Acta Scientiarum

http://periodicos.uem.br/ojs/acta
ISSN on-line: 1807-8648
Doi: 10.4025/actascihealthsci.v40i1.37813

CIÊNCIAS DA SAÚDE / HEALTH SCIENCES

Evaluation of oxidative DNA damage in elderly patients with type 2 *Diabetes mellitus* living in Ivoti, State of Rio Grande do Sul

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ABSTRACT. Due to the increase in life expectancy and changes in eating habits, the elderly and obese population has increased in recent years. The objective of this study was to analyze the correlation between type 2 *Diabetes mellitus* (DM2) and oxidative DNA damage in elderly residents of the municipality of Ivoti, State of Rio Grande do Sul. This study had an exploratory, descriptive, cross-sectional and quantitative approach based on the data bank of the institutional project of the Feevale University. There was a predominant population of married women, retired, with monthly income up to 2 minimum wages, with education until to the 4th grade of fundamental school and bilingual. Statistical difference was detected for fasting glycemia, HbA1c and 8-hydroxydioxy-2-guanosine (8-OHdG) between DM2 and control subjects, as well as a positive Spearmann correlation between HbA1c and 8-OHdG in patients with DM2. It was possible to identify through fasting glycemia and HbA1c that elderly people who had poor glycemic control also showed a significant increase in the production of reactive oxygen species and consequent DNA damage when compared to the elderly with good glycemic control.

Keywords: DNA damage; oxidative stress; hyperglycemia; aging.

Avaliação do dano oxidativo ao DNA em idosos portadores de *Diabetes mellitus* tipo 2 residentes em Ivoti/RS

RESUMO. Em virtude do aumento da expectativa de vida e mudanças nos hábitos alimentares, a população idosa e obesa tem aumentado nos últimos anos. O objetivo deste trabalho foi analisar a correlação existente entre *Diabetes mellitus* tipo 2 (DM2), e o dano oxidativo ao DNA em idosos residentes do munícipio de Ivoti/RS. Esse estudo teve origem exploratória, descritiva, transversal e de abordagem quantitativa a partir do banco de dados do projeto institucional da Universidade Feevale. Houve uma população predominante de mulheres casadas, aposentadas, com renda mensal de até dois salários mínimos, com escolaridade até a quarta série e bilíngues. Obteve-se diferença estatística para as variáveis glicemia de jejum, hemoglobina glicada (HbA1c) e 8-hydroxydioxy-2-guanosine (8-OHdG) entre os portadores de DM2 e grupo controle, além de uma correlação de Spearmann positiva entre HbA1c e 8-OHdG nos portadores de DM2. Foi possível identificar que idosos que possuíam mau controle glicêmico por meio das análises de glicemia de jejum e HbA1c, apresentavam também aumento significativo em relação à produção de espécies reativas de oxigênio e consequente dano ao DNA quando comparados aos idosos com bom controle glicêmico.

Palavras-chave: dano ao DNA; estresse oxidativo; hiperglicemia; envelhecimento.

Introduction

In recent years, due to population growth, urbanization and longer life expectancy, the number of elderly and obese individuals has been increasing in several contries, especially in developing and developed contries (Reis Filho et al., 2011; Sociedade Brasileira de Diabetes [SBD], 2014). Accompanying this process, the number of individuals with diabetes has also increased (SBD, 2014).

Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders that has in common hyperglycemia due to defects in insulin action, its secretion or both (SBD, 2014). About 20% of people over 65 years old have DM2 and approximately 90% of DM2 patients are overweight or obese, with a higher fat deposit in the central region, and may increase the risk of developing DM2 complications by up to 10 times (Reis Filho et al., 2011; Varaschim et al., 2012; SBD, 2014).

The main clinical manifestation of DM is hyperglycemia and its prolonged persistence is harmful to the organism (Sumita & Andriolo, 2008). Chronic hyperglycemia is toxic to the organism and,

in addition to the obesity of most patients with DM2, leads to an oxidative stress trigger, with increased mitochondrial superoxide anion production, increased non-enzymatic glycation of proteins, as well as through the activation of various cellular transcription factors (Sumita & Andriolo, 2008; Netto et al., 2009; SBD, 2014).

Oxidative stress and endothelial dysfunction are considered early events in the development of both micro- and macrovascular complications of DM (SBD, 2014). Oxidative stress is defined as the state of imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses presenting, as a consequence, damage to proteins, carbohydrates, lipids and DNA, and is increased in diabetes from the early stages, worsening with the evolution of the disease (Varaschim et al., 2012; SBD, 2014)

Oxidative DNA damage can be measured by means of the 8-hydroxydioxy-2-guanosine (8-OHdG) biomarker (Black, Bot, Scheffer, & Penninx, 2016). 8-OHdG is both a mitochondrial and nuclear biomarker that reflects oxidative DNA damage and is among the 20 modifications that can be performed under conditions of oxidative stress (Geyik, Altunisik, Neyal, & Taysi, 2016). When the excess hydroxyl (OH-), one of the free radicals produced, reaches the guanine base, it becomes a modified base called 8-OHdG, which is one of the main modifications in the DNA molecule produced by reactive oxygen species (Bolajoko, Mossanda, Adeniyi, Akinosun, Fasanmade, & Moropane, 2008; Black et al., 2016). Serum levels of 8-OHdG have been demonstrated in patients with DM2 compared to individuals without DM2 and are associated with the progression of various diseases such as diabetes, cancer and aging (SBD, 2014).

The aging process is marked by a series of changes in gene expression, where several proteins gradually increase or decrease their concentration in the cells through regulatory shifts in translation and transcription of genes due to DNA damage caused by oxidative stress, either from the aging process itself and deterioration of homeostasis or from other chronic non-communicable diseases that affect the body, especially DM2 (Rattan, 2013). Thus, it is important to deepen the knowledge about oxidative DNA damage in the elderly, especially in DM2 patients.

Objectives

This study aimed to analyze the correlation between DM2 and oxidative DNA damage in elderly residents of the municipality of Ivoti, State of Rio Grande do Sul. A sociodemographic profile, fasting blood glucose, glycated hemoglobin and 8-OHdG levels in elderly patients with DM2 and elderly without DM2 (control group) were performed.

Methods

Considering the proposed objective, the study had an exploratory, descriptive, transversal and quantitative approach from the data bank of the institutional project of the Feevale University, entitled 'Study of capillary cortisol as a stress and depression biomarker in the elderly', in partnership with the Municipal Council of the Elderly and the Secretariat of Health and Social Assistance of the Municipality of Ivoti, State of Rio Grande do Sul. This study was approved by CEP of Universidade Feevale (31238314.4.0000.5348).

The sample of this study was composed of 160 elderly people between 60 and 79 years old, of both sexes, living in the city of Ivoti, State of Rio Grande do Sul, and enrolled in the Basic Health Units of the city. The inclusion criteria were: being 60 years old or older, residing in the municipality of Ivoti, not being institutionalized or hospitalized, and having mental and health conditions to have independence and autonomy to participate in the study. Elderly individuals who presented dementia, or were hospitalized or institutionalized were excluded. Elderly patients with a history of DM2 and HbA1c values $> 6.5\%$ were used as a criterion for DM2 classification. The elderly who did not present a history of DM2 and values of HbA1c ≤ 6.5 were considered as a control group.

The municipality of Ivoti, State of Rio Grande do Sul, has a population estimated at 21,460 people in 2013, area of the territorial unit of 63,161 km^2 and a population density of 314.71 inhabitants per km^2. The municipality is within the metropolitan region of the State of Rio Grande do Sul, with a predominantly German ethnic identity and a high human development rate (Instituto Brasileiro de Geografia e Estatística [IBGE], 2013).

Data and biological samples referring to the present study were collected between February and June 2015 and stored in an electronic database. From this database, data were collected regarding socio-demographic profile, fasting blood glucose, glycated hemoglobin and 8-OHdG levels of 160 elderly subjects. The fasting blood glucose assay was performed by LabTest Liquiform kits, HbA1c by liquid chromatography and 8-OhdG by Elisa through the HT 8-oxo-dG ELISA kit II from Trevigen.

We used statistical descriptive analyses and Student's t-test in Excel spreadsheets, as well as non-parametric correlations, such as Mann-Whitney U-test of independent samples and Spearman correlation test by the SPSS software 22.

Results

Through the data analysis it was possible to survey the socio-demographic profile of the elderly residents of the municipality of Ivoti, State of Rio Grande do Sul, which included gender, monthly income, schooling, language, marital status and occupation. The mean age of the participants was calculated with the sample separated according to sex, obtaining 68 ± 5.7 years for women and 69 ± 5.3 years for men (mean ± standard deviation). Table 1 lists the socio-demographic data of the elderly:

Table 1. Distribution of absolute frequency and percentage of variables gender, family income, language, schooling, marital status and occupation.

Variables	Category	Frequency	Percentage (%)
Gender	Female	118	73.8
	Male	42	26.2
Marital status	Single / Divorced	22	13.8
	Married	92	57.5
	Widowed	46	28.7
Occupation	Retired	160	100
Family income	Until to 02 minimum wages	93	58.1
	More than 02 minimum wages	25	15.6
	More than 03 minimum wages	35	21.9
	I do not know / did not answer	7	4.4
Schooling	Up to 4th grade	68	42.5
	5th to 8th grade	55	34.4
	High School	22	13.8
	Higher Education	10	6.3
	Illiterate	5	3.0
Bilingual	Yes	110	68.8
	No	40	25.0
	Did not answer	10	6.2

Descriptive data presented as frequency and percentage.

Table 1 lists the predominance of female participants, married and with family income of 02 minimum wages. All the elderly reported being retired. Regarding to schooling, 42.5% of the elderly studied until the 4th grade, and 34.4% of the elderly studied from 5 to 8th grade. The region of Ivoti was colonized by German families in 1826 (Prefeitura Municipal de Ivoti, 2016). This explains why 68.8% of the participants speak another language, in this case, German and its dialects.

Table 2 presents the values found from the sex-separated sample on the variables fasting glycemia, HbA1c and 8-OHdG.

These results were also obtained in other studies: Barbosa et al. (2016), who correlated risk factors among university students aged 16 to 62 years, did not obtain significance between the sexes for fasting glycemia; Vasques et al. (2007) and Rezende et al. (2006) performed similar studies on overweight, central adiposity and body mass index, and found no statistical difference in fasting glycemia between the sexes, only in the group with increased values of the parameters evaluated.

Table 2. Analysis of fasting glycemia, HbA1c and 8-OHdG of the sample according to gender (median and interquartile range).

Variable	Gender	P25	Median	P75
Fasting Glycemia (mg dL^{-1})	Female	87.00	98.00	111.25
	Male	90.80	98.50	107.00
HbA1c (%)	Female	5.30	5.60	6.30
	Male	5.20	5.60	6.03
8-OHdG ($\mu g\ mL^{-1}$)	Female	2.39	4.02	6.57
	Male	1.66	2.82	6.53

Values expressed as the median and interquartile ranges by Mann-Whitney U-test ($p > 0.05$).

Regarding 8-OHdG values, some studies also report a higher 8-OHdG level in men. Black et al. (2016) studied health indicators and reported a lower level of 8-OHdG in women when compared to men of the same age, although with no statistical difference. Nihi et al. (2010) when studied the association between body fat, inflammation and oxidative stress also found higher levels of 8-OHdG in men, with no statistical difference between the sexes. Irie, Tamae, Iwamoto-Tanaka and Kasai (2005) analyzed urinary 8-OHdG and detected significantly higher levels in males, smokers and alcoholics.

In order to classify the patients into DM2 and non-DM2 groups, the frequency test was used for the HbA1c values found. Patients with HbA1c > 6.5 added to the history of DM2 were considered as having DM2. On the other hand, the elderly with HbA1c ≤ 6.5 and no history of DM2 were considered as control group. Thus, we obtained a number of 27 elderly patients with DM2 and 133 elderly patients for the control group. According to the Guidelines of the Brazilian Diabetes Society (2015-2016) (SBD, 2016), approximately 20% of the Brazilian population has *Diabetes mellitus*. The findings described above corroborate the guidelines, since we found approximately 20% of the elderly population studied with a diagnosis of DM2. From the sample separated between DM2 and control subjects, the fasting glycemia, HbA1c and 8-OHdG of the two groups were analyzed by the Mann-Whitney U-test. There was a statistical difference between the two groups for the three analyzed variables (Table 3).

Glycemia refers to the concentration of glucose in the blood. Diabetic patients have defects in the action and secretion of insulin, a hormone responsible for stimulating the entry of glucose into the cells to be used as energy, raising their concentration in the blood and thus their glycemia (Sumita & Andriolo, 2008; Varaschim et al., 2012).

This significant difference found in the present study on glycemia values between control group and patients with DM2 was also observed in a study by Bolajoko et al. (2008).

Table 3. Analysis of fasting glycemia, HbA1c and 8-OHdG of the separated sample in control group and patients with DM2 (median and interquartile range).

Variable	Gruop	P25	Median	P75	P
Fasting Glycemia (mg dL^{-1})	Control	87.00	95.00	105.00	< 0.001
	DM2	139.00	161.00	199.00	
HbA1c (%)	Control	5.30	5.50	5.80	< 0.001
	DM2	6.70	7.50	9.00	
8-OHdG ($\mu g\ mL^{-1}$)	Control	1.91	3.45	6.03	< 0.01
	DM2	3.07	5.27	9.65	

Values expressed as the median and interquartile ranges by Mann-Whitney U-test ($p < 0.05$).

The amount of glucose bound to hemoglobin is directly proportional to the mean blood glucose concentration and the half-life of the erythrocytes, being able to provide an evaluation of the average glycemic control in the period from 60 to 90 days before blood collection for the examination (Sumita & Andriolo, 2008). DM2 carriers have irregular blood glucose concentration, raising their HbA1c levels and, when compared to the control group, a significant difference was found. This difference between the HbA1c values between control group and diabetics was also reported by Bolajoko et al. (2008).

Most individuals with DM2 are overweight or obese, being in a chronic low-intensity inflammatory process that stimulates oxidative stress (Nihi et al., 2010). Nihi et al. (2010) confirmed that individuals who have high body fat were associated with higher levels of inflammation and therefore more ROS production due to the activation of the inflammatory cascade by adipokine production by adipose tissue. From this, it is possible to understand the significant difference detected between 8-OHdG levels in patients with DM2 and control group, which are corroborated by Bolajoko et al. (2008). Sena, Nunes, Louro, Proença and Seiça (2007) studied antioxidant effects in rats and found high levels of 8-OHdG in the urine of diabetic and hyperlipidemic rats when compared to control rats.

From these findings, the variables HbA1c and 8-OHdG were correlated through the Spearman test, obtaining positivity for the group of DM2 patients. Figure 1 illustrates the levels of 8-OHdG relative to HbA1c of the control group (≤ 6.5%). Applying Spearman's correlation test, a trend was not obtained, since the values ≤ 6.5% are within the recommended range, unrelated to the level of free radicals produced and consequent DNA damage.

Figure 2 shows the levels of 8-OHdG relative to HbA1c of DM2 carriers (> 6.5%). The Spearman correlation coefficient ($r^2 = 0.258$; $p < 0.001$) indicated a positive correlation between 8-OHdG and HbA1c levels. There is a tendency expressed in Figure 2, where the higher HbA1c%, the higher the 8-OHdG levels, since the decompensated HbA1c values are related to the increase in the reactive oxygen species production and increased oxidative DNA damage.

The constant hyperglycemia present in patients with DM2 results in an increase in HbA1c levels, leading to harmful damage to the organism, such as the promotion of advanced glycation, hyperosmolality and by increasing the levels of sorbitol inside the cell.

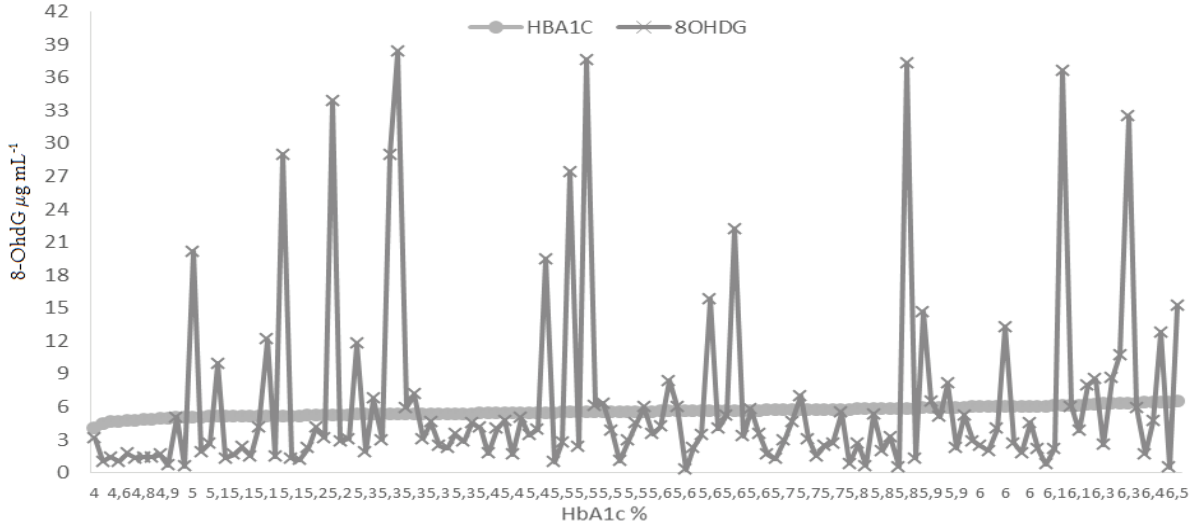

Figure 1. Relationship between HbA1c x 8-OHdG of the control group (133 elderly). Negative Spearman correlation between HbA1c (%) and 8-OHdG (µg mL^{-1}).

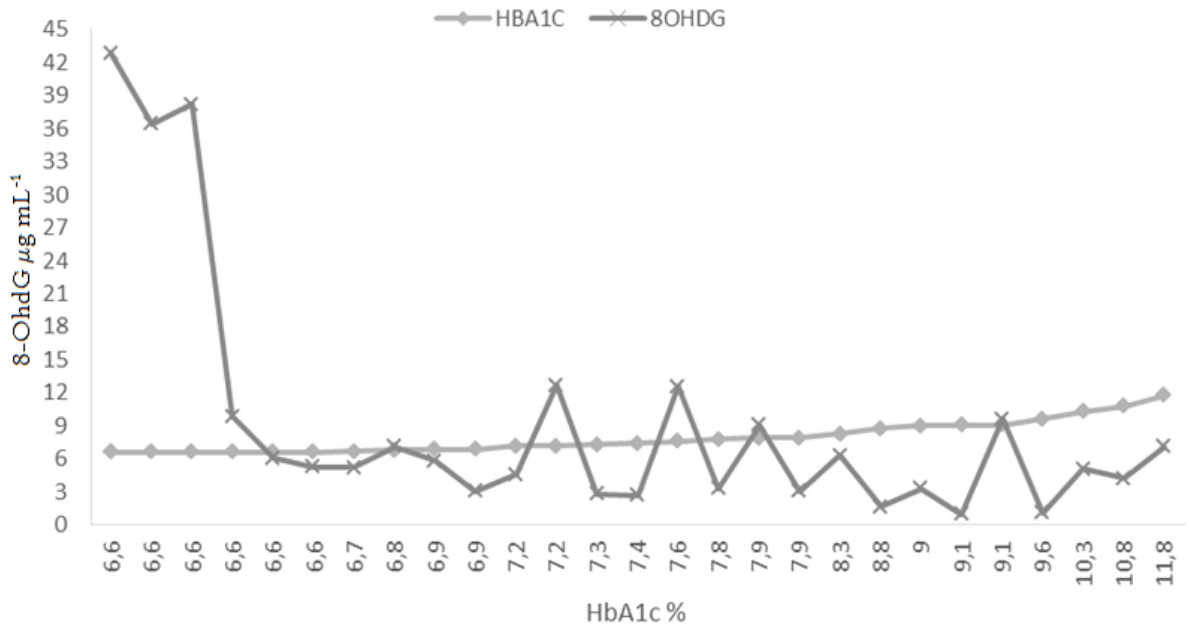

Figure 2. Relationship between HbA1c x 8-OHdG of DM2 carriers (27 elderly). Positive Spearman correlation ($r^2 = 0.258$ and $p < 0.001$) between HbA1c (%) and 8-OHdG (μg mL^{-1}).

In addition, oxidative stress is triggered, with increased mitochondrial superoxide anion production, increased non-enzymatic glycation of proteins and activation of various cellular transcription factors, which can reach DNA molecules and form, in greater quantity, fragments of 8-OHdG (Sumita & Andriolo, 2008; Netto et al., 2009; SBD, 2014). When analyzing Figure 2, it is possible to perceive the positive trend: the higher the HbA1c%, the higher the levels of 8-OHdG, different from the analysis illustrated in figure 01, where there is no relationship between 8-OHdG and HbA1c values. Bolajoko et al. (2008) found a strong correlation between HbA1c and glycemia with level of oxidants and activity of antioxidant enzymes, indicating that the higher HbA1c and glycemia, the higher oxidation, therefore, increased oxidative damage.

Aging itself is a pro-oxidant condition and together with chronic hyperglycemia, characteristic of *Diabetes mellitus*, promotes an increase in oxidative stress and the development of extensive and irreversible organic lesions, since immune and antioxidant defenses are impaired (Guimarães-Souza, Yamaleyeva, Lu, Ramos, Bishop, & Andersson, 2015; Avelar, Storch, Castro, Azevedo, Ferraz, & Lopes, 2015). ROS can react with and damage DNA, protein, carbohydrate and lipid molecules and consequently lead to tissue damage, metabolic disorders, alteration in cell signaling, biological breakdown, among others (Avelar et al., 2015; Cohen, Pechy, Petry, Correa, Caravatto, & Tzanno-Martins, 2015).

The action of free radicals on DNA, especially the hydroxyl radical (OH-) results in the occurrence of oxidative damages causing structural alterations, including nitrogenous, purine and pyrimidine bases, deoxyribose sugar and DNA-protein cross-links (Avelar et al., 2015; Cao et al., 2016). Intensive and frequent attack of these radicals can result in mutagenesis, genomic instability, and changes in DNA structure, such as single or double DNA strand breaks, base pair mutations, rearrangements, deletions, insertions, sequence enlargements, as well as large chromosomal changes and point mutations (American Diabetes Association [ADA], 2014; Cao et al., 2016). As a consequence, these alterations may influence several comorbidities, such as hypertension, cardiovascular diseases, micro- and macrovascular complications such as neuropathy, nephropathy and retinopathy, as well as carcinogenesis and neurodegenerative diseases (Avelar et al., 2015).

Several studies have shown several adverse effects of diabetes, even cognitive impairment from DNA damage caused by oxidative stress. The occurrence of cognitive deficits and the development of Alzheimer's disease (AD), changes in vascular reactivity and cerebral lipid metabolism, neuroinflammation, diabetic retinopathy, among others, are consequences of the contribution of DM2 or insulin resistance, responsible for maintaining hyperglycemic levels and lead the body to a chronic inflammatory process capable of stimulating oxidative stress (SBD, 2014).

Conclusion

As society ages, older people's health problems challenge different care models. The organism undergoes changes in its functioning, losing the adaptive capacity of the immune system, antioxidant and physiological responses to adapt to the environmental stress and chronic diseases, such as *Diabetes mellitus*. It was possible to identify through fasting glycemia and HbA1c analyzes that elderly people who had poor glycemic control also showed a significant increase in the production of reactive oxygen species and consequent DNA damage when compared to the elderly with good glycemic control.

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Received on June 22, 2017.
Accepted on November 10, 2017.