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The effect of sleeve gastrectomy on serum irisin levels in patients with morbid obesity

Wpływ gastrektomii rękawkowej na poziom irisiny w surowicy pacjentów z chorobliwą otyłością

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Abstract

Introduction: Irisin, a recently identified myokine, is associated with increased energy expenditure and has a potential role in obesity. Therefore, we investigated circulating irisin levels in morbidly obese patients undergoing sleeve gastrectomy (SG).

Materials and methods: Thirty morbidly obese patients undergoing SG and 30 healthy subjects were included. All participants were evaluated at baseline and again at three months post-SG. Body weight and height, the lipid profile, and plasma glucose, HbA1c, insulin, and irisin levels were measured at each visit.

Results: The two groups had similar mean age and sex distribution. Serum irisin was significantly lower in the morbidly obese subjects compared with the controls ($p = 0.003$) and negatively correlated with BMI, body weight, insulin levels, and HOMA-IR ($p = 0.006$, $p = 0.011$, $p = 0.046$, $p = 0.048$, respectively). When the morbidly obese patients were re-evaluated three months post-SG, their weight and BMI had significantly decreased (both $p = 0.001$). Similarly, the insulin, HbA1c, HDL-cholesterol, and HOMA-IR values significantly decreased ($p = 0.001$, $p = 0.028$, $p = 0.006$, and $p = 0.001$, respectively). However, irisin levels remained unchanged ($p = 0,267$).

Conclusion: Although the irisin levels were significantly lower in the morbidly obese subjects, they did not change after SG-induced weight loss. **(Endokrynol Pol 2016; 67 (5): 481–486)**

Key words: *irisin; obesity; bariatric surgery; sleeve gastrectomy; insulin*

Streszczenie

Wstęp: Irisina jest niedawno poznaną miokiną, która jest związana ze wzmożonym zużyciem energii i która odgrywa potencjalna rolę w rozwoju otyłości. Dlatego też autorzy pracy badali stężenie krążącej irisiny u pacjentów chorobliwie otyłych poddawanych rękawkowej gastrektomii (SG).

Materiał i metody: Do badana włączono trzydziestu chorobliwie otyłych pacjentów poddanych SG oraz 30 zdrowych ochotników. U wszystkich badanych pacjentów dokonano oceny wyjściowej oraz ponownie po 3 miesiącach po wykonaniu SG. Podczas każdej wizyty mierzono: masę ciała i wzrost, profil lipidowy, stężenie glukozy w osoczu, poziom HbA1c, insuliny raz irisiny.

Wyniki: W obu grupach stwierdzono zbliżony rozkład średniej wieku i płci. Stężenie irisiny w surowicy było istotnie niższe u pacjentów z chorobliwą otyłością w porównaniu z grupą kontrolną ($p = 0,003$) i negatywnie korelowało z BMI, masą ciała, stężeniem insuliny i HOMA-IR (odpowiednio: $p = 0,006$, $p = 0,011$, $p = 0,046$, $p = 0,048$). W momencie wykonywania oceny u chorobliwie otyłych pacjentów po 3 miesiącach od SG ich masa ciała i BMI uległy istotnej redukcji (dla obu parametrów $p = 0,001$). Również stężenie insuliny HbA1c , cholesterolu frakcji HDL i HOMA-IR uległy istotnemu obniżeniu (odpowiednio: $p = 0,001$, $= 0,028$, $p = 0,006$ i $p = 0,001$). Niemniej stężenie irisiny nie uległy zmianie ($p = 0,267$).

Wnioski: Mimo że stężenie irisiny było istotnie niższe u pacjentów z chorobliwą otyłością nie uległo ono zmianie przy spadku masy ciała indukowanym SG. **(Endokrynol Pol 2016; 67 (5): 481–486)**

Słowa kluczowe: *irisina; otyłość; chirurgia bariatryczna; gastrektomia rękawkowa; insulina*

Introduction

Obesity has become a major health problem in recent decades and has reached epidemic proportions, not only in high-income countries but also in most middle-income societies, as reported by the World Health Organisation (WHO) in 2014. During the last three decades, the prevalence of obesity has increased enormously, and it is usually assumed that environmental changes are the main causes, although genetic bases can undoubtedly be involved [1]. In 2008, according to the WHO, 1.4 billion adults were overweight and 500 million adults were

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obese worldwide. It has been projected that 2/3 of the world's population may be overweight (2.2/3.3 billion) or obese (1.1/3.3 billion) by 2030 [1]. Obesity has also become one of the most important public health problems in our country. According to the TURDEP-I and TURDEP-II surveys, the average age-standardised body mass index (BMI) has increased from 26.6 to 28.6 kg/m^2, and the average waist has increased from 87.2 to 94.5 cm in 12 years in Turkey. Compared with TURDEP-I, the rate of increase for obesity was 40% and for central obesity was 35% during the last 12 years in TURDEP-II [2].

Obesity is associated with increased rates of mortality and morbidity [3, 4], including insulin resistance and type 2 diabetes mellitus, hypertension, dyslipidaemia, cardiovascular disease, stroke, sleep apnoea, gallbladder disease, hyperuricaemia and gout, and osteoarthritis. Although the pathogenesis of obesity is extremely complex and far from being unravelled, the key component of the obesity epidemic is long-term dysregulation of energy balance, comprising increased energy intake and/or reduced energy expenditure.

Bariatric surgery is currently the most effective treatment for severe obesity [5]. While mechanical restriction of food intake is a dominating contributor to the weight loss observed after bariatric surgery, weight loss is often greater than expected by restriction alone [6]. There is a growing body of evidence that the hormonal effects of bariatric surgery are also responsible for the weight loss [7]. However, the extent and sustainability of postsurgical weight loss markedly differs between individuals [8]. This heterogeneity is determined by a wide range of factors related to the type of surgery, patient demographics, and psychosocial factors, as well as biological factors that regulate energy intake, storage, and expenditure [9, 10]. Because the various available bariatric surgeries are heterogeneous in terms of the anatomical alterations made, it is important to consider each procedure separately, as the resulting mechanisms involved in weight loss are quite different. The four most commonly undertaken procedures are as follows, in order from least to most invasive: laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion [11]. The outcome of bariatric surgery on insulin sensitivity and secretion is different in relation to the type of surgery methods performed [12]. In fact, while RYGB enhances insulin secretion after a meal, thus improving glucose metabolism, Bilio-Pancreatic Diversion acts through the amelioration of insulin sensitivity allowing a subsequent reduction of insulin hypersecretion, which is a typical feature of the insulin resistance state. LAGB action is mediated uniquely through the weight loss, and the effect of SG is proposed to be mediated by the decrease in ghrelin levels because ghrelin is mainly produced by the fundus of the stomach, but this is still to be elucidated [12, 13].

In SG, a partial gastrectomy is performed, in which the majority of the greater curvature of the stomach is removed and a tubular stomach is created [7]. An SG constitutes the upper abdominal component of the biliopancreatic diversion with a duodenal switch. SG results in approximately 60–70% of excess body weight loss after two years, positioning it between LAGB and RYGB in terms of weight loss efficacy [14]. As most of the ghrelin-producing cells of the stomach are removed with the partial gastrectomy, ghrelin levels decrease from day one to at least five years postoperatively [15–17]. In addition to being a restrictive procedure, SG also results in more rapid delivery of nutrients to the small intestine; thus, glucagon-like-peptide 1 (GLP-1) levels have been shown to rise in response to meals in SG patients [18, 19]. Additionally, PYY has been found to increase postprandially to levels comparable to RYGB [18–20]. Increased adiponectin and decreased leptin levels following SG have also been reported [21].

Irisin, the most recently identified myokine, is the extracellular cleaved product of fibronectin type III domain containing 5 (FDNC5) and is regulated by peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1 alpha (PGC1α) [22]. Studies in mice have shown that FDNC5/irisin overexpression induces browning and enhances thermogenesis in white adipose tissue, contributing to improvements in glucose homeostasis and insulin resistance. This myokine has been shown to increase energy expenditure and has therefore been proposed to play a potential role in obesity [23].

In humans, the existing data regarding irisin levels in relation to obesity, type 2 diabetes mellitus (T2D), and metabolic syndrome are inconclusive [24]. Although the effect of bariatric surgery (LAGB or RYGB) on irisin levels has been studied previously, the effect of SG on irisin levels has not been evaluated. Therefore, the aim of this study was to assess changes in circulating irisin concentrations in obese subjects following SG.

Material and methods

This investigation is a case control study. Thirty morbidly obese subjects (age 31.47 ± 7.17 years, BMI 44.23 ± ± 3.23 kg/m^2, males/females = 5/25) were recruited to this study after being approved for bariatric surgery in accordance with NIH criteria for bariatric surgery, which recommended consideration of surgical weight loss for all patients with BMI > 40 kg/m^2 (unless surgery would pose a significant risk). All of the patients with morbid obesity were evaluated before SG and three months after SG. The control group included 30 healthy subjects (age 31.13 ± 6.89 years, BMI 21.86 ± 2.39 kg/m^2, males/females = 8/22).

All of the study subjects were non-diabetic. Other inclusion criteria included having normal renal and hepatic function, thyroid function, fasting plasma glucose (FPG), and calcium levels. Exclusion criteria were known chronic diseases (hyperparathyroidism, hypercortisolism, chronic renal disease, chronic liver disease, cancer history, previous intestinal operation, and cardiovascular disease) and previous or current treatment with drugs affecting glucose metabolism (thiazides, glucocorticoid, oestrogen, and androgen therapy). All participants provided written informed consent to participate, as approved by the Ethics Committee of the Izmir Tepecik Training and Research Hospital (Date: February 04, 2015; Meeting Number: 1; Decision: 7) and in accordance with the Declaration of Helsinki.

Clinical and pre-operative evaluations

The height of each subject was measured to the nearest 0.1 cm using a stadiometer. Body weight was measured using a digital weighing scale (ADE — Germany — Type MZ 10023). BMI was calculated using the Quetelet formula, which states that BMI equals weight in kilograms divided by the square of height in metres (kg/m^2). Overweight was defined as a BMI of 25 to 29.9 kg/m^2, and obesity was defined as a BMI ≥ 30 kg/m^2. Severe obesity was defined as a BMI ≥ 40 kg/m^2.

All patients underwent evaluation by a bariatric multidisciplinary team (endocrinologist, dietitian, psychiatrist, anaesthesiologists, cardiologist, chest physicians, and surgeons) before undergoing SG. Candidates for surgery were informed about the procedure and completed an extensive preoperative workup as indicated by the multidisciplinary group.

Measurement of biochemical parameters and irisin levels

All blood samples were processed for serum and plasma within 90 minutes of collection and stored at –80 °C.

Plasma glucose levels were measured using the hexokinase method on an Olympus AU 2700 analyser (Olympus Diagnostics, GmbH, Hamburg, Germany). Serum insulin levels were measured using direct chemiluminescence technology on a Siemens Immulite 2000 XPI analyser (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Glycated haemoglobin (A1C) analysis was performed by affinity chromatography HPLC on a Primus Ultra2 Analyser (Primus Corporation, Kansas City, Kansas, USA). Homeostasis model assessment for insulin resistance (HOMA-IR) (25) was calculated as (fasting insulin [units per millilitre] X fasting plasma glucose [milligrams per decilitres]/18)/22.5.

Lipid parameters (total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)) were enzymatically measured using Abbott commercial kits on an Abbott Architect C8000 auto analyser (Abbott Laboratories, USA).

Plasma irisin protein concentrations were measured using a specific ELISA kit (SunRedBio, Shanghai, China) (sensitivity: 0.157 ng/mL; assay range: 0.2–60 ng/mL).

Obese subjects were re-evaluated three months after SG.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences software version 15.0 (SSPS, Inc., Chicago, Illinois, USA). An alpha level of 0.05 was used to determine statistically significant differences. Shapiro-Wilk tests were performed to assess the normal distribution of continuous variables. Data are reported as the mean ± standard deviation (SD) for normally distributed variables. Variables that are not normally distributed are reported as medians with minimum and maximum values. Discrete variables were evaluated using chi-square tests. Normally distributed values of continuous variables between the case and control groups were evaluated with the independent t test. Non-normally distributed values of continuous variables between the case and control groups were evaluated with the Mann-Whitney U test. Case group values before and after operation were correlated using the paired-samples t test for normally distributed values; the Wilcoxon test was performed for non-normally distributed values. $p<0.05$ was considered statistically significant.

Results

There were 13 males and 47 females in the study, with a mean age of 31.3 ± 6.97 years. Comparing males and females, there were no differences in age, BMI, FPG, A1C, insulin, and irisin levels. The gender distribution was similar between the obese (male/female: 5/25) and control groups (male/female: 8/22) ($p = 0.347$). The mean age (years) was similar between the obese (31.47 ± ± 7.17) and control groups (31.13 ± 6.89) ($p = 0.855$) (Table I). As expected, weight and BMI were higher in obese subjects ($p = 0.001$ and $p = 0.001$, respectively). Although FPG levels were not significantly different between the two groups ($p = 0.131$), insulin levels and HOMA-IR were higher among the obese subjects than in the control group ($p = 0.001$ and $p = 0.001$, respectively). LDL and total cholesterol levels were significantly higher in the obese group compared with the control group ($p = 0.04$ and $p = 0.014$, respectively). Although HDL levels were higher in the control group and TG levels were higher in the obese group, the differences were not statistically significant ($p = 0.427$ and $p = 0.200$, respectively). HbA1C levels were lower in the obese group than in the control group ($p = 0.001$) (Table II).

Table I. *Clinical characteristics of participants*
Tabela I. *Charakterystyka kliniczna badanych*

	Obesity group (n = 30)	Control group (n = 30)	p value
Age (years)	31.47 ± 7.17	31.13 ± 6.89	0.855
Gender/Male (%)	5 (16.7)	8 (26.7)	0.347
Female (%)	25 (83.3)	22 (73.3)	

Serum irisin levels were significantly lower in morbidly obese subjects compared with the controls (p = 0.003).

Spearman's correlation analysis revealed that serum irisin levels in all subjects were negatively correlated with BMI (r = –0.350, p = 0.006), body weight (r = –0.326, p = 0.011), insulin level (r = –0.259, p = 0.046), and HOMA IR(r = –0.254, p = 0.048) but were not correlated with FPG, A1C, and lipid parameters.

When the morbidly obese patients were re-evaluated three months after SG, weight and BMI were significantly decreased (p = 0.001 and p = 0.001, respectively). Likewise, insulin and HbA1c levels and HOMA-IR values decreased significantly three months after SG (p = 0.001, p = 0.028, and p = 0.001, respectively). Furthermore, whereas FPG, LDL, TG, and total cholesterol levels did not change significantly after SG (p = 0.223, p = 0.120, p = 0.249, and p = 0.299, respectively), HDL levels decreased significantly (p = 0.006). However irisin levels did not change after SG (p = 0.267) (Table III).

Table II. *The Comparison of anthropometric and metabolic parameters between obese and control groups*
Tabela II. *Porównanie parametrów antropometrycznych oraz metabolicznych między grupą otyłych pacjentów i grupą kontrolną*

	Obesity group (n = 30)	Control group (n = 30)	p value
BMI [kg/m^{2}]	44.23 ± 3.23	21.86 ± 2.39	0.001
Weight [kg]	121.27 ± 12.34	60.29 ± 10.83	0.001
Fasting glucose [mg/dL]	91.03 ± 5.34	88.67 ± 6.56	0.131
A1c (%)	4.79 ± 0.19	5.34 ± 0.22	0.001
Total cholesterol [mg/dL]	200.10 ± 34.18	175.12 ± 29.40	0.014
LDL [mg/dL]	132.67 ± 34.78	102.06 ± 27.56	0.004
HDL [mg/dL]	47.13 ± 9.03	50.06 ± 12.89	0.427
TG [mg/dL]	Median: 104 Min-Max: 50–237	Median: 74 Min-Max: 48–366	0.200*
Insulin	Median: 33.64 Min-Max: 12.0–120	Median: 6.81 Min-Max: 2.11–17.70	0.001*
HOMA-IR	Median: 7.52 Min-Max: 2.47–28.15	Median: 1.47 Min-Max: 0.39–3.85	0.001*
Irisin [ng/mL]	Median: 6.44 Min-Max: 3.71–61.61	Median: 9.72 Min-Max: 4.21–102.51	0.003*

*Mann-Whitney U test

Discussion

Obesity has become a major health problem and is associated with an increased risk in all-cause and CVD mortality. The biomedical, psychosocial, and economic consequences of obesity have substantial implications for human health and well-being. Due to the limited medical therapeutic options, the tendency toward bariatric surgery has been increasing. Bariatric surgery involves changes in the gastrointestinal anatomy and has been shown to be effective for treating obesity and obesity-associated comorbidities.

Irisin, the most recently identified myokines, is proteolytically processed from the FNDC5 gene product prior to being released into the circulation and is regulated by PPARγ coactivator 1 alpha (PGC1-α), but its pathophysiology remains largely unknown. There is recent evidence regarding its role in the browning of subcutaneous adipocytes and in thermogenesis via increased uncoupling protein-1 levels, its role in exercise physiology, and its association with metabolic and anthropometric parameters. This myokine has been shown to increase energy expenditure and has therefore been proposed to have a potential role in obesity and T2D treatment [22, 23]. Since its discovery, a number of original studies have addressed various aspects of the biology of irisin. Although the effects of LAGB or RYBG surgery on irisin levels have been studied before, to our knowledge this is the first study to evaluate circulating irisin levels and investigate the potential relationship between irisin concentrations and weight loss after SG.

Irisin was previously found to be reduced in patients with type 2 diabetes [26, 27] and metabolic syndrome [28]. Liu JJ et al. found a significant positive association between serum irisin and FPG but not with other glucose/Lipid markers. Choi YK et al. found negative correlations between serum irisin levels and two-hour plasma glucose (Oral Glucose Tolerance Test), A1C, and triglycerides, but only the negative association with two-hour plasma glucose persisted after multiple regression analysis. Additionally, Espes et al. reported increased irisin levels in patients with long-standing type 1 diabetes [29] and found that irisin levels correlated with lower insulin requirements [29].

Table III. *Anthropometric and metabolic parameters of obese patients before and three month after surgery*

Tabela III. *Parametry antropometryczne i metaboliczne otyłych pacjentów przed i trzy miesiące po zabiegu*

n = 30	Before SG mean ± SD	Three months after SG mean ± SD	p value
Weight [kg]	121.27 ± 12.34	100.30 ± 11.79	0.001
BMI [kg/m^2]	44.24 ± 3.23	36.47 ± 2.97	0.001
Fasting glucose [mg/dL]	91.1 ± 5.34	89.63 ± 6.92	0.223
A1c (%)	4.79 ± 0.20	4.68 ± 0.25	0.028
Total cholesterol [mg/dL]	200.10 ± 34.18	193.0 ± 32.18	0.299
LDL [mg/dL]	132.67 ± 34.78	121.77 ± 26.25	0.120
HDL [mg/dL]	47.13 ± 9.03	42.07 ± 6.50	0.006
TG [mg/dL]	Median: 104 Min-Max: 50–237	Median: 117.50 Min-Max: 83–238	0.249**
Insulin	Median: 33.64 Min-Max: 12.0–120	Median: 9.70 Min-Max: 6.50–26.41	0.001**
HOMA-IR	Median: 7.52 Min-Max: 2.47–28.15	Median: 2.13 Min-Max: 1.38–5.93	0.001**
Irisin [ng/mL]	Median: 6.44 Min-Max: 3.71–61.61	Median: 6.86 Min-Max: 2.84–62.6	0.267**

** Wilcoxon test

There are conflicting results regarding irisin levels in obesity, with elevated levels found in some studies [30, 31] and decreased levels found in others [32]. Pardo M et al. observed that irisin levels were positively correlated with body weight, BMI, fat mass, and resting energy expenditure and suggested that fat mass was the main contributing factor for elevated irisin levels in obese patients [31]. Likewise, Stengal A et al. reported a positive correlation between irisin levels and BMI, fat mass, fat-free mass, and insulin levels in obese patients and proposed that increased irisin levels in obesity might indicate a physiological function to improve glucose tolerance, which is often impaired in obese subjects [30]. In contrast with these findings, a study by Huh et al., which included 117 middle-aged women with BMIs ranging from 20.0 to 47.7 kg/m^2, revealed that irisin levels were only correlated with muscle mass evaluated by bicep circumference, fat-free mass, and BMI [33]. Additionally, irisin levels were positively correlated with serum glucose, ghrelin, GH, and IGF-1 and negatively correlated with total and HDL cholesterol. However, irisin levels in that study were not compared between obese and lean subjects. Consistent with the results of Moreno-Navarrate et al. [34], our study revealed lower irisin levels in morbidly obese patients, with respect to control subjects. We also observed a negative correlation between irisin levels and body weight, BMI, insulin levels, and HOMA-IR. This effect can be explained by decreased irisin levels possibly being associated with insulin resistance and metabolic syndrome. Additionally, the lower irisin levels observed in morbidly obese patients might suggest a loss of browning of subcutaneous adipose tissues.

In addition to the association of irisin with obesity, the association of irisin with weight loss has also been studied [33, 35, 36]. In a study by Crujeiras et al., insulin levels were found to be higher in obese patients and significantly correlated with weight, BMI, waist circumference, and fat mass. After weight loss with a hypocaloric diet, the irisin levels were decreased, suggesting that the irisin levels reflected the body fat mass and that circulating irisin levels were conditioned by the adiposity level [35]. In another study, it was reported that irisin predicted the insulin resistance onset in association with weight regain and suggested that irisin could be secreted as an adaptive response to counteract the deleterious effect of excess adiposity on glucose homeostasis[36]. Joo Young Huh studied the effect of bariatric surgery on patients with obesity. In this study, fourteen subjects who had undergone either LAGB or RYGB surgery were evaluated at baseline and at six months postoperatively. Significant decreases in circulating irisin levels were observed (112.7 ± 32.2 *vs.* 98.6 ± 22.1) with a decrease in BMI from 50.2 ± 10.6 to 41.4 ± 8.5. The statistical significance of the decrease was lost when adjusted for fat-free mass, suggesting that muscle mass is the primary predictor of circulating irisin levels. Insulin and leptin levels were also reported to be decreased after weight loss [33]. In contrast with the study by Huh et al., our study included 30 morbidly obese patients who underwent SG. When the morbidly obese patients were re-evaluated three months after SG, weight and BMI were found to be significantly decreased ($p = 0.001$ and $p = 0.001$, respectively); irisin levels remained unchanged. Additionally, we observed decreased insulin and HbA1c levels and HOMA-IR values after surgery. The difference in the change in irisin levels between the study of Huh et al. and ours can be explained by several mechanisms; first, the possible difference in leptin levels. Since in a study of Gutierrez et al., in subcutaneous adipose tissue explants from non-obese subjects, leptin produced a decrease in FNDC5 expression, it was proposed that FNDC5 expres-

sion could be regulated by leptin [37]. However, we did not evaluate leptin levels in our study. Second, because muscle mass has been proposed to be a predictor of irisin levels, no change in irisin levels might reflect the similar muscle mass before and after surgery in obese patients in our study. However, we did not evaluate fat mass and fat-free mass separately. And third, the difference in type of bariatric surgery might be responsible for the difference in the change in irisin levels, but there are only two studies that evaluated the effect of bariatric surgery on irisin levels and LAGB or RYGB surgery was performed in these studies [33, 36]. There is no data regarding the effect of SG on irisin levels, so this hypothesis needs to be investigated.

In addition to not evaluating body composition and leptin levels, our study has several limitations. Our study sample was small, which may affect the statistical power of our study. We also did not evaluate FNDC5 gene expression in adipose tissue, which would strengthen our hypothesis. However, to our knowledge this is the first study to investigate the effects of SG on serum irisin levels.

In conclusion, we found significantly decreased irisin levels in morbidly obese patients, and there was a negative correlation between BMI and the newly identified myokine irisin, but it remained unchanged after SG. These results suggest that irisin may not be involved in the amelioration of obesity and insulin resistance by SG. Further studies are necessary to discover the mechanisms underlying the regulation of irisin levels and its physiological effects in humans. The effect of irisin on weight loss failure or recidivism after a hypocaloric diet or bariatric surgery must also be investigated.

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