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Genotoxic markers in patients with diabetes mellitus (Literature review)

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This paper considers studies aimed at identifying markers of genotoxicity (chromosomal aberrations, micronuclei, and DNA damage assessed by the DNA comet assay) in patients with both gestational diabetes mellitus (GDM) and diabetes type 1 and 2 (T1DM and T2DM, respectively), as well as possible changes in the levels of these genotoxic markers under the influence of medicines and nutritions. Patients with T2DM are characterized by an increased level of genotoxicity markers. The results of genotoxicity markers in patients with T1DM and GDM studies are contradictory, however, they indicate the presence of an increased genotoxic load rather than its absence. The levels of genotoxic damage in diabetic patients may be reduced by physical exercises, diet, and/or hypoglycemic drugs. Metformin, Afobazole and Noopept are recommended for experimental and clinical studies as possible drug candidates that reduce the levels of genotoxic biomarkers in diabetic patients.

Keywords: diabetes mellitus type 1 and 2; gestational diabetes; chromosomal aberrations; micronuclei; DNA comet assay; DNA damage; genotoxicity; antimutagenicity.

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Генотоксические маркеры у больных сахарным диабетом (обзор литературы)

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В работе рассмотрены исследования, направленные на выявление маркеров генотоксичности (хромосомные аберрации, микроядра и повреждения ДНК, регистрируемые методом ДНК-комет) у пациентов с гестационным сахарным диабетом (ГСД) и сахарным диабетом (СД) 1-го и 2-го типов, а также возможные изменения уровней этих генотоксических маркеров под влиянием лекарственных препаратов и диет. Больные СД 2-го типа характеризуются увеличенным уровнем маркеров генотоксичности. Результаты исследований маркеров генотоксичности у пациентов с СД 1-го типа и ГСД противоречивы, однако, свидетельствуют скорее о наличии повышенной генотоксической нагрузке, чем об ее отсутствии. Уровни генотоксических повреждений у больных СД могут быть снижены под влиянием физических упражнений, диет и/или гипогликемических лекарств. К экспериментальному и клиническому изучению в качестве возможных лекарственных кандидатов, снижающих уровни генотоксических биомаркеров у больных диабетом, рекомендованы метформин, Афобазол® и Ноопепт®.

Ключевые слова: сахарный диабет 1-го и 2-го типов; гестационный диабет; хромосомные аберрации; микроядра; метод ДНК-комет; повреждения ДНК; генотоксичность; антимутагенность.

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INTRODUCTION

In 2017, there were 463 million people globally with diabetes mellitus (DM). According to forecasts the number of people with this pathology will increase steadily in the medium term and will reach 693 million by 2045 [1–3]. In the Russian Federation at the beginning of 2019, there were 4,584,575 patients with DM (3.12% of the population of the Russian Federation), including 256.2 thousand patients with type 1 diabetes (T1DM), 4.24 million people with type 2 diabetes (T2DM), (92.49% of the total number of DM patients), and 89.9 thousand patients with other types of DM. According to the statistics, since 2000, the number of DM patients in Russia has grown 2.2-fold [4].

General ideas about the pathogenesis of DM and its complications have been discussed repeatedly and in detail in the modern literature. They are summarized schematically in Figure 1 [5–9]. Oxidative stress caused by hyperglycemia and an integral part of the pathogenesis of DM, as well as the associated processes of lipid peroxidation, represents a source of reactive oxygen species and overoxidized lipids. Many studies represent free radical DNA damage as the main mechanism of endogenous mutagenesis [10].

Against the background of existing ideas about the medical significance of genotoxic lesions, their role in the occurrence of neoplasms, hereditary diseases, and miscarriages [11], we can explain the interest in the study of genotoxicity markers in DM patients.

This review aimed to analyze the results of studies performed using the most common markers of genotoxicity in patients with T1DM, T2DM, and gestational diabetes and to discuss possible methods of reducing genotoxicity in such category of patients.

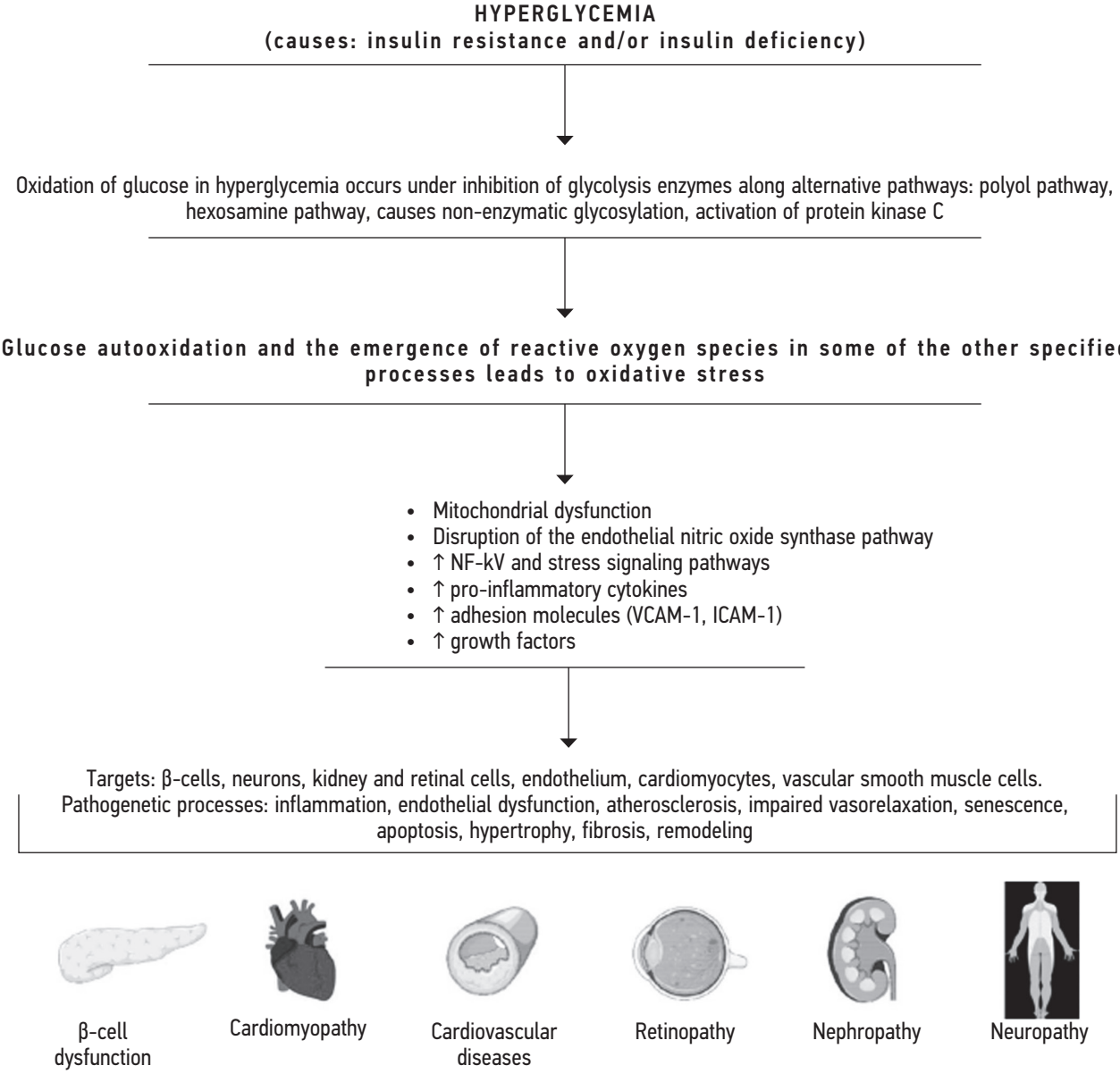

Figure 1. Medical significance of oxidative damage to nucleic acids, lipids, and proteins in hyperglycemia ([9], significantly modified)

MATERIALS AND METHODS

Literature search was performed from January 1, 1990 to January 31, 2021 using the MedLine/PubMed scientific literature database (National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA, http://www.ncbi.nlm.nih.gov/PubMed) and the scientific electronic library of the Russian Science Citation Index (http://elibrary.ru). The search was performed using the keywords "diabetes", "micronuclei", "DNA comet", "chromosomal aberrations", and the corresponding Russian-language translations for Russian sources. When searching the PubMed database, we additionally used the "humans" filter. We considered studies published both in Russian and English languages for which full-text versions of articles were available, as well as those indexed by DOI for English sources.

Articles focused on identifying the most verified and widely used genotoxic markers in peripheral blood lymphocytes were recognized as acceptable for registration and analysis, subject to the following criteria:

1) the balance of the populations surveyed by gender and age in the group of patients and healthy volunteers, each of which exceeded 10 people;

2) the use of verified cytogenetic research methods [chromosomal aberrations (CA) test, the cytokinesis-block micronucleus (MN) cytome assay, registration of DNA damage by the DNA comet assay];

3) availability of acceptable statistical analysis, presentation of mean values for groups with standard errors or standard deviations;

4) compliance with ethical standards during the study, approval of the study protocol by the Ethics Committee.

From the full-text versions of the articles, information was selected about the research subjects (the number of subjects in each group, gender, age, duration of disease, concomitant diseases and medications, smoking status, alcohol consumption, and nutritional quality) and biomarkers studied, as well as the actual research results, such as "mean ± SD". Only publications containing a detailed description of the study design and results were considered in detail.

During the discussion of the results, the data obtained in the analysis of genotoxicity markers in the cells of the buccal and lingual epithelium were also recorded, as well as other results of interest from the perspective of assessing the modification of genotoxicity in this category of patients.

RESULTS

An electronic search in the MedLine/PubMed database yielded a total of 598 publications, and among them, 50 original research articles were selected, on the basis of full-text reviews, that met the selected inclusion criteria. MN or CA in peripheral blood lymphocytes (PBL) were used as biomarkers of genotoxicity in 14 cases, and DNA damage assessed by the DNA comet assay in 36 cases. The information collected is summarized in Tables 1 and 2.

The subjects of the study were patients with type 1 or 2 diabetes or gestational diabetes. Unless otherwise indicated in the table, patients with bacterial infections, cancer, or hepatitis C or B and those who were HIV positive were excluded. Patients must not have taken immunosuppressants or antibiotics for at least 1–3 months before the study and must not have undergone X-ray examination or radiation therapy for more than 6 months before the study. Control groups consisted of healthy volunteers living in the same region, matched by age and gender to the patient groups, and the presence of gestational diabetes during pregnancy. Medical history and information about recent medical procedures and medications taken were collected from study participants. In some studies that used questionnaires, data were also collected on smoking status, alcohol consumption, nutritional quality, and lifestyle. Peripheral blood was collected for research by venipuncture. The protocols of all mentioned studies were approved by the Ethics Committees.

Patients with gestational diabetes mellitus (GDM)

In 2019, 16% of pregnancies (20 million births) ended in the birth of children with hyperglycemia, mainly due to gestational diabetes [12, 13]. The search identified only four studies of genotoxicity biomarkers in patients with gestational diabetes. Two of them were focused on the analysis of cytogenetic status [14, 15], and the assessment of DNA damage was discussed in two studies [16, 17].

The results of cytogenetic studies did not coincide; however, they shared a common tendency. Some researchers [14] revealed an increase in the levels of CA in patients compared with a comparable sample of healthy pregnant women. Other researchers [15] registered a moderate but statistically insignificant increase in the level of CA when compared between pregnant women with GDM and without DM and newborns in mothers with and without GDM. The authors explained the absence of the initially assumed cytogenetic effect by a relatively short period of exposure to an increased glucose level (the average gestational period for detecting GDM is 25.4 ± 5.6 weeks), as well as by proper control over the level of glycemia during pregnancy.

An increased level of DNA damage in PBL, defined as the average value of the percentage of DNA in the comet tail, was observed in two studies [16, 17], the total sample of which consisted of 160 patients and 155 healthy pregnant women. The discovered phenomenon was explained by the authors as a consequence of hyperglycemia, obesity, hypertension, and/or insulin resistance.

Lymphocytes from infants born from GDM mothers were also examined. As a result, a positive correlation was established between the mean level of glucose in the mother's blood and an increased level of DNA damage in the children [18]. In addition, newborns of mothers with GDM had a higher level of DNA damage in umbilical cord blood cells compared with those of mothers with euglycemia [19].

Table 1. Results of studies of cytogenetic markers of genotoxicity in lymphocytes of patients with diabetes mellitus

First author, country [1] and year of publication	Source	Group size		Average age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied cohort of patients (concomitant diseases, drugs taken), comments	"Number of MN per 1000 binuclear cells, ‰" or "Number of CA per cell" (*M* ± SD)		Multiplicity of excess
		P (m/f)	C (m/f)	P	C				P	C	
Patients with gestational diabetes mellitus											
M. Toljic et al., Serbia, 2017	[14]	37 (0/37)	31 (0/31)	33 (24–40)	31 (20–44)	Not applicable	–	Pregnant women who had not previously been diagnosed with DM were included; blood was sampled in the period between weeks 24 and 28. A group of patients with mild gestational hyperglycemia was also included	12.76 ± 6.31**	6.32 ± 3.37	2.02
M. Witczak et al., Poland, 2017	[15]	35 (0/35)	30 (0/30)	32 ± 4	30 ± 7	Not applicable	5.2 ± 0.5	Pregnant women with GDM were included. The level of CA in the blood of their newborns was also assessed	0.0065 ± 0.0138 (CA)	0.0045 ± 0.009 (CA)	–
Patients with type 1 diabetes mellitus											
O. Mihaljevic et al., Serbia, 2018	[21]	13 (6/7)	19 (9/10)	10.4 ± 3.9	11.9 ± 3.7	–	10.24 ± 2.03	–	7.77 ± 2.95**	2.10 ± 1.99	3.7
M. Witczak et al., Poland, 2014	[22]	17 (0/17)	40 (0/40)	30 ± 4	31 ± 6	16 ± 7.6	6.3 ± 1.0	The study included women with type 1 DM in trimester I of pregnancy, taking folic acid at a dose 400 μg. The umbilical cord blood lymphocytes from newborns were also sampled	2.35 ± 1.07** (1.42 ± 0.60* in newborns)	0.86 ± 0.90 (0.67 ± 0.79 in newborns)	2.73 (2.11 in newborns)
N. Cinkilic et al., Turkey, 2009	[23]	35 (20/15)	15 (9/6)	32 ± 10	39 ± 9	1–22	8.37 ± 1.36	The study included patients in whom type 1 DM was detected before the age of 30 years, insulin therapy for up to 1 year	0.009 ± 0.012 (CA), 1.83 ± 1.15 (MN)	0.007 ± 0.009 (CA) 1.53 ± 0.64 (MN)	–

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Table 1 (continued)

First author, country [1] and year of publication	Source	Group size		Average age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied cohort of patients (concomitant diseases, drugs taken), comments	"Number of MN per 1000 binuclear cells, ‰" or "Number of CA per cell" ($M \pm SD$)		Multiplicity of excess
		P (m/f)	C (m/f)	P	C				P	C	
Patients with type 2 diabetes mellitus											
M. Salimi et al., Iran, 2016	[25]	50 (22/28)	50 (25/25)	58 ± 10	57 ± 10	10–20	9.22 ± 1.76 vs. 5.0 ± 0.5 (in the control group)	Information on the drugs taken was not provided. A group of patients with T2DM and nephropathy was included separately (50 patients, m/f ratio was 32/18; average age was 60 ± 11; the duration of the disease was 1–20 years; HbA1c was 7.5 ± 1.82) [2]	4,4 ± 0,7** (in the group of patients with T2DM and nephropathy 7.54 ± 2.52)	2.5 ± 0.3	1.8
M. Prasad et al., India, 2015	[26]	22 (13/9)	42 (30/12)	60 ± 12	58 ± 11	0.08–20	–	Information on the drugs taken was not provided. The additional group included 20 patients with peripheral neuropathy, with a m/f ratio of 7/13; average age of 58 ± 11; and disease duration of 10–20 years	6 ± 7** (in the group of patients with neuropathies 5 ± 0.5)	0.3 ± 0.5	20.0
M.K. Harishankar et al., India, 2015	[46]	147 (61/86)	54 (25/29)	52 ± 1	–	0.5–10	–	Metformin and/or glimepiride. Additionally, the MN level in the cells of the urothelial epithelium was assessed	16.1 ± 0.3*	2.5 ± 0.2	6.4
R. Saraswathy et al., India, 2014	[24]	50 (31/19)	50 (31/19)	52 ± 9	52 ± 9	9.02 ± 6.78	–	Information on the drugs taken was not provided. 50 patients with diabetic neuropathy were also included, with a m/f ratio of 31/19; average age of 58 ± 11; and disease duration of 0.5–30	0.03 ± 0.02* (CA) (0.086 ± 0.04** in the group of patients with neuropathy)	0.014 ± 0.0001	2.1 (6.1)
S.C. Corbi et al., Brazil, 2014	[41]	30 (12/18) 30 (10/20)	30 (12/18)	48 ± 8 50 ± 7	39 ± 4	6.2 ± 4.2 5.2 ± 6.6	10.4 ± 1.9 (6.6 ± 0.9) vs. 5.4 ± 0.21 (in the control group)	Patients with dyslipidemia and periodontitis with high and low levels of glycated hemoglobin were included	5.42 ± 3.80** (8.17 ± 5.41)	1.57 ± 0.79	3.4

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Table 1 (continued)

First author, country [1] and year of publication	Source	Group size		Average age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied cohort of patients (concomitant diseases, drugs taken), comments	"Number of MN per 1000 binuclear cells, ‰" or "Number of CA per cell" ($M \pm SD$)		Multiplicity of excess
		P (m/f)	C (m/f)	P	C				P	C	
D.N. Binici et al., Turkey, 2013	[27]	50 (15/35)	30 (8/22)	58 ± 13	44 ± 14	5.4 ± 4.3	8.93 ± 2.56	Sulfonylurea and/or metformin	3.5 ± 1.0**	1.8 ± 0.7	1.9
S.K. Shettigar et al., India, 2012	[29]	25 (14/11)	24 (11/13)	58 ± 11 (m) / 51 ± 15 (f)	56 ± 10 (m) / 49 ± 7 (f)	Information was not provided	9.7 ± 1.3 vs. 7.9 ± 1 (in the control group)	Information was not provided	No differences were revealed 11.3 ± 3.5 (m) / 11.0 ± 3.9 (f)	9.3 ± 3.1 (m) / 11.8 ± 4.6 (f)	–
R.P. Palazzo et al., Brazil, 2012	[28]	22 (12/10)	22 (5/17)	63 ± 9	63 ± 8	1.5 ± 0.9	–	Patients receiving maintenance hemodialysis therapy were included; the intake of ACE inhibitors, hypoglycemic drugs, diuretics, in some cases, recombinant erythropoietin and iron hydroxide	5.5 ± 4.0*	3.5 ± 2.8	1.6
S.A. Supriya et al., India, 2011	[81]	46 (24/22)	25 (16/9)	55.2	50.5	Over 8 years	–	Patients with autonomic neuropathy (varying degrees of coronary artery disease) were included	15.2 ± 2.3*	10.6 ± 1.2	1.4
L.M. Martínez-Pérez et al. Mexico, 2007	[82]	15 (5/10)	10 (2/8)	49 ± 7	46 ± 4	Information was not provided	–	Oral hypoglycemic drugs	6.53 ± 2.03**	3.10 ± 1.79	2.1

* $p < 0.05$; ** $p < 0.001$. [1] State where patients were enrolled in the study. [2] Hereinafter, in brackets, the data are presented as the number of patients in the group (men/women); average age; diabetes duration; and the level of glycated hemoglobin, mg/dl.

Note. SD – standard deviation; P – patient group, C – control groups, PBL – peripheral blood lymphocytes, HbA1c – glycated hemoglobin, MN – micronucleus, CA – chromosomal aberrations, GDM – gestational diabetes mellitus. Studies that revealed no statistically significant difference between the groups of patients and healthy volunteers are highlighted in color.

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Table 2. Results of studies of genotoxic markers in lymphocytes of patients with diabetes mellitus by the DNA comet assay (alkaline version, unless otherwise indicated)

First author and year of publication	Source	Group size		Age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied patient population (concomitant diseases, medications taken), comments	Multiplicity of excess of % DNA in the comet tail, significance of differences from the control group
		patients (m/f)	control (m/f)	patients (m/f)	control (m/f)				
Patients with gestational diabetes mellitus									
R.B. Gelaleti et al., Brazil, 2015	[16, 83]	46 (0/46)	41 (0/41)	31 ± 5	30 ± 6	Not applicable	6.33 ± 0.90	Pregnant women who had not previously been diagnosed with DM were included; blood was sampled in the period between weeks 24 and 28. A group of female patients with mild gestational hyperglycemia was also included (24; 32 ± 4; 5.74 ± 0.67)	Only the presence of a difference was mentioned, without specifying the multiplicity of the excess *
J. Basu et al., India, 2018	[17]	114 (0/114)	114 (0/114)	26 ± 5	24 ± 4	Not applicable	6.00 ± 0.66	Pregnant women who had not previously been diagnosed with DM were included; blood was sampled in the period between weeks 24 and 28	The authors register an approximately 8–10-fold increase in the level of DNA damage, but the registration of the result differed from that recommended ** [63]
Patients with type 1 diabetes mellitus									
O. Mihaljevic et al., Serbia, 2018	[21]	13	19 (9/10)	10.4 ± 3.9	11.9 ± 3.7	–	10.24 ± 2.03	–	The authors recorded an approximately 2–5-fold excess of the level of DNA damage; however, registration of the result differed from that recommended ** [63]
N. Wyatt et al., UK, 2006	[84]	11	24	18–77	18–77	23.7	–	Metformin (dosages not specified)	~1.5*
J. Varvarovská et al., Czech Republic, 2004	[85]	50 (29/21)	30	11.96 ± 4.69	–	4.25	9.5 ± 2.5	–	No differences were revealed
Y. Dinçer et al., Turkey, 2003	[39]	45 (21/24)	40 (17/23)	32 ± 8	35 ± 6	9 ± 6	7.04 ± 0.85	Among the complications, microangiopathies, retinopathies, and neuropathies were observed	The authors recorded an approximately 1.2–1.5-fold excess of the level of DNA damage; however, the registration of the result differed from that recommended ** [63]

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Table 2 (continued)

First author and year of publication	Source	Group size		Age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied patient population (concomitant diseases, medications taken), comments	Multiplicity of excess of % DNA in the comet tail, significance of differences from the control group
		patients (m/f)	control (m/f)	patients (m/f)	control (m/f)				
S. Sardaş et al., Turkey, 2001	[51]	15	30	Information was not provided	Information was not provided	5.2 ± 8.1	–	The study included smokers (26 in the T2DM group, 11 in the control). No medication information was provided. Vitamin E supplementation reduced the level of DNA damage	The authors recorded an approximately 1.7-fold excess of the level of DNA damage; however, the registration of the result differed from that recommended * [63]
M.P. Hannon-Fletcher et al., UK, 2000	[43]	50 (30/20)	50 (28/22)	36 ± 2	38 ± 1	–	7.71 ± 0.03	Thirteen diabetic patients had at least one complication, namely retinopathy, nephropathy, neuropathy, and macrovascular diseases, eight patients were smokers. No significant differences were revealed in lymphocytes, monocytes, and whole blood; however, in the neutrophil fraction, the levels of DNA damage were significantly higher ($p < 0.001$) than those in the control group	No differences were revealed
S. Astley et al., UK, 1999	[42]	49 (31/18)	42 (20/22)	39 ± 7	40 ± 9	15.2 ± 5	9.0 ± 1.2	Thirteen patients had a history of retinopathy, and eight had patients had neuropathy. Vitamin E supplementation (400 IU/day) for 8 weeks did not have a significant effect on the level of DNA damage	No differences were revealed
A.R. Collins et al., Slovakia, 1998	[86]	10 (10/0)	10 (10/0)	48 ± 8	43 ± 6	15.6	11.0 ± 2.9	Eight patients had chronic complications (neuropathy and/or retinopathy); 2 patients had no diabetic complications	2.3 *
D. Anderson et al., UK, 1998	[61]	22 (11/11)	20 (9/11)	55 ± 7	50 ± 13	Over 5 years	7.61 ± 0.31	Information on the drugs taken was not provided	No differences were revealed

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Table 2 (continued)

First author and year of publication	Source	Group size		Age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied patient population (concomitant diseases, medications taken), comments	Multiplicity of excess of % DNA in the comet tail, significance of differences from the control group
		patients (m/f)	control (m/f)	patients (m/f)	control (m/f)				
Patients with type 2 diabetes mellitus									
A. Rao et al., India, 2020	[87]	50	50 (+50)	30–60	30–60	Information was not provided	<7	The experimental group included patients with T2DM and periodontitis without any concomitant systemic diseases. The control group consisted of both healthy volunteers and patients with periodontitis, but without T2DM or other systemic diseases	No differences were revealed (however, the mean values were higher in the T2DM group, $p = 0.515$)
A. Raghav et al., India, 2018	[88]	100	50	56 ± 10	57 ± 12	Information was not provided	–	Information was not provided. Half of the DM patients also had a history of chronic kidney disease	3.5–4.8 ** (depending on the absence or presence of kidney pathologies)
M. Pittaluga et al., Italy, 2015	[58]	12 (12/0)	12 (12/0)	62 ± 4	61 ± 4	Over 5 years	6.7 ± 0.2 vs. 5.5 ± 0.1 (in the control group)	Metformin as monotherapy or in combination with repaglinide or gliclazide. Significant ($p < 0.05$) decrease from baseline after 4 months of moderate training	No differences were revealed
S.A. Bukhari et al., Pakistan, 2015	[89]	80 (40/40)	80 (40/40)	Cohorts included young and elderly patients	Cohorts included young and elderly patients	Information was not provided	Over 7.5	Information on the drugs taken was not provided	The authors register an approximately 2–3-fold excess of the level of DNA damage; however, the registration of the result differed from that recommended ** [63]
A. Merecz et al., Poland, 2015	[90]	120 (67/53)	146 (77/69)	64 ± 12	65 ± 15	Information was not provided	–	Information on the drugs taken was not provided. A group with neuropathies was also included [89 (42/47); 66 ± 11], in which an increased level of DNA damage was revealed ($p < 0.001$)	1.2–2 ** (depending on the genotype)

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Table 2 (continued)

First author and year of publication	Source	Group size		Age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied patient population (concomitant diseases, medications taken), comments	Multiplicity of excess of % DNA in the comet tail, significance of differences from the control group
		patients (m/f)	control (m/f)	patients (m/f)	control (m/f)				
D.J. Xavier et al., Brazil, 2015	[91]	27 (11/16)	16 (7/9)	53 ± 9	53 ± 7	10.1 ± 4.0	–	Metformin and/or insulin	The authors recorded an approximately 2.3-fold excess of the level of DNA damage; however, the registration of the result differed from that recommended * [63]
D.J. Xavier et al., Brazil, 2014	[56]	10 (3/7)	12 (7/9)	46 ± 12	53 ± 7	6.9	9.9 ± 2.0, after treatment 9.2 ± 2.1	Insulin and/or oral hypoglycemic drugs, as well as drugs for treatment of concomitant pathologies. For 7 days, the patients adhered to a diabetic diet, after which the level of DNA damage decreased significantly ($p < 0.05$)	The authors recorded an approximately 2.3-fold excess of the level of DNA damage, however, the registration of the result differed from that recommended * [63]
E. Müllner et al., Austria, 2013	[48]	76 (34/42)	21 (6/15)	65 ± 7	63 ± 6	Information was not provided	7.26 ± 1.08	Oral hypoglycemic drugs and/or insulin. After 4 weeks of increased consumption of vegetables and vegetable oil, a decrease in the level of DNA damage was observed	No differences were revealed
E. Tatsch et al., Brazil, 2012	[37]	32 (14/18)	30 (16/14)	57 ± 6	54 ± 7	10.7 ± 6	7.7 ± 1.7 vs. 5.2 ± 0.7 (in the control group)	in 9% of those treated with insulin alone, in 72% of those treated with oral hypoglycemic drugs, and in 19% of those treated with a combination thereof	The authors recorded an approximately 5–6-fold excess of the level of DNA damage, however, the registration of the result differed from that recommended * [63]
R.P. Palazzo et al., Italy, 2012	[28]	22 (12/10)	22 (5/17)	63 ± 9	63 ± 8	1.5 ± 0.9	–	Patients receiving maintenance hemodialysis therapy, ACE inhibitors, hypoglycemic drugs, diuretics, and in some cases, recombinant erythropoietin and iron hydroxide were included	2.2 * (the version of the DNA comet assay is not specified)

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Table 2 (continued)

First author and year of publication	Source	Group size		Age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied patient population (concomitant diseases, medications taken), comments	Multiplicity of excess of % DNA in the comet tail, significance of differences from the control group
		patients (m/f)	control (m/f)	patients (m/f)	control (m/f)				
S.I. Salem et al., Egypt, 2012	[92]	28 (8/20)	25 (10/15)	53 ± 5	53 ± 7	9.7 ± 2.1	9.6 ± 2 vs. 3.4 ± 0.6 (in the control group)	Patients with a history of smoking, coronary heart disease, congestive heart failure, chronic liver diseases, diabetic nephropathy, rheumatic diseases, and cancer, as well as subjects who had recently undergone radiological procedures (1 month previously), were not included in the study. None of the patients took antioxidant supplements	12.2 **
J. Kasznicki et al., Poland, 2012	[93]	16 (6/10)	19 (10/9)	64 ± 12	65 ± 14	Information was not provided	9.44 ± 1.68 vs. 5.5 ± 0.3 (in the control group)	Information was not provided. An additional group included patients with T2DM and distal symmetric polyneuropathy, where DNA damage was significantly ($p < 0.001$) higher than in the group of patients with T2DM without neuropathy	3.1 *
M. Arif et al., Bangladesh, 2010	[38]	32 (18/14)	25 (15/10)	47 ± 5	49 ± 8	5.6 ± 1.8	8.1 ± 2.88 vs. 2.92 ± 0.64 (in the control group)	Information was not provided. Patients without systemic comorbidities and those not taking antioxidant drugs were included	1.8 ** (DNA comet assay is presented in a neutral environment)
V. Manfredini et al., Brazil, 2010	[94]	11	18	55 ± 7	49 ± 9	~3 years	7.8 ± 2	Metformin. Also included was a group of patients with T2DM with dyslipidemia who received simvastatin therapy (20 mg/day; $n = 14$) or did not receive it ($n = 9$); the level of DNA damage in group 1 was significantly lower than that in the group 2 and higher in both than in the control ($p < 0.05$)	4.0 *

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Table 2 (continued)

First author and year of publication	Source	Group size		Age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied patient population (concomitant diseases, medications taken), comments	Multiplicity of excess of % DNA in the comet tail, significance of differences from the control group
		patients (m/f)	control (m/f)	patients (m/f)	control (m/f)				
E. Ibarra-Costilla et al., Mexico, 2010	[60]	71 (21/50)	14 (3/11)	40–70	40–50	Over 5 years	Over 8.88 ± 1.35	Information on the drugs taken was not provided	No differences were revealed
D.A. Vasiliev et al., Russia, 2008	[95]	17 (0/17)	14 (0/14)	57 ± 3	53 ± 1	Diagnosed for the first time	–	Information on the drugs taken was not provided	No differences were revealed
P.B. Bagatini et al., Brazil, 2008	[96]	25 (13/12)	20 (7/13)	63 ± 9	62 ± 9	2.13 ± 2.08	–	Patients who received maintenance hemodialysis therapy, ACE inhibitors, hypoglycemic drugs, diuretics, and, in some cases, recombinant erythropoietin and iron hydroxide were included	The authors recorded an approximately 1.5–2-fold excess of the level of DNA damage, however, the registration of the result differed from that recommended * [63]
M. Lodovici et al., Italy, 2008	[35]	39 (16/23)	18 (10/8)	41–79	35–70	Information was not provided	7.16 ± 0.19	Metformin as monotherapy or in combination with glibenclamide	2.1 *
A. Sliwinska et al., Poland, 2008	[97]	30 (15/15)	30 (12/18)	60 ± 10	64 ± 12	11.0 ± 7.6	8.1 ± 1.7	Metformin and/or insulin	3.4 **
F. Song et al., China, 2007	[98]	92 (48/44)	113 (64/51)	50 ± 10	52 ± 11	Diagnosed for the first time	7.73 ± 2.19 vs. 5.00 ± 0.46 (in the control group)	Information on the drugs taken was not provided	2.6 *

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Table 2 (continued)

First author and year of publication	Source	Group size		Age, years		Disease duration, years	HbA1c, mg/dl	Characteristics of the studied patient population (concomitant diseases, medications taken), comments	Multiplicity of excess of % DNA in the comet tail, significance of differences from the control group
		patients (m/f)	control (m/f)	patients (m/f)	control (m/f)				
J. Blasiak et al., Poland, 2004	[99]	52 (41/11)	55 (43/12)	61 ± 5	59 ± 6	Information was not provided	8.5 ± 0.4	Oral hypoglycemic drugs (sulfonylurea and/or metformin) and/or insulin. Neither patients nor control groups took antioxidant supplements	1.6 *
V. Pitozzi et al., Italy, 2003	[100]	14 (9/5)	14 (7/7)	62 ± 5	61 ± 4	Information was not provided	7.0 ± 0.3	Metformin as monotherapy or in combination with other drugs	No differences were revealed
Y. Dinçer et al., Turkey, 2002	[36]	63 (33/30)	41 (21/20)	52 ± 6	50 ± 8	Over 10 years	8.4 ± 2.6 vs. 5.5 ± 0.3 (in the control group)	55/63 patients had a history of complications (retinopathy, neuropathy, nephropathy, angiopathy). No medication information was provided. The patients did not take antioxidant vitamins or supplements	The authors recorded an approximately 1.8-fold excess of the level of DNA damage; however, the registration of the result differed from that recommended ** [63]
S. Sardaş et al., Turkey, 2001	[51]	48	30	Information was not provided	Information was not provided	5.1 ± 5.2	–	The study included smokers (26 patients in the T2DM group, 11 patients in the control). No medication information was provided. Vitamin E supplementation reduced the level of DNA damage	The authors register an approximately 2.5-fold excess of the level of DNA damage; however, the registration of the result differed from that recommended * [63]
D. Anderson et al., UK, 1998	[61]	23 (15/8)	20 (9/11)	60.5 ± 5.4	50.1 ± 12.8	Over 5 years	7.1 ± 0.5 vs. 4.4 ± 0.1 (in the control group)	Information on the drugs taken was not provided	No differences were revealed

* $p < 0.05$; ** $p < 0.001$.

Note. HbA1c – glycated hemoglobin. Studies which revealed no statistically significant difference between the groups of patients and healthy volunteers are highlighted in color.

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Thus, at the present stage of research development, it can be concluded that the level of genotoxicity markers is increased both in pregnant women with GDM and their newborns. It is noteworthy that these data are aligned with the results of V.V. Zabrodina, who showed an increase in the levels of DNA damage in pregnant rats and their offspring in a model of streptozotocin-induced diabetes [20]. Nevertheless, it should be borne in mind that nowadays, data of a very limited range of clinical genotoxic studies are available, and a confident conclusion about the genotoxic profile of GDM patients can only be made on the basis of additional results of new independent studies.

Patients with type 1 diabetes mellitus

As a result of the search, 12 articles were selected, including 3 studies using cytogenetic parameters in the PBL of T1DM patients as a biomarker, and 9 studies using DNA damage detected using the DNA comet assay.

In 2 of 3 cytogenetic studies [21, 22], an increased value of MN levels in T1DM patients was revealed [65 patients (26 men, 39 women) were analyzed in total] compared with control groups (74 healthy volunteers, 18 men, 56 women). Study 3 presented only a tendency toward an increase in the CA level in T1DM patients, which was not supported by statistical significance [23].

It is noteworthy that in the group of pregnant T1DM patients, the average number of MN per 1000 cells was significantly higher ($p < 0.001$) than that in the control group of pregnant women. A similar effect was observed in the corresponding groups of newborns ($p < 0.05$). At the same time, there were no significant correlations between the incidence of MN in mothers with T1DM and that in their newborns, the duration of diabetes, or HbA1c levels [22]. This finding is clearly consistent with the data obtained in the study of patients with hyperglycemia due to GDM (see above).

Analysis of DNA damage in patients with T1DM by the DNA comet assay resulted in an ambiguous picture. In four out of nine studies, there were no significant differences between the groups of patients with T1DM (265 patients in total) and the control groups of healthy volunteers (265 subjects). High significance ($p < 0.01$) was revealed only in two out of five studies, indicating an increase in DNA damage in this category of patients. The authors associate the absence of an increased level of DNA damage with a high living standards and an appropriate drug therapy for patients. Thus, despite the formal predominance of studies indicating an increase in genotoxic markers in T1DM patients, the study of genotoxicity markers in this category of patients requires additional research.

Patients with type 2 diabetes mellitus

In comparison with other types of DM, T2DM is the most common disease. Most of the analyzed studies focused on the assessment of genotoxic markers in T2DM. MN were selected as a genotoxicity biomarker in 9 of 34 publications selected for the review, and DNA damage detected by the DNA comet assay was found in 25. A study that met all the inclusion criteria, in which the classical CA method was used, was presented by only one study [24].

In 10 studies focused on the analysis of MN or CA in PBL, 487 patients (219 men and 268 women) and 337 control subjects (165 men and 172 women) were examined. Summary data on age, duration of therapy, and the frequency of MN, as well as the multiplicity factor of the MN frequency in the group of patients compared with the control group are presented in Table 1. In 9 out of 10 studies focused on the analysis of MN or CA, the significance of the differences between groups of patients and the control group was shown, and the significance was high in 6 cases ($p < 0.001$). Two studies [25, 26] showed a correlation between the duration of disease and the incidence of MN, while two others [27, 28] did not justify this correlation. In one study [29], no differences were revealed; the authors explained this by the small size of the surveyed sample of patients, and a small difference between the groups in terms of the levels of glycated hemoglobin HbA1c (9.7 ± 1.3 vs. 7.9 ± 1 mg/dL).

These data are consistent with the results of studies, in which the authors chose the level of MN in the cells of the buccal and lingual epithelium as a biomarker as less invasive methods for obtaining a biomaterial. Thus, in a recent study [30], it was demonstrated that in T2DM patients, the MN level in the cells of the buccal (0.52 ± 0.27 vs. 0.07 ± 0.06‰; $p < 0.001$) and lingual (0.41 ± 0.21 vs. 0.06 ± 0.05‰; $p < 0.001$) epithelium was increased in comparison with that in a group of healthy volunteers of the same age. A similar result was obtained a little earlier by Russian scientists (0.52 ± 0.04 vs. 0.34 ± 0.05‰; $p < 0.05$) [31], as well as by other researchers [32] on a large group of female patients ($n = 146$), when the level of MN in the cells of the buccal epithelium was 1.85 ± 1.4 vs. 0.29 ± 0.4‰ in the control group.

In 25 studies focused on the analysis of the level of DNA damage, assessed by the DNA comet assay in PBL, 1,090 patients were examined (in several studies, the gender of the patients was not specified), and 945 were the control volunteers. A significant increase in the level of damage was revealed in 18 out of 25 publications focused on the study of DNA damage by the DNA comet assay in the PBL of T2DM patients, while in 8 cases the significance was high ($p < 0.001$). At the same time, in 7 out of 25 studies, such a result was not observed, which the authors explained by good control over glycemic status and/or low study power.

The first information on the possible induction of cytogenetic damage in T2DM patients appeared around half a century ago [33, 34]. Based on recent findings showing an increase in the levels of genotoxic markers in T2DM patients in most studies (27 out of 34), it is logical to infer an increased genotoxic load in these patients.

It is noteworthy that several of the cited authors set themselves the task of identifying correlations between the

levels of glycated hemoglobin and genotoxicity biomarkers. Some of them indicated the presence of such a relationship with DNA damage [35–38] or MN [29, 32] in patients with T2DM or DNA damage in T1DM patients [39], while others did not reveal it in patients with T2DM [27, 40, 41] and T1DM [23, 42, 43]. Our own attempts to identify such correlations based on a generalized analysis were unsuccessful.

Thus, the question of the relationship between genotoxicity markers and levels of glycated hemoglobin remains open to date and can only be resolved with a significant expansion of the samples available for analysis.

GENOTOXIC BIOMARKERS IN NUTRITIOLOGICAL AND PHARMACOLOGICAL CORRECTION OF HYPERGLYCEMIA

An integral factor potentially capable of influencing the levels of genotoxic markers in DM patients is the use of drugs and diet to control patients' glycemic status. Their effect can be expressed both as a direct genotoxic effect and as a comutagenic or antimutagenic modification of the action of endogenous genotoxicants, which are products of free radical reactions during oxidative stress, which inevitably accompanies hyperglycemia.

Currently, in published literature there are results of several studies focused on the targeted assessment of the cytogenetic status of patients undergoing therapy with hypoglycemic drugs and/or receiving the diet therapy.

The common design feature of most studies is the absence of a comparable group of T2DM patients not receiving therapy. This does not enable clear differentiation of the effects of endogenous genotoxicants, which are products of oxidative stress that are possible in T2DM, from the effects of exogenous medicinal or dietary factors. In all such cases, it is appropriate to suggest integrative genotoxic effect in the "therapeutic effect – disease" system, rather than the identification of a genotoxic or genotoxicant-modifying effect of a single drug and/or dietary factor.

An increase in the levels of genotoxic markers with drug therapy and/or diet therapy has been demonstrated in several studies. CA levels in PBL increased in T2DM patients receiving chlorpropamide therapy (daily doses were 100–400 mg) compared with a group of healthy, age- and gender-matched volunteers [44].

In T2DM patients who received daily therapy with a combination of pioglitazone (30 mg/day) and glimepiride (4 mg/day) for the long term (over 5 years), an increased frequency of micronuclei in buccal epithelium cells was observed compared with a group of healthy, age- and gender-matched volunteers (8.63 ± 2.23 vs. 2.93 ± 1.4‰; $p < 0.001$) [45].

A greater than 5-fold excess MN level was revealed in the cells of the urothelial epithelium in T2DM patients taking metformin and/or glibenclamide (doses not indicated) in comparison with a group of healthy volunteers (24.98 ± 2.87 vs. 5.02 ± 1.01‰; $p < 0.001$). At the same time, the analysis showed a significant increase in the number of MN in patients taking only metformin (23.02 ± 4.44) or a combination of metformin and glimepiride (24.98 ± 2.87‰) relative to that in subjects taking only glimepiride (17.52 ± 3.28) [46].

In T2DM patients treated with sitagliptin (100 mg/day), thiazolidinediones with pioglitazone (30 mg/day), or rosiglitazone (4 mg/day) or those receiving medical dietary therapy [50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from protein, with cholesterol not exceeding 300 mg/day, and fiber 35 g/day] for 6 months [47], the frequency of PBL with MN was significantly higher in the pharmacological treatment groups (1.5 ± 0.9, 2.6 ± 1.2 and 2.2 ± 1.1‰, respectively) in comparison with the nutritional control group (1.0 ± 0.6‰). At the same time, in a comparison of the drug treatment groups with each other, the frequency of MN was significantly lower ($p < 0.01$) in the sitagliptin therapy group, which may indicate a higher genotoxic potential of treatment with thiazolidinediones in comparison with the pyrazine inhibitor of dipeptidyl peptidase-4.

In this study, the number of cells with CA was also assessed. The above findings concerning a more intense cytogenetic status in patients receiving pharmacotherapy were also valid for the total number of CA (0.07% ± 0.02%, 0.14% ± 0.05%, 0.15% ± 0.05% vs. 0.04% ± 0.03%) [47]. It is fair to note that the last given indicators are not entirely clear, since they are an order of magnitude less than the values of the spontaneous level of chromosomal mutagenesis in humans, which is generally accepted to be estimated at 1%–3% of aberrant PBL.

Thus, evidence of an increase in genotoxic markers in patients under the influence of hypoglycemic drugs was presented in singular studies, which are unconfirmed and insufficiently convincing. The issue of the genotoxic effects of hypoglycemic drugs in treated patients requires more extensive research.

More convincing and numerous examples demonstrate a decrease in the levels of genotoxic markers under the influence of pharmacological and/or nutritional factors.

A decrease in DNA damage ($p < 0.001$) was revealed in T2DM patients after an 8-week period of additional daily consumption of 300 g of a mixture of vegetables, including various cruciferous species, as well as spinach, carrots, and legumes in combination with vegetable oil (25 ml per day) rich in polyunsaturated fatty acids. A decrease in DNA damage was registered as early as week 4 of the study and persisted for 8 weeks after diet cessation [48]. It is noteworthy that the same group of researchers did not reveal the effect of a similar diet on the MN levels in buccal epithelial cells in T2DM patients [49].

Regular consumption of green tea (twice daily, 150 ml 1% w/v) for 12 weeks led to a significant ($p < 0.001$) reduction in the level of DNA damage in T2DM patients in a placebo-controlled (water) study [50]. Vitamin E intake (900 mg/day)

for 12 weeks resulted in a significant ($p < 0.05$) decrease in the level of DNA damage in PBL identified by the DNA comet assay in smokers and nonsmokers with T2DM [51]. A decrease in the frequency of MN in buccal epithelial cells was registered in two independent studies in T2DM patients with daily folic acid intake (5 mg orally three times a day) for 30 days [52–54]. No effect of regular consumption of low doses of the known antioxidant vitamin C on MN levels in peripheral blood cells of patients with T2DM or prediabetes was revealed [40]. However, this fact is not very informative, since the authors did not provide data on the initial provision of patients with this essential element of antioxidant protection in humans. Long term treatment with simvastatin (20 mg/day over 2 years) reduces oxidative damage to DNA in patients with dyslipidemic T2DM [55].

Information about the possibility of reducing the levels of genotoxic biomarkers was confirmed in studies where patients received a diet in combination with drugs. In particular, it was shown that, after a 7-day hospitalization during which T2DM patients adhered to a diabetic diet with a low sugar content under glycemic control (insulin, metformin), the level of DNA damage decreased significantly ($p < 0.05$), however, it did not reach the level of the control group of healthy volunteers ($p < 0.05$) [56]. Moreover, it was convincingly demonstrated that, with metformin monotherapy (on average 1.7 ± 0.9 g/day) for more than 5 months, the frequency of MN in the PBL of patients was inversely proportional to the concentration of metformin in the blood plasma of T2DM patients ($p = 0.009$) [57].

Thus, it can be stated that drugs used to control hyperglycemia or diet are not indifferent to the genotoxic status of DM patients. It is important to note that exercise and other environmental factors can also reduce the levels of genotoxic biomarkers. For example, 4 months of moderate physical training three times a week significantly reduces the levels of DNA damage ($p < 0.05$) [58], and bariatric surgery leads to a significant decrease in the level of MN in the peripheral lymphocytes of T2DM patients 1 year after surgery ($p < 0.05$) [59].

DISCUSSION

The results of the analysis of various genotoxic events in diabetes are heterogeneous, primarily in terms of DNA damage indices. Several authors [60, 61] suggest that this can be explained by the choice of cohorts of patients with different disease durations. Indeed, permanent oxidative stress can lead to activation of adaptive mechanisms on various levels, from the antioxidant defense system to DNA repair. Along with this, it should be mentioned that the methodology for registering DNA damage by the DNA comet assay was established relatively recently [62]. In this regard, the discrepancies revealed can be explained by the peculiarities of the instrumental part of the studies, which often cause interlaboratory discrepancies in the results of this test [63]. In addition, in the cited studies, various protocols for the obtaining and storage of the tested samples were used, which also has an impact on the estimated values [64].

Given the possibility of artifactual distortions in the results of the DNA comet assay and fewer studies denying an increase in DNA damage in hyperglycemia, as well as the obvious consistency among studies revealing a correlation of DNA damage in DM with cytogenetic biomarkers of CA and MN, we can reasonably infer an increase in DNA damage in diabetic patients.

The available pool of experimental data is obviously insufficient for a confident conclusion about an increase in genotoxicity markers in T1DM patients and, in part, GDM. The continuation of research in this field is all the more important because it is necessary to answer the question of whether antimutagenic protection and, consequently, efforts to develop it are needed for this category of patients.

The totality of the above information enables goals to be set for rationalizing the therapy of GDM, T2DM and, in the future, T1DM, considering the effect on genotoxicity markers. This is all the more important because DNA damage is a trigger for carcinogenesis and increases with the development of tumors. Diabetes, as shown for T2DM, is associated with an increased risk of developing cancer of the liver, pancreas, endometrium, colon and rectum, breast, and bladder. However, the link may be partly due to common risk factors for the two diseases, such as aging, obesity, diet, and physical inactivity [65, 66]. In addition to the direct or indirect effect of reactive oxygen species on DNA through lipid peroxidation and/or peroxynitrite, it should also be noted that, according to new data, the Akt/tuberin signaling pathway may be involved in the process of DNA damage [67, 68].

DNA damage initiates cell death and, therefore, can be considered as a factor in the development of cyto- and histopathogenesis in DM [69], which determines the need to develop methods of antimutagenic protection in DM not only in terms of prevention of oncogenesis, but also the prevention of degenerative processes.

From the point of view of rationalizing therapy, metformin attracts particular attention. First, this dimethylbiguanide derivative, an oral antiglycemic drug, is the most frequently prescribed first-line treatment for T2DM worldwide [70]. Secondly, there are experimental studies proving its antimutagenic properties. For example, oral single or daily 4- or 8-week administration of metformin at doses of 100, 500, and 2500 mg/kg significantly reduces the levels of bone marrow cells with CA and MN in a rat model of streptozotocin diabetes in a dose-dependent manner [71]. A similar effect was observed using the same experimental model of diabetes after daily 4-week oral administration of metformin at a dose of 50 mg/kg in combination with pioglitazone (1 mg/kg) when registering MN in bone marrow cells [72]. Metformin, at doses of 62.5, 125, and 250 mg/kg after 7-day daily administration, significantly dose-dependently reduced the frequency of polychromatophilic erythrocytes in the bone

marrow of male Swiss albino mice 24, 48, or 72 hours after intraperitoneal administration of the cytostatic antitumor drug Adriamycin at a dose of 15 mg/kg [73]. Data from in vitro studies also indicate the protective effect of metformin against ionizing radiation and several chemical agents [74]. Third, the single but direct finding described above indicates its ability to reduce MN levels during monotherapy in T2DM patients [57]. It can also be contrasted with a single study [46], which showed the co-mutagenic effect of metformin. Certainly, inversion of the protective effect is not uncommon among antimutagens [75]. Nevertheless, this finding has not yet been confirmed either clinically or experimentally, while the evidence for the antimutagenic effects of metformin has been reproduced in the studies of various authors. Hence, there is an obvious recommendation for research aiming to extend the understanding of the antimutagenic/anticarcinogenic properties of metformin in experimental and clinical trials. As a result, hypoglycemic therapy may be enriched with new opportunities to prevent the genotoxic complications of diabetes.

It is possible that, for antigenotoxic prophylaxis in diabetic patients, it is advisable to use antimutagenic vitamin therapy, possibilities for which were discussed earlier [75, 76], as well as the well-known anxiolytic Afobazole®, which demonstrated experimentally antimutagenic properties [77] as well as antidiabetic and cytoprotective activity in a model of streptozotocin-induced diabetes [78] and a model of GDM in rats [79]. Noopept® is also an interesting drug, which has neuroprotective and nootropic properties and showed antidiabetic activity in a model of streptozotocin-induced diabetes in mice in combination with antigenotoxic activity in cells of the pancreas, liver, and kidneys [80].

CONCLUSION

Biomarkers of genotoxicity in diabetic patients are of significant interest to researchers. The summarized results are heterogeneous, and a more extensive study of biomarkers of genotoxicity in DM is required, with the use of modern approaches and generally accepted standardized protocols.

At the current stage, it is appropriate to state that T2DM patients are characterized by an increased level of genotoxicity markers, which indicates the risk of oncological diseases in them. The results of studies of genotoxicity markers in patients with T1DM and GDM are contradictory and represented by a small number of studies; however, they indicate an increased genotoxic load rather than its absence.

The levels of genotoxic damage, and therefore, the risk of carcinogenesis, can be reduced in diabetic patients under the influence of exercise, diet and/or hypoglycemic drugs. Metformin, Afobazol® and Noopept® may be recommended for experimental and clinical studies as possible drug candidates that reduce the levels of genotoxic biomarkers in diabetic patients.

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