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White matter microstructure and cognitive decline in metabolic syndrome: A review of diffusion tensor imaging

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Abbreviation list: metabolic syndrome (MetS); type 2 diabetes (T2DM); blood pressure (BP); diffusion tensor imaging (DTI); gray matter (GM); white matter (WM); magnetic resonance imaging (MRI); fractional anisotropy (FA); mean diffusivity (MD); axial diffusivity (AD); radial diffusivity (RD); white matter hyperintensities (WMH); body mass index (BMI); high density lipoprotein (HDL); low density lipoprotein (LDL); familial hypercholesterolemia (FH); Reactive oxygen species (ROS); nitric oxide (NO)

Abstract

Metabolic syndrome is a cluster of cardiovascular risk factors defined by the presence of abdominal obesity, glucose intolerance, hypertension and/or dyslipidemia. It is a major public health epidemic worldwide, and a known risk factor for the development of cognitive dysfunction and dementia. Several studies have demonstrated a positive association between the presence of metabolic syndrome and worse cognitive outcomes, however, evidence of brain structure pathology is limited. Diffusion tensor imaging has offered new opportunities to detect microstructural white matter changes in metabolic syndrome, and a possibility to detect associations between functional and structural abnormalities. This review analyzes the impact of metabolic syndrome on white matter microstructural integrity, brain structure abnormalities and their relationship to cognitive function. Each of the metabolic syndrome components exerts a specific signature of white matter microstructural abnormalities. Metabolic syndrome and its components exert both additive/synergistic, as well as, independent effects on brain microstructure thus accelerating brain aging and cognitive decline.

Keywords: metabolic syndrome; white matter mictrostructure; white matter abnormalities; diffusion tensor imaging; cognitive decline; brain

1. Introduction

Aging can be defined as the combined effects of time, genetics, behavior and enviroment on all body functions, leading to their progressive decline. Aging affects all body organs and systems and brain aging is related to consistent differences in brain structure, decreased regenerative capacity for repair, impaired maintenance of synaptic and cognitive functions including memory function, and transition to dementia [1, 2]. Magnetic resonance imaging (MRI) shows that the volume of the frontal lobe presents the greatest decline with aging (approximately 12%), followed by the volume of the temporal lobe (approximately 9%), while modest volume declines are observed in occipital and parietal lobes [3]. The effects of age on cognition vary greatly in the general population as well as in associated conditions and diseases that occur earlier in life.

Metabolic syndrome (MetS) is a group of metabolic disorders that occur together and increases the risk of cardiovascular disease [4-7], stroke [8, 9], and type 2 diabetes mellitus (T2DM) [10-12]. MetS is considered a global epidemic by the World Health Organization [13] and it affects approximately 20% of adults in the Western world [14]. According to the International Diabetes Federation [15] at least three of the following criteria have to be present for its diagnosis: increased waist circumference (population and/or country cut-off), increased triglycerides (≥150 mg/dl or in treatment), reduced high density lipoprotein (HDL) cholesterol (<40 mg/dl in men, <50 mg/dl in women or in treatment), increased blood pressure (BP) (systolic ≥130 mmHg and/or diastolic ≥85 mmHg, or in treatment) and increased fasting glucose (>100 mg/dl or in treatment).

The impact of MetS on cognition and risk of development dementia is well documented [16, 17]. Numerous studies reported changes in memory, visuospatial and executive functioning, processing speed and daily functional activities in adults with MetS relative to healthy controls [18-21]. However, there is little evidence regarding the impact of MetS on brain structure and its link to cognitive and functional decline. With the advent of diffusion tensor imaging (DTI) in MetS, new results characterizing changes in the white matter (WM) microstructure have emerged. DTI allows to detect abnormalities in WM microstructure that are no visible on conventional MRI, and thus it is a promising tool to identify microstructural brain damage secondary to MetS processes.

2. Methods

This review concentrates on the effects of MetS and its components on cognitive functioning and WM microstructural integrity as measured by DTI in non-demented adults. We present the results of previous studies that linked changes in diffusion parameters and cognitive

performance, and provide a brief overview of potential future directions in the current therapeutic guidelines to control the impact of MetS on the brain.

For this literature review an electronic search was undertaken in Pubmed from January 2000 up to May 2017. Only studies published in English were included. The keywords used were "diffusion tensor imaging", "DTI", "microstructural white matter", "white matter disease", "cerebral small vessel disease", "magnetic resonance imaging", "MRI", "metabolic syndrome", "obesity", "body mass index", "BMI", "waist circumference", "hyperglycemia", "chronic hyperglycemia", "glucose intolerance", "insulin resistance", "type 2 diabetes", "T2DM", "hypertension" "high blood pressure", "dyslipidemia", "hypercolesterolemia", "cognition", "cognitive impairment", "cognitive dysfunction", "cognitive function" "atrophy", "white matter hyperintensities", "infarcts".

3. Role of DTI in clinical studies

DTI is a relatively novel MRI technique that identifies changes in the WM microstructure [22], by quantifying directional diffusion. DTI has become one of the most powerful imaging tools available to understand the pathophysiological mechanisms of diseases like T2DM [23, 24], ischemic stroke [25], and hypertension [26] and their relationships to cognitive deficits. DTI is based on the assumption that water molecules follow a physiological perpendicular path through the long axis of neural fibers and bundles, formed by the integrity of the axons and the thick myelin membrane surrounding them [27]. Any alteration in the integrity of the WM fibers (eg. demyelination) will result in changes in the water diffusion and consequently in the DTI parameters [28]. These subtle abnormalities will subsequently lead to disruptions in the connectivity between different brain regions and contribute to a decline in the cognitive performance in patients.

Fractional anisotropy (FA) and mean diffusivity (MD) are the main DTI-metrics used to identify alterations in WM organization and interconnectivity. These imaging parameters provide information about the density of the WM fiber, diameter of the axon and degree of myelination based on a quantitative measure of the diffusion anisotropy [29]. Additionally, DTI allow us to identify changes in the integrity of the axon with the metric of axial diffusivity (AD), and information regarding the quality of the myelin sheath with the measure of radial diffusivity (RD). This is especially important considering that these alterations in WM tracts may disturb functional connectivity and the information transfer between different brain regions, potentially leading to cognitive deficit. A number of clinical studies of the last decade have revealed alterations in FA and/or MD in several brain diseases and disorders such as multiple sclerosis, schizophrenia, traumatic brain injury, amyotrophic lateral sclerosis, amnestic mild cognitive impairment and Alzheimer's disease [30-35]. All of them have found important WM microstructural alterations complementary to or not seen otherwise in conventional MRI scans.

4. Metabolic Syndrome

The associations between MetS and brain health are etiologically quite complex (see a conceptual model in the Figure 1). MetS components share common pathways leading to metabolic, inflammatory, and microvascular disturbances that may futher contribute to WM microstructural damage and cognitive decline [47]. However, the individual componets also have their specific signatures in the brain. Specifically, genetic factors may contribute to the changes at the cellular and vascular levels, with concomittteant effects of oxidative stress and inflammation. Insulin resistance alters insulin signaling and its functions in the brain, as well as glucose metabolism [48]. Brain hyperglycemia and oxidative stress can lead to the formation of glycated end products and neuroinflammation [49, 50]. Oxidative stress could lead to blood brain barrier alterations [51], neuronal cell damage and glucose toxicity [48]. Insulin resistance in its turn increases oxidative stress [52] leading to a vicious circle.

4.1 Molecular basis for cellular and vascular mechanisms of MetS

Altered insulin signaling in the brain attenuates phosphatidylinositol-3 kinase function and protein kinase B activation leading to reduced glucose transport and increased apoptosis, decreased glucose and energy metabolism and reduced adenosine triphosphate production which contributes to cognitive decline [53]. Decreased intraneuronal glucose metabolism induced by insulin resistance compromises the generation of O-N-acetylglycosamine throught the hexosamine biosynthetic pathway, which O-N-acetylglycosamine competes protein phosphorylation and help in the prevention of cognitive decline, dementia and Alzheimer's disease [54]. Insulin resistance also leads to endothelial dysfunction due to alterations in vasoreactivity, microvascular blood flow, cellular glucose and lipid metabolism which leads to increased levels of reactive oxygen (ROS) and nitrogen species and overconsumption of endothelial-derived nitric oxide (NO) in combination with NO decreased synthethis or release [55]. This leads to a vicious circle where endothelial dysfunction alters the capacity of capillary network to expand, attenuates microcirculatory blood flow to metabolically active tissues and prevents insulin to reach target tissues, while vascular damage that occurs from oxidative stress and lipid deposition on the vessel wall induces an inflammatory response which further deteriorates insulin resistance and endothelial dysfunction [48, 52, 55, 56]. Altered endothelial integrity leads to cerebral hypoperfusion either through small vessel disease and altered vasoregulation [56] or through arterial stiffness, macrovascular disease and infarcts [57].

4.2 MetS and MRI findings

MetS components are known to exert an individual effect on brain structure and function as it will be discussed later in detail, but evidence on the effect of MetS as a whole remain inconclusive. The MRI findings describing the impact of MetS and MetS individual components are outlined in the Table 1 and are discussed in detail below. MetS was associated with lower global brain volume [36], silent lacunar infarcts [37, 38], periventricular WM hyperintensities (WMH), subcortical WM lessions [39] and increased cerebrospinal fluid (CSF) [40] . On the other

hand, others failed to demonstrate a reduced brain volume or focal ischemic lessions in patients with MetS even though worse cognitive performance was observed compared to controls [41]. MRI findings of individual MetS components show an independent association of impaired glucose metabolism, abdominal obesity, and elevated triglycerides with global brain atrophy, while elevated body mass index (BMI), BP, and fasting glucose were independently associated with silent lacunar infarcts [36-38]. Elevated BP and/or fasting glucose and/or dyslipidemia were also associated with large vessel infarcts, WMH and subcortical WM lesions [36, 39].

4.3 MetS and DTI findings

Evidence that suggest the association between MetS and impairment of WM integrity and microstructural damage is growing (Table 2). A reduced FA was found in the corpus callosum, right external capsule, and deep WM of the right frontal lobe of MetS patients compared to controls [42, 43]. Changes in FA of the corpus callosum in the frontal lobe were associated with cognitive impairment and more specifically with reduced processing speed [44]. Furthermore, lower FA and higher RD values in angular gyri and higher AD values in the left post-central gyrus in patients with MetS were associated with worse verbal learning and memory performance [45]. The negative effect of MetS on WM microstructure was present in adolescents with MetS as well, who presented with reduced FA in the corpus callosum, optic radiations, and medial longitudinal fasciculi compared to controls [40]. These findings suggest that impairments in metabolism even at a young age could negatively impact brain health and could potentially lead to cognitive decline later in life. All these studies had a case-control design and only one study examined the effect of MetS on WM microstructure prospectively finding reduced FA and increased RD in the corpus callosum and dorsal cingulum bundle with increasing severity of MetS [46]. The study demonstrated that in normally appearing WM, the rate of change during a two year period varies across WM regions and among individuals contrary to cross-sectional studies that present a rather uniform age-related WM deterioration across brain regions and this change was exacerbated by metabolic risk [46]. Therefore, MetS could negatively impact WM microstructure regardless of age, and may contribute to worse cognitive outcomes and accelerated brain aging.

All MetS components contribute to microstructural WM damage but is still under question if there is any component that has a greater effect over the others. Bender and Raz showed in 96 healthy adults 17-78 years old that subclinical elevation in metabolic risk indicators predicted greater microstructural integrity damage indicating an additive/synergistic effect of the MetS components [46]. However, it is still questionable whether all MetS components contribute the same. Sala et al. found that all MetS components i.e. serum HDL cholesterol, triglycerides, BMI, and diastolic BP were independent factors of microstructural brain tissue integrity [73]. Alfaro

et al., has shown that hyperglycemia was the component mediating the WM abnormalities in patients with MetS [45]. However, other studies have examined some of the MetS components without analyzing or considering the additive/synergistic effects of other componenents (e.g. T2DM studies where diabetic patients are also obese or overweight and frequenly have dyslipidemia and hypertension) [74] thus not being able to indicate one component over the other. Specifically, high BP in midlife and late life and high glucose levels in midlife but not late life, were associated with worse late-life WM microstructural integrity, but no adverse association between lipids and WM microstructural integrity was supported by these data [75]. T2DM was found to have an additive/synergistic effect to hypertension on WM microstructural alterations in the frontal lobe [76]. Others showed that the reduced WM integrity observed in obese patients with T2DM compared to lean normoglycemic individuals was mostly explained by the elevated BMI (21% of the variance) and not by T2DM per se [77]. Verstynen et al. studied the mediating pathways between elevated adiposity and WM integrity abnormalities and showed that BP regulation explained most of the variance (12.58%), followed by dyslipidemia (7.93%), inflammation (6.59%) and glucose regulation (1.71%) all of them accounting for 49.69% of the total variance [78]. Furthermore, they showed that these factors could have antagonist effects on the diffusion signal i.e. a globally distributed immunity-linked negative component (inflammation and glucose regulation) and a more localized vascular-linked positive component (BP and dyslipidemia) [78]. In addition, dyslipidemia was found to mediate WM integrity abnormalities in obesity in prefrontal areas involved in executive functioning and decision-making [79] while vascular and inflammatory markers were found to explain the effect of BMI on WM integrity in fornix and middle/posterior regions of the corpus callosum [80]. Allen et al. suggested that at least two mechanisms could explain the association between elevated adiposity and WM miscrostructural damage and more specifically they proposed one pathway that involves elevated BP that negatively affects global WM integrity and reduces integrity of the myelin sheath, and at least one other adiposity-specific pathway that leads to axonal integrity damage [81]. Considering the above it is hard to conclude which MetS component could lead to a greater WM mictrostructural damage and the role of combined and cumulative effects of individual components, therefore larger prospective randomized-control studies are needed. In the following sections we will discuss the impact of each individual MetS components on WM integrity.

4.4 Pathophysiology of micro- and macrovascular dysfunction in MetS

Another potential pathophysiological mechanism that has been reported linked to MetS and cognitive dysfunction is the presence of microvascular alterations that lead to WM destruction. Through a process of intracranial atherosclerosis [58], microcirculatory alteration can potentially induce a state of chronic hypoperfusion that contribute to the development of axonal and glial changes [59]. Postmortem studies, have indicated that intracranial

microvasculature are specially sensitive to the ROS present in MetS and respond to oxidative stress with the accelerated atherogenesis [60]. Moreover, these pathological changes have been linked to the formation of leukoaraiosis, which has been identified as a risk factor for the development of cognitive dysfunction and AD [61]. Although further studies are required, it has been found that MetS is associated with the formation of silent brain infarction, periventricular white matter hyperintesitives and subcortical white matter lesions [39], which are all linked to cognitive dysfunction [62]

Hypertension further contributes to vascular damage and cognitive impairment by its effects on the structure and function of cerebral blood vessels through atherosclerosis and lipohyalinosis, rearrangement of the cellular architecture and changes in the composition of the vascular wall, alterations in functional hyperemia, autoregulation and endothelial function, reduced compensatory capacity of the cerebral circulation and increased susceptibility of the brain to vascular insufficiency [63]. ROS are involved in the structural remodeling of cerebral blood vessels and in the functional alterations induced by hypertension, while some of these effects are mediated by vascular nitrosative stress induced by peroxynitrite derived from nicotinamide adenine dinucleotide phosphate oxidase-derived superoxide and NO [63]. Obesity-induced hyperleptinemia could lead to cognitive decline through the phosphatidylinositol-3 kinase/protein kinase B and mitogen-activated protein kinases/extracellular signal-regulated kinases signaling pathways [64, 65]. Furthermore, the obesity related dysregulation of the hypothalamic-pituitary-adrenal axis and hypercortisolemia could lead to hippocampal dentritic atrophy and cognitive deficits [66, 67]. Lastly, dyslipedimia could lead to cognitive decline through atherosclerosis [68]. Hypertriglyceridemia could promote cognitive impairment possibly by impairing maintenance of the N-methyl-d-aspartate component of hippocampal long-term potentiation and by contributiong to leptin resistance [69]. Reduced HDL levels could also deteriorate cognition as HDL and apolipoprotein A-I/HDL prevents hippocampal atrophy, improves synaptic growth and plasticity and reduces inflammation and oxidative stress [70, 71]. HDL carries the antioxidative enzyme paraoxonase 1, the low levels of which have been linked to cognitive function impairment [70, 72]. The outcome of these individual or synergistic actions may manifest as structural brain changes, WM microstructural damage and functional decline of degenerative or vascular origin. As a result, brain aging and cognitive decline are accelerated. Figure 1 provides an overview of these mechanisms that are also discussed in the individual parts of the MetS components below.

5. Obesity

Obesity is considered an epidemic of the modern era as its worldwide prevalence was doubled between 1980 and 2014 and in 2014 more than 1.9 billion adults were overweight and over 600 million (13% of world’s adult population) of those were obese [82]. By 2025 it is estimated that

global obesity prevalence will reach 18% in men and surpass 21% in women while severe obesity will surpass 6% in men and 9% in women [83]. Obesity was estimated to account for 0.7-2.8% of a country's total healthcare expenditures and obese people were found to have about 30% greater medical costs than normal-weight individuals [84]. Overweight and obesity have been linked to several comorbidities including T2DM, several types of cancer and cardiovascular disease, asthma, gallbladder disease, osteoarthritis and chronic back pain [85]. Furthermore, obesity may lead to exacerbate cognitive decline and it has been related to several progressive and age-related neurodegenerative diseases such and Alzheimer's disease [86]. Obesity, mostly abdominal, is the most prevalent manifestation of MetS [87] and although most of its health consequences have been broadly examined, less is known about its effects on the brain.

5.1 Obesity and MRI findings

Modern neuroimaging is widely used to study and understand the brain pathology in obesity. BMI has been associated with brain structural and functional abnormalities [88] (Table 1). Obesity is associated with global brain atrophy [36, 89-93] and regional atrophy in both gray matter (GM) and WM, and although a consistent reduction in GM volume with increasing BMI has been observed [91, 93-99], alterations in WM are more complex and less conclusive [91, 93-95, 97, 100-103]. Furthermore, there is evidence that increased BMI is accociated with increased WMH [104], decreased cerebral blood flow [105], increased CSF [106] and silent brain infarcts [39] and silent lacunar infarcts [37]. Since MRI cannot assess WM integrity, DTI has been used to explore microstructural changes in WM microstructure in obesity, and this research field has just begun to grow.

5.2 Obesity and DTI findings

An increasing BMI has been associated with a decrease in WM integrity as assessed by reduced FA and/or altered AD, MD and RD in both genders in several brain regions like corticospinal tracts, brainstem, anterior and posterior thalamic radiation, inferior fronto-occipital fasciculus, inferior and superior longitudinal fasciculus, corpus callosum, uncinated fasciculus, internal capsule, cingulum, mammillary bodies, optic radiation and corona radiate, middle and superior cerebellar peduncles, medial lemniscus regions of the midbrain, infundibulum, perithalamic WM and perihippocampal WM in the temporal lobe (Table 2), areas related to numerous functions including motor control, coordination, reward seeking, motivation/drive, inhibition, emotional regulation, learning, cognitive control, memory, decision making and impulsive control [107-114]. Women may be more prone to the obesity-related WM microstructural alterations as a negative association between FA and BMI and a positive association between RD and BMI in corpus callosum was found only in women, while a negative association between AD and BMI was noticed in the corpus callosum of both genders [115]. This might be either

because males have higher myelination than females [116] or modest demyelination might be not detectable enough in males [115]. Howewer, the sample size of the study was small [115] and conclusions should be interpreted with causion. It seems that obesity does not affect WM integrity only in adults but also in their offspring as a negative association between maternal adiposity and FA of the offspring has been found [117]. Furthermore, it was shown that healthy obese children have reduced regional GM, increased WM and differences in WM microstructures in several brain regions compared to their healthy normal-weight counterparts [118]. Consideraing the above, obesity negatively impacts WM microstructure regardless of age and this is linked to non-beneficial alterations in a wide range of functions including cognitive health and memory that may increase the risk for cognitive decline and memory loss later in life.

Most DTI studies in obesity have examined differences in diffusion characteristics that give insight into localized changes in WM microstructure. Other DTI studies have focused on fiber tracts in order to evaluate the relative connectivity between brain regions and networks. Specifically, obesity-related alterations of GM density in brain regions involved in executive control and habit learning were found to be associated with alterations of WM fiber bundles within the corpus callosum [119]. Furthermore, alterations in MD and AD with increasing BMI in the corticospinal tract, anterior thalamic radiation and superior longitudinal fasciculus indicate changes in fiber tracts linking limbic structures with prefrontal regions that could accelerate aging and cognitive decline in obese individuals [120]. This was also supported by lower FA values with increasing BMI in brain regions connecting frontal and temporal lobes [121], as well as with shorter fiber bundle length in the temporal lobe [122] in older adults, changes that precede cognitive dysfunction. In adolescents, BMI was inversely associated with verbal and spatial working memory accuracy which was mediated by reduced FA in superior longitudinal fasciculus and left inferior longitudinal fasciculus, WM fiber tracts that link cortical regions important for cognitive and executive functions [123]. On the other hand, other researchers have not found similar effects in normal weight children and adolescents [124]. In any case, available evidence points to the fact that obesity is associated with brain damage that could accelerate brain aging.

Obesity is also linked with deteriorating chances in the brain reward system making the loss of weight much more challenging and its health consequencies, including brain damage, more difficult to be reversed. Fiber density differences have been observed in several brain areas of the reward system between normal-weight and overweight/obese individuals [125], showing an altered connectivity and probably communication between key regions of the reward network and other related networks [126]. A disruption of a larger taste reward circuitry has been suggested by Shott et al., who found decreased GM across the taste reward system and reduced WM integrity in the corona radiata, sagittal stratum, and external capsule, fiber tracts

that connect frontal with limbic and subcortical brain regions [127]. A significant negative correlation was also found between BMI and the number of WM tracks connecting midcingulate cortex and subcortical regions involved in decision making and impulsive control [114]. In chronic dieters, a reduced structural integrity in the WM tract connecting the inferior frontal gyrus that is related to cognitive control and the orbitofrontal cortex that is related to reward was found with higher body fat percentage [128]. This marked negative impact of excess adiposity on the reward circuit indicate the great difficulty of reversing obesity and thus its metabolic disturbunces, the increased risk for chronic diseases as well as the earlier cognitive and memory impairment.

The majority of these studies have a cross-sectional design and no cause-effect relationship could be established between increasing BMI and reduced WM integrity and connectivity. Several mechanisms have been proposed though to explain the association between increased BMI and WM microstructural alterations (Figure 1). Obesity is associated with chronic low-grade inflammation [129] and inflammation in the hypothalamus [130] which may affect energy balance regulation and contribute to the obesity-associated insulin resistance and consequently to WM metabolism and integrity alterations [131]. Patients with abnormal DTI metrics within hypothalamus had higher values of BMI, fat mass, inflammatory markers, carotid-intima media thickness, hepatic steatosis and lower scores on cognitive tests [132]. Cholesterol profile abnormalities could be another mechanism to partly explain the reduced WM microstructural integrity in obesity as a negative association between abnormal cholesterol profiles and FA was found in the left and right prefrontal lobes in obese but not lean individuals [133]. The early elevated plasma low density lipoprotein (LDL) levels might, also, affect the WM integrity in the right frontal region, mostly in men [107]. Other proposed mechanisms are hypertension, hypothalamic–pituitary–adrenal axis dysregulation, oxidative stress, hyperleptinemia, reduced endothelian integrity and vascular reactivity, reduced cerebral blood flow, leading to cerebral hypoperfusion and cognitive and neurodegenerative changes [64, 67, 88, 134]. Genetic factors cannot be excluded as obesity and reduced WM integrity may share common genetic risk factors [135] such as the obesity risk gene neuronal growth regulator 1 that was found to be associated with lower WM integrity (2.2% lower average FA per allele) [136]. Longitudinal studies are of outmost importance to shed more light into the field and understand the cause and effect relationship between increased BMI and WM microstructural changes. Exercise seems to be neuroprotective and improve WM integrity in obese individuals [137]. WM integrity is greater with higher aerobic fitness and lower BMI, associations noticed in different hemispheres showing that hemispheric dominance patterns for aerobic fitness and obesity in relation to cognitive decline might exist [113]. Furthermore, exercise induced weight-loss in obese individuals increased structural brain plasticity in brain areas functionally related to gustation and cognitive processing such as the insular cortex, the hippocampus, and the left

cerebellar regions [138] indicating that the adverse effects of excess weight in the brain could be partly reversible with exercise.

6. Hyperglycemia

Glucose metabolism is a complex process that involves numerous regulatory pathways including central autonomic neural networks, hormonal and cardiovascular system activities [139, 140]. Being glucose the primary source of energy to the brain, alterations in glycemic metabolic processes can lead to impairment in brain structure and functionality (Figure 1). The presence of chronic hyperglycemia has been linked to the formation of ROS and proinflammatory cytokines [52, 141] that generate oxidative stress and inflammatory changes throughout the body which have been linked to micro- and microvascular alterations [142, 143]. Abundance evidence shows that there is a strong correlation between hyperglycemia and cerebral microvascular disease, alterations of the blood brain barrier, neuronal injury and brain tissue loss [48, 56]. Chronic hyperglycemia has also been implicated in the development of advanced glycation end products, that further contribute to vascular damage and cognitive deterioration through neuroinflammation pathways [49, 143]. Brain insulin resistance which is another important risk factor for cognitive deterioration which has been associated with alterations in regional cerebral glucose metabolism and brain atrophy in adults [144, 145]. Brain insulin is essential for neuroprotection, neurovascular coupling, and normal cerebral metabolism [146, 147], and any alteration in insulin signaling may further contribute to funcational and cognitive decline.

6.1 Hyperglycemia and MRI findings

Numerous research studies in the past decade have reported changes in cerebral structure [148], endothelial dysfunction and impaired cerebral vasoreactivity [149], that have been associated with an acceleration of functional decline and severe cognitive deficits in patients with T2DM [150]. The longer the disease duration and the higher levels of hemoglobin A1c, a marker of glycemic control, were linked with worse cognitive performance in T2DM patients [151]. This evidence is supported by longitudinal studies showing that higher levels of hemoglobin A1c are linked to a faster decrease in cognitive function in T2DM compared to non-T2DM populations [152, 153]. Neuroimaging studies using MRI have shown that in patients with T2DM a higher prevalence of lacunar infarcts and GM atrophy [154, 155] exists in comparison to controls without T2DM (Table 1). Few other studies have reported a generalized global atrophy [156, 157], increased CSF [148] as well as regional reductions in brain structures particularly in the hippocampus and amygdala [158, 159] (Table 1). However, evidence of the relationship between T2DM and WM is not consistent in the literature [160-162]. This lack of consensus between T2DM and abnormalities in WM structure has been attributed to a decrease in the sensitivity of MRI to detect microstructural WM changes or WMH [163]. DTI

has given new insights to the deleterious effects T2DM has on the WM network. The following section gives an overview of the existing evidence linking T2DM and changes in the microstructural WM integrity, and how these effects are associated with subtle cognitive decrements in T2DM.

6.2 Hyperglycemia and DTI findings

Several cross-sectional studies have reported significant differences in the microstructural WM in T2DM as compared to controls [23, 163] (Table 2). These results suggest that T2DM is associated with an increased risk factor for WM microstructural alterations, detectable before the structural conventional MRI abnormalities.Alterations in the WM integrity may represent early stages on WM disease and lead to disruptions in the communication between different brain regions and subsequently to cognitive deterioration. One of the first studies using DTI in T2DM found a negative association between declarative memory impairment and left temporal stem FA [164]. A negative correlation between the left external capsule FA and left anterior limb of the internal capsule FA correlated with executive function in T2DM [165]. Expanding these results, negative associations were reported between information-processing speed and MD of the uncinate fasciculus, inferior longitudinal fasciculus and splenium of corpus calosum and between memory and MD of the inferior longitudinal fasciculus in patient with T2DM, but not control subjects [23]. These associations were independent of WMH, and lacunar infarcts. Recently, DTI measures were evaluaed in a population of T2DM with mild cognitive impairment, T2DM with normal cognition and healthy controls [166]. It was found that not only T2DM- mild cognitive impairment group but also T2DM with normal cognition showed changes in RD parameters in several regions, including external capsule, temporal lobe, right frontal lobe and corona radiate [166]. These results suggest that changes in brain microstructural WM integrity are already present in early stages of the disease and can contribute to increase the risk of cognitive impairment. Although the cross-sectional design of these studies limits the causality of the results, the consistency of the findings across populations makes evident that chronic hyperglycemia is linked with WM microstructural integrity, and that these changes are associated with cognition even when no evidence of other MRI findings are present.

To summarize, evidence has shown that chronic hyperglycemia is associated with microsctructural WM abnormalities, with most of these changes present in the frontotemporal region [164-166]. DTI changes were also associated with cognitive performance in the T2DM population, but not in the controls [23, 164-166]. These subtle cognitive deficits were especially observed in information-processing speed, executive function and memory [164-166]. Given the relatively new nature of these evidence, and the lack of longitudinal studies, it is difficult to determine a causality between the changes described in DTI parameters and the presence of chronic hyperglycemia. However, the amount of evidence gathered from the previous studies

allows us to determine that there's a clear association between microstructural WM changes, hyperglycemia and cognitive functionality.

7. Hypertension

Hypertension affects approximately one third of the global population and is considered the leading preventable cause of premature death worldwide [167]. Hypertension has been part of the MetS definition since its first description in 1923 [15] and seems to impact brain structure and function.

7.1 Hypertension and MRI findings

The relationship between hypertension and cognitive decline has been studied numerously as hypertension leads to small vessel disease and plaque formation, arterial hypertrophy and cerebral vasoconstriction, all of them leading directly or indirectly through cerebral circulation dysregulation and reduced cerebral blood flow to atrophy or WM lessions, silent lacunar infarcts [37, 38], increased CSF volume [168] and finally to dementia, vascular dementia and Alzheimer's disease [169]. Hypertension is considered a major risk factor for the development of WMH, WM lessions, lacunes and cerebral microbleeds [170, 171] and is related to brain volume reductions, specifically in hippocampus, which may play a significant role to neurodegeneration in Alzheimer's disease [172, 173] (Figure 1; Table 1).

7.2 Hypertension and DTI findings

Hypertension seems to negatively impact WM mictrostructure and cognitive function (Table 2). Hypertension was associated with lower FA in both normal appearing WM and WM lessions and with higher MD in WM lessions in patients with small vessel disease [174]. Specifically, the odds ratios for the risk of impaired microstructural integrity assessed by FA in hypertensive patients were 3.1 and 2.1 in normal appearing WM and WM lessions, respectively, compared to normotensive patients [174]. Hypertensive patients presented decreased FA and increased MD in the left superior longitudinal fasciculus that connects areas of fronto-parietal networks involved in executive function, attention, control and working-memory processing and had decreased executive functions and attention compared to normotensive patients [175]. This was supported by the study of Maillard et al., who found increased systolic BP to be linearly associated with decreased regional FA and increased MD in the anterior corpus callosum, the inferior fronto-occipital fasciculi, and the fibres that project from the thalamus to the superior frontal gyrus in yound adults [176]. Hypertensive patients, and mostly those with uncontrolled hypertension, had a lower FA in the splenium and a significantly higher MD in both the anterior body and the splenium of the corpus callosum compared to controls indicating impaired microstructural integrity associated with lower cognitive function [177]. The authors of this

study also found that 14 to 60% of the relation between reduced callosal microstructural integrity and global cognitive function was explained by small vessel disease elsewhere in the WM [177]. In another study, lower integrity of the splenium of the corpus callosum predicted elevated systolic BP which in turn was associated with brain connectivity variations in cognitively healthy adults and slower information processing; associations mediated by the functional connectivity of the right superior temporal gyrus with the resting-state ventral attention network [178]. The duration of the disease and control of hypertension were not fould to significantly affect the hypertension effect on WM integrity but the genetic makeup played an important role as decreased FA and increased MD were found in the uncinate fasciculus and inferior fronto-occipital fasciculi of hypertensive patients, with even lower FA and higher MD values in Apolipoprotein E4 carriers [179]. According to longitudinal studies greater and variable systolic BP levels were associated with lower WM integrity of frontoparietal and medial temporal tracts (uncinate and superior lateral fasciculi bilaterally) over a ten year follow-up period, independent of markers of arterial stiffness or cardiometabolic conditions (age, race, stroke history, antihypertensive medication use) [180]. On the other hand, another study found no association between hypertension and WM variability either at baseline or at the seven year follow-up [181]. The mechanisms of how hypertension affects WM integrity have not been not fully elucidated (Figure 1). Axonal loss or dysfunction assessed by N-acetylaspartate reductions seems to be a principal process of WM mictrostructural damage in hypertension [182]. Increased aortic arch stiffness has been also proposed to explain the relationship between hypertension and DTI measures of brain injury as it is associated with incipient brain injury before overt brain abnormalities become apparent [183]. This probably happens through increased aortic arch stiffness involvement in the pathogenesis of WMH, vascular dysautoregulation due to arterial remodeling leading to reduced WM blood flow, hypoxemia and myelin break-down or through exaggerated flow reversal and plaque embolism or greater pressure and/or flow transmission from the aorta to the cerebral circulation or disproportionate stiffening of the aortic arch with little change in carotid artery stiffness that may facilitate transmission of excessive pulsatile energy into the cerebral microcirculation [183]. In addition hypertension seems to disrupt endothelial cell integrity and increase blood-brain barrier leakage, oxidative stress, brain cell toxicity and small vessel disease-related brain damage [184, 185].

In conclusion, available evidence indicate hypertension, particularly increased systolic BP, as an important factor for WM microstructural damage and cognitive decline. Antihypertensive therapy has been suggested to reduce the risk of impaired microstructural integrity and delay cognitive decline [174, 177], although this is not supported by other studies [176, 179]. More research is needed to fully understand the underlying mechanisms and the effect of

hypertension treatment as well as more longitudinal studies to determine the cause and effect relationship between hypertension and WM microstructure alterations.

8. Dyslipidemia

Dyslipidemia has been recognized as a major cause of cerebrovascular and cardiovascular disease (170). However, the relationship between dyslipidemia and cognition is more complex and contradictory.

A large cross sectional study of 1037 post-menopausal women revealed an association between high LDL and total cholesterol levels and cognitive impairment [186]. A longitudinal study of 1159 elderly Chinese individuals found an association between elevated total cholesterol and LDL and accelerated cognitive decline [187]. On the contrary, other large studies of older adults have found an association between higher triglycerides [188] and LDL and better cognitive performance [189]. Furthermore, a recent longitudinal study of 192 adults with Alzheimer's disease, rising LDL levels were associated with a trend towards improvement in functional performance [190]. Given the well established role of lipid lowering therapy with statins in cardiovascular disease secondary prevention, the potential of statins in the treatment and prevention of dementia has been explored in several randomized controlled trials. A recent re-analysis of data from a prior, negative trial of simvastatin in Alzheimer's disease after completion of a longer follow-up revealed a non significant trend towards slowing of disease progression from mild to moderate stage [191]. This effect was seen only in Apolipoprotein E4 carriers.

These findings, however, are contradicted by a meta-analysis of two large trials including a total of 26340 patients 40 years and older with cardiovascular risk factors, which found no evidence that statin therapy prevents cognitive decline or dementia [192]. Similarly, a meta-analysis of 4 large randomized trials of statin treatment in patients with Alzheimer's disease found no effect on cognitive performance[193]. There is a marked paucity of studies focused on vascular dementia which conceptually would be more likely to be related to dyslipidemia.

8.1 Dyslipidemia and MRI findings

The major limitation of dyslipidemia studies on brain structure is that dyslipidemia rarely occurs in isolation and it is usually accompanied by hypertension and impaired glucose metabolism. In that regard, patients with familial hypercholesterolemia (FH) present a unique opportunity to examine the effect of isolated dyslipidemia on brain structure. A study of 39 young individuals (aged 6-48) with heterozygous FH on statin treatment found no difference in the number of silent brain infarcts and WMH compared to 25 age-matched healthy controls

despite significantly higher cholesterol levels in the FH group [194]. A smaller case control study of young adults with homozygous FH yielded similar results despite markedly higher cholesterol concentrations in the FH group [195]. Two similar case-control studies middle-aged, hypertension-free adults with heterozygous FH and age-matched controls found no difference in WM lesions despite significantly higher serum cholesterol levels [196, 197]. Lastly, a larger study explored the occurrence of WMH in 33 older than 65 years with heterozygous FH [198]. They were compared to middle aged counterparts with FH and healthy controls of similar age. Among these 33 older adults with FH, those who were older had more WMH. However there was no difference in the number of WMH when compared to younger, middle aged adults with FH or healthy adults of similar age [198]. Lastly, a study of 82 healthy and cognitively intact adults revealed a robust association between elevated LDL levels and lower GM volume, but no association with WM volume[199].

8.2 Dyslipidemia and DTI findings

Data on the effect of dyslpidemia on WM microstructural integrity are very sparse. In one cross-sectional study of 125 older adults having underwent MRI with DTI, an association between higher cholesterol levels and lower FA was found for several areas within the right hemisphere [200]. When adjusting for age, gender and mean arterial BP, the associations remained significant for the superior longitudinal fasciculus, right hemisphere precentral WM, right hemisphere caudal middle frontal WM and the right precuneus. The reason for the right hemisphere predilection is uncertain. This relationship between cholesterol and FA was driven almost exclusively by LDL, whereas triglyceride levels had the least potent association with WM integrity. Elevated LDL was associated with higher RD and AD values in the aforementioned areas. The effect was more potent on RD in anterior regions and AD in posterior regions.

Taken together, these findings suggest no independent association between dyslipidemia and traditional imaging markers of WM disease such as silent infarcts, WM volume atrophy and WMH. The isolated effect of dyslipidemia on WM microstructure is inadequately studied.

9. Limitations

The studies on the effects of MetS and its components on WM mictrostructure, cognition and aging have several limitations. One of the major limitations is that most of the studies have a cross-sectional design that does not allow causal inference and prospective studies for understanding the cause and effect relationship of MetS and the reduced microstructural brain tissue integrity are of outmost importance. Another limitation is that in most studies the examination of the individual MetS components is not always feasible, because in most cases

the components co-exist i.e. T2DM with obesity, obesity with hypertenstion, etc, thus it is not always easy to draw clear conclusions on the individual effects of MetS components. Therefore, larger prospective studies that would allow to separate the individual components into the separate groups and also study the interactions among them prospectively are needed.

10. Summary

A growing body of evidence indicates that MetS is associated with increased brain microstructural damage, worse cognitive performance and increased risk for dementia and Alzheimer's disease. All MetS components have an individual negative impact on WM integrity, but their itneractions and cumulative effects are not well known. Hyperglycemia with brain inuslin resistance, hypertention and obesity have been studied the most and the results suggest the most robust negative effects on WM integrity and brain structure. Research is still lacking in understanding the additive and cumulative effects of each MetS component as most of the studies have examined either the individual components by themselves or some but not all of them. This piece of knowledge would be very important for the future direction of interventions for the prevention and treatment of cognitive decline and dementia. Furthermore, the mechanisms that lead to WM microstructural damage need to be further elucidated as all MetS components have distinct but also share similar mechanisms and pathways but the picture is still not very clear about which mechanisms are the most prevalent ones and how everything is linked. MetS is an important condition with several impacts on brain health, affects all age groups and should not be underestimated when it comes to cognitive and memory decline and brain aging. More studies of prospective design are needed as well studies on the mechanisms, therapy and additive/cumulative effects of the separate MetS components.

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Figure 1 Legend

Figure 1: Conceptual model that describes the main mechanisms by which metabolic syndrome and its components lead to structural and functional brain abnormalities, accelerate brain aging and cognitive decline. Cellular, vascular and genetic factors as well as inflammation and oxidative stress are the main contributors to this complicated process.

Abbreviations: neuronal growth regulator 1 (NEDR1); apolipoprotein E4 (ApoE4); reactive oxygen species (ROS); blood brain barrier (BBB); small vessel disease (SVD); macrovascular disease (MVD); gray matter (GM); white matter (WM); white matterhyperintensities (WMH); fractional anisotropy (FA); mean diffusivity (MD); axial diffusivity (AD); radial diffusivity (RD)

Table 1. Brain anatomical and functional abnormalities for Metabolic Syndrome and individual Metabolic Syndrome components

	Brain Anatomical and Functional Alterations			**Cognitive Alterations**
Metabolic Syndrome	GM	↓ - ↓↑	Lower global brain volume [36] No focal ischemic lesions [41] No changes [41]	Cognitive impairment [47], slower processing speed [44]
	WM	↑ ↑	Periventricular WMH [39], Subcortical WM lesions [39]	
	Infarcts	↑ ↑	Infarcts [39] Silent lacunar infarcts [37, 38]	
	CSF	↑	Increased CSF [45]	
Obesity ↑Waist Circumference [15]	GM	↓ ↓	Lower global brain volume [36, 89-93] Lower GM volumes [91, 93-99]	Worse cognitive decline [86]
	WM	↓ ↑ ↓↑ ↑ -	Lower WM volume [94, 101, 102] Increased WM volume [95, 97] No change [91, 93], Increased WMH [104] Multiple findings [103]	
	Infarcts	↑ ↑	Infarcts [39] Silent lacunar infarcts [37]	
	CSF	↑	Increased CSF [106]	
Hyperglycemia >100 mg/dl Fasting glucose [15]	GM	↓ ↓	Lower global brain volume [36, 148, 151, 154, 155, 161, 201] Hippocampal atrophy [158, 159]	Worse cognitive decline [152, 153]
	WM	↑ ↑ ↓↑	WMH [151, 162] Periventricular WMH [39] No change [148, 155, 159],	
	Infarcts	↑ ↑ ↑	Infarcts [39] Silent lacunar infarcts [37, 38, 159, 202] Cortical/subcortical infarcts [151]	
	CSF	↑ ↓↑	Increased CSF [148] No changes [163, 203]	
Hypertension ≥130 mmHg SBP ≥85 mmHg DBP [15]	GM	↑ ↓↑	Hippocampal atrophy [172, 173] No atrophy [180]	Worse executive function, [175, 177]
	WM	↑	WMHs [36, 180, 204-208]	

		↑ ↑	Periventricular hyperintensity [39] Subcortical WM lesions [39, 171]	
	Infarcts	↑ ↓ ↑	Infarcts [39] Silent lacunar infarcts [36-38] Microbleeds [170, 171]	
	CSF	↑	Increased CSF volume [168]	
Dyslipidemia TGL (≥150 mg/dl) HDL ((<40 mg/dl men; <50 mg/dl women) [15]	GM	↓	Lower global brain volume [199]	Cognitive impairment [186, 187] Improvement cognitive performance [189] Improvement functional performance [188, 190]
	WM	↑ ↓↑	Subcortical WM lesions [39] No changes [194-197]	
	Infarcts	↑ ↓↑	Silent lacunar infarcts [37] No changes [194, 195]	
	CSF	-	-	

GM: gray matter; WM: white matter; WMH: white matter hyperintensities CSF: Cerebrospinal fluid SBP: Systolic Blood Pressure DBP: Diastolic Blood Pressure

Table 2. DTI findings for Metabolic Syndrome and individual Metabolic Syndrome components

	DTI Microstructural abnormalities			**Cognitive Alterations**
Metabolic Syndrome	FA	↓	Reduced FA in corpus callosum [40, 46], right external capsule, deep white matter of the right frontal lobe [42, 43], angular gyri [45], optic radiations, medial longitudinal fasciculi [40], dorsal cingulum bundle [46]	Cognitive impairment [44, 47]
	MD	↓↑	No change [45]	
	AD	↑	Increased AD values in L post-central gyrus [45]	
	RD	↑	Increased RD in angular gyri [45], dorsal cingulum bundle [46]	
Obesity	FA	↓	Reduced FA in superior and inferior right longitudinal fasciculus [108], medial lemniscus regions of the midbrain, corona radiate [110], mammillary bodies [109], right inferior occipito-frontal fascicle, thalamic radiation (including optic radiation) [108, 109], internal capsule [108, 110], corticospinal tracts [107-109], corpus callosum [108, 109, 111, 112, 115], cingulum [108, 110, 113, 114], middle and superior cerebellar peduncles [110, 120], uncinate fasciculus [108, 121], right brainstem [107], corona radiate [110]	Altered motor control, coordination, reward seeking, motivation/drive, inhibition, emotional regulation, learning, cognitive control, memory, decision making and impulsive control [107-114] spatial working memory [123] Accelerates aging and cognitive decline [120]
	MD	↓ ↑ ↓↑	Reduced MD in uncinate fascicles and inferior occipito-frontal fascicles [109], bilateral corticospinal tract and anterior thalamic radiation [120] Increased MD in corpus callosum [111] and right superior longitudinal fasciculus [120] No change [108]	
	AD	↓	Reduced AD in corpus callosum [111, 115], bilateral corticospinal	

			tract and anterior thalamic radiation [120]	
		↑	Increased AD in right corona radiata and superior longitudinal fasciculus [111, 120]	
		↓↑	No change [108]	
	RD	↑	Increased RD in corpus callosum [111, 115]	
		↓	Lower RD in the right middle cerebellar peduncle [120]	
		↓↑	No change [108]	
Hyperglycemia	FA	↓	Reduced FA in cingulate bundle and uncinated fasciculus [209], frontal and temporal lobes [163, 164]	Poor cognitive performance (20, 121-123) Impaired declarative memory [164], information-processing speed [23] executive function [165] (121-123)
	MD	↑	Increased MD in bilateral frontal lobe, cerebellum, temporal lobe, left parahippocampal gyrus, left fusiform gyrus, left cuneus [163], superior longitudinal fasciculus, uncinated fasciculus, inferior longitudinal fasciculus, corpus calosum splenium [23]	
	AD			
	RD	↑	Increased RD in bilateral frontal lobes [163]	
Hypertension	FA	↓	Reduced FA in right anterior thalamic radiation, left cingulum cingulated gyrus, forceps major, superior longitudinal fasciculus [176, 180], corpus callosum splenium [177]	Decreased executive function, attention, control and working-memory processing and attention [175] lower cognitive function [177]
	MD	↑	Increased MD in bilateral anterior thalamic radiation, bilateral corticospinal tract, forceps major, superior longitudinal fasciculus [176], anterior corpus callosum body and splenium [177]	
	AD	↓↑	No change [181]	
	RD	↓↑	No change [181]	
Dyslipidemia	FA	↓	Reduced FA in superior longitudinal fasciculus, right precentral WM, right causal	Cognitive impairment [186, 187]

			middle frontal, right precuneus [200]	
	MD	-	No reports	
	AD	↑	Increased AD in superior longitudinal fasciculus, right precentral WM, right causal middle frontal, right precuneus [200]	
	RD	↑	Increased RD in superior longitudinal fasciculus, right precentral WM, right causal middle frontal, right precuneus [200]	

FA: fractional anisotropy; MD: medial diffusivity; AD: axial diffusivity; RD: radial diffusivity

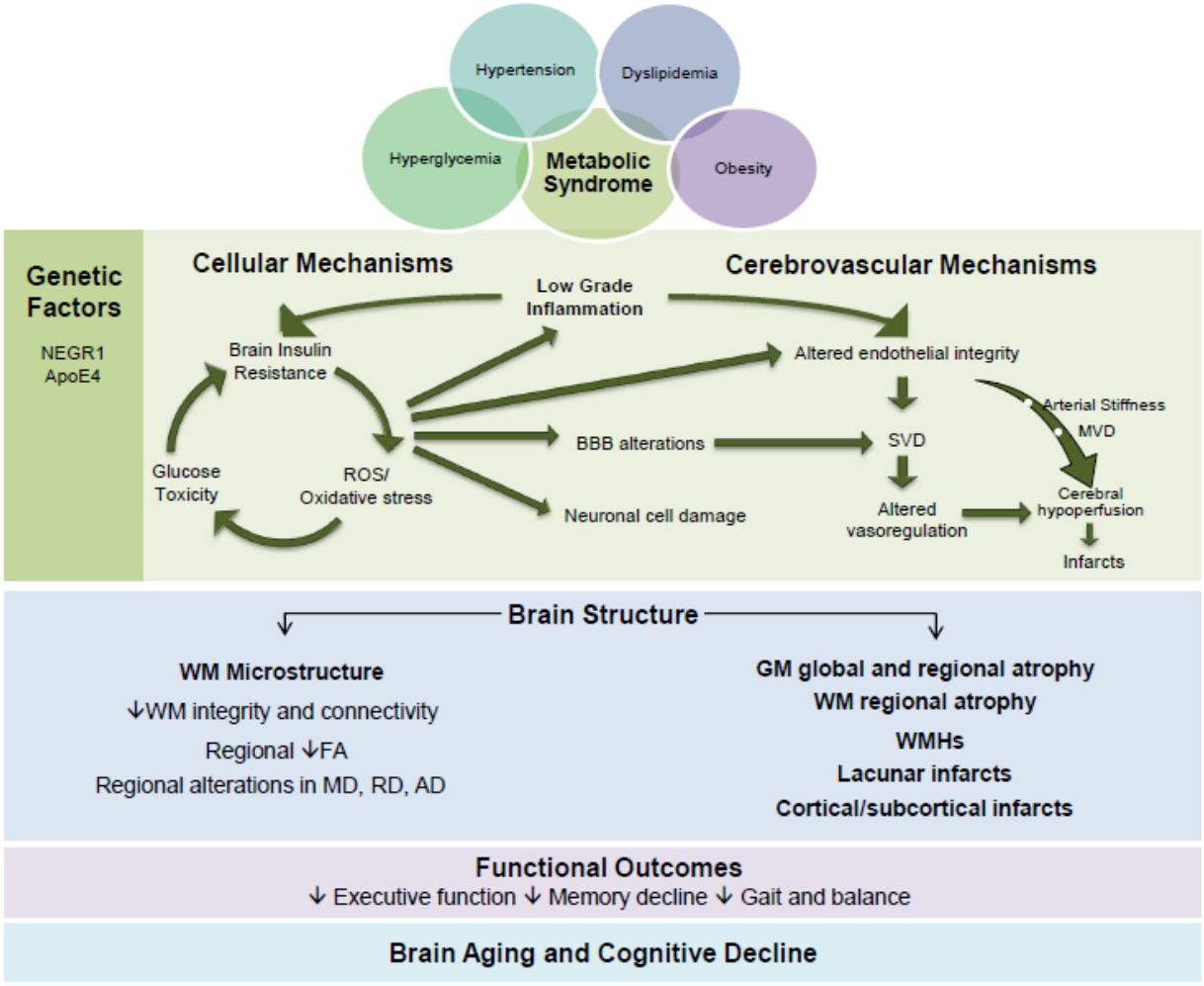

Figure 1