International Journal of Modern Medicine
VOLUME03 ISSUE11
PUBLISHED DATE: - 12-11-2024
DOI: https://doi.org/10.55640/ijmm-03-11-04
Page 18-24
eISSN: 2156-5198 pISSN: 2156-518X

RESEARCH ARTICLE

FEATURES OF MANIFESTATION OF NONALCOHOLIC STEATOHEPATITIS IN OBESE PATIENTS AFTER LAPAROSCOPIC SLEEVE GASTRECTOMY

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Abstract: The state of energy starvation is the main phenomenon of the early postoperative period of bariatric surgery. All organs and systems of the body undergo such changes. Under normal physiological conditions, with the development of energy hunger, there is an excitation of metabolic centres in the hypothalamic-pituitary system of the brain. Transmitted impulses from chemoreceptor cells increase lipolysis, which ultimately leads to the mobilisation of large amounts of fatty acids from the fat depot to the liver. Excessively high concentrations of ketone bodies due to rapid weight loss are accompanied by the development of ketonemia, the severity of which depends not only on the compensatory capabilities of the body but also on the condition of the liver. Ketonemia is one of the common side effects reported by patients after bariatric surgery. Despite this, the evidence for the incidence of ketonemia after various bariatric surgeries and the mechanism of the development of this phenomenon is very limited. In this regard, this scientific article is devoted to the features of the manifestation of ketonemic syndrome in obese patients after the most popular type of bariatric surgery - laparoscopic longitudinal resection of the stomach.

Key words: Obesity, bariatric surgery, longitudinal resection of the stomach, postoperative complications, ketonemic syndrome.

INTRODUCTION

The frequency of bariatric surgeries worldwide has increased significantly in recent decades. So, 10 years ago, about 500 thousand bariatric surgeries were performed, today, this figure has increased tenfold [1].

In the perioperative and early postoperative periods, the surgeon will closely monitor surgical complications such as anastomosis failure, deep vein thrombosis, and infection. An experienced nutritionist, as a rule, helps at the beginning of the meal and its gradual passage. Going forward, regular follow-up with the surgeon, including eventually annual lifelong follow-up, is important to assess success in weight loss and consolidate necessary lifestyle changes [2].

Bariatric surgery leads to a significant improvement in glucose homeostasis and type 2 diabetes [3]. Bariatric surgery can improve dyslipidemia by altering diet, various endocrine and inflammatory factors, bile acid metabolism, and possibly even the gut microbiome [4].

Ketonemia is one of the common side effects reported by patients after bariatric surgery [5].

Despite this, the evidence for the incidence of ketonemia after various bariatric

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surgeries and the mechanism of the development of this phenomenon is very limited. Several studies that have examined this problem have provided information on the prevalence of ketonemia after bariatric surgery. For example, one study found that ketonemia affected 73% of patients undergoing Roux-en-Y gastric bypass [6], while another study reported ketonemia in 82% of patients undergoing laparoscopic Roux-en-Y gastric bypass grafting and 46% of patients undergoing laparoscopic regulated gastric banding [7].

It is known that an increase in the concentration of free fatty acids in the blood plasma, even in the presence of only overweight or obesity of the first degree, can lead to insulin resistance. Accordingly, the clinical significance of the above-described mechanisms of insulin resistance development can be characterised by the balance of a high level of free fatty acids in the blood plasma and the source of their production. In this case, such a mechanism is more possible if the patient has non-alcoholic steatohepatitis. In other words, the combination of obesity and non-alcoholic steatohepatitis can be considered the key to the development of insulin resistance and, in the future, type 2 diabetes mellitus. An important role in the development of insulin resistance in patients with nonalcoholic steatohepatitis should be assigned to muscle lipotoxicity on the part of free fatty acid metabolites. Muscle resistance to insulin is fully established even in non-obese individuals with non-alcoholic steatohepatitis if they have insulin resistance of adipose tissue.

In this regard, the purpose of our study was to study the features of the clinical and laboratory manifestation of ketonemic syndrome as a complication after bariatric surgery in patients with non-alcoholic fatty liver disease.

METHODS

The results of laparoscopic longitudinal resection of the stomach performed in 111 obese patients were analysed. Among them, 69% of patients were female. The mean age of the patients was 46.6±7.1 years; the mean body mass index was 38.7±6.98 kg/m2. On average, there were 2.16 concomitant diseases per patient. The most common concomitant diseases were pathologies of the gastrointestinal tract (32%), including non-alcoholic fatty liver disease. In second place were diseases of the endocrine system (19.3%), mainly in the form of type 2 diabetes mellitus and diseases of the cardiovascular system (18.8%), which was expressed by the presence of coronary heart disease, arterial hypertension and varicose veins of the lower extremities. All patients were divided into three groups: control – patients with obesity and without non-alcoholic fatty liver disease; the main one is patients with non-alcoholic steatohepatitis; and comparative – patients with non-alcoholic steatohepatitis.

The research methods were aimed at identifying the degree of development of the ketonemic syndrome and included the determination of ketone bodies in the patient's biological media: in the condensate of exhaled air, in the blood and in the urine.

Special research methods were included in the protocol developed by us, which was reviewed and approved by the Bioethics Committee of the Ministry of Health of the Republic of Uzbekistan. These studies were carried out as a baseline value in the postoperative period during the 5th, 10th, 30th, 90th, 180th and 365th days after surgery.

The significance of the differences between the samples, which were close to the norm in terms of the nature of the distribution, was established according to the parametric

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Student's test with a 95% reliable probability interval. The criterion for the statistical reliability of the conclusions obtained was considered to be the generally accepted in medicine value p<0.05.

RESULTS

Ketone excretion through exhaled air condensate in patients from the comparative and study groups corresponded on average to the second stage of the ketonemic syndrome (35.16±4.06 ppm), which was 5.9 times higher than the values of patients in the control group (p<0.01) – Table 1.

Table 1

Comparative dynamics of changes in the level of ketosis in exhaled air condensate (ppm) after laparoscopic longitudinal resection of the stomach

DYNAMICS	GROUPS OF PATIENTS					
	Control		Comparative		Main	
	M	m	M	m	M	m
Before surgery	0,31	0,03	2,18	0,69	8,12	2,15
5-day	0,35	0,01	13,99	2,18*	22,90	5,29*
10- day	0,41	0,09	48,91	6,08*	58,29	7,83*
1-month	21,82	0,09*	55,13	8,19*	68,90	8,91*
3 -month	12,29	0,12*	27,63	4,83*	50,71	6,38*
6-month	0,28	0,08	12,25	2,59*	32,38	4,51*
12--month	0,26	0,05	11,94	0,05*	18,91	3,99*

***p<0.05 – significantly to the indicator of the preoperative period**

In the patients of the comparative group, as early as on the 5th day after laparoscopic longitudinal resection of the stomach, there was a 6.4-fold increase in ketosis in the condensate of exhaled air compared to the preoperative period (p<0.05), while in the patients of the study group, there was a 2.8-fold increase (p<0.05), which was apparently due to the presence of initial high values of this parameter in the patients of this group.

In the subsequent terms of the study, the patients of the comparative group showed a progressive increase in ketosis in the condensate of exhaled air, which reached a peak value in 1 month after surgery (p<0.05), corresponding to the third stage of the ketonemic syndrome. At the same time, on the 10th day and 3 months after surgery, the level of ketosis in the condensate of exhaled air was already equal to the second stage of physiological bariatric ketonemic syndrome.

6-12 months after surgery, checking the level of ketosis in the exhaled air condensate showed the presence of values corresponding to the first stage of ketonemic syndrome. In general, in the patients of the comparative group, in the early postoperative period, ketone excretion through the condensate of exhaled air averaged 39.34±1.45 ppm, which corresponded to the second stage of ketonemic syndrome, and in the long-term period, this indicator averaged 17.27±2.49 ppm, which corresponded to the first stage of ketonemic syndrome.

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In the patients of the main group, already on the 10th day after laparoscopic longitudinal resection of the stomach, the level of ketosis in the condensate of the excreted air reached the level of the third and even the fourth stage of the development of ketonemic syndrome, and 1 month after surgery - exclusively the fourth stage of this pathological process. Three months after laparoscopic longitudinal resection of the stomach, the studied value decreased to the level of the third stage of the development of the ketonemic syndrome and, in subsequent terms – to the level of the second and first stages. In general, in the patients of the study group, in the early stages after surgery, ketone excretion through the condensate of exhaled air was 50.03±7.34 ppm, which corresponded to the third stage of ketonemic syndrome, and in the separated period, this indicator was equal to 34.0±4.96 ppm, which corresponded to the second stage of ketonemic syndrome.

Thus, in contrast to the patients of the comparative group, in the case of non-alcoholic steatohepatitis (the main group of patients), the release of ketones through the condensate of exhaled air was characterised by higher values with the achievement of a severe stage of the ketonemic syndrome.

In patients of the comparative and study groups after laparoscopic longitudinal resection of the stomach, the mean level of ketonemia was 1.87±0.24 mmol/L and 2.99±0.43 mmol/L, respectively. In the early stages after laparoscopic longitudinal resection of the stomach, the mean level of ketonemia in the patients of the comparative group was 2.32±0.28 mmol/L, which corresponded to the second stage of the ketonemic syndrome, and in the patients of the study group - 4.06±0.6 mmol/L, which corresponded to the third stage of the ketonemic syndrome. In the long term, after laparoscopic longitudinal resection of the stomach, the average level of ketonemia in the patients of the comparative group was 1.43±0.19 mmol/L, which corresponded to the first stage of the ketonemic syndrome, and in the patients of the study group - 1.92±0.26 mmol/L, which corresponded to the second stage of the ketonemic syndrome (Table 2).

Table 2

Comparative dynamics of changes in the level of ketone bodies in the blood serum (mmol/l) after laparoscopic longitudinal resection of the stomach

DYNAMICS	GROUPS OF PATIENTS					
	Control		Comparative		Main	
	M	m	M	m	M	m
Before surgery	0,15	0,06	0,31	0,07	0,43	0,05
5-day	0,35	0,09*	1,42	0,13*	1,08	0,13*
10- day	0,41	0,11*	2,52	0,31*	3,09	0,49*
1-month	1,48	0,13*	3,01	0,39*	8,00	1,18*
3 -month	1,02	0,08*	2,04	0,42*	3,03	0,48*
6-month	0,28	0,05*	1,13	0,09*	1,52	0,12*
12--month	0,26	0,03	1,11	0,07*	1,22	0,18*

***p<0.05 – significantly to the indicator of the preoperative period**

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The level of ketonuria in patients of the comparative and study groups reflected the general dynamics of patients with nonalcoholic fatty liver disease. As early as on the 5th day after laparoscopic longitudinal resection of the stomach, the level of ketonuria was noted to be 1.9 times higher than the reference values ($p<0.05$) in the patients of the comparative group and only 1.4 times ($p>0.05$) in the patients of the study group. The insignificant difference between the baseline value and day 5 of the postoperative period was due to the initial high level of ketonuria, which, although within the reference values, was nevertheless almost 2 times higher than in patients of the comparative group ($p<0.05$). However, already on the 10th day of the postoperative period, we revealed a significant difference ($p<0.05$) between the level of ketonuria among the patients of the comparative and study groups (Table 3).

Table 3

Comparative dynamics of changes in the level of ketone bodies in urine (mmol/l) after laparoscopic longitudinal resection of the stomach

DYNAMICS	GROUPS OF PATIENTS					
	Control		Comparative		Main	
	M	m	M	m	M	m
Before surgery	0,21	0,07	0,27	0,02	0,50	0,11
5-day	0,18	0,04	0,52	0,09*	0,68	0,18
10- day	0,23	0,03	0,85	0,17*	1,68	0,32*
1-month	0,55	0,07*	1,66	0,22*	2,32	0,49*
3 -month	0,57	0,09*	1,63	0,37*	1,41	0,29*
6-month	0,47	0,11*	0,81	0,18*	0,55	0,19
12--month	0,39	0,08*	0,55	0,17*	0,53	0,28

***p<0.05 – significantly to the indicator of the preoperative period**

In general, in patients of the comparative and study groups after laparoscopic longitudinal resection of the stomach, the mean level of ketonuria was 1.0±0.2 mmol/L and 1.2±0.29 mmol/L, respectively. An interesting fact is that in the patients of the comparative group, the average level of ketonuria in the early and remote periods after laparoscopic longitudinal resection of the stomach was stable (1.01±0.16 mmol/L and 1.0±0.24 mmol/L, respectively), while among the patients of the study group, the level of ketonuria in the early period after surgery, which was 1.56±0.33 mmol/L, corresponding to the second stage of the ketonemic syndrome. In the long term, after laparoscopic longitudinal resection of the stomach, the level of ketonuria in the patients of the study group was equal to 0.83±0.25 mmol/l, which corresponded to the first physiological bariatric stage of the ketonemic syndrome.

DISCUSSION

In humans, the rate of very low-density lipoprotein secretion increases linearly with an increase in intrahepatic triglyceride accumulation, but the export of very low-density liver lipoproteins is insufficient to

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normalise the liver triglyceride content in nonalcoholic fatty liver disease [8].

Under the condition of hyperproduction of very low-density lipoproteins in the liver, it is possible to reduce the level of cholesterol bound to high-density lipoproteins. This, in turn, culminates in the formation of low-density lipoprotein cholesterol molecules, which have a high density despite their relatively small size. Such changes are specific markers of the triad of both nonalcoholic steatohepatitis and other insulin-resistant conditions [9].

Necrotic processes in the liver in nonalcoholic steatohepatitis may be stimulated due to low plasma adiponectin levels [10]. Low plasma levels of adiponectin contribute to the development of fatty liver and dysregulation of very low-density lipoproteins [11].

Studies by A. Gastaldelli et al. [12] showed the possibility of increasing the concentration of the hormone adiponectin in blood plasma with the help of thiazolidine, which in turn led to an improvement in both metabolic and histological changes in the liver. This process proceeded due to increased control of liver lipogenesis by adiponectin.

There is considerable interest in understanding the role of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the development of cardiovascular disease [13].

The prerequisites for this interest were the conclusions that there is a close relationship between nonalcoholic steatohepatitis and type 2 diabetes mellitus, metabolic syndrome, and the development of cardiovascular diseases [14].

CONCLUSION

After laparoscopic longitudinal resection of the stomach, non-alcoholic steatohepatitis in obese patients is manifested by hyperketonemia (from 0.43 mmol/l to 4.06 mmol/l), hyperketonuria (from 0.5 mmol/l to 1.56 mmol/l) and a high concentration of ketosis in the condensate of exhaled air (8.5 times), which leads to the development of a pronounced ketonemic syndrome already in the early stages of the postoperative period. All this may indicate the ongoing active reactions of lipolytic action on the functional state of the liver already in the early stages after laparoscopic longitudinal resection of the stomach.

Conflict of interest – none

Study funding – not provided

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