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GENOTOXIC BIOMARKERS IN PATIENTS ON HEMODIALIASIS

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❀ It is generally recognized that genotoxic damage have essential etiopathogenetic significance, and its prevention is an important measure to preserve human life and health. In the framework of this concept, literature information on studies of genotoxic biomarkers in patients with various hemodialysis regiments has been reviewed and summarized, and ways to prevent detectable genotoxicity have been identified. Based on the analysis of the known data, it was concluded that patients of this group have an increased level of DNA and chromosome damage in peripheral blood lymphocytes. Based on the results of individual studies, it was shown that one of the strategies for reducing genotoxicity may be the improvement of hemodialysis therapy methods and regimes, as well as pharmacological and nutritional correction of genotoxic effects.

❀ **Keywords:** hemodialysis; hemodiafiltration; genotoxicity; DNA damage; chromosomal aberrations; micronuclei.

ГЕНОТОКСИЧЕСКИЕ БИОМАРКЕРЫ У ПАЦИЕНТОВ, НАХОДЯЩИХСЯ НА ГЕМОДИАЛИАЗЕ

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❀ Общепризнано, что генотоксические поражения имеют существенное этиопатогенетическое значение, а их предупреждение является важной мерой сохранения жизни и здоровья человека. В рамках этой концепции рассмотрены и обобщены литературные сведения об исследованиях генотоксических биомаркеров у пациентов с различными вариантами гемодиализа. На основе анализа известных данных сделано заключение, что пациенты этой группы имеют повышенный уровень повреждений ДНК и хромосом в лимфоцитах периферической крови. На основе результатов отдельных работ показано, что одной из стратегий уменьшения генотоксичности может быть совершенствование методов и режимов гемодиализной терапии, а также фармакологическая и нутрициологическая коррекция генотоксических эффектов.

❀ **Ключевые слова:** гемодиализ; гемодиафильтрация; генотоксичность; повреждения ДНК; хромосомные аберрации; микроядра.

INTRODUCTION

Modern international recommendations [1] define chronic kidney disease (CKD) as a decrease in kidney function for at least 3 months up to a glomerular filtration rate of <60 ml/min per 1 · 73 m^2 [2, 3]. Risk factors for this pathology include smoking, hyperlipidemia, and metabolic syndrome [4–6].

CKD is a progressive condition, and subsequent end-stage renal failure requires replacement therapy such as hemodialysis (HD), hemodiafiltration (HDF), peritoneal dialysis (PD), or kidney transplantation [7, 8].

In 2018, 3.4 million patients underwent dialysis worldwide. The number of patients with CKD who need dialysis is increasing at a relatively constant rate of approximately 6% per year. Social trends contribute to the increase in the number of patients, particularly population aging and increased incidence of diabetes and hypertension [9–11].

In Russia, 54,953 patients with end-stage chronic renal failure were receiving renal replacement therapy at the end of 2018 [12]. This accounts for 374.4 cases per 1 million populations with a growth rate of 6.4% in 2018. Moreover, 42,621 (77.6%) patients with CKD received HD and 2,585 (4.7%) patients received PD.

Patients with CKD undergoing regular HD are diagnosed relatively more often with cardiovascular, oncological, neurodegenerative, and some other diseases [2, 13–15]. Moreover, studies

revealed an increase in the frequency of genotoxicity markers in such patients, which may be the most important cause of the onset and development of the above pathologies [16–18].

This work aimed to summarize and analyze the results of studies to identify verified genotoxic biomarkers in patients with CKD before and after HD, PD, and HDF, as well as to consider the possibilities of preventing genotoxicity during dialysis.

MATERIALS AND METHODS

Literature searches were conducted up to February 2020 using the MedLine/PubMed scientific literature database (National Library of Medicine, National Institutes of Health, Bethesda, MD, USA; http://www.ncbi.nlm.nih.gov/PubMed) and scientific electronic library of Russian Science Citation Index (http://elibrary.ru). Key search terms included for the English and Russian sources were respectively as follows: "hemodialysis," "predialysis," "hemodiafiltration," "peritoneal dialysis," "гемодиализ," "предиализ," "гемодиафильтрация," "перитонеальный диализ" in combination with "micronuclei," "микроядра," or "DNA-comet," and the "метод ДНК-комет". We considered studies published both in English and Russian languages with full-text versions of articles available.

From full-text articles, the following information about the study subjects were collected: number of subjects in groups, sex, age, duration of dialysis therapy, comorbidities, medications taken, smoking status, alcohol consumption, nutritional quality, intensity of therapy, biomarkers studied, cytogenetic methods used, as well as the results of the study as "mean ± standard error of the mean" for studies investigating the micronuclei (MN) level and qualitative result by the DNA-comet assay. Only publications containing a clear description of the design and results of the study were considered.

Collected data were summarized in tables. The mean values for the studied population were calculated with the standard deviation of the mean, as well as the fold of excess of the biomarkers in groups of patients compared with controls in each study.

RESULTS

Literary search results

An electronic search in the MedLine/PubMed database revealed a total of 123 records, including 38 original research articles which were selected based on abstracts. Given the limited studies in this field and all of them are of particular interest, the results of all these studies are presented in this review and will be mentioned in the appropriate subsections. Collected information is summarized in tables and presented in Appendices 1 and 2. Data are presented as a total number of patients (men/women); mean age ± standard error of the mean, years; mean duration of therapy ± standard error of the mean, years; and significance. If any information was not mentioned in the original article, a dash is written in the corresponding column.

Patients with CKD who regularly (3–4 times a week for 3–4 h) underwent HD procedures were enrolled in the study. The control groups were composed of healthy volunteers living in the same region and age and sex were matched with the patient groups, in some cases, among patients with kidney disease, without a history of HD therapy. Medical history, information about recent medical procedures (including radiography), as well as medicines administered were collected from the study participants. In some studies, questionnaires were used, which collected data on smoking status, alcohol consumption, nutritional quality, and lifestyle. Peripheral blood for tests was collected by vein puncture. The protocols of all studies analyzed were approved by Ethics Committees.

Upon further consideration of the full-text versions, 16 publications that met the following inclusion criteria were selected for the statistical analysis:

(1) The study populations in the experimental and control (unexposed) groups were matched by sex and age, and each group had more than 10 participants.
(2) The average age of the patients was >45 years.
(3) The average duration of dialysis therapy was >6 months.
(4) Cytogenetic research methods (counting of MN and/or chromosomal aberrations) and/or the DNA-comet assay were used to con-

sider DNA damage. The listed biomarkers and methods in the standard protocols were verified by leading genotoxicology guidelines [19–21].

(5) Statistical analyses applicable to the research task were available and errors of statistical conclusion were minimized, as recommended by the relevant guidances [22–24], and mean values for groups with standard errors (SD) were presented.

(6) Compliance with ethical standards during the study and approval of the study protocol by the Ethical Committee.

In these 16 publications, MN in peripheral blood lymphocytes (PBLs) were selected as a biomarker in seven studies, and DNA damage detected by the DNA-comet assay was chosen in nine studies. Among these studies, no studies without established genotoxic effects of HD were found.

MN in PBLs

In seven studies focused on the analysis of MN in PBLs, data from 242 patients (143 men and 99 women; mean age, 60.4 ± 4.3 years; mean duration of therapy, 6.0 ± 4.3 years) and 174 controls (90 men and 84 women; mean age, 53.0 ± 7.3 years) were analyzed. Summarized data on age, duration of therapy, frequency of MN, and fold of excess MN in the patient group compared with the control group are presented in Table 1.

All studies showed significant differences ($p < 0.05$) in the number of MN in the PBLs of patients compared with controls, and in four cases, the significance was high ($p < 0.001$).

Table 1

Summary review of the results of studies of cytogenetic damage in lymphocytes identified by counting the number of micronuclei in patients with chronic renal failure undergoing hemodialysis compared with volunteers without kidney pathologies

First author, year of publication and country	Source	Group size		Average age, years		Duration of therapy, years	Frequency of MN per 1,000 binuclear cells, ‰, mean ± SE		Fold of excess
		P (M/F)	C (M/F)	P	C		P	C	
Mamur et al., 2019, Turkey	[25]	60 (43/17)	26 (17/9)	57 ± 23	40 ± 21	4.0 ± 3.1	4.6 ± 3.4 **	0.7 ± 1.5	6.6
Palazzo et al., 2012, Brazil	[26]	22 (12/10)	22 (5/17)	63 ± 9	63 ± 8	1.5 ± 0.9	5.5 ± 4.0 *	3.5 ± 2.8	1.6
Schupp et al., 2011, Germany	[27]	14 (7/7)	14 (7/7)	69 ± 10	53 ± 13	7.7 ± 5.7	21.1 ± 2.9 **	12.5 ± 0.2	1.7
Sandoval et al., 2010, Spain	[28]	98 (60/38)	57 (33/24)	62 ± 2	52 ± 2	3.5 ± 0.3	11.4 ± 0.9 **	6.9 ± 0.6	1.7
Roth et al., 2008, Brazil	[29]	20 (10/10)	20 (10/10)	50 ± 10	51 ± 11	7.6 ± 5.5	2.8 ± 2.7 *	0.9 ± 1.1	3.1
Fragedaki et al., 2005, Germany	[30]	12 (5/7)	12 (7/5)	58 ± 13	53 ± 11	3.6 ± 1.8	29.1 ± 5.9 *	13.2 ± 3.0	2.2
Stopper et al., 1999, Germany	[31]	16 (6/10)	23 (11/12)	64 ± 11	59 ± 16	14.3 ± 4.1	44.3 ± 13.7 **	15.3 ± 4.7	2.9
Total		242 (143/99)	174 (90/84)	60 ± 6	53 ± 7	6.0 ± 4.3	–	–	–

Note. SE, standard error (mean-root square error), *$p < 0.05$; **$p < 0.001$. P, patients; C, controls.

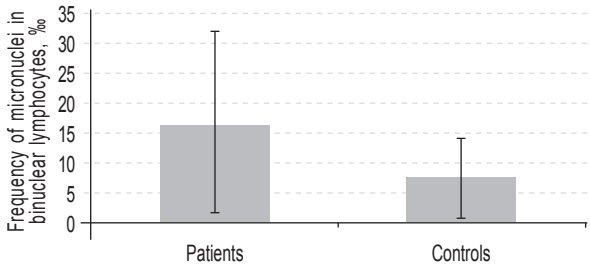

Fig. 1. Frequency of micronuclei in the lymphocytes of hemodialysis patients and controls, mean ± SEM ($n = 7$, $p < 0.05$)

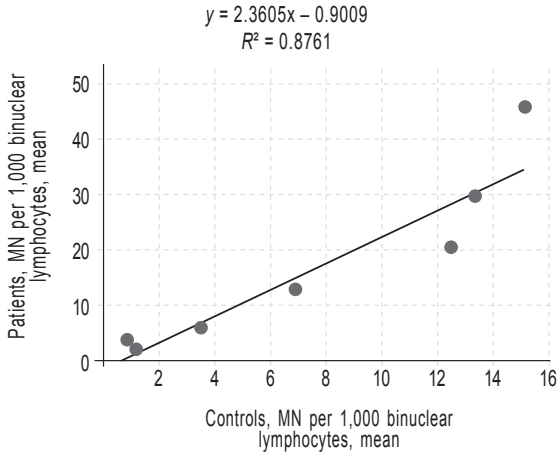

Fig. 2. Correlation of the frequency of micronuclei (MN) in the binuclear lymphocytes of patients undergoing hemodialysis and controls. Each point on the graph represents the mean for one study ($n = 7$)

The analysis of summarized data also revealed a more than 2.5-fold excess in the number of MN (2.8 ± 0.7; $p < 0.05$) (Fig. 1). No correlation was found between the average duration of HD therapy and the number of MN in PBLs ($R^2 = 0.0014$).

A positive correlation ($R = 0.88$, $p < 0.001$) was found between data for patients and controls (Fig. 2), which indicated a generally good agreement between the results of studies by different authors. Indirectly, this correlation indicates the proper composition of the control groups for variables that affect the number of MN in the lymphocytes, i.e., age, sex, nutrition, alcohol consumption, smoking status, as well as the acceptability of the cytokinesis-block MN assay in the lymphocytes of the study subjects for similar biomonitoring research. Thus, a significant increase was found in the number of MN in HD patients.

DNA damage measured by the DNA-comet assay

The results of biomonitoring studies using the DNA-comet assay cannot be quantitatively compared because of a high interlaboratory variability (Table 2) [32]. In four of nine studies, researchers

Table 2

Summary review of the results of studies of cytogenetic damage in lymphocytes detected by the DNA-comet assay in patients with chronic renal failure undergoing hemodialysis compared with volunteers without kidney pathologies

First author, year of publication and country	Source	Group size		Average age, years		Duration of therapy, years	Significance of differences from the control group [a]
		P (M/F)	C (M/F)	P (M/F)	C (M/F)		
Mamur et al., 2016, Turkey	[33]	60 (43/17)	26 (17/9)	57 ± 23	40 ± 21	4.0 ± 3.1	$p < 0.001$
Ersson et al., 2013, Sweden	[34]	31 (20/11)	10 (4/6)	69 ± 12	59 ± 7	3.5 ± 3.5	$p < 0.001$
Palazzo et al., 2012, Brazil	[26]	22 (12/10)	22 (5/17)	63 ± 9	63 ± 8	1.5 ± 0.9	$p < 0.05$
Stoyanova et al., 2009, Spain	[35]	77 (49/28)	176 (111/65) [b]	62 ± 2	67 ± 1	4.3 ± 0.5	$p < 0.05$
Bagatini et al., 2008, Brazil	[36]	25 (13/12)	20 (7/13)	63 ± 9	62 ± 9	2.13 ± 2.08	$p < 0.05$
Horoz et al., 2006, Turkey	[37]	22 (11/11)	22 (10/12)	47 ± 9	42 ± 8	2.7 ± 3	$p < 0.05$
Domenici et al., 2005, Brazil	[38]	51 (29/22)	9 (1/8)	52 ± 17	32 ± 6	4.34 ± 2.38	$p < 0.05$
Kan et al., 2002, Turkey	[39]	36 (24/12)	36 (24/12)	49 ± 14	49 ± 14	3.5 ± 2.6	$p < 0.001$
Stopper et al., 2001, Germany	[40]	26 (16/10)	21 (9/12)	64 ± 13	48 ± 17	8.2 ± 7.5	$p < 0.001$
Total		350 (217/133)	342 (188/154)	58 ± 8	51 ± 12	3.8 ± 1.9	–

Note. [a] Hereinafter, the significance is indicated in accordance with the information provided in the text of the original article. [b] In this study, the control group included patients who did not receive hemodialysis but had renal failure of varying severity (2–5). P, patients; C, controls.

revealed a high significance ($p < 0.001$) of an increase in DNA damage in patients compared with controls, and the remaining five studies reported significance ($p < 0.05$). Thus, an increase in DNA damage evaluated through the DNA-comet assay was found in HD patients.

Description of the results of studies not included in the main review

An exhaustive meta-analysis is impossible due to the high variability of the study populations, which affects the cytogenetic status. The main "disturbing" factors included ethnic characteristics, lifestyles, concomitant diseases, characteristics of drug therapy, and other factors (Appendices 1 and 2). Moreover, creatinine levels, sex, age, smoking status, and alcohol consumption do not affect the genotoxic effect of HD treatment [29].

The most significant research results of the analyzed studies not covered by the previous presentation, as not fully consistent with the principles of a systematic review, are given below.

In addition to the MN level in the PBLs of patients, a study [25] also examined the total number of chromosomal aberrations [60 (43/17); 57 ± 23; 4.0 ± 3.1]*. In comparison with the control group [26 (17/9); 40 ± 21], a significant ($p < 0.001$) increase in the level of chromosomal aberrations (CA) was found (0.06 ± 0.03 vs. 0.04 ± 0.02 CA/cell), and the most common structural aberrations in patients with CKD were chromatid breaks. Similar data were obtained in an earlier study [41], where a significant increase in the frequency of CA (2.9% vs. 0.3%) was found in the PBLs of HD patients [44 (25/19); 48 (18–74); 0.8–30], in comparison with the PBLs of healthy volunteers [24 (12/12); 32].

Results of studies of the cytogenetic status in children at the predialysis stage and HD are interesting [42–44]. These studies found that the frequency of MN in the PBLs of patients on predialysis [17 (9/8); 13 ± 5; 3.5 ± 3.2] and of HD patients therapy [15 (7/8); 15 ± 3; 2.5 ± 2.3] is more than 5.5 times higher (9.2 ± 2.6 and 9.1 ± 4.9 vs. 1.6 ± 1.0‰, respectively; $p < 0.001$) than those in healthy volunteers [20 (11/9); 13 ± 4]. In addition, in the analysis of the frequency of MN in buccal epithelial cells, excess of more than 6-fold of the biomarker level was found, compared with controls [9.6 ± 7.6 vs. 1.5 ± 1.3‰; $p < 0.001$], which was some extent higher than the frequency of MN in patients at the predialysis stage (8.3 ± 8.5 vs. 1.5 ± 1.3; $p < 0.001$). The same patient groups showed a significant difference in the level of DNA damage assessed through the DNA-comet assay ($p < 0.001$).

In addition to PBLs, non-invasive assessment of genotoxicity markers in buccal epithelial cells is becoming increasingly popular in biomonitoring studies. Thus, a study [45] revealed a significant difference in the level of DNA damage in buccal epithelial cells in HD patients [35 (13/22); 52 ± 1; 2.1 ± 0.6] in comparison with healthy volunteers [21 (8/13); 51 ± 2] and an increased level of MN frequency (6.3 ± 0.3 vs. 1.9 ± 0.2; $p < 0.001$).

Another study [46], which aimed to investigate the relationship between DNA damage in the salivary glands of HD patients in comparison with age-matched volunteers without kidney pathologies, demonstrated that DNA damage in patients with CKD who were not undergoing dialysis (10; 33–66) was significantly greater than those in controls (10; 36–69; $p < 0.05$). In addition, DNA damage was lower in patients receiving dialysis (69; 25–87) than in controls (69; 35–89; $p < 0.001$). This indicates the apparent tissue specificity of genotoxicity in the examined group of patients.

The level of DNA damage in PBLs is increased in patients with end-stage renal failure undergoing HD [40 (23/17); 45 ± 13; 3; $p < 0.001$] compared with that in controls (21 (11/10); 41 ± 11), and this indicator was found to correlate significantly with the level of leptin in the serum ($p < 0.05$, beta = 0.508) [47].

A comparative study of the frequency of MN in reticulocytes with MN in the PBLs of patients under standard [9 (4/5); 64 ± 8] and daily

* Hereinafter: the total number of patients (men/women); mean age ± standard error of the mean, years; mean duration of therapy ± standard error of the mean, years, are indicated in brackets. This data presentation format is presented in the "Literary search results" section.

[9 (7/2); 46 ± 4] HD procedures showed that both biomarkers were significantly lower in the daily dialysis group (29.2 ± 6.4 vs. 15.8 ± 3.7; 0.92 ± 1.07 vs. 0.68 ± 0.53‰). However, the predictability of reticulocytes in assessing genomic damage under chronic exposure has been questioned due to their short lifespan [48].

In HD patients, analysis revealed a reduced number and impaired function of endothelial progenitor cells (EPCs), which, under physiological conditions, contribute to the restoration of vascular damage. Researchers [49] analyzed the effect of one HD session on the number of CD34-labeled cells, including cells of the EPC subtype, using the DNA-comet assay, and revealed a higher basal level of genomic damage in the HD group [30 (16/14); 55 ± 11; 2.7 ± 1.6] than in the control group [30 (15/15); 60 ± 13]; it statistically significantly increased ($p < 0.001$) after an HD session and returned to the level of intact parameters in the interdialysis period.

Iron deficiency anemia is common in HD patients. Iron supplements often used to prevent this condition increase DNA damage [50, 51].

Thus, both within the systematic approach and in the analysis of each study, HD patients are characterized by increased levels of genotoxic biomarkers, which cause various pathologies [52]. Hence, there is a need to consider possible options for prevention of genotoxic damage.

Possible methods to prevent genotoxicity

In a study with a small sample of patients, a decrease in the level of DNA damage in PBLs was noted during the transition from HD [7 (2/5), 73 ± 7, 3.9 ± 4.0] to HDF (the HDF therapy duration was 0.6 ± 0.3; $p < 0.05$) [53].

The dependence of the manifestations of genotoxicity on HD methods and protocols has been confirmed in a previous study [54]. When alteration from HD to an online HDF procedure [34 (25/10); 62 ± 2; 2.2 ± 0.4], in which high-flux synthetic membranes and ultrapure dialysis fluids are used, the level of genetic damage in PBLs decreased significantly ($p = 0.048$) compared with that in control patients who did not change their approach to therapy [15 (9/5); 59 ± 4; 1.5 ± 0.6] [54].

The same group of researchers obtained similar results when assessing MN in PBLs [55], i.e., in 33 patients (25/8; 62 ± 2; 1.9 ± 0.4) undergoing stable HD, the frequency of MN in PBLs decreased significantly (8.9 ± 1.3 vs. 5.9 ± 0.6‰; $p < 0.05$) after a 6-month period of switching to a new online HDF therapy.

Subsequent studies have confirmed the possibility of genotoxicity reduction due to the regimen and/or changes in procedures. In particular, the start of standard HD therapy (5; the duration of therapy was approximately 0.5 years) did not cause changes in the genomic damage in PBLs. Alteration from HD to HDF (7; the duration of HDF therapy was approximately 0.6 years) reduced DNA damage ($p < 0.05$) but did not affect the frequency of MN. In a crossover study, the frequency of MN in PBLs was significantly lower in HD patients daily but in shorter sessions than in patients undergoing standard HD therapy (3–4 times a week, 3–4 h) [56].

A pilot study [57] demonstrated that the type of dialyzer membrane and intradialysis iron infusion significantly affected the level of DNA damage in PBLs. Consecutive changes in the membrane type every 4 weeks in HD patients (9; 54–87) revealed that the total DNA damage was the same for cellulose membranes coated with polysulfone and vitamin E, while a significant increase in the level of damage was noted for cellulose diacetate membrane ($p < 0.001$). In addition, in patients receiving intravenous infusion of iron (5 ml of a complex of sodium gluconate and iron in sucrose containing 62.5 mg of Fe) during HD, the total DNA damage further increased (10; 55–87; $p < 0.005$), which is consistent previous data [50, 51].

Among uremic toxins, homocysteine levels are elevated in most patients and correlated with the degree of genotoxic damage in PBLs. Homocysteine accumulation is reduced when folic acid and vitamin B_{12} are added to the diet. The effect of folic acid (15 mg 3 times a week) and vitamin B_{12} (IV, 1 mg once a week) administration on the frequency of MN in the PBLs of HD patients [27 (19/8); 64 ± 9; 9.0 ± 5.7] was monitored for

17 weeks. Ultimately, the greatest effect on reducing the frequency of MN compared with the initial level was achieved with the combined use of the two vitamins (31.4 ± 6.7 vs. 37.6 ± 16.9‰; $p < 0.05$) [58].

Angiotensin II (ANG II) and advanced glycation end products are known to be genotoxic *in vitro*, but the effect is mitigated when treated with candesartan, a type 1 ANG II receptor blocker. A study tested [27] whether oral administration of candesartan (dose range, 4–16 mg/day, for 4.5 months) influenced DNA damage in patients with CKD undergoing HD therapy [15 (10/5); 64 ± 15; 6.2 ± 4.1] compared with a similar group of patients not taking candesartan [14 (7/7); 69 ± 10; 7.7 ± 5.8]. The study revealed the frequency of MN decreased by 27.7% in the candesartan group.

Another study [59] evaluated the effect of neuromuscular electrical stimulation (NMES) of the quadriceps muscle in patients with CKD [10 (8/2); 65 ± 5; 2.3 ± 2.7] during an HD session (3 times a week for 8 weeks) on the genome damage using the DNA-comet assay. That study revealed that intradialytic NMES leads to a significant time-dependent decrease in the level of DNA damage after 4 and 8 weeks compared with the baseline ($p < 0.001$). However, this case was not explained adequately.

In addition to attempts to reduce genotoxic damage by varying dialysis therapy, pharmacological and nutritional prevention measures were applied. For example, a study [39] evaluated the effect of vitamin E administration (600 mg/day, daily for 14 weeks) in HD patients [36 (24/12); 49 ± 14; 3.5 ± 2.6] using the DNA-comet assay. The study found that the level of DNA breaks in the lymphocytes before vitamin E intake was significantly higher than that in the group of healthy volunteers [36 (24/12); 49 ± 14; $p < 0.001$], but after 14 weeks of vitamin E intake, the level of damage decreased toward the level before vitamin E intake ($p < 0.001$), but still differed significantly from the control values ($p < 0.001$). The authors associate this gene-protective effect to the antioxidant potential of vitamin E.

Unlike earlier studies, another study [60] used a different approach and evaluated the effect of using polysulfone membranes coated with vitamin E during HD sessions on the levels of genetic damage in patients [29 (13/16); 69 ± 2; 1.7 ± 0.4] in whom MNs were counted and the DNA-comet assay was used. The researchers found a minor but significant decrease in the level of DNA oxidative damage under to the initial level ($p < 0.05$), and no similar effect on the frequency of MN was revealed.

An attempt was made to correct genomic damage by adding fruit juice rich in polyphenols and anthocyanins [red grapes (40%), blackberries (20%), cherries (15%), black currants (15%), and elderberry (10%)] to the diet of HD patients (21 (14/7)). After a 4-week daily intake of 200 ml of juice, DNA damage significantly decreased according to the DNA-comet assay ($p < 0.001$); however, after cancellation and a 3-week washing period, the indicators returned to their previous values [61].

Another study [62] showed that the addition of unfermented grape juice (100 ml at the end of each HD session for 6 months) to the diet of HD patients [25 (15/10); 66 ± 3; 3 ± 0.5] reduced significantly ($p < 0.05$) the level of the DNA oxidative damage (the DNA-comet assay), which was not detected in a similar group of patients without diet modification [14 (9/5); 60 ± 5; 2 ± 0.6].

DISCUSSION

The results of this review unequivocally indicate that patients with progressive CKD have an increased level of DNA and chromosomal damage in PBLs, by DNA-comet and cytokinesis-block micronucleus assays. Thus, the number of MN in the PBLs of patients undergoing HD therapy is almost 3 times higher than that in nephrologically healthy volunteers, matched by sex and age. In addition, based on the results of all studies on DNA damage assessed by the DNA-comet assay, a significant difference in the level of DNA damage was found in HD patients.

The biomarkers indicate an increased risk of the occurrence of corresponding diseases, such as oncological and neurodegenerative diseases [20, 63, 64]. One of the possible consequences of dialysis is oxidative stress, which might lead

to varying degrees of DNA damage [65], which is a source of gene mutations and clastogenic and aneugenic effects [31]. Genotoxic changes underlie carcinogenesis and occurrence of hereditary diseases and can be also involved in the aging process and pathogenesis of neurodegenerative diseases and diabetes.

A recent study with a 4-year follow-up of 123 HD patients point at a relationship between a high level of genetic damage, identified using the DNA-comet assay, at the beginning of the study and an increased risk of mortality from any medical cause [76/47; 62 ± 15; 3.1 ± 3.8; $p < 0.05$] [66]. Patients undergoing dialysis are at increased risk of having hepatocellular disease and cancers of the kidney, bladder, urinary tract, and thyroid gland [67–69]. The relationship among the duration of HD therapy, recurrence of urothelial carcinoma of the bladder, and overall survival in patients undergoing maintenance HD has been demonstrated [70].

Research directions in the prevention of genotoxicity during HD are certain. There are two complementary strategies for preventing long-term genotoxic-related pathologies in CKD. The first one is based on the knowledge of the existing correlation between the degree of DNA damage and/or the frequency of chromosomal abnormalities and CKD severity and the duration of dialysis treatment [28, 40], and strategy is aimed at improvement of HD therapy methods. Its implementation is supported by the results of studies cited earlier, which indicate that the severity of genotoxicity depends on treatment duration and intensity and the use of more or less sparing methods of dialysis therapy. HDF or daily HD appears to be more sparing types of renal maintenance therapy in terms of maintaining and preventing cancer complications. A study [30] showed that in patients with end-stage kidney failure, daily HD is associated with less genome damage than standard HD (3 times a week), which may result from the rapid removal of toxic substances, including glycation end products. For other reasons, HD specialists also point the need for shorter but daily dialysis procedures [71].

The second strategy is based on the well-known advances in the search and study of antimutagenic agents [72, 73]. Pharmacological and nutritional correction of genotoxicity is important in light of the constant somatogenic vital threat associated with the treatment of patients with end-stage CKD. The information described above, indicating a decrease in genotoxicity levels in HD patients under the influence of known food antimutagens (vitamin E, folic acid and vitamin B_{12}, and anthocyanins and polyphenols in juices), illustrates the possibilities of this approach. The use of pharmacological agents for prevention is even more attractive, as they combine antigenotoxic activity with the main type of pharmacological activity and can be prescribed to a patient for direct indications, for example, for the relief of anxiety disorders that occur inevitably in patients with chronic diseases, including those with CKD and on regular dialysis [1, 74]. These can be known psychotropic compounds (such as afobazole, mexidol), certain immunomodulators, and drugs of other pharmacological groups with confirmed antimutagenic activity [72].

In addition, the integration of antimutagens into HD therapy requires further clinical investigations, since the aforementioned studies are still pilot ones conducted on insufficient number of samples and thus cannot be the basis for direct treatment recommendations. The unjustified use of antimutagens with an antioxidant action can bear direct harm due to the dose-dependent inversion of the protective effect in the pro-oxidant action inherent in these compounds. This is explicitly confirmed in a previous study [75] demonstrating that Carnicor, acting as an antioxidant and neuroprotector, increased significantly the frequency of MN and DNA damage in the PBLs of HD patients. Afobazole is essentially the only antimutagen that does not exhibit inversion of effects in a wide range of doses for different modes of use [76].

CONCLUSIONS

Thus, on the one hand, the hemodialysis procedure is essential for a significant number of CKD patients. On the other hand, HD is accompanied by genotoxic effects that cause life-threatening diseases in the medium and long term. Hence, efforts are necessary to optimize HD

therapy aimed at reducing or completely arresting genotoxic effects. They can be implemented both through the improvement of instrumentation and/or modes of application and through the use of nutritional and pharmacological antimutagenic compounds.

Appendix 1

Summary review of the results of studies of cytogenetic damage in lymphocytes in patients with chronic renal failure detected by cytokinesis-block micronucleus assay

First author, year of publication and country	Source	Group size		Average age, years		Duration of therapy, years	Aspects of the studied patient population (concomitant diseases, drugs taken)	Frequency of MN per 1,000 binuclear cells, ‰, mean ± SE [a]	
		P (M/F)	C (M/F)	P	C			P	C
Predialysis									
Aykanat et al., 2016, Turkey	[42–44]	17 (9/8)	20 (11/9)	13 ± 5	13 ± 4	3.5 ± 3.2	Patients with CKD were enrolled. Drugs: cyclosporin, tacrolimus, or rapamycin in combination with mycophenolate mofetil steroid or alone, vitamin supplements, antihypertensive drugs, erythropoietin, anti-osteoporosis drugs, iron preparations, calcium acetate and citrate, antibiotics, analgesics	9.2 ± 2.6 **	1.6 ± 1.0
Stopper et al., 1999, Germany	[31]	19 (14/5)	23 (11/12)	56 ± 15	59 ± 16	Information has not been provided	Patients with chronic renal failure were enrolled; two patients had type 2 diabetes. Patients with acute or chronic infection, and cancer; and patients receiving antiviral, cytostatic, or immunosuppressive drugs; as well as patients with a history of radiation therapy were excluded from the study	28.2 ± 9.4 *	15.3 ± 4.7
Rangel-López et al., 2013, Mexico	[77]	23 (12/11)	61 (27/33)	49 ± 18	39 ± 9	Information has not been provided	Patients with CKD were enrolled, and approximately half of them had type 2 diabetes. Patients with cancer, bacterial infections, hepatitis C or B, HIV, or liver failure or those receiving immunosuppressive therapy were excluded from the study	46.2 ± 4.3 **	24.4 ± 9.5

Appendix 1 (continued)

First author, year of publication and country	Source	Group size		Average age, years		Duration of therapy, years	Aspects of the studied patient population (concomitant diseases, drugs taken)	Frequency of MN per 1,000 binuclear cells, ‰, mean ± SE [a]	
		P (M/F)	C (M/F)	P	C			P	C
Hemodialysis									
Mamur et al., 2019, Turkey	[25]	60 (43/17)	26 (17/9)	57 ± 23	40 ± 21	4.0 ± 3.1	Patients with chronic renal failure were enrolled; 43% of them had type 2 diabetes. They also had a history of hypertension and hepatitis B and C. No information on the drugs taken was provided	4.6 ± 3.4**	0.7 ± 1.5
Pastor et al., 2018, Spain	[75]	214 (135/79)	–	65 ± 15	—	2.6 ± 3.1	Patients with end-stage renal disease were enrolled. Comorbidities included hypertension, diabetes, cardiovascular diseases, and kidney transplantation. Patients were taking erythropoietin-stimulating drugs	8.6 ± 6.0	–
Aykanat et al., 2016, Turkey	[42–44]	15 (7/8)	20 (11/9)	15 ± 3	13 ± 4	2,5 ± 2,3	Patients with CKD were enrolled. Drugs: cyclosporine, tacrolimus, or rapamycin in combination with mycophenolate steroid mofetil or alone, vitamin supplements, antihypertensive drugs, erythropoietin, anti-osteoporosis drugs, iron preparations, calcium acetate citrate, antibiotics, and analgesics	9.1 ± 4.9	1.6 ± 1.0
Rodríguez-Ribera et al., 2016, Spain	[55]	33 (25/8)	–	62 ± 2	–	1.9 ± 0.4	Patients with CKD were enrolled. Comorbidities included hypertension, cardiovascular diseases, oncological diseases, diabetes, and dyslipidemia. Medications taken were folic acid, vitamins B and C, L-carnitine, ACE inhibitors, statins, vitamin D, sevelamer hydrochloride, calcium, venofer, and erythropoietin	8.9 ± 1.3	–

Appendix 1 (continued)

First author, year of publication and country	Source	Group size		Average age, years		Duration of therapy, years	Aspects of the studied patient population (concomitant diseases, drugs taken)	Frequency of MN per 1,000 binuclear cells, ‰, mean ± SE [a]	
		P (M/F)	C (M/F)	P	C			P	C
Rangel-López et al., 2013, Mexico	[77]	35 (15/20)	61 (27/33)	47 ± 17	39 ± 9	–	Patients with CKD were enrolled, and approximately half of them had type 2 diabetes. Patients with oncological diseases, bacterial infections, hepatitis C or B, HIV, or liver failure or on immunosuppressive therapy were excluded from the study	29.7 ± 15.6 *	24.4 ± 9.5
Palazzo et al., 2012, Brazil	[26]	22 (12/10)	22 (5/17)	63 ± 9	63 ± 8	1.5 ± 0.9	Patients with type 2 diabetes were enrolled. They were taking ACE inhibitors, agents that lower blood sugar levels, and diuretics. Some patients received recombinant erythropoietin and iron hydroxide	5.5 ± 4.0 *	3.5 ± 2.8
Schupp et al., 2011, Germany	[27]	14 (7/7)	14 (7/7)	69 ± 10	53 ± 13	7.7 ± 5.7	Patients with end-stage renal diseases were enrolled. The drugs taken included various antihypertensive drugs (beta-blockers, calcium channel antagonists, loop diuretics, etc.). Patients with acute or chronic infections, carcinomas, or congestive heart failure were excluded from the study	21.1 ± 2.9 **	12.5 ± 0.2
Sandoval et al., 2010, Spain	[28]	98 (60/38)	57 (33/24)	62 ± 2	52 ± 2	3.5 ± 0.3	Patients with chronic renal failure were enrolled. The history also included cardiovascular pathology, cancer diseases, dyslipidemia, and diabetes	11.4 ± 0.9 **	6.9 ± 0.6
Roth et al., 2008, Brazil	[29]	20 (10/10)	20 (10/10)	50 ± 10	51 ± 11	7.6 ± 5.5	Patients with chronic renal failure were enrolled. No information on concomitant diseases and medications taken was provided	2.8 ± 2.7 *	0.9 ± 1.1

Appendix 1 (continued)

First author, year of publication and country	Source	Group size		Average age, years		Duration of therapy, years	Aspects of the studied patient population (concomitant diseases, drugs taken)	Frequency of MN per 1,000 binuclear cells, ‰, mean ± SE [a]	
		P (M/F)	C (M/F)	P	C			P	C
Stopper et al., 2008, Germany	[58]	27 (19/8)	–	64 ± 9	–	9.0 ± 5.7	Patients with indications for HD in the presence of various renal pathologies were enrolled. The exclusion criteria were bacterial or viral infections and malignant neoplasms. Drugs taken included ACE inhibitors, angiotensin receptor blockers, beta-blockers and calcium channel blockers, loop diuretics, statins, erythropoietin, and vitamin complexes	31.4 ± 6.7	–
Fragedaki et al., 2005, Germany, Slovakia	[30]	12 (5/7)	12 (7/5)	58 ± 13	53 ± 11	3.6 ± 1.8	Patients with end-stage renal failure were enrolled. Patients with diabetes, bacterial or viral infections (HCV, HBV, or HIV), malignant neoplasms, or liver failure or those receiving treatment with anti-inflammatory, cytostatic, or immunosuppressive drugs were excluded from the study	29.1 ± 5.9 *	13.2 ± 3.0
Stopper et al., 1999, Germany	[31]	16 (6/10)	23 (11/12)	64 ± 11	59 ± 16	14.3 ± 4.1	Patients with chronic renal failure were enrolled. Patients with acute or chronic infection, cancer patients, and patients receiving antiviral, cytostatic, or immunosuppressive drugs, as well as those with history of radiation therapy were excluded from the study	44.3 ± 13.7 **	15.3 ± 4.7

Appendix 1 (continued)

First author, year of publication and country	Source	Group size		Average age, years		Duration of therapy, years	Aspects of the studied patient population (concomitant diseases, drugs taken)	Frequency of MN per 1,000 binuclear cells, ‰, mean ± SE [a]	
		P (M/F)	C (M/F)	P	C			P	C
Hemodiafiltration									
Rodríguez-Ribera et al., 2016, Spain	[55]	33 (25/8)	–	62 ± 2	–	0.5	Patients with CKD were enrolled. Comorbidities included hypertension, cardiovascular pathology, cancer diseases, diabetes, and dyslipidemia. Drugs taken were folic acid, vitamins B and C, L-carnitine, ACE inhibitors, statins, vitamin D, sevelamer hydrochloride, calcium, venofer, and drugs stimulating erythropoiesis	5.9 ± 0.6	–
Peritoneal dialysis									
Roth et al., 2008, Brazil	[29]	20 (11/9)	20 (11/9)	49 ± 13	49 ± 13	1.8 ± 1.6	Patients with chronic renal failure were enrolled. Information on concomitant diseases or medications taken was not provided	1.4 ± 1.5	1.6 ± 1.9
Rangel-López et al., 2013, Mexico	[77]	33 (13/20)	61 (27/33)	51 ± 16	39 ± 9	Information has not been provided	Patients with CKD were enrolled, and approximately half of them had type 2 diabetes. Patients with cancer, bacterial infections, hepatitis C or B, HIV, or liver failure or on immunosuppressive therapy were excluded from the study	41.9 ± 14.0**	24.4 ± 9.5

Note. [a] SE, standard error (mean-root square error). * $p < 0.05$; ** $p < 0.001$. P, patients; C, control groups; MN, micronuclei; HD, hemodialysis; CKD, chronic kidney disease; ACE inhibitors, angiotensin-converting enzyme inhibitors. The study in a pediatric patient population is marked gray.

Appendix 2

Summary review of the results of studies of cytogenetic damage in lymphocytes in patients with chronic renal failure and damage was identified using the DNA-comet assay

First author, year of publication and country	Source	Group size		Age, years		Duration of therapy, years	Aspects of the studied patient population (comorbidities, drugs taken)	Significance of differences from the control group
		P (M/F)	C (M/F)	P (M/F)	C (M/F)			
Predialysis								
Aykanat et al., 2016, Turkey	[42–44]	17 (9/8)	20 (11/9)	13 ± 5	13 ± 4	3.45 ± 3.24	Patients with CKD were enrolled. Drugs: cyclosporine, tacrolimus, or rapamycin in combination with mycophenolate mofetil steroid or alone, vitamin supplements, antihypertensive drugs, erythropoietin, anti-osteoporosis drugs, iron preparations, calcium acetate and citrate, antibiotics, and analgesics	$p < 0.001$
Corredor et al., 2015, Spain	[64]	101 (57/44)	187 (119/68)	67 ± 1	56 ± 1	Information has not been provided	Patients with CKD stages 4–5 were enrolled, and approximately $^1/_3$ had diabetes. Such patients had a history of hyperlipidemia, cardiovascular pathologies, hypertension, and cancer diseases	$p < 0.001$
Rangel-López et al., 2013, Mexico	[77]	33 (13/20)	61 (27/33)	51 ± 16	39 ± 9	Information has not been provided	Patients with CKD were enrolled, about half of them had type 2 diabetes. Patients with cancer, bacterial infections, hepatitis C or B, HIV, or liver failure or on immunosuppressive therapy were excluded from the study	$p < 0.05$
Stopper et al., 2001, Germany	[40]	23 (12/11)	21 (9/12)	65 ± 11	48 ± 17	Information has not been provided	Patients with indications for HD in the presence of various renal pathologies were enrolled. These patients had a history of diabetes and amyloidosis. No drug information was provided.	$p < 0.001$

Appendix 2 (continued)

First author, year of publication and country	Source	Group size		Age, years		Duration of therapy, years	Aspects of the studied patient population (comorbidities, drugs taken)	Significance of differences from the control group
		P (M/F)	C (M/F)	P (M/F)	C (M/F)			
Hemodialysis								
Schardong et al., 2018, Brazil	[59]	10 (8/2)	–	65 ± 5	–	2.33 ± 2.7	Patients with CKD were enrolled. Patients had a history of hypertension, diabetes, autoimmune disorders, cancer, and cardiovascular diseases	–
Aykanat et al., 2016, Turkey	[42–44]	15 (7/8)	20 (11/9)	15 ± 3	13 ± 4	2.48 ± 2.3	Patients with CKD were enrolled. Drugs taken included cyclosporine, tacrolimus, or rapamycin in combination with mycophenolate mofetil steroid or alone, vitamin supplements, antihypertensive drugs, erythropoietin, anti-osteoporosis drugs, iron preparations, calcium acetate and citrate, antibiotics, and analgesics	$p < 0.001$
Mamur et al., 2016, Turkey	[33]	60 (43/17)	26 (17/9)	57 ± 23	40 ± 21	4.0 ± 3.1	Patients with chronic renal failure were enrolled, and 43% of them had type 2 diabetes. History included hypertension and hepatitis B and C. Information on the drugs administered was not provided	$p < 0.001$
Corredor et al., 2015, Spain	[64]	209 (129/90)	187 (119/68)	65 ± 1	56 ± 1	2–8	Patients with CKD stages 4–5 were enrolled, and approximately $^1/_3$ of them had diabetes. History included hyperlipidemia, cardiovascular pathologies, hypertension, and oncological diseases	$p < 0.001$
Ersson et al., 2013, Sweden	[34]	31 (20/11)	10 (4/6)	69 ± 12	59 ± 7	3.5 ± 3.5	Patients with chronic renal failure were enrolled. Patients with acute infection were excluded from the study. Moreover, 26% of the patients had diabetes	$p < 0.001$

Appendix 2 (continued)

First author, year of publication and country	Source	Group size		Age, years		Duration of therapy, years	Aspects of the studied patient population (comorbidities, drugs taken)	Significance of differences from the control group
		P (M/F)	C (M/F)	P (M/F)	C (M/F)			
Rangel-López et al., 2013, Mexico	[77]	33 (13/20)	61 (27/33)	51 ± 16	39 ± 9	Information has not been provided	Patients with CKD were enrolled, and about half of them had type 2 diabetes. Patients with cancer, bacterial infections, hepatitis C or B, HIV, or liver failure or on immunosuppressive therapy were excluded from the study	$p < 0.001$
Palazzo et al., 2012, Brazil	[26]	22 (12/10)	22 (5/17)	63 ± 9	63 ± 8	1.5 ± 0.9	Patients with type 2 diabetes were enrolled. They were taking ACE inhibitors, blood sugar-lowering agents, and diuretics, and some patients used recombinant erythropoietin and iron hydroxide	$p < 0.05$
Stoyanova et al., 2015, Spain	[35]	77 (49/28)	176 (111/65)[a]	62 ± 2	67 ± 1	4.3 ± 0.5	Patients with CKD were enrolled, and approximately $^1/_3$ of them had type 2 diabetes. History included cardiovascular pathologies. Drugs taken were vitamins B, C, and D and folate	$p < 0.05$
Bagatini et al., 2008, Brazil	[36]	25 (13/12)	20 (7/13)	63 ± 9	62 ± 9	2.13 ± 2.08	Diabetic patients undergoing hemodialysis were enrolled. Drugs taken were antihypertensive drugs (ACE inhibitors), hypoglycemic agents and diuretics; and human recombinant erythropoietin and iron hydroxide. Patients with a viral disease (hepatitis, HIV) were excluded from the study	$p < 0.05$

Appendix 2 (continued)

First author, year of publication and country	Source	Group size		Age, years		Duration of therapy, years	Aspects of the studied patient population (comorbidities, drugs taken)	Significance of differences from the control group
		P (M/F)	C (M/F)	P (M/F)	C (M/F)			
Horoz et al., 2006, Turkey	[37]	22 (11/11)	22 (10/12)	47 ± 9	42 ± 8	2.7 ± 3	Patients with CKD were enrolled. Drugs taken were antihypertensive drugs (beta-blockers, calcium channel blockers, ACE inhibitors, and angiotensin II receptor type 1 blockers), phosphate binders, and erythropoietin injections. Patients with hepatitis B or metabolic or autoimmune pathologies were excluded from the study	$p < 0.05$
Domenici et al., 2005, Brazil	[38]	51 (29/22)	9 (1/8)	52 ± 17	32 ± 6	4.34 ± 2.38	Patients with CKD were enrolled. Information on concomitant diseases and medications used was not provided	$p < 0.05$
Kan et al., 2002, Turkey	[39]	36 (24/12)	36 (24/12)	49 ± 14	49 ± 14	3.5 ± 2.6	Patients with CKD were enrolled. Patients with diabetes, chronic respiratory failure, intercurrent infection, or malignant tumors were excluded from the study	$p < 0.001$
Stopper et al., 2001, Germany	[40]	26 (16/10)	21 (9/12)	64 ± 13	48 ± 17	8.2 ± 7.5	Patients with indications for HD in the presence of various renal pathologies were enrolled. History included diabetes and amyloidosis. No drug information was provided	$p < 0.001$
Peritoneal dialysis								
Domenici et al., 2005, Brazil	[38]	22 (10/12)	9 (1/8)	58 ± 16	32 ± 6	2.7 ± 1.3	Patients with CKD were enrolled. Information on concomitant diseases and medications used was not provided	$p < 0.05$

Appendix 2 (continued)

First author, year of publication and country	Source	Group size		Age, years		Duration of therapy, years	Aspects of the studied patient population (comorbidities, drugs taken)	Significance of differences from the control group
		P (M/F)	C (M/F)	P (M/F)	C (M/F)			
Hemodiafiltration								
Stopper et al., 2001, Germany	[40]	15 (5/10)	21 (9/12)	65 ± 8	48 ± 17	5.2 ± 3.0	Patients with indications for HD in the presence of various renal pathologies were enrolled. History included diabetes and amyloidosis. No drug information was provided	$p < 0.001$

Note. [a] In this study, the control group included patients who were not undergoing HD but had renal failure of varying severity (2–5). P, patients; C, controls; HD, hemodialysis; ACE inhibitors, angiotensin-converting enzyme inhibitors; CKD, chronic kidney disease; the study in a pediatric patient population is marked gray.

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