



## CO-MORBID PATHWAY LINK BETWEEN METABOLIC SYNDROME AND DEPRESSION AMONG ELDERLY – A NARRATIVE REVIEW

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### Abstract

The WHO ranked depression as the third-leading cause of burden of disease worldwide and projected that the disease will rank first by 2030. Depression is associated with higher prevalence of many somatic disorders, such as metabolic, cardiovascular and autoimmune diseases. Moreover, elderly with an impaired metabolic status, such as obesity or insulin resistance, who are strongly associated with the pre-diabetic stage, suffer more frequently from depression. Through more research studies, the relationship between metabolic syndrome and depression has been noticed primarily among elderly. More studies proved evidence that the pathogenesis of depression and metabolic syndrome includes endocrine and immune system, inflammatory response, activation of Hypothalamic Pituitary Axis. As the clinical treatment of depression is limited, exploring the co morbidity of depression and metabolic syndrome helps to identify new treatment strategies and further reduce the morbidity and mortality rate of depression among elderly. Depression may cause significant changes in elderly life which includes clinical mortality, decreased life span, diminished daily activity and loss of quality of life. The present review aims to analyze data on association between depression and metabolic syndrome in elderly.

### Methods

Database searches were performed in Medline, Pubmed and PsycINFO for assessing the association between depression and metabolic syndrome in elderly.

### Results

Current available data in the literature concerning the impact of Metabolic Syndrome on depression among elderly based on inconsistent evidence. Components of metabolic syndrome and factors associated with depression may show differential findings based on age, therefore larger quality studies are still needed in the field.

**Keywords:** Metabolic syndrome, obesity, type 2 diabetes, hypertension, depression, elderly

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**DOI:** 10.53555/ecb/2022.11.8.42

## Introduction

Metabolic syndrome is a web of cardio vascular risk factor that includes hypertension, visceral adiposity, impaired fasting blood sugar, dyslipidemia which increases morbidity and mortality. Increased lifespan is associated with an increased risk of age related diseases and an increased burden rate of chronic disease. Genetic and clinical factors play a significant role in causing increased risk of developing CVD, Stroke and diabetes. Metabolic syndrome is treated as major health problems worldwide- WHO. It has become significantly relevant as it is common among elderly population worldwide.<sup>[30]</sup> In recent times metabolic syndrome is strongly associated with an increased risk of developing mental illness that includes major depressive episode, ADHD, schizophrenia, Alzheimer's disease, PTSD. According to the WHO, there are more than 300 million elderly with depression in the world, accounting for 4.4% of the world's population. In 2020, depression will become the second largest global disease burden after cardiovascular disease, with an economic burden of about \$2.5 trillion, accounting for 10% of the total disease burden worldwide. <sup>[16, 30]</sup>

## Objectives

The present review aimed to identify the association between Metabolic Syndrome and depression among elderly.

## Methods

### Search strategy and selection criteria

Database searches were performed in Medline, pubmed and PsycINFO, using the following strategy: "metabolic syndrome" OR "syndrome x" AND "depression" OR "major depressive disorder" OR mild depressive disorder AND "elderly" OR "older" OR "aged" OR "senior". No limits were placed on publication dates or fields. Inclusion criteria were: (1) original articles which dealt with Metabolic Syndrome in samples aged  $\geq 60$  years old and (2) studies in which depression is assessed as an outcome. Articles were excluded if one or more of the following features was identified: (1) middle-aged adults (<60 years old) (2) studies did not apply the Metabolic Syndrome components; (3) studies were written in languages other than English; and (4) studies consisted of posters, conference papers, reviews, case reports or essays.

### Data Analysis

Thematic analysis was conducted in accordance with five steps: coding, theme generation, defining themes, and collecting. The themes emerged are depression and metabolic syndrome, depression and obesity, depression and type 2 diabetes, depression and inflammatory response. The thematic analysis helps in identifying the existing relationship between them through comparative study and through data conclusions were drawn. The articles are retrieved by using PRISMA guidelines. The flowchart of article selection according to PRISMA guidelines are described in Figure 1.

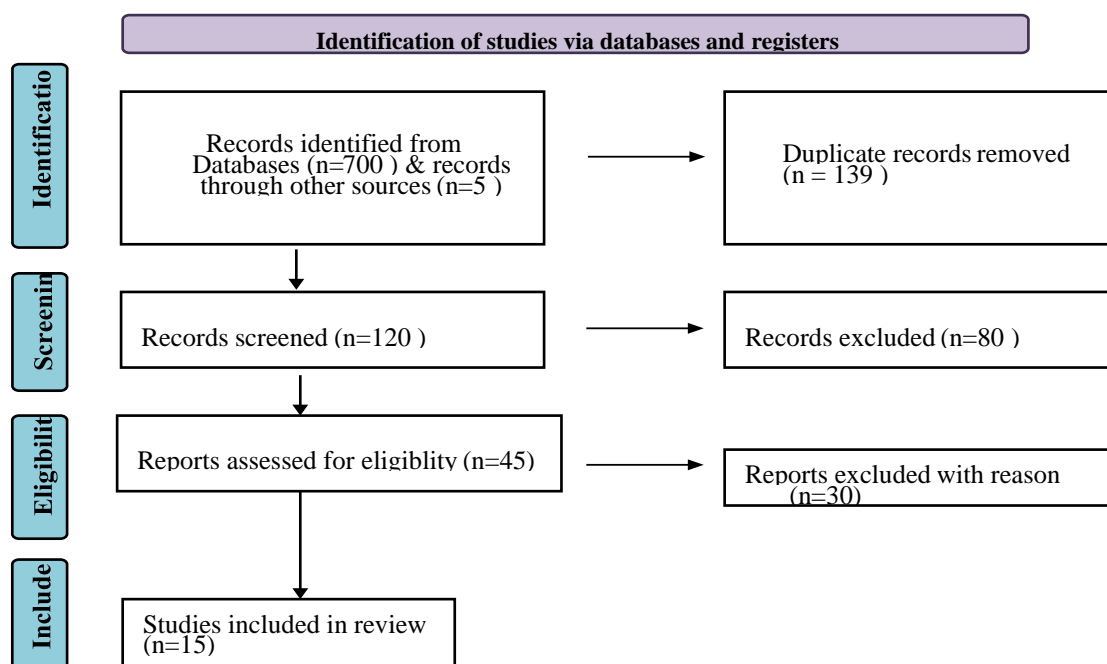


Figure 1: presents the flowchart of article election according to PRISMA guidelines

**Table1:** Comparison of research studies of different authors

Author(s)	Year	Country	Study Title	Study Design	Main idea of the literature
Victoria Limon <sup>1</sup> , Miryoung Lee <sup>2</sup> , Brandon Gonzalez <sup>2</sup> , Audrey C Choh <sup>2</sup> , Stefan A Czerwinski <sup>2</sup>	2020	Tibet	Impact of metabolic syndrome on mental health-related quality of life and depressive symptoms	Longitudinal study	Mets was adversely associated with depressive symptoms and poor mental health-quality of life.
Jing-Hong Liu, YuXi Qian, Qing-Hua Ma, Hong-Peng Sun, Yong Xu, ChenWei Pan.	2020	China	Cross-sectional study on Depressive symptoms and metabolic syndrome components among older Chinese adults	Cross sectional	There was a negative association between depressive symptoms and elevated systolic BP ( $\geq 130$ mm Hg)
Kourosh Shahbazi, Marjan Hosseinzadeh Taghvaei, Seyed Kamal Solati, Arsalan Khaledifar, Mahdi Shahnazari.	2021	Iran	Effectiveness of Mindfulness-based Stress Reduction on Hypertension among elderly with Metabolic Syndrome	Experimental study	Mindfulness therapy was effective on each component of the metabolic syndrome among cardiovascular patients with hypertension
Ali Bijani, Seyed Reza Hosseini, Reza Ghadimi, Simin Mouodi	2020	Amirkola	Association of Metabolic Syndrome and Its Components with Survival of Older Adults.	Prospective study	Metabolic syndrome significantly decreased the survival rate of older adults after adjusting age, gender and number of chronic diseases.
Xujuan Zheng, Hongbo Yu, Xichenhui Qiu, Sek Ying Chair, Eliza Mi-Ling Wong, Qun Wang.	2020	North China	The effects of a nurse-led lifestyle intervention program on cardiovascular risk, self-efficacy and health promoting behaviours among patients with metabolic syndrome.	Two arm randomized control trial	Decreased cardiovascular risk, self-efficacy for nutrition, stress dimension were found in the lifestyle intervention group.
Diana C Parra, Julie Loebach Wetherell, Alexandria Van Zandt, Ross C Brownson, Janardan Abhishek, Eric J Lenze	2019	USA	Older adults' perspectives on initiating exercise and mindfulness practice	Qualitative study	This study indicates that mindfulness training and exercise can serve as tools to cultivate important health lifestyle qualities among older adults, who are in the midst of mental, social, emotional and physical change
Afsaneh Bakhtiari, Maryam Hashemi, Seyed Reza Hosseini, Shabnam Omidvar, Ali Bijani, and Farzan Khairkhan	2018	Iran	The Relationship between Depression and Metabolic Syndrome in the Elderly Population.	Cohort study	This association highlights the relevance of norepinephrine signal and sympathetic nervous activity disturbance for the emergence of depressive symptoms in the elderly.
Luiz Gustavo Ruas et al.	2016	Brazil	Components of the metabolic syndrome and depressive symptoms in community-dwelling older people.	Cross sectional study	High triglyceride level was the individual component that showed the strongest association with depressive symptoms
Carpenter, K. M., Hasin, D. S., Allison, D. B., and Faith, M. S.	2000	USA	Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study.	SURVEY DESIGN	BMI was associated with both major depression and suicidal ideation.
Chaitoff, A., Swetlik, C., Ituarte, C., Pfoh, E., Lee, L. L., Heinberg, L.L.	2019	Ohio	Associations Between Unhealthy WeightLoss Strategies and Depressive Symptoms.	Survey design	Unhealthy weightloss strategies are associated with increased odds of depression.
Fentie Dilnessa, Derese Tariku, Yazie Bekele, and Getachew Yibeltal.	2021	Eastern Ethiopia.	Metabolic syndrome and associated factors among severely ill psychiatric and non-psychiatric patients	Comparative cross-sectional study	There is a high burden of metabolic syndrome and its components in patients with severe psychiatric disorders.
Heo1, M., Pietrobelli, A., Fontaine, KR., Sirey1 J.A., Faith, MS.	2006	USA	Depressive mood and obesity in US adults: comparison and moderation by sex, age, and race	Survey design	The relationship between the depressive mood and obesity is dependent upon gender and age.
Herva, A., Rasanen, P., Miettunen. J., Timonen, M., Lakso, K., Veijola, J.	2006	Finland	Co-occurrence of metabolic syndrome with depression and anxiety in young adults:	Cohort study	Association between Psychological distress
Jabben, N., Nolen, W.A., Smit, J.H., Vreeburg, S.A., Beekman, A.T.,	2013	Netherland	Co-occurring manic symptomatology influences HPA axis alterations in depression.	Meta analysis	Two major subtypes of depression are associated with different biological correlates with inflammatory and metabolic dysregulation in atypical depression and HPA-axis hyperactivity
Jorntorp B & Rosmond R	2000.	Sweden	Pathogenesis of metabolic syndrome and depression.	Survey design	Saliva cortisol have indicated that the problem is complex with both high and low secretion of cortisol, perhaps depending on the status of the function of the hypothalamicpituitary-adrenal gland axis
Lamers, F., Bot, M., Jansen, R., Chan M. K., Coope, JD., Bahn, S., and Penninx, B. W. J. H.	2016	USA	Serum proteomic profiles of depressive subtypes,	Systematic review	Diagnosis of depression continues to be based on clinical signs, biomarkers may be a valuable tool for stratifying particular patients with the disorder.

Depression in the elderly leads to poor health status, slow recovery rate, unbearable physical pain, high financial costs in relation to health care, and poor quality of life and also increased risk of stroke, cardio vascular disease, hip fractures, and death rates from other illnesses [6] Metabolic Syndrome was adversely associated with depressive symptoms and poor Mental Health-Quality of Life. [41]

There is evidence to prove that both obesity and depression are related and they may either co-occur or may occur in a sequence that is with one leading to the other.[7] One suggested sequence is that obesity precedes depression since obese persons are at greater risk of depression for many reasons including physical inactivity [12], poorer quality of life [11] and social prejudice. [21] The reverse temporal sequence has also been suggested based on observations that depressed people may gain weight through the effects of antidepressant

medications, [23] impaired sleep quality [20] and a sedentary life style. Metabolic syndrome significantly decreases the survival rate of elderly after adjusting age, gender and number of chronic diseases. [9]

The pathogenesis of metabolic syndrome is influencing the vital organs strongly in causing major inflammation leading to mental illness among elderly worldwide. Early diagnosis and treatment that includes risk factor modification and life style changes effectively helps in preventing the complication of metabolic syndrome. Factors related to metabolic syndrome includes obesity, diabetes, hypertension, dyslipidemia have been associated with presence of depression. [10, 27]

### Diagnostic criteria

The diagnostic criteria of metabolic syndrome has been described in **Table 2**

**Table 2: Diagnostic criteria**

	CADI (Metabolic syndrome criteria for Asian Indians)	AHA/NHLBI	IDF	JIS	NCEP-ATP III
<b>Abdominal Obesity Men :</b>	<b>Waist</b> >90cm/35.4 inches	≥102 cm	≥94 cm	≥94 cm	≥102 cm
<b>Women:</b>	>80cm/31.5 inches	≥88 cm	≥80 cm	≥80 cm	≥88 cm
<b>Triglycerides</b>	>150mg/dL	≥1.7 mmol/L or receiving treatment	≥1.7 mmol/L or receiving treatment	≥1.7 mmol/L or receiving treatment	≥1.7 mmol/L
<b>HDL Men:</b>	<40mg/dL	<1.0 mmol/L	<1.0 mmol/L <1.3 mmol/L (women)	<1.0 mmol/L <1.3 mmol/L (women)	<1.0 mmol/L <1.3 mmol/L (women)
<b>Women:</b>	<50mg/dL	<1.3 mmol/L (women) or receiving treatment	or receiving treatment	or receiving treatment	or receiving treatment
<b>Blood Pressure</b>	≥130/≥85 mm Hg	≥130/85 mm Hg or receiving treatment	≥130/85 mm Hg or receiving treatment	≥130/85 mm Hg or receiving treatment	≥130/85 mm Hg
<b>Fasting Glucose</b>	≥100 mg/dL	≥5.6 mmol/L or T2DM	≥5.6 mmol/L or T2DM	≥5.6 mmol/L or T2DM	≥6.1 mmol/L
*CADI – Coronary artery disease in Asian Indians *IDF - International Diabetes Federation * JIS - Joint Interim Societies, * NCEP-ATP III - National Cholesterol Education Program-Adult Treatment Panel * AHA/NHLBI - American Heart Association and National Heart Lung and Blood Institute * T2DM - Type 2 diabetes mellitus					

### Common risk factors

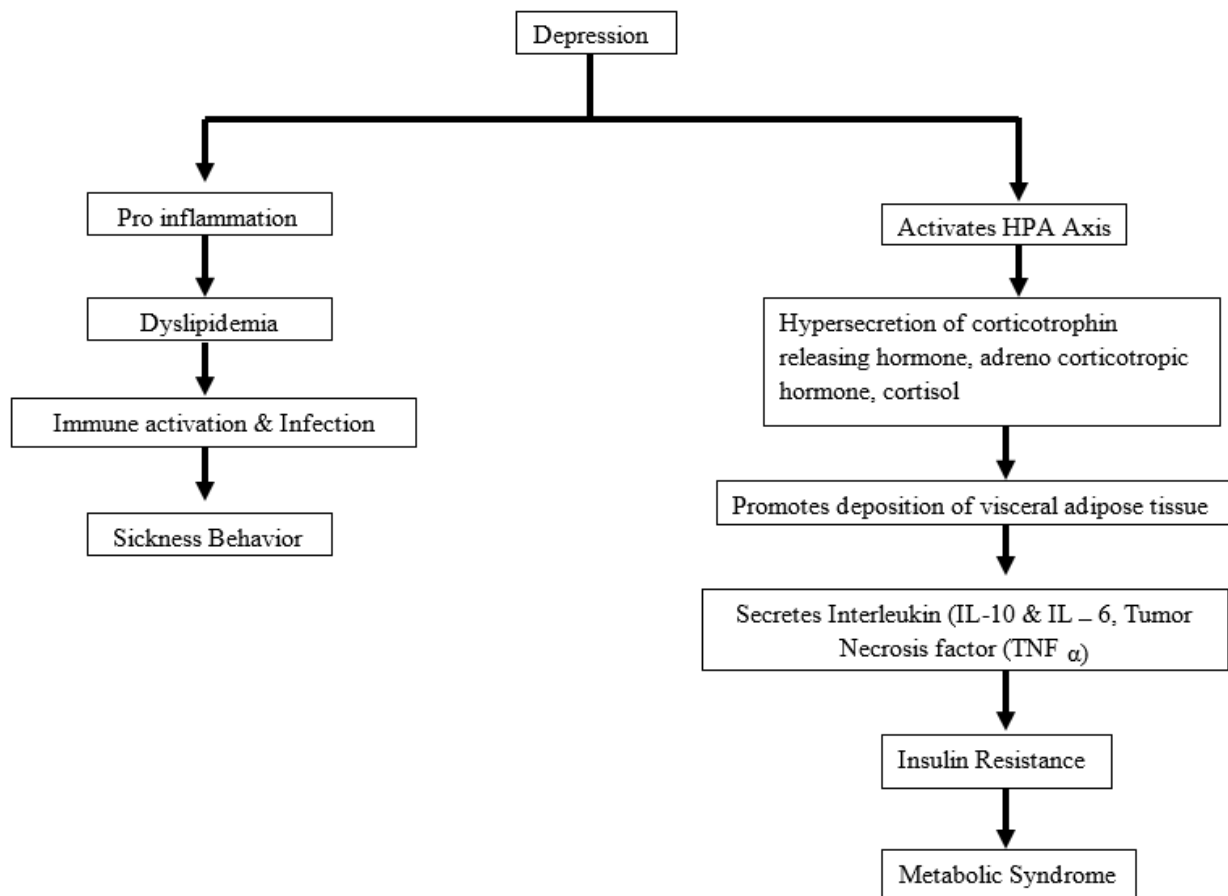
The causes of metabolic syndrome are multifactorial. The bio physiological factors such as dysregulation of HPA axis, impaired insulin resistance, visceral adiposity are more likely to cause inflammation in the blood vessels. Health related behaviors such as smoking, alcohol, drug usage, lack of physical activity, unhealthy dietary habits are likely to contribute metabolic syndrome. Hormonal imbalances such as cortisol high serum levels of C – reactive protein are also play a major role. Societal factors such as rapid urbanization, increased aging population, sedentary life style, dietary changes all these factors greatly influences the morbidity of metabolic syndrome.

### Depression and Metabolic syndrome

Globally depression is considered as one of the most prevalent psychiatric disorder among elderly population. By 2030 depression will rise to first place in contributing to the disease burden globally. This is due to the facts that depression has greater impact on activities of daily living, instrumental activities of daily living, thereby affecting public health causing high suicidal and financial crisis. Depression causes greater impact on physical health, overall mortality risk and also contributing to the risk of cardio vascular outcomes, diabetes, hypertension, obesity, high CRP, low HDL. Metabolic Syndrome might aggravate depressive symptoms in the elderly

because of the inter relation between depression and non-communicable diseases, such as diabetes, hypertension, and dyslipidemia.<sup>[27]</sup> Depression results in increased activity of the HPA axis causing decreased estrogen levels, which eventually leads to menopause and increased visceral fat eventually, and this most likely

contributing to Metabolic Syndrome in women.<sup>[7]</sup> This qualitative study indicates that older adults with metabolic syndrome have changes in the mental, social, emotional and physical behavior which affects the qualities of healthy life style in later life.<sup>[28]</sup>



**Figure 2:** Schematic representation of link between depression and Metabolic Syndrome

Recent research studies evidence that there is a energy metabolism dysfunction in psychiatric disorder.<sup>[31]</sup> Human brain constitutes 2% of the whole body weight and paradoxically is responsible for 25% of total body glucose utilization. The study revealed that there is a reduction in blood flow and glucose metabolism in the caudate nucleus, prefrontal cortex.

Study revealed that there is a high burden of metabolic syndrome among clients with myocardial infarction due to high smoking and alcohol habits, non compliance of medical care.<sup>[10]</sup> The contributing factors associated with metabolic syndrome have high frequency rates in clients with myocardial infarction. Elderly were found to be significantly more likely to have metabolic syndrome. As we age, there will be less sensitivity to muscle fat and other tissues leading to

insulin resistance and dyslipidemia and also get stiffer arteries leading to increased blood pressure. Another study in Italy (2011) on depressed patients over 65 years showed that depressive symptoms also starts by an increase in Waist Circumference in older ages and that the Metabolic Syndrome alone is not a factor for developing depression but may increase the persistence of depression.<sup>[34]</sup> Physicians are aware that obesity is considered as the potential contributing factor leading to coronary artery disease and premature death in depressive disorder. Mood - related factors, ie mania or depression, weight loss, decreased physical activity, medication side effects, drug abuse, poor diet, smoking, alcohol.<sup>[32]</sup>

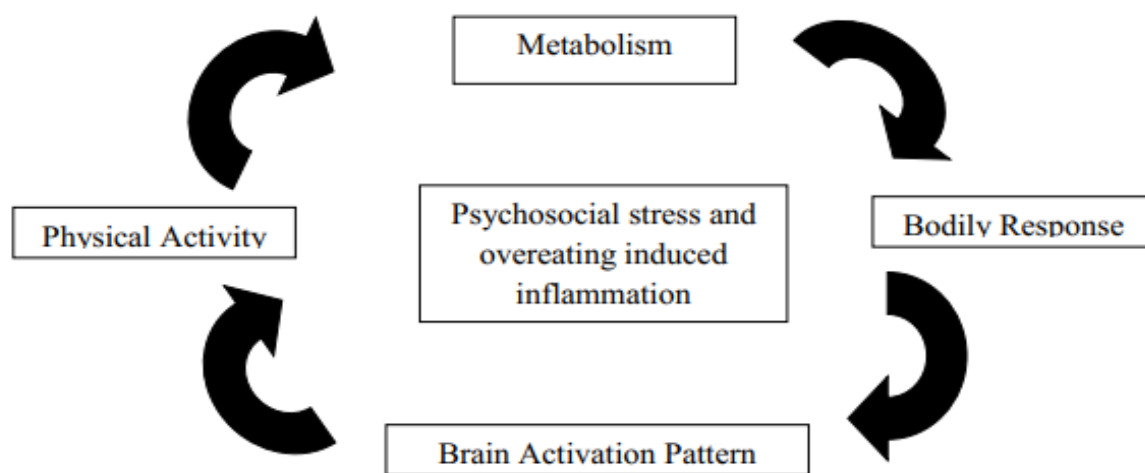
People with known stressors lead to increase in calorie intake and obesity.<sup>[1]</sup> Some with unknown stressors may experience loss of appetite, sleeplessness resulting in less food intake and

weight loss. Recent research studies proved that unhealthy weight loss strategy may lead to the occurrence of depressive symptoms related to report 47% increased risk of depression.<sup>[8]</sup> Cross sectional survey was conducted and revealed that there is a significant relationship between waist circumference, low HDL and depression.<sup>[26]</sup>

### Depression and Obesity

Obesity is frequently associated with neuro endocrine changes particularly involving hypothalamic pituitary adrenal axis. There is

growing evidence revealing that activated stress system act as a triggering factor for mood disorders. It also revealed that there is a strong role of obesity and brain functioning through inflammatory response and HPA axis.<sup>[18]</sup> The depression associated with behavioral symptoms such as poor physical activity and imbalanced diet, may affect metabolic diseases such as obesity, diabetes, hypertension in the body of elderly population. Psychiatric illness associated with the accumulation of visceral fat leading to the pathogenesis of metabolic syndrome.<sup>[17]</sup>



**Figure3:** Vicious cycle of psychosocial stress and inflammation

A study found that there is a increased risk of cardiovascular diseases, decreased self efficacy for nutrition, stress dimension among elderly with metabolic syndrome.<sup>[43]</sup> The association between high level of cholesterol components and depressive symptoms signifies the emergence of depression among elderly with lipid abnormalities.<sup>[30]</sup>

### Depression and Type 2 Diabetes

Elders with a history of diabetes accelerate ageing and reduce lifespan, thus enhancing the morbidity of T2DM.<sup>[21]</sup> The strong relationship exists between depression and type 2 diabetes. Studies showed that psychosocial stress or overeating induced inflammation invokes a vicious cycle that can affect metabolism, the bodily stress response, brain activation patterns and the physical activity of the individual.<sup>[31]</sup> It has now been proved that a particular type of depression namely the atypical depression, can be associated with chronic low-grade inflammation, which also occurs along with pre-diabetes or Type 2 Diabetes Mellitus.<sup>[19]</sup>

The relevance of association between norepinephrine signal and sympathetic nervous activity disturbance highlights the emergence of depressive symptoms in the elderly.<sup>[7]</sup>

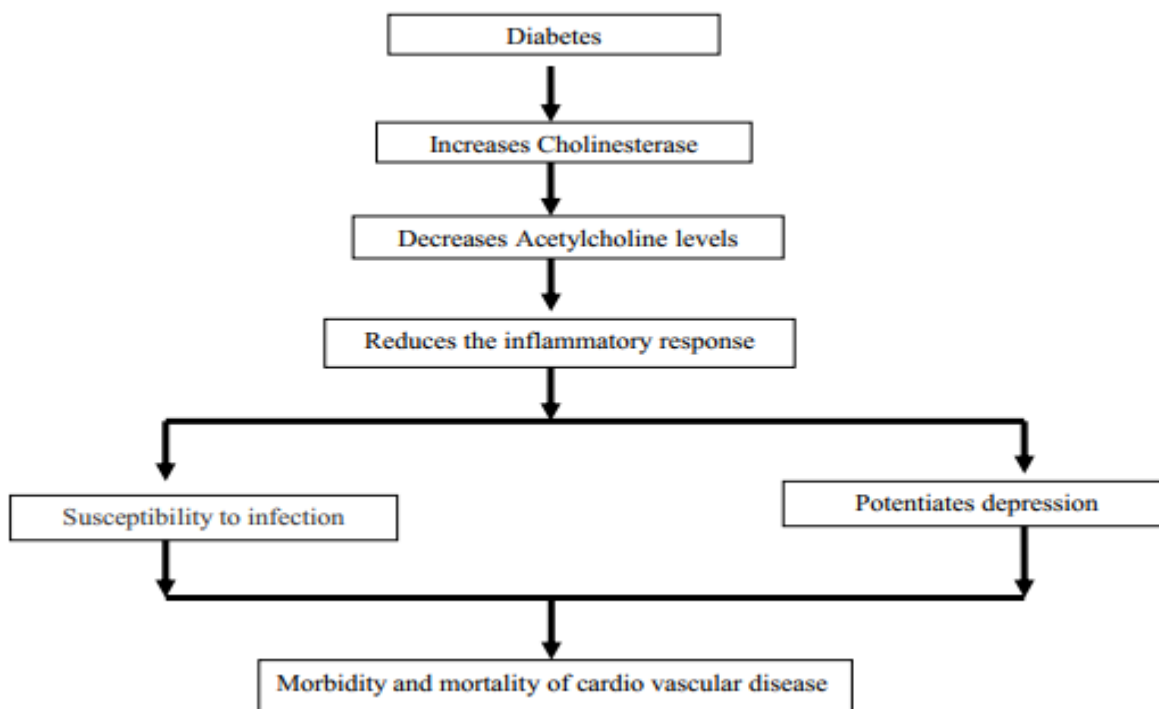
The possible pathways such as increased norepinephrine, arousal and movement of energy stores, alterations of serotonin-mediated platelet activation could increase the risk of hypertension among elderly with depression.<sup>[19]</sup>

### Depression and Inflammatory response

Research studies proved that over activity of angiotensin converting enzyme2 in corticotropic releasing hormone which inhibits HPA axis activation and the release of adreno corticotropic hormone which in turn drives adrenal glucocorticoid secretion resulting in depression, anxiety disorders, PTSD etc.<sup>[35, 36]</sup>

Other studies also showed that the emergence of HPA-axis (hypothalamicpituitary-adrenal) activation occurs due to stress caused by depression. The hyperactivity of HPA-axis leads to increased secretion of androgens, sexual steroids

and growth hormones, which can also cause metabolic changes in the body.<sup>[7]</sup>



**Figure 4:** Schematic representation of link between depression and inflammatory response

There was a negative association between depressive symptoms and elevated systolic BP ( $\geq 130$  mm Hg). A cross-sectional study on Depressive symptoms and metabolic syndrome components among older Chinese adults aimed to examine associations of depressive symptoms with Metabolic Syndrome and its components in older Chinese adults.<sup>[22]</sup> An experimental study was conducted on elderly with metabolic syndrome and suggested that there is a strong association between each component of metabolic syndrome among elderly leading to cardio vascular complication.<sup>[35]</sup>

### Conclusion

The pathogenesis of depression is unique to each individual. Depression has variety of co morbidity with several metabolic components like type 2 diabetes, obesity and hypertension resulting in cardiovascular morbidity and mortality. The co relational link between depression and other diseases should be studied deeply by exploring its impact on individual and society as a whole, thereby helpful in designing the novel interventional strategies. Hence more researchers are needed to conduct in order to increase the life span, decrease the morbidity and improve the quality of life among elderly.

### Conflicts of interest

There is no conflict of interest

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