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DNA damage and efficacy of DNA repair in patients with type 2 diabetes and coexisting colorectal cancer

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KEY WORDS

colorectal cancer, DNA damage, DNA repair, oxidative stress, type 2 diabetes

ABSTRACT

INTRODUCTION Numerous epidemiological studies have indicated that the frequency of developing certain types of cancer, including colorectal cancer (CRC), is higher in patients with type 2 diabetes. The possible causes of this association have not been fully clarified. It has been suggested that chronic hyperglycemia-related oxidative stress leading to oxidative DNA damage and impaired DNA repair may contribute to increased risk of cancer in type 2 diabetes.

OBJECTIVES The aim of the study was to evaluate the level of DNA damage and efficacy of DNA repair in patients with CRC with and without type 2 diabetes in comparison with healthy controls.

PATIENTS AND METHODS The alkaline comet assay was used to assess the level of endogenous oxidative and H_2O_2-induced DNA damage and the efficacy of DNA repair in the lymphocytes of patients with type 2 diabetes, with CRC, with type 2 diabetes and CRC, and of healthy people (a total of 32 patients).

RESULTS The highest levels of endogenous oxidative and H_2O_2-induced DNA damage were found in the lymphocytes of patients with type 2 diabetes and CRC. Additionally, the capacity of DNA repair was significantly decreased in patients with CRC with and without type 2 diabetes.

CONCLUSIONS Our findings support the hypothesis that an increased risk of cancer in type 2 diabetes may be associated with oxidative DNA damage; however, impaired DNA repair seems to play a major role in carcinogenesis in people with and without type 2 diabetes.

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INTRODUCTION Recent evidence has indicated an association between some types of cancer such as liver, pancreatic, colorectal, esophageal, stomach, kidney, endometrial, and breast cancer with diabetes mellitus, especially with type 2 diabetes.[1] It is estimated that about 371 million people worldwide have diabetes, and this number has been increasing dramatically.[2,3] Therefore, there is a high probability that the number of people with diabetes and cancer will also rapidly increase. In this context, it should be underlined that colorectal cancer (CRC) is the fourth most common cause of cancer death in the global population.[4]

The relationship between diabetes and cancer has not been sufficiently clarified. However, several possible underlying mechanisms have been postulated, including obesity, insulin resistance, elevated levels of insulin and insulin-like growth factor 1, and chronic hyperglycemia.[5,6]

It is widely accepted that hyperglycemia leads to the overproduction of mitochondrial reactive oxygen species (ROS) via 4 principal mechanisms: protein kinase C activation, activation of the hexosamine and polyol pathways, and formation of advanced glycation end-products with the subsequent formation of sustained cellular oxidative stress.[7-10] Furthermore, patients with diabetes have reduced levels of intracellular antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase and low levels of nonenzymatic antioxidants such as vitamins A and E.[11]

Endogenous ROS actively react with DNA and other cellular components such as lipids and proteins, thus causing their damage. Alterations to DNA in the form of oxidized bases, modifications

TABLE Clinical characteristics of the study group

	Controls (n = 8)	Type 2 diabetes (n = 8)	CRC (n = 8)	Type 2 diabetes and CRC (n = 8)
age, y	79.50 ±2.00	68.00 ±16.00	69.00 ±8.00[b]	78.50 ±6.50[g]
sex (female/male)	4/4	3/5	2/6	4/4
BMI, kg/m^2	28.00 ±1.41	31.50 ±5.94	26.00 ±3.60	24.00 ±2.00[b,d]
FPG, mM	4.96 ±0.25	8.11 ±2.17[b]	5.28 ±0.89	5.88 ±1.02[a,c,e]
HbA_{1c}, %	5.55 ±0.45	7.20 ±1.61[a]	5.92 ±0.55	6.39 ±0.73[a]
duration of type 2 diabetes, y	–	8.63 ±3.20	–	9.5 ±4.50

Data are expressed as means ± standard deviation.

a $P < 0.05$ b $P < 0.01$ compared with controls
c $P < 0.05$ d $P < 0.01$ compared with type 2 diabetes
e $P < 0.05$ compared with CRC

Abbreviations: BMI – body mass index, CRC – colorectal cancer, FPG – fasting glucose plasma, HbA_{1c} – glycated hemoglobin

of sugar moieties, and strand breaks are mainly repaired by base excision repair.[12] The impairment of the DNA repair system leads to insufficient removal of DNA damage from cells.[13]

It has been suggested that both DNA damage and repair play an important role in neoplastic transformation.[14] However, a number of studies exploring the effect of hyperglycemia on the DNA repair system, which plays a critical role in the maintenance of genomic DNA stability in type 2 diabetes, is limited.[15,16] Therefore, the objective of this study was to assess the extent of endogenous oxidative and H_2O_2-induced DNA damage and the capacity for repair in patients with type 2 diabetes with and without CRC in comparison with nondiabetic patients without cancer. We assume that the results of this study could add to our knowledge about the role of an efficient DNA repair system in patients with type 2 diabetes and concurrent CRC.

PATIENTS AND METHODS

Patients Eight patients with type 2 diabetes, 8 patients with CRC, 8 patients with type 2 diabetes and CRC, and 8 potentially healthy individuals were recruited into the study. All patients were hospitalized at the Department of Internal Medicine, Diabetology and Clinical Pharmacology in Zgierz, Poland. The study was approved by the local ethics committee of the Medical University of Lodz. Each participant gave written consent to participate in the study. Type 2 diabetes was diagnosed on the basis of the recommendations of the American Diabetes Association.[17] The diagnosis of CRC was established according to the recommendations of the American Cancer Society.[18] The inclusion criteria were age older than 18 years and CRC with or without type 2 diabetes. Patients were excluded if they had metastases, inflammatory bowel disease, thyroid disease, a family history of CRC, history of chemotherapy or radiotherapy, other types of cancer, and other types of diabetes. The control group consisting of healthy volunteers without diabetes and cancer was recruited from the employees of our department. The clinical characteristics of the study group are presented in the **TABLE**.

Isolation of lymphocytes Blood samples were drawn from the antecubital vein of each participant before breakfast. Peripheral blood lymphocytes were isolated by centrifugation (15 min, 280 × *g*) in a density gradient of Gradisol L (Aqua Medica, Łódź, Poland).

Lymphocyte treatment To assess DNA damage and repair in peripheral blood lymphocytes, alkaline single-cell gel electrophoresis was used. H_2O_2 was used as a factor that causes oxidative stress and contributes to various types of DNA damage.

To evaluate the level of DNA damage, lymphocytes were incubated with or without H_2O_2 at a final concentration of 10 mM and 20 mM on ice for 10 min. If DNA repair was effective, H_2O_2-treated lymphocytes were washed and suspended in a fresh medium for 2 h at 37°C. Subsequently, the level of DNA damage was measured at 15, 30, 60, and 120 min of repair incubation.

Comet assay The comet assay under alkaline conditions was performed according to Singh et al.[19] with minor modifications that were described previously.[20,21]

Previously treated or nontreated lymphocytes suspended in low melting point agarose (0.75%) were spread onto microscope slides that were precoated with normal melting point agarose (0.5%). The cells were then placed in lysis buffer for 1 h at 4°C (NaCl, 2.5 M; EDTA, 100 mM; TritonX-100, 1%; and Tris, 10 mM; pH 10). Next, the slides were placed in unwinding buffer (NaOH, 300 mM; EDTA, 1 mM; pH >13). The electrophoresis was conducted at 0.73 V/cm (28 mA) for 20 min. Subsequently, the slides were washed with distilled water, drained, and stained with 4',6-diamidino-2-phenylindole dihydrochloride (DAPI, 2 mg/ml). Incubation with DAPI was conducted under dark conditions at a temperature of 4°C at least for 30 min. The comets were

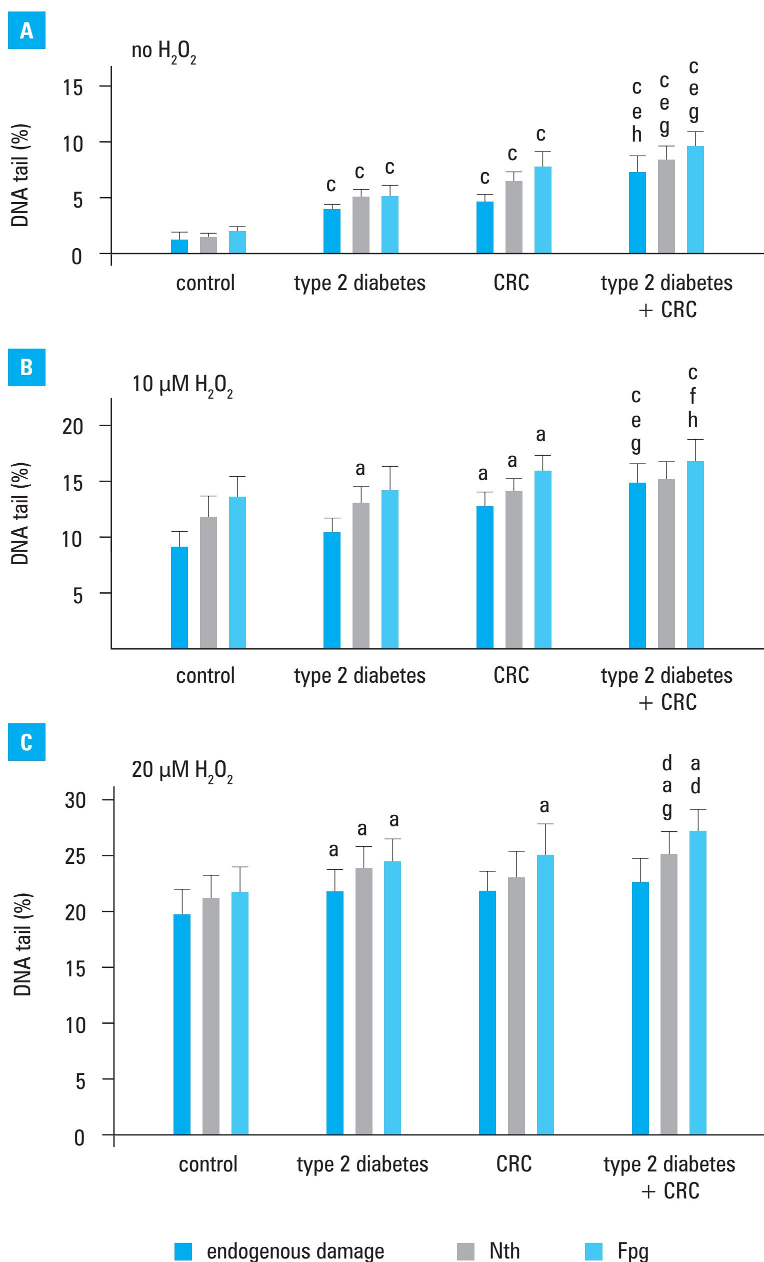

FIGURE 1 Endogenous oxidative (**A**) and H_2O_2-induced (**B**, **C**) DNA damage in the study groups; data are expressed as means ± standard error of the mean

a $P < 0.05$ **b** $P < 0.01$ **c** $P < 0.0001$ compared with controls
d $P < 0.05$ **e** $P < 0.01$ **f** $P < 0.0001$ compared with patients with type 2 diabetes
g $P < 0.05$ **h** $P < 0.01$ **i** $P < 0.0001$ compared with patients with CRC

Abbreviations: Fpg – formamidopyrimidine-DNA glycosylase, Nth – endonuclease III, others – see TABLE

observed under a fluorescence microscope at a magnification of ×200 attached to a video camera with ultraviolet (UV-1), a filter block, and personal computer equipped with the Lucia-Comet v. 4.51 analysis software. The percentage of DNA in the tail of the comet was analyzed from 50 cells in each sample.

DNA repair enzyme treatment Formamidopyrimidine-DNA glycosylase (Fpg) and endonuclease III (Nth) were used to assess the level of oxidative DNA damage. Fpg plays a key role in the first stage of the base excision repair. This enzyme generates apurinic/apyrimidinic sites by cutting and removing mainly 7,8-dihydro-8-oxo-2`deoxyguanine and 2,6-diamino-4-hydroxy-5-N-methyl formamidopyrimidine from DNA.[13,22,23] Nth, a restriction endonuclease, is responsible for the detection of oxidized pyrimidines and then transforming them into DNA strand breaks that are detected by the comet assay.[23]

To examine the ability of the enzymes to recognize oxidized bases, the cells were incubated with or without H_2O_2, lysed, and then treated with Nth and Fpg enzymes. The slides were washed in enzyme buffer (HEPES-KOH, 40 mM; KCl, 0.1 mm; EDTA, 0.5 mM; bovine serum albumin, 0.2 mg/ml; pH, 8.0) and drained. Then, 25 µl of enzyme buffer or a mixture of enzyme buffer with 1 µg/ml of the enzyme was placed on slides, covered by cover slips and incubated for 30 min at 37°C.[23,24] Subsequently, the cells were placed in unwinding buffer and electrophoresis was conducted.

Data analysis The clinical data were expressed as mean ± standard deviation. The values of the comet assay in this study were expressed as the mean ± standard error of the mean from 4 independent experiments. If no significant differences between variations were found, as assessed by the Snedecor–Fisher test, the differences between the means were evaluated using the *t* test. A *P* value of less than 0.05 was considered statistically significant. All statistical calculations were performed using STATISTICA v. 10.0 package (StatSoft, Tulsa, Oklahoma, United States).

RESULTS

DNA damage **Endogenous oxidative DNA damage** DNA damage of lymphocytes not induced by any treatment was considered as endogenous DNA damage. We observed that patients with type 2 diabetes and CRC had the highest level of endogenous DNA damage. Moreover, it was significantly higher in patients with CRC compared with controls as well as in patients with type 2 diabetes compared with controls.

DNA damage of lymphocytes treated with Fpg and Nth was considered as endogenous oxidative DNA damage. The level of DNA damage of Nth-treated and Fpg-treated lymphocytes were significantly higher in patients with both type 2 diabetes and CRC compared with controls, patients with type 2 diabetes, and patients with CRC. The treatment with Nth and Fpg revealed a significantly increased level of DNA damage in the lymphocytes of patients with CRC compared with controls and a lower level compared with patients with type 2 diabetes and CRC. In patients with type 2 diabetes, the levels of DNA damage in lymphocytes treated with Nth and Fpg were significantly higher compared with controls and lower compared with patients with type 2 diabetes and CRC. The levels of endogenous oxidative DNA damage are shown in FIGURE 1A.

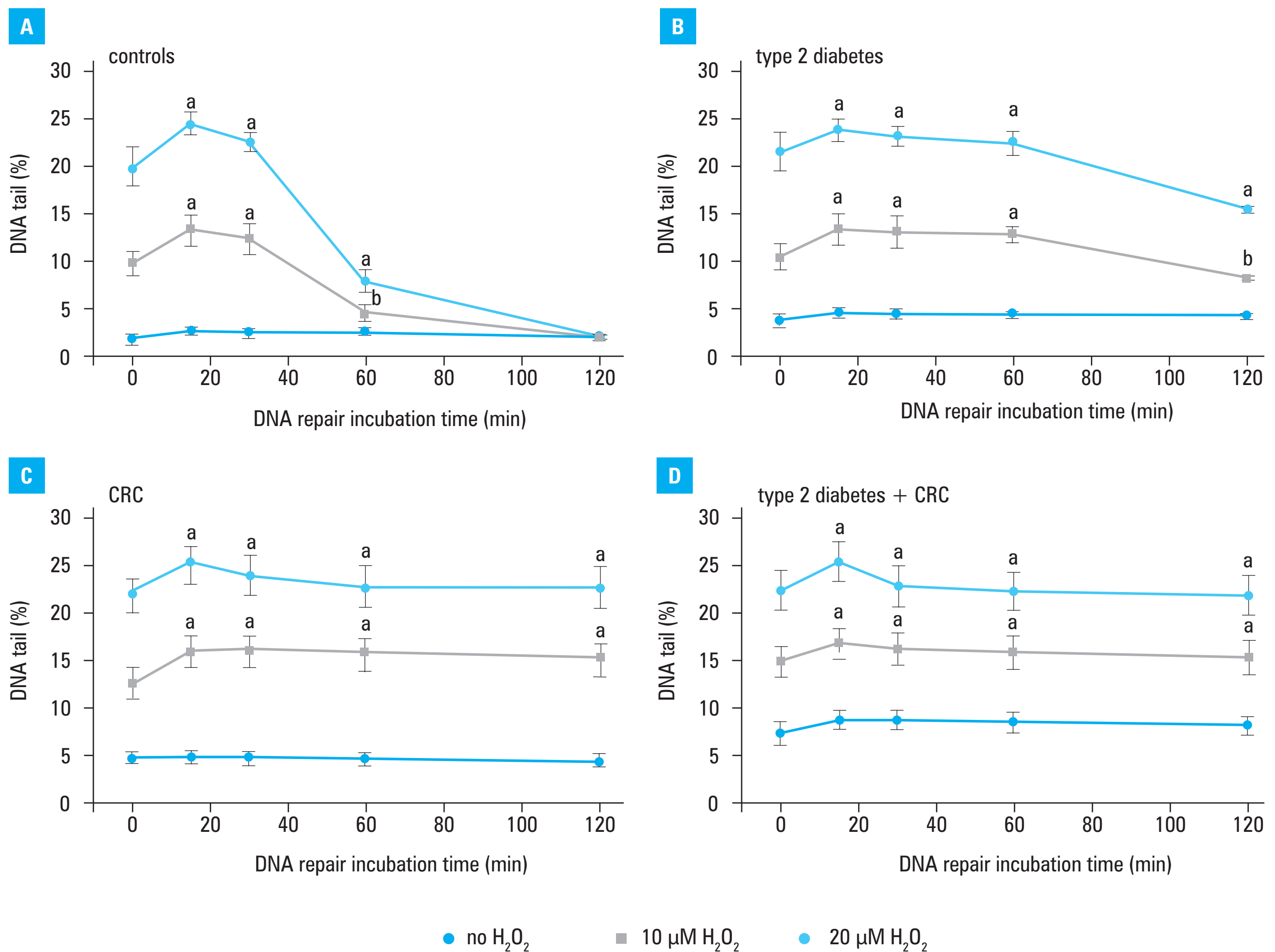

FIGURE 2 Efficacy of DNA repair in the lymphocytes of patients with colorectal cancer (CRC) with and without type 2 diabetes in comparison with controls; data are expressed as means ± standard error of the mean

a P <0.05

b P <0.0001 compared with untreated lymphocytes (negative control)

H_2O_2-induced DNA damage Susceptibility of lymphocytes to oxidative stress was detected by the measure of DNA damage after the treatment with H_2O_2 (10 µM and 20 µM) for 10 min on ice. Additionally, the analysis of DNA damage after exposure to Fpg and Nth was performed. DNA damage induced by 10 µM H_2O_2 is presented in FIGURE 1B. A significantly higher level of DNA damage induced by 10 µM H_2O_2 was observed in patients with CRC compared with controls. Patients with type 2 diabetes and CRC had a significantly higher level of DNA damage induced by 10 µM H_2O_2 compared with controls, patients with type 2 diabetes, and patients with CRC. The treatment with Nth resulted in an increased level of DNA damage induced by 10 µM H_2O_2 in patients with CRC with and without type 2 diabetes compared with controls. The analysis with Fpg showed a significantly higher level of DNA damage in patients with CRC compared with controls. The treatment with Fpg revealed a significantly increased level of DNA damage induced by 10 µM H_2O_2 in patients with type 2 diabetes and CRC compared with controls, patients with type 2 diabetes, and patients with CRC.

A significantly higher level of DNA damage induced by 20 µM H_2O_2 was observed in patients with type 2 diabetes compared with control. The analysis with Nth showed a significantly higher level of DNA damage induced by 20 µM of H_2O_2 in patients with type 2 diabetes compared with controls. A significantly higher level of DNA damage induced by 20 µM H_2O_2 treated with Nth was observed in patients with type 2 diabetes and CRC compared with controls, patients with type 2 diabetes, and patients with CRC. The treatment with Fpg revealed an increased level of DNA damage induced by 20 µM H_2O_2 in patients with type 2 diabetes alone and those with CRC alone compared with controls. The treatment with Fpg showed the highest level of DNA damage induced by 20 µM H_2O_2 in patients with type 2 diabetes and CRC compared with controls and patients with type 2 diabetes. DNA damage induced by 20 µM H_2O_2 is presented in FIGURE 1C.

Efficacy of DNA repair The efficacy of the repair of H_2O_2-induced DNA damage was measured as the level of DNA in the tail of the comet at 0, 15, 30, 60, and 120 min of DNA repair incubation. The efficacy of DNA repair is presented in FIGURE 2. In contol subjects, DNA damage induced by 10 µM and 20 µM H_2O_2 was repaired during 120 min of incubation. In patients with type 2 diabetes, H_2O_2-induced DNA damage was not completely repaired during 120 min of incubation, and in patients with CRC and patients with type 2 diabetes and CRC, it was not repaired during 120 min of incubation.

DISCUSSION In our study, we focused on whether DNA damage and repair may be associated with the risk of CRC in patients with type 2 diabetes. We showed that the lymphocytes of patients with type 2 diabetes and CRC had the highest level of endogenous oxidative and 10 μM H_2O_2-induced damage. However, the levels of DNA damage in the lymphocytes of patients with type 2 diabetes alone and those with CRC alone were similar. These results may indicate that patients with type 2 diabetes and CRC may be more prone to oxidative stress.

To the best of our knowledge, this has been the first study to explore the level of DNA damage in the lymphocytes of patients with type 2 diabetes and coexisting CRC. The results of this study are in line with those demonstrating an increased level of DNA damage in the lymphocytes of patients with type 2 diabetes and other types of cancer cells. Rehman et al.[25] reported that the level of oxidative DNA damage induced by a DNA-damaging agent is higher in type 2 diabetes. Al-Aubaidy et al.[26] observed a higher level of 8-hydroxy 2'-deoxy-guanosine in patients with prediabates and type 2 diabetes than in healthy individuals. Interestingly, the evaluation of biopsy material obtained from patients with CRC revealed that cancer cells had a higher level of oxidative DNA damage that normal cells.[27]

Several studies revealed that patients with malignancy have a decreased activity of antioxidant enzymes, which may predispose them to increased DNA damage.[28,29] Moreover, lower expression and activity of catalase and cytosolic superoxide dismutase under oxidative stress have been reported.[30] Our findings at least partially support these observations because we found an increased level of DNA damage induced by H_2O_2 both in the lymphocytes of patients with type 2 diabetes and those with CRC.

Our data indicated that DNA repair was more efficient in the lymphocytes of patients with type 2 diabetes than in those with CRC both with and without type 2 diabetes. We hypothesize that disturbances in DNA repair in patients with CRC may be associated with an inappropriate process of the elongation and ligation of DNA repair. Moreover, mutations in the genes that regulate cell survival, i.e., *APC*, *TP53*, *PTEN*, *K-Ras*, *BRAF*, and in those that participate in DNA repair, i.e., *XCRR1*, DNA polymerase β gene, should be considered. Several recent studies have indicated positive associations between CRC and mutations in the *TP53, K-ras, BRAF,* and *APC* genes.[31-34] Mutations in the gene encoding DNA polymerase β, participating in the final step of DNA repair, were also found in patients with colon cancer.[35] Moreover, the 194Trp allele and the 399Gln allele of the *XCRR1* gene participating in the base excision repair pathway have been reported to correlate with an increased risk of the early onset of CRC in the Egyptian population.[36]

Our study has a few limitations. First, our sample size was relatively small. Second, the comet assay detects single and double strand breaks and DNA modifications that produce strand breaks only under alkaline conditions. Third, the comet assay used in our study allows to analyze global DNA repair but is insufficient to analyze the specific pathways of DNA repair.

In conclusion, our preliminary findings support the concept that an increased risk of cancer in type 2 diabetes may be associated with oxidative DNA damage; however, the reduced efficacy of DNA repair seems to play a predominant role in carcinogenesis in patients with and without type 2 diabetes. Further studies are needed to clarify the association between type 2 diabetes and CRC.

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ARTYKUŁ ORYGINALNY – KONKURS STUDENCKI 2014*

Uszkodzenia DNA oraz efektywność naprawy DNA u pacjentów z cukrzycą typu 2 ze współistniejącym nowotworem jelita grubego

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SŁOWA KLUCZOWE

cukrzyca typu 2, naprawa DNA, nowotwory jelita grubego, stres oksydacyjny, uszkodzenia DNA

STRESZCZENIE

WPROWADZENIE Liczne badania epidemiologiczne wskazują, że częstość rozwoju pewnych typów nowotworów, w tym jelita grubego (*colorectal cancer* – CRC), jest większa wśród osób chorujących na cukrzycę typu 2. Możliwe przyczyny tego związku nie są w pełni poznane. Sugeruje się, że stres oksydacyjny związany z przewlekłą hiperglikemią prowadzi do oksydacyjnych uszkodzeń DNA oraz upośledzonej naprawy DNA, co może się przyczyniać do zwiększonego ryzyka nowotworu u chorych z cukrzycą typu 2.
CELE Celem badania było określenie poziomu uszkodzeń DNA i efektywności naprawy DNA u pacjentów z CRC z współistniejącą cukrzycą typu 2 lub bez niej w porównaniu z osobami zdrowymi.
PACJENCI I METODY Poziom uszkodzeń DNA endogennych, oksydacyjnych i indukowanych nadtlenkiem wodoru (H_2O_2) oraz efektywność naprawy DNA w limfocytach pacjentów z cukrzycą typu 2, pacjentów z CRC oraz pacjentów z cukrzycą typu 2 i CRC, a także zdrowych osób (łącznie 32 osoby), mierzono za pomocą alkaicznej wersji testu kometowego.
WYNIKI Największe nasilenie endogennych, oksydacyjnych oraz indukowanych H_2O_2 uszkodzeń DNA zaobserwowano w limfocytach pacjentów z cukrzycą typu 2 i CRC. Dodatkowo efektywność naprawy DNA była znamiennie zmniejszona u pacjentów z CRC bez cukrzycy typu 2 lub z cukrzycą typu 2.
WNIOSKI Nasze wyniki wspierają hipotezę, że wzrost ryzyka wystąpienia nowotworu u chorych na cukrzycę typu 2 może być związany z oksydacyjnymi uszkodzeniami DNA, jednak wydaje się, że to upośledzona zdolność do naprawy uszkodzeń DNA odgrywa główną rolę w karcynogenezie u chorych z cukrzycą typu 2 i bez niej.

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