THE INFLUENCE OF NATURAL, PREFORMED PHYSICAL FACTORS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH THE METABOLIC SYNDROME ON THE COMPENSATION OF CARBOHYDRATE METABOLISM ACCORDING TO THE RESULTS OF CONTINUOUS GLUCOSE LEVEL MONITORING

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**Abstract.** In recent years, rehabilitative and preventive areas of medicine have become relevant. Restorative treatment and rehabilitation with the use of complex resort therapy in patients with type 2 diabetes have been relevant in recent years.

The purpose of our study was to investigate the variability of glycaemia in patients with type 2 diabetes mellitus with MS under the influence of natural and preformed physical factors at the Subsidiary Enterprise “Sanatorium “Morshynkurort” in Morshyn.

Continuous glucose monitoring (CGM) was performed using the Metronic Guardian Connect system in 48 patients with type 2 DM and MS for an average of 14 days before and after the treatment. Daily monitoring of blood glucose was performed using the “iPro Metronic” device. We’ve used the traditional indicators of glycaemia variability according to the recommendations of the American Diabetes Association. All patients with type 2 DM and MS had signs of the abdominal obesity, which was evidenced by an increase not only in BMI, but also in waist size (WS). Their WS was 112.06±5.59 in men and 107.64±2.46 in women. After the performed course of treatment, the HOMA IR index decreased 3-fold (p<0.05). The content of fasting insulin in blood after 3 months of treatment reliably decreased at 45%, which indicates a significant contribution of sanatorium-spa therapy in overcoming hyperinsulinemia and insulin resistance in general. For optimal diabetes control, in addition to HbA₁c, we must consider CGM and % Time in range (TIR) (time in target range). TIR: (3.9–10.0 mmol/l) in the studied patients before the treatment was 53.30±5.90% and significantly differed from patients after the treatment – 72.53±7.41% (p<0.05) (with a norm of >70%). TIR should be used as a target point, as an indicator of glycemie control in routine clinical practice.

Under the influence of natural and preformed physical factors in the conditions of the resort “Morshynkurort” – medical center in Morshyn, in patients with type 2 DM with MS, the variability of glycaemia according to CGM data is likely to decrease, which makes it possible to achieve strategic goals and criteria for the effectiveness of treatment of DM. CGM plays an important role in evaluating the effectiveness and safety of treatment, including the prevention of hypoglycaemia.

**Key words:** type II diabetes mellitus, metabolic syndrome, insulin resistance, continuous glucose monitoring, hypoglycaemia, treatment.

**Introduction.** Diabetes mellitus (DM) is a complex chronic disease that requires constant medical care with multifactorial risk reduction strategies using extraglycemic control [4]. In recent years, rehabilitative and preventive areas of medicine are relevant. In particular, medical rehabilitation involves a complex approach including ways to accelerate restitution, stimulate reparative-regenerative processes, identify and strengthen compensatory mechanisms, correct the body’s general resistance and immunity. In this regard, the widespread use of mineral healing waters for medical rehabilitation, disease prevention and population health improvement is becoming more and more popular. The resorts of Ukraine use mineral waters of different chemical composition, microbial cenosis, and biological activity [1,3]. Subsidiary enterprise “Sanatorium “Morshynkurort” is located in the center of the Morshyn balneological resort, known in Ukraine and beyond, among thousands of hectares of ecologically clean Carpathian forests [3]. Mineral water treatment contributes to the normalization of metabolism – it has a positive effect on the level of cholesterol, B-lipoproteins, reduces the level of sugar in blood and increases glucose tolerance in patients with DM, increases oxidative processes, thus leading to weight loss in people with obesity; has a favorable effect on water-electrolyte exchange, acid-alkaline balance in the human body, on metabolism of the heart muscle; provides the necessary amount of magnesium, which contributes to the normalization of the biogenesis of the large intestine due to the growth of bifido- and lactobacteria in its content, a decrease in the number of conditionally pathogenic microflora, helps to reduce tissue hypoxia of liver cells, which improves their function, naturally reduces intoxication of the body and plays an important role in the vital activity of the body [3, 2].

Compensation – a condition in which, under the influence of antidiabetic treatment of patients with diabetes mellitus, normalization of glycemia, as well as indices of lipid metabolism, blood pressure, and body weight has been achieved [4]. An increase in the level of HbA₁c determines the development and progression of chronic diabetic micro- and macroangiopathies [7,9]. HbA₁c monitoring is the most useful method of determining the state of metabolic control and the only method of obtaining informative data available from the point of view of their relationship with late micro- and macroangiopathies [8,10]. However, HbA₁c is a limited measure as an index of glycemic control status, as it shows average
blood glucose values. According to scientists, until today there was an era of HbA1c, because it was considered as: the main glycemic marker for the intensification of therapy, the main glycemic marker of the quality of diabetes control and the effectiveness of drugs, a diagnostic criterion for diabetes mellitus and various metabolic disorders, a standard marker of the risk of developing chronic complications, a target index of intensification of therapy algorithm in clinical practice and research [5, 6]. However, the average level of glycemia does not reflect the real situation, does not indicate past hypoglycemia or high variability of glycemia, the accuracy of determining the level of HbA1c may be impaired in the case of: hemoglobinopathies, iron deficiency anemia, CKD, liver diseases, individual lifespan of erythrocytes, unknown genetic factors that lead to glycation disorder, CKD, liver diseases, individual lifespan of erythrocytes, unknown genetic factors that lead to glycation disorder, kidney disease, and the main glycemic marker of the quality of diabetes control and the effectiveness of drugs, a diagnostic criterion for diabetes mellitus and various metabolic disorders, a standard marker of the risk of developing chronic complications, a target index of intensification of therapy algorithm in clinical practice and research [5, 6]. However, the average level of glycemia does not reflect the real situation, does not indicate past hypoglycemia or high variability of glycemia, the accuracy of determining the level of HbA1c may be impaired in the case of: hemoglobinopathies, iron deficiency anemia, CKD, liver diseases, individual lifespan of erythrocytes, unknown genetic factors that lead to glycation disorder, does not provide complete information about diabetes control compared to continuous monitoring of glucose level [11]. Continuous glucose monitoring (CGM) measures the level of glucose in the interstitial fluid. Thanks to new trends in glucose measurement, the variability of glycemia can more be accurately determined, namely the amplitude of fluctuations. According to the latest recommendations, achieving diabetes compensation and low glycemic variability will allow achieving strategic aims and criteria for the effectiveness of diabetes treatment [12]. CGM plays an important role in evaluating the efficacy and safety of treatment, including the prevention of hypoglycemia development, and may be appropriate for some patients with type 2 DM [4].

**Aim.** The aim of our study was to investigate the variability of glycemia in patients with type 2 diabetes with MS under the influence of natural and preformed physical factors.

**Materials and methods**

Continuous glucose measurement (CGM) was carried out using the Metronic Guardian Connect system in 48 patients with type 2 diabetes and MS for an average of 14 days (patients of the endocrinology department of the communal non-profit enterprise of the regional clinical hospital of the Ivano-Frankivsk Regional Council and the subsidiary enterprise “Sanatorium “Morshynkurort”, Morshyn”) before and after the treatment. Daily monitoring of blood glucose was performed using the “iPro Metronic” device. We’ve used traditional indices of glycemia variability according to the recommendations of the American Diabetes Association: Time below range (TBR): <54 mg/dl (<3 mmol/l) – <1% was considered the norm; Time below range (TBR): <69 mg/dl (3.8 mmol/l) – <4%; Time in range TIR: 70 – 180 mg/dl (3.9–10.0 mmol/l) – >70%; Time above range (TAR): >181 mg/dl (10.1 mmol/l) – <25%; Time above range TAR: >250 mg/dl (13.9 mmol/l) – <5%; Glucose Variability CV (coefficient of variation) – ≤36%; Average Glucose – goal <154 mg/dl (8.6 mmol/l); Glucose Management Indicator (GMI) – HbA1% level according to CGM – goal < 7%; < 8%.

Patients with type 2 DM with MS followed an oral glucose-lowering therapy (received monotherapy with metformin and sulfonylurea derivatives, as well as combined therapy with metformin and other groups of glucose-lowering drugs) and basal-bolus insulin therapy. Drinking treatment with mineral water from spring No. 6, physiotherapy, massage, hydrotherapy-baths and showers was carried out on the basis of the subsidiary enterprise “Sanatorium “Morshynkurort” for three weeks. IDF criteria, 2005, were used to detect signs of MS in the examined persons. According to the structure of the work, elements of typological sampling (stratification randomization) were used in the controlled clinical trial of MS patients with type 2 DM.

All examined patients with type 2 diabetes were divided into 2 groups: the group of patients with type 2 diabetes with MS before and after the treatment – 48 patients. The degree of IR was determined by the size of the waist circumference (WW), IR indices: the HOME-IR index (Homeostasis Model Assessment Insulin Resistance) and the Caro index. The HOMA IR indicator was calculated according to the formula: HOMA IR=fasting blood glucose (mmol/l)×fasting blood insulin (µU/l)/22.5 [Matthew DR, 1985]; the Caro index was calculated according to the formula: ratio: glucose (mmol/l)/insulin (µU/l) [CaroAA, 2004]. Using BMI indicators, the degree of general obesity was assessed according to the recommendations of the WHO (1997) and the International Diabetes Federation (2005). BMI was considered normal - less than 24 kg/m2; OT - less than 80 cm in women, less than 94 cm in men, HOMA IR which does not normally exceed 2.77, Caro index, which normally exceeds 0.33. A general clinical examination of patients was performed as well as determination of fasting blood glucose and postprandial glycemia, blood glycemic profile by the glucose oxidase method using the “Exan” apparatus. Biochemical studies: glycated hemoglobin (HbA1c) by chromatographic method using a test system (fully automated analyzer) to determine the content of hemoglobin D-10TM of the company “BioRad” (USA). The concentration of endogenous insulin (EI) was determined by a set of reagents DRG (USA). The statistical processing of the results obtained was performed using the statistical data analysis package “STATISTICA” on a Pentium-IV personal computer and the application of parametric and non-parametric methods of evaluating the obtained results.

**Results**

According to our data, the average age of 48 patients with type 2 DM with MS was 54 years, of which 26 were men and 22 were women. Abdominal obesity, which is determined by waist circumference (cm) according to the criteria given by the IDF, should be included among
the characteristic signs of insulin resistance. All patients with type 2 DM and MS had signs of abdominal obesity, which was evidenced by an increase not only in BMI, but also in WS. Their waist size was 112.06±5.59 in men and 107.64±2.46 in women. After the course of treatment, the NOMA IR index decreased 3-fold (p<0.05). The content of fasting insulin in the blood after 3 months of treatment reliably decreased at 45%, which indicates a significant contribution of sanatorium-spa therapy in overcoming hyperinsulinemia and insulin resistance in general.

Table 1 represents the dynamics of changes in carbohydrate metabolism indices in MS patients with type 2 DM. 3 months after the start of treatment, a decrease in fasting glycemia was registered: at 33%, compared to the values before the treatment (p<0.05). After the treatment, the level of postprandial glycemia in patients reliably decreased at 25% (p<0.05).

Determination of the EI level in blood, calculation of the Caro index, HOMA-IR are informative for the verification of the presence of IR in patients with MS. We ascertained a reliable difference in the EI index in the group of patients with type 2 DM with MS after treatment compared to patients before the treatment almost 1.8-fold (p<0.05). The analysis of hemoglobin glycation (HbA1c) shows that under the influence of basic therapy, its content in blood after 3 months of treatment reliably decreased at 15% (p<0.05). It should also be emphasized that compensation of diabetes in terms of glycemia and HbA1c under the influence of basic therapy was achieved in 36% of patients.

CGM was performed using the Metronic Guardian Connect system in 48 patients with type 2 DM and MS. The absence of hypoglycemia is an essential condition for the successful and safe treatment of patients, therefore the time in the range of less than 3.8 mmol/l and 3.0 mmol/l (Time below range (TBR): <3 mmol/l) in patients with DM with MS was 0.19±0.07% and probably did not differ in patients after the treatment – 0.11±0.89 (p<0.05); Time below range (TBR): (<3.8 mmol/l) in patients with diabetes mellitus with MS before treatment was – 1.7±0.89%, after the treatment it probably decreased up to 0.91±0.54% (p<0.05); Time in range TIR: (3.9–10.0 mmol/l) in the studied patients before the treatment was 53.30±5.90% and probably differed from patients after the treatment – 72.53±7.41 (p<0.05) (with a norm of >70%); Time above range (TAR): (>10.1 mmol/l) in patients with DM with MS was 43.33±5.96% and significantly differed from patients after treatment – 24.47±7.96 (p<0.05) (norm <25%); Time above range (TAR: >13.9 mmol/l) in patients with diabetes mellitus with MS before treatment was 22.1±3.91%, in patients after treatment – 11.42±2.89% (norm <5%); Glucose Variability CV in patients with diabetes mellitus with MS before treatment

| Table 1. Indices of carbohydrate metabolism in MS patients with type 2 DM under the influence of natural, preformed physical factors (M±m) |
|-----------------|---------------------------------|---------------------------------|
| Indices         | Type 2 DM with MS before treatment n=48 | Type 2 DM with MS after treatment n=48 |
| Endogenous insulin, mc IU/ml               | 28.45±2.49 | 15.85±2.40*  |
| HOMA IR index                                      | 10.32±0.80 | 3.37±2.38*   |
| Caro index                                          | 0.34±0.01* | 0.36±0.56    |
| Fasting blood glucose, mmol/l                     | 9.53±0.24  | 6.48±0.31*   |
| Postprandial glycemia, mmol/l                    | 11.54±0.28 | 8.70±0.29*   |
| HbA1c%                                                | 9.39±0.40  | 7.99±0.31*   |
| Glucose Management Indicator (GMI) % po CGM         | 8.26±1.05  | 6.26±1.05    |
| Time below range (TBR): <3 mmol/l, %              | 0.19±0.07  | 0.11±0.89*   |
| Time below range (TBR (<3.8 mmol/l), %             | 1.7±0.89   | 0.91±0.54*   |
| Time in range TIR: (3.9–10.0 mmol/l), %            | 53.30±5.90 | 72.53±7.41*  |
| Time above range (TAR): (час вище діапазону) (>10.1 mmol/l), % | 43.33±5.96 | 24.47±7.96*  |
| Time above range TAR (>13.9 mmol/l), %            | 22.1±3.91  | 11.42±2.89*  |
| Glucose Variability CV,%                          | 44.10±4.89 | 29.64±7.06*  |
| Average Glucose, mmol/l                           | 10.1±0.52  | 8.45±1.36    |

Notes: 1.* – the difference is reliable in relation to the indices of the comparison group (p<0.05).
was 44.10±4.89%, which probably differed in patients with diabetes mellitus after the treatment – 29.64±7.06% (p < 0.05), (norm ≤ 36%); Average Glucose in patients with DM with MS was 10.1±0.52 mmol/l, after treatment – 8.45±1.36 mmol/l, which indicates that the goal was achieved (target<8.6); Glucose Management Indicator (GMI) – the level of HbA1c% according to CGM in patients with diabetes mellitus with MS was 9.6 ± 1.19% after the treatment – 8.3 ± 2.05 (target < 7%; < 8%), (see Table 1).

Conclusions

1. HbA1c does not indicate previous hypoglycemia or high variability of glycemia, does not provide complete information about diabetes control.
2. For optimal diabetes control, in addition to HbA1c, we must consider CGM data and % Time in range (TIR). TIR should be used as a target point and an index of glycemic control in routine clinical practice.
3. Under the influence of natural and preformed physical factors in the conditions of the subsidiary enterprise “Sanatorium “Morshynkurort” medical center in Morshyn, in patients with type 2 DM with MS, the variability of glycemia according to CGM data is likely to decrease, which makes it possible to achieve strategic goals and criteria for the effectiveness of DM treatment.
4. CGM plays an important role in evaluating the effectiveness and safety of the treatment, including the prevention of hypoglycemia development.

Ethical standards: The written informed consent was obtained from each patient before the treatment.

Conflict of interest: The Authors declare no conflict of interest

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