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One-week intervention period led to improvements in glycemic control and reduction in DNA damage levels in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Hyperglycemia leads to increased production of reactive oxygen species (ROS), which reduces cellular antioxidant defenses and induces several DNA lesions. We investigated the effects on DNA damage of a seven-day hospitalization period in patients with type 2 diabetes mellitus (T2DM) to achieve adequate blood glucose levels through dietary intervention and medication treatment, compared with non-diabetic individuals.

Methods: DNA damage levels were evaluated by the alkaline comet assay (with modified and without conventional use of hOGG1 enzyme, which detects oxidized DNA bases) for 10 patients and 16 controls. Real time PCR array method was performed to analyze the transcriptional expression of a set of 84 genes implicated in antioxidant defense and response to oxidative stress in blood samples from T2DM patients ($n = 6$) collected before and after the hospitalization period.

Results: The seven-day period was sufficient to improve glycemic control and to significantly decrease ($p < 0.05$) DNA damage levels in T2DM patients, although those levels were slightly higher than those in control subjects. We also found a tendency towards a decrease in the levels of oxidative DNA damage in T2DM patients after the hospitalization period. However, for all genes analyzed, a statistically significant difference in the transcriptional expression levels was not observed.

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Conclusions: The study demonstrated that although the transcriptional expression of the genes studied did not show significant alterations, one-week of glycemic control in hospital resulted in a significant reduction in DNA damage levels detected in T2DM patients, highlighting the importance of an adequate glycemic control.

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1. Introduction

T2DM is a chronic, progressive, heterogeneous, and poorly understood metabolic disease, which develops as a consequence of insulin resistance and pancreatic β-cell dysfunction, leading to extracellular hyperglycemia [1–3]. It is estimated that 382 million people have diabetes worldwide, with T2DM accounting for approximately 90% of all diagnosed cases [4]. In addition, the prevalence of T2DM has increased dramatically, mainly due to a high-calorie diet and sedentary lifestyle, which contribute to excess body weight [5]. Hyperglycemia is widely recognized as a link between diabetes and diabetic complications [3,6]. One of the major hypotheses to explain the onset of diabetic complications is the increase in oxidative stress due to the accumulation of reactive oxygen species (ROS) as a consequence of hyperglycemia [3,7].

ROS accumulation can lead to the depletion of cellular antioxidant defenses, such as vitamins E and C as well as glutathione peroxidase [10]. Consistent with the fact that hyperglycemia can trigger ROS generation, reduced levels of glutathione have been reported both in cells exposed to high glucose concentrations and in leukocytes of patients with diabetes [8,9], suggesting that the antioxidant defense system is compromised in those patients [10]. Also, in T2DM, signaling pathways may be deregulated, such as fatty acid metabolism, protection against lipid-induced oxidative stress, pro-inflammatory cytokines, and DNA repair [11].

In addition, overproduction of ROS can induce several DNA lesions, including oxidized bases, abasic sites, DNA strand breaks, and DNA-protein cross-links [12]. The 8-position of guanine is highly susceptible to ROS attack, generating 8-hydroxy-2′-deoxyguanosine (8-OHdG) [13]. The latter is an extensively studied DNA lesion and has been considered as a biomarker of oxidative DNA damage [14]. Furthermore, several studies have reported high levels of 8-OHdG in peripheral blood lymphocytes from patients with diabetes [15,16]. The presence of 8-OHdG can be measured by the alkaline comet assay employing the hOGG1 enzyme, a glycosylase that removes 8-OHdG, generating alkali-labile sites, which causes DNA breaks that can be detected by the comet assay [14].

Extracellular chronic hyperglycemia leads to increased oxidative stress due to an elevated generation of ROS [3,7,17], which, in turn, can cause DNA lesions [12]. The present study aimed to investigate the effects of a seven day-glycemic management on the levels of DNA damage in T2DM patients compared with the control group (individuals without diabetes) by performing the alkaline comet assay. In addition, we aimed to examine whether the intervention affects the transcriptional expression levels of a gene set with roles in oxidative stress and antioxidant defense, by comparing samples obtained from patients with T2DM before and after hospitalization.

2. Subjects

A total of 10 T2DM subjects (3 males and 7 females) participated in the present study, aged between 30 and 61 years (mean 46.4 ± 12.3 years) and with an average duration of diabetes of 6.9 years. The main clinical characteristics are described in Table 1. All patients were hospitalized for a

Table 1 – Clinical characteristics of patients with type 2 diabetes mellitus.

Patient	Age (years)	Gender	Height (cm)	BH			AH			HT	DLP	MR	MN
				Fasting Plasma glucose (mmol/L)	HbA1c (% –mmol/mol)	Weight (kg)	Fasting plasma glucose (mmol/L)	HbA1c (% –mmol/mol)	Weight (kg)				
1	30	M	174	8.9	8.6–71	101	5.7	8.4–68	96	X	X	–	–
2	38	M	171	8.1	8.0–64	96	4.8	7.6–60	93.5	–	–	X	–
3	44	F	153	12.3	6.9–52	57	10.8	6.9–52	56.5	–	–	–	–
4	45	F	154	12.2	9.8–84	74.7	4.3	8.3–67	73.1	–	X	–	–
5	37	F	160	19.4	13.2–121	97.5	11.6	12.8–116	94.3	X	–	–	–
6	61	M	168	13.3	10.6–92	84	6.8	9.3–78	82.2	X	X	–	X
7	33	F	159	4.9	11.8–106	77.4	4.4	10.3–89	NA	–	–	–	–
8	64	F	145	10.2	12.0–108	39	4.6	12.8–116	39.6	–	X	X	–
9	51	F	166	9	9.7–83	100	5.2	7.5–59	95	X	X	–	–
10	61	F	157	14.3	8.5–69	75	5.2	8.0–64	73.1	–	X	–	–

BH: before hospitalization; AH: after hospitalization; HbA1c: glycated hemoglobin; HT: hypertension; DLP: dyslipidemia; MR: mild retinopathy; MN: mild nephropathy; NA: not avaliable. X: denotes the presence of the corresponding comorbidity.

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