past two years, her plasma insulin levels were 21–36 μIU/mL (normal range 6–29 μIU/mL) and plasma leptin levels were 89–130 ng/mL (normal range 0.5–12.7 ng/mL).

In 2009, the patient was treated with a 6-month placement of intragastric balloon. In six months the patient lost 21 kg (from

131 kg to 110 kg) with a concomitant improvement of both IR, LR, and PCOS indicating, as reported in the literature, weight loss has a pivotal role in the etiopathogenesis of both IR and LR, and improved menstrual frequency. Unfortunately, although weight loss and lifestyle modifications are the first line treatment in PCOS, IR, and LR, they are associated with low adherence and sustainability over time. Therefore, the patient completely regained this weight loss three months after the balloon was removed, with a concomitant deterioration of both IR and LR.

After considering overall clinical history and a careful preoperative multidisciplinary clinical screening, the patient was considered eligible for obesity surgery. Patient’s clinical characteristics before surgery (baseline) are reported in Table 1 and Fig. 1a, and clearly show high levels of hyperinsulinemia, hyperleptinemia, IR (HOMA index 11.9 vs normal range 0.23–2.5), dyslipidaemia, enlarged liver associated with high levels of transaminases, PCOS, and amenorrhoea.

The patient then underwent a laparoscopic sleeve gastrectomy (LSG) for correction of her obesity. During the operation, there

Table 1
Patient characteristics at baseline e during the follow-up.

| Clinical characteristics | Baseline | Post-LSG(6 months) | Post-LSG(12 months) | Post-LSG(24 months) | Post-LSG(36 months) |
|-------------------------------------------------|-------------|--------------------|---------------------|---------------------|---------------------|
| Age (years) | 27 | 27 | 28 | 29 | 30 |
| Height (cm) | 1.68 | 1.68 | 1.70 | 1.71 | 1.72 |
| Body Weight (kg) | 141 | 105.7 | 91.4 | 74.3 | 69.4 |
| BMI (kg/m ²) | 49.9 | 37.5 | 31.6 | 25.4 | 23.4 |
| Leptin (range 0.5–12.7 ng/mL) | 123.2 | 30.8 | 11.3 | 2.3 | 1.9 |
| Glucose (range 70–110 mg/dL) | 164 | 102 | 86 | 79 | 74 |
| Insulin (range 6–29 μIU/mL) | 29.4 | 21.3 | 11.5 | 6.1 | 2.9 |
| Glycated Hemoglobin (range 5–20%) | 9.2 | 6.4 | 6.1 | 5.9 | 5.7 |
| Homa index (range 0.23–2.5) | 11.9 | 5.36 | 2.44 | 1.19 | 0.53 |
| Liver left lobe size (rage 9–10 cm) | 16.3 | 11.2 | 11.6 | 11.2 | 11.2 |
| Liver right lobe size (rage 12–14 cm) | 21.2 | 13.9 | 12.8 | 12.1 | 13.4 |
| Total cholesterol (normal value <190 mg/dL) | 251 | 189 | 174 | 161 | 154 |
| HDL (normal value >45 mg/dL) | 39 | 44 | 45 | 51 | 62 |
| LDL (normal value <100 mg/dL) | 154.8 | 107 | 94.6 | 83.4 | 67.2 |
| Total cholesterol/HDL ratio (normal value <4.5) | 6.43 | 4.3 | 3.9 | 3.1 | 2.5 |
| Triglycerides (normal value <150 mg/dL) | 286 | 190 | 172 | 133 | 124 |
| GOT (range 7–45 U/L) | 49 | 24 | 21 | 23 | 16 |
| GPT (range 8–43 U/L) | 43 | 21 | 19 | 17 | 19 |
| GGT (range 6–29 U/L) | 35 | 25 | 22 | 19 | 17 |
| Menstrual cycles | Amenorrhoea | Irregular | Normal | Normal | Normal |

Homa index = homeostatic model assessment.
HDL = high density lipoprotein.
LDL = low density lipoprotein.
GOT = glutamic oxaloacetic transaminase.
GPT = glutamic pyruvic transaminase.
GGT = gamma-glutamyl transferase.

were no intra-operative complications. Post-operative course was uneventful. On day 5, a routine upper gastrointestinal gastrografin swallow study was performed and showed no evidence of leak or obstruction. Therefore, she was discharged home in a stable condition. After discharge on the fifth postoperative day, the patient assumed a liquid diet that was changed to puree-based after 15 days, and after four additional weeks, to soft solid food. The patient was also instructed to regularly follow an enriched protein diet [9], to take daily vitamin supplements, and physical activity was encouraged. Obviously, the surgery goals were to decrease total body weight and improve lipid and hepatic profile, IR, LR, and consequently the PCOS. Patient presence at scheduled follow-up visits (6, 12, 24 and 36 months) was 100%.

Patient's postoperative clinical characteristics are reported in Table 1 and Fig. 1b. In particular, the patient lost 35.3 kg six months after surgery, and 49.6 kg, 66.7 kg and 71.6 kg, at 12, 24 and 36 months after the surgery, respectively. At postoperative month 36, BMI was 23.4 kg/m² that on the basis of BMI categories is considered a healthy weight. More importantly, patient levels of insulin and leptin started to improve at postoperative month 6 to become normal at postoperative month 24. At postoperative month 36, plasma insulin and leptin levels were 2.9 μIU/mL and 1.9 ng/mL, respectively, for insulin and leptin range values (Table 1) this is considered normal. Furthermore, as shown in Fig. 1, patient's ovaries that at baseline (a) had characteristic aspects related to PCOS, at postoperative month 36 (b) may be defined as normal. In fact, the patient reported that starting from postoperative month 12 her menstrual cycle became regular with a frequency range of 27–31 days.

3. Discussion

The relationship between leptin, IR in PCOS is still a matter of debate. Patients become LR by the same mechanism associated with IR, through a continuous overexposure to high levels of hormone [10–12]. Over time, if the body is exposed to excess leptin, it will become resistant, just as it can become resistant to insulin. While there is currently no medical treatment for LR, IR is often successfully treated with the use of insulin-lowering agents or ISDs. Pharmacotherapy is also used in PCOS, including the oral contraceptive pill and ISDs. In fact, the recognition of IR as a principal factor in the pathogenesis of PCOS has led to the use of ISDs for PCOS treatment. For instance, troglitazone is a drug that improves IR and hyperinsulinemia without altering leptin levels [13]. By contrast, metformin, an insulin sensitizer widely used for treating type 2 diabetes mellitus, considerably reduces serum leptin concentration in obese and non-obese PCOS patients [14]. However, some women are unresponsive to this type of pharmacotherapy.

To our knowledge, only one case of a 16-year-old Caucasian male with LR and successfully treated with bariatric surgery has been reported in the medical literature [15]. To our knowledge, this is the first report of bariatric surgery in a morbidly obese patient suffering from concomitant IR, LR, PCOS, and unresponsive to ISDs. In the present case the patient was effectively treated with SG.

4. Conclusion

Bariatric surgical procedures, such as SG, are currently the most effective therapy for the treatment of obesity. In the present report,

SG was applied to resolve an intricate endocrinological framework confirming its therapeutic value not only in effectively determining weight loss but also as endocrine/metabolic surgery able to treat multifactorial endocrinopathy. The underlying molecular mechanisms contributing to these benefits remain largely undetermined, despite offering tremendous potential to reveal new targets for therapeutic intervention, mostly in those patients unresponsive to classical pharmacotherapy.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Conflict of interest

The authors of this manuscript declare no conflict of interest regarding any commercial label or pharmaceutical industry.

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