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Review

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Cognitive Impairments and Associated Structural Brain Changes in Metabolic Syndrome and Implications of Neurocognitive Intervention

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Currently, metabolic syndrome has become a global health problem. Alterations in neurocognitive functions among patients with metabolic syndrome are important issues in this disorder. In this paper, studies on metabolic syndrome were reviewed and their importance emphasized for the benefit of experts and policy makers. Metabolic syndrome activates inflammatory mediators that disrupt brain metabolism. These mediators can be activated by metabolic inflammation and microvascular disorders and may further cause damage to the white matter and impair cognitive function. These alterations can result in serious changes in cognitive abilities. The association between cognitive changes and metabolic syndrome has been independently evaluated in several studies. In addition, some areas of research in the field of metabolic syndrome include the effectiveness of neurocognitive interventions to enhance normal behaviors or reduce risky behaviors in patients. Structural brain correlates of health-related behaviors provide a basis for designing more effective behavioral interventions by identifying the corresponding brain regions and using behavioral interventions.

Key words: Brain structure, Metabolic syndrome, Neurocognitive intervention

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INTRODUCTION

Metabolic syndrome, a non-communicable disease (NCD), has become a global health problem. The World Health Organization has cited the metabolic syndrome as a highly prevalent disease.[1] Metabolic syndrome is a collection of clinical and laboratory abnormalities that cause many problems in an individual and is associated with an increased risk of NCDs such as cardiovascular disease and diabetes mellitus. In addition to the health problems, metabolic syndrome also lowers the quality of life and increases economic burden. The risk factors for metabolic syndrome can cause health problems. The worldwide prevalence of this disease in the elderly ranges from 20% to 25%. Nearly 20% of residents in western Iran and 30% of Tehran residents suffer from metabolic syndrome. Obesity, a risk factor for metabolic syndrome, causes the death of 100,000 Americans annually.[2-4] Other challenges include the incidence of obesity and diabetes mellitus in children and adolescents, which has recently become a health concern.[5,6]

Currently, neurocognitive dysfunctions in patients with metabolic syndrome is an important issue associated with the disorder, however the issue has not been well addressed.[6,7] Therefore, in the present study, a literature search was performed to determine the

structural brain changes in metabolic syndrome patients. Finally, after selecting the relevant studies, the relationship between metabolic systems, neurocognitive impairment, and brain structure in metabolic syndrome were the areas of particular focus. Brain mapping studies were used for confirmation of findings.

BRAIN STRUCTURAL CHANGES IN METABOLIC SYNDROME

Mediators associated with metabolic syndrome are correlated with pathways that activate metabolic inflammation and microvascular disorders and may further cause damage to the brain white matter and reduce cognitive function (Fig. 1).[8] Many complications of metabolic syndrome can be attributed to glucose fluctuation, an important indicator of the disorder. Insulin resistance is a serious condition in metabolic syndrome which can cause fluctuations in blood glucose and increase serum insulin levels in the affected patients. It is well-known that insulin resistance can alter insulin signaling in the brain, and with oxidative stress, can cause glycation of the brain tissue and lead to brain inflammation.[2]

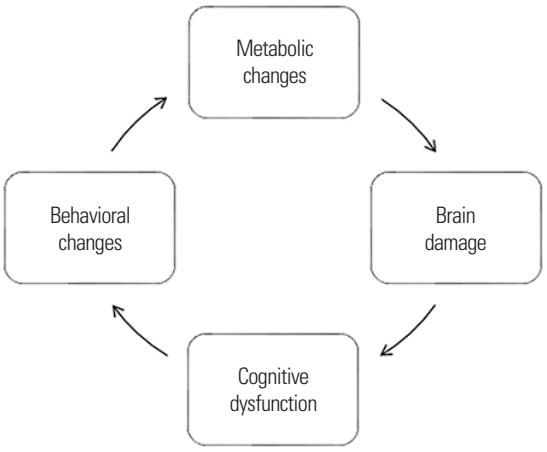

Figure 1. Metabolic changes, brain damage, cognitive dysfunction, and behavioral changes are in a cyclic relationship and any change in one part can affect the others.

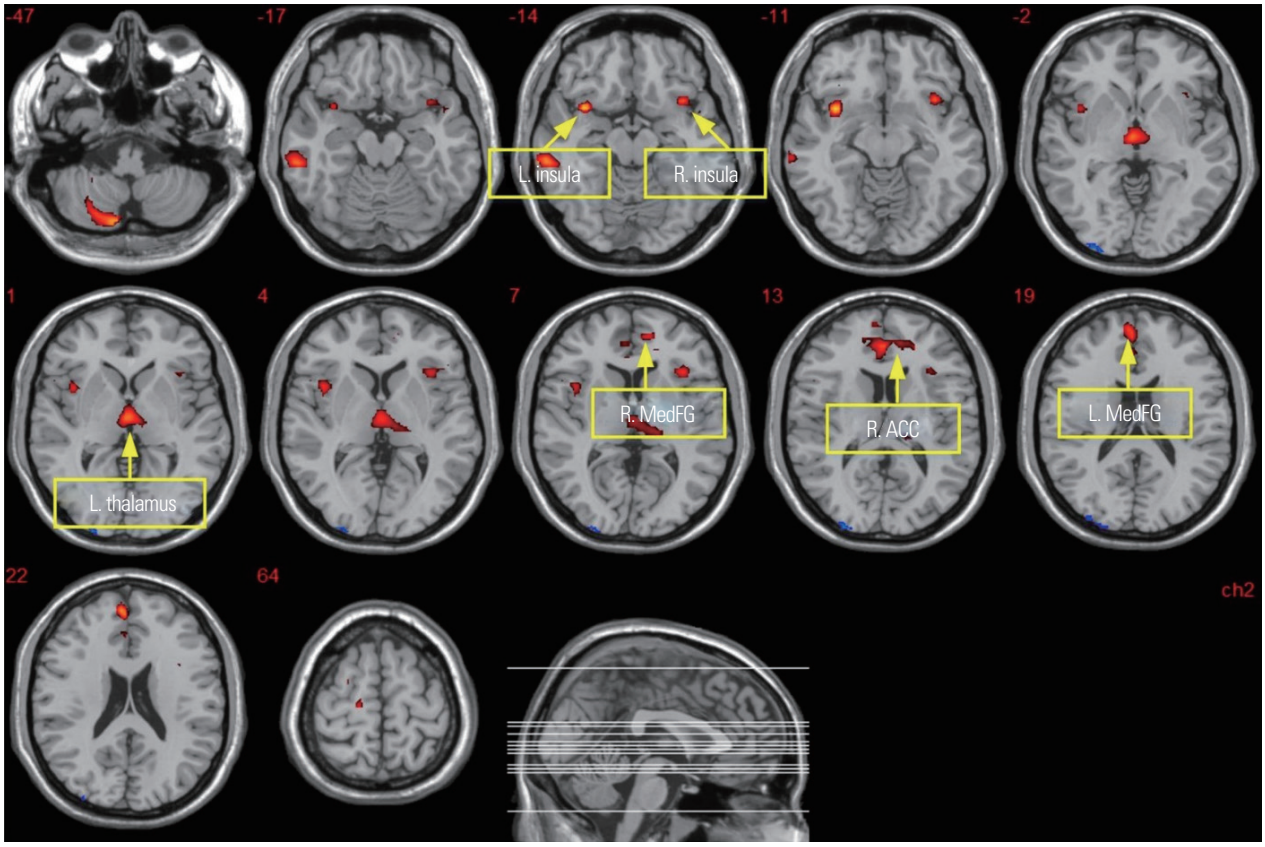

Figure 2. The red regions are reductions in grey matter volume in obese patients versus normal weight patients. The blue regions are increases in grey matter volume in obese patients versus normal weight patients. L, left; R, right; MedFG, medial frontal gyrus; ACC, anterior cingulate cortex (P=0.005, cluster size >50). Reprinted from Wang H, et al. Sci Rep 2017;7:40595.[9]

A high glucose level in the brain associated with metabolic syndrome is observed in a variety of cognitive dysfunction including dementia. In addition, obesity and hypertension are considered modifiable factors in dementia and severe degeneration of the brain (Fig. 2).[9] In previous studies, the control of metabolic syndrome was shown to slow down the process of brain degeneration in both white and grey matter tissues.[4,10] Metabolic syndrome was a risk factor not only for diabetes mellitus and cerebrovascular disorders but also forthe progression of Alzheimer disease.[11]

Furthermore, metabolic syndrome can accelerate the onset and progression of cerebral small vessel dysfunctions by causing changes in the structure and function of the blood vessels, which can lead to mild bleeding, white matter damage, and brain atrophy.[12] Most of these atrophies occur in deep areas of the white matter, especially in the right frontal lobe, brain gyri, optic radiations, and dorsal cingulum bundle.[2]

In addition to direct effects on brain tissue, metabolic syndrome can cause indirect damage, which has not been fully addressed. For example, sedentary lifestyle, a risk factor for metabolic syndrome, decreases oxygenation and circulation and can cause long-term damage to neural structures. Thus, brain oxygenation and elimination of toxic substances are significantly improved by changing lifestyle and promoting physical activity. This process independently can also improve brain function and subsequently, quality of life.[6]

COGNITIVE CHANGES IN METABOLIC SYNDROME

In addition to numerous studies conducted on the structural changes in the brain of patients with metabolic syndrome, the association between cognitive changes and metabolic syndrome has been independently evaluated in several studies. The attention and neuromuscular connections were reduced in cognitive tasks associated with the parietal and occipital lobes in elderly patients with metabolic syndrome.[13,14] Based on various study results regarding metabolic syndrome effects on brain structure and consequent changes in brain tissue integrity and decrease of cognitive ability,[4] obesity, hypertension, and hyperglycemia apparently have the greatest effect in reducing cognitive performance and abilities.[2,15] The effects of metabolic syndrome on cognitive skills included a decreased decision-making ability, reduced memory function, and decline in the reward system, and apparently a reduction of cognitive efficiency can decrease the individual's ability in the attributed skills.[16]

Metabolic syndrome is not the only cause of impaired brain metabolism and the resulting cognitive and structural changes. Currently, metabolic disorders have attracted increased attention among metabolic diseases. In addition, due to the high prevalence of metabolic syndrome and diabetes mellitus, as well as the slowing down of metabolism in all organs including the brain, the importance of metabolic syndrome has increased. For example, brain metabolism plays a major role in pathogenesis of some neurological disorders such as Alzheimer's disease[17-19] by hypometabolism-promoted Aβ deposition.[20] Furthermore, the findings based on proton magnetic resonance spectroscopy have shown the alteration of metabolite concentration in various areas of the brain in different neurometabolic disorders such as multiple sclerosis,[21] brain tumors,[22,23] epilepsy,[24,25] Alzheimer disease,[26-28] and dementia[29] is significantly correlated with cognitive decline. Based on the abovementioned studies, metabolic diseases of the brain can lead to changes in the structure and function of brain areas associated with cognition; most metabolic diseases of the brain cause changes in neuronal structure and cognitive decline.

In several studies, significantly decreased grey matter volume in the cerebellum, thalamus, pre-central/post-central gyrus, middle temporal gyrus, superior parietal lobule, and increased grey matter volume in the pallidum and hippocampus were observed in patients with obesity.[30-32]

COGNITIVE NEUROLOGICAL INTERVENTIONS IN METABOLIC SYNDROME AND THEIR EFFECTIVENESS

In some areas of research in the field of metabolic syndrome, the effectiveness of neurocognitive interventions to enhance normal behaviors or reduce risky behaviors in patients is investigated. For example, in a study conducted by Garcia-Silva,[33] 48 cognitive behavioral interventions such as saying "no" effectively, anger control, and appetite control, were taught to volunteers with metabolic syndrome. After 3–6 months, biochemical indices and body mass index were remeasured and significant changes were observed in

these indices. The main change due to the interventions was the success of individuals in following a diet for metabolic syndrome. In another study, researchers showed that cognitive-behavioral therapy over the course of 12 months had a positive effect on weight loss in obese patients. However, behavioral interventions without the involvement of cognitive methods, did not have any significant effect on weight loss.[34] Another study by Augustijn et al.[35] on children showed that cognitive interventions, along with other interventions, could be effective in controlling weight and binge-eating behavior. A combination of cognitive interventions and other interventions such as physical activity promotion can lead to permanent changes in the behavior, habits and lifestyle of children. The authors found a significant increase in total ($P < 0.001$) and cerebellar ($P < 0.001$) grey matter in patients with obesity after the multidimensional intervention compared with healthy children.

In several studies, the relevance and effectiveness of these interventions on structural changes in the brain were investigated and the mechanisms of cognitive intervention effects were evaluated. In a study by Shigaeff et al.,[13] significant increases in the grey matter volume and total brain mass were observed when food choices and dietary behaviors were modified (which consists of a set of nutritional behaviors). The volunteers who participated in the study were adults with metabolic syndrome. In a meta-analysis study recently conducted, cognitive therapy significantly reduced binge-eating episodes and abstinence from binge-eating.[36]

CONSIDERATION OF STRUCTURAL BRAIN CHANGES TO DESIGN EFFECTIVE INTERVENTIONS

Attention to behavioral patterns in metabolic syndrome is important in two aspects. First, the behaviors associated with metabolic syndrome including high-risk behaviors such as abnormal nutritional habits and sedentary lifestyle should be addressed. Most of the interventions in this area are cognitive behavioral interventions to create true beliefs, normal behaviors, and promote healthy lifestyles. Second, the behavioral changes caused by cognitive impairments are associated with structural disorders of the brain due to metabolic syndrome.[1,3,4] For example, the effects of metabolic syndrome on memory have been shown in several studies, and this cognitive impairment can lead to serious behavioral problems in patients.[14-16]

Therefore, an important goal of cognitive-behavioral interventions in metabolic syndrome is the consideration of various disorders. Cognitive-behavioral interventions in both preventive and therapeutic dimensions should be added to clinical guidelines for metabolic syndrome management to prevent the behavioral disorders caused by cognitive impairments in patients. In addition, structural brain correlates of health-related behaviors provide a basis for designing more effective behavioral interventions by identifying the corresponding brain regions and using brain-targeted behavioral interventions.[33-35]

Consequently, large studies should be performed to fully understand the map of structural changes in the brain of subjects with metabolic syndrome, the corresponding behaviors, interventions to manage the behaviors, and prevent future structural brain disorders.

CONCLUSION

Most of the neurocognitive interventions studied in patients with metabolic syndrome have been designed to modify lifestyles, promote normal behaviors, and reduce risky behaviors, but less attention has been given to the neural capacities needed to institutionalize and maintain normal health behaviors, a subject generally studied in social neuroscience. Human behavior is coded in the brain, and the development of a specific part of the brain is needed for manifestation of human behavior. For example, some parts of the cerebral cortex such as the superior medial frontal are associated with appetite control behavior and the development of brain capacity in this area is associated with such behavior. Interventions to activate or develop this part of the cortex should be performed to provide the neural capacity needed to manifest and maintain the appetite-related behavior. Otherwise, other interventions, even if they have short-term effects, will not lead to sustainable behavior in the long-term. Therefore, in metabolic syndrome, the first step in behavioral interventions to establish sustainable behavior and lifestyle modification is to identify the neural correlates of the normal behaviors and focus on their development or activation concordant with the patient's age. Cognitomics is the evaluation of the relation-

ship between diseases and cognitions and may provide relevant answers.[37]

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: AP; drafting of the manuscript: FM and SN; critical revision of the manuscript: SA and PKM; administrative, technical, or material support: SN.

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