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# Genotoxic properties of hypoglycemic drugs (systematic review)

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According to the literature genotoxic properties of about a half of hypoglycemic drugs have not been investigated in accordance with the recommended methodology, and studies of the mutagen-modifying activity of antidiabetic drugs are sporadic. Based on the available published data, it is impossible to conclude about either presence or absence of genotoxic / antigenotoxic potential of antidiabetic drugs. There is evidence of the antimutagenic activity of metformin; in relation to other drugs, studies of mutagen-modifying activity have not been carried out or are represented only by a few articles. Further study of the genotoxic properties of hypoglycemic drugs is required in accordance with modern approaches and requirements, as well as an assessment of their mutagen-modifying activity.

**Keywords:** diabetes; chromosomal aberrations; micronuclei; DNA comet assay; DNA damage; genotoxicity; antigenotoxicity.

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## Генотоксические свойства гипогликемических лекарств (систематический обзор)

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Анализ литературных данных показал, что около половины гипогликемических препаратов не исследованы в отношении их генотоксических свойств в соответствии с рекомендованной методологией, а исследования мутаген-модифицирующей активности противодиабетических средств имеют спорадический характер. На основании доступных опубликованных данных невозможно составить исчерпывающее заключение о наличии или отсутствии генотоксической/антигенотоксической активности у препаратов, используемых для лечения пациентов с диабетом. Имеются свидетельства в пользу антимутагенной активности метформина, в отношении других препаратов исследования мутаген-модифицирующей активности не проводились или представлены единичными работами. Требуется дальнейшее изучение генотоксических свойств гипогликемических препаратов в соответствии с современными подходами и требованиями, а также оценка их мутаген-модифицирующей активности.

**Ключевые слова:** диабет; хромосомные aberrации; микроядра; метод ДНК-комет; повреждения ДНК; генотоксичность; антигенотоксичность.

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## INTRODUCTION

Diabetes mellitus (DM) refers to a group of metabolic diseases characterized by abnormally increased plasma glucose concentrations or hyperglycemia, and is classified as type 1 (T1DM) or type 2 (T2DM). If untreated, DM leads to chronic degenerative diseases of the heart, kidneys, and the nervous system, including the retina. The International Diabetes Federation has characterized DM as a global epidemic [1]. By 2030, the number of patients with T2DM is predicted to increase globally to 439 million people [2].

Numerous epidemiological studies and meta-analyses indicate a link between DM and cancer incidence, as well as mortality from liver, pancreatic, colon, kidney, endometrial, and breast cancer [3]. Patients with a combination of DM and cancer have an increased risk of mortality from any cause compared with patients without a history of DM [4].

Mutagenesis has been generally recognized and comprehensively substantiated to trigger carcinogenesis [5, 6]. The increase in markers of genotoxicity in DM patients was noted repeatedly. It is associated with the formation of genotoxic reactive oxygen species (ROS) during hyperglycemia-induced oxidative stress [7–11].

Several hypoglycemic drugs are available to manage DM. However, it is not known whether these drugs contribute to genotoxicity in diabetic patients. These drugs may have their own genotoxic activities, as well as enhance (co-mutagens) or weaken (antimutagens) the effects of exogenous and endogenous genotoxicants, in particular ROS [12].

*This work aimed to systematically review and analyze the results of previous studies of genotoxic activity and mutagen-modifying properties of hypoglycemic drugs in experimental eukaryotic test systems *in vitro* and *in vivo*.*

## MATERIALS AND METHODS

Literature search was conducted to include articles published from January 1, 1990 to March 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 Russian Science Citation Index (RSCI) scientific electronic library (<http://elibrary.ru>). For certain instances when the understanding of a class of drugs required a more extensive review of its history, an additional literature search to include articles published earlier than 1990 was performed. The results from this supplementary search are specifically indicated with the dates in the text.

Key search terms for studies on the genotoxic activities of oral hypoglycemic drugs included the international nonproprietary names of drugs classified as group A10 “Drugs for the treatment of DM” in the anatomical-therapeutic-chemical drug classification system [13], in combination with the terms “genotoxicity” or “genotoxic,” “mutagen” or “mutagenic”, and the corresponding equivalents for English-language sources. The review included genotoxicological studies performed by chromosomal aberrations test (CA) and/or the cytokinesis-block micronucleus (MN) cytome assay, evaluation of DNA damage by the DNA comet assay and the following criteria:

- conducted *in vivo* on mammals or *in vitro* in cultures of eukaryotic somatic non-immortalized cell lines;
- performed in compliance with the standard practices of evaluating genotoxicity, including the presence of positive and negative controls and appropriate statistical analyses;
- published in peer-reviewed scientific journals in the English or Russian languages, with full-text versions of articles available.

From the full-text articles, information on the test systems (species of animals, cells used), experimental design, (doses, routes and frequency of administration, concentration, exposure time, etc.), and results of the study were collected.

In the absence of information on the genotoxicological properties of a specific drug in the Pubmed and RSCI databases, an additional search was performed on the official websites of regulatory agencies, namely European Medicinal Agency (EMA) and the U.S. Food and Drug Administration (FDA).

## RESULTS AND DISCUSSION

The antidiabetic drug classes included in the systematic search were insulin and its analogs, insulin secretion stimulants [sulfonylurea derivatives, meglitinides, analogs of glucagon-like peptides 1 (GLP-1), dipeptidyl peptidase 4 (DPP-4) inhibitors], insulin sensitivity sensitizers that increase the glucose disposal (biguanides, thiazolidinediones), and drugs with other mechanisms of action [alpha-glucosidase inhibitors and sodium glucose cotransporter type 2 (SGLT2) inhibitors].

### Insulin and its analogs

Insulin and its analogs are widely used to treat patients with T1DM and T2DM. Insulin is required in patients with T2DM who fail to achieve glycemic control after initiating lifestyle changes and oral antidiabetic drugs, as well as during pregnancy, in the postoperative period, and in other acute conditions [14].

Current regulatory requirements do not require genotoxicity studies of insulin and its analogs for the registration of their drug products (DPs). Using our search strategy, no study available in the literature met the above-defined inclusion criteria. However, there were studies that determined the outcomes of interest in immortalized cell lines as presented in Table 1. In particular, one study aimed to elucidate the possible contribution of insulin to tumorigenesis and levels of genotoxic biomarkers of oxidative stress in DM [15]. It was revealed that a minimum human insulin concentration of

10 nM in human lymphocytes and 0.5–1 nM in human colon adenocarcinoma cells (HT29) resulted in an increase in the levels of DNA damage and MN *in vitro* 24 h after treatment. Normally, the concentration of fasting insulin in the blood in the morning is an order of magnitude lower than these values (0.04 nM). However, in hyperinsulinemia and in the postprandial state, the concentrations could exceed 1 nM, and the plasma insulin concentration in ZDF rats (Zucker diabetic fatty) reaches 1.67 nM. Data from specialized clinical trials note an increased risk of cancer in patients who use insulin or its analogs [17].

**Table 1.** Studies of the genotoxic and mutagenic properties of insulin and its analogs *in vitro* and *in vivo*

| International nonproprietary name | Test system  | Treatment conditions  | Measured biomarker                                  | Effect  | Literature source |
|-----------------------------------|--|---|---|---|-------------------|
| Recombinant human insulin         | Cell lines of adenocarcinoma (MCF 7) and BT 474 human breast carcinoma   | 10 nM for 24 h  | DNA damage (DNA comet assay), MN frequency          | Significant effects in both test systems for both biomarkers              | [18]              |
|                                   | Cell lines of human colon adenocarcinoma (HT29), human colon cancer (Caco 2), primary cell line of rat colon, human lymphocytes  | Within 2 h (HT29 and Caco 2) or 6 days (HT29; 50% medium change daily and addition of fresh insulin at concentrations of 0.5–1, 1–2, and 10–20 nM), 30 min of the primary colon cell line (10, 100, and 2000 nM) and 24 h for lymphocytes (10 and 100 nM) | DNA damage (DNA comet assay), MN frequency          | Significant dose-dependent effects in all concentrations and test systems | [15]              |
| Insulin lispro                    | According to the manufacturer's information, insulin lispro does not induce MN induction in the bone marrow of male and female ICR mice <i>in vivo</i> and the induction of CA in Chinese hamster ovary (CHO) cells (primary data not presented)                       |   |   |   | [19]              |
| Insulin aspart                    | According to the FDA and EMA, insulin aspart does not exhibit mutagenic activity in tests for recording CA in human peripheral blood lymphocytes, in a test for recording MN in mice <i>in vivo</i> (primary data not presented)                                       |   |   |   | [20, 21]          |
| Insulin glulisine                 | According to the FDA and EMA, insulin glulisine does not exhibit mutagenic activity <i>in vitro</i> and <i>in vivo</i> CA recording tests (primary data not presented)   |   |   |   | [22, 23]          |
| Insulin glargine                  | Cell lines of adenocarcinoma (MCF-7) and BT 474 human breast carcinoma   | 10 nM for 24 h  | Level of DNA damage (DNA comet assay), MN frequency | Significant effect in both test systems for both biomarkers               | [18]              |
| Insulin detemir                   | According to the FDA and EMA, insulin detemir does not exhibit mutagenic activity in tests for recording CA in human lymphocyte cells <i>in vitro</i> and in bone marrow cells of CD-1 mice <i>in vivo</i> up to a dose of 7500 nM/kg (primary data are not presented) |   |   |   | [24, 25]          |
| Insulin degludec                  | Genotoxicity study data are not presented in the available literature  |   |   |   |                   |

*Note.* Here and below in Tables 2–6. MN – micronuclei, CA – chromosomal aberrations. Hereinafter, in the tables, studies are highlighted in gray, which reveal significant genotoxic activity of the compound in comparison with the negative control.

Current available data is insufficient to provide basis for evaluating the genotoxicity of insulin. Whether insulin or its excipients in the formulations directly causes the findings reported is unknown. Based on the general understanding of the mechanisms of induced mutagenesis and the known effects of insulin, it could be assumed that genotoxicity due to insulin is improbable.

### Oral hypoglycemic drugs

Information on the results of genotoxicity and mutagenicity studies of the main classes of hypoglycemic drugs is presented in Tables 2–6. Thirty-two drugs were included in the analysis.

For 6 of these drugs (19 %), no data on their genotoxic activities was available in the literature (buformin, gemigliptin, evogliptin, gosogliptin, dulaglutide, and ipragliflozin). For 10 of these DPs (31 %), only documents from the websites of regulatory authorities in Europe and/or the USA were available and did not include specifications of the experimental design or presentation of primary data (saxagliptin, alogliptin, exenatide, liraglutide, lixisenatide, semaglutide, canagliflozin, ertugliflozin, repaglinide). For these drugs, it was indicated that cytogenetic studies were performed in accordance with current regulatory requirements *in vitro* and *in vivo*, and no data was found indicating genotoxic properties in them.

Experimental data on genotoxicity or mutagenic effects were available only for 16 drugs (50 %), performed in either *in vivo* (for 13 drugs, 41 %) or *in vitro* (for 8 drugs, 25 %) systems as summarized in Tables 2–6. Mutagenic effects *in vivo* was noted in sulfonylurea derivatives of chlorpropamide [27], tolbutamide [28] and gliquidone [29], as well as in a thiazolidinedione derivative pioglitazone [30, 31]. The genotoxic activity *in vivo* was demonstrated by rosiglitazone [32], and *in vitro* by metformin [9, 38] and sitagliptin [33]. The absence of genotoxicity or mutagenicity was demonstrated *in vivo* for glibenclamide, carbutamide, glipizide, gliquidone, gliclazide, glimepiride, dapagliflozin, and empagliflozin.

**Biguanide derivatives.** Metformin is the most commonly used drug for treatment of prediabetes, gestational DM, and T2DM in the last 65 years [34]. According to various estimates, metformin is prescribed to 70 %–85 % of T2DM patients annually for long-term daily use [35, 36]. The widespread use of metformin has captured the interest of research groups to assess its genotoxicity (Table 2).

Analysis of the data given in Table 2 shows that metformin administered orally or intraperitoneally at doses

ranging from 95.4 to 2500 mg/kg does not result in the induction of CA or MN in laboratory rodents. Rather, metformin exhibited antimutagenic properties under these sets of conditions in streptozotocin-induced DM model in rats [37]. A similar decrease in MN in bone marrow cells was observed in the same model after daily 4-week oral administration of 50 mg/kg metformin combined with 1 mg/kg [41].

The absence of genotoxic activity *in vivo* in metformin agrees with results obtained *in vitro* using cell cultures of rodents and human lymphocytes at maximum doses from 50  $\mu\text{M}$  in some cases and up to 114.4  $\mu\text{g/ml}$  in others Table 2. However, one study showed that metformin can induce DNA damage in p53-deficient Chinese hamster ovary CHO-K1 cells was shown using the DNA comet assay [38]. However, the strength of evidence from this set of data is low because the authors used unverified indicators that differ significantly from generally accepted ones [42]. Lastly, it is worth noting that a significant decrease in the levels of genotoxic biomarkers was observed in several clinical studies in patients with T2DM while taking metformin [7].

In turn, the antimutagenic effect of metformin, established in experiments with streptozotocin DM, is supported by a number of independent studies which used chemical mutagens [43]. Metformin after 7-day daily administration significantly reduced the frequency of MN in polychromatophilic erythrocytes in the bone marrow of male Swiss albino mice 24, 48, or 72 h after intraperitoneal administration of the cytostatic antitumor drug Adriamycin [44]. This observation was seen using metformin doses of 62.5, 125, and 250 mg/kg and occurred in a dose-dependent manner. Data from *in vitro* studies also indicate a protective effect of metformin against the induction of CA and MN after exposure to ionizing radiation [45] and DNA damage (% DNA in the comet tail) induced by 1 mM cumene hydroperoxide in human lymphocytes [46].

The protective effect of metformin extends to its ability to reduce the mutagenic effects of other hypoglycemic DPs [47]. The cytogenetic effects of sitagliptin and vildagliptin [0.04 mg/(kg per day)] alone or with metformin (0.2 mg metformin) in pregnant female mice and their embryos were evaluated. In the absence of metformin, both these drugs exerted mutagenic and toxic effects on pregnant females and embryos. In contrast, no similar effects were registered when either of these drugs were combined with metformin.

Furthermore, metformin has antiradical [48], reparative [49], and proapoptotic [50] effects, each of which can contribute to the observed antimutagenic effects.

**Table 2.** Studies of genotoxic and mutagenic properties of biguanide derivatives *in vitro* and *in vivo*

| International nonproprietary name | Test system  | Treatment conditions   | Effect biomarker   | Effect   | Literature source |
|-----------------------------------|--|--|--|--|-------------------|
| Metformin                         | Wistar albino rats, male, control or model of streptozotocin-induced diabetes mellitus (65 mg/kg intraperitoneally, single dose) | Single dose, <i>per os</i> in doses of 100, 500, and 2500 mg/kg    | Frequency of MN and CA in bone marrow cells 24 h after administration                | No effect in control rats, significant decrease in MN and CA levels in rats with diabetes mellitus (in two higher doses)                                     | [37]              |
|                                   | Wistar albino rats, male, control or model of streptozotocin-induced diabetes mellitus (65 mg/kg intraperitoneally, single dose) | Daily for 4 or 8 weeks, <i>per os</i> in doses of 100 or 500 mg/kg | Frequency of MN and CA in bone cells brain 24 h after the last injection             | No effect in control rats, a significant decrease in the MN level in rats with diabetes mellitus (at a dose of 500 mg/kg 4 and 8 weeks after administration) | [37]              |
|                                   | Swiss albino mice, females   | Once, intraperitoneally at doses of 95.4, 190.8, and 333.9 mg/kg   | MN frequency in bone marrow cells 24 h after administration                          | No effect; cytotoxicity at the highest dose  | [38]              |
|                                   | Chinese hamster ovary cells, CHO-K1 <i>in vitro</i>  | 114.4 and 572 µg/ml  | DNA damage (DNA comet assay, alkaline version) and CA frequency 24 h after treatment | Significant increase in the level of DNA damage in both concentrations (maximum with a lower one); no effect on the level of CA was found                    | [38]              |
|                                   | Culture of human lymphocytes   | 114.4 µg/ml for 72 h   | DNA damage (DNA comet assay, alkaline version) and MN frequency                      | No effect  | [39]              |
|                                   | Culture of human lymphocytes   | 12.5, 25, and 50 µM for 72 h                                       | Frequency of MN and CA   | No effect  | [40]              |
|                                   | Rat NRK kidney epithelial cells  | 3, 12, and 48 µM for 2 and 24 h with/without insulin (10 nM)       | DNA damage (DNA comet assay, alkaline version) and NM frequency                      | Significant reduction in DNA damage and MN frequency compared to insulin treatment only  | [9]               |
| Buformin                          | Genotoxicity study data are not presented in the available literature  |  |  |  |                   |

This antimutagenic effect translates well when measuring outcomes directly related to cancer. Metformin has been shown to possess antitumor activity [51]. Lastly, in a number of meta-analyses, patients taking metformin have been shown to have a lowered risk of lung, pancreatic, prostate, and breast cancer, as well as in mortality in cancer patients, compared with patients receiving insulin or sulfonylurea derivatives [52–55].

Two plausible mechanistic pathways underlying the benefit of using metformin as a means of cancer prevention have been proposed previously, namely (1) an indirect pathway associated with its ability to reduce the

insulin levels by slowing tumor proliferation in patients with hyperinsulinemia; and (2) a direct action against the respiratory Complex I of the electron transfer chain in the mitochondria of preneoplastic and neoplastic cells, which ultimately reduces the energy consumption of the target cell [56]. Both pathways of action involve stimulation of adenosine monophosphate-activated protein kinase (AMPK) by metformin, which inhibits the target of rapamycin (mTOR) in mammals. AMPK activation decreases cell proliferation and can trigger cell cycle arrest and apoptosis [57, 58]. Today, in addition to these two possibilities of antitumor prophylaxis, it is quite

appropriate to suggest an antimutagenic pathway, for example, by suppressing the genotoxicity of ROS arising during oxidative stress DM.

**Sulfonylurea derivatives.** It is known that the use of the first generation of drugs in this group (tolbutamide, chlorpropamide, acetohexamide, and tolazamide) was associated with an increased risk of thyroid cancer due to their antithyroid action [59]. Currently, the second generation of sulfonylureas (glipizide, glimepiride, glimepiride, and glycidone) are widely used and can provide relatively better glycemic control with fewer side effects. Information on the results of the study of genotoxicity of sulfonylurea derivatives is presented in Table 3.

Additionally, the results of studies performed in the 1980s investigating the cytogenetic properties of chlorpropamide and tolbutamide should be mentioned as reference [27, 28]. In these studies, a dose-dependent mutagenic effects of these drugs were demonstrated when used in doses 1–2 orders of magnitude higher than the therapeutic doses used in humans. These findings provide a compelling argument in favor of refinement of future studies to measure the genotoxicity of chlorpropamide and tolbutamide based on contemporary protocols. Moreover, no studies on the DNA-damaging effects *in vitro* or *in vivo* have been done for any of the drugs in this group, and the mutagenicity data of the first-generation sulfonylurea derivatives created several decades ago [27, 64] requires reassessment [26].

**Thiazolidinediones.** Currently, pioglitazone is the only thiazolidinedione available in the market. Rosiglitazone was withdrawn because it increased the risk of myocardial infarction, and troglitazone was withdrawn due to its hepatotoxicity [65, 66] (Table 4).

In cultures of human lymphocytes, pioglitazone at concentrations exceeding 108  $\mu\text{M}$  demonstrated concentration-dependent MN induction [68]. In rat lymphocytes and hepatocytes, a significant dose-dependent increase

in the level of DNA damage was observed using the DNA comet assay after daily oral administration of pioglitazone for 14 days at doses of 10, 20, and 40 mg/kg [30].

There are separate data indicating a dose-dependent MN decrease in bone marrow cells of rats after 4 weeks of daily oral administration of pioglitazone at doses of 20, 40, and 80 mg/kg in the model of streptozotocin-nicotinamide DM [67].

An unambiguous interpretation of the presented data is difficult and require further verification in future independent studies.

**GLP-1 analogs and DPP-4 inhibitors.** The available literature presents no primary results of studies on the genotoxic activity of glucagon-like peptide analogs. Information from the websites of regulatory agencies reports that they have no genotoxic effects (Table 5). At the same time, there are indications in the literature on the possible carcinogenic potential of drugs in this group [69, 70]. From a practical point of view, these drugs have been in the market for a relatively short period of time only, which precludes the assessment of their long-term effects in humans [71]. Therefore, the conduct of independent studies on their genotoxic activity, which enables the prediction of their carcinogenicity using short-term tests, is of primary importance [6, 72] and remains an urgent task of contemporary genotoxicology.

Among DPP-4 inhibitors, only sitagliptin and vildagliptin were studied for their genotoxic and mutagenic activities. No information on these parameters is available for other drugs in the class, namely, saxagliptin, alogliptin, gemigliptin, evogliptin, and gosogliptin. Data on sitagliptin are conflicting. In one study, the drug at concentrations of 250, 500, and 1000  $\mu\text{g/ml}$  did not affect the frequency of CA and MN after 24 and 48 h of *in vitro* treatment of human lymphocytes [77]. However, in another study, it caused a significant increase

**Table 3.** Studies of genotoxic and mutagenic properties of sulfonylurea derivatives *in vitro* and *in vivo*

| International nonproprietary name | Test system                         | Treatment conditions  | Effect biomarker  | Effect    | Literature source |
|-----------------------------------|-------------------------------------|---|---|-----------|-------------------|
| Glibenclamide                     | Culture of human lymphocytes        | 0.6, 10, 100, 240, and 480 $\mu\text{M}$ for 72 h             | Frequency of MN   | No effect | [60]              |
|                                   | Chinese hamsters, males and females | Once <i>per os</i> at a dose of 10 mg/kg                      | SCE in bone marrow cells 24 h after administration                | No effect | [27]              |
|                                   | Swiss albino mice, male             | Twice with an interval of 24 h at doses of 4, 8, and 16 mg/kg | Frequency of MN in bone marrow cells 6 h after the last injection | No effect | [28]              |

**Table 3 (continued)**

| International nonproprietary name | Test system  | Treatment conditions   | Effect biomarker  | Effect  | Literature source |
|-----------------------------------|--|--|---|---|-------------------|
| Chlorpropamide                    | Chinese hamsters, C57BL/6J mice, males and females                                 | Therapeutic dose 7.1 mg/kg, as well as 71, 177.5, 497, and 710 mg/kg, single dose, <i>per os</i> | SCE in bone marrow cells 24 hours after administration            | Significant dose-dependent effect in both test systems  | [27]              |
|                                   | Mice NMRI, C3H, C57BL/6J, Chinese hamsters, Sprague-Dawley rats, males and females | Twice after 24 h at a dose of 355 mg/kg, <i>per os</i>   | MN in bone marrow cells 6 h after the last injection              | Significant increase in MN levels in all mice test systems; no effect in rats and hamsters                                  | [28]              |
| Tolbutamide                       | Chinese hamsters, C57BL/6J mice, males and females                                 | Therapeutic dose 28.6 mg/kg, as well as 286, 1430, and 2002 mg/kg, single dose, <i>per os</i>    | SCE in bone marrow cells 24 h after administration                | Significant dose-dependent effect in both test systems  | [27]              |
|                                   | Mice NMRI, C3H, C57BL/6J, Chinese hamsters, Sprague-Dawley rats, males and females | Twice after 24 h at a dose of 1430 mg/kg, <i>per os</i>  | MN in bone marrow cells 6 h after the last injection              | Significant increase in MN levels only in line C57BL mice; no effect in other test systems                                  | [27]              |
|                                   | Swiss albino mice, male  | Twice with an interval of 24 h at doses of 500, 1000, and 2000 mg/kg                             | Frequency of MN in bone marrow cells 6 h after the last injection | Significant (in two higher doses) dose-dependent increase in MN level   | [28]              |
| Carbutamide                       | Chinese hamsters, males and females  | Once <i>per os</i> at a dose of 715 mg/kg  | SCE in bone marrow cells 24 h after administration                | No effect   | [27]              |
| Glipizide                         | Chinese hamsters, males and females  | Once <i>per os</i> at a dose of 15 mg/kg   | SCE in bone marrow cells 24 h after administration                | No effect   | [27]              |
| Gliquidone                        | Chinese hamsters, males and females  | Once <i>per os</i> at a dose of 85 mg/kg   | SCE in bone marrow cells 24 h after administration                | No effect   | [27]              |
|                                   | Swiss albino mice, male  | <i>Per os</i> at a dose of 30 mg/kg once or daily for 10 or 20 days                              | MN in bone marrow cells 24 h after the last injection             | Significant ( $p < 0.01$ ) dose-dependent increase in the level of MN cells was noted in both cases multiple administration | [29]              |
|                                   | Swiss albino mice, male  | Once <i>per os</i> at doses of 30, 60, and 120 mg/kg   | CA in bone marrow cells 7 days after administration               | Significant ( $p < 0.01$ ) dose-dependent increase in the level of cells with CA was registered for all doses               | [29]              |



**Table 3 (continued)**

| International nonproprietary name | Test system   | Treatment conditions   | Effect biomarker                                       | Effect  | Literature source |
|-----------------------------------|---|--|--|---|-------------------|
| Gliclazide                        | Swiss albino and OF1 mice   | Once at doses of 1, 2, and 3 g/kg  | MN in peripheral blood cells 24 h after administration | No effect   | [61]              |
|                                   | Culture of human lymphocytes  | 5, 25, 50, and 100 µM without/with subsequent irradiation (1.5 Gy after 3 h) | MN frequency after 72 h of exposure                    | No effect (without irradiation), significant concentration-dependent decrease in the level of damage caused by irradiation, in all concentrations | [62]              |
| Glimepiride                       | Wistar rats, male, diabetes model, intraperitoneal administration of streptozotocin (65 mg/kg) and nicotinamide (230 mg/kg) | Daily for 4 weeks per os at doses of 0.175, 17.5, and 175 mg/kg              | Frequency of MN in bone marrow cells                   | Significant dose-dependent decrease in the level of cells with MN compared to control ( $p < 0.001$ )   | [63]              |

in the frequency of CA when used at a concentration of 1000 µg/ml after 24 h and at concentrations of 31.25, 62.5, 125, 500, and 1000 µg/ml (but not at a concentration of 250 µg/ml) after 48 h, and increased the frequency of MN only at the highest concentration of 1000 µg/ml [33]. In a pilot clinical study, the genotoxic and cytotoxic effects of sitagliptin in lymphocytes of T2DM patients after a 6-month course of treatment were demonstrated [82].

With regard to their mutagenic and toxic effects, an *in vivo* study showed that sitagliptin and vildagliptin had harmful effects on pregnant females and their foetus [47]. Reduction of this detrimental effect using metformin combinations is described above.

Although the existing data are insufficient for the drawing of precise conclusions, available results indicate the need for a systematic genotoxicological study of these groups of drugs using experimental and clinical studies.

**SGLT2 inhibitors.** Inhibitors of the sodium glucose cotransporter type 2 (SGLT2 inhibitors) promote the excretion of glucose in the urine in an insulin-independent manner. The drugs of this group, dapagliflozin and empagliflozin, did not induce cytogenetic changes in the cells of the peripheral blood and/or bone marrow of rats [83, 84]. However, no data on their genotoxic activities was available (Table 6).

As in the previous drug classes, it should be noted that studies of the genotoxic activity of the drugs in this group are insufficient.

Overall, our results demonstrate that current data on the genotoxicity of hypoglycemic drugs are incomplete, fragmentary, uncoordinated, and contradictory. Almost half of the known hypoglycemic drugs have not been tested adequately for genotoxicity. This observation does not differ from that in other drug groups, with more than half of which have not yet been fully investigated

**Table 4.** Studies of genotoxic and mutagenic properties of thiazolidinediones *in vitro* and *in vivo*

| International nonproprietary name | Test system               | Treatment conditions  | Effect biomarker   | Effect   | Literature source |
|-----------------------------------|---------------------------|---|--|--|-------------------|
| Rosiglitazone                     | Sprague-Dawley rats, male | Daily <i>per os</i> for 14 days at doses of 0.5, 1, and 2 mg/kg | DNA damage (DNA comet assay) in peripheral blood cells and hepatocytes | Significant dose-dependent increase in the level of DNA damage in hepatocytes compared to control in all doses ( $p < 0.001$ ); in lymphocytes, the effect is only in the two higher doses | [32]              |

**Table 4 (continued)**

| International nonproprietary name | Test system  | Treatment conditions   | Effect biomarker  | Effect  | Literature source |
|-----------------------------------|--|--|---|---|-------------------|
| Pioglitazone                      | Sprague-Dawley rats, male  | Daily for 14 days <i>per os</i> at doses of 10, 20, and 40 mg/kg   | DNA damage (DNA comet assay) in peripheral blood cells and hepatocytes    | Significant dose-dependent increase in the level of DNA damage in lymphocytes and hepatocytes compared with control ( $p < 0.001$ )                         | [30]              |
|                                   | Wistar albino rats, male, diabetes model – intraperitoneal streptozotocin administration (65 mg/kg) and nicotinamide (230 mg/kg) | Daily for 4 weeks <i>per os</i> at doses of 20, 40, and 80 mg/kg   | Frequency of CA and MN in bone marrow cells 24 h after the last injection | Significant dose-dependent decrease in the level of both biomarkers in comparison with the diabetes group, and to the control level in the two higher doses | [67]              |
|                                   | Culture of human lymphocytes   | 100 $\mu\text{M}$ with/without pretreatment with vitamin B <sub>12</sub> cell cultures (13.5 $\mu\text{g}/\text{ml}$ ) | Frequency of CA and SCE after 24 h of exposure                            | Significant increase in the level of both biomarkers ( $p < 0.01$ ); pretreatment with vitamin B <sub>12</sub> reduces the genotoxic effect                 | [31]              |
|                                   | Culture of human lymphocytes   | 4, 12, 36, 108, 324, and 972 $\mu\text{M}$   | MN level after 72 h   | Significant concentration-dependent increase in MN level at concentrations above 108 $\mu\text{M}$  | [68]              |

for genotoxicity according to the accepted protocols [64]. The issue underlying these does not seem to be the lack of genotoxicity analysis of new drugs entering the market but the outdated evaluation of already available hypoglycemic drugs. Because the pathogenesis of DM is accompanied by oxidative and coupled carbonyl stress, resulting in the formation of genotoxic products [8–10], the combination of the effects of these endogenous mutagens with the potential genotoxicity of the drug used is highly undesirable. Therefore, a systematic study on the genotoxicity of these antidiabetic drugs, in accordance with current requirements, is needed.

Another potential source of concern is the possible presence of co-mutagenic effects in hypoglycemic drugs, which has not been mandatorily tested until now [91]. Our analysis of the literature shows that this type of study has not been proactively performed in drugs of this group. Co-mutagens can significantly enhance the genotoxic effects. For example, the co-mutagenic properties

of calcium channel blockers are well known [92, 93]. Further experimental (in appropriate biomodels) or clinical confirmation of the co-mutagenic activity of these drugs will make these extremely undesirable as anti-hypertensive drugs in patients with DM. Thus, hypoglycemic drugs used in the treatment of patients with DM should be tested for co-mutagenicity.

Regardless of whether genotoxicity in DM can be considered a consequence of pathognomonic oxidative stress or manifestations of the effects of the use of drugs with genotoxic activity, it is essential to note that most comorbid DM diseases are characterized by increases in DNA damage in their pathogenesis. This pathology has been shown in chronic degenerative heart diseases [94] and the development of atherosclerosis [95, 96], nephropathy [97], neuropathy and retinopathy [98–100], and cancer [101, 102]. Thus, it is desirable to consider the use of drugs with combined hypoglycemic and antimutagenic activity as an option for DM therapy.

**Table 5.** Studies of genotoxic and mutagenic properties of GLP-1 analogs and DPP-4 inhibitors *in vitro* and *in vivo*

| International nonproprietary name         | Test system                     | Treatment conditions  | Effect biomarker   | Effect   | Literature source |
|---|---------------------------------|---|--|--|-------------------|
| Analogues of GLP-1                        |                                 |   |  |  |                   |
| Exenatide                                 |                                 | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented)              |  |  | [73]              |
| Liraglutide                               |                                 | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented)              |  |  | [74]              |
| Lixisenatide                              |                                 | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented)              |  |  | [75]              |
| Semaglutide                               |                                 | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented)              |  |  | [76]              |
| Dulaglutide                               |                                 | Genotoxicity study data are not presented in the available literature   |  |  |                   |
| Dipeptidyl peptidase 4 (DPP-4) inhibitors |                                 |   |  |  |                   |
| Sitagliptin                               | Pregnant mice and their embryos | 0.04 mg/(kg · day) <i>per os</i> from the day 3 to the day 18 day of pregnancy without or in combination with metformin [0.2 mg/(kg · day)] | CA frequency in bone marrow cells of mice on the day 19 of pregnancy and in hepatocytes of embryos | Significant more than 2-fold excess of CA level in the case of bone marrow and 3-fold excess in embryonic cells; a decrease in the level of CA when administered together with metformin almost to the control values  | [47]              |
|   | Culture of human lymphocytes    | 250, 500, and 1000 µg/ml with/without metabolic activation  | Frequency of CA, SCE and MN after 24 and 48 h  | No effect  | [77]              |
|   | Culture of human lymphocytes    | 31.25, 62.5, 125, 250, 500, and 1000 µg/ml  | DNA damage (DNA comet assay), frequency of CA, SCE and MN after 24 and 48 h                        | Significant increase in the frequency of CA and SCE at the highest concentration within 24 h and at all concentrations (except for 250 µg/ml for CA and 31.25 and 62.5 µg/ml for SCE) after 48 h compared with control ( $p < 0.05$ ), the frequency of MN are only in the highest concentration ( $p < 0.05$ ), sitagliptin increased significantly the mean intensity of the comet tail and the moment of the tail only at two concentrations (62.50 and 1000 µg/ml for intensity, 125 and 1000 µg/ml for tail moment) and tail length at all concentrations (except 125 and 500 µg/ml) ( $p < 0.05$ ) | [33]              |

**Table 5 (continued)**

| International nonproprietary name | Test system  | Treatment conditions  | Effect biomarker   | Effect  | Literature source |
|-----------------------------------|--|---|--|---|-------------------|
| Vildagliptin                      | Human lymphocyte culture   | 125, 250, and 500 µg/ml with or without metabolic activation  | Frequency of CA, SCE and MN after 24 and 48 h  | No effect   | [77]              |
|                                   | Pregnant mice and their embryos  | 0.04 mg/(kg · day) <i>per os</i> from the day 3 to the day 18 of pregnancy without/ in combination with metformin [0.2 mg/(kg · day)] | CA frequency in bone marrow cells of mice on the day 19 of pregnancy and in hepatocytes of embryos | Significant more than 2-fold excess of CA level in the case of bone marrow and 3-fold excess in embryonic cells; a decrease in the level of CA when administered together with metformin almost to the control values | [47]              |
| Saxagliptin                       | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented) |   |  |   | [78, 79]          |
| Alogliptin                        | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented) |   |  |   | [80]              |
| Linagliptin                       | Human peripheral blood mononuclear cell culture  | 0.5, 1, 2.5, 5, 10, 25, 50, and 100 mg/l  | CA frequency after 72 h of exposure  | No effect   | [81]              |
| Gemigliptin                       | Genotoxicity study data not presented in the available literature  |   |  |   |                   |
| Evogliptin                        | Genotoxicity study data not presented in the available literature  |   |  |   |                   |
| Gosogliptin                       | Genotoxicity study data not presented in the available literature  |   |  |   |                   |

Moreover, this stresses the need to study the antimutagenicity of drugs already used in DM.

Analysis of the literature indicates that among hypoglycemic drugs, only metformin has been tested for antimutagenic activity. The studies performed are fragmentary, and this issue requires further in-depth analysis. For this purpose, a proven technique for studying the antimutagenicity of pharmacological agents can be used

[12, 103, 104]. In addition, a number of drugs that exhibit antimutagenic effect [105] can potentially be suitable as complementary treatment interventions for DM.

Among drugs that lower glucose levels, insulin and insulin secretion stimulants notable for their potential to increase the risk of cancer. Their mechanisms of action include signaling of insulin receptors and insulin-like growth factor I (IGF-1R), which enhance cell

**Table 6.** *In vitro* and *in vivo* studies of the genotoxic and mutagenic properties of sodium glucose cotransporter type 2 (SGLT2) inhibitors

| International nonproprietary name | Test system                            | Treatment conditions  | Effect biomarker   | Effect    | Literature source |
|-----------------------------------|--|---|--|-----------|-------------------|
| SGLT2 inhibitors                  |  |   |  |           |                   |
| Dapagliflozin                     | Sprague-Dawley rats, males and females | Daily for 1 month <i>per os</i> at doses of 25, 100, 150, and 200 mg/kg   | CA in peripheral blood cells 24 h after the last injection         | No effect | [83]              |
|                                   | Sprague-Dawley rats, males and females | Daily for 3 days <i>per os</i> at doses of 350, 700, or 1050 mg/kg or for 14 days at doses of 75, 150, 200, and 250 mg/kg | Frequency of MN in bone marrow cells 24 h after the last injection | No effect | [83]              |

**Table 6 (continued)**

| International nonproprietary name | Test system  | Treatment conditions  | Effect biomarker                                   | Effect    | Literature source |
|-----------------------------------|--|---|--|-----------|-------------------|
| Canagliflozin                     | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented) |   |  |           | [85]              |
| Empagliflozin                     | Wistar Han rats, males and females   | Daily for 3 days <i>per os</i> at doses of 100, 300, 1000, and 2000 mg/kg | Frequency of MN in polychromatophilic erythrocytes | No effect | [84]              |
|                                   | Chinese hamster cell culture   | 5, 10, and 20 $\mu$ M with or without metabolic activation                | Frequency of cells with MN                         | No effect | [86]              |
| Ertugliflozin                     | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented) |   |  |           | [87]              |
| Ipragliflozin                     | Genotoxicity study data are not presented in the available literature<br>Other hypoglycemic drugs                              |   |  |           |                   |
| Rapiginide                        | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented) |   |  |           | [88]              |
| Exenatide                         | According to EMA, does not exhibit genotoxic activity in <i>in vivo</i> and <i>in vitro</i> tests (primary data not presented) |   |  |           | [89]              |

proliferation and, possibly, carcinogenesis. In contrast, insulin sensitizers (metformin) have an anticancer effect by stimulating the regulatory pathway of AMPK, peroxisome proliferator activated gamma receptor (PPAR- $\gamma$ ), and the transcription factor, Egr-1 [17]. This raises the question of whether thiazolidinediones, another class of insulin sensitizers, could also have antimutagenic activity, similar to metformin. Finally, available data undoubtedly supports the use of metformin as the drug of choice among hypoglycemic agents.

## CONCLUSION

Almost half of the drugs used in the treatment of patients with DM have not been studied for genotoxic

activity in accordance with current methodological requirements. Studies on the mutagen-modifying activity of antidiabetic agents are sporadic and were performed beyond the previously recommended approaches [12, 104].

In most cases, the results of preclinical assessment of genotoxic potential do not provide adequate information for us to arrive at a reasonable conclusion regarding the presence or absence of genotoxic/antigenotoxic potential in drugs used to treat DM. Further studies on the genotoxic and mutagen-modifying properties of hypoglycemic drugs are required and should be performed in accordance with current approaches and standards.

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