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ABOUT COVER

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Retrospective Study

Role of nutritional ketosis in the improvement of metabolic parameters following bariatric surgery

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Abstract

BACKGROUND

Ketone bodies (KB) might act as potential metabolic modulators besides serving as energy substrates. Bariatric metabolic surgery (BMS) offers a unique opportunity to study nutritional ketosis, as acute postoperative caloric restriction leads to increased lipolysis and circulating free fatty acids.

AIM

To characterize the relationship between KB production, weight loss (WL) and metabolic changes following BMS.

METHODS

For this retrospective study we enrolled male and female subjects aged 18-65 years who underwent BMS at a single Institution. Data on demographics, anthropometrics, body composition, laboratory values and urinary KB were collected.

RESULTS

Thirty-nine patients had data available for analyses [74.4% women, mean age 46.5 ± 9.0 years, median body mass index 41.0 (38.5; 45.4) kg/m², fat mass 45.2% ±

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6.2%, 23.1% had diabetes, 43.6% arterial hypertension and 74.4% liver steatosis]. At 46.0 ± 13.6 d post-surgery, subjects had lost $12.0\% \pm 3.6\%$ of pre-operative weight. Sixty-nine percent developed ketonuria. Those with nutritional ketosis were significantly younger [42.9 (37.6 ; 50.7) years *vs* 51.9 (48.3 ; 59.9) years, $P = 0.018$], and had significantly lower fasting glucose [89.5 (82.5 ; 96.3) mg/dL *vs* 96.0 (91.0 ; 105.3) mg/dL, $P = 0.025$] and triglyceride levels [108.0 (84.5 ; 152.5) mg/dL *vs* 152.0 (124.0 ; 186.0) mg/dL, $P = 0.045$] *vs* those with ketosis. At 6 mo, percent WL was greater in those with postoperative ketosis ($-27.5\% \pm 5.1\%$ *vs* $23.8\% \pm 4.3\%$, $P = 0.035$). Urinary KBs correlated with percent WL at 6 and 12 mo. Other metabolic changes were similar.

CONCLUSION

Our data support the hypothesis that subjects with worse metabolic status have reduced ketogenic capacity and, thereby, exhibit a lower WL following BMS.

Key Words: Obesity; Ketone bodies; Bariatric surgery; Weight loss; Glucose metabolism; Lipid metabolism

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Core Tip: Ketone bodies might act as potential metabolic modulators besides serving as energy substrates. Acute postoperative caloric and carbohydrate restriction after bariatric metabolic surgery (BMS) leads to increased lipolysis, inducing ketogenesis. We report that the majority, but not all patients undergoing BMS, develop nutritional ketosis. Patients with nutritional ketosis had significantly lower baseline fasting glucose and triglyceride levels *vs* those without ketonuria. Weight loss was greater in those with postoperative ketonuria, and urinary ketones positively correlated with percent weight loss. These observations suggest that subjects with worse gluco-metabolic status have reduced ketogenic capacity, which might blunt the metabolic response to BMS.

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INTRODUCTION

Ketogenesis primarily occurs in the liver at rates proportional to total fat oxidation under conditions of reduced glucose availability such as fasting or very low-calorie ketogenic diets (VLCKDs). In brief, under these conditions, lipolysis-derived free fatty acids (FFAs) undergo beta-oxidation and are broken down into acetyl CoA, which is then converted to ketone bodies (KB), namely acetone, acetoacetate (AcAc), and beta-hydroxy butyrate (BHB), in the mitochondrial matrix of hepatocytes. KBs, namely BHB, AcAc and acetone, transfer lipid-derived energy from the liver, which cannot use them as a fuel, to extrahepatic organs (*e.g.*, central nervous system, heart, skeletal muscle, kidney), serving as an energy substrate alternative to glucose[1]. Over the past few years, the interest in KBs and nutritional ketosis has progressively increased, largely due to the discovery that, besides serving as energy substrates, KBs may also exert favourable metabolic effects[2,3], serving as metabolic regulators and signalling molecules. In particular, BHB exerts antioxidant and anti-inflammatory effects, may affect epigenetics by inhibiting histone deacetylation, suppresses the activity of the sympathetic nervous system and reduces lipolysis and, through unknown mechanisms, to play a role in appetite suppression[4,5]. In healthy individuals, even small increases in KB levels were shown to lower glucose and circulating FFA independent of insulin and glucagon[6], and to attenuate the glycaemic response to an oral glucose tolerance test by increasing insulin sensitivity[7], suggesting a direct metabolic effect of KBs. Bariatric metabolic surgery (BMS) offers a unique opportunity to study

nutritional ketosis, avoiding the complexity of a nutritional intervention such as VLCKD that would need greater effort from patients and also greater costs[8]. Similar to VLCKDs, BMS involves a marked energy deficit that results in massive mobilization of FFAs from adipose tissue and therefore ketogenesis[9,10]. The role of BMS in achieving sustained weight loss (WL), improving obesity-related comorbidities and reducing mortality is well established[11]. However, not all subjects respond to a similar extent[12], those with cardiometabolic abnormalities such as diabetes (especially when long-standing or poorly controlled) and arterial hypertension exhibiting poorer WL after surgery[13,14]. To the best of our knowledge, no studies have assessed the relationship between ketogenic capacity, as reflected by KB production in response to marked calorie restriction, and WL after BMS. We hypothesized that subjects with reduced ketogenic capacity are poorer responders to BMS in terms of WL 6 mo surgery.

MATERIALS AND METHODS

Study design

This was an observational, retrospective, single-centre study part of the KETO-BMS study. Male and female subjects aged 18–65 years who underwent laparoscopic sleeve gastrectomy at San Raffaele Scientific Institute from May 2016 to November 2018 and had urinary KB measured within two months of surgery and a follow-up of at least 6 mo were included. The protocol was approved by the Institutional Ethics Committee, and all patients provided informed consent. All patients underwent routine assessments prior to BMS, including medical history, physical examination, measurement of anthropometrics [height (cm), weight (kg) and body mass index (BMI), calculated as the ratio between the weight and the height squared, waist circumference (WC)], body composition (measured by electric bio-impedance in the fasting state using a BIA AKERN device and the software Bodygram PLUS software, Akern, Montachiello, Italy). Metabolic parameters including fasting plasma glucose (FPG), total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides were collected. During the first 8 wk after surgery, patients meet with a registered dietitian and subsequently with a staff physician for nutritional assessment and guidance. As per institutional protocols, during this time frame patients move from clear liquids to pureed foods, progressively increasing to approximately 750–900 kcal daily, depending on protein requirements (up to 1.5g/kg IBW). After the first 8 wk, patients move to solid foods and gradually increase the daily energy intake. Assessments are scheduled every 3–6 mo for the first 12 mo, and annually thereafter. Follow-up outpatient visits include medical history review, physical examination, measurement of anthropometrics, and laboratory assessments as per current recommendations[15].

KB production

KB production was assessed by the presence of acetoacetic acid in urine using an automated dipstick urinalysis (Aution MAX and Aution Sticks, Menarini Diagnostics, Florence, Italy). This is a semiquantitative method that detects urinary acetoacetic acid at concentrations ranging from 5 mg/dL to 150 mg/dL.

Statistical analysis

Descriptive statistics were obtained for all study variables. Normality was assessed with the Shapiro-Wilk test. Continuous variables were expressed as mean \pm SD or median (25th–75th percentile), depending on data distribution. Categorical variables were summarised as counts and percentages. Missing data were not imputed. The *t*-test, Welch *t*-test, or Mann-Whitney *U*-test were used for between-group comparisons, depending on variable distribution. The Fisher's exact test was used to assess the association between categorical variables and KB production.

Our primary objective was to examine the relationship between KB production and WL at 6 mo after BMS. One-way analyses of covariance were conducted to examine the effect of sex and pre-operative cardiometabolic conditions [diabetes mellitus (DM), hypertension, dyslipidaemia] on WL at 6 mo, with age included as a covariate. Bivariate correlation analyses were performed to examine the relationship of WL at 6 mo with pre-operative BMI, fat mass, FPG, total cholesterol, triglycerides and post-operative urinary KBs. Relevant variables that were significantly correlated were included in a hierarchical multiple-regression analysis, while controlling for sex, age and BMI. All variables were screened for violations of the assumptions relevant to

each of the statistical analysis performed. Statistical significance was set at $P < 0.05$. Statistical analysis was conducted using IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, United States: IBM Corp.).

RESULTS

Patient population

A total of 39 patients were included in the analysis. Patient characteristics are depicted in [Table 1](#). Patients were middle-aged, mostly females. Metabolic-associated fatty liver disease was the most prevalent obesity complication, followed by dyslipidaemia, hypertension and DM.

KB production

Most patients (69.2%) developed ketosis after a mean of 46.0 ± 13.6 d from surgery. Time from surgery was similar between those who did or did not develop ketosis (44.6 ± 15.0 d *vs* 49.0 ± 9.5 d, respectively; $P = 0.351$). Patients with ketosis were significantly younger and had significantly lower pre-operative FPG and triglyceride levels, but greater LDL cholesterol ([Table 2](#)). Urinary KBs were inversely correlated with age (Spearman's $\rho -0.519$, $P = 0.001$), FPG (Spearman's $\rho -0.366$, $P = 0.024$), and positively correlated with LDL cholesterol (Spearman's $\rho 0.426$, $P = 0.011$). There was no correlation between urinary KBs and BMI ($P = 0.936$), WC ($P = 0.619$), percent fat mass ($P = 0.768$), total cholesterol ($P = 0.368$), HDL cholesterol ($P = 0.618$) or triglycerides ($P = 0.095$).

WL after surgery

Mean WL at 6 mo was $26.4\% \pm 5.1\%$ of pre-operative weight in the whole group. WL at 6 mo was significantly greater in patients who had developed post-operative ketosis ($P = 0.035$; [Figure 1](#)). Time of assessment was similar between those who did or did not develop ketosis (6.1 ± 0.9 mo *vs* 6.1 ± 0.5 mo, respectively; $P = 0.931$). In 35 patients who had available data at 12 mo (89.7% of the total, 24 and 11 in the group with and without ketosis, respectively), WL also tended to be greater in those with post-operative ketosis ($P = 0.067$, [Figure 1](#)). Time of assessment was similar between those who did or did not develop ketosis (11.9 ± 0.9 mo *vs* 12.1 ± 1.2 mo, respectively; $P = 0.590$).

Urinary KB (Spearman's $\rho 0.398$, $P = 0.012$) significantly correlated with WL at 6 mo, whereas age ($P = 0.290$), BMI ($P = 0.056$), fat mass ($P = 0.735$), FPG ($P = 0.680$), total cholesterol ($P = 0.508$) and triglycerides ($P = 0.976$) did not. After adjustment for age, there was a statistically significant difference in WL at 6 mo between males and females, $F(1, 36) = 5.221$, $P = 0.028$, partial $\eta^2 = 0.127$. There was no statistically significant difference between patients with or without DM, hypertension, or dyslipidaemia, therefore these variables were not included in the regression model. At hierarchical multiple regression, urinary KBs and male sex emerged as significant predictors of WL at six months. The full model statistically significantly predicted WL at 6 mo, $R^2 = 0.31$, $F(4, 34) = 3.76$, $P = 0.012$ ([Table 3](#)). Urinary KBs also correlated with WL at 12 mo (Spearman's $\rho 0.356$, $P = 0.036$).

Laboratory variables at 6 mo were available for a subgroup of patients. No statistically significant differences in percent change from pre-surgery to 6 mo were detected between groups ([Figure 2](#)), although patients who had developed nutritional ketosis tended to have a greater percent increase in HDL cholesterol and greater percent reductions in total and LDL-cholesterol, whereas those who did not develop ketosis tended to have a greater reduction in triglycerides.

DISCUSSION

In this analysis of patients who underwent BMS, we found that KB production during marked calorie restriction after surgery predicted WL at 6 mo. Patients who developed nutritional ketosis had greater WL at 6 mo and tended to have a greater WL at 12 mo after surgery, as compared with those who did not develop nutritional ketosis.

Little information is available on KB production after BMS. Crujeiras *et al* [9] reported that patients who underwent BMS developed mild ketosis at one month after surgery. Thereafter, KBs decreased and returned to pre-operative levels at 3 mo. The association between nutritional ketosis and WL was not explored in that study, which

Table 1 Pre-operative patient characteristics

	All 39	Missing
Age, yr	46.5 ± 9.0	-
Male, <i>n</i> (%)	10 (25.6)	-
Hypertension, <i>n</i> (%)	17 (43.6)	-
Diabetes mellitus, <i>n</i> (%)	9 (23.1)	-
Dyslipidaemia, <i>n</i> (%)	22 (56.4)	-
MAFLD	29 (74.4)	-
Waist circumference (cm)		2
Males	129.7 ± 6.2	
Females	114.1 ± 13.3	
BMI, kg/m ²	41.0 (38.5; 45.4)	-
Fat mass (%)	45.2 ± 6.2	5
Plasma glucose (mg/dL)	91.0 (84.0; 98.3)	1
Total cholesterol (mg/dL)	193.1 ± 29.6	3
HDL cholesterol (mg/dL)	48.0 (42.0; 58.0)	4
LDL cholesterol (mg/dL)	115.1 ± 28.0	4
Triglycerides (mg/dL)	118.5 (102.3; 159.3)	3

MAFLD: Metabolic-associated fatty liver disease; BMI: Body mass index; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

had a different aim. There may be different explanations for the association between post-operative nutritional ketosis and the greater WL at 6 mo observed in our study. It has been reported that conditions of altered glucose metabolism such as type 2 DM negatively impact WL after BMS[16,17]. Ketogenic capacity might be a proxy of glucometabolic health. Previous studies suggested that ketogenic capacity is impaired in women with obesity as compared to normal-weight controls[18], in the pathogenesis of non-alcoholic liver disease and progression to non-alcoholic steatohepatitis, and even hepatocellular carcinoma[19-21]. Furthermore, studies in mice indicate that impaired ketogenesis may play a role in fatty liver injury and dysregulated glucose homeostasis[22-24]. Patients who did not develop nutritional ketosis in our cohort had significantly higher FPG and triglycerides, indicating worse glucometabolic status. Impaired ketogenesis may be responsible for a diminished extraction of available fat, altered acetyl-CoA balance in mitochondria, and diversion of non-disposed FFAs to other metabolic pathways, possibly including lipogenesis [23]. Conversely, better WL and metabolic responses to BMS in patients with adequate ketogenic capacity might be due to efficient clearance of excess FFAs released from adipose tissue. It has been known for more than 40 years that KBs may have roles beyond serving as energy substrates[25]. Specifically, BHB appears to exert antioxidant and anti-inflammatory effects, to inhibit histone deacetylation and to play a role in appetite suppression[4,5]. In healthy individuals, even small increases in circulating KBs were shown to reduce glucose and triglyceride levels, and to hamper the glycaemic response to an oral glucose load by increasing insulin sensitivity[6,7]. At the time of KB assessment, WL was similar between patients with or without ketosis. However, it is tempting to speculate that exposure to mild ketosis led to an improvement of mitochondrial bioenergetics and metabolic health[3,26,27], which in turn resulted in improved subsequent WL. Despite having significantly higher LDL cholesterol prior to surgery, patients who developed nutritional ketosis exhibited a numerically greater reduction in LDL at 6 mo as compared with patients who did not develop nutritional ketosis (Figure 2). During ketogenesis, acetyl-CoA is converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by mitochondrial HMG-CoA synthase, an enzyme that is also involved in cholesterol synthesis[28]. It is possible that, in conditions of low glucose and high FFA availability, an increase in ketogenesis results in lower rates of *de novo* cholesterol synthesis.

Table 2 Comparison of pre-operative characteristics between subjects who developed (patients with post-operative ketosis) or did not develop (patients without post-operative ketosis) ketosis after surgery

	KB+ (n = 27)	KB- (n = 12)	P value
Age, yr	42.9 (37.6; 50.7)	51.9 (48.3; 59.9)	0.018
Female, n (%)	20 (74.1)	9 (75.0)	1.000
Hypertension, n (%)	11 (40.7)	6 (50.0)	0.730
Diabetes mellitus, n (%)	4 (14.8)	5 (41.7)	0.102
Dyslipidaemia, n (%)	14 (51.9)	8 (66.7)	0.494
MAFLD	20 (74.1)	9 (75.0)	0.683
Waist circumference ¹ (cm)	119.3 ± 13.5	115.3 ± 14.0	0.421
BMI, kg/m ²	41.0 (38.7; 45.4)	40.1 (35.9; 45.6)	0.663
Fat mass (%)	45.6 ± 6.2	44.2 ± 6.1	0.552
Plasma glucose (mg/dL)	89.5 (82.5; 96.3)	96.0 (91.0; 105.3)	0.025
HbA1c (mmol/mol)	37.0 (35.8; 41.0)	38.5 (36.0; 46.3)	0.305
Total cholesterol (mg/dL)	197.1 ± 25.8	183.9 ± 36.4	0.222
HDL cholesterol (mg/dL)	48.0 (42.5; 53.0)	49.0 (39.5; 62.0)	0.843
LDL cholesterol (mg/dL)	121.0 ± 23.5	100.2 ± 33.9	0.045
Triglycerides (mg/dL)	108.0 (84.5; 152.5)	152.0 (124.0; 186.0)	0.020

¹Pooled data for males and females, as there were only 2 males in the patients without post-operative ketosis group.

MAFLD: Metabolic-associated fatty liver disease; BMI: Body mass index; HbA1c: Glycated haemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; KB: Ketone bodies; WL: Weight loss.

Table 3 Hierarchical regression analysis for weight loss at 6 mo

Variable	Weight loss at 6 mo					
	Model 1		Model 2		Model 3	
	B	β	B	β	B	β
Constant	30.300 ^b		22.386 ^b		16.984	
Age	-0.106	-0.186	-0.113	-0.199	-0.032	-0.057
Sex (male)	4.038 ^a	0.305	3.756 ^a	0.325	4.391 ^a	0.380
BMI			0.200	0.201	0.203	0.204
Urinary KB					0.074 ^a	0.365
R ²	0.157		0.196		0.307	
F	3.351 ^a		2.852		3.759 ^a	
ΔR ²	0.157		0.040		0.110	
ΔF	3.351 ^a		1.722		5.402 ^a	

^aP < 0.05.

^bP < 0.01.

BMI: Body mass index; KB: Ketone bodies.

Differences in KB production might also be due to differences in diet macronutrient composition. A limitation of our study is that we did not record food intake in the first weeks following BMS. However, all patients received standard dietary recommendations, and compliance was reviewed by dietitians at follow-up assessments. Ketosis develops in conditions of reduced glucose availability and marked calorie restriction [29], such as in the first weeks after BMS. Following BMS, protein-rich foods are prioritized over other foods in order to prevent excess loss of fat-free mass[30]. It is

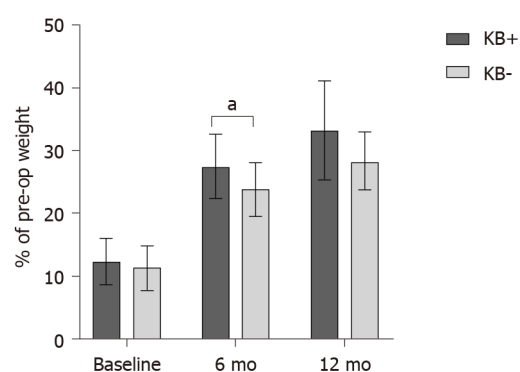


Figure 1 Weight loss at baseline (46.0 ± 13.6 d post-surgery), 6 mo and 12 mo after surgery. KB+: Patients with post-operative ketosis; KB-: Patients without post-operative ketosis. * $P < 0.05$.

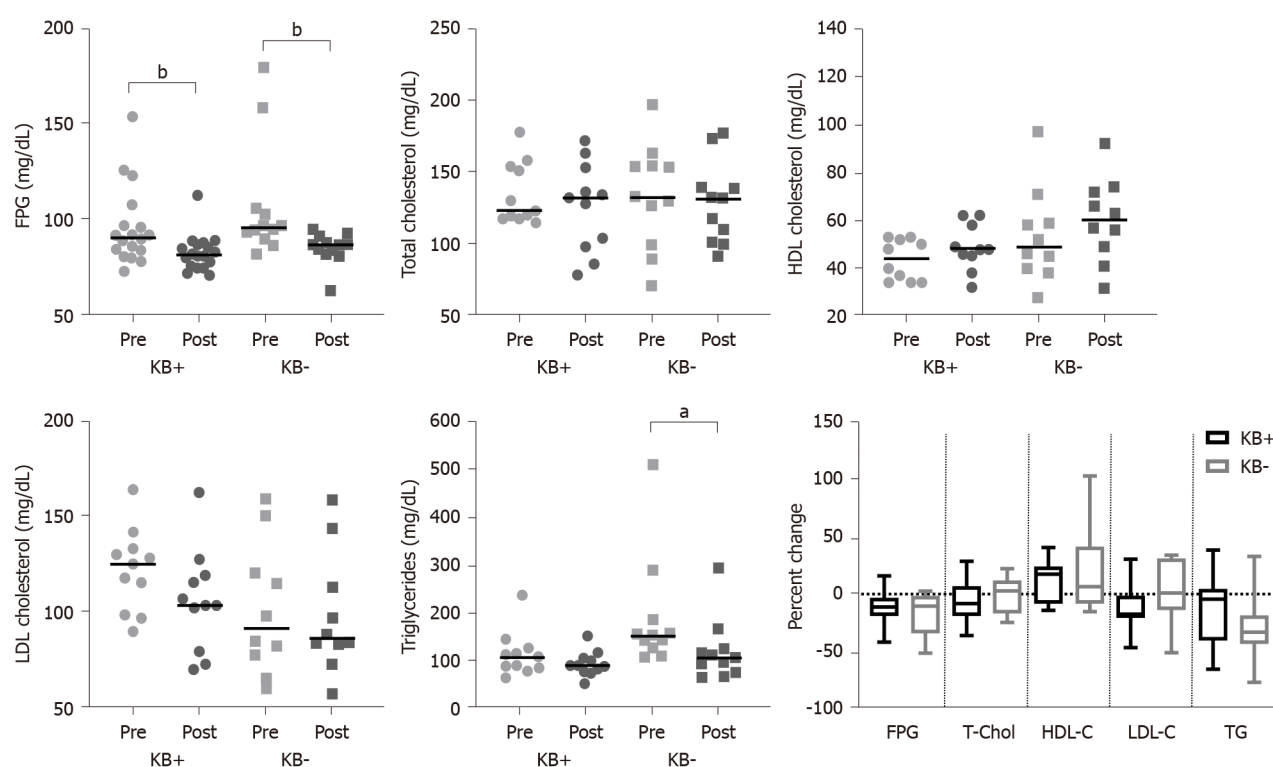


Figure 2 Changes in metabolic parameters at 6 mo after surgery. FPG: Fasting plasma glucose; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; KB+: Patients with post-operative ketosis; KB-: Patients without post-operative ketosis. * $P < 0.05$. ^a $P < 0.01$.

unlikely that some patients ingested relatively high amounts of carbohydrates in the first postoperative weeks. On the other hand, it is possible that some greatly restricted carbohydrates to allow adequate protein intake. Deriving energy from proteins is an expensive process for the body, which may lead to calorie consumption and greater WL as compared with diets that rely on carbohydrates as the main energy source[31-33]. In fact, during carbohydrate restriction most of the body's glucose requirements are satisfied by gluconeogenesis from amino acids, a process that requires approximately 400-600 kcal/d[32]. In other settings, several studies have demonstrated that very-low carbohydrate ketogenic diets are associated with greater WL as compared to other dietary regimens[34-36]. Diet composition in the first postoperative weeks might influence subsequent WL even in patients undergoing BMS. Other potential limitations are the relatively small sample size and the availability of data on WL at 12 mo only for a subgroup of patients, which might explain the lack of a statistically significant between-group difference in WL at this timepoint. Finally, we did not formally assess the level of physical activity throughout the 12-month follow-up to detect differences that might influence WL. In general, changes in physical activity during the first 6 mo after BMS (*i.e.*, the timepoint for the assessment of the primary

outcome in this study) are small and unlikely to affect WL[37]. We cannot exclude that changes in physical activity during the following months influenced WL at 12 mo.

CONCLUSION

In conclusion, it is possible that both metabolic status and diet composition influenced KB production in our cohort. Urinary KBs are easy to measure, and could be an early predictor of WL after BMS. Increasing evidence indicates that nutritional ketosis may have several health benefits[2,22,38-49]. Our findings add to this knowledge, suggesting that patients who develop nutritional ketosis following BMS might have greater WL and better metabolic responses to BMS.

ARTICLE HIGHLIGHTS

Research background

Ketone bodies (KB) derived from free fatty acid (FFA) metabolism serve as energy substrates in conditions of reduced glucose availability, but also as metabolic regulators and signalling molecules. Bariatric metabolic surgery (BMS) involves a marked energy deficit that results in massive mobilization of FFAs from adipose tissue, resulting in the activation of ketogenesis. It is not known whether all subjects undergoing BMS become ketotic, and whether there is a relationship between ketogenic capacity and weight loss (WL) following BMS.

Research motivation

We hypothesized that subjects with reduced ketogenic capacity are poorer responders to BMS in terms of WL. Characterization of the relationship between ketogenic capacity and WL following BMS will help understand the metabolic actions of KB and find out whether KB could be used as a predictor of BMS-induced WL.

Research objectives

We assessed the relationship between KB production in the first weeks after BMS and WL at 6 mo. We also assessed the relationship of KB with metabolic parameters and WL at 12 mo.

Research methods

For this retrospective study, we analyzed data from 39 patients who underwent laparoscopic sleeve gastrectomy, had urinary KB measured within two months of surgery and a follow-up of at least 6 mo. KB production was assessed by the presence of acetoacetic acid in urine using an automated dipstick urinalysis. We compared patients who developed post-operative ketosis with those who did not. The relationship of WL at 6 mo with pre-operative anthropometrics, body composition and metabolic parameters, and with post-operative urinary KBs was studied using bivariate correlation analyses. Variables that were significantly correlated were included in a hierarchical multiple-regression analysis, while controlling for sex, age and BMI.

Research results

This was the first study to specifically assess the relationship of ketogenic capacity with weight and metabolic outcomes. Most, but not all patients (69.2%), developed ketosis after a mean of 46.0 ± 13.6 d from surgery. Patients with ketosis were significantly younger [42.9 (37.6; 50.7) years *vs* 51.9 (48.3; 59.9) years, $P = 0.018$] and had significantly lower pre-operative fasting plasma glucose [89.5 (82.5; 96.3) mg/dL *vs* 96.0 (91.0; 105.3) mg/dL, $P = 0.025$] and triglyceride levels [108.0 (84.5; 152.5) mg/dL *vs* 152.0 (124.0; 186.0) mg/dL, $P = 0.020$], but greater LDL cholesterol [121.0 ± 23.5 mg/dL *vs* 100.2 ± 33.9 mg/dL, $P = 0.045$]. WL at 6 mo was significantly greater in patients who had developed post-operative ketosis ($27.5\% \pm 5.1\%$ *vs* $23.8\% \pm 4.3\%$ in the groups with and without ketosis, respectively; $P = 0.035$). At hierarchical multiple regression, urinary KBs and male sex emerged as significant predictors of WL at 6 mo.

Research conclusions

In keeping with the growing body of evidence indicating that nutritional ketosis has

several health benefits, our findings suggest that patients who develop nutritional ketosis following BMS might have greater WL and better metabolic responses to BMS.

Research perspectives

Our findings should be considered hypothesis-generating. Further research is needed to confirm these data in larger populations, and to assess the relationship between ketogenic capacity and metabolic responses to BMS with more sophisticated techniques.

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