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STATE OF DIFFERENT LINKS OF HORMONAL-METABOLIC CHANGES IN PATIENTS WITH METABOLIC SYNDROME AND OBESITY

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The article is devoted to the problem of surgical treatment of patients with metabolic syndrome and obesity. Research methods: general clinical, anthropometric, laboratory, morphological; mathematical and statistical. It has been established that in order to select the optimal surgical tactics and predict complications in the postoperative period, it is necessary to additionally determine the insulin level. It has been proven that metabolic syndrome and obesity negatively affect the state of carbohydrate metabolism, production of inflammatory cytokines and cortisol. Assessment of changes in the structure of comorbidities (hypertension, joint pain) had no significant differences and in all groups was positive. The analysis of complications in all groups showed the absence of significant problems during the postoperative period, and there are minor differences of no discussion interest.

Key words: obesity, insulin resistance, metabolic disorders, metabolic syndrome, surgical treatment, diabetes mellitus.

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СТАН РІЗНИХ ЗВ'ЯЗКІВ ГОРМОНАЛЬНО-МЕТАБОЛІЧНИХ ЗМІН У ПАЦІЄНТІВ З МЕТАБОЛІЧНИМ СИНДРОМОМ ТА ОЖИРІННЯМ

Стаття присвячена проблемі хірургічного лікування пацієнтів з метаболічним синдромом та ожирінням. Методи дослідження: загальноклінічні, антропометричні, лабораторні, морфологічні; математично-статистичні. Встановлено, що для вибору оптимальної хірумилицяргічної тактики та прогнозування ускладнень у післяопераційному періоді необхідно додатково визначати рівень інсуліну. Доведено, що метаболічний синдром та ожиріння негативно впливають на стан вуглеводного обміну, продукцію запальних цитокінів та кортизолу. Результати зміни показників супутніх захворювань (артеріальна гіпертензія, біль у суглобах) не мали різких відмінностей і в усіх респондентів мали позитивну динаміку. Аналіз ускладнень в усіх групах вказав на відсутність видимих проблем у післяопераційний період, відтак незначні відмінності не мають дискусійного підґрунтя.

Ключові слова: ожиріння, інсулінорезистентність, метаболічні порушення, метаболічний синдром, хірургічне лікування, цукровий діабет.

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As early as in the twentieth century, scientists concluded and later confirmed that obesity and insulin resistance create the pathophysiological foundation of further metabolic disorders with different clinical manifestations, first as single disorders (for example, coronary heart disease or hypertension), and then as metabolic expansion of almost all organs and tissues implemented in the form of numerous diseases that answer the description of Pickwick syndrome [4]. Therefore, the study of metabolic features of the

body in patients with surgical profile, timely diagnosis of metabolic syndrome, obesity, their impact on the course of surgical diseases, determining the presence or absence of weight loss on the pathological range of pathophysiological and biochemical changes already formed is extremely important [5].

At the current level of development of medical science, it is proven that only surgical treatment of metabolic syndrome provides long-term, reliable, compliant results [9, 10, 11]. The analysis of mortality in patients with type 2 diabetes showed that it was 92 % lower after gastric bypass surgery than with conservative therapy, and the elimination of hyperinsulinemia and insulin resistance significantly reduced the risk of oncogenesis and premature mortality [8].

Metabolic syndrome X, as the name implies, reflects a complex of metabolic changes in organs and tissues of the whole organism, and not an isolated organ. First, it is worth mentioning the physiological role of insulin, which plays an important role in the body's metabolic process. Normally, glucose utilization depends on both the level of insulin in the body and the concentration of glucose in the blood. With the development of hyperglycemia, there is a compensatory non-oxidative consumption of glucose, while insulin increases its oxidation. That is, the clinical detection of hyperglycemia is not yet a risk factor for the development of carbohydrate disorders and diabetes [5]. With a corresponding increase in insulin production, all the negative effects of hyperglycemia are offset by its accelerated oxidation. That is why, now there is the focus not on blood glucose levels, but on insulin levels and insulin resistance index (HOMA-IR index) in the detection of carbohydrate metabolism disorders, as obtained experimental evidence of the importance of insulin concentration in ensuring tissue sensitivity. It has been established that insulin, as well as other hormones, can realize its biological effect only through the receptor apparatus of the cell. Therefore, it has been found that as we age, even with normal glucose and insulin production, adipocytes, especially as they increase in volume, develop receptor deficiency, which leads to the development of carbohydrate tolerance. After reducing fat mass (weight loss), insulin sensitivity is restored [7].

The purpose of the study was to consider the state of various links of hormonal and metabolic changes in patients with metabolic syndrome and obesity before and after restrictive bariatric surgery (by content of insulin, glucose, cortisol).

Materials and methods. The clinical part of the study consisted of examination and questionnaires of 809 patients (population cohort) of the surgical clinic at the Zaporizhzhia Medical Academy of Postgraduate Education, MOH of Ukraine, located on the basis of the Zaporizhzhia City Multidisciplinary Clinical Hospital 9, O.O. Shalimov National Institute of Surgery and Transplantation of the NAMS of Ukraine and patients who applied for outpatient counseling. The survey was carried out in accordance with the order of the MOH of Ukraine dated April 2, 2010 No. 297. These parameters were used as a criterion for selecting patients for the next in-depth study to diagnose or exclude metabolic syndrome (MS) and obesity (O).

The survey was performed in the mode of continuous screening by random sampling. That is, all patients who were treated in the hospital, when performing a “slice of one day” were performed anthropometric examinations (measuring height, weight, abdomen) to detect obesity in general and visceral obesity in particular. Blood pressure parameters blood glucose level was evaluated. After performing bariatric surgery, patients underwent re-examination of glucose, insulin, HOMA-IR index after 10 – 12 months (group 3). Depending on the obesity degree (I, II or III), it was also divided into subgroups – respectively 3A, 3B, 3C.

Based on the above data, is both scientific and practical interest in studying the state of insulin production in obese patients, taking into account the initial body weight and postoperative weight loss, as well as identifying features of glucose utilization, determining the insulin resistance index, comparing the results with the state of the receptor apparatus of adipocytes (according to immunohistochemical study).

In order to solve these issues, group 1 (comparison group) of 20 patients without MS and O was formed. The second group (group 2) was formed of 40 patients with MS and O and was divided into subgroups: 2A – patients with grade I obesity, 2B – patients with grade II obesity and 2C – patients with grade III obesity, their blood content was studied for checking insulin, glucose, HOMA-IR index before restrictive bariatric surgery. At the same time, patients with a clinical diagnosis of diabetes were excluded from the study. After performing ofriatric surgery, patients underwent re-examination of glucose, insulin, HOMA-IR index after 10–12 months (group 3). Depending on the degree of obesity (I, II or III), it was also divided into subgroups – respectively, 3A, 3B, 3C.

All patients were divided into groups according to their body mass index. The first group included 60 patients with the body mass index (BMI) of 20.0–24.9, i.e. with normal weight; to the second – 59 patients with excess body weight (BMI 25.0–29.9); to the third – 117 patients with obesity of grade I (BMI

30.0–34.9); to the fourth – 51 patients with grade II obesity (BMI 35.0–39.9); to the fifth – 44 patients with grade III obesity, i.e. with morbid obesity, in which the BMI exceeded 40.0. Among the surveyed patients, there were men – 65, women – 266. The mean age in the group with obesity grade I – 47.3 years; grade II – 47.7 years; grade III – 51.0 years).

Materials and methods. Life history and disease of all patients was studied, anthropometric, general clinical and laboratory-instrumental studies were performed. The circumference of the abdomen was measured at the level of the navel with a centimeter tape. All patients were examined before and after surgery. By type of surgery, they were distributed as follows: gastroplication, laparoscopic longitudinal resection of the stomach (LLRS), others. Patients were observed for one to three years. Insulin and glucose were determined by standard methods. To assess insulin resistance, the HOMA-IR index was calculated by the formula: HOMA-IR=fasting glucose (mmol/l)×fasting insulin (μOd/ml)/22.5. The normative index was less than 2.7.

Digital data analysis was performed using the program "Statistic Soft 6.0". The obtained results were presented in the form of M±m values. The mean values in the groups were compared using non-parametric Mann-Whitney U-test.

Results of the study and their discussion. Detailed examination shows that in the first degree of obesity, the glucose level slightly exceeded the upper threshold in only one patient before surgery. In the postoperative period, all indicators corresponded to the median value. Similar data were observed in second-degree obesity. Only one patient had a small excess of the upper threshold before surgery, and in the postoperative period, all indicators corresponded to the median. Only at the obesity of the III degree, insignificant excess of the top standard value is revealed in three patients. After the surgery, all indicators were normal. That is, neither biochemical nor clinically significant impairment of glucose levels in patients with severe obesity was observed.

The results of the research are presented in table 1.

Table 1

Data on carbohydrate metabolism parameters before and after restrictive operations

Group	Insulin, μIU / ml)	Glucose, mmol/l	Index HOMA-IR
Group 1 *n*=20	8.48±0.74	4.62±0.17	1.72± 0.16
Group 2 *n*=40	25.31±4.31	4.80±0.14	5.54±0.99
Group 2A *n*=6	12.69±0.96	4.71±0.33	2.65±0.27
Group 2B *n*=10	16.14±1.61	4.83±0.25	3.55±0.50
Group 2C *n*=24	32.28±6.82	4.82±0.20	7.10±1.57
Group 3 *n*=39	7.43±0.69	3.73±0.12	1.26±0.14
Group 3A *n*=5	6.31±0.76	3.71±0.35	1.02±0.13
Group 3B *n*=10	6.14±0.60	3.59±0.27	0.97±0.11
Group 3C *n*=24	8.21±1.06	3.79±0.15	1.44±0.21

Given the data the mean glucose, indices in all groups and in patients with normal body weight and in patients with MS and O both before and after surgery did not exceed the mean physiological limits. However, it should be borne in mind that the diagnosis of "diabetes" was the exclusion criterion and patients with such a diagnosis formed a special group for further observation.

It was found that the average insulin level in obese patients was 3.0 times higher than in the comparison group ($p<0.001$). Nevertheless, at the same time, this indicator only slightly exceeded the upper limit of the physiological norm.

The study of insulin levels at different degrees of obesity indicates certain features. If the level of glucose almost met the norm even in severe obesity, the level of insulin in the group of obese patients differed. In mild and moderate levels of obesity, no changes in insulin levels were observed. Moreover, with severe obesity, the average insulin level increased by 3.8 times ($P<0.001$). However, these figures are not a verdict for patients with morbid obesity.

Laboratory-confirmed hyperinsulinemia was registered in 20 % of patients, with an average insulin level of 70.15 μIU/ml, which is 2.8 times higher than the upper limit of the allowable norm and 8.3 times higher than the comparison group. In the remaining 80 % of patients, neither hyperinsulinemia nor hyperglycemia was recorded. However, due to the fact that insulin resistance begins to develop with normal insulin and glucose levels, but their ratio is disturbed, and only when decompensation is confirmed hyperglycemia and hyperinsulinemia, the indicator (HOMA-IR index) was determined, which reflects the state of insulin resistance.

In patients with obesity in the preoperative period, even with the normative values of glucose and insulin, the average HOMA-IR index (5.54) was by 3.2 times higher than in the comparison group. In the group with first-degree obesity, the index of insulin resistance was increased by 1.5 times (P<0.01), with second-degree obesity – by 2.1 times (P<0.005), and with third-degree obesity – by 4.1 time (P≤0.001). At the same time, normal values were registered only in 3 patients out of 40 (namely in 7.5 %), and in other cases (92.5 %) insulin resistance was recorded. However, the "normality" of these indicators is a big question. The low HOMA-IR index figures are due to very low insulin levels (0.2 and 0.4 μIU/ml) in two out of three cases, which essentially indicates depletion of the insular apparatus of the pancreas that means undiagnosed diabetes.

According to existing data, low insulin level causes the development of insulin resistance as well as high one. Thus, insulin resistance is not confirmed in only one case out of 40, namely in 2.5 %. This may be due to the body's good compensatory capacity, but it is also possible that this condition is temporary and later transforms into IR.

The obtained data once again confirm that it is not possible to focus only on the absolute values of glucose and/or insulin in the clinical and biochemical assessment of the patient's condition. Taking into account only these indicators, without determining their ratio, characteristic of insulin resistance, it leads to false negative results and lack of diagnosis of insulin resistance, which creates grounds for the formation of the basis for the development of subsequent IR-induced pathological conditions, up to carcinogenesis.

After bariatric surgery in a state of carbohydrate metabolism, there is a clear positive dynamic. The average insulin level decreased by 3.4 times (p<0.001). No cases of hyperinsulinemia have been reported. Glucose levels were 22.3 % lower than in the preoperative period. In addition, no case of hyperglycemia, even with grade III obesity, was detected.

However, the most convincing argument in favor of the positive effect of bariatric surgery is the dynamics of the insulin resistance index.

Determination of the HOMA-IR insulin resistance index convincingly demonstrated the positive effect of restrictive bariatric operations on the state of carbohydrate metabolism, on the desensitization of insulin cell receptors, on the restoration of insulin sensitivity. Thus, in the postoperative period, the average insulin resistance (HOMA-IR) decreased by 4.4 times (P<0.001). Moreover, its normalization was recorded in almost all patients. The HOMA-IR index exceeded the normative values only in two of 39 patients (5.2 % of cases). But at the same time, it decreased by 4.8 times (from 16.65 to 3.47) and 3.4 times (from 16.64 to 4.91) in these same patients.

Individual paired analysis before and after surgery in each patient also indicates a positive effect of restrictive surgery on the phenomenon of insulin resistance at any degree of obesity and the possibility of its correction by surgery.

It is known that the pathogenetic effect of bariatric surgery is to reduce the amount of fat mass and, accordingly, reduce the mechanical and aggressive metabolic effects on the patient's body. Therefore, the analysis of changes in the state of carbohydrate metabolism have been conducted in the work depending on the severity of weight loss.

Maximum changes and normalization of insulin resistance have been shown to be closely related to normalization of body mass index. It is not weight loss in kilograms that is most important for the restoration of carbohydrate metabolism, but the maximum normalization of body mass index. Thus, in patient A., history No. 2231, body mass index after surgery became 22.3 with postoperative weight loss of 12 kg and all indices were fully normal. The same was observed in patient K., history No. 2554, body mass index was 44.6 with the weight loss of 74 kg after surgery, carbohydrate metabolism improved significantly, but the HOMA-IR index did not return to normal and was 4.91 (it was 16.64 before surgery).

Genetic determination of the impaired insulin response to hyperglycosemia, its implementation requires external action, which triggers changes in hormonal homeostasis and long-term existence causes metabolic instability with clinical manifestations. This may be a purely external, even short-term effect, but with pronounced fluctuations in the hormonal background; less significant, but long-lasting actions; a combination of any small action with age-related changes or additional pathological processes. Therefore, it is necessary to study separately, first of all, the contra-insular hormone cortisol, in order to determine the genesis of insulin resistance in MS and O.

Chronic stress is realized in stress-induced obesity, hyperglycemia and AH. Less is known about what further changes in cortisol are observed in long-term and progressive obesity. Since the effect of cortisol depends entirely on the level and duration of its production, it is necessary to study the content of cortisol in patients with MS and O of varying severity. Data on the level of cortisol in the examined patients are given in table 2.

Table 2

Cortisol content in patients with metabolic syndrome and obesity, nmol/l

Categories of patients	Amount of patients	Cortisol indicator	The degree of authenticity
Comparison group	23	621.65±58.34	
Before surgery			
Patients with MS and O	40	406.38±30.33	p≤0.001
Patients with I degree MS and O	6	373.90±57.20	p≤0.005
Patients with II degree MS and O	10	408.24±35,19	p≤0.005
Patients with III degree MS and O	24	413.73±46,97	p≤0.005
After surgery			
Patients with MS and O	40	688.88±42.25	p – nd
Patients with I degree MS and O	6	577.41±71.91	p – nd; p^1≤0.02
Patients with II degree MS and O	10	704.71±90.72	p – nd; p^1≤0.005
Patients with III degree MS and O	24	710.15±57.12	p – nd; p^1≤0.0001

p – with the comparison group; p^1 – between groups before and after surgery.

The results of the study indicate that the mean concentration of cortisol is in the range of mean physiological parameters in the comparison group, namely answers normal values. Contrary to expectations, the average cortisol content was reduced by 34.6 % (p≤0.001) in patients with MS and O. Moreover, the content of cortisol is significantly (p≤0.003756, p≤0.001846, p≤0.004024) lower at each degree of obesity (with obesity of the first degree – by 39.9 %, with obesity of the second degree – by 34.3 %, with obesity of III degree – by 33.4 %) than in the comparison group. At the same time, no significant difference between the level of cortisol in the blood in obesity of varying severity was found (p>0.05), although there is a tendency to increase the content of cortisol as obesity progresses.

After surgery, with a steady reduction in body weight, cortisol levels increased by 69.5 %, which even exceeded the physiological norm by 2.8 %. The obtained data allow to make assumptions about the presence of "fatigue" or the development of refractoriness of the cortisol-producing apparatus of the adrenal glands in metabolic syndrome and obesity and the possibility of restoring its reactive state on the background of long-term weight loss.

Comparative analysis of different obesity degrees shows that the lower the primary degree of obesity is, the easier it is to restore cortisol-producing function of the adrenal glands. Thus, cortisol levels are fully restored and do not exceed the upper limit of the physiological norm with first-degree obesity after restrictive surgery and a steady (during the year) weight loss. With moderate obesity after surgery, cortisol levels exceeded the upper range of normal values by 5.2 % and the indicators of the comparison group – by 13.4 %. In severe obesity (grade III) in the remote postoperative period, the cortisol content exceeded the upper limit of normal by 6.0 % and the indices of the comparison group – by 14.2 %.

Thus, the results of the cortisol content study give grounds to assert the negative effect of MS and OJ on cortisol-producing function of the adrenal glands; the fundamental possibility of restoring the physiological production of cortisol, even with long-standing obesity; positive effect of bariatric surgery on the functional state of the adrenal glands due to weight loss. A comparative analysis of the results obtained at different degrees of obesity shows that the lower the primary degree of obesity, the easier it is to restore cortisol-producing function of the adrenal glands.

Determining the characteristics of the carbohydrate status of patients proved that bariatric surgery really affects the level of insulin in the blood, restores the sensitization of insulin receptors, which leads to the normalization of insulin resistance. Thus, the level of blood glucose in the preoperative period in patients of both groups did not differ significantly (4.92 mmol/l – group with gastroplication and 4.76 mmol/l – group with LLRS). There was a tendency to lower glucose levels in the postoperative period in both groups, but not probable. Moreover, in both pre- and postoperative periods, glucose levels did not exceed the normative physiological parameters. As for insulin, the situation is changing. In the preoperative examination, the mean insulin level in patients of both groups did not differ significantly and approached the upper limit of the norm (respectively, 25.22 μIU/ml in the group with gastroplication and 26.44 μIU/ml in the group with LLRS). In the postoperative period, there is a probable decrease in blood insulin: in the first group it decreased by 3.6 times, and in the second one – by 3.3 times.

After performing restrictive bariatric surgery, insulin resistance was completely normalized, reaching average physiological values, which indicates the restoration of the sensitivity of the receptor apparatus to insulin and reducing the risk of mortal complications. Assessment of changes in the structure of comorbidities (hypertension, joint pain) had no significant differences and in both groups was positive.

The analysis of complications in both groups showed the absence of significant problems during the postoperative period, and there are minor differences of no discussion interest.

In the last decade unconditional preference is given to surgical treatment of metabolic syndrome. During this period was created a separate department of "metabolic surgery", since 1991 was published a specialized surgical journal "Obesity Surgery". All this due to the fact that at the present stage of development medical science only surgical treatment of MS gives long-term, reliable, compliant results [6, 7, 8]. Thus, conducted by some authors [10, 11] analysis of mortality in patients with diabetes type 2 showed that when gastric bypass surgery mortality was 92 % lower, than in conservative therapy, and the elimination of hyperinsulinemia and insulin resistance allowed significantly reduce the risk of oncogenesis and premature mortality. Our work logically fits into modern research on the problem described in the article, is a practical embodiment of the latest ideas in medicine in bariatric surgery of world medical practice. This is consistent with numerous current data on the reality of treating type 2 diabetes with bariatric surgery [2].

Conclusions

Performing restrictive bariatric operations that reduce the patient's body weight leads to a reduction and elimination of quantitative and qualitative disorders of pro-inflammatory cytokine production, which reflects a decrease in the intensity or cessation of inflammatory and destructive processes that develop in patients with MS and O. Therefore, we can draw the following conclusions on the basis of the above:

1. When assessing the carbohydrate status of patients with MS and O, as well as elderly patients, it is necessary to focus not on glucose indicators, but to determine one-stage glucose, insulin and HOMA-IR index. Only the index of insulin resistance makes it possible to exclude the presence of carbohydrate disorders characteristic of this pathology in the elderly group and in people with MS and O.

2. Normalization and positive dynamics in the state of insulin resistance are closely related to the normalization of body mass index, which can be optimized during restrictive bariatric surgery. 3. Metabolic syndrome and obesity adversely affect the cortisol-producing function of the adrenal glands, creating conditions for reducing its function. Weight loss achieved through bariatric surgery helps to restore the physiological production of cortisol.

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