Acute and Chronic Effects of Exercise in Health

Cognitive screening and depressive symptoms in hypertensive and diabetic women

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Abstract - Aim: The objective of this study was to compare the global cognitive function and depressive symptoms in hypertensive and/or diabetic middle-aged and elderly women (52-76 years old). **Methods:** Sixteen participants with hypertension (HT) and 12 with hypertension and type 2 diabetes mellitus (HT+DM) were included; sociodemographic data, anthropometric measurements, and blood pressure were analyzed, and questionnaires for cognitive screening (Mini-Mental State Examination - MMSE) and depressive symptoms (Geriatric Depression Scale - GDS-30) were administered. For statistical analysis, independent Student's t-test, chi-square test (dichotomous variables), and the Mann-Whitney test (ordinal variables) were used and $p < 0.05$ was adopted. **Results:** Results indicate that there were no significant differences pertaining to depressive symptoms (HT = 7.4 ± 5.5; HT+DM = 10.2 ± 4.6 points; p = 0.1658) and global cognitive function (HT = 22.3 ± 4.2; HT+DM = 21.0 ± 3.2 points; p = 0.4015) between hypertensive women and hypertensive and diabetic women, contradicting the hypothesis that the presence of two comorbidities would intensify cognitive impairment and mental health. However, clinically relevant cognitive decline (HT = 63%; HT+DM = 75%; $\chi^2 = 0.4834$) and depressive symptoms (HT = 38%; HT+DM = 33%; $\chi^2 = 0.8199$) were found in both groups. **Conclusion:** It has been shown that the presence of two comorbidities: type 2 diabetes mellitus and hypertension, does not intensify cognitive impairment and mental health when compared to hypertension alone in middle-aged and elderly women.

Keywords: elderly, cognitive function, comorbidity, type 2 diabetes mellitus, hypertension.

Introduction

The aging process is directly associated with key physiological, morphological, and psychological changes that contribute to the loss of functional capacity, autonomy, and quality of life. In this sense, arterial hypertension, and type 2 diabetes mellitus (T2DM) are conditions that commonly affect individuals aged 60 years or over[1]. In addition, changes in mental health are observed, in which depression, cognitive deficit, and dementia are among the most prevalent disorders[2].

Depression being a risk factor for cognitive decline is well established in the literature, with evidence indicating that depressive symptoms are common in diabetic patients with a 24% high risk of developing the comorbidity[3,4]. Some studies have suggested that the hypothalamic-pituitary-adrenal (HPA) axis is deregulated in people with depression[5,6] and cognitive decline[7,8]. In fact, high serum cortisol was associated with low brain volumes and impaired memory in asymptomatic younger to middle-aged adults, with the association being evident particularly in women[9]. Associated with this is the fact that the HPA axis also appears to be altered in individuals with T2DM, causing hormonal imbalance and elevated levels of cortisol, a common biomarker of depression and diabetes[6,10,11].

Studies suggest that diabetes is an important risk factor for cognitive decline and motor dysfunction due to progressive muscle atrophy[12,13]. A study published by Strachan et al.[14] suggests that the effects of T2DM on cognition are multifactorial, reflecting the metabolic com-

plexity of diabetes. Acute hyperglycemia could cause reduced cognitive function, mainly decrements in working memory and attention. Patients with hyperglycemia also experienced reduced happiness and energy levels, and their levels of tension rose. In addition, factors such as hypertension, dyslipidemia, systemic inflammation, hyperinsulinemia, accumulation of advanced glycation end products (AGEs), depression, and dysregulation in the HPA axis may contribute to the cognitive decline associated with T2DM. The mechanism underlying these effects is unclear; however, it has been discussed that acute changes in blood glucose concentration could alter the regional cerebral blood flow and also cause osmotic changes in the cerebral neurons, as well as insulin resistance and chronic hyperglycemia that might impair cognition by promoting cerebral microvascular disease[14].

Similarly, hypertension has been associated with cognitive impairment. Patients with hypertension present lower performance in several domains of cognition, such as global cognition, memory, executive function, attention, and processing speed, than patients who are normotensive[15]. In addition, the low performance in cognitive tests intensifies with the severity of hypertension. Hereupon, researchers pointed out that blood pressure could be an early biomarker for cognitive impairment in individuals without dementia or stroke[16]. The mechanisms that explain the relationship between high blood pressure and cognitive impairment are not completely elucidated, and some evidence indicates that exposure to hypertension could damage the brain microcirculation, causing cognitive impairment[16,17].

In terms of epidemiology, the prevalence of hypertension in 65 years old corresponds to 65%[18], while dementia is approximately 8%, mainly in women that live longer than men[19,20]. Given the increased life span, women are becoming a growing body of the population to spend a significant period at an age associated with increased cardiovascular and dementia risk. Indeed, endogenous estrogen is an innate protection in women that is lost at the menopausal transition when cardio- and cerebro-vascular risk increases to reach that of the male population[21].

Considering the high prevalence of hypertension with aging, the additional presence of diabetes could contribute to impaired mental health and cognitive decline, especially in middle-aged and elderly women. Thus, this study aimed to compare the global cognitive function and depressive symptoms in women with diabetes and/or hypertension. Additionally, analyses of the association between the parameters were included. The hypothesis is that the presence of two comorbidities, hypertension and diabetes, could intensify cognitive impairment and affect mental health, which could point out the importance of early screening in women affected by both conditions.

Methods

Ethical aspects

The study was approved by the Research Ethics Committee of the Universidade Estadual do Sudoeste da Bahia (CAAD nº 27221414.3.0000.0055), respecting the ethical precepts of the resolution of the National Health Council, and an informed consent form was obtained from all the participants.

Participants

This was a cross-sectional study conducted with participants of the *Núcleo Interdisciplinar de Estudos e Extensão em Cuidados à Saúde da Família em Convibilidade com Doenças Crônicas* (Interdisciplinary Center for Studies and Extension in Family Health Care in Convenience with Chronic Diseases - NIEFAM), in Jequié, Bahia, Brazil. Recruitment took place between August and September 2018. Participants included 28 women, aged 52 to 76 years, previously diagnosed with T2DM and/or hypertension, with pathologies controlled by drugs and who attended the NIEFAM's continuous program of functional training, conducted three times a week for at least one year. The participants were classified as type 2 diabetics and/or hypertensive, according to diagnosis previously made by the specialized doctors from the Brazilian primary health care system and following the national guidelines[22,23]. Failure to complete one or more survey questionnaires was considered an exclusion criterion.

Groups

The women were divided into two groups according to their diagnosis, 16 participants with hypertension (HT) and 12 with hypertension and diabetes mellitus (HT +DM). Information on the pathologies and sociodemographic data, such as age, education, and marital status, were collected through a structured anamnesis. In addition, participants' anthropometric measurements and blood pressure were recorded, and cognitive screening and depressive symptoms assessment was carried out in both groups.

Anthropometric assessments

Body mass (Tech Line® portable digital scale), height (Sanny® fixed stadiometer), and waist, as well as abdominal and hip circumferences (Cescorf® anthropometric tape measure), were measured. The abdominal circumference was measured as the largest perimeter between the last rib and the iliac crest, usually located at the level of the umbilical scar; hip circumference was measured at the level of maximum protrusion of the gluteal muscles, above the gluteal fold; and waist circumference was performed at the natural level of the

waist, considering the smallest perimeter above the iliac crest and below the last rib[24]. Body Mass Index (BMI) was determined by the body mass/height ratio[2], and the calculation of waist to hip ratio (WHR) was obtained by dividing the waist circumference (cm) by hip circumference (cm).

Blood pressure measurement

To measure resting blood pressure (BP), the procedures recommended by the current Brazilian Guidelines on Hypertension were followed[22]. After remaining at rest for 20 min in a sitting position and quiet environment, the measurement was performed on the left arm by an auscultatory technique using a stethoscope and aneroid sphygmomanometer on three non-consecutive days, in which the mean of the measurements was considered the resting BP.

Depressive symptoms evaluation

Depressive symptoms were investigated using the Geriatric Depression Scale (GDS-30)[25]. The instrument comprises 30 items on feelings and behaviors that occurred in the last week, with dichotomous responses (yes/no) ranging from 0 to 30 points. Results equal to or above 10 points suggest the presence of clinically relevant depressive symptoms.

Cognitive function assessment

The Mini-Mental Status Examination (MMSE)[26] is a cognitive screening tool used worldwide for global cognition. The test presents a sensitivity of 85% and specificity of 90% for the detection of dementia[27]. In Brazil, the MMSE was translated into Portuguese by Bertolucci et al.[28]. The instrument includes questions related to concentration, orientation, language/praxis, memory, and attention. The score can vary from 0, which indicates the greatest degree of cognitive impairment of the individuals, up to a maximum of 30 points, which corresponds, in turn, to a better cognitive capacity. The participants had heterogeneous educational levels; hence, cutoffs were adjusted to the level of education. The following cutoff scores were used to identify abnormal cognition in this study: ≤20 for those illiterates; ≤25 for those with 1-4 years of education; ≤26.5 for those with 5-8 years of education; ≤28 for those with 9-11 years of education; and ≤29 for those with ≥11 years of education[29].

Statistical analysis

Central tendency and dispersion values were used according to data distribution and verified by the Shapiro-Wilk test. Then, the groups were compared by Student's *t*-test for independent samples. The chi-square test (χ^2) was used for dichotomous categorical variables (classification in the GDS and the MMSE) and the Mann-Whitney test for ordinal categorical variables (education, marital status, BMI, and WHR). According to the data distribution, the Spearman test was chosen to analyze the correlation between cognitive function and depressive symptoms. The data were analyzed using the statistical packages GraphPad Prism version 5.0 and Statistical Packages for the Social Sciences (SPSS) version 20. For all analyses, $p < 0.05$ was adopted.

Results

Table 1 describes the sociodemographic, anthropometric, and hemodynamic information, in which no differences between the groups are verified. The participants had a mean age of 64.1 ± 7.0 years for the HT group, 69.1 ± 7.4 years for the HT+DM group, and both groups were overweight, considering the BMI classification. Most participants had one to four years of schooling (HT: 43.9%; HT+DM: 50.0%). Regarding marital status, 68.8% of the HT group was married, while 58.8% of the HT+DM group was widowed.

Resting BP was at normal levels according to the Brazilian Guideline on Hypertension[22], and since this was a population with hypertension, all participants had their pathology controlled by medication.

Table 1 - Characteristics of the participants.

	HT	HT+DM	p-value
n	**16**	**12**	
Age (years)	64.1 ± 7.0	69.1 ± 7.4	0.0804
Education			
Illiterates	0 (0%)	3 (25.0%)	0.0700
1-4 years	7 (43.8%)	6 (50.0%)	
5-8 years	2 (12.5%)	1 (8.3%)	
9-11 years	6 (37.5%)	2 (16.7%)	
Marital status			
Single	1 (6.3%)	1 (8.3%)	0.1890
Married	11 (68.8%)	4 (33.3%)	
Widowed	4 (25.0%)	7 (58.3%)	
Body mass (kg)	69.3 ± 10.8	65.7 ± 10.6	0.3761
BMI (kg/m^2)	28.7 ± 3.8	27.7 ± 4.5	0.5444
Abdominal circumference (cm)	100.9 ± 10.3	99.2 ± 9.7	0.6485
Waist circumference (cm)	93.5 ± 10.9	93.2 ± 10.9	0.9450
Hip circumference (cm)	104.7 ± 8.5	101.8 ± 9.8	0.4021
WHR	0.89 ± 0.08	0.92 ± 0.08	0.4912
SBP (mm Hg)	125.6 ± 8.1	126.7 ± 10.0	0.7796
DBP (mm Hg)	76.9 ± 6.0	76.7 ± 7.1	0.9385

HT: Hypertensive group; HT+DM: Hypertensive-diabetic group; BMI: Body Mass Index; WHR: Waist to hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. Mann-Whitney test (categorical variables) and Student's t-test for independent samples (ordinal variables).

Regarding the results obtained by the GDS-30, 4 participants with HT+DM presented clinically relevant depressive symptoms, with a group mean corresponding to 10.2 ± 4.6 points, while 6 participants with HT presented depressive symptoms, with a group mean corresponding to 7.4 ± 5.5 (p = 0.1658; χ^2 = 0.8199), as shown in Figure 1. There was no significant difference between the groups, both for absolute values and classification of the groups based on the GDS-30 cutoff score.

In the cognitive evaluation using the MMSE, the HT group reached 22.3 ± 4.2 points, with 63% of the group below the cutoff point, and the HT+DM group, in turn, reached 21.0 ± 3.2 points, with 75% below the cutoff point (χ^2 = 0.4834). There was no significant difference between the groups, both for the absolute values obtained by the MMSE and cutoff scores according to the schooling proposed by Brucki et al.[29], as well as the association between cognitive functions and depressive symptoms were verified. No significant correlation was found (r_s = −0.11; p = 0.56).

Discussion

This study aimed to compare the global cognitive function and depressive symptoms in middle-aged and elderly women with hypertension and women with hypertension and diabetes. The main results indicated that there was no difference between the groups, contradicting the hypothesis that the presence of two comorbidities could intensify cognitive impairment and mental health. However, despite the absence of a significant difference,

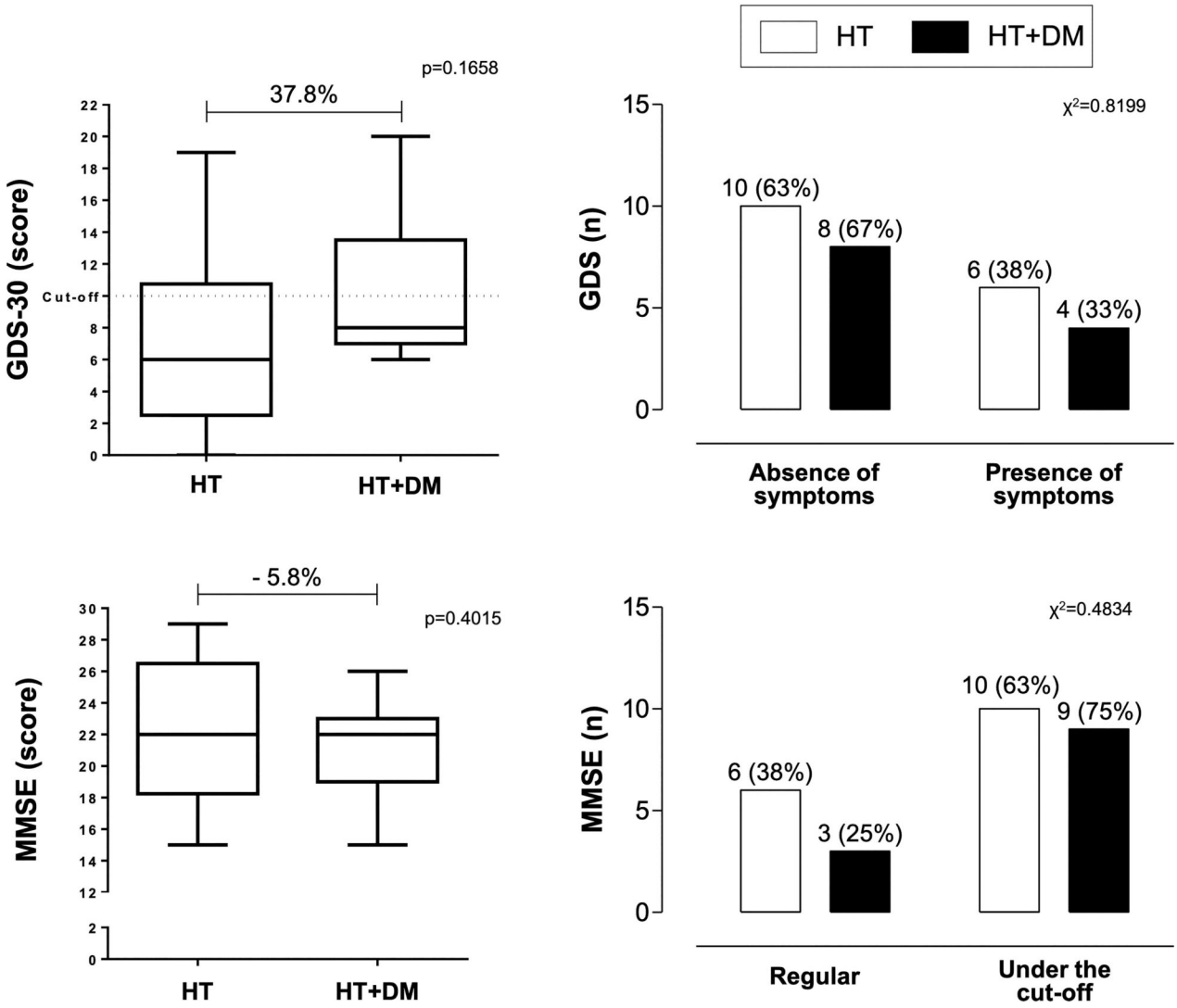

Figure 1 - Cognitive screening and depressive symptoms in hypertensive and diabetic women physical activity practitioners. HT: Hypertensive group; HT+DM: Hypertensive-diabetic group; GDS-30: Geriatric Depression Scale; MMSE: Mini-Mental State Examination. Chi-square test (dichotomous categorical variables) and Mann-Whitney test (categorical variables).

women with cognitive decline and clinically relevant depressive symptoms were present in both groups.

It has been estimated that 10% to 30% of the Brazilian elderly population has impairment of cognitive functions or depressive symptoms[30], and the female gender was the sociodemographic factor most consistently associated with depressive disorders[31]. In a recent systematic review, Gutiérrez-Rojas et al.[31] highlighted that the prevalence of depressive symptoms is expressed differently between genders, with greater predominance in females, indicating differences in the expression of serotonin transporter polymorphisms associated with depression[32], as well as in the response of cellular immunity to stress and depression[33].

The presence of depressive symptoms or a clinical picture of depression may be directly related to cognitive losses[34,35], which reinforces the need to verify how these variables present themselves in populations susceptible to the onset of mental health changes. In this study, 63% of the participants in the group with hypertension presented MMSE results below those established in the literature, while in the group with hypertension and diabetes, this percentage was 75%. Although there was no significant difference between the groups, the values draw attention and reinforce the high prevalence of cognitive losses in middle-aged and elderly women with some type of chronic disease.

The score obtained in the MMSE were corrected adopting the cutoffs according to the level of education, in which some questions depend on writing, capacity to calculate, reading, and other demands related to previous learning. Considering the population in Brazil has heterogeneous educational levels, adjusted cutoffs were suggested to avoid false-positive results[36]. On the other hand, unexpected scores below the cut-off were found in the present study, indicating poor performance. Thus, given the extent of adoption of the test and its sensitivity and specificity, glucose levels and blood pressure could influence cognitive performance. Previous studies demonstrated that insulin resistance had a relation to the brain metabolism in older adults with prediabetes[37], in which insulin resistance is high in mild cognitive impairment and Alzheimer's disease[38]. On the other hand, patients who are normotensive perform better than patients with hypertension in different types of cognitive tests, including MMSE[15]. Indeed, in patients with preserved MMSE, high blood pressure values were associated with a reduction of cognitive function[39]. A previous study showed that in postmenopausal elderly women aged 60 to 84 years, hypertension and T2DM were associated with cognitive decline[40]. In the aforementioned study, arterial hypertension and DM were analyzed in isolation with cognitive decline, which partially limits the joint influence of the diseases on cognition.

However, T2DM and hypertension jointly further impaired executive functions in middle-aged women when compared to normotensive diabetics, revealing the marked effect on cognitive decline in the presence of both diseases[41]. In contrast, a comparison, including a group of women with diabetes without hypertension, was not performed in the present study, while in Petrova et al.'s study[41] there was no hypertension group without diabetes, which could contribute to a better understanding.

Although the mechanisms between dementia, hypertension, and DM need to be clarified, it is recognized that the last two represent important risk factors for the development of Alzheimer's disease (AD)[42]. Individuals with T2DM are twice as likely to develop AD than patients who present only insulin resistance[43,44]. Similarly, among the cardiovascular risk factors, hypertension in middle age is considered a major population attributable fraction for the development of dementia[45]. The mechanisms on how hypertension and T2DM are linked to cognitive functions are complex, and its understanding is limited by a lack of research. One of the ways proposed to explain the relationship between cognitive decline and cardiovascular diseases are the changes arising from aging in the blood vessels and inflammatory response[40]. Aging *per se* contributes to an increased inflammatory response in the central nervous system, in which there is proliferation and activation of the astrocytes and microglia[46]. These cells are considered part of the neurovascular unit, and together with the cerebral blood flow, are essential for its proper functioning[40].

Regarding the presence of depressive symptoms, when the study data are presented in percentage values, it is observed that 37.5% of participants in the HT group and 33.3% in the HT+DM group presented relevant symptoms. There were no statistical differences between the groups. Controversially, a comparative study between elderly individuals with T2DM and a control group without the disease, with a mean age of 68.8 years, identified that those diagnosed with DM showed worse cognitive performance and high GDS scores[47]. Although this association is concrete, the cause and effect relationship between the two clinical conditions is not adequately explained[48]; however, two main theories explain this relationship: first, it may be related to the increase of catecholamines in individuals with depressive symptoms, triggering the increase in blood glucose levels; and second, considering the neurochemical effects on the central systems, decreasing the activity of some amines, such as serotonin, dopamine, and norepinephrine, which are related to the mood state[3].

There is evidence that the presence of depression in individuals with hypertension was associated with a high risk of stroke and mortality from cardiovascular events[49]. Santos et al.[50] suggest that the presence of depressive symptoms can negatively impact the quality of life of

individuals with hypertension. Furthermore, a higher prevalence of depressive disorders was found in individuals with hypertension compared to the control group without the pathology, as well as an association between high diastolic BP and low levels of physical activity[51]. Thus, the presence of arterial hypertension in women across both groups in the present study may have been a factor that contributed to there being no differences in the results of depressive symptoms, regardless of associations with another comorbidity.

The main limitations of this study are the absence of a control group for comorbidities, such as women who are normotensive without T2DM, as well as more refined measures to evaluate cognitive screening. Thus, the results of the present study should be interpreted with caution. Additionally, further studies adopting the sample size calculation, control group, objective measures of cognition, such as neuroimage, assessing physical activity levels, as well as the time of engagement in physical activities, and the medicine in use by the participants could clarify the discussion about cognitive status and depressive symptoms associated with hypertension and diabetes in women. On the other hand, the tests used in the present study to evaluate global cognition and depressive symptoms could represent options for public health actions when, considering simple, accessible, and reliable tools that could be replicated in other locations. To monitor the effects of aging associated with chronic diseases on mental health, the MMSE and GDS are valuable instruments for the early screening of women with diabetes and/or hypertension.

To the best of our knowledge, few studies investigated the relationship between comorbidities and depressive symptoms or cognitive performance, indicating the lack of scientific literature. Considering that the aging process associated with hormonal changes may leave the female gender more susceptible to the development of cardiovascular and metabolic diseases, further studies are needed to evaluate the association between comorbidities in women's mental health-related aspects (Figure 2).

Although previous studies show that cardiovascular risk factors do not necessarily undo the beneficial effects of exercise on cognition in individuals with cognitive impairment[52], regular physical activity remains an auxiliary treatment for chronic, cardiovascular, and mental diseases. The participants in our study consisted of women who had been exercising for at least one year, and it is feasible that the non-observation of a difference between HT and HT+DM could be based on the fact that physical exercise contributes to preventing great impairment of cognitive function in HT+DM. Although not to focus on this study, it is well demonstrated in the literature that encouraging the practice of physical activity to promote active aging in middle-aged women may contribute to the prevention of other diseases, prolong autonomy, and in some cases, prevent or delay the progressive decline of the dementia process, and help to maintain quality of life and mental health[53-55].

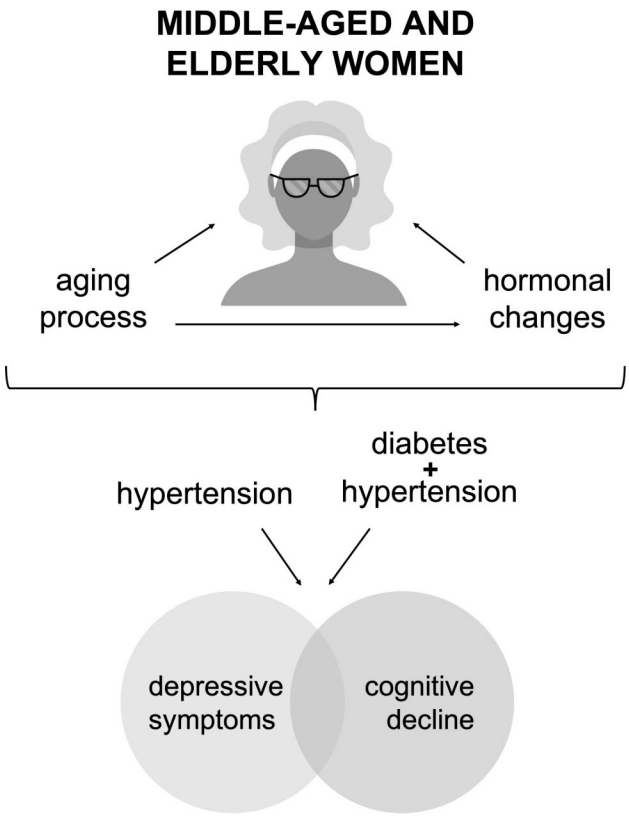

Figure 2 - Middle-aged and elderly women are more susceptible to the development of cardiovascular and metabolic diseases due to the aging process associated with hormonal changes after menopause transition. However, it has been shown that the presence of two comorbidities: T2DM and hypertension, does not intensify cognitive impairment and mental health, when compared with hypertension alone.

Conclusion

The results of this study indicate that there was no difference in depressive symptoms and global cognitive function between middle-aged and elderly women with hypertension and women with hypertension and diabetes. However, despite the absence of a significant difference, cognitive decline and clinically relevant depressive symptoms were found in both groups, drawing attention to the fact that regardless of the condition, it was important to carry out an early screening of women with diabetes and/or hypertension.

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