

## **Correlation of DNA damage in type 2 diabetes to glycemic control**

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### **ABSTRACT**

**Background:** Diabetes is associated with excessive production of reactive oxygen species (ROS) which can damage cellular macromolecules. The aim of the study was to detect oxidative DNA damage in type 2 diabetic patients and to correlate it with glycemic control.

**Aim of work:** to assess the percentage of DNA damage in patients with type 2 diabetes and the relation with glycemic control and lipid profile.

**Patients and methods:** The present work included 28 diabetic patients as well as 25 age and sex matched healthy volunteers served as control. Single cell gel electrophoresis (SCGE) was used to assess DNA damage in 28 patients with type 2 diabetes and 25 age and sex matched healthy controls. Moreover, glycemic as well as lipid profiles were also estimated in those subjects.

**Results:** The percent of DNA damage of peripheral blood mononuclear cells was higher in diabetic patients ( $45.1 \pm 9.2$ ) compared to healthy controls ( $3.70 \pm 0.85$ ) ( $p < 0.001$ ). The percent of DNA damage correlated positively with BMI, fasting blood glucose, HbA1C, serum cholesterol, serum triglycerides, HDL cholesterol and LDL cholesterol ( $p < 0.001$ ). However, there was no significant difference in percent of DNA damage between hypertensive patients ( $36.2 \pm 4.6$ ) and non hypertensive patients ( $37.2 \pm 4.6$ ). Pearson correlation analysis showed a significant positive correlation between DNA damage and body mass index, glycated hemoglobin, total cholesterol, triglycerides and low density lipoprotein cholesterol.

**Conclusion:** Type 2 diabetic patients have more oxidative DNA damage than normal controls and this damage increase with poor diabetic control, obesity and hyperlipidemia. Thus, DNA damage in the peripheral blood of diabetic patients assessed by comet assay can be applied as a new and non expensive technique for monitoring patients with type-2 diabetes.

**Key words:** diabetes, DNA damage.

### **Introduction**

Diabetes is one of the most challenging

health problems in the 21st century. Its complications including; overweight,

coronary artery disease, peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness result in increasing disability, reduced life expectancy and enormous health costs [Pan *et al.*, 2007 and Vengopal & Iyer 2010]. The prevalence of diabetes is increasing globally, the number of diabetics is expected to increase to 438 million by 2030 [IDF, 2009]. Type 2 diabetes is associated with several complications, such as atherosclerosis, retinopathy, neuropathy and nephropathy. Experimental evidence indicates that these complications are mainly because of the production of excessive free radicals, which result in oxidative damage to biomolecules [Dandona *et al.*, 1996]. Oxidative damage may also affect DNA and this could have teratogenic or carcinogenic consequences [Chandie *et al.*, 2006 and Yfjord & Bodvarsdottir 2005].

Single cell gel electrophoresis (SCGE) or comet assay, is a sensitive, simple, inexpensive, and rapid method that can be used to detect DNA damage of individual cells and reveal the presence of double-strand breaks, single-strand breaks and alkali labile sites [Hartmann *et al.*, 2003]. Therefore, it has been widely used in studies on DNA repair, genetic toxicology, radiation, pollution and ageing [Pan *et al.*, 2007]. The Comet assay was generally very sensitive in assessing genotoxic damage, making it a good biomarker of induced

DNA damage (Baumgartner *et al.*, 2012). The aim of this study was to assess the percentage of DNA damage in patients with type 2 diabetes and the relation with glycemic control and lipid profile

### **Patients and methods**

Twenty-eight patients with type 2 diabetes were recruited from the outpatient clinic of Medical Services Unit at the National Research Center in the period from November 2009 to June 2010. They were 8 men and 20 women with age ranging from 45 to 61 years with mean age  $52.5 \pm 5.3$  years. Twenty-five healthy volunteers, 10 men and 15 women, age ranging from 45 to 60 years with mean age  $53.1 \pm 6.7$  years age, served as control group. We excluded any patient with a history of smoking, coronary artery disease, congestive heart failure, chronic liver disease, diabetic nephropathy, rheumatic disease, cancer and subjects who had recently undergone radiological procedures (a month previously).

Patients were subjected to detailed history for collection of demographic data and recording of relevant medical history and medications. Thorough clinical examination including neurological examination and height and weight measurement for calculation of body mass index were also done for all patients. None of the patients were taking antioxidant supplement. Patients were fully informed and consented in

advance according to the approval of the ethical committee of the National Research center.

#### **Laboratory methods:**

Five milliliters of venous blood was withdrawn from both the healthy individuals and patients fasting for 14 hours into two sterile vaccutainers; one containing EDTA and the other without additives to separate serum.

Serum samples were assayed, within 2 hours, for fasting blood glucose, glycated hemoglobin (HbA1c) and lipid profile including cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C) using the automated clinical chemistry analyzer Olympus AU 400 analyzer. Low density lipoprotein cholesterol (LDL-C) was calculated by Friedewald formula. [Friedewald, 1972]. DNA damage was assessed by the Comet Assay.

#### **Measurement of Comet Assay**

##### **Cell preparation**

Peripheral blood leukocytes were isolated by centrifugation (30 min at 1300g) in Ficoll-Paque density gradient (Pharmacia LKB Biotechnology, Piscataway, NJ, USA). After centrifugation, leukocytes were aspirated and washed twice by phosphate-buffered saline at pH 7.4 (PBS).

##### **Preparation of cell microgels on slides:**

The comet assay was performed according to Singh and colleagues [Singh *et al.*, 1988]

with modifications according to Blasiak and colleagues [Blasiak *et al.*, 2003]. Cell microgels were prepared as layers. The first layer of gel was made by applying 100  $\mu$ l of normal melting point agarose (0.7%) onto a precleaned microscope charged slides and coverslipped gently. The coverslip was removed after the agarose solidified at 4°C. Low melting-point agarose (0.5%) was prepared in 100 mmol/L PBS and kept at 37°C. Approximately, 1500 of peripheral blood leukocytes were mixed with the low melting-point agarose and 100  $\mu$ l of the mixture was applied to the first gel layer. The slides were then covered with a coverslip and placed at 4°C for solidification. After the second layer solidified, the coverslips were removed from the cell microgels. A final layer of low-melting agarose was added followed by coverslips, left to solidify for 10 minutes then the coverslips were removed.

##### **Lysis of cells, DNA unwinding, gel electrophoresis, DNA staining**

The slides were covered with 100 ml of ice-cold freshly prepared lysis solution buffer pH 10 (2.5 mol/L NaCl, 100 mmol/L EDTA, 1% sodium hydroxide, 10 mmol/L Tris, 1% Triton X-100, 10% DMSO ) for at least 1 h. After draining, microgels slides were treated with DNA unwinding solution (300 mmol/L NaOH, 1 mmol/L EDTA, pH 13) for 30 min at 4°C, and placed directly into a horizontal gel electrophoresis chamber filled with

DNA-unwinding solution. Gels were run with constant current (300 mA at 4°C) for 30 min. After electrophoresis, the microgels were neutralized with 0.4 M Tris base at pH 7.5 for 10 min. The slides were stained with 20 µl ethidium bromide (10 µg/ml).

***Visualization and analysis of Comet Slides***

The slides were examined at 40× magnification using an inverted fluorescence microscope (IX70; Olympus, Tokyo, Japan) equipped with an excitation filter of 549 nm and a barrier filter of 590 nm, attached to a video camera (Olympus). Damaged cells were visualized by the “comet appearance”, with a brightly fluorescent head and a tail to one side formed by the DNA containing strand breaks that were drawn away during electrophoresis. Samples were analyzed by counting the damaged cell out of 100 cells per slide to calculate the percent of damage.

***Statistical Analysis:***

Data are presented as mean ±SD. The compiled data were computerized and analyzed by SPSS PC+, version 14. The following tests of significance were used: t test between means to analyze mean difference. A value of  $p \leq 0.05$  was considered significant,  $p < 0.001$  was considered highly significant and  $p > 0.05$  was considered insignificant. Pearson's multiple correlation coefficients {r} were used to determine the correlation of the studied parameters to each other.

**Results:**

The study included 28 patients with type 2 diabetes and 25 healthy individuals as control group. The mean age of the patients was  $53.1 \pm 6.7$  years. Demographic and laboratory data for the patients and controls are shown in table (1).

The percent of DNA damage correlated positively with BMI, and lipid profile including; serum cholesterol, serum triglycerides, HDL cholesterol and LDL cholesterol as presented in table (2). Regarding glycemic control; there was a high statistical significant correlation ( $p < 0.001$ ) as represented in figure (2). However, there was no significant difference in percent of DNA damage between hypertensive patients ( $36.2 \pm 4.6$ ) and non hypertensive patients ( $37.2 \pm 4.6$ ). Images of single cell gel electrophoresis are classified according to the degree of damage after migration through electrophoresis & visualized by the digital camera fitted fluorescent microscope as shown in figure (1). It reveals an intact DNA in normal healthy subjects (figure 1a), while a high degree of DNA damage clarified by a slightly pointed end due to the migration of fragmented DNA through electrophoresis (tailed) was presented as figure 1b. The percentage of DNA damage was higher in patients compared to controls ( $p < 0.001$ ).

**Table (1):** Demographic and laboratory data of patients and controls

<b>Variables</b>	<b>Diabetic patients (n=28)</b>	<b>Controls (n=25)</b>
Age (years)	52.5 ± 5.3	53.1± 6.7
Sex: (M/F)	8/20	10/15
BMI (Kg/m <sup>2</sup> )	36.8±4.5*	25.1±2.1
Duration (years)	9.7±2.1	-
Hypertension (no / %)	10/ 35.7%	-
Peripheral neuropathy (no %)	5 /17.8%	-
Fasting blood glucose (mmol/l)	10.3±1.9*	4.8±0.35
HbA <sub>1C</sub> (%)	9.6±2*	3.4±0.6
Cholesterol (mmol/l)	5.9±1.3*	4.1±0.5
Triglycerides (mmol/l)	22.3±4.1**	8.5±1.0
HDL cholesterol (mmol/l)	0.75±0.12**	1.0±0.05
LDL cholesterol ( mmol/l)	3.9±0.81*	2.0±0.3
LDL / HDL (ratio)	5.2 ± 0.4**	2 ± 0.27
DNA damage (%)	45.1±9.2*	3.7±0.85

Data are represented as mean ± SD. M; male, F; female, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein

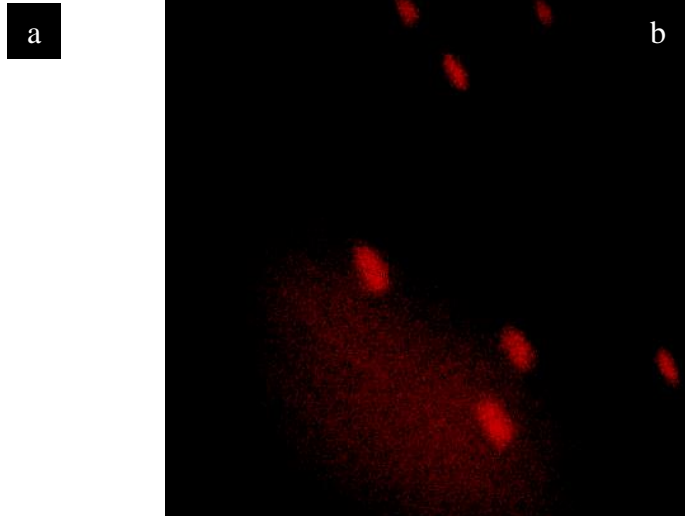
\* p<0.001,\*\* p<0.05.

**Table (2):** Correlation between DNA damage and demographic and laboratory data

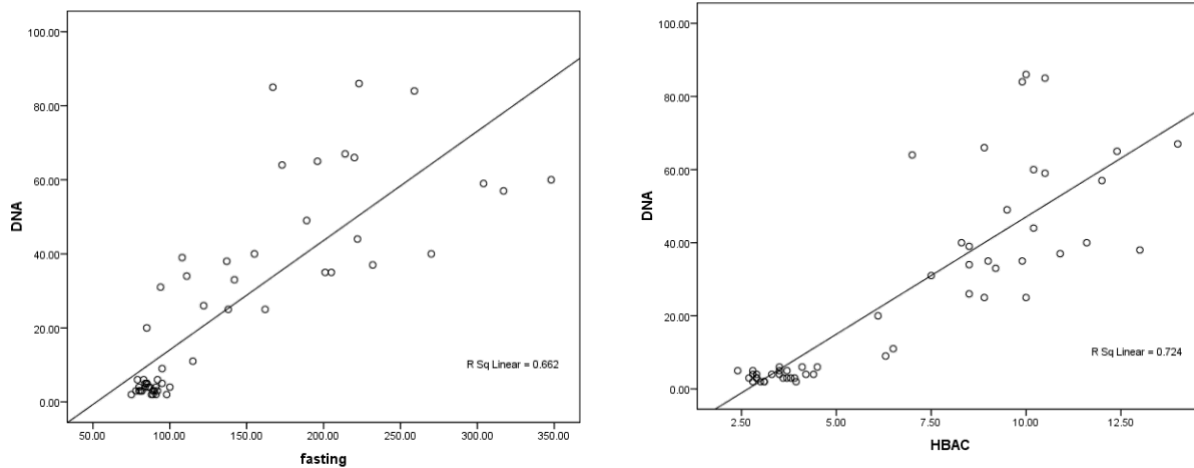
<b>Variables</b>	<b>r</b>	<b>p</b>
Age	0.084	0.54
BMI	0.73	<0.001*
Duration	0.062	0.75
Fasting blood glucose	0.81	<0.001*
HbA <sub>1C</sub> ,%	0.85	<0.001*
Cholesterol	0.6	<0.001*
Triglycerides	0.6	<0.001*
HDL cholesterol	0.1	0.45
LDL cholesterol	0.67	<0.001*

BMI: body mass index, HDL: high density lipoprotein

LDL: low density lipoprotein, \* p is highly significant



**Figure (1):** DNA damage in the studied subjects



**Figure (2):** Correlation of DNA damage with glycemic control.

## Discussion

Hyperglycemia results in oxidative stress due to increased production of reactive oxygen species (ROS). Excessive levels of ROS lead to the damage of proteins, lipids, and DNA and consequently the development of late diabetic complications [Evans et al., 2002]. Also nuclear and mitochondrial DNA damage

may promote a great number of mutations which in turn may lead to malignant transformation [Dandona *et al.*, 1996 and Ohrr *et al.*, 2005]. In the present study, we used single cell gel electrophoresis (SCGE) method to detect oxidative damage in lymphocyte DNA as it is a sensitive, simple method to detect very low levels of damage.

[Hong-Zhi *et al.*, 2007]. Matrinez-Alfaro and his colleagues [Martinez *et al.*, 2006] suggested that the modified comet assay could prove to be a convenient and sensitive biomonitoring tool for individuals occupationally or voluntarily exposed to tinner inhalation.

In the present study, the percent of DNA damage of peripheral blood mononuclear cells was higher in diabetic patients compared to healthy controls. Studies concerning DNA damage and DM revealed contradictory results. Several studies revealed increased extent of DNA damage in type 2 DM patients compared to controls [Pitozzi *et al.*, 2003, Blasiak *et al.*, 2004 and Choi *et al.*, 2005]. On the other hand other studies failed to find association between DM and DNA damage in insulin and in non insulin dependent DM. [Hannon *et al.*, 2000 and Ibarra *et al.*, 2010].

The contradictory results may be related to different methodology used for assessment of the DNA damage whether using restriction enzymes, or general total DNA damage (without restriction enzyme) [Hong-Zhi *et al.*, 2007] or to differences in the characteristics of the examined patients. When correlating DNA damage with different

demographic and laboratory data, we did not find significant correlation with age. However previous study found positive association between age and DNA damage in healthy controls [Lotovici *et al.*, 2005]. The lack of such association in our patients is probably because of the effect of diabetes itself and the narrow age range.

We reported a significant positive correlation between DNA damage and HbA<sub>1C</sub> but not with the duration of diabetes. Goodarzi and his colleagues [Goodarzi *et al.*, 2010] reported significant positive correlation between urinary 8-hydroxydeoxyguanosine (8-OHdG) and HbA<sub>1C</sub>. 8-hydroxydeoxyguanosine has been regarded as a biomarker of oxidative DNA damage *in vivo*. Hyperglycemia causes glucose auto-oxidation, glycation of proteins, and activation of polyol metabolism. It has also been demonstrated that hyperglycaemia is associated with increased production of free radicals in the mitochondria and may contribute to a greater DNA damage [Robertson, 2004]. The lack of association with duration has been reported by other authors in diabetes and in chemical exposure and they suggested

that long term chronic exposure cause adaptation of response to damage. [Anderson *et al.*, 1998 and Thorpe *et al.*, 2004].

One of the complications of diabetes is atherosclerosis. Atherosclerosis is associated with DNA damage that increases with progression of atherosclerosis. DNA damage has been found in atherosclerotic plaques and in circulating cells of patients with atherosclerosis. [Andreassi *et al.*, 2003 and Marlinet *et al.*, 2002]. This widespread occurrence lead authors to suggest that factors that promote DNA damage are attributable, at least in part, to systemic stimuli, such as risk factors that promote atherosclerosis. [Mercev *et al.*, 2010].

As compared to the non-diabetic controls, type 2 diabetic subjects have increased triglycerides levels and decreased high-density lipoprotein cholesterol (HDL), but relatively small differences in low-density lipoprotein cholesterol (LDL). The excess risk in the diabetic subjects is only partially explained by the standard risk factors measured in these subjects.

Increased clearance of HDL particles from the plasma space may also be

operative particularly in patients with hypertriglyceridemia. Singla and his colleagues., 2009 suggested that LDL uptake by fibroblasts may be impaired in type 2 diabetics. This leads to increase in LDL: HDL ratio in type 2 diabetics.

Moreover, in the current study we found significant positive correlation between DNA damage and serum total cholesterol, LDL-c and triglycerides. It is not known whether DNA damage in diabetes directly promotes atherosclerosis, or is byproduct of dyslipidemia of diabetes. Some cholesterol oxidation products (oxysterols) lead to the generation of reactive oxygen/nitrogen species (ROS/RNS) that can cause DNA damage, also, ROS are involved in oxidation of LDL, which is considered a fundamental step in the initiation and progression of atherosclerosis [van der Komer *et al.*,2009].

We found a significant positive correlation between DNA damage and BMI. Recent studies revealed increase DNA damage in obesity with significant positive correlation with cholesterol, triglycerides and LDL-c [Bukhari *et al.*, 2010 and Al- Aubaidy & Jelinek, 2011]. These indicate that obesity and



dyslipidemia in type 2 diabetes may be predisposing or aggravating factors for DNA damage (Murata *et al.*, 2012).

Finally, it can be concluded from the present study that type 2 diabetic patients have more oxidative DNA damage than normal controls and this damage increases with poor diabetic control. As well as, obesity and hyperlipidemia may aggravate oxidative DNA damage. Thus, DNA damage in the peripheral blood of diabetic patients assessed by comet assay can be applied as a new and non expensive technique for monitoring patients with type-2 diabetes.

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الملخص العربي

**العلاقة بين تلف الحمض النووي في النوع الثاني من داء السكري و التحكم في نسبة السكر في الدم**

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يرتبط داء السكري بزيادة في إنتاج أنواع الأوكسجين النشط التي يمكن من تدمير الجزيئات الكبيرة داخل الخلايا.

تهدف هذه الدراسة إلى تحديد التلف المؤكسد في الحمض النووي في مرضى داء السكري النوع الثاني و إيجاد علاقة بالتحكم بمستوى السكر في الدم.

تضمنت هذه الدراسة على 28 مريض بداء السكري النوع الثاني و 25 من المتطوعين الأصحاء كمجموعة ضابطة. تم استخدام تقنية الفصل الكهربائي أحادي الخلية لتحديد التلف في الحمض النووي.

كما تم أيضا تحديد بروفيل الدهون و مستوى السكر في الدم في الأشخاص محل الدراسة. نسبة التلف في الحمض النووي في مرضى داء السكري النوع الثاني كانت أعلى ( $45,1 \pm 21,2$ ) مقارنة بالمجموعة الضابطة ( $3,7 \pm 1,3$ ).

أرتبط حدوث تلف في الحمض النووي بكل من مؤشر كتلة الجسم، مستوى السكر الصائم، الهيموجلوبين السكري، مستوى الكوليسترول، الدهون الثلاثية، الكوليستيرول عالي الكثافة، الكوليستيرول منخفض الكثافة.

من الدراسة يمكن إستنتاج أن النوع الثاني من مرضى داء السكري لديهم تلف مؤكسد في الحمض النووي أكثر من المجموعة الضابطة و هذا التلف يزيد مع عدم التحكم في سكر الدم، السمنة، زيادة الدهون في الدم.

بالتالي فإن تلف الحمض النووي في مرضى داء السكري النوع الثاني يمكن اكتشافه بإستخدام تقنيات جديدة و غير مكلفة لمتابعة هؤلاء المرضى.