ОРИГИНАЛЬНАЯ СТАТЬЯ

THE USE OF A VITAMIN-MINERAL COMPLEX IN THE COMBINED THERAPY OF PATIENTS WITH OBESITY AND TYPE 2 DIABETES MELLITUS: A CLINICAL TRIAL

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ABSTRACT. Low caloric diet is used in the complex treatment of patients with diabetes mellitus and obesity. However, the reduced caloric food can inadvertently lead to decreased intake of micronutrients. The main goal of the research was to assess the necessity and effectiveness of the vitamin-mineral complex in the treatment of type 2 diabetes with obesity.

Methods: 80 females suffering from type 2 diabetes and obesity, ranging from 40 to 65 years old participated in the study. The total patients were divided into two groups, each containing 40 patients. All patients were given a personalized diet and 1000mg of metformin every day. The experimental group, besides that, received vitamin-mineral complex. The biochemical analysis of the blood, composition of the body, and the complaint on micronutrient deficiency were taken before the experiment and after 14 days of the therapy.

Results: Supplementation of the vitamin-mineral complex was associated with higher blood serum levels of vitamins B_6, B_{12}, B_9, C, D, potassium, calcium, magnesium and zinc, and lower levels of glucose. Clinical manifestations, associated with micronutrient deficiency, were significantly decreased in patients who were given vitamin-mineral complex. All these changes were valid both in relation to the initial level in the study group and to the indicators after treatment in the control group.

Conclusion: Micronutrient supplements may be a very important part of the combined therapy of patients with diabetes mellitus and obesity.

KEYWORDS: nutrition, micronutrients, personalised diet therapy, supplements.

INTRODUCTION

Diabetes is a rapidly increasing disease, with its global headcount reaching approximately 422 million adults (WHO | Global Report on Diabetes, 2017). Obesity is a key factor to cause type 2 diabetes, which has made it one of the most important medical and social problems in the world. Even worse, its prevalence in the past three decades has increased by almost 30–50% (Ng et al., 2014). Currently, obesity is considered not only as the most important risk factor for cardiovascular diseases and type 2 diabetes (according to the World Health Organization), overweight and obesity influence the development of type 2 diabetes mellitus by 44 – 57%, coronary heart disease by 17–23%, arterial hypertension by 17%, gallstone disease by 30%, osteoarthritis by 14% and malignant neoplasms by 11%) (James et al., 2015), but also for reproductive dysfunction and cancerous diseases (Ligibel et al., 2014; Shawe, 2014). It is worth remarking that almost half of the obese patients actually develop disorders of carbohydrate metabolism (Dreval' et al., 2010). Poor glycaemic and metabolic control in obese patients are the main causes, which lead to type 2 diabetes. The medical, social and economic significances are associated with its steadily increasing prevalence and corresponding complications (Dedov, 2012; Velazquez et al., 2018).

The patients with type 2 diabetes are treated with less caloric diet, but the same dietary plan is associated with less intake of micronutrients, which, in turn, results in worsening of diabetes (Damms-Machado et al., 2012). On the other hand, metformin, an essential hypoglycaemic drug, has also been

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associated with a decrease of several vitamins (B_{12}, B_9 and D) (Kos et al., 2012; Xu et al., 2013). In this way, the negative feedback loop is one of the culprits for deteriorating already stressed health condition of the patients.

The progression of type 2 diabetes can be induced and driven by a deficiency of a number of micronutrients.

Vitamins that affect diabetes and vice versa. According to several studies, a lack of vitamin D increases the risk of developing type 2 diabetes (Gupta et al., 2011; Vujosevic et al., 2014) and obesity (Muscogiuri et al., 2010). Obesity, in turn, increases the deficiency of vitamin D as it is distributed in higher magnitude in fatty tissue (Lapik et al., 2020), which may also indirectly decrease the level of vitamin B_{12} (Curic et al., 2018). Moreover, vitamin D is not only obtained from food but also those synthesized endogenously in the skin.

Thus, the main negative effect of the obesity is associated with the deposition of 25(OH)D and an increase in the catabolism of calcidiol in adipose tissue with the formation of inactive 24,25-dihydroxyvitamin D_3 (Blum et al., 2008). In addition, it was found that the concentration of leptin (which controls the biosynthesis of vitamin D) increases with overweight (MacDonald et al., 2008). Abdominal obesity and a lowered level of 25(OH)D are synergistic factors that increase the risk of insulin resistance (Kabadi et al., 2012). In a research conducted by Huang et al., in patients with type 2 diabetes, the degree of insulin resistance was found to be inversely proportional to 25(OH)D (Huang et al., 2013). In type 2 diabetes, chronic hyperglycaemia is accompanied by an increase in the rate of autoxidation of glucose, leading to an increase in the number of free radicals and the development of oxidative stress. This is considered as the main mechanism of β-cell damage, which accelerates the transition of insulin-independent diabetes to insulin-dependent (Evans et al., 2003).

In this regard, vitamins A, E, C and lipoic acid are helping in the prevention and treatment of type 2 diabetes as they possess antioxidant properties (Garcia-Bailo et al., 2011). A 2017 meta-analysis showed that vitamin C supplements help to reduce glycaemia and basal insulin secretion in patients with type 2 diabetes. However, no association was found with postprandial insulin levels and HbA1c concentrations. Also, no effect of ascorbic acid on carbohydrate metabolism was detected in patients without type 2 diabetes (Ashor et al., 2017). The mechanism of this phenomenon is not completely clear.

Vitamins of group B can improve the structural and functional states of peripheral nerves in type 2 diabetes (Strokov I.A. and Strokov K.I., 2009). In any type 2 diabetes mellitus, especially with prolonged course and in severe decompensation of the disease, the exchange of water-soluble vitamins (thiamine, pyridoxine, riboflavin, nicotinic and pantothenic acids) is disrupted (Kodentsova et al., 2000).

Macro and trace elements that affect diabetes and vice versa. It was found that chromium deficiency is accompanied by impaired glucose metabolism, lipid metabolism, a decrease in the number of insulin receptors and the development of insulin resistance (Ngala et al., 2018). Some studies have shown that an increased level of glucose in the blood serum enhances the elimination of chromium from the body that results in a decrease in its level in patients with type 2 diabetes (Cefalu et al., 2002). An increment of tissue sensitivity to insulin, a reduction in the level of glucose and lipids in blood serum, as well as glycated haemoglobin were observed in type 2 diabetes patients with an additional intake of chromium (Balk et al., 2007). However, along with this, there is evidence that this group of patients did not have a positive effect when taking supplements containing chromium (Landman et al., 2014).

Zinc is involved in secretion and storage of insulin (Jayawardena et al., 2012). The highest concentration of zinc is observed in beta cells of the pancreas in insulin-secreting granules (Chabosseau et al., 2016). During the process of storage of insulin, its dimers aggregate around two zinc atoms and form a less soluble hexamer – a storable form of insulin (Capdor et al., 2013; Shan et al., 2014; Li, 2014; Maruthur et al., 2015). Moreover, zinc is involved in the regulation of activity of the insulin receptor and insulin-signalling pathway (Wijesekara et al., 2009; Shan et al., 2014). Hyperglycaemia is accompanied by a decrement of zinc in patients with type 2 diabetes (Saharia et al., 2013). A decrease in insulin production and an increase in insulin resistance are observed with zinc deficiency, which ultimately escalates the risk of type 2 diabetes (Kazi et al., 2008; Saharia et al., 2013). A negative correlation was established between the levels of glycated haemoglobin and zinc in blood serum in this group of patients. But diabetes itself can disrupt zinc homeostasis in the body (Saharia et al., 2013).

In patients with type 2 diabetes, there is often a reduction in the concentration of zinc in plasma and

red blood cells whereas an increment is observed in the urine (Al-Timimi, 2014). Moreover, zinc absorption in the digestive tract is reduced in patients with type 2 diabetes (Jansen et al., 2012; Sinha et al., 2014). Several studies have shown a reduction in fasting glucose, serum insulin and glycosylated haemoglobin in patients with type 2 diabetes when supplements were taken (Oh et al., 2008; Parham et al., 2008). Jansen et al. have found in their study that serum zinc concentrations were significantly reduced in patients with diabetes as compared with the control group. Besides it, patients with type 2 diabetes treated with insulin had lower serum zinc levels as compared with patients without insulin therapy (Jansen et al., 2012). A 2017 meta-analysis showed that serum zinc concentration is significantly lower in patients with type 2 diabetes. According to the review, the increase in zinc intake (as diet therapy or the use of supplements) significantly improves glycaemic concentration since it reduces the concentration of HbA1c in the blood (de Carvalho et al., 2017). Many studies have shown that the additional intake of zinc-containing supplements in patients with type 2 diabetes helps to reduce the levels of glycaemia, glycated haemoglobin and prevents the progression of diabetic nephropathy (Oh et al., 2008; Jayawardena et al., 2012). The combined intake of zinc and chromium contributes to lowering not only basal and postprandial glycaemia but also total cholesterol and serum triglycerides in patients with type 2 diabetes (Gunasekara et al., 2011).

Several authors consider hypomagnesaemia as a serious predictor of type 2 diabetes (Everett et al., 2006; de Carvalho et al., 2017). It is involved in many intracellular processes, which are important for glucose metabolism. Several studies have found a decrease in serum magnesium concentrations in patients with impaired fasting glycaemia, impaired glucose tolerance and type 2 diabetes (Simmons et al., 2010; Liu et al., 2011; Lecube et al., 2012; Ferdousi et al., 2013). The opposite results were found in another study (Yu et al., 2012). Reason for decreased magnesium concentration is due to non-optimal glycaemic and metabolic control (Dasgupta et al., 2012). However, Mooren believes that the main mechanism for the development of hypomagnesaemia in impaired glucose metabolism involves a decrease in the reabsorption capacity of the kidneys as a result of exposure to hyperglycaemia.

In addition to it, glucosuria promotes hyperosmolar polyuria, which also reduces the ability of the renal tubules to reabsorb cations (Mooren, 2015). Anyway, a decrease in the intracellular concentration of magnesium disrupts the action of tyrosine kinase, which in turn contributes to the deteriorating insulin resistance (Barbagallo et al., 2007). There are studies, which have revealed an association of hypomagnesaemia with development of insulin resistance, progressive diabetic retinopathy and nephropathy (Barbagallo et al., 2007; Dasgupta et al., 2012). A negative correlation was established among the serum magnesium, glucose and glycated haemoglobin. A number of clinical studies have shown that a supplement of magnesium significantly reduces basal glycaemia, improves insulin sensitivity and plays an important role in the prevention of vascular complications in patients with type 2 diabetes (Lopez-Ridaura et al., 2004; Song et al., 2006; Shaikh et al., 2011).

In type 2 diabetes, levels of magnesium, calcium and potassium are decreased (Afridi et al., 2008). With the additional intake of potassium and magnesium, a hypotensive effect was noted in patients with type 2 diabetes and hypertension (Gilleran et al., 1996).

However, the significance of certain elements in diabetic patients has not been fully understood yet.

Table 1. Constituents of the vitamin-mineral complex

Component	Content (per day)	% from RDA (Norms…, 2009)[2]
Vitamin C	90 mg	100
Vitamin E	18 mg	120
Beta-carotene	2 mg	40
Vitamin B_6	6 mg	300
Vitamin B_1	2.4 mg	160
Vitamin B_2	1.5 mg	83
Vitamin B_{12}	1.5 µg	50
Nicotinamide	7.5 mg	38
Pantothenic acid	3 mg	60
Vitamin B_9	300 µg	75
Biotin	30 µg	60
Zinc	12 mg	100
Chromium	200 µg	400

For optimal status of vitamins and bioelements, patients are required to consume large portions of food products, which will inevitably lead to excess calorie intake and obesity. 90% of patients with type 2 diabetes have obesity with varying severity (Niswender, 2010). Regarding this issue, diet therapy is an indispensable component of the complex treatment in these patients. However, providing only a balanced diet meal restricts patient from receiving the necessary vitamins and elements due to the different bioavailability of micronutrients from different food. Therefore, the use of vitamin-mineral complexes (VMC) should be considered as an integral part of personalized diet therapy for type 2 diabetes as they help to reduce the risk of vascular complications, as the deficient of micronutrients exacerbates the course of diabetes and increase the risk of different complications, including cardiovascular complications (Tutelyan, 2009; Spirichev, 2011).

The aim of the study was to assess the importance of the use of micronutrient additives in the complex treatment of patients with diabetes mellitus.

MATERIAL AND METHODS

Research design. The research was a randomized controlled prospective trial. Upon admission to the clinic, subjects were randomly assigned to an experimental or control group.

80 females, ranging ages of 40 – 65 years old, who had been suffering from type 2 diabetes and obesity of grade I – II were included in the study. The experimental group had a pre-prandial glycaemic level of 7.2 ± 0.2 mmol/L, whereas it was 7.3 ± 0.3 mmol/L in the control group. Both the groups were given the same drug therapy – 1000 mg of metformin each day. Patients with severe cardiovascular, infectious, neurological and dermatological complications and patients taking insulin therapy or other glucose controlling therapy except as described above were exempted from taking part in the research. Those subjects who required a change in hypoglycaemic therapy during the study were excluded.

All the patients received a personalized diet (1700 ± 200 kcal/day). The energy value of the personalized diet for each patient was determined individually based on data obtained by indirect calorimetry using a physical activity coefficient of 1.4 (low physical activity), followed by a reduction in the calorie content of 500 kcal/day. All the patients continued to take 1000mg of metformin per day. Patients of the experimental group received VMC (constituents of VMC are in table 1) and were additionally given 71 mg of magnesium and 235 mg of potassium.

Before and after a 3-week course of therapy, serum biochemical parameters were monitored, as well as an assessment of body composition.

Body composition parameters (the content of fatty and lean mass, subcutaneous fat, total fluid) were evaluated by bioimpedanceometry using an "InBody 720" multi-frequency analyzer (Biospace, South Korea).

Glycated haemoglobin (HbA1c), pre-prandial and postprandial glycaemic levels were determined using a "One Touch ® Ultra ™" ("LifeScan", Inc., USA) glucometer and a "KONELAB Prime 60i" biochemistry analyser ("Thermo Scientific", Finland). Low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG), serum biochemical parameters (total cholesterol, alanine and aspartate aminotransferase (ALT, AST) activity, uric acid, urea, creatinine) were determined on a "KONELAB Prime 60i" biochemistry analyser ("Thermo Scientific", Finland). The immunoassay was used with the "Axis Homocysteine EIA" kit ("AXIS – SHIELD", Great Britain) to determine serum homocysteine (HC). The "Vitamin C kit" ("Immunodiagnostic AG", Germany) was used to photometrically determine serum vitamin C, the content of vitamin B_6 and folate in blood serum were identified by using the microbiological method using the "ID – Vit Vitamin B_6" and "ID – Vit Folic acid" ("Immunodiagnostic AG", Germany). The enzyme-linked immunosorbent assay (ELISA) was used with the "ID – Vit Vitamin B_{12}" ("Immunodiagnostic AG", Germany) and "25-Hydroxy Vitamin D EIA" ("Immunodiagnostic systems", UK) to determine the concentration of vitamin B_{12} and 25-hydroxyvitamin D in the blood serum. The concentration of bioelements (potassium, magnesium, calcium, zinc, phosphorus) in the blood serum was determined by colorimetric methods using the set "OJSC" ("Vital Development Corporation", Russia), on a "KONELAB Prime 60i" biochemistry analyser ("Thermo Scientific", Finland). The insulin and C-peptide were measured by using the immunoassay method with the help of standard materials: "Insulin ELISA" and "C-Peptide ELISA" ("DRG Instruments GmbH", Germany). Insulin resistance index (HOMA-IR) was calculated using the formula;

*index HOMA-IR = (fasting glycaemia (mmol/L) * insulin level)/22.5.*

The prevalence of clinical manifestations of micronutrient deficiencies was evaluated under the reference book of Spirichev (Spirichev VB, 2004).

The research was held in the Clinic of the Federal State Budgetary Institution of Science "Federal Research Centre of Nutrition, Biotechnology and Food Safety".

Ethical review. All the patients had given informed consent about the experiment. The research was approved by the Ethical Committee of Federal Research Centre of Nutrition, Biotechnology and Food Safety (protocol no. 17 (24.10.2012)). The study was carried out in accordance with the Helsinki Declaration of the World Medical Association (1964) and its subsequent editions. All the subjects voluntarily took part in the experiment after proper consent had been taken.

Statistical analysis. The sample size was not calculated before the investigation. The sample size was determined by the admission to the clinic of patients who meet the inclusion criteria and the absence of contraindications.

SPSS 21.0 ("IBM", USA) was used for statistical data processing. The results were presented as mean values with some standard error of the mean ($M \pm m$). Student *t*-test and one-way analysis of variance (ANOVA) were calculated to define the significance of differences in the samples. Spearman correlation analysis method was used for pairing relationship between two or more features. The significance level was determined to be significant at $p < 0.05$.

RESULTS

At the initial examination, patients with type 2 diabetes were optimally provided with vitamin C. Before treatment, the content of 25-hydroxyvitamin D in the blood serum of patients from the control group was slightly higher than in the experimental group. At the same time, marginal provision of vitamin D (11–20 ng/ml) was detected in 62% of the patients of the experimental group and 54% in the control group, which is probably due to a decrease in the endogenous synthesis of vitamin D in the skin in these patients due to an age-related reduction in the concentration of 7-dehydrocholesterol (age of patients ranged from 40 to 65 years).

Before starting the therapy, serum calcium levels in the patients were found to be below the optimal level, which is probably due to vitamin D deficiency in the very patients. At the initial inspection, the content of vitamin B_6 in the blood serum of patients from the control group was significantly higher than in the main one. Before the treatment, the content of vitamin B_{12} in the blood serum was found below the optimal level in 13% of the patients of the experimental group and 7% of the patients of the control group. The folate content in the blood serum of the patients of the experimental group and the control group was within the normal range. The concentration of potassium in the blood serum of patients of the experimental group was significantly lower than in the control group. In primary inspection, 17% of the patients of the experimental group had lower magnesium content in the blood serum than the recommended level.

This is probably due to a deficiency of vitamin B_6 (the serum content in patients with magnesium deficiency was below normal – 2.7 ± 0.8 μgm/L) which improves the absorption of magnesium in the gastrointestinal tract. The serum phosphorus content in patients of both groups before treatment was within normal values.

When assessing the micronutrient status in patients with type 2 diabetes and obesity, a decrease in the level of 1 micronutrient was observed in 40% of patients, a reduction in the levels of 2 micronutrients was noticed in 31% of patients and a decrement in the levels of 3 micronutrients – in 6% of patients.

A correlation analysis revealed a negative relationship between the level of vitamin C and glucose, HbA1c and insulin in blood serum ($r = –0.763$; $r = –0.409$; $r = –0.345$ respectively, $p < 0.05$), magnesium – with glucose and insulin ($r = –0.580$; $r = –0.339$ respectively, $p < 0.05$), zinc – with glucose, HbA1c and insulin ($r = –0.671$; $r = –0.221$; $r = = –0.253$ respectively, $p < 0.05$).

When evaluating the effectiveness of personalized therapy with the inclusion of VMC in patients of the experimental group, a decrease in the intensity and frequency of non-specific clinical manifestations of vitamin deficiency was observed. No significant positive dynamics was observed in the control group (Fig. 1).

A positive change was detected in the study of the body's composition during the process of therapy, which was manifested in the form of a decrease in body weight and obesity degree mainly. This was mainly due to the change in the fat mass (Table 2).

The dynamics of biochemical parameters of blood in patients with type 2 diabetes and obesity are presented in Table 3, which reflects the effects of treatment in both groups.

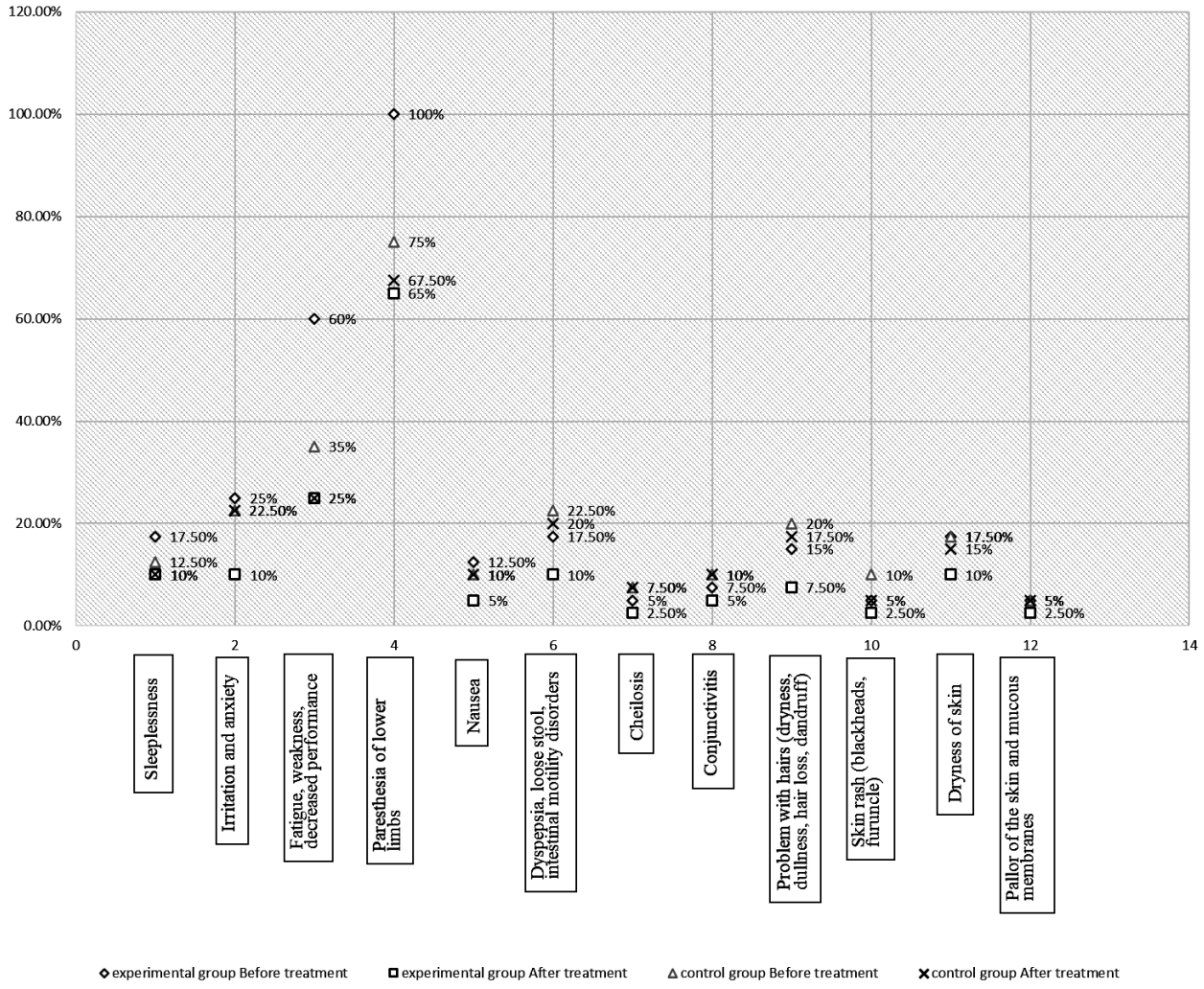

Fig. 1. *Dynamics of nonspecific clinical manifestations of vitamin deficiency in patients of the experimental group during treatment*

Table 2. ***Change in anthropometric parameters and indicators of body composition in patients with type 2 diabetes and obesity during therapy (M ± m)***

Indicator	The experimental group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Body weight, kg	97.8 ± 1.6	93.5 ± 1.5*	97.9 ± 1.9	93.7 ± 1.8*
BMI, kg/m²	37.5 ± 0.6	35.2 ± 0.6*	37.6 ± 0.6	35.5 ± 0.6*
Waist circumference (WC), cm	114.8 ± 2.4	109.2 ± 2.3*	114.9 ± 2.5	109.0 ± 2.4*
Thigh circumference (TC), cm	107.9 ± 1.8	104.0 ± 1.7*	108.4 ± 1.9	104.1 ± 1.7*
WC/TC, units	1.06 ± 0.04	1.05 ± 0.03*	1.06 ± 0.04	1.05 ± 0.02*
Fat mass, kg	47.3 ± 1.2	45.5 ± 1.1*	47.8 ± 1.3	45.6 ± 1.1*
Subcutaneous fat, kg	45.4 ± 0.7	44.0 ± 0.6*	45.7 ± 0.8	44.2 ± 0.7*
Lean body mass, kg	50.9 ± 0.7	50.4 ± 0.7	52.8 ± 1.1	52.2 ± 1.1
Visceral fat area, cm²	215.2 ± 5.4	197.7 ± 4.2*	211.6 ± 5.2	193.7 ± 4.8*
Total liquid, kg	37.2 ± 0.5	35.8 ± 0.4*	38.7 ± 0.6	37.2 ± 0.5*

N o t e : * – $p < 0.05$ from the indicator before treatment.

Table 3. ***Change in biochemical parameters of serum in patients with type 2 diabetes and obesity, and index HOMA-IR before and after treatment (M ± m)***

Indicators	The experimental group		Control group		Reference values (Nazarenko and Kishkun, 2006)
	Before treatment	After treatment	Before treatment	After treatment	
Glucose, mmol/L	7.2 ± 0.2	5.4 ± 0.1**'*	7.3 ± 0.3	6.2 ± 0.2*	4–5.4
Total cholesterol, mmol/L	5.5 ± 0.2	4.3 ± 0.1*	5.4 ± 0.1	4.2 ± 0.2*	<5.2
HDL cholesterol, mmol/L	1.4 ± 0.03	1.3 ± 0.03	1.2 ± 0.04	1.1 ± 0.04	1–1.3
LDL cholesterol, mmol/L	3.2 ± 0.1	2.5 ± 0.1*	3.1 ± 0.1	2.4 ± 0.1*	<3.4
Triglycerides, mmol/L	2.1 ± 0.1	1.5 ± 0.06*	2.3 ± 0.1	1.6 ± 0.06*	<1.7
Creatinine, μmol/L	60.4 ± 1.7	58.9 ± 1.8	61.5 ± 1.8	60.2 ± 1.7	60–110
Urea, mmol/L	4.6 ± 0.1	4.3 ± 0.2	5.2 ± 0.2	5.0 ± 0.2	2.5–7.1
Total bilirubin, μmol/L	13.8 ± 0.8	12.8 ± 0.6	14.6 ± 0.6	13.9 ± 0.7	1.7–20
ALT, IU/L	36.3 ± 2.0	33.3 ± 1.7	35.8 ± 3.5	31.6 ± 2.3	29–33
AST, IU/L	30.2 ± 1.6	28.0 ± 1.2	30.3 ± 3.5	29.2 ± 2.0	5–40
Insulin, μIU/ml	15.0±1.4	16.8±1.0**	12.4±1.1**'*	15.2±0.8*	2.0–25.0
C–peptide ng/ml	3.7±0.3	4.0±0.2	3.5±0.2	3.9±0.3	0.5–3.2
Index HOMA–IR	4.8±0.5	5.5±0.5**	2.9±0.4**'*	4.2±0.5*	<2.77

N o t e : * – the reliability of intra-group differences ($p < 0.05$) before and after treatment; ** – significance of differences ($p < 0.05$) of the experimental group from the control group.

Table 4. Changes in provision of the micronutrient in patients with type 2 diabetes and obesity during therapy (M ± m)

Concentration of micronutrients in blood serum	Normal levels	The experimental group		Control group	
		Before treatment	After treatment	Before treatment	After treatment
Vitamin C, mg/L	4–15	10.9 ± 0.4	14.4 ± 0.3**'*	12.0 ± 0.2	10.6 ± 0.2*
25 (OH) D, ng/ml	20–60	20.5 ± 0.8	24.4 ± 0.9**'*	21.0 ± 1.1	20.4 ± 0.8
Vitamin B_6, μg/L	4.8–17.7	6.9 ± 1.4**	16.4 ± 1.4**'*	10.9 ± 1.6	6.8 ± 0.8
Vitamin B_{12}, pg/ml	200 – 1300	383.2 ± 45.3	811.2 ± 88.4**'*	430.6 ± 50.8	396.9 ± 43.7
Homocysteine, μmole/L	4 – 12	14.1 ± 1.2	10.5 ± 1**'*	13 ± 1.3	13.3 ± 1.6
Folate, μg/L	3 – 24	16.8 ± 1.3	22.1 ± 1.5**'*	18.3 ± 2.6	16.1 ± 1.7
Potassium, mmol/L	3.8 – 5.3	4.41 ± 0.06**	4.83 ± 0.03**'*	4.61 ± 0.07	4.59 ± 0.07
Magnesium, mmol/L	0.7 – 1.2	0.748 ± 0.008	0.825 ± 0.008**'*	0.750 ± 0.009	0.714 ± 0.008*
Calcium, mmol/L	2.15 – 2.57	2.22 ± 0.02	2.34 ± 0.01**'*	2.24 ± 0.01	2.22 ± 0.02
Zinc, mmol/L	9 – 14	12.8 ± 0.2	14.5 ± 0.2**'*	12.9 ± 0.2	11.8 ± 0.2*
Phosphorus, μmol/L	0.81 – 1.55	1.18 ± 0.01**	1.17 ± 0.02**	1.33 ± 0.04	1.24 ± 0.02*

N o t e : * – the reliability of intra-group differences (p < 0.05) before and after treatment; ** – significance of differences ($p < 0.05$) of the experimental group from the control group.

Patients had a significant decrease in the total serum cholesterol content from the initial level (by 1.2 ± 0.2 mmol/L in patients of the experimental group, 1.2 ± 0.1 mmol/L in patients of the control group), LDL (0.7 ± 0.1 mmol/L in the experimental group and 0.7 ± 0.2 in the group of comparison, $p < 0.05$) and triglycerides (by 0.6 ± 0.2 mmol/L in the experimental group and 0.7 ± 0.2 mmol/L in the control group, $p < 0.05$). During treatment, a decrease in glycaemia was observed in the experimental group of patients by an average of 1.8 ± ± 0.3 mmol/L and by 1.1 ± 0.2 mmol/L in the control group, $p < 0.05$.

During treatment, a decrease in the blood serum HC was observed on average by 25% in patients of the experimental group. This may probably be due to the additional intake of vitamins of group B as part of the VMC. Apart from this, an increment of HC by 3% was observed in patients of the control group. Moreover, there was a significant decrease in glucose level in the experimental group as compared with the control group. The control group also showed a decrease in glucose level, but it was not statistically significant.

During hypocaloric diet therapy, there was a propensity towards the reduction of the status of vitamins and bioelements in the control group and a significant increment of these readings in the experimental group (Table 4).

Finally, the level of insulin in both of the groups were in normal range, but the levels of C-peptide were found to be higher than reference value (Table 3).

DISCUSSION

It was found that the level of glucose was significantly reduced in experimental group, which is probably due to the intake of VMC, as it was abstained in control group. The micronutrient status in the experimental group became significantly more favourable, while in the control group the concentrations of vitamins and macro and trace elements remained unchanged or even slightly decreased. Positive dynamics was also noted in the experimental group regarding complaints of micro symptoms of micronutrient deficiency, which was not observed in the control group.

Due to the reduced caloric intake by the patients of type 2 diabetes, the supply of all essential dietary micronutrients was hampered. In such conditions, use of VMC in combined therapy of type 2 diabetes had a significant effect on the progression of the disease (Issa, 2017). The data obtained indicate a need for additional inclusion of VMC in the hypocaloric diet, which will prevent the deterioration of micronutrients in this category of patients during treatment. Patients with diabetes usually have micronutrient deficiencies, which may cause complications triggered by diabetes. Obese people often lack vitamin D and other fat-soluble vitamins due to dissipation of hydrophobic substance in higher fat mass (Muscogiuri et al., 2010; Gupta et al., 2011; Vujosevic et al., 2014). People with obesity and diabetes have increased excretion and thereby need for vitamins of group B, vitamin C, Mg, Zn, Cr, V, Mn and other micronutrients. Addition of VMC in the therapy of diabetes improved the concentration of different micronutrients: in the experimental group, the serum concentration of vitamins C, B_6, B_9, B_{12}, potassium and magnesium after treatment were higher ($p < 0.05$) than in control group.

In the beginning of the study, many symptoms of micronutrient deficiency were observed like paraesthesia of lower limbs, fatigue, weakness, irritation, sleeplessness, nausea, dyspeptic syndrome, cheilosis, conjunctivitis and the dryness of skin. It is very important to note that the use of VMC contributed to a significant decrease in glycaemia in patients.

After the course, the levels of vitamin C, B_6, B_9, B_{12}, potassium, magnesium and zinc were significantly increased when compared with initial level and with patients of the control group. Phosphorus was only the element whose level was statistically lower after treatment in the experimental group as compared to the control group. Pallor of the skin can be associated with a decrease in vitamins C, B_9, B_{12}, potassium and zinc supply. This may be due to involvement of these micronutrients in the proper functioning of the skin (Tveden-Nyborg and Lykkesfeldt, 2013; Elias and Williams, 2018; Galchenko and Nazarova, 2019a; Galchenko and Nazarova, 2019b). Similarly, dryness of skin is usual in subjects with the decreased serum concentrations of vitamins C and B_6, which might be explained by necessity of vitamin C in collagen synthesis (Tveden-Nyborg and Lykkesfeldt, 2013). In the same way, skin peeling may be related to the deficiency of the same vitamins and zinc (Galchenko and Nazarova, 2019b). Moreover, skin rashes may be found at a decreased level of vitamin B_6. Besides this, there can be an affinity towards haemorrhage when there is decreased blood concentration of vitamin C. This is due to impaired collagen biosynthesis and perhaps HIF-1α hydroxylation (Stipanuk and Caudill, 2012). The problems of hair are prominent

in people with lower levels of vitamin B_6 and zinc since they play vital role in growth and development of the hair (Galchenko and Nazarova, 2019b). Conjunctivitis, cheilosis, geographic tongue and glossitis are another set of problems due to the deficient of vitamin B_6. In addition to these, gastric symptoms like a decrease in appetite and nausea may be also related to a decreased blood concentration of vitamin B_6. On the other hand, increased affinity towards infection was suspected to be due to the lack of vitamin C and zinc. It is well known that vitamin C contributes to immune defence by supporting various cellular functions i.e. innate and adaptive immune system (Carr et al., 2017). Apart from this, anaemia was suspected to be associated with deficiency of vitamin B_6, B_9, B_{12} and zinc. Similarly, neurological symptoms, as polyneuritis was found to be the result of vitamin B_6 deficiency and the symptoms like seizure were due to vitamin B_6 and magnesium deficiency (Galchenko and Nazarova, 2019a). That is due to neurotransmitter forming function of the vitamin B_6 (Brown et al., 2019). Finally, symptoms like irritation, anxiety, fatigue and tiredness may be associated with a reduced level of vitamins C (Stipanuk and Caudill, 2012) and magnesium (Galchenko and Nazarova, 2019a).

During the experiment, the physique of the patients in the experimental group and the control group remained unchanged with respect to each other, both groups showed approximately the same changes in body composition. The micronutrient status probably plays a much smaller role in the dynamics of body composition indicators than the macronutrient one.

CONCLUSION

As the patients with diabetes and obesity have increased risk of development of micronutrient deficiency, that relatively increases the risk of complications related with diabetes mellitus and obesity, use of VMC therapy is one of the most important aspects in the treatment.

Limitations. The group, on which the experiment was conducted, was small in size, which may have resulted in difficulty to achieve the highest significance in statistical analysis. Similarly, there was heterogeneity in the group due to difference in age, anthropometrical parameters and the initial micronutrient status.

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ИСПОЛЬЗОВАНИЕ ВИТАМИННО-МИНЕРАЛЬНОГО КОМПЛЕКСА В КОМБИНИРОВАННОЙ ТЕРАПИИ ПАЦИЕНТОВ С ОЖИРЕНИЕМ И САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА: РАНДОМИЗИРОВАННОЕ, КОНТРОЛИРУЕМОЕ КЛИНИЧЕСКОЕ ИССЛЕДОВАНИЕ

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РЕЗЮМЕ. В комплексном лечении пациентов с сахарным диабетом и сопутствующим ожирением используют низкокалорийную диету. Однако снижение энергетической ценности рациона приводит и к снижению поступления микронутриентов. Главная задача настоящего исследования - оценка важности и эффективности использования витаминно-минерального комплекса в лечении таких пациентов.

Методы. В исследовании приняли участие 80 женщин, страдавших от сахарного диабета 2-го типа с сопутствующим ожирением, в возрасте от 40 до 65 лет. Пациентки были разделены на 2 группы по 40 человек. Все испытуемые получали персонализированную диетотерапию и 1000 мг метформина ежедневно. Экспериментальная группа, помимо этого, получала витаминно-минеральный комплекс. В начале исследования, а также по истечении 14 дней терапии были проведены биохимический анализ крови, исследование состава тела и осмотр в сочетании с опросом для выявления симптомов дефицита отдельных микронутриентов.

Результаты. Прием витаминно-минерального комплекса ассоциировался с более высокими сывороточными концентрациями витаминов B_6, B_{12}, B_9, C и D, а также калия, кальция, магния и цинка, и более низкими – глюкозы. Клинические проявления микронутриентных дефицитов значительно уменьшились у пациентов, которые получали витаминно-минеральный комплекс. Все эти изменения были справедливы как по отношению к показателям в основной группе до лечения, так и к значениям, которые были обнаружены в контрольной группе после него.

Заключение. Микронутриентная поддержка является важной составляющей комплексной терапии пациентов с сахарным диабетом и сопутствующим ожирением.

КЛЮЧЕВЫЕ СЛОВА: питание, микронутриенты, персонализированная диетотерапия, БАД.