Metabolic Syndrome and Central Nervous System

Subjects: Others

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The metabolic syndrome (MS) is a set of cardio-metabolic risk factors that includes central obesity, hyperglycemia, hypertension, and dyslipidemias. The syndrome affects 25% of adults worldwide. The definition of MS has evolved over the last 80 years, with various classification systems and criteria, whose limitations and benefits are currently the subject of some controversy. Likewise, hypotheses regarding the etiology of MS add more confusion from clinical and epidemiological standpoints. The leading suggestion for the pathophysiology of MS is insulin resistance (IR).

IR can affect multiple tissues and organs, from the classic “triumvirate” (myocyte, adipocyte, and hepatocyte) to possible effects on organs more recently considered, such as the central nervous system (CNS). In consequence, it has been proposed that mild cognitive impairment (MCI) and Alzheimer’s disease (AD) may be clinical expressions of CNS involvement. However, the association between MCI and MS is not understood.

The bidirectional relationship that seems to exist between these factors raises the questions of which phenomenon occurs first and whether MCI can be a precursor of MS.

metabolic syndrome | insulin resistance | diabetes mellitus type 2 | mild cognitive impairment | Alzheimer’s disease

1. Introduction

El síndrome metabólico (SM) es un grave problema de salud pública. Afecta a alrededor del 25 % de la población general y, lo que es más alarmante, a alrededor del 40 % de los adultos mayores de 40 años en todo el mundo [1][2]. La definición de este síndrome ha evolucionado recientemente para incluir un grupo de al menos tres de cinco anomalías cardiometabólicas. Estas condiciones incluyen presión arterial alta, obesidad central, resistencia a la insulina (RI), triglicéridos sanguíneos elevados y dislipidemia aterogénica[3], que en conjunto conducen a un mayor riesgo de patologías cardiometabólicas[4][5][6], así como otras enfermedades, como la artritis [7] y algunos tipos de cáncer [8].

Asimismo, la presencia de trastornos relacionados con la EM también juega un papel en la fisiopatología de los trastornos neurológicos [9], reflejando la asociación entre las deficiencias en la secreción y acción de la insulina y el deterioro cognitivo leve (DCL)[10]. MCI se define como una disfunción cognitiva que excede lo que normalmente se espera para la edad y el nivel educativo, pero que no cumple con los criterios de un trastorno neurocognitivo mayor. La funcionalidad general se conserva en MCI [11] y puede describirse mejor como un estado intermedio

entre el deterioro cognitivo característico del envejecimiento y las principales afecciones neurocognitivas, como la enfermedad de Alzheimer (EA) [12][13].

Por lo tanto, se proponen diferentes hipótesis para explicar la asociación MCI/MS [14]. Parece existir una relación cíclica entre la RI y el deterioro cognitivo, y surge la pregunta de qué fenómeno ocurre primero[15]. Además, si el deterioro cognitivo precede a la RI, se convierte en un factor de riesgo para desarrollar EM. Por lo tanto, esta revisión describe brevemente la historia de la EM y discute los hallazgos clínicos y preclínicos que respaldan el papel de la EM y la RI como elementos de los mecanismos fisiopatológicos del deterioro cognitivo.

While most reviews on the topic focus on the MS-to-MCI relationship, this review goes beyond this by looking at the inverse relationship, examining available evidence regarding a new hypothesis that suggests that cognitive impairment could have a role in the development of IR and the appearance of MS. Among the mechanisms to be highlighted in this regard, the hyperphosphorylation of tau proteins and the formation of amyloid β (Aβ) plaques are proposed as alterations that go beyond the pathophysiology of Alzheimer's disease (AD), and their role in the pathophysiology of insulin alterations is examined.

2. Metabolic Syndrome: Historical Aspects

The first studies of MS started almost 100 years ago when Eskil Kylin, in 1921, and Gregorio Marañón, in 1922, independently published in the same journal (Zentralblatt für Innere Medizin) papers with the same title, "diabetes mellitus and hypertension" [16][17]. Yet, not until 1981 did Hanefeld and Leonhardt use the term "metabolic syndrome" for the first time [18].

In 1988, Gerald Reaven hypothesized that IR was a common etiological factor for a group of disorders he termed "Syndrome X" At this time, the fundamental pathophysiological role of IR was known. This mechanism had been studied by researchers, such as Randle [19]. In subsequent years, DeFronzo, Ferrannini, and others used the term "Insulin Resistance Syndrome", proposing that available evidence suggested its presence was the cause of MS [20].

The cause of MS and its components have been debated worldwide since the end of the 20th century. Many organizations, such as the World Health Organization (WHO) [21], the European Group for the Study of Insulin Resistance (EGIR) [22], the Adult Treatment Panel III (ATP-III) [23], the American Association of Clinical Endocrinologists (ACE/AACE) [24], and the International Diabetes Federation (IDF) [25], have proposed evolving diagnostic criteria. Some criteria have been progressively discarded and replaced with criteria that can be easily applied in daily clinical practice.

Finally, the IDF, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity made a joint statement in 2009 that concluded that a diagnosis of MS requires the presence of three or more of the following criteria: high abdominal circumference as defined for each geographical region, triacylglycerides (TAG)

greater than or equal to 150 mg/dL, HDL levels less than 50 mg% in women or less than 40 mg% in men, systolic blood pressure (SBP) greater than or equal to 130 mmHg or diastolic blood pressure (DBP) greater than or equal to 85 mmHg, and glycemic levels greater than 100 mg/dL [3]. We now consider that the evolution of diagnostic criteria has reached a maturity level that makes it difficult to incorporate new criteria that are both easily recognized and provide useful clinical information [26]. IR continues to be the most widely accepted hypothesis to describe MS pathophysiology that involves various organs and associations with numerous diseases [27].

3. Mild Cognitive Impairment and Metabolic Syndrome: Molecular Basis

Epidemiological, clinical, and experimental evidence provides a solid basis for the hypothesis that IR is the pathophysiological origin for dyslipidemias, high blood pressure, and disorders in glucose homeostasis [28]. As studies of MS continued, a relationship emerged between obesity, the syndrome's most prevalent individual criterion, and neurological alterations [29]. This association necessitates additional consideration of the pathophysiological mechanisms involved and how they are interconnected.

Epidemiological [30], neuroimaging [31], and animal modeling studies are available to characterize MS pathophysiology, accompanying diseases, and individual components in the development of neurodegenerative diseases and associated cognitive impairment [32]. The connection between diabetes mellitus (DM) and AD and the connection between obesity and cognitive impairment are two areas that have been investigated in depth, including reports of statistically significant relationships [10][33][34].

The hippocampus plays an important role in learning and memory. The effect of IR on hippocampal function has been widely studied [35]. administered high- and low-fat diets to different groups of rats, using bromodeoxyuridine (BrdU) to observe synaptogenesis after 4 weeks. This result could reflect the role of lipid alteration, a component of MS, in cognitive decline.

studied long-term neuronal potentiation (LTP) in the dentate gyrus (DG) of the hippocampus in mice receiving different combinations of a high-fat diet and antioxidants. Mice fed a high-fat diet showed lower LTP levels compared with control animals. In contrast, mice that received antioxidants displayed elevated LTP [36]. These effects might be mediated by an increase in free radical production caused by the high-fat diet, leading to oxidative stress (OS).

Production of reactive oxygen species (ROS) results in increased levels of amyloid precursor peptide-β (AβPP) and increased expression and accumulation of amyloid-β 42 One pathway for increased ROS production is increased insulin levels that lead to changes in normal NADPH oxidase (NOX4) pathway function. This aberrant metabolism is perpetuated because elevated ROS leads to activation of casein kinase 2 (CK2) and consequent activation of the retromer. This action signals the degradation of glucose receptor, GLUT4, leading to a continued increase in glucose levels in the blood and, therefore, increased production of insulin [37]

The metabolic syndrome (MS) and its components cause brain alterations such as neuroinflammation, hyperphosphorylation of Tau, formation of beta amyloid plaques, and vascular changes (not represented in the figure). This is achieved through changes in the signaling of hormones such as adiponectin, leptin, and insulin. These changes are clinically expressed as mild cognitive impairment (MCI), Alzheimer's disease (AD), and major vascular neurocognitive disorder.

An associated hypothesis is that, along with neurofibrillary tangles and amyloid-beta plaques, inflammation has a critical role in the pathophysiology of the disease [38]. In vitro studies show that high levels of insulin affect the degradation and elimination of Aβ. During hyperinsulinemia, IDE degrades insulin preferably to Aβ, promoting its oligomerization into insoluble aggregates [39]. In vivo experiments in rats corroborate these findings, showing that elimination of Aβ is reduced in the presence of high levels of insulin [40].

Insulin receptors provide an alternative explanation for IR effects on the hippocampus and other brain structures [41]. These receptors are abundant in metabolic active brain areas and exert their effects at the neuronal level via PI3K and mitogen-activated protein kinases (MAPK) pathways [42]. These pathways, when activated by insulin, promote angiogenesis in the brain. This disruption might underlie the concomitant synaptic anomalies, memory disorders, decreases in neurogenesis at the hippocampus level, alterations in cognition, and decreases in levels of brain-derived neurotrophic factor (BDNF) [41].

Conversely, tau protein (TP) helps stabilize microtubules and its alteration results in the formation of neurofibrillary tangles [43]. Further, IR induces hyperphosphorylation of TP and induces cognitive impairment in human and animal models [44][45]. Thus, IR is associated with poorer performance on cognitive tests and higher levels of phosphorylated PT in cerebrospinal fluid (CSF) in cognitively normal individuals and carriers of the APOE allele ε4 [10][46].

One mechanism underlying this phenomenon involves glycogen synthase kinase-3β (GSK3β), a tau kinase regulated by insulin via the protein kinase B (AKT) pathway. Decreased brain insulin signaling caused by IR induces chronic exposure of neurons to high levels of insulin or an eventual decrease in insulin levels, resulting in PI3K dysfunction and reduced AKT-dependent phosphorylation. Downstream, GSK3β is activated, and ultimately TP is hyperphosphorylated[47][48] . The production of advanced glycation end products (AGEs) from OS damage via GSK3β receptors (RAGE) also increases the activity of GSK3β by an alternate pathway involving c-Jun N-terminal kinase (JNK)[49] .

A recent study showed protein kinase Moreover, insulin deficiency influences hyperphosphorylated TP level by decreasing the activity of protein phosphatase 2 (PP2A) PP2A is the primary tau phosphatase involved in AD and its deregulation is associated with TP hyperphosphorylation[50] . Similarly, hypothermia, common in chronic DM, also leads to inhibition of PP2A activity[51] .

Another pathological mechanism in AD is truncation of TP by proteolytic enzymes, such as caspases, peptidases, and thrombins that promote tau aggregation and formation of the central component of neurofibrillary tangles (NFT)

[52] . DM stimulates apoptosis through the activation of caspases in affected tissues. Through hyperglycemia, DM might increase tau aggregation by activating caspases, thus contributing to AD risk[53] . Kim et al. demonstrated such increased tau aggregation in the brain of db/db rats using in vivo and in vitro type 2 diabetes mellitus (T2DM) animal models [54].

[55]Alterations in hormones involved in MS, such as leptin and adiponectin, are also linked to cognitive impairment[56] . Both hormones affect the metabolism of fatty acids and glucose as well as energy metabolism and food intake . Their function in neuroplasticity, learning, and cognition[57][58] is now known via reports of leptin and adiponectin receptor expression in brain regions such as the hippocampus and neocortex[59] .

Recent studies in animal models show that leptin deficiency or resistance is associated with cognitive disorders, such as reductions in LTP, long-term neuronal depression (LTD), and alterations in spatial memory[60] . Further, leptin modulates the production and elimination of Aβ in AD by inhibiting the formation of AβPP and increasing APOEε4-induced amyloid filament elimination[61][62]. . Leptin resistance in AD is associated with diminished activity in these pathways and increased cognitive impairment [63].

Additionally, adult rats deprived of adiponectin display several common characteristics of AD, including deposition of Aβ, TP phosphorylation, and neuroinflammation [64]. This observation is corroborated by Kim et al., who demonstrated that adiponectin receptor suppression also produced an AD-like phenotype [65] Thus, hormone deficiencies might be involved in AD pathogenesis. However, studies in humans are controversial since available information for the association of adiponectin and leptin levels in the blood and CSF with cognitive impairment is inconclusive[66] .

Micro- and macrovascular changes observed in MS, such as hypertension and DM, are also associated with brain alterations, such as vascular neurocognitive disorder. However, several recent studies note the contribution of vascular risk factors in AD. Mechanisms for this accelerating cognitive decline are not fully elucidated[67] .

Hypertension leads to alterations observed in magnetic resonance imaging (MRI), such as white matter lesions (WML), lacunar infarcts, microhemorrhages, and microinfarcts. All these abnormalities are part of a spectrum called small vessel cerebral disease (SVD), which is common in AD[68] . Other mechanisms might involve large arteries via endothelial dysfunction that progresses to the formation of atherosclerotic plaques in the carotid or intracranial arteries. Such damage can cause ischemic events in brain regions related to cognition[69] .

The consequences of MS on the development of cognitive impairment have been studied in depth[70] , but the inverse relationship in which pathophysiological mechanisms of AD, such as hyperphosphorylation of TP and the formation of amyloid complexes-β, lead to the appearance of MS is largely unstudied.

Interestingly, TPs, in addition to microtubule stabilization, also interact with insulin signaling pathway components in the brain. The N-terminal portion of TP can bind to homology 3 (SH3) domains of the Src family of tyrosine kinases, including domains of the p85 alpha subunit of PI3K, a key protein in the insulin signaling pathway. Under

pathological conditions, hyperphosphorylation of TPs can lead to loss of functionality, triggering alterations in insulin signaling that eventually generate altered fasting glycemia and DM. The ability of TPs to interact with SH3 domains is inversely correlated with the degree of phosphorylation, suggesting that scaffolding properties of TPs are regulated by their phosphorylation status[71] .

Further, co-immunoprecipitation studies of mouse brain tissue and N1E115 cells indicate that TPs bind to phosphatase and tensin homologous protein (PTEN), a negative insulin signal translocation regulator that catalyzes dephosphorylation of phosphatidylinositol triphosphate (PIP3) to PIP2. Thus, TP, by interacting with and inhibiting PTEN, promotes insulin signaling . These studies raise the possibility that insulin helps maintain adequate brain activity due to TP and, conversely, pathological forms of TP could be harmful due to a loss of protein function. This suggestion is supported by a study that showed that TP removal was accompanied by loss of inhibitory effects of insulin on PTEN in the hippocampus, resulting in brain IR.

Concurrently, the absence of TP reduced the anorexigenic effect of insulin in the hypothalamus after intracerebroventricular injection of TP [72]. Previously, such injection induced increased food intake, weight gain, adiposity, hyperinsulinemia, and glucose intolerance in rodents with insulin receptor deletion in the hypothalamus[73] [74]. These effects produce alterations in energy metabolism that may increase the risk of suffering from obesity, DM, and MS.

However, its function in peripheral tissues is not fully understood[75] [76]. Wijesekara et al. investigated TP actions on β-cell function and glucose homeostasis using a tau KO rat model. Rats showed weight gain, defects in glucose signaling, and IR, leading to DM and ultimately MS. Thus, TP might be crucial for normal energy metabolism in peripheral tissues

In vitro and in vivo studies suggest that Aβ may also contribute to IR through various mechanisms. Aβ competitively inhibits the binding of insulin to its receptor [77]and activates the JAK2/STAT3/SOCS-1 signaling pathway to produce IR in the liver [78]. Further, the oligomer Aβ (AβO), a highly toxic species of Aβ, causes deregulation of N-methyl-D-aspartate (NMDA) receptors and leads to the production of excessive ROS. This effect is probably due to mitochondrial dysfunction[79] .

This deregulation might lead to alterations in insulin signaling, since increased ROS activates several serine kinases, such as an inhibitor of the nuclear factor kappa-B kinase beta subunit (IKK-β), protein kinase C (PKC), and JNK. ROS can cause OS and damage at mitochondrial and cellular levels. This stress generates mitophagy and, at high levels of stress, apoptosis. The elimination of mitochondria by mitophagy results in a decrease in oxidation and consequent accumulation of lipids, leading to IR and T2DM[80] .

Conversely, AβO causes a rapid and substantial loss of insulin receptors in dendrites and inhibition of insulin receptor autophosphorylation associated with NMDA activity[81] . Additionally, an increase in levels of IR markers p(Ser)-IRS-1 and p-JNK were observed in neurons after intracerebroventricular injection of AβO in vivo in monkeys [82].

Aβ and TP have also been linked to alterations in leptin signaling. Bonda et al. showed that TP hyperphosphorylation leads to the formation of NFT and dysfunction in intracellular trafficking networks in the hippocampus. Thus, the leptin receptor in its long form (Ob-Rb) becomes unable to reach cell membranes, hindering its access to circulating free leptin and interrupting signaling. This activity might lead to increased food intake and weight gain with subsequent development of obesity and long-term MS[83] ; leptin in the hippocampus is associated with regulating food intake and processing food-related memories[84] .

Elevated levels of Aβ1-42 produced by beta-site amyloid cleaving enzyme 1 (BACE1) increase leptin resistance in the hypothalamus, which is associated with decreased sensitivity to exogenous leptin throughout the body and exacerbation of body weight gain in rats fed high-fat diets. Thus, countering BACE1 activity may be protective against metabolic disorders[85] .

The above findings affirm cognitive impairment as a key trigger of alterations in insulin signaling in the hypothalamus. The latter region is the primary regulator of body weight via controlling food intake and peripheral metabolism[86] . Thus, cognitive impairment might lead to metabolic changes that precede the development of MS and its complications.

4. Mild Cognitive Impairment and Metabolic Syndrome: Epidemiological Basis

Evidence concerning the relationship of MS and its components with MCI has accumulated in the last few years to the point where grouping these disorders into a single clinical entity, the cognitive–metabolic syndrome, may be appropriate . Below, it summarizes clinical and epidemiological information on the MCI and MS relationship and its components.

Cardio-metabolic risk factors and MS affect cognition and increase the risk of major neurocognitive disorders[87][88][89] . Speed of processing, attention, and executive functions are the most frequently affected domains[90][91] . Thus, an association is often reported between risk factors, such as hyperlipidemia, T2DM, obesity, hypertension, and physical inactivity, and models of risks of cardiovascular disease (CVD) with the risk of MCI and major neurocognitive disorders.

Strong evidence of a link between high blood pressure in middle age and poorer cognitive function in old age is available[92][93] . Different prospective studies in older people show that increased blood pressure is associated with worse cognitive function[94] . The risk of cognitive impairment can increase up to 2.8 times [95]. In older women, risks may increase by up to 20% [96].

Obesity, defined by a high abdominal circumference or a body mass index (BMI) ≥ 30, is also associated with poor cognitive function[97][98] . Individuals with high BMI during middle age show low scores among various cognitive tests[99] . Further, long-term obesity is linked to lower cognitive performance and an increased risk of neurocognitive impairment in older people[100][101][102] .

Several epidemiological studies and meta-analyses provide evidence for an effect of hyperlipidemia, hypertriacylglycerolemia, and HDL-C levels on cognitive performance in individuals with and without major neurocognitive disorders. Further, hypertriacylglycerolemia is associated with low scores in verbal tests[103][104] . Low concentrations of this lipoprotein are associated with poor and decreased memory in middle-aged adults , while in older people, low levels are associated with major neurocognitive disorders[105] . In contrast, improvement in cognitive test performance is reported for subjects over 75 years old with high HDL-C [106],[107] which is also associated with a significant decrease in the appearance of major neurocognitive disorders .[108]

Hyperinsulinemia, glucose intolerance, and T2DM are other cardio-metabolic risk factors that recently have been associated with cognitive impairment and different major neurocognitive disorders[109] . Hyperinsulinemia and impaired glucose tolerance, both indicators of a prediabetic state and an increased risk of developing DM, are associated with cognitive dysfunction and an increased risk of developing MCI .[110][111][112][113] These premorbid states are associated with reduced long-term memory scores[114] and impaired verbal fluency [115]. These lower scores correlate with an increased risk of developing cognitive impairment and MCI[116][117][118][119][120][121].

Several studies associate different elements of MS with cognitive functions. However, few studies of MS as a clinical entity and its relationship with MCI or its progression to major neurocognitive disorders are available. MS was associated with an increased risk of developing cognitive impairment in older women[122]. , who concluded that MS is associated with an increased incidence of major neurocognitive disorders and an increased risk of progression from MCI to such disorders, respectively.

Effects of components of MS on cognitive function, the risk of MCI, and major neurocognitive disorders.

Abbreviations: MS: metabolic syndrome; MCI: mild cognitive impairment; BP: blood pressure; CAMCOG: Cambridge Cognitive Examination; MMSE: Mini-Mental State Examination; CV: coefficient of variation; BMI: body mass index; OR: odds ratio; HR: hazard ratio; CI: confidence interval; AD: Alzheimer’s disease; HDL-c: high-density lipoprotein; DM: diabetes mellitus.

The impact of MS on cognitive function is not limited to adults. There is also evidence that suggests that MS components may be detrimental in younger populations. The presence of T2DM, obesity, and hypertension in children and adolescents is associated with poorer performance in overall functioning, and declines in executive function, memory, attention, and intelligence quotient (IQ) .

Cardiovascular and metabolic risk factors are modifiable and their timely identification and consequent management could prevent MCI or its progression to major neurocognitive disorders[90] . Thus, lifestyle changes, including increased physical activity and implementation of healthy diets, and antihypertensive, hypolipidemic, and insulin-sensitizing drugs are important considerations for the management of premorbid state characteristics of MS [123].

Changes in lifestyle and physical activity positively impact cognitive function[124][125]. . Physical activity is associated with better scores on tests of executive function, processing speed, and improvement in global cognitive function. These benefits were found both in healthy older subjects and in older subjects with MCI or major neurocognitive disorders[126] [127][128][129].

Better results are obtained if physical activity is combined with a healthy diet. Supplementation with B-vitamins, folic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and flavonoids is associated with improved cognitive performance, particularly memory, in subjects with MCI[130] . Similarly, both cognitively normal individuals and those with MCI are reported to be at less risk of developing MCI or AD if they maintain high adherence to a Mediterranean diet [131]. Similar results are associated with Mediterranean-DASH diets[132] , low-carbohydrate diets (keto-diet) , and fish PUFA diets[133] .

Additionally, a causal relationship between antihypertensive drugs and improved cognitive function is supported by available evidence. Antihypertensive drugs, especially calcium channel blockers and renin–angiotensin system blockers, have a protective effect on cognitive decline and decrease the risk of AD and neurocognitive vascular disorders in older people [134]. Similarly, treatment with antihypertensive drugs reduces the risk of major neurocognitive disorders by 9% and shows improvement in all cognitive domains, except language[135] . Longitudinal studies that included older individuals without major neurocognitive disorders who were undergoing antihypertensive therapy produced supporting results[136] [126].

Controlling glycemic concentrations and increasing peripheral insulin sensitivity are strategies that might positively affect cognitive function [137]. A recent meta-analysis showed that treatment with metformin or sulfonylureas is associated with a significant decrease in cognitive impairment in patients with T2DM. In contrast, the use of insulin aggravated the dysfunction[138] . However, other studies show no association between the use of antidiabetic drugs and improvement in cognitive function[139][140] .

Finalmente, a diferencia de los medicamentos antihipertensivos y antidiabéticos, los hipolipidemiantes, como las estatinas, no afectan el riesgo de progresión a MCI o trastornos neurocognitivos mayores de ningún tipo[141][142] . De hecho, varios estudios clínicos y epidemiológicos no informan una asociación significativa entre el uso de estatinas y la reducción del deterioro cognitivo[143][144][145][146].

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