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Comparative Estimation of the Influence on The Level of Glycosylated Hemoglobin of Hygienic Toothpastes in Patients with Type II Diabetes Mellitus

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Abstract

The aim of the study is to comparatively analyze the effect of INFANETIM Technology® BROWN LINE toothpaste on the contents level of glycosylated hemoglobin in patients with type II diabetes mellitus.

Methods: We examined 205 patients with controlled type II diabetes mellitus who had the disease for no more than 3 years and randomized 200 of them (1:1). The study and control groups enrolled 100 patients each: using INFANETIM Technology® BROWN LINE toothpaste or any other toothpaste with standard hygienic properties that does not have antidiabetic indications for 36 weeks. The change in the level of glycosylated hemoglobin, the frequency of diabetic complications, the frequency of carious and inflammatory processes in the oral cavity were determined.

Results: At the beginning of the study both groups showed a stable level of glycosylated hemoglobin less than 7,5%, no diabetic complications, comparable indicators of carious and inflammatory processes in the oral cavity. After 36 weeks of the study a decrease in glycemia was found in patients using INFANETIM Technology® BROWN LINE toothpaste in comparison

with control group. The incidence of carious and inflammatory processes in the oral cavity was significantly higher in the control group.

Keywords: Diabetes mellitus, Infanetim, Toothpaste, Glycosylated hemoglobin.

Introduction

Diabetes mellitus (DM) is one of the most common diseases in the world [1]. The growth in the number of patients with this pathology over the past centuries has shown us the true face of this epidemic of non-infectious origin [1].

According to statistics from WHO experts, by the end of 2017, more than 425 million people worldwide suffer from diabetes. The International Diabetes Federation predicts 629 million people will suffer from diabetes by 2045, most of whom live in low- and middle-income countries. These are mainly patients with type II diabetes. Each year 1.6 million deaths occur from diabetes-related causes. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. [1]

The most dangerous consequences of the global epidemic of diabetes are its systemic vascular complications - nephropathy, retinopathy, damage to the great vessels of the heart, brain, arteries of the lower extremities. It is these complications that are the main cause of disability and mortality in patients with diabetes.

It's worth noting that diabetes seems to be superbly manageable. Changes in habits and lifestyle, pharmacotherapy and regular screening for complications can maintain a high quality of life for patients throughout their lives. However, due to the social significance of the disease, discussion of the prospects for combating diabetes and issues of additional patient care occupy an important place, including among dentists [8].

The oral cavity of patients with diabetes is subject to increased stress due to high levels of glucose in the salivary fluid [9,10]. Increased sugar levels cause dry mouth [11,12], which in turn contributes to acid-base imbalance. Gingivitis or periodontitis is detected in diabetic patients 2-3 times more often than in healthy individuals [13,14]. These factors dictate a new comprehensive approach to oral care for patients with diabetes. This approach is based on a drug specially developed for patients with diabetes with a multidirectional mechanism of action, which reduces the risk of developing bacterial and inflammatory diseases and, in particular, increases the effectiveness of concomitant hypoglycemic therapy of the underlying disease in people with type 2 diabetes.

A toothpaste specially developed for diabetics is a necessary element of the comprehensive management of a patient with diabetes in any variant of the course of the disease. The development of caries, inflammation and loss of teeth due to weakening of the periodontium, circulatory disorders and regeneration processes in the oral cavity can be avoided by switching to appropriate dental care products.

The modern dental market offers a wide range of toothpastes for patients with diabetes: DiaDent, Elmex and many others. Basically, they contain tannins, pectins, chlorhexidine and have anti-inflammatory, strengthening and antibacterial properties.

BROWN LINE toothpaste is an additional development of INFANETIM Technology®, aimed at lowering blood sugar and normalizing metabolic processes, working through the complex of plant ingredients, synergizing in hypoglycemic, anti-insulin-resistance, and vasculoprotective effects. The mechanism of glucose lowering is mostly conditioned by bean shells, and galega herb known for their systemic pharmacological action concerning sugar metabolism.

The basis of the toothpaste is made up of herbal ingredients:

• Bean shells (Valve fructuum Phaseoli vulgaris). The hypoglycemic effect of beans is associated with the presence of flavonoids in it, which contribute to the normalization of carbohydrate metabolism, as well as the presence of a sufficient amount of the amino acid arginine, which is involved in the synthesis of insulin.

• Blueberry shoots (CormiVaccinii). Blueberry shoots (mainly in

leaves) contain tannins (up to 20% of dry raw materials), flavonoids, as well as salts of potassium, magnesium, manganese, iron, copper and chromium. Leaf extracts prevent the death of animals with a removed pancreas. The pharmacological effect is associated with the presence of flavonoids (anthocyanins) in the raw material. The high content of minerals in blueberry leaves contributes to an increase in tissue sensitivity to insulin and a decrease in glycemic levels.

• Galega herb (HerbaGalegae). It has been experimentally established that the presence of guanidine alkaloids in a plant causes a prolonged hypoglycemic effect. Goat's rue herb extract increases the glycogen content in the liver and glucose tolerance, inhibits hepatic insulinase. Galegin has a hypoglycemic effect. The plant also has a diuretic, diaphoretic, antimicrobial and anti-inflammatory effect.

• Roots of chicory (Radices Cichorii). A decoction from the roots is widely used in mild forms of diabetes, with cholecystitis as a choleretic agent and kidney disease as a diuretic. Chicory is also used for skin diseases associated with metabolic disorders.

• Ginkgo leaves (Folia Ginkgo). Ginkgo leaves contain the so-called ginkgobilobids, biflavonoids, terpene lactones, trace elements. Ginkgo biloba significantly improves microcirculation in the brain tissues and prevents blood clots. Ginkgo extracts help to restore the structure of the vascular wall and reduce its permeability, thereby preventing the risk of hemorrhagic stroke. Ginkgo flavonoids and trace elements, being natural antioxidants, neutralize the action of free radicals and prevent the destruction of endogenous nitric oxide, thereby increasing its vasodilating effect, as well as preventing the oxidation of low density lipoproteins and the development of atherosclerosis of the cerebral vessels. The consequence of the direct action on the neurons of the brain is the maintenance of the normal activity of the number of cholinergic and adrenergic receptors in the cells of the brain.

Toothpaste INFANETIM Technology® BROWN LINE provides gentle care for the oral cavity due to the main natural components of the composition and does not damage tooth enamel. Being a complex-component system, INFANETIM Technology paste allows you to maintain a neutral environment for a long time, ensuring the maintenance of the acid-base balance, which prevents the process of stone deposition and the formation of caries.

The INFANETIM Technology® BROWN LINE toothpaste contains no parabens, fluorides and aggressive abrasives.

The aim of this study

To assess the glycemia and hygienic state of organs and tissues of the oral cavity in type 2 diabetes mellitus in order to develop recommendations for improving oral hygiene in the system of comprehensive prevention of periodontal diseases in this category of patients.

Methodology

The present study is a randomized controlled open-label prospective study. It was carried out on the basis of the M.E. Zhadkevich, dental clinic "Moscow State University of Medicine and Dentistry named after A.I. Evdokimov" of the Russian Ministry of Health and the Clinic of Oncoimmunology and Cytokine Therapy.

We examined patients with controlled type 2 diabetes (n = 170). The degree of diabetes control was determined by the target level of glycosylated hemoglobin.

All patients gave informed consent (approved by the Institutional Review Board before the enrollment of the first patient) to conduct the study in an outpatient setting and as part of a dental appointment.

The inclusion of patients was carried out taking into account the following key parameters of inclusion / exclusion: patients with type 2 diabetes of any sex from 48 to 69 years old with a baseline glycosylated hemoglobin value of less than 7.5% and patients with no more than 3 years of diabetes history.

Patients with a history of allergic reactions or comorbid conditions that, from the investigator's point of view, could affect follow-up outcomes were not included in the study. Also excluded were patients with moderate to severe ketonuria and acidosis (based on the results of a general urinalysis), patients with confirmed macro- and microvascular complications of diabetes mellitus. The study did not include pregnant and lactating patients.

The exclusion of patients from participation in the study was

made on the basis of the following criteria: the patient's refusal to participate or the development of a serious adverse event.

Patients pledged to follow protocol procedures, have their blood sugar measured regularly (at least twice a day), and continue to take prescribed hypoglycemic medications on a regular basis. Also, patients had to keep a diary and write down all measurements and medications taken there, as well as record the time of brushing their teeth.

Patients in the study group used INFANETIM Technology® BROWN LINE toothpaste twice daily for 36 weeks. In the comparison group, the use of any toothpaste with standard hygienic properties (cleansing and refreshing), no antidiabetic indication and no special additives was allowed. The application of the toothpaste in the comparison group took place in the same regimen: 2 times a day every day for 36 weeks.

Prior to the start of the study, all patients were trained in Bass brushing technique using medium-hardness and floss brushes. The use of standard hygienic rinses (cleansing and refreshing, without special medicinal additives) and irrigators with water was allowed.

The study methodology used clinical and laboratory examination methods to evaluate effectiveness parameters. Clinical methods included: study of complaints, medical history, family history, the presence of concomitant diseases, pharmacotherapy regimen of the underlying and concomitant diseases.

Before starting to use the paste and during the final examination after 36 weeks, the level of glycosylated hemoglobin (%), PMA indices (papillary-alveolar index as modified by Parma, 1960), Green-Vermillion oral hygiene index and CPITN (Community Periodontal Index of treatment Needs), reflecting the presence and severity of gingivitis and periodontitis, the intensity of dental caries (KPU index - caries + filling + removed), as well as the prevalence of gingivitis and periodontitis in these groups.

Periodontal diseases were diagnosed according to the classification (adopted in 2001 at a meeting of the presidium of periodontology) [15].

The patient visited both endocrinologist and stomatologist – obligatory members of research team. The detailed guidelines were done to the investigators performing the effectiveness evaluation through a series of trainings.

The depth of the periodontal canal was measured with a graduated probe from the gingival margin to the bottom of the pocket.

Index teeth are probed to determine the depth of pockets, the presence of subgingival calculus and bleeding gums as part of the CPITN score. The probing force should not exceed 20 g. A practical test to determine this force is to place the tip of the probe under the thumbnail and press until whitening appears. To feel the subgingival calculus, use the least possible force to move the ball tip of the probe along the tooth surface. The tip of the inserted probe should be moved according to the anatomical configuration of the root surface. The appearance of pain during probing indicates the use of too much force. When determining the depth of the gingival pocket, the tip of the probe should be inserted carefully, the insertion depth corresponds to the colored markings. The total length of the pocket is examined, for which the depth is determined at at least 6 points of each tooth: medial-buccal, mid-buccal, distal-buccal, medial-lingual, middle-lingual, distal-lingual. Inspection and registration of data, calculation of the CPITN according to the rating scale:

4 - pocket over 6 mm;

3 - pocket 3.5-5.5 mm;

2 - there is no periodontal pocket, but there is a phenomenon of gum inflammation, tartar, defects in fillings or crowns;

1 - bleeding immediately after the end of probing, observed directly with the eye or with the help of a mirror, no tartar, no pockets;

0 - periodontal intact.

The PMA index assesses the degree of inflammation in the periodontium. To determine it, the gums of each tooth are stained with a Schiller-Pisarev solution, consisting of 1 g of crystalline iodine, 2 g of potassium iodide, 40 ml of distilled water. The inflamed areas of the gums can turn brown in color due to the presence of glycogen. Lack of coloration meant 0 points, coloration of the gingival papilla (P) - 1 point, coloration of the marginal gingiva (M)

- 2 points, coloration of both marginal and alveolar gums (A) - 3 points. The PMA index is calculated using the following formula:

PMA = Sum of indicators (points) x 100/90, -

where 90 - 3 (averaging coefficient) x 30 (the number of all teeth - after 15 years is taken as 30).

The PMA index should normally be equal to 0. With an increase in the intensity of gingivitis, the digital value of the index grows.

With a mild degree of gingivitis, the PMA index is less than 30%, with an average degree - 31-60%, with a severe degree - more than 61%.

The Greene-Vermillion Oral Hygiene Index allows for a separate assessment of the amount of dental plaque and tartar. To determine the index, 6 teeth are examined: 16, 11, 26, 31 - vestibular surfaces 36, 46 - lingual surfaces. Plaque assessment can be carried out visually or using staining solutions (Schiller-Pisarev, fuchsin, erythrosine).

Plaque assessment codes and criteria:

0 - no plaque detected;

1 - soft plaque covering no more than 1/3 of the tooth surface, or the presence of any amount of colored deposits (green, brown, etc.);

2 - soft plaque covering more than 1/3, but less than 2/3 of the tooth surface;

3 - soft plaque covering more than 2/3 of the tooth surface.

Determination of supra- and subgingival calculus is carried out using a dental probe.

Codes and criteria for the assessment of calculus:

0 - tartar was not detected;

1 - supragingival calculus, covering no more than 1/3 of the tooth surface;

2 - supragingival dental calculus, covering more than 1/3, but less than 2/3 of the tooth surface, or the presence of separate deposits of subgingival calculus in the cervical region of the tooth;

3 - supragingival calculus, covering more than 2/3 of the tooth surface, or significant deposits of subgingival calculus around the cervical region of the tooth.

The calculation of the index is made up of the values obtained for each component of the index, dividing by the number of surfaces examined by summing both values.

Formula for calculation:

OHS = SUM OF FLIGHT VALUES / NUMBER OF SURFACES + SUM OF VALUES OF STONE / NUMBER OF SURFACES

Interpretation of the index (values of OHS oral hygiene status):

- 0.0-1.2 good
- 1.3-3.0 satisfactory
- 3.1-6.0 bad

The intensity of tooth decay is determined by the value of the DMFT index, where D is the number of carious (untreated) teeth, M is the number of extracted teeth or tooth roots to be removed, F is the number of filled (cured) teeth. The sum characterizes the intensity of the carious process in the patient. The average indicator of the intensity of caries per group of patients is determined by the formula:

Intensity of caries = The sum of individual indicators of DMFT / The number of patients with caries among the surveyed.

Dynamic observation makes it possible to determine the increase in the intensity of caries or the true incidence of caries by the difference in the DMFT indices on examinations as the average number of teeth in which new carious cavities have appeared over a certain period (in our case, about 9 months).

At the completion visit (at 36 weeks), the fact of the development of complications, carious and inflammatory processes in the oral cavity was recorded, and compliance with the use of the paste and keeping a diary was assessed.

Thus, all participants in the study underwent a standard clinical and laboratory examination, an examination by an endocrinologist, and an assessment of their dental status.

Statistics

The data were statistically processed using the R and MS Excel software packages. Taking into account the quantitative and qualitative nature of the variables, as well as the sample size and its normal distribution, determined using the Shapiro-Wilk test, when comparing these two groups, Pearson's $\chi 2$ and t-test were used. A p-value less than 0.05 was statistically significant.

Results

205 people were examined. After the screening stage, 200 patients were selected that met all inclusion / exclusion criteria. Each group was randomized to 100 patients. During the study, 25 patients dropped out early for various reasons . The final analysis included 88 patients in the study group and 87 patients in the control group - a total of 175 people (Figure 1).

The average age of all examined was 53.3 ± 4.1 years. The level of glycated hemoglobin is 6.419%.

All patients who were followed up had stable hypoglycemic therapy, which did not change during the entire study, as evidenced by the entries in the patient diaries and the endocrinologist's conclusions at the completion visit. There were no significant differences in screening between the groups. The majority of patients (92-95%) in both groups took metformin (mono- or in combination). Thus, the influence of basic therapy on the results obtained

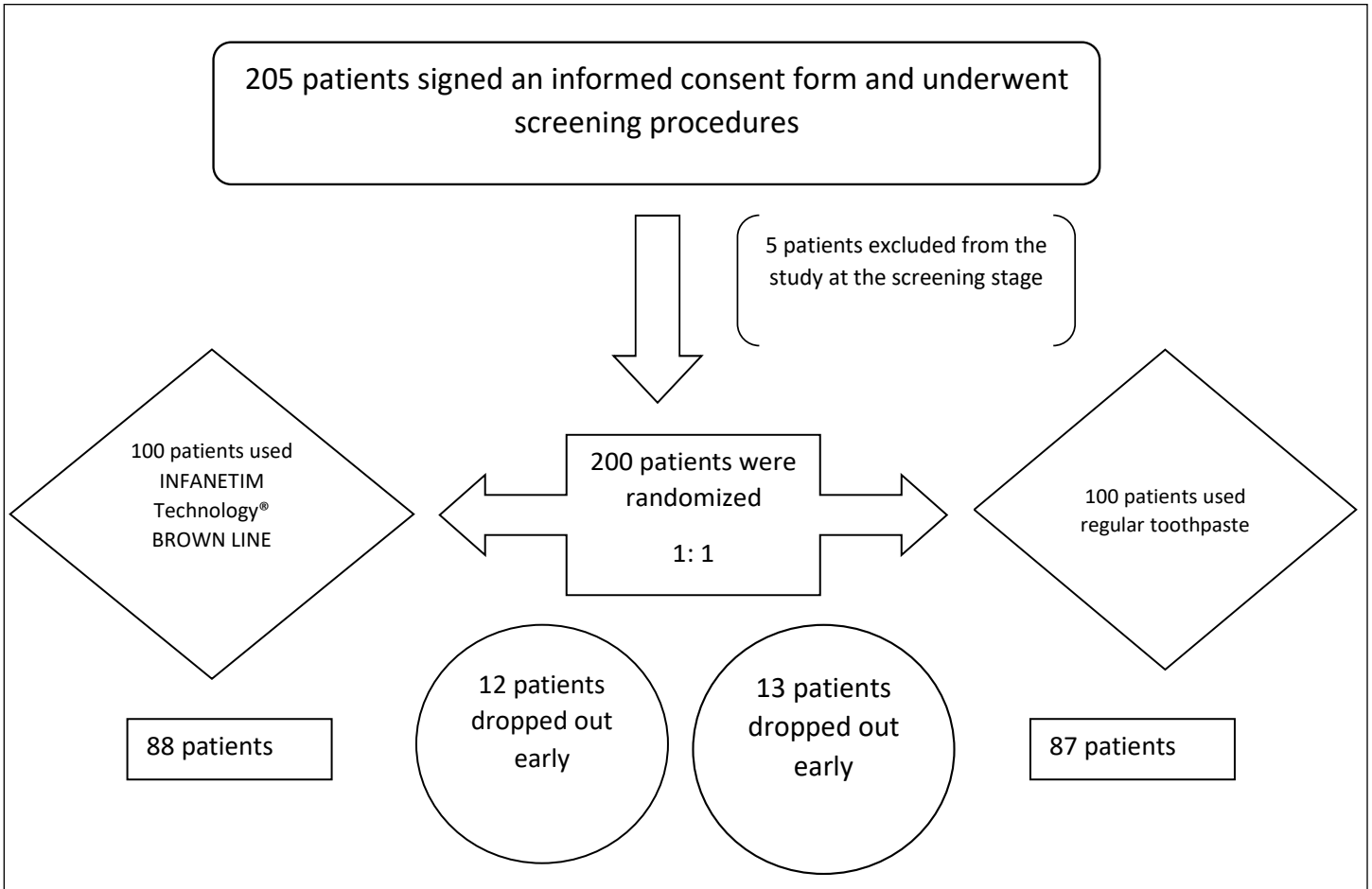

Figure 1: Patient Allocation

12 patients in the study group withdrew informed consent, 10 were found to be non-compliant based on the results of the patient diary check at the completion visit. 2 patients in the comparison group did not contact after randomization, 5 patients with drew informed consent, 6 patients were found to be non-compliant based on the results of the patient diary check at the completion visit.

is excluded. For the rest of the critical parameters, the sample was also homogeneous.

Patients included in the study showed initially comparable glycosylated hemoglobin values when compared between groups. No patient reported diabetic complications at the screening visit. One third of the patients showed signs of gingivitis and periodontitis. One fifth of the patients had an active (untreated) carious process. An unsatisfactory OHS was registered in almost all patients (3-4) (Table 1).

In patients who have used INFANETIM Technology® BROWN LINE toothpaste for 36 weeks, a clinically significant decrease in the level of glycosylated hemoglobin with a final mean of less than 6% corresponds to the state of very well controlled diabetes mellitus.

In more than 70% of cases in the study group, gingivitis was not detected, in other patients of the group, inflammation of a mild severity was recorded, as evidenced by a decrease in the PMA index compared to the initial data (26,15 vs. 35,20 at Visit 0), as well as a

Table 1: The ratio of patient groups by baseline parameters before the start of the study

Indicator	Patients in the study group (M ± SD) N = 88	Control group patients (M ± SD) N = 87	P
Age, years	53,2±3,3	54,0±4,9	0,46
HbA1c, %	6,400±0,9	6,438±0,84	0,74
Diabetic, years	1,91±1,00	1,6±1,23	0,83
Complications, %	0	0	1,00
Gingivitis, %	31,82±1,0	35,63±8,1	0,51
Periodontitis, %	30,68±6,58	32,18±1,26	0,15
Caries, %	23,86±7,95	20,69±5,94	0,47
CPITN	3,15±0,6	3,81±0,2	0,11
PMA	35,20±3,1	31,16±1,1	0,07
OHS	4,11±1,91	3,13±1,73	0,20
DMFT	13,32±2,4	14,41±1,3	0,72

M – Mean; SD – Standard Deviation; P – p-value; HbA1c – Glycosylated hemoglobin; CPITN – Community Periodontal Index of treatment Needs; PMA – Papillary-Alveolar Index as modified by Parma, 1960; OHS –Greene-Vermillion Oral Hygiene Index; DMFT – Decayed, Missed and Filled Tooth Index

statistically significant difference between the groups at the end of the research ($p<0.05$).

The frequency of such manifestations of periodontal diseases as the presence of a periodontal pocket, gingival recession and a false periodontal pocket was 3 times higher in the control group than in the study group. We draw the readers' attention to the fact that the average depth of the periodontal pocket, measured at the completion visit, is also greater in the control group and was 5.21 ± 1.3 mm, which corresponds to the average severity of periodontitis. In the study group, the depth of the periodontal pocket was on average 3.86 ± 0.38 mm, which corresponds to mild periodontitis.

The fact of the presence of new carious cavities was recorded 2 times less often in the group of patients using INFANETIM Technology® BROWN LINE toothpaste, which was reflected, among other things, in a more pronounced negative increase in the intensity of caries by the difference in the dental indices of DMFT.

The CPITN index indicators in the comparison group indicated the prevalence of type II-III recession among patients with signs of periodontitis, in the study group patients predominantly recession was detected within the attached gums.

Almost all indices (except for OHS) showed statistically significant differences between groups at the study completion visit ($p <0.05$) (Table 2).

Thus, the incidence of caries and periodontal disease in patients of the comparison group was significantly higher than in patients using INFANETIM Technology® BROWN LINE toothpaste.

Discussion

The results of the study showed a significant decrease in glycosylated hemoglobin in patients in the group who had used INFANETIM Technology® BROWN LINE toothpaste for 36 weeks. The statistical significance of the difference in the level of glycosylated hemoglobin between the groups at the end of the study reached differences that are at the borderline of statistical significance ($p = 0.05$), it can be assumed that with an increase in the sample of patients, the main indicators might show significant differences. It should be noted that the average decrease in the indicator for the study group was 0.478%, which is a clinically significant change [16,17]. At the same time, in the control group, the decrease was less pronounced, within the margin of error, and did not reach clinical significance (0.249%). Therefore, to prove the pilot hypothesis about significant lowering of glucose level in patients with diabetes using INFANETIM Technology® BROWN LINE toothpaste for at least 36 weeks, a study with bigger sample size should be recommended. Besides, a profound research with widen biochemical check-up for triglycerides, cholesterol, and glycemia should be considered. Glucose tolerance curves were not available in this study as the patients were not disciplined enough to work with the diary records accurately, so the next study should foresee the instruments of distant monitoring of patient measurements.

With good blood glucose control and the achievement of the recommended target HbA1c levels, the risk of diabetes complications is significantly reduced. Patients included in the study had target levels of this indicator and were in the zone of minimal risk of complications. To study the effects of toothpaste on reducing the risk of complications, it is necessary to conduct a study with the participation of patients with high levels of glycosylated hemoglobin.

The Greene-Vermillion oral hygiene index showed no difference between the groups, but found an improvement in this indicator by the end of the study in both groups. The authors suggest that the effect is associated, firstly, with a fairly high compliance of patients with the procedure for brushing teeth (analyzed on the basis of data from patient diaries) and, secondly, with teaching the Bass technique and introducing dental floss, rinses and irrigators into hygienic use, which resulted in a satisfactory oral hygiene performance.

The study was focused on the patients with type II diabetes mellitus that is well-controlled and the follow-up period was too short to assess long term effectiveness and patients compliance. Longer period of study and observation with the participation of patients with uncontrolled form of the disease is required to assess the effect of the toothpaste on the risk of complications.

Table 2: The ratio of patient groups at the end of the study

Indicator	Study group (M ± SD) N = 88	Control group (M ± SD) N = 87	P
HbA1c, %	5,717±0,8	6,189±0,71	0,05(*)
Complications, %	0	0	1,00
Gingivitis, %	27,27±2,0	35,63±2,1	0,02*
Periodontitis, %	10,23±2,9	33,33±4,1	0,02*
Caries, %	10,23±4,32	21,84±3,77	0,03*
CPITN	2,13±1,0	3,14±0,4	0,04*
PMA	26,15±7,1	35,17±1,6	0,02*
OHS	1,71±1,51	1,72±0,01	0,72
DMFT	5,43±1,3	11,86±0,7	0,02*
Increaseintheintensityofcaries	-7,89	-2,55	0,01*

Conclusion

The results of the study showed a significant positive effect of the INFANETIM Technology® BROWN LINE toothpaste on the condition of hard tissues of teeth and periodontium in patients with compensated type II diabetes mellitus compared with the control group who used ordinary oral care products.

The use of INFANETIM Technology® BROWN LINE toothpaste showed good dynamics not only in changing the dental status of patients with diabetes mellitus, but also made it possible to reveal a clinically significant decrease in the level of glycemia after 36 weeks of use, which opens up new possibilities for the successful complex management of patients with type II diabetes.

References

1. WHO, Diabetes (N.A.) Available at: https://www.who.int/health-topics/diabetes#tab=tab_1(accessed 09/20/2021);
2. Martin, A., Komada, MR., Sane, DC. (2003) Abnormal angiogenesis in diabetes mellitus. Med Res Rev, 23(2): 117-145.
3. (2007) KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. KDOQI. Am J Kidney Dis, 49(2 Suppl 2): S12-154.

4. Feldman, EL., Callaghan, BC., Pop-Busui, R., Zochodne, DW., Wright, DE., Bennett, DL., (2019) Diabetic neuropathy. Nat Rev Dis Primers, 5(1): 42.

5. Bourne, RR., Stevens, GA., White, RA., Smith, JL., Flaxman, SR., Price, H., et al. (2013) Lancet Global Health, 1: e339-e349.

6. Klein, R., Klein, BE., Moss, SE., Cruickshanks, KJ. (1998) The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology, 105(10): 1801-1815.

7. Martin, A., Komada, MR., Sane, DC. (2003) Abnormal angiogenesis in diabetes mellitus. Med Res Rev, 23(2): 117-145.

8. Ship, JA. (2003) Diabetes and oral health: an overview. J Am Dent Assoc, 134(1): 4S-10S.

9. Mata, AD., Marques, D., Rocha, S., Francisco, H., Santos, C., Mesquita, MF., (2004) Effects of diabetes mellitus on salivary secretion and its composition in the human. Mol Cell Biochem, 261(1-2): 137-142.

10. Manfredi, M., McCullough, MJ., Vescovi, P., Al-Kaarawi, ZM., Porter, SR. (2004) Update on diabetes mellitus and related oral diseases. Oral Dis, 10(4): 187-200.

11. Meurman, JH., Collin, H., Niskanen, L., Töyry, J., Alakuijala, P., Keinänen, S., (1998) Saliva in non-insulin-dependent diabetic patients and control subjects: The role of the autonomic nervous system. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 86(1): 69-76.

12. Sreebny, LM., Vissink, A. (2010) Dry Mouth, The Malevolent Symptom: A Clinical Guide. Hoboken, NJ., Wiley-Blackwell.

13. Preshaw, PM., Alba, AL., Herrera, D., Jepsen, S., Konstantinidis, A., Makrilakis, K., (2012) Periodontitis and diabetes: a two-way relationship. Diabetologia, 55(1): 21-31.

14. Bascones-Martínez, A., Muñoz-Corcuera, M., Bascones-Ilundain, J. (2015) [Diabetes and periodontitis: A bidirectional relationship]. Med Clin (Barc), 145(1): 31-35.

15. Ower, P. (2019) New classification system for periodontal and peri-implant diseases. Dental Update, 46(1): 8-11.

16. Lenters-Westra, E., Schindhelm, RK., Bilo, HJ., Groenier, KH., Slingerland, RJ. (2014) Differences in interpretation of haemoglobin A1c values among diabetes care professionals. Neth J Med, 72(9): 462-466.

17. Russian clinical guidelines for the treatment of type II diabetes mellitus in adults. https://rae-org.ru/system/files/documents/pdf/saharnyy_diabet_2_tipa_u_vzroslyh.pdf (accessed 09/20/2021).