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SERIC LEVELS OF C-REACTIVE PROTEIN AND MYELOPEROXIDASE AND PARAMETERS OF GLYCEMIC CONTROL IN DIABETICS TYPE 2

NÍVEIS SÉRICOS DE PROTEÍNA C-REATIVA E MIELOPEROXIDASE E PARÂMETROS DE CONTROLE GLICÊMICO EM DIABÉTICOS TIPO 2

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ABSTRACT

The objective of the study was to evaluate the serum levels of C-reactive protein (CRP) and myeloperoxidase (MPO) and glycemic control parameters in patients with type 2 diabetes mellitus (T2DM). This was a comparative study conducted with 86 individuals of both sexes, aged 20 to 59 years with a 1:1 ratio between control and T2DM. Body weight, body mass index, waist circumference, fasting glucose, insulinemia, glycated hemoglobin percentage, homeostasis model assessment insulin resistance (HOMA-IR), ultrasensitive CRP and MPO were evaluated. Regarding glycemic control, 55.8% and 86.1% of diabetics had glycated hemoglobin and fasting glucose above 7% and 130 mg / dL, respectively. CRP and MPO values were significantly higher ($p < 0.05$) in the diabetic group, where 51.2% had CRP above 3 mg / L. There was no statistically significant association ($p < 0.05$) between glycemic control parameters and CRP concentrations. A high proportion of diabetics presented inadequate glycemic control and high concentrations of ultra-sensitive CRP, although no relationship was found between glycemic control parameters and CRP.

Keywords: Diabetes; Inflammation; Glycemic Control.

RESUMO

O objetivo do estudo foi avaliar os níveis séricos de proteína C reativa (PCR) e mieloperoxidase (MPO) e parâmetros de controle glicêmico em pacientes com Diabetes mellitus tipo 2 (DM2). Trata-se de um estudo comparativo realizado com 86 indivíduos de ambos os sexos, na faixa etária de 20 a 59 anos com proporção de 1:1 entre grupo controle e DM2. Foram avaliados peso corporal, índice de massa corporal, circunferência da cintura, glicemia de jejum, insulinemia, percentual de hemoglobina glicada, modelo de avaliação da homeostase da resistência à insulina (HOMA-IR), PCR ultrassensível e MPO. Em relação ao controle glicêmico, 55,8% e 86,1% dos diabéticos apresentaram hemoglobina glicada e glicemia de jejum acima de 7% e 130 mg/dL, respectivamente. Os valores de PCR e MPO foram significativamente maiores ($p<0,05$) no grupo diabético, onde 51,2% apresentaram PCR acima de 3 mg/L. Não houve associação estatisticamente significativa ($p<0,05$) entre os parâmetros de controle glicêmico e as concentrações de PCR. Uma alta proporção de diabéticos apresentou controle glicêmico inadequado e altas concentrações de PCR ultrassensível, embora não tenha sido encontrada relação entre parâmetros de controle glicêmico e PCR.

Palavras-chave: Diabetes, Inflamação, Controle Glicêmico.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized as a multifactorial metabolic dysfunction in which glucose intolerance and chronic hyperglycemia are present and occur due to defects in insulin secretion and/or action (ADA, 2020).

According to the International Diabetes Federation (IDF, 2019), the estimated number of adults with diabetes worldwide is 463 million, and projections indicate that the total number will increase to 578 million in 2030 and 700 million in 2045. Approximately 7.4% (13 million) of Brazilians suffer from diabetes, and Brazil ranks 4th in the ranking of countries with the highest notifications of diabetes cases, behind only China, India and the United States (SBD, 2019).

Chronic hyperglycemia is a determining factor in triggering several serious complications that reduce the quality and life expectancy of diabetic individuals, such as nephropathy, neuropathy, retinopathy, lower limb amputation and even cardiovascular events, considered the main cause of the increase in deaths in the diabetic population (COSTA *et al.*, 2017).

Among the possible mechanisms linked to the presence of hyperglycemia in the presence of chronic inflammation are alterations in signaling pathways linked to the production of reactive species and modifications in insulin receptor (IR) phosphorylation, resulting in the interruption of the signaling process (GOMES; ACCARDO, 2019).

On the other hand, insulin resistance results in a disturbance in the lipid and cytokine homeostasis and in the production of adipocytokines, resulting in an increase in the inflammatory process, which in turn leads to an increase in the synthesis of cells (neutrophils, monocytes), cytokines like to interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) and proinflammatory proteins such as C-reactive protein (CRP) (REHMAN; AKASH, 2016; BURHANS *et al.*, 2018).

CRP is an acute phase inflammatory protein considered as a sensitive and poorly specific marker of inflammation. It is synthesized by hepatocytes and regulated primarily by IL-6, thus being a distal marker of inflammation (SPROSTON; ASHWORTH, 2018). Its activation is implicated in the reduction of the activity of the enzyme Nitric Oxide Synthase Endothelial (eNOS), reducing the availability of nitric oxide and increasing the concentration of endothelin (ET-1), a substance with regulatory action of the adhesion molecules, which leads to a lower endothelium-mediated vasodilation, resulting in increased risk of endothelial dysfunction and cardiovascular disease (NEVES; NEVES; OLIVEIRA, 2016).

High plasma concentrations of CRP significantly increase the risk of cardiovascular events, such as myocardial infarction, stroke and peripheral vascular disease, even among adults who did not present previous chronic processes (SHARIF; VAN DER GRAAF; CRAMER, 2021). Its determination is generally considered useful in patients with intermediate cardiovascular risk, as in the case of T2DM, a disease in which the risk for cardiovascular events is considered intermediate to high (BADIMON *et al.*, 2018).

However, the prognostic importance of CRP in patients with T2DM is still controversial, since although some studies show an association between this biomarker and the occurrence of cardiovascular events (CARDOSO; LEITE; SALLES, 2016) others did not obtain these results (SHARIF; VAN DER GRAAF; CRAMER, 2021). So, the objective of the study was to evaluate serum levels of C-Reactive Protein and Myeloperoxidase and parameters of glycemic control in type 2 diabetics.

MATERIALS AND METHODS

Subjects and study design

A comparative study of an analytical design was conducted with 86 individuals of both sexes, aged 20 to 59 years. Participants were divided into two groups, group type 2 diabetes (T2DM, n = 43) and control group (individuals without the disease, n = 43). Patients in the T2DM group had confirmed disease for at least 6 months before starting the study, and they were treated with oral hypoglycemic agents alone and had no complications due to the disease. In addition, participants in both study groups had no active infectious processes or who were active 3 months prior to the study, severe chronic inflammatory disease, and were non-smokers.

Assessment of nutritional status

The overall nutritional status was assessed using the Body Mass Index (BMI) and ranked from the BMI cut-off points for adults, according to categories proposed by the World Health Organization (WHO, 2000). The evaluation of central adiposity was performed by waist circumference, classified according to the WHO cut-off points (WHO, 2008), associated with cardiovascular risk and development of metabolic complications described in action levels.

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Evaluation of Glycemic Control

Analyzes of serum fasting glucose concentrations were performed using the dry chemistry method; the percentage of glycated hemoglobin was realized by the ion exchange chromatography method. The evaluation of the glycemic control of type 2 diabetic patients was performed according to the American Diabetes Association (ADA, 2020) criteria, which considers glycemia control to be altered in adults, fasting glycemia values above 130 mg/dL and values above 7% for glycated hemoglobin.

Characterization of the Insulin Resistance

The determination of insulin concentrations was performed by the chemiluminescence method. The evaluation of insulin resistance was fulfilled by calculating the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), from the fasting insulin and glucose concentrations, using the formula of Matthews *et al.* (1985).

Determination of Serum C-Reactive Protein Concentration (CRP)

The determination of the CRP concentration was performed according to the immunoturbidimetry method, using an ultra-sensitive Labtest® kit. The analysis was done according to the manufacturer's recommendations. Values > 1.0 mg/L were considered as indicative of active inflammatory processes.

Determination of Plasma Activity of Myeloperoxidase (MPO)

The measurement of MPO activity was performed based on the oxidation rate of the o-dianisidine substrate in the presence of H_2O_2 and evidenced by the change in absorbance measured at 450 nm (BRADLEY *et al.*, 1982). The activity was calculated from the maximum reaction rate, and the result was expressed as U MPO/µL of sample. An MPO unit is defined as the amount of H_2O_2 (µmol) degraded per minute.

Statistical analysis

Data were analyzed in the Stata® program, v.12 (Statacorp, College Station, Texas, USA). Normality of distribution was verified by application of the Shapiro-Wilk test. The Mann Whitney test was performed to compare the means of independent samples. The chi-square test (χ^2) was used to identify the existence of associations between the study variables. The nonparametric data were submitted to logarithmic transformation, and Pearson's correlation coefficient was applied to identify the correlations. The level of significance was set at $p < 0.05$ and 95% confidence interval.

Ethical aspects

The study was approved by the Research Ethics Committee of Federal University of Piauí, by means of Consubstantiated Opinion Nº 1.522.965 and the adherence to the study was confirmed by sign'ing the Free and Informed Consent Term.

RESULTS

General characteristics of participants

The mean time of disease in diabetics was 4.3 ± 4.2 years, of these, 30.2% were with the disease more than 5 years. There was a predominance of females in both groups (69.8%). Table 1 shows the mean values, median and confidence interval of age and anthropometric parameters used to evaluate the nutritional status of the control group and type 2 diabetic patients. There was a statistically significant difference for the variables of weight, body mass index and waist circumference ($p < 0.05$).

Table 1. Mean values, median and confidence interval of age, body weight, height, body mass index and waist circumference of the control group and type 2 diabetic patients.

Variables	Control (n=43) Mean ($CI_{95\%}$) Median	Diabetics (n=43) Mean ($CI_{95\%}$) Median	Values of *p*

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Age (years)	50.3 (48.4 – 52.2) 51.0	49.8 (47.7 – 51.9) 51.0	0.903
Weight (kg)	58.0 (55.7 – 60.4) 56.5	68.3 (65.4 – 71.3) 67.7	<0.001*
Stature (cm)	155.7 (153.3 – 158.2) 155.0	156.7 (153.2 – 160.1) 154.0	0.822
BMI (kg/m^2)	23.9 (23.3 – 24.4) 23.8	28.2 (27.2 – 29.2) 27.8	<0.001*
WC (cm)	83.6 (81.3 – 85.8) 85.0	96.8 (94.5 – 99.2) 96.0	<0.001*

BMI: body mass index; WC: waist circumference; 95% CI: 95% confidence interval;
* Statistically significant difference; Mann-Whitney U-test.

Glycemic Control of Type 2 Diabetic Patients

The majority of diabetics (86,05%) presented glycemia values above the limits defined as good glycemic control (<130 mg/dL), and 55.81% presented HbA1c percentage above the clinical goal defined at level < 7%, in accordance with the ADA recommendations (ADA, 2020).

Evaluation of serum levels of CRP and plasma MPO activity

Table 2 shows the mean values, median and confidence interval of serum CRP concentrations and plasma MPO activity in the control and diabetic groups. There was a statistically significant difference between the groups in relation to the CRP and MPO ($p < 0.05$).

Table 2. Mean, confidence interval and median values of serum concentrations of PCR and MPO of the study participants.

Parameters	**Controls (n=43)**	**Diabetics (n=43)**	**Values of *p***
	Mean ($IC_{95\%}$) Median	**Mean ($IC_{95\%}$) Median**	
CRP (mg/dL)	0.9 (0.8 -1.1) 0.7	3.0 (2.2 – 3.8) 3.0	<0.001
MPO (U MPO/µL)	0.64 (0.42 – 0.86) 0.51	1.7 (0.13 – 3.28) 0.25	0.049

PCR: C-reactive protein; MPO: Myeloperoxidase.
* Significantly different values between type 2 diabetic patients and control group, Mann-Whitney U test ($p < 0.05$).

Figure 1 shows that most participants in the control group had CRP concentrations below 1 mg/L and more than 50% of diabetics had concentrations greater than 3 mg/L. There was a statistically significant difference between the groups ($p < 0.05$).

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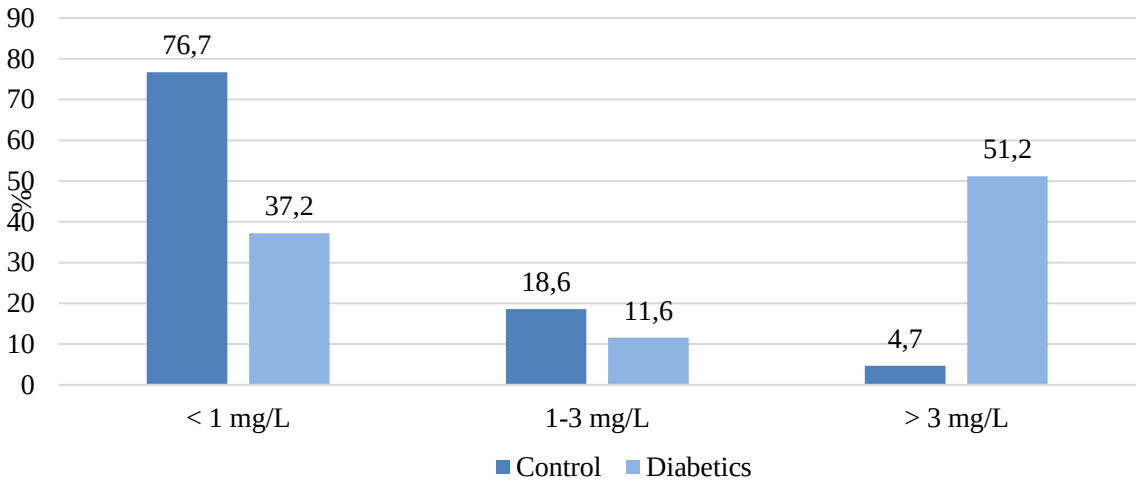
Figure 1. Percentage distribution of study participants according to serum concentrations of CRP.



Chi-square test (p = 0.01).

Table 3 presents the correlation analysis between the glycemic control parameters and the serum concentrations of CRP in type 2 diabetics and in the control group. No statistically significant correlations were found.

Table 3: Correlation between glycemic control parameters and serum concentrations of CRP in the control and diabetic patients.

Variables	Controls (n=43)		Diabetics (n=43)	
	r	*p*	R	*P*
Glucose (mg/dL)	0.093	0.554	0.258	0.095
Glycated Hemoglobin (%)	-0.160	0.304	0.169	0.280
Insulin (U/mL)	-0.131	0.403	-0.120	0.442
HOMAir	-0.087	0.578	0.015	0.923

HOMAir = Homeostasis Model Assessment. Pearson's linear correlation with parameters of glycemic control.

DISCUSSION

In this study, patients with type 2 diabetes undergoing treatment had inadequate glycemic control as well as elevated CRP levels. The systemic inflammation, estimated by the CRP, was not related to the glycemic control parameters evaluated.

Glycemic control, assessed by fasting glycemia and percentage of glycated hemoglobin in most diabetic patients in the present study, was not in line with the treatment goals of the disease, although all diabetics reported on therapy with oral hypoglycemic agents. Similar results were found by Rossaneis *et al.* (2019) when evaluating the glycemic control of type 2 diabetic adults aged 40 years or older, found that 68.9% of diabetics had glycated hemoglobin levels < 7%.

Among the main factors involved in the metabolic control of type 2 diabetes individuals are the disease time associated with inadequate glycemic control, the gradual reduction of β-pancreatic cells and their functional loss (SKYLER *et al.*, 2017). In addition, the progression of the disease is related to the appearance of several comorbidities resulting from macro and microvascular changes, leading to greater metabolic dysfunction in these patients (DUNCAN; COUSIN; NAGHAVI, 2017; EL-AAL, 2018).

Regarding the evaluation of the presence of systemic inflammation, estimated by the ultra-sensitive

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CRP, the groups of type 2 diabetic patients had higher concentrations of the biomarker when compared to the control group. This result is in agreement with the study of Elimam *et al.* (2019) in Egypt, who evaluated the condition of subclinical inflammation in patients with DM2 with poor glycemic control and in a group of healthy controls with paired characteristics. It is also noteworthy that other studies have demonstrated increased risk of disease and insulin resistance associated with increased CRP values.

PCR is an inflammatory marker that plays an important role in cardiovascular disease (ABOLHASANI *et al.*, 2019). However, because it is considered a low specific marker for inflammatory processes, it would not be pertinent to affirm that the high values of this marker found in diabetics is indicative of a greater risk of atherosclerotic process. However, it was also verified in this study increased MPO enzyme activity, which besides being a marker of endothelial oxidative stress, participates in pro-atherogenic activities related to the evolution of cardiovascular disease. Furthermore, MPO appears to play an important role in the link between inflammation and cardiovascular disease. MPO and CRP act together in the atherosclerotic process, although they participate in different metabolic pathways (RUSCICA *et al.*, 2020; MARTIN, 2021).

Moreover, it is important to consider that the majority of diabetics in this study had high BMI, which may also have contributed to high CRP levels. It is known in this literature that obesity influences CRP concentrations, since excess adipose tissue contributes to increased IL-6 and TNF-α expression, and these cytokines stimulate hepatic CRP production (UEMURA *et al.*, 2017).

As to the relation between the concentrations of ultra-sensitive CRP and the glycemic control parameters evaluated (fasting glycemia, glycated hemoglobin, serum insulin and HOMA-IR), no correlation was found in any of the groups evaluated. In contrast, studies demonstrate that percentages of glycated hemoglobin are positively related to CRP levels (WEI, 2019). On the other hand, Tutuncu *et al.* (2016) found no association between CRP and fasting glycemia after adjusting for confounding factors, although a correlation of this inflammation marker with glycated hemoglobin was found.

It is relevant to consider that CRP levels can be modulated by various clinical and environmental parameters. In this sense, it is noteworthy that in this study, diabetics were on oral hypoglycemic therapy, and as described in some studies (CONSUELO *et al.*, 2020), its use may constitute a confounding factor for CRP levels. In addition, some factors may explain in part the lack of association between the evaluated parameters, such as the sample size and the great variability of the data.

Although there was no correlation between CRP concentrations and glycemic control parameters, this marker was high and, considering the high proportion of participants with excess body adiposity, pro-atherogenic lipid profile, higher MPO and inadequate glycemic control, the results found here indicate a greater risk of atherogenic processes in diabetics. These findings reflect the importance of diabetics to maintain good glycemic control, as well as the need for more specific interventions that contribute to the reduction or delay of complications related to the disease.

CONCLUSION

In conclusion, a high proportion of type 2 diabetic patients presented inadequate glycemic control and high concentrations of ultra-sensitive CRP, although no correlation was found with the glycemic control parameters evaluated in these patients. In this study we also verified the increased activity of the MPO enzyme in the type 2 diabetics group.

Considering the importance of glycemic control in the progression of type 2 diabetes, as well as the effects of systemic inflammation on the risk of developing comorbidities and reducing the survival of these patients, there is a need for actions aimed at promoting the metabolic control of this group.

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