An Acad Bras Cienc (2024) 96(3): e20230844 DOI 10.1590/0001-3765202420230844
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

BIOMEDICAL SCIENCES

Diabetes and hypertension in elderly women: interactions between severity and failure to control inflammation

PAULO HENRIQUE B. LIMA, CAROLINE V. GONCALVES, ISRAEL S. RIBEIRO, MARIA POLIANA L. GALANTINI, IGOR P.R. MUNIZ, GILVANÉIA S. SANTOS & ROBSON A.A. DA SILVA

Abstract: Elderly women are more susceptible to the development of chronic non-communicable diseases. Among these, diabetes *mellitus* (DM) and systemic arterial hypertension (SAH) stand out. This work aimed to carry out an expanded study on the interactions of anthropometric, biochemical and inflammatory parameters associated with the risk of severity in elderly women with hypertension and diabetes. The study involved the evaluation of 126 elderly women with hypertension and diabetes *mellitus*. The women were divided according disease severity (low, moderate, high and very high). Anthropometric data were collected by bioimpedance analysis. The inflammatory and biochemical data were obtained from volunteer blood samples. Waist circumference, waist circumference/height ratio, and systolic and diastolic pressures increased with severity. Biochemical marker levels increased with risk of severity, except HDLc. In the very high risk group, there was a higher IL-1β, IFN-γ and TNF-α production, however, lower IL-10 levels were observed. The very high risk group showed change values for the IL-10/IL-1β, IL-10/IL-17 and IL-10/TNF-α ratios. The results showed to be extensively altered in the very high risk group, where the inflammatory profile loses its responsiveness. This is the first study that shows an expanded view of the different parameters evaluated in elderly women with hypertension and diabetes.

Key words: Diabetes *mellitus*, systemic arterial hypertension, elderly, inflammation.

INTRODUCTION

Given the metabolic and hormonal changes in women in the postmenopausal period, they are more susceptible to the development of chronic noncommunicable diseases (NCDs) (Orsatti et al. 2008, Steiner et al. 2014). In this scenario, NCDs are long-term and slowly progressive multifactorial diseases, especially heart disease and diabetes *mellitus* (World Health Organization 2014, Malta et al. 2020, Westphal et al. 2021).

In the scenario of NCDs, systemic arterial hypertension and diabetes *mellitus* are interrelated diseases, causing metabolic, hormonal, inflammatory and blood pressure alterations that configure one of the main risk factors for the development of severe complications such as increased risk and severity of the disease (De Souza et al. 2008).

In this sense, biomarkers can be used as a tool for risk assessment and offer a better understanding of disease processes. In addition, they can provide an objective measure of the severity of the disease, collaborating with future actions in the prediction and stratification of risk groups, contributing to the monitoring of clinical interventions in different groups, such

as elderly women (Badawi et al. 2010, Dhingra & Vasan 2012, Skevaki et al. 2016).

Hormonal changes in postmenopausal women directly influence body composition (Dong 2014, Lopes et al. 2021). The increase in fat mass and hypertrophied adipose tissue, alters physiological responses by increasing pro-inflammatory signals such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-17 and IL-1β (Barry et al. 2016). In addition, regulatory cytokines, such as IL-10, are responsible for maintaining homeostasis in adipose tissue, being related to protection against atherogenesis and control of inflammatory responses. In the same way, studies also indicate that IL-10 is related to the reduction of TNF-α production (Barry et al. 2016). In view of the above, increasing evidence demonstrates that inflammation also plays a crucial role in the pathogenesis and development of systemic arterial hypertension (SAH) and type 2 diabetes *mellitus* (T2DM) (Teixeira et al. 2014, Mikael et al. 2017).

The generation of reactive oxygen species promoted by chronic hyperglycemia, observed in individuals with T2DM, leads to endothelial dysfunction with vascular injury, promoting, respectively, morphofunctional changes and increased expression of inflammatory mediators, such as TNF-α, IL-6, and IL-1β, causing metabolic and cardiovascular problems, such as, systemic arterial hypertension (Santos et al. 2017). In this way, an established inflammatory state results in an increase in the serum concentrations of several pro-inflammatory cytokines, such as, the interleukins IL-6, IL-1β, IL-17, TNF-α and IFN-γ as well as a reduction in the concentrations of regulatory cytokines such as IL-10 (Chehimi et al. 2017, Xia & Rao & Zhong 2017, Ribeiro et al. 2021, Galantini et al. 2022, Gonçalves et al. 2022).

Chronic low-grade inflammation that characterizes aging in elderly women is the result of a complex imbalance between pro- and anti-inflammatory responses, which decreases in reliability and efficiency, resulting in greater progression and susceptibility to NCDs (Baylis et al. 2013, Pawelec et al. 2020). Therefore, this work aimed to obtain a better understanding about the interactions of anthropometric, biochemical and inflammatory parameters and the severity of these diseases in elderly postmenopausal women with T2DM and SAH.

METHODOLOGY

Population study

The study involved the evaluation of 126 women aged between 60 and 80 years, with a positive diagnosis of systemic arterial hypertension (SAH) and type 2 diabetes *mellitus* (T2DM), assisted at the Family Health Units (USF) in Vitória da Conquista- BA. Participation was voluntary and the sample size was defined by convenience. As inclusion criteria, a minimum age of 60 and a maximum of 80 was applied. Exclusion criteria were defined by the diagnosis of autoimmune diseases, presence of self-reported inflammation and/or use of anti-inflammatory drugs. All participants were invited to sign the Free and Informed Consent Form or the dactyloscopy identification.

The evaluation consisted of the application of a semi-structured questionnaire on socioeconomic data, use of medication and practice of physical activity, anthropometric evaluation, analysis of body composition estimated by bioimpedance, measurement of blood pressure and blood samples collection for biochemical dosages and measurement of cytokines.

Anthropometric assessment

The body mass index (BMI) was calculated from the ratio between weight (Kg) and height (m^2) (BMI= weight Kg/height m^2) protocol

recommended by Lipschitz 1994. To classify the nutritional *status*, the cutoff points for the elderly proposed by the Protocols of the Food and Nutritional Surveillance System - SISVAN, of the Brazilian Ministry of Health were used. The recommendation of the SISVAN Protocol is the use of specific BMI cutoff points to the elderly: <22 kg/m^2 - underweight; ≥22 and <27 kg/m^2 - eutrophic; ≥27 kg/m^2 – overweight. The values for waist circumference (WC) were obtained by circling the individuals with a flexible measuring tape at the waist line (in the narrowest region between the chest and the hip, at the midpoint between the last rib and the iliac crest), without compressing the tissues and at the moment of expiry. The cutoff points recommended by the Brazilian Society of Cardiology in the VII Brazilian Guideline on Dyslipidemia and Prevention of Atherosclerosis were used according to the degree of risk for cardiovascular diseases. The analysis of the estimated body composition was performed using a bioimpedance device coupled to the scale (*Plenna*, SP, Brazil). After checking height, age and height values were entered into the device. The values obtained were then recorded as BMI (Kg/m ^{2}), fat mass (%), lean mass (%), bone mass (%), body water (%) and basal metabolism (Kcal/day).

Blood pressure measurement

Blood pressure and pulse were measured using an automatic digital blood pressure device (G-TECH, model BP3AA1-1). The measurement was carried out with the individuals sitting comfortably for at least 5 minutes (feet on the floor), in a calm environment and with the right arm positioned at heart level. For the purposes of data analysis, the average of the values obtained from two blood pressure measurements, taken at intervals of approximately 10 minutes, was used.

Dosage of biochemical markers

To assess the glycemic and lipid profile of the participants, peripheral blood samples were collected by venipuncture, after a maximum fast of 12 hours. Serum concentrations of triglycerides, total cholesterol and fractions, and glucose were then measured. The determination of serum concentrations was carried out according to the specifications of the manufacturer Bioclin, for the following kits, monoreagent cholesterol (K083), enzymatic HDL (K015), monoreagent triglycerides (K117) and monoreagent glucose (K088).

Cytokine dosages by ELISA

IL-1β, TNF-α, IL-10, IL-17A, INF-γ and TNF-α cytokines were measured by the ELISA method, according to the recommendations of the manufacturers of the Quantikine ® Kits (R&D systems).

Criteria for dividing the groups

Using the reformulated risk stratification method proposed by the European Society of Cardiology (Mancia et al. 2013), the groups were divided based on the clinical criterion of hypertension, correlating them with the risk factors: family history, age, BMI, WC, WC/HC ratio, uncontrolled blood glucose ≥ 126 mg/dL (patients who do not respond to prescribed pharmacological treatment), physical inactivity and dyslipidemias (cholesterol > 200; LDL > 160; HDL < 35; triglycerides >200). With the association between hypertension and risk factors, it was possible to divide he group into low risk, moderate risk, high risk, and very high risk, according to the risk of developing cardiovascular diseases (Mancia et al. 2013, Galantini et al. 2022).

Statistical analysis

Statistical analysis of the data was performed using the GraphPad-Prisma Version 8.0 program

(GraphPad Software, CA, USA). Numerical variables were expressed as mean ± standard deviation. The normality of data distribution was verified using the Shapiro-Wilk test. Since the variables did not present a normal distribution, comparisons among the low, moderate, high and very high risk groups were performed using the non-parametric Kruskal -Wallis test, followed by Dunn's post test. Multivariate analysis of correlations were obtained through the RStudio software, using the Corrplot package. Differences were considered statistically significant and were used when $p<0.05$, with a 95% confidence interval. RStudio software was also used to create Bayesian networks. The packages used to build the networks were: bnlearn and bnviewer.

Ethical considerations

The project was approved by the Ethics Committee for Research Involving Human Beings (UFBA/IMS), in accordance with Resolution 466/12 (CNS/CONEP). The project approval protocol is 27439114.4.0000.5556.

RESULTS

Characterization of the study group

Our study population consisted of 126 women aged between 60 and 80 years, with a positive diagnosis of SAH and T2DM. In this population, the drugs that were being used to control blood pressure were: the angiotensin receptor antagonist, losartan potassium (95%), the thiazide diuretic, hydrochlorothiazide (89%), in addition to the beta-adrenergic receptor blocker, propranolol (60%). For glycemic control, the most commonly used oral hypoglycemic agents in the studied population were metformin (89%), a biguanide, and a second-generation sulfonylurea, glibenclamide (60%). For the control of dyslipidemia, the main drug was simvastatin.

Blood pressure parameters increase and lean mass decreases with the increased risk of severity in elderly women

Waist circumference was higher in the very high risk group when compared to the low risk group. In line with this result, the waist circumference/height ratio was also different, with an increase in the very high risk group compared to the other groups. Lean mass decreases with increasing risk of severity, this finding is observed when comparing the low and very high risk groups. Furthermore, systolic and diastolic pressures increased in parallel with increasing severity across groups. Systolic blood pressure shows differences among moderate, high and very high risk groups (Table I).

All concentrations of biochemical markers increased with risk of severity, except HDLc

Most concentrations of biochemical markers increased with the risk of severity, with emphasis on the very high risk group when compared to the other groups. This goes for the following biochemical markers in the blood: Triglycerides, Cholesterol, LDLc and VLDLc. In contrast, HDLc decreased with the severity of the groups. There was a difference in relation to the serum glucose concentration, with an increase in the very high risk group when compared to all other groups of elderly women (Table II).

TNF-α concentration increased concomitantly with severity and cytokine ratios show different patterns among groups

From the inflammatory data, it was possible to observe that the serum concentration of TNF-α increased with the severity, where differences were observed among the different risk groups. IFN-γ however showed difference with increase between high and very high risk groups. In general, these two cytokines had their highest serum concentrations in the very high risk group (Table III). Meanwhile, the anti-inflammatory

Table I. Anthropometric, hemodynamic and body composition data of elderly women with SAH and T2DM according to stratification into low, moderate, high and very high risk groups.

parameters	low risk	moderate risk	high risk	very high risk	p
	n= 6	n=12	n=20	n=88	
Weight (kg)	61.02(±12.71)	66.74(±7.33)	69.05(±11.46)	72.96(±13.68)	0.2505
BMI (kg /m ^{2})	24.77(±4.04)	27.97(±3.20)	29.16(±3.30)	30.28(±5.25)	0.1287
WC (cm)	84.50(±10.55) †	97.25(±7.42)	97.60(±8.88)	109.2(±95.28)†	0.045
HC (cm)	94.67(±8.96)	102.0(±6.75)	102.7(±6.39)	105.6(±12.62)	0.2616
WC/HC ratio (cm)	0.89(±0.05)	0.95(±0.06)	0.94(±0.06)	1.04(±0.95)	0.2525
WC/Height Ratio	0.54(±0.06) †	0.63(±0.05)	0.63(±0.05)	0.70(±0.63)†	0.0447
Fat mass (%)	26.98(±6.61)	32.45(±2.92)	32.12(±5.47)	33.61(±4.61)	0.1391
Lean mass (%)	18.62(±7.57) †	13.95(±2.82)	13.29(±4.81)	11.85(±2.70)†	0.011
Bone mass (%)	9.86(±1.04)	8.43(±0.95)	9.27(±2.06)	8.55(±1.42)	0.0425
Water (%)	52.68(±3.90)	49.33(±2.13)	49.44(±3.76)	49.28(±7.10)	0.2296
metabolism (Kcal/day)	1,252(±157.0)	1,264(±70.75)	1,308(±154.2)	1,377(±150.8)	0.0144
Systolic pressure (mmHg)	137.3(±14.43)	134.5(±10.10)$^{\#}$	147.5(± 6.56)*	155.0(±19.48)$^{\#*}$	0.0002
Diastolic pressure (mmHg)	89.08(±6.71)	86.13(±4.14)	86.43(±5.11)*	92.02(±8.14)*	0.0054
Pulse (ppm)	82.17(±14.08)	75.08(±9.94)	78.23(±11.76)	78.51(±11.81)	0.5738

The normality of data distribution was verified using the *Shapiro-Wilk test*. The ANOVA test was used for variables with normal distribution. The non-parametric *Kruskal -Wallis* test was used for variables that did not present normal distribution, followed by Dunn's post-test. † indicated for comparison with the low-risk group. $^{\#}$ indicated for comparison with the moderate risk group. * Indicated for comparison with the high risk group. Different symbols indicate statistical difference (p< 0.05) between groups. Numerical variables were expressed as mean ± standard deviation. WC: Waist circumference; HC: Hip Circumference; BMI: Body Mass Index.

cytokine IL-10 decreased in the very high risk group compared to the other analyzed groups. The group of very high risk elderly women had lower values for the IL-10/IL-1β, IL-10/IL-17 and IL-10/TNF-α ratios when compared to high risk elderly women (Table III).

Elderly women at very high risk show changes in their correlations between markers

Through the analysis of the *corrplot* (Figure 1) it was possible to observe the correlations of anthropometric, biochemical and inflammatory data of elderly women with SAH and T2DM in the different risk groups. These correlations were different among the groups, mainly in relation to the very high risk group, where lower correlation forces and the emergence of other interactions are observed. This fact was observed in the anthropometric parameter, where the fat mass was positively correlated with weight, WC and HC in the different risk groups of elderly women with hypertension and diabetes. However, with the increase in the level of severity, there is a reduction in their correlation strength.

With regard to biochemical parameters, correlations differ among groups. In the low risk group, LDLc shows a negative correlation with WC and fat mass, however it correlates positively with lean mass. Despite the reduction in the strength of correlations observed with the increase in the risk of severity, new significant correlations were observed in the high and

very high risk groups. In the high and very high risk groups, cholesterol, LDLc, Triglycerides and VLDLc showed positive correlations with weight and HC. Glucose also shows correlations in the very high risk group, in terms of systolic blood pressure and all the biochemical parameters analyzed: HDLc, LDLc, triglycerides and VLDLc, except for cholesterol (Figure 1).

It is also worth highlighting the role of cytokines, where the same pattern regarding the loss of correlations among the different groups is also observed. Among them, IL-10 curiously, there is a reduction in the strength of correlation with the increase in the level of severity in the elderly groups. IL-10 in the low-risk group positively correlates with the WC/HC ratio, diastolic blood pressure. It is also observed in the same group, a positive correlation between TNF-α and IL-1β.

With increasing risk of severity, IL-10 in the moderate risk group positively correlates with biochemical parameters: triglycerides, VLDLc, and glucose. Cytokines IL-17, IL-1β and TNF-α negatively correlate with HDLc. However, it should be noted that in the high and very high risk groups, the IL-10 correlation forces become less intense and negative. In the high risk group, TNF-α is positively correlated with the cytokines IL-17 and IL-1β. IL-17 is positively correlated with BMI, the same fact is observed in IL-1β with diastolic blood pressure and with IL-17. It is worth highlighting IL-10, where it correlates negatively with IL-17. Still in this same group, TNF-α correlated negatively with HDLc and positively with IL-10.

In the very high risk group, the lowest intensity of correlations is observed, in addition to the emergence of new interactions with the biochemical parameters. IFN-γ is positively correlated with IL-1β and TNF-α with glucose. TNF-α negatively correlates with HDLc. Likewise, IL-10 negatively correlates with basal metabolism, cholesterol and LDLc (Figure 1).

DISCUSSION

Aging is a dynamic process marked by changes in the individual (De Araujo Silva et al. 2006). This event in elderly women is marked by a reduction in serum levels of female sex hormones. This affects different metabolic pathways and inflammatory mechanisms that alter body composition. In addition, weight gain, characteristic of the elderly population, is

Table II. Biochemical parameters of postmenopausal women with SAH and T2DM according to severity.

parameters	low risk	moderate risk	high risk	very high risk	p
	n= 6	n=12	n=20	n=88	
Glucose (mg/dL)	115.0(± 9.55) †	114.8(± 9.77)#	118.4(±15.47)†#*	187.6(±36.35)#*	<0.0001
Triglycerides(mg/dL)	115.8(±18.19)†	126.0(±21.98)#	138.8(±23.86)*	181.3(±36.06)†#*	<0.0001
Cholesterol (mg/dL)	196.2(±12.89)	198.5(±12.26)#	199.9(±20.54)*	231.9(±42.85)#*	0.0001
LDLc (mg/ dL)	107.4(± 3.80) †	111.1(± 9.58)#	115.0(± 18.96)*	154.6(±43.96)†#	<0.0001
VLDLc (mg/dL)	23.13(± 3.62) †	25.21(± 4.41)#	27.67(± 4.86)*	36.27(±7.23)#*	<0.0001
HDLc (mg/dL)	65.90(±10.96)	63.30(± 6.31)#	57.81(±10.87)*	41.09(±10.01)#*	<0.0001

The normality of data distribution was verified using the *Shapiro-Wilk test*. The ANOVA test was used for variables with normal distribution. The non-parametric *Kruskal -Wallis* test was used for variables that did not show normal distribution. Numerical variables were expressed as mean ± standard deviation. † indicated for comparison with the low-risk group. # indicated for comparison with the moderate risk group. * Indicated for comparison with the high risk group. Different symbols indicate statistical difference (p< 0.05) between groups. HDL: High Density Lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low density lipoprotein.

strongly associated with hypertension and T2DM (Lopes et al. 2021). Our results demonstrate, in an expanded analysis, that body composition, biochemical markers and inflammatory parameters are involved with the increased risk of severity in elderly women with hypertension and diabetes. In addition, our data brings to light important alterations in the inflammatory profile, alterations that are linked to the development of a pro-inflammatory profile related to a greater metabolic and systemic imbalance.

The postmenopausal period, on average, promotes a loss of 0.6% of lean mass per year (Buffa et al. 2011). These modifications are associated with an increase in fat mass, which tends to accumulate in the central or visceral region, in addition to a reduction in bone mass. The atrophy of this muscle associated with age, as it happens in elderly women, is called sarcopenia (Toth et al. 2000). In view of these findings, based on the anthropometric assessment, we observed that lean mass in elderly women decreases with an increase in the risk of severity (Table I). Thus, the loss of lean mass, or age-associated atrophy in the studied group, may be associated with functional limitation and disability that increases the risk of mortality (Buffa et al. 2011). In addition, changes in the lipid and glycemic profile, inflammatory cytokines, and oxidative metabolism play important roles in age-related muscle atrophy (Leite et al. 2012).

Another important finding in relation to the anthropometric data of the studied population is the WC and the WC/Height ratio, where an increase can be observed between the elderly women in the low risk group and those in the very high risk group. Studies show that the increase in WC and the WC/Height ratio are related to a higher risk of development and progression of T2DM in women, and even correlate with the increase in systolic blood pressure and overweight (Okęcka-Szymańska et al. 2011, Lopes et al. 2021).

Individuals with T2DM are at increased risk for dyslipidemia since insulin resistance

Table III. Inflammatory markers in postmenopausal women with SAH and T2DM according to severity.

parameters	low risk	moderate risk	high risk	very high risk	p
	n= 6	n=12	n=20	n=88	
IL-17A (ng/mL)	0.34(±0.29)	0.81(±0.89)	0.40(±0.49)	1.25(±1.60)	0.177
IL - 1β (pg/mL)	16.10(±20.23)	23.91(±13.39)	20.02(±19.33)	29.92(±17.65)	0.0658
IFN - γ (pg/mL)	3.01(±3.97)	4.03(±3.76)	2.70(± 3.33)*	5.23(± 3.14)*	0.0043
TNF - α (ng/mL)	0.18(±0.29)†	0.38(±0.53) #	0.58(±0.65)*	2.38(± 1.99)† # *	<0.0001
IL-10 (pg/mL)	45.44(±81.21)	44.12(±55.60)	87.68(±87.28)*	39.77(±62. 14)*	0.0293
IL-10/IL-1β	0.43(±0.22)	2.46(± 5.80)	23.68(± 42.41)*	2.16(± 4.52)*	< 0.05
IL-10/IL-17	1,202(±2,846)	173.2(±356.7)	1,442(± 2,329)*	233.0(±852.2)*	< 0.05
IL-10/TNF-α	38.23(±4.05)	58.85(±24.92)	89.31(±66.72)*	35.26(±49.47)*	< 0.01
IL-10/ IFN-γ	4.85(±6.12)	24.98(±38.20)	30.15(±37.25)	18.56(±38.72)	0.2499

The normality of data distribution was verified using the *Shapiro-Wilk test.* The ANOVA test was used for variables with normal distribution. The non-parametric *Kruskal -Wallis* test was used for variables that did not show normal distribution. Numerical variables were expressed as mean ± standard deviation. † indicated for comparison with the low-risk group. # indicated for comparison with the moderate risk group. * Indicated for comparison with the high risk group. Different symbols indicate statistical difference (p< 0.05) between groups. IL-17A: Interleukin 17; IL-1β: Interleukin 1 beta; TNF-α: Tumor necrosis factor alpha; IL-10: Interleukin 10; IFN-γ: Interferon gamma.

is related to changes in the metabolism of circulating lipoproteins (Freitas-Dias et al. 2015). After menopause, there is an increase in serum cholesterol concentrations, especially total cholesterol, low-density lipoprotein (LDLc) and triglycerides. However, it is marked by a reduction in high-density lipoprotein (HDLc). These lipid changes occur with the reduction of ovarian hormones, justified by the increased cardiovascular risk and development of metabolic diseases in postmenopausal women (Fonseca et al. 2017, Lopes et al. 2021).

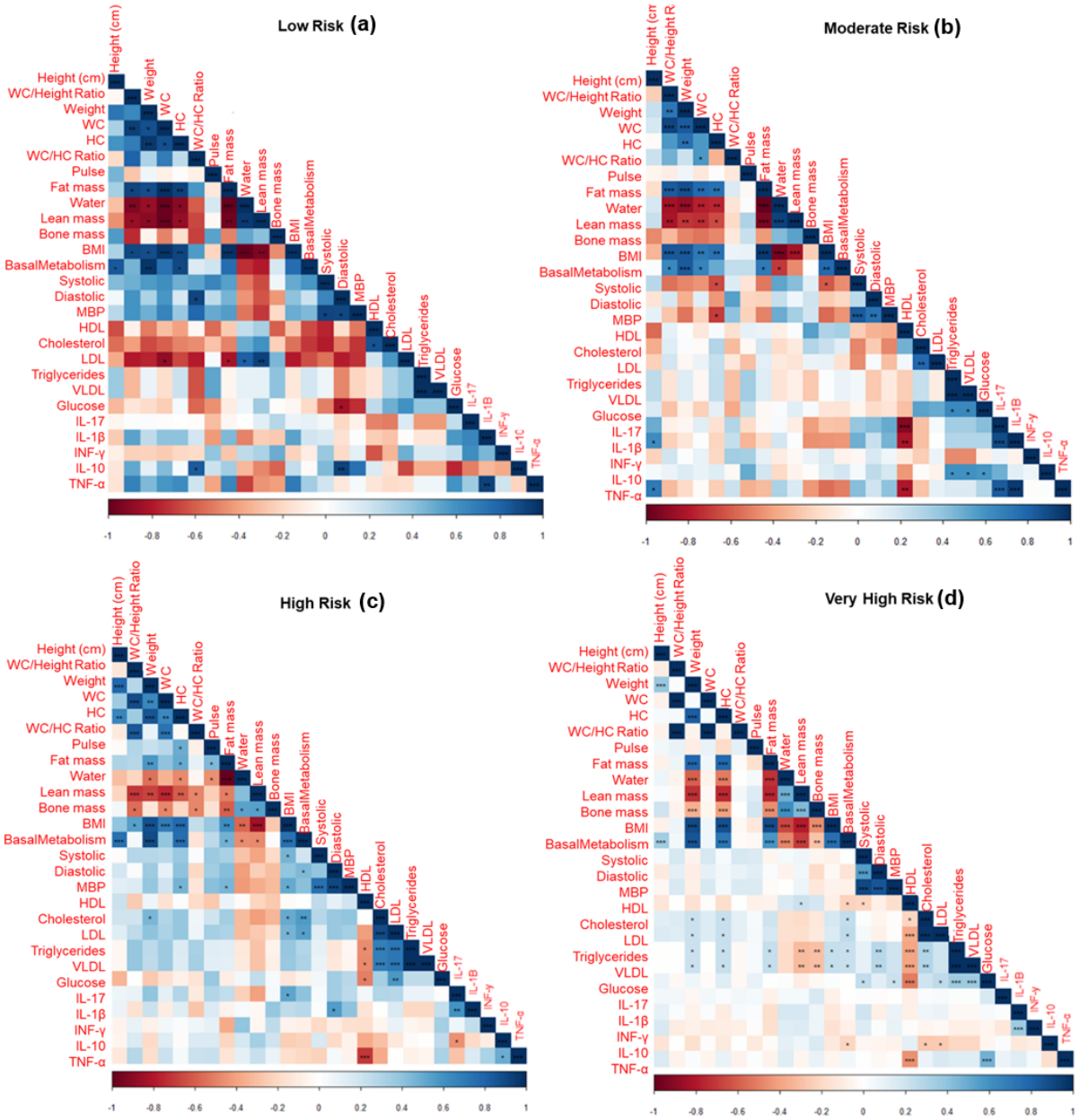

Figure 1. **Correlations between anthropometric data, blood pressure, biochemical and immunological markers. (a) Low risk, (n= 6). (b) Moderate risk, (n= 12). (c) High risk, (n= 20). (d) Very high risk, (n= 88). Positive correlations are indicated in blue and reverse correlations in red. Darker color tones indicate higher r-values. p values are indicated based on *Spearman rank correlation tests* (* p <0.05; ** p <0.01; *** p <0.001).**

Therefore, all biochemical markers expressed in elderly women, increased significantly in relation to the risk of severity, among these triglycerides, cholesterol, LDLc and VLDLc. However, a reduction in HDLc levels was observed with increasing severity in the groups (Table II). Evidence suggests that low levels of HDLc may also contribute to the pathophysiology of T2DM through direct effects on plasma glucose. Thus, HDLc can influence glucose homeostasis through mechanisms that include insulin secretion, increased insulin sensitivity and direct glucose uptake by muscle (Drew et al. 2012, Fonseca et al. 2017).

Given the above, even under drug treatment, the very high risk group of elderly women with hypertension and diabetes has the highest serum glucose concentration (Table II). Differences in relation to serum glucose concentrations were observed between high risk groups when compared to all other analyzed groups. It is known that the increase in glycaemia exacerbates the pro-inflammatory state of T2DM and SAH, aggravating its clinical course (Gündogan et al. 2009).

All the modifications that affect postmenopausal women exhibit changes in body composition, lipid and inflammatory profile that predispose to the development and complications of chronic diseases, such as T2DM and SAH. Thus, aging is associated with low-grade inflammation, characterized by increased serum concentrations of pro-inflammatory cytokines, as well as decreased serum concentrations of anti-inflammatory cytokines (Lopes et al. 2021, Ribeiro et al. 2021, Dos Santos et al. 2021, Gonçalves et al. 2022).

In the aging process, changes in TNF-α production have been related to hyperglycemia and hyperinsulinemia. Evidence suggests that TNF-α may contribute to T2DM by inducing β-cell apoptosis through NF-κB (Dunmore & Brown 2012, Kahn & Cooper & Del Prato 2014, Nalini et al. 2017). Our data are in agreement, since the higher the degree of severity in elderly women with hypertension and diabetes, the higher the serum level of TNF-α. It is known that TNF-α is one of the cytokines found in high concentrations in the elderly and that it may also be related to obesity, insulin resistance, sarcopenia and atherosclerosis (Renna et al. 2013, Rong et al. 2018, Gonçalves et al. 2022).

Continuing the progression of severity observed in the elderly groups, the cytokines IL-1β and INF-γ showed their highest concentrations in the very high risk group (Table III). Studies indicate that the increase in serum concentrations of IL-1β is greater in hypertensive individuals when compared to healthy individuals, as well as in people with hypertension and diabetes (Dayre et al. 2018). Some studies show positive correlations between IL-1β and INF-γ in cardiovascular complications, while IFN-γ is considered to be involved in the pathogenesis of diabetes *mellitus* and heart disease (Dayre et al. 2018).

Another dual character cytokine analyzed was IL-10. It is known that IL-10, produced mainly by macrophages and lymphocytes, acts by regulating the immune system, significantly inhibiting the expression and/or synthesis of pro-inflammatory cytokines, in addition to inhibiting the activity of macrophages and T cells (Speretta et al. 2014). It has also been demonstrated that IL-10 exerts essential control over biochemical parameters, such as LDLc, VLDLc, HDLc, triglycerides and glucose, improving aspects related to T2DM and SAH (Jung & Choi 2014).

The intense production of inflammatory mediators, such as cytokines, may be able to generate a major dysfunction in the coordination of the immune system. Individuals who have non-transmissible chronic diseases can relate

to a disorganized response of immune system cells, leading to a fragility of these defense systems (Bonyek-Silva et al. 2020). In this way, we observed that the anti-inflammatory cytokine IL-10 was decreased in the very high risk group compared to the other groups analyzed. This result suggests that the greater the risk of severity, the lower the anti-inflammatory responsiveness.

As expected, the elderly women in the very high risk group had higher concentrations of the pro-inflammatory cytokines IFN-γ and TNF-α. IFN-γ, in turn, plays a role in the development of age-associated inflammation by inducing reactive oxygen species in the bone marrow, which induces the release of more IFN-γ and thus sustains a pro-inflammatory cycle vicious (Pangrazzi et al. 2017, Ribeiro et al. 2021). TNF-α is one of these cytokines that is found in high concentrations in the elderly and that may also be related to obesity, insulin resistance, sarcopenia and atherosclerosis (Dos Santos et al. 2021).

An interesting pattern was also reported in the ratio between the anti-inflammatory cytokine IL-10 and the pro-inflammatory cytokines examined in this study. The ratios observed between IL-10 and the other cytokines IL-10/IL-1β, IL-10/IL-17 and IL-10/ TNF-α were lower in relation to very high-risk elderly women compared to elderly women of high risk. Thus, the group of elderly women at very high risk had lower values for the ratios IL-10/IL-1β, IL-10/IL-17 and IL-10/TNF-α. Ribeiro et al. (2021) demonstrated that the increased IL-10/IL-17 ratio can be a good predictor of the inflammatory state of elderly women. However, this response differs when we stratify the group of elderly women with hypertension and diabetes, according to the degree of severity presented in this study.

Through multivariate analysis of *corrplot* (Figure 1), we observed that the correlations become less evident in the different groups of elderly women with hypertension and diabetes. In this context, the interactions between the analyzed parameters begin to be lost as the risk increases, suggesting that there is a loss of responsiveness and control in the inflammatory context. The group of elderly women at very high risk presents new correlations with biochemical and inflammatory parameters, reinforcing the idea that elderly women at very high risk and with NCDs are at increased risk for dyslipidemia, since insulin resistance is related to changes in metabolism of the lipids. Furthermore, hyperstimulation of the immune system is involved in adipose tissue inflammation and may be associated with a weaker cellular response, leading to uncontrolled inflammation in the high risk group (Sell et al. 2012, Galantini et al. 2022).

CONCLUSIONS

The data from this study demonstrate an expanded analysis from anthropometric, biochemical and inflammatory parameters to stratification in risk levels of severity, in elderly women with hypertension and diabetes. The evaluated parameters showed to be extensively altered in the very severe risk group when compared to the other groups. The reduction of female sex hormones alters body composition, especially lean mass, WC and the WC/Height ratio. These parameters are closely related to the progression of complications and injuries of non-transmissible chronic diseases such as SAH and T2DM.

Biochemical markers, especially glucose, were also correlated with increased severity in the studied groups. It is known that the increase in glycemia increases the pro-inflammatory state, consequently the progression of diseases (Galantini et al. 2022). Therefore, the

inflammatory response loses its responsiveness as the severity increases, since the serum concentrations of IL-10 and the ratios between the cytokines IL-10/IL-1β, IL-10/IL-17 and IL-10/TNF-α change as risk increases in elderly women with hypertension and diabetes.

In view of this, there are no studies that show an expanded view of several markers in elderly women with hypertension and diabetes, and their association according to the risk of severity. In this sense, our study is of fundamental importance, as it demonstrates the loss of inflammatory responsiveness in elderly women with a higher risk of severity.

Acknowledgments

This work was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil, and by Universidade Federal da Bahia – Instituto Multidisciplinar em Saúde - Campus Anísio Teixeira (UFBA-IMS-CAT).

REFERENCES

BADAWI A ET AL. 2010. Type 2 diabetes mellitus and inflammation: Prospects for biomarkers of risk and nutritional intervention. Diabetes Metab Syndr Obes 3: 173-186. Doi: 10.2147/dmsott.s9089. PMID: 21437087; PMCID: PMC3047967.

BARRY JC ET AL. 2016. Hyporesponsiveness to the anti-inflammatory action of interleukin-10 in type 2 diabetes. Sci Rep 6: 1-9.

BAYLIS D ET AL. 2013. Understanding how we age: insights into inflammaging. Longev healthspan 2(1): 8.

BONYEK-SILVA I ET AL. 2020. Unbalanced production of LTB4/PGE2 driven by diabetes increases susceptibility to cutaneous leishmaniasis. Emerg Microbes Infect 9(1): 1275-1286.

BUFFA R ET AL. 2011. Body composition variations in aging. Coll Anthropol 35(1): 259-265.

CHEHIMI M, VIDAL H & ELJAFARI A. 2017. Pathogenic role of il-17-producing immune cells in obesity, and related inflammatory diseases. J Clin Med 6(7).

DAYRE A, BUTKOWSKI EG & JONG B DE. 2018. Inflammation and oxidative stress markers in diabetes and hypertension. J Inflamm Res 11: 61-68.

DE ARAUJO SILVA TA ET AL. 2006. Aging-associated sarcopenia: Etiologic aspects and therapeutic options. Brazilian Journal of Rheumatology 46(6): 391-397.

DE SOUZA S ET AL. 2008. Qualidade De Vida De Indivíduos Com Diabetes Mellitus E Hipertensão Acompanhados Por Uma Equipe De Saúde Da Família Quality of Life for Diabetic and Hypertensious Individual Accompanied By the Family Health Team La Calidad De Vida De Los Pacientes Diabéti. Texto Contexto Enferm, Florianópolis, 17(4): 672-679.

DHINGRA R & VASAN RS. 2012. Age as a risk factor. Med Clin N Am 96(1): 87-91.

DONG X. 2014. Association between Elder Abuse and Metabolic Syndromes: Findings from the Chicago Health and Aging Project. Gerontology 61(5): 389-398.

DOS SANTOS DC ET AL. 2021. Gender-related differences in the modulation of anthropometric, biochemical, and immune markers by physical activity in hypertensive and diabetic individuals. An Acad Bras Cienc 93: 1-13.

DREW BG ET AL. 2012. The emerging role of HDL in glucose metabolism. Nat Rev Endocrinol 8(4): 237-245.

DUNMORE S & BROWN J. 2012. The role of adipokines in b -cell failure of type 2 diabetes. J Endocrinol 216: T37-T45.

FONSECA MIH, DA SILVA IT & FERREIRA SRG. 2017. Impact of menopause and diabetes on atherogenic lipid profile: Is it worth to analyse lipoprotein subfractions to assess cardiovascular risk in women? Diabetol Metab Syndr 9(1): 1-13.

FREITAS-DIAS R ET AL. 2015. Exercise increases pancreatic b -cell viability in a model of type 1 diabetes through IL-6 signaling. The FASEB Journal 29: 1805-1816,

GALANTINI MPL ET AL. 2022. The sweet fuel of inflammation: New perspectives on the complex web that interconnects diabetes. Exp Gerontol 167: 111905. ISSN 0531-5565. https://doi.org/10.1016/j.exger.2022.111905.2022.

GONÇALVES CV ET AL. 2022. Inflammaging and body composition: New insights in diabetic and hypertensive elderly men. Exp Gerontol 170: 112005, ISSN 0531-5565. https://doi.org/10.1016/j.exger.2022.112005.

GÜNDOGAN K ET AL. 2009. Prevalence of metabolic syndrome in the Mediterranean region of Turkey: evaluation of hypertension, diabetes mellitus, obesity, and dyslipidemia. Metab Syndr Relat Disord 7(5): 427-434.

JUNG UJ & CHOI MS. 2014. Obesity and its metabolic complications: The role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci 15(4): 6184-6223.

KAHN SE, COOPER ME & DEL PRATO S. 2014. Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. The Lancet 383(9922): 1068-1083.

LEITE LE DE A ET AL. 2012. Envelhecimento, estresse oxidativo e sarcopenia: uma abordagem sistêmica. Rev Bras Geriatr Gerontol 15(2): 365-380.

LIPSCHITZ DA. 1994. Screening for nutritional status in the elderly. Prim Care 21(1): 55-67.

LOPES DPS ET AL. 2021. Regular physical activity reduces the proinflammatory response in older women with diabetes and hypertension in the postmenopausal phase. Exp Gerontol 152: 111449. ISSN 0531-5565. https://doi.org/10.1016/j.exger.2021.111449.

MALTA DC ET AL. 2020. Noncommunicable diseases, risk factors, and protective factors in adults with and without health insurance. Cienc Saude Colet 25(8): 2973-2983.

MANCIA G ET AL. 2013. ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34(28): 2159-2219.

MIKAEL L DE R ET AL. 2017. Envelhecimento Vascular e Rigidez Arterial. Arq Bras Cardiol 109(3): 253-258.

NALINI M ET AL. 2017. Correlation of various serum biomarkers with the severity of diabetic retinopathy. Diabetes Metab Syndr 11(Suppl 1): S451-S454. Doi: 10.1016/j.dsx.2017.03.034. Epub 2017 Apr 8. PMID: 28420575.

OKĘCKA-SZYMAŃSKA J ET AL. 2011. Effects of age, gender and physical activity on plasma lipid profile. Biomed Hum Kinet 3: 1-5.

ORSATTI FL ET AL. 2008. Indicadores antropométricos e as doenças. Rev Bras Ginecol Obstet 30(4): 182-189.

PANGRAZZI L ET AL. 2017. "Inflamm-aging" influences immune cell survival factors in human bone marrow. Eur J Immunol 47(3): 481-492.

PAWELEC G ET AL. 2020. The conundrum of human immune system "senescence". Mech Ageing Dev 192: 111357.

RENNA NF, DE LAS HERAS N & MIATELLO RM. 2013. Pathophysiology of Vascular Remodeling in Hypertension. Int J Hypertens 2013: 808353.

RIBEIRO IS ET AL. 2021. Regular physical activity reduces the effects of inflammaging in diabetic and hypertensive men. Exp Gerontol 155: 111558.

RONG Y ET AL. 2018. Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6 , anti-inflammatory cytokine IL-10. BMC Geriatr 18: 308.

SANTOS ALM ET AL. 2017. Alzheimer's disease and type 2 diabetes mellitus: what is the relationship? Rev Bras Neural 53(4): 17-26.

SELL H, HABICH C & ECKEL J. 2012. Adaptive immunity in obesity and insulin resistance. Nat Rev Endocrinol 8(12): 709-716.

SKEVAKI C ET AL. 2016. Immune biomarkers in the spectrum of childhood noncommunicable diseases. J Allergy Clin Immunol 137(5): 1302-1316.

SPERETTA GF, LEITE RD & DUARTE ACDO. 2014. Obesity, inflammation and exercise: focus on TNF-alpha and IL-10. Pedro Ernesto University Hospital Magazine 13(1): 61-69.

STEINER ML ET AL. 2014. Evaluation of food consumption, anthropometric measurements and time since menopause in postmenopausal women. Brazilian Journal of Gynecology and Obstetrics 37(1): 16-23.

TEIXEIRA BC ET AL. 2014. Inflammatory markers, endothelial function and cardiovascular risks. J Vasc Bras 13(2): 108-115.

TOTH MJ ET AL. 2000. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes 24(2): 226-231.

WESTPHAL G ET AL. 2021. Tratamento multiprofissional da obesidade sobre o risco cardiometabólico e a aptidão física relacionada à saúde de mulheres com obesidade severa. Revista Saúde e Desenvolvimento Humano 9(2): 1-11.

WORLD HEALTH ORGANIZATION. 2014.Global Status Report On Noncommunicable Diseases 2014.

XIA C, RAO X & ZHONG J. 2017. Role of T Lymphocytes in Type 2 Diabetes and Diabetes-Associated Inflammation. Jf Diabetes Res 2017, Article ID 6494795, 6 pages.

How to cite
LIMA PHB, GONCALVES CV, RIBEIRO IS, GALANTINI MPL, MUNIZ IPR, SANTOS GS & SILVA RAA. 2024. Diabetes and hypertension in elderly women: interactions between severity and failure to control inflammation. An Acad Bras Cienc 96: e20230844. DOI 10.1590/0001-3765202420230844.

Manuscript received on September 16, 2023; accepted for publication on April 4, 2024

PAULO HENRIQUE B. LIMA[1]
https://orcid.org/0000-0002-1672-8632

CAROLINE V. GONCALVES[1]
https://orcid.org/0000-0003-0895-1583

ISRAEL S. RIBEIRO[2]
https://orcid.org/0000-0002-1262-1387

MARIA POLIANA L. GALANTINI[1]
https://orcid.org/0000-0001-9423-5334

IGOR P.R. MUNIZ[1, 3]
https://orcid.org/0000-0003-1842-6432

GILVANÉIA S. SANTOS[1]
https://orcid.org/0000-0002-5075-6872

ROBSON A.A. DA SILVA[1]
https://orcid.org/0000-0003-1361-1591

[1]Universidade Federal da Bahia, Instituto Multidisciplinar em Saúde, Campus Anísio Teixeira, Rua Rio de Contas, 58, Bloco 17, Lote 58, Candeias, 45029-094 Vitória da Conquista, BA, Brazil

[2]Universidade Federal do Sul da Bahia, Centro de Formação em Ciências da Saúde, Praça Joana Angélica, 58, São José, 45988-058 Teixeira de Freitas, BA, Brazil

[3]Universidade Estadual do Sudoeste da Bahia/ UESB, Departamento de Ciências da Saúde, Campus Vitória da Conquista, Estr. Bem Querer, Km 04, 45031-300 Vitória da Conquista, BA, Brazil

Correspondence to: **Robson Amaro Augusto da Silva**
E-mail: robson.amaro@gmail.com, ramaro@ufba.br

Author contributions

Paulo H. B. Lima: Conceptualization, Validation, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing. Israel S. Ribeiro: Term, Conceptualization, Methodology, Validation, Investigation. Caroline V. Gonçalves: Validation, Investigation, Data Curation. Maria P. L. Galantini and Igor P. R. Muniz: Validation, Investigation, Data Curation. Gilvaneia S. Santos: Term, Conceptualization, Methodology, Resources, Supervision. Robson A. A. da Silva: Term, Conceptualization, Methodology, Resources, Supervision, Project administration.