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ALZHEIMER'S DISEASE, GLYCEMIA AND GLYCATED HEMOGLOBIN - REVIEW ALZHEIMER'S DISEASE AND DIABETES

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Abstract: Introduction: Alzheimer's disease (AD) is a multifactorial syndrome and diabetes and decreased brain glucose metabolic rate may be involved in the onset and progression of AD. Changes in insulin signaling pathways and decreased brain energy resulting from low glucose availability are factors that favor AD. Objective: To evaluate the relationship between glycemia, diabetes and AD. Method: Descriptive systematic review using the following descriptors: Alzheimer's disease and blood glucose. Twenty-five original articles were selected, all studies were in human modal with evidence of Alzheimer's disease and the analysis of glycemia or/and glycated hemoglobin (HbA-1c). Results: 1,165 individuals with a mean age of 72.4 years were identified. Of these, 54.6% had normal blood glucose and 98.1% had HbA1-c in the prediabetes and diabetes range. Considering glycemia and HbA1-c parameters, 16.6% were classified as diabetic. Conclusion: The data showed the association between hyperglycemia, increased HbA-1c and pre-diabetes and diabetes with AD. They also suggest that, as AD is clinically manifested years after the onset of diabetes, maintaining normoglycemia and preventing the onset of pre-diabetes and diabetes may minimize the development of AD.
Keywords: Alzheimer's Disease, Blood Glucose, Glycated Hemoglobin, Dementia, Diabetes

INTRODUCTION

Alzheimer's disease (AD) is a multifactorial and progressive neurodegenerative disease that affects millions of people. Neurodegeneration leads to the progressive loss of nervous system functions, especially cognitive functions such as language, judgment, attention and executive functions, culminating in dementia[1,2]. As defined by the Brazilian Society of Geriatrics and Gerontology[3], "AD is a syndrome with memory impairment (altered ability to learn new information or remember old information) associated with impairment in at least one of the cognitive functions (language, gnosias, praxias or executive functions) and which interferes with the individual's social and/or professional performance and represents a decline in relation to the previous level of functioning."

AD is the most common form of dementia in the elderly. The name "Alzheimer's disease" comes from the first study published on the subject by the German psychiatrist and neuropathologist Alois Alzheimer[1]. It is associated with genetic factors, with mutations in the amyloid precursor proteins presenilin1 and presenilin2 and modifiable, non-genetic risk factors, such as insulin resistance and diabetes[4].

MOLECULAR BASIS OF ALZHEIMER'S DISEASE

Numerous studies have been carried out to uncover the cascade of events that lead to AD and to counteract the dysregulation of brain homeostasis, mainly through nutritional, environmental and pharmacotherapeutic approaches. The aim is to prevent the onset and progression of the disease.

Studies into the molecular basis of AD indicate some hypotheses[1], such as (a) hypothesis of alterations in neurotransmitters-decrease in cholinergic neurons and in the expression of the enzyme choline acetyltransferase and increase in the enzyme acetylcholinesterase, which successively catalyze the synthesis and degradation of the neurotransmitter acetylcholine, leading to depletion of acetylcholine[2]; activation of glutamate receptors as a result of alterations in cellular energy metabolism, leading to alterations in calcium homeostasis and neuronal apoptosis; (b) Aβ-amyloid plaque formation hypothesis - aggregation of peptides

resulting from irregular enzymatic cleavage of the amyloid precursor glycoprotein[2]; (c) neurofibrillary degeneration hypothesis-hyperphosphorylation and decreased affinity of TAU proteins for microtubules, destabilizing the integrity of the cytoskeleton and precipitating proteins in the cytosol[2]; (d) oligomeric hypothesis - aggregation of Aβ-amyloid peptides and TAU proteins into oligomers alters synaptic plasticity and leads to neuronal death, a hypothesis that justifies the neurotoxicity of Aβ-amyloid peptides[4]; (e) metallic/oxidative stress hypothesis - redox ions, such as copper(II), iron(III); non redox-active ions, such as zinc(II); antioxidant ions, such as selenium and some ions considered toxic, such as aluminum, lead and mercury, favor the aggregation of Aβ-amyloid peptides and an increase in free radicals and oxidative stress in the brain; (f) diabetes hypothesis - decrease in insulin receptors and concentration[5], (g) energy hypothesis - decrease in cerebral glucose metabolic rate and mitochondrial dysfunction[4,5,6] and (h) hypothesis of altered intestinal microbiota[2]. Figure 1 shows the interaction between the hypotheses proposed to explain the molecular basis of AD.

The complexity of the pathology and the slow involvement of the nervous system, from the first biochemical alterations until the clinical stage is evident, indicates that different hypotheses may be associated in the development of AD. The mechanism of formation of TAU protein aggregates and the formation of Aβ-amyloid plaques may be due to oxidative stress and insulin resistance. TAU protein phosphorylation and the formation of Aβ-amyloid plaques may contribute to or be formed as a result of the dysregulation of metal homeostasis in synapses. However, the order of the factors that lead to AD is questionable, considering that the toxicity of the accumulation of Aβ-amyloid peptides could lead to oxidative stress and insulin resistance in the brain.

On the other hand, disturbances in the intestinal microflora result in increased production of cytotoxic deoxycholic bile acid and immunogenic lipopolysaccharides and amyloids that can be deposited in the brain, leading to an increase in reactive oxygen species, neuroinflammation, insulin resistance and neurodegeneration. The alteration of the intestinal microbiota also influences the formation and absorption of the neurotransmitters serotonin and GABA, increases the production of nitric oxide and causes axonal degeneration, neuroinflammation, with an increase in pro-inflammatory cytokines and reactive oxygen species and neurodegenerative disorders[2].

Altered glucose metabolism, mitochondrial dysfunction, oxidative stress, altered calcium homeostasis and insulin resistance may be the triggering events for the other mechanisms proposed for the development of AD.

Insulin resistance in the brain can impair intracellular signaling processes and facilitate increased toxicity of amyloid Aβ peptides, Tau hyperphosphorylation, oxidative stress and neuroinflammation, resulting in neurodegeneration. Diabetes, resulting from insulin resistance, leads to decreased insulin signaling in the central nervous system, altering brain metabolism and influencing memory processing, brain morphology and synaptic communication[7,8].

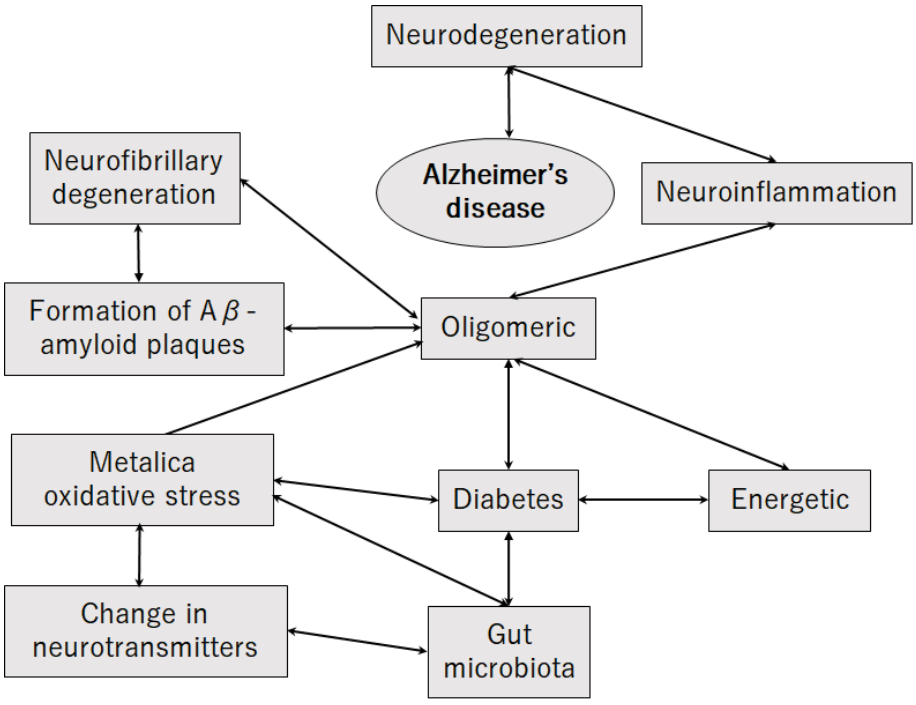

Figure 1: Molecular basis of AD. Prepared by the authors.

INSULIN RESISTANCE, DIABETES AND ALZHEIMER'S DISEASE

Insulin, a hormone produced by the beta cells of the islets of Langerhans in the pancreas, is secreted into the blood plasma. The cerebral influx of insulin of plasma origin occurs through the blood-brain barrier, mediated by an active transport system by specific receptors[7,8]. There is also evidence of insulin synthesis in the central nervous system[7]. Insulin acts by binding to glycoprotein receptors on cell membranes. In the central nervous system, insulin binding is greatest on receptors in the olfactory bulb, cerebral cortex and hippocampus[8].

In brain cells, the insulin-linked receptor undergoes molecular modifications and signals intracellular changes such as glucose homeostasis and energy metabolism, which may explain the increased susceptibility to AD among diabetics. The receptors also signal protein synthesis and amyloid clearance and the activity of enzymes related to TAU protein phosphorylation. Insulin also regulates calcium influx, the expression and levels of acetylcholine, norepinephrine, epinephrine, GABA, NMDA and AMPA and the preservation of synaptic connections essential for memory. Dendrite formation, neuronal integrity, apoptosis and neurogenesis are related to perfect insulin-mediated signaling[5,7,8].

The decrease in the synthesis of anti-amylogenic proteins and the consequent increase in Aβ-amyloid peptides are due to the decrease in insulin in the central nervous system. Aβ-amyloid peptides can also competitively inhibit insulin binding to membrane receptors, which results in low functionality of insulin receptors. Taken together, these data suggest that insulin resistance may be a potential target for the prevention and treatment of AD

Glucose, the main energy source used by the brain[9], comes from blood plasma and from the conversion of astrocyte glycogen into glucose, which is stimulated by the activation of glial adrenoceptors. Glial glucose uptake for neuronal utilization occurs via insulin-

sensitive type 1 transporters (GLUT1)[7], whose expression is regulated by plasma glucose[9]. Therefore, the balanced neuronal glucose level depends on astrocytes and glucose transporters that are expressed in glial cells[7]. Thus, cerebral insulin resistance, due to a decrease in the activity of GLUTs, also reflects a decrease in the absorption and consequent neuronal energy metabolism of glucose. Therefore, insulin resistance and impaired insulin signaling not only affect systemic blood glucose levels, but also cause various degenerative processes in neuronal cells.

Neuronal glucose uptake is not totally dependent on insulin because neurons have insulin-independent glucose transporters; thus, insulin resistance partially impairs neuronal energy metabolism and mainly affects insulin signaling pathways. The malfunctioning of the insulin signaling pathways and the decrease in energy resulting from the low availability of glucose are factors that favor AD. It is likely that AD arises and manifests clinically years after the onset of insulin resistance and diabetes, providing possible explanations for the connection between diabetes and AD[7,8] and making it possible to implement strategies to prevent the development of AD.

GLYCEMIA, DIABETES AND ALZHEIMER'S DISEASE

Peripheral insulin resistance and hyperglycemia, observed in diabetes, are associated with a higher risk of dementia and AD[9,10,11,12,13]. Lower cerebral glucose metabolic rates have been observed in individuals with increased serum glucose levels[14]. Peripheral hyperglycemia, increased insulin secretion and insulin resistance lead to the deposition of amyloid plaques in the brains of cognitively normal adults. Imaging studies suggest that amyloid plaques begin to form 10-15 years before the onset of clinical dementia[9,11]. Therefore, individuals with cerebral amyloid plaques, in the absence of cognitive alterations, are at greater risk of cognitive decline, cerebral atrophy and progression to AD.

DIET AND ALZHEIMER'S DISEASE

It is well established that diets with a higher intake of sucrose (sugar), high glycemic index foods and carbohydrates in general are linked to hyperglycemia, insulin resistance and type 2 diabetes, risk factors for AD and cognitive decline.

Diets containing the nutrients vitamin B-12, vitamin D, zinc and omega-3 fatty acids have been associated with lower deposition of Aβ amyloid peptides. On the other hand, increased brain amyloid is associated with higher intake of sugary drinks and high glycemic index diets[11]. The Mediterranean diet, with a low glycemic index, moderate alcohol consumption and the intake of fats with omega-3 fatty acids and vegetables with a high level of folate and selenium, may decrease the risk of AD[4].

Although brain cells preferentially use glucose as an energy source, in situations of glucose deficit, such as prolonged fasting and diabetes, neurons start to use ketone bodies and lactate as an energy substrate.

Ketone bodies, synthesized in the liver mainly from fatty acids, correspond to acetoacetate and β-hydroxybutyrate molecules. These are released into the blood and used by cells in extrahepatic tissues that have mitochondria, because the energy metabolism of ketone bodies occurs through the Krebs cycle. Insulin resistance impairs glucose uptake but does not interfere with the cellular uptake of ketone bodies. Thus, in AD, the uptake of ketone bodies by brain cells is not altered and they can be used to minimize neuronal energy deficiency. Ketogenic interventions, which increase the availability of ketone bodies to the brain, improve some

cognitive outcomes in AD[15]. Ketogenesis, resulting from normal plasma glucose levels, has been shown to be successful for treating diabetes and AD[16].

The aim of this study was to evaluate, through a systematic review of the literature, the relationship between glycemia, diabetes and AD. This relationship can support the proposal of dietary planning, considering that it is a modifiable risk that can influence the deposition of cerebral Aβ-amyloid peptides and minimize the development of AD.

MATERIAL AND METHOD

This article is a descriptive systematic review of works published in the *Scientific Electronic Library Online* (SciELO) and *U.S. National Library of Medicine* (Pubmed) databases, following the method proposed by the *standard check-list Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*. The descriptors used were: *Alzheimer's disease [MeSH] and Food Intake [MeSH]*.

The articles for the statistical analysis were selected at first by title and abstract, and then by proof of Alzheimer's disease and quantitative analysis of blood glucose in the form of glycemia and/or glycated hemoglobin (HbA-1c). Original articles were included, with studies on human beings and excluded were those that evaluated athletes or pregnant women, as well as those that dealt with other subjects, other diseases, diagnostic tests, review articles, animal studies and articles not available in full. The flowchart for selecting the material used is described in Figure 2.

Data on the number of individuals, age, blood glucose and HbA-1c values were extracted from the selected studies, organized in *Microsoft Excel* 2016 spreadsheets, analyzed using descriptive statistics using the statistical 2022 *software* and a significance level of 95% ($p < 0.05$) and presented in tables and figures shown in the results of this study.

RESULTS

The results were analyzed by compiling data from journals that identified blood glucose and/or HbA-1c values in 1,165 individuals with diagnosed AD. The blood glucose and HbA-1c values indicated by the Brazilian Diabetes Society[17] were used as a reference: fasting normoglycemia when plasma glucose concentration is less than 100 mg/dL and HbA-1c is less than 5.7%; pre-diabetes or increased risk for diabetes, with glycemia ≥ 100 and < 126 mg/dL and HbA-1c ≥ 5.7 and < 6.5% and established diabetes with glycemia ≥ 126 mg/dL and HbA-1c ≥ 6.5%.

The tables below show the data on blood glucose, HbA-1c, age and the number of individuals included in the studies. The data has been subdivided into individuals with normal blood glucose (Table 1), with blood glucose classified as pre-diabetic and with hyperglycemia, which leads to the classification of diabetics (Table 2).

Original data on number of individuals (n), age (years), glycemia (mg/dL, mean and standard deviation) and HbA-1c (%, mean and standard deviation) from the studies listed in the first column.

Original data on number of individuals (n), age (years), glycemia (mg/dL, mean and standard deviation) and HbA-1c (%, mean and standard deviation) from the studies listed in the first column.

The statistical analysis of the data as a whole, considering the average presented in each study, is shown in Table 3. The average age of the individuals was 72.4 (±4.2) years, and no significant difference was found in the age of the individuals in the glycemia, pre-diabetes and diabetes groups. The majority of individuals with AD had normal glycemia (54.6 %) and HbA1-c in the pre-diabetes range (53.3 %). There was a statistical difference ($p<0.05$) in blood glucose between the diabetes group and the other two groups.

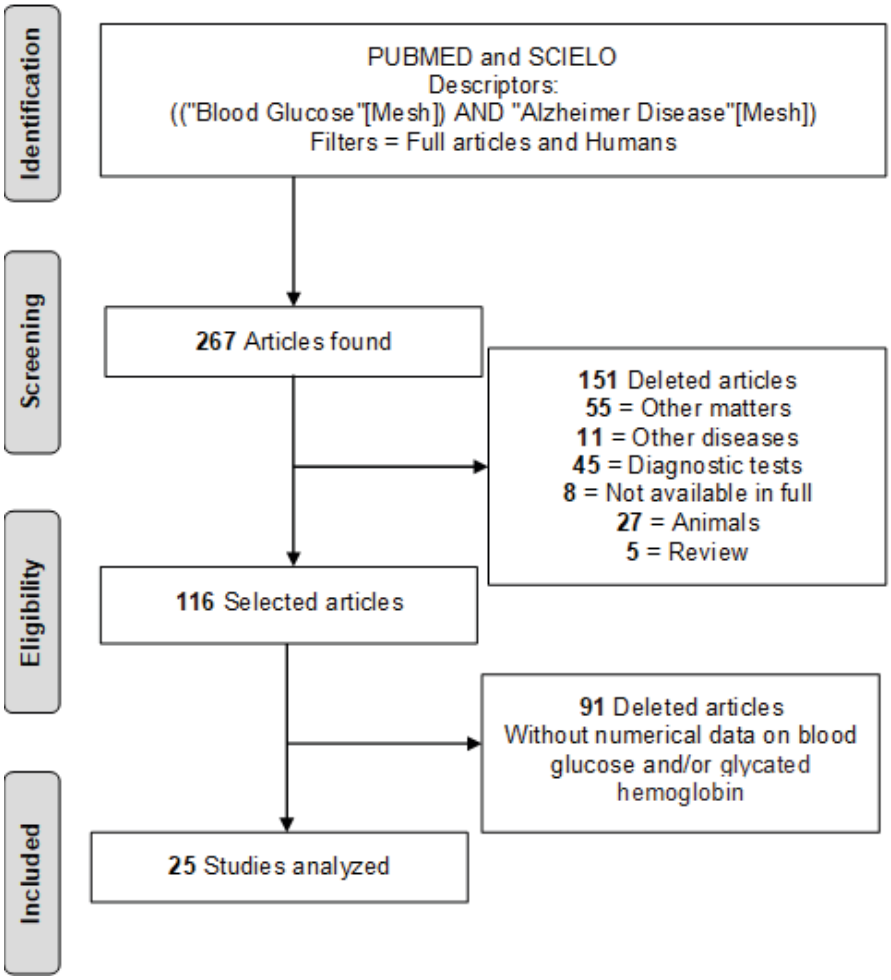

Figure 2: Flowchart of the selection of articles. Prepared by the authors.

STUDIES/GROUPS	INDIVIDUALS (n)	AGE (years)	BLOOD GLUCOSE (mg/dL)	HbA-1c (%)
Apostolova et al[18]	87	74,2 (5,3)	98,4 (15,8)	-
Craft et al[19]	10	69,1 (6,9)	99,5 (9,3)	5,2 (0,4)
Craft et al[20]	19	71,6 (9,5)	99,4 (12,2)	-
Craft et al[20]	12	73,1 (8,0)	98,7 (10,9)	-
Cutler et al[21]	6	67,0 (-)	84,3 (9,5)	-
Fisman et al[22]	9	-	95,3 (11,2)	-
Fujisawa et al[23]	108	72,6 (7,9)	85,2 (10,3)	-
Isik, Bozoglu[24]	40	76,9 (5,6)	93,5 (12,6)	-
Isik et al[25]	31	76,9 (5,6)	93,5 (9,8)	-
Ramdane et al[26]	150	75,3 (7,7)	88,9 (13,2)	-
Razay, Wilcock[27]	12	72,3 (-)	93,5 (12,6)	-
Razay, Wilcock[27]	12	73,1 (8,0)	98,7 (10,9)	-

Table 1 - Age, glycemia and HbA-1c of individuals with normal glycemia.

STUDIES/GROUPS	INDIVIDUALS (n)	AGE (years)	BLOOD GLUCOSE (mg/dL)	HbA-1c (%)
Burns et al[14]	31	75,8 (6,3)	101,9 (15,9)	-
Craft et al[19]	10	69,1 (5,9)	102,3 (13,8)	-
Craft et al[29]	32	72,0 (9,0)	104,8 (11,0)	-
Craft et al[30]	5	73,5 (3,0)	103,9 (2,1)	-
Craft et al[30]	17	74,6 (1,1)	101,6 (2,2)	-
Dominguez et al[10]	10	73,2 (6,2)	109,2 (26,5)	6,4 (1,4)
Dominguez et al[10]	29	73,3 (5,4)	-	6,0 (0,6)
Exalto et al[31]	58	71,0 (8,0)	-	5,7 (0,7)
Exalto et al[32]	61	73,0 (7,0)	100,7 (32,4)	5,9 (0,8)
Foley et al[33]	80	67,9 (9,4)	-	5,8 (0,6)
Foley et al[33]	27	67,9 (9,1)	-	5,9 (0,8)
Riviere et al[34]	6	82,3 (4,8)	104,0 (27,0)	-
Riviere et al[34]	13	78,2 (5,2)	105,9 (30,9)	-
Papas et al[35]	7	73,6 (4,7)	-	6,0 (0,3)
Thome et al[36]	15	69,7 (7,8)	-	5,8 (0,6)
Ogawa et al[38]	40	82,1 (6,0)	-	7,9 (1,5)
Padala et al[39]	8	67,6 (7,9)	-	8,4 (1,3)
Moran et al[12]	27	75,5 (6,2)	132,0 (41,9)	-
Chen et al[37]	30	65,4 (8,2)	142,1 (80,9)	11,2 (3,3)
Shimada et al[40]	103	70,7 (5,6)	147,1 (38,2)	9,7 (1,7)
Chen et al[37]	30	65,5 (8,3)	323,7 (84,5)	11,0 (3,2)
Chen et al[37]	30	65,7 (8,5)	325,5 (80,9)	11,2 (3,4)

Table 2 - Age, glycemia and HbA-1c of pre-diabetic and diabetic individuals.

	BLOOD GLUCOSE (mg/dL)			HbA1-c (%)		
	INDIVIDUALS		BLOOD GLUCOSE Mean (standard deviation)	INDIVIDUALS		HbA1-c % Mean (standard deviation)
	n	%		n	%	
Normoglycemia	487	54,6	94,1 (5,2)	10	1,9	5,2 (0,0)
Pre-diabetes	185	20,7	103,8 (2,5)	287	53,3	5,9 (0,2)
Diabetes	220	24,7	214,1 (90,4)	241	44,8	9,9 (1,3)

Table 3 - Comparative analysis of blood glucose and HbA-1c data from normoglycemic, pre-diabetic and diabetic individuals.

Blood glucose and HbA-1c data calculated from the means of the original studies and represented by mean and standard deviation (SD). *p<0.05 for the diabetes group compared to the normoglycemia and pre-diabetes groups.

DISCUSSION

By analyzing Tables 1 and 2 above, it was possible to see that most of the individuals who took part in the studies were over 60 years old. According to data from the Brazilian Society of Geriatrics and Gerontology[3], the worldwide prevalence of dementia increases with age, from 1.2% in the 65 to 69 age group to 16.4% in the 85 to 89 age group. In Brazil, it is estimated that AD affects 7.7 out of every 1,000 individuals over the age of 65. The preliminary, pre-clinical phase, with changes in neuronal proteins but no evidence of morphological or functional changes, can begin in the fourth decade of life.

The HbA-1c results (Table 3) indicate that the majority of individuals with AD (98.1%) had pre-diabetes and diabetes. HbA-1c enables early diagnosis of chronic hyperglycemia and also eliminates the need for fasting, which can be an error factor when assessing glycemia[41]. Considering the blood glucose results (table 3), 45.4% of individuals with AD can be classified as diabetic or pre-diabetic. The blood glucose values of the diabetic group were statistically different (p<0.05) from the group of individuals with normal blood glucose and pre-diabetics, confirming that 24.7% of individuals with AD have hyperglycemia. These data corroborate the hypothesis that hyperglycemia may be associated with the deposition of amyloid plaques in the brain and a greater risk of dementia and AD[9,10,11,12,13].

Since the diagnosis of diabetes since 2009 has been based on HbA-1c and fasting blood glucose values[42], it can be inferred that fasting blood glucose alone is not a sufficient parameter for assessing diabetes. Therefore, of the total number of individuals (n = 1,165) who took part in the study, 16.6% (n = 193) were classified as diabetic because their fasting blood glucose and HbA-1c levels were ≥ 126 mg/dL and HbA-1c ≥ 6.5, as stipulated for diabetics by the Brazilian Diabetes Society[17].

CONCLUSION

The data show an association between hyperglycemia, increased HbA-1c and pre-diabetes and diabetes with AD. It also suggests that, as the formation of amyloid plaques is preliminary to the clinical picture of dementia, maintaining normoglycemia and not developing pre-diabetes and diabetes may minimize the development of AD.

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