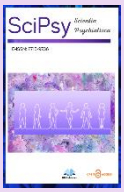

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The Relationship between Metabolic Syndrome and Depression: A Literature Review

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A B S T R A C T

Depressive disorders are a group of disorders with characteristics of loss of happiness, feeling useless or desperate, withdrawn or uninterested in common activity, and loss of energy or hypoactivity almost every day. Metabolic syndrome (MetS) is a clustering of conditions consist of central obesity, dyslipidemia, glucose intolerance, and hypertension. Both diseases are considered important risk factors of morbidity and cause of quality of life impairment. Some mechanisms are submitted to explain the correlated mechanism between MetS and depression.

1. Introduction

Depressive disorders are a group of disorders with characteristics of loss of happiness, feeling useless or desperate, withdrawn or uninterested in common activity, and loss of energy or hypoactivity almost every day.[1,2] Depression is one of the most frequent mental disorders that causes disability and effects on quality of life with 16,2% lifetime prevalence.[3] Depression prevalence and incidence increases globally and is visualized as second death cause by 2030.[4] Individuals with depression commonly present with other comorbidities. Metabolic syndrome (MetS) is one of comorbidities that can be found along with depression.[3] Depression and MetS have been recognized enough in many studies as important risk factors of morbidity and cause of quality of life impairment.[3,5,6]

Metabolic syndrome (MetS) is a clustering of conditions consist of central obesity, dyslipidemia, glucose intolerance, and hypertension.[7] MetS increases individual risk factors of both cardiovascular disease and type 2 diabetes, especially in old age.[5,8,9] Based on International Diabetes Federation (IDF), approximately 20–25% adult population in the world have MetS.[7] MetS, including related metabolic biomarkers, is thought to be related to depression.[4] Individuals with one or more metabolic disorder show a higher risk of depression development.[9] MetS is considered to have association with early and late depression with 1%-5% prevalence in older.[8] MetS is suggested significantly associated with depression at age 60 years or more.[2] However, variation on individual risk still have important role affecting comorbidity of MetS and depression in different population.[5] These differences are caused by

heterogeneity and complexity of both MetS and depression as multifactorial diseases, for examples, lifestyle factors related metabolic disorders (e.g., chronic alcohol consumption and smoking habits, and also reduced physical activity) show a higher risk of depression incidence.[5,9] MetS and depression's co-occurrence is suggested to have overlapping pathophysiological between these conditions.[4] Therefore, a comprehensive study is necessary to evaluate depression risk among metabolic syndrome patients and its possible correlation. [3,5,9]

Metabolic syndrome

Metabolic syndrome is a bundle of conditions consists of central obesity, dyslipidemia, hypertension, and insulin resistance.[5,8,10] MetS people have a higher risk for cardiovascular disease CVD), diabetes mellitus (DM), and other complications with higher mortality. Many MetS patients are also reported having depression with poor quality of life.[11] MetS development is related to unhealthy lifestyle, such as smoking and alcohol drinking habit, poor diet with high fat and calorie, inadequate physical exercise, and commonly increased by age being. Research reported MetS prevalence is higher in women and/or people at age 60 years or older.[10]

Metabolic syndrome is characterized by the presentation of at least three conditions or more of the following conditions: 1) fasting blood glucose ≥ 110 mg/dL) or use of antidiabetic medication; 2) hypertriglyceridemia ≥ 150 mg/dL) or use of anti-hypertriglyceridemia medication; 3) HDL < 40 mg/dL in men or < 50 mg/dL in women; 4) blood pressure (BP) of ≥130/85mm Hg or use of antihypertensive medication; and 5) waist circumference ≥ 90 in men or ≥ 80 cm in women.[7]

Metabolic inflammation is characterized by alteration of circulating cytokine profiles, tissue infiltration of immune cell, and activation of inflammatory pathways within its parenchyma. In obese individuals, TNF-α level and proinflammatory cytokine are increased in adipose tissue and cause regulatory impairment of blood glucose levels mediating by insulin. This mechanism is used as a main explanation to understand inflammation and insulin resistance relationship and role of obesity on type 2 DM development.[5]

In obese individuals, most circulating proinflammatory cytokines are elevated and thus cause metabolic inflammation and metabolic dysfunction. IL-1β, IL-6, and TNF-α activate stress kinase (e.g., IKK, JNK, p38 MAPK) in muscle and fat, lead to phosphorylate inhibitory serine accumulation on IRS1 (insulin receptor substrate 1) and directly affect insulin receptor downregulation and signal transduction blockade. IL-12 and IFN-γ are cytokines which play important roles in immune system activation. IL-12 contributes to naive $CD4^+$ T cells (Th1) differentiation and IFN-γ contributes to macrophages' pro-inflammatory M1 polarization and induces insulin resistance. This activation of immune system is found in obesity and insulin resistance relationship. In addition, chemokines (CCL2 and CXCL1) are known as chemoattraction which promote migration of immune cells from bone marrow into tissues.[5]

Leukocytosis can be found in metabolic syndrome with increased total monocyte, neutrophil, and lymphocyte counts. This laboratory finding correlates significantly with body mass index (BMI), percentage of body fat, and insulin resistance. Increasing in non-classical and intermediate monocytes and decreasing in classical monocytes are found in obese patients' blood. Classical monocytes are correlated with higher CCR expression (CCL receptor). Surface chemokine receptors levels (CCR2 and CCR5) also increase in obesity. Moreover, in obese patients, chemokines CCL2 and CCL5 promote greater migration of monocytes from bone marrow to blood and lead to tissue infiltration.[5]

Management of MetS is primarily focused on lifestyle modification. Many studies support lifestyle modification as an effective choice in achieving the target, improving depression, and better quality of life.[11,12] Duration of lifestyle management varies from weeks to years.[11] Lifestyle management, improving

physical activity and healthy diet, has good effects on health, improve quality of life and depression status in MetS, especially in middle-aged and older women based on recent study. In elderly with poor health status and limitation, low-grade physical activity can be alternative and effective enough for health improvement.[2]

Depression

Depression is one of the most frequent mental disorders that can affect both males and females.[13] Depression affects emotion, motivation, and cognitive domain in negative way. More than 300 million people are estimated to have depression and end with suicide in the most severe cases.[5] Depression is related to increased morbidity and. So that, depression is cited as one of leading causes of worldwide impairment.[5] Depression is commonly found in the elderly and associated with chronic course and poor prognosis in comparison with younger age. Almost 50% of old age cases suffer long duration depression. Physiological changes related to age may contribute to poor results.[14] Depressive symptoms in older adults cause poorer condition compared to other chronic medical conditions.[13]

Depression is also associated with metabolic syndrome in many cases.[14] Depression is thought as important factor of type 2- DM and cardiovascular disease. Some studies showed that depression may be associated with MetS especially in women.[10]

Association of metabolic syndrome and depression

Metabolic syndrome is associated with depression and poor quality of life.[15] Individuals with depression are more likely having MetS compared to non-depressed individuals.[4] Depressive symptoms are frequently present in women with MetS than others.[15] Several studies showed an increased risk for depression development in individuals with metabolic syndrome and its components. Metabolic syndrome has a 1.49 times higher risk of developing depression.[8] Although the association between metabolic syndrome and depression has been reported by many studies,[8] correlated mechanism of both conditions is still unclear. There are some suggested hypotheses from several studies.[4] Otherwise, some studies also suggested depression as a risk factor of MetS with similar mechanism.[1]

The relationship between metabolic syndrome and depression is considered to be affected by lifestyle factors, such as alcohol drinking, cigarette smoking, and low physical activity.[10] Adverse health behaviors lead to a higher incidence of MetS in depressed patients.[4] Metabolic and behavioral risk factors have potential risk factors for depression development in adult population in general.[10]

Depression-MetS components association are mediated by different pathways. Metabolic syndrome components are associated with depressive symptoms incidence, including central obesity, hypertriglyceridemia, and low HDL cholesterol level.[13] Waist circumference or central obesity is considered as the most important influencing factor of MetS and depressive symptoms onset.[16] Underweight and severe obesity are also considered as increased risk factors of depression incidence.[10]

Study showed a significant association between MetS and depression incidence in women. The possible reason for this condition is sex hormone-related depressive symptoms as a mediating factor.[9] In addition, women present a higher cortisol level in chronic stress which is considered as a mediator in depression and Mets. High density of cortisol-glucocorticoid receptor binding in the visceral fat promotes lipoprotein lipase and causes lipid mobilization inhibition and results in increasing visceral fat. In older age, increasing stress response and cortisol levels are associated with low sex steroid levels that cause higher risk of depression. Thus, adult age or older women are more vulnerable in Mets and depression.[15]

Some pathophysiologies; including hypothalamus–pituitary–adrenal (HPA) axis and autonomic nervous system disturbances, chronic inflammation, oxidative stress, and peripheral hormones (e.g., leptin and ghrelin); are also considered as related mechanisms

between MetS and depression.[10] In depression, there is hypothalamic–pituitary–adrenal axis activation that impacts visceral fat accumulation by increasing corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol secretion.[1,4,16] Recently, studies introduced mechanisms correlating MetS and depression and showed chronic and low-grade inflammation, including increased circulating proinflammatory cytokines levels, blood leukocyte count alteration, and immune cells accumulation in tissues, as possible mechanisms. These chronic oxidative and inflammatory stress states promote cytokines inducing depressive-like behavior by neurotransmitter synthesis and signal transduction interruptions. Insulin resistance is commonly accompanied by obesity and also suggested as increased risk of MetS. Peripheral hormones (leptin and ghrelin) are also thought to have role in mood regulation. Physical activity and diet patterns have important roles in MetS and depression. So that lifestyle modification with increased exercise and a healthy diet pattern become a strategy therapy of choice.[9]

In addition, genetic abnormality or ACTH receptor, glucocorticoid, and aldosterone dysfunction are also considered to have role in MetS and depression.[16] Another study showed no correlation between MetS and depression remission time, disease severity, and course of disease in older persons with a formally diagnosed depression. However, MetS-depression patients have to be clinically followed for other reasons to their improve quality of life.[8]

2. Conclusion

Depression is one of the most frequent mental disorders that can be found along with metabolic syndrome. Depression and MetS have been recognized enough in many studies as important risk factors of morbidity and cause of life quality impairment. The correlated mechanism between metabolic syndrome and depression is still unclear, but there are some suggestion hypotheses from several studies, such as lifestyle factor, hypothalamus–pituitary–adrenal (HPA) axis and autonomic nervous system disturbances, chronic inflammation, oxidative stress, and peripheral hormones, that are thought as main mechanism of disease.

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