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A Review of Inflammatory Markers in Metabolic Syndrome

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Abstract: The conditions included in the definition of metabolic syndrome typically include central obesity (excessive fat accumulation around the waist), insulin resistance, hyperglycemia (elevated blood sugar levels), dyslipidemia (abnormal levels of lipids in the blood), and hypertension (high blood pressure). Having any three or more of these conditions is considered to be indicative of metabolic syndrome. Metabolic syndrome (MetS) is emerging as a major public health problem with pro-inflammatory changes leading to Insulin Resistance and Cardiovascular Disease (CVD) at a very young age. Metabolic syndrome (MetS) is a global health concern; metabolic syndrome is becoming more common in our country. It is found to be a risk factor for insulin resistance and abnormal adipose tissue . Clinical symptoms of the syndrome could include abdominal obesity, hypertension, diabetes, hypertriglyceridemia, and low HDL cholesterol. So far various studies have been conducted on the effect of inflammatory markers like Serum Uric acid (UA), serum homocysteine, Leptin, Lp(a) etc. Most of them have reported a positive correlation between these inflammatory markers and the various components of (MetS) like abdominal obesity, elevated Blood pressure, Fasting blood Glucose and Lipid profile abnormalities like elevated Triglycerides (TAG) and low High Density Lipoprotein-Cholesterol (HDL-C). Various studies have reported a positive correlation between serum uric acid and Serum Homocysteine and Lp(a) in causing endothelial dysfunction and premature Cardiovascular events. Hence a review of the studies pertaining to the various inflammatory markers was done. There was an association of various inflammatory markers like uric acid, homocysteine, MDA, lipoprotein and others. More awareness must be created even at the high school level regarding the ill effects of sedentary lifestyle the likely hood of metabolic syndrome. An early identification of surging biomarker levels in high-risk children may find new cases at an earlier stage to prevent upcoming diabetes mellitus and its complications.

Key words: Metabolic syndrome (MetS); pro-inflammatory; Cardiovascular Disease (CVD); Serum homocysteine; Triglycerides (TAG).

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1. INTRODUCTION

Metabolic syndrome is a cluster of metabolic abnormalities, including central obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension, that increase the risk of cardiovascular disease and type 2 diabetes. Inflammation has been suggested as a key factor linking these metabolic abnormalities and playing a role in the development and progression of metabolic syndrome. Numerous studies have identified elevated levels of various inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and others, in individuals with metabolic syndrome. These markers are produced by adipocytes, liver cells, and immune cells, and their increased production has been associated with insulin resistance, oxidative stress, and other features of metabolic syndrome[1,2,3]. In addition to being associated with the presence of metabolic syndrome, elevated levels of inflammatory markers have also been found to predict the development of cardiovascular disease and type 2 diabetes in individuals with metabolic syndrome. This highlights the importance of measuring and monitoring levels of these markers in individuals with metabolic syndrome, as well as the potential utility of anti-inflammatory therapies for reducing the risk of these complications. Overall, the available evidence supports the role of inflammation in the development and progression of metabolic syndrome. Further research is needed to fully understand the mechanisms underlying this relationship, as well as to evaluate the efficacy of anti-inflammatory interventions in improving outcomes in individuals with metabolic syndrome. As the name suggests Metabolic syndrome (MetS) includes a cluster of factors that increases the risk of Cardiovascular Disease (CVD) and Type2 Diabetes Mellitus (T2DM) at an earlier age. Metabolic syndrome is a global public health concern.[1] Its major components are central obesity, dyslipidemia[2], hypertension, hyper insulinaemia and glucose intolerance[3], which are risk factors for cardiovascular disease.[4]

1.1 Role of Uric acid

Various studies have postulated that inflammatory markers like serum Uric acid, Homocysteine, Highly sensitive C-Reactive Proteins (HsCRP) etc. are positively associated with MetS which may result in cardiovascular events at an earlier age. Uric acid has strong reducing properties and it is also a free-radical scavenger. Several studies have indicated that serum uric acid is an important inflammatory marker and may be useful in the assessment of cardiovascular risk. Elevated uric acid levels have also been associated with insulin resistance (IR), metabolic syndrome (MetS) and T2DM.[5,6] Several epidemiologic studies show a strong association between elevated serum levels of uric acid with obesity, insulin resistance, MetS, diabetes, essential hypertension [7] and renal disease. Uric acid is produced from xanthine and hypoxanthine by the action of the enzyme xanthine oxidase which uses molecular oxygen as electron acceptor and generates superoxide anion and reactive oxygen species (ROS).[5,6,7] Under conditions of increased oxidative stress, there is depletion of the local antioxidants.[8] Elevated levels of UA in the serum may be a risk factor for lipid abnormalities leading to endothelial dysfunction, chronic inflammation, atherosclerosis, Hypertension and Cardiovascular diseases[9-11]. It has been shown experimentally that uric acid stimulates the synthesis of monocyte chemo-attractant protein-1, Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor- α (TNF-α) [12], all of which are pro-inflammatory molecules and stimulate production of CRP in the liver.[13] Oxidative stress and chronic low-grade inflammation could be the basic problem of hyperuricemia and MetS. MetS was determined to be linked with hyperuricemia. Many additional analyses that previously identified risk factors for MetS still found hyperuricemia to be independently associated with MetS. The findings of the preceding studies indicate a requirement to comprehend the metabolic pathways of UA in order to explain its impact on MetS. Prospective clinical trials evaluating the impact of UA and UA control on MetS and co - occurring medical outcomes should really be conducted in the future.

1.2 Role of homocysteine

Homocysteine, a sulphur containing amino acid formed from methionine is yet another inflammatory marker whose normal level is 5-15 µmol/litre. An increase in plasma homocysteine has been associated with pro-inflammatory and pro-thrombotic consequences. Hyperhomocystinemia causes endothelial dysfunction by reducing Nitric oxide and vasodilatation which worsens oxidative stress leading to proliferation of smooth muscle and intimal thickening. We wished to detail the inflammatory markers and their association with Mets in this review.

2. METHODOLOGY

The writer searched web sites like PubMed and Google Scholar using the keywords "Inflammatory markers" or "Inflammation" and "Metabolic Syndrome". The writer reviewed case reviews and series, retrospective and potential studies, systematic opinions and meta-analyses and different narrative critiques.

2.1 Databases

To detail the search techniques, To identify relevant studies, a computerised search was developed and executed in cooperation with a knowledgeable university librarian. Ovid MEDLINE Epub Ahead of Print, In-Process, & Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid MEDLINE 1946 to July 2021, Ovid EMBASE (1974 to July 2021), CINAHL (1982 to July 2021), and AMED were searched (1985 to July 2021).

2.2 Rationale of selection

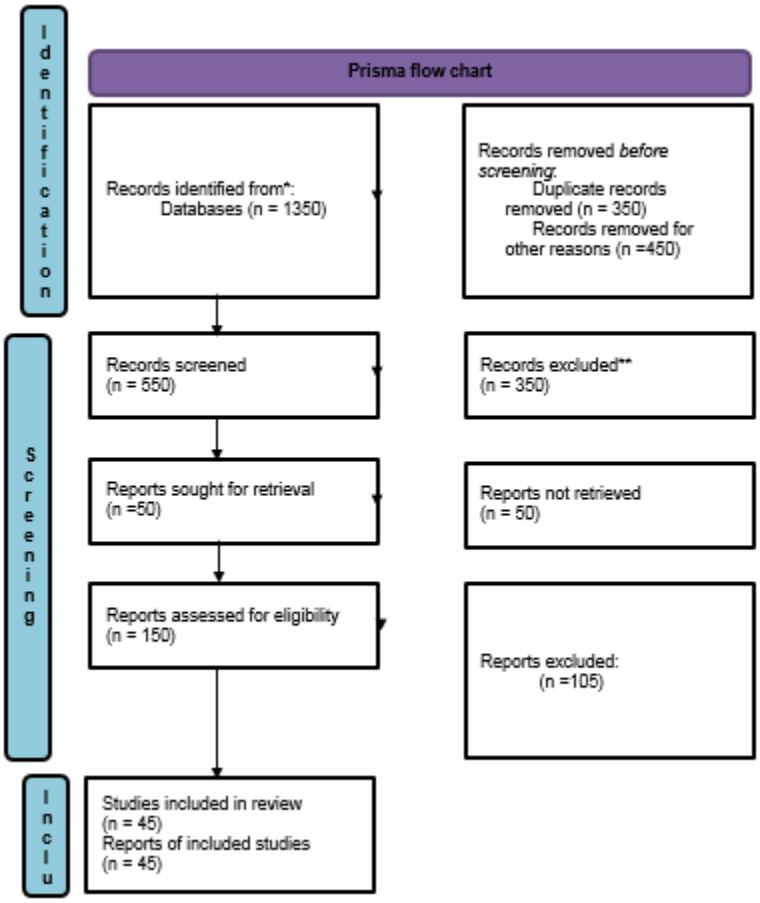
Based on each database, key words pertaining to the domains of inflammatory biomarkers and metabolic syndrome were utilized for searching with subheadings and word truncations. The searches were not limited to a single language.

2.3 Inclusion

Cross-sectional, longitudinal cohort, or case control studies that examined the link between inflammatory biomarkers and MET symptoms and outcomes in humans were considered suitable for inclusion. Cross-sectional studies, in which data is collected at a single point in time, were also frequently used to assess prevalence and associations.

2.4 Exclusion

Any study with patients with full and established diabetes or which involved the presence of any other systemic illness like Rheumatoid arthritis which can alter the biomarkers were excluded.



3. DISCUSSION

3.1 The patient criteria for metabolic syndrome is tabled below

Table 1 showing Patient criteria for metabolic syndrome

Criteria	Definition
Central obesity	Waist circumference ≥40 inches (102 cm) in men or ≥35 inches (88 cm) in women
Triglycerides	≥150 mg/dL (1.7 mmol/L)
High-density lipoprotein (HDL) cholesterol	<40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.3 mmol/L) in women
Blood pressure	≥130/85 mmHg
Fasting glucose	≥100 mg/dL (5.6 mmol/L)

3.2 Does uric acid play a role ?

Several studies have shown that hyperuricemia is one of the risk factors of metabolic syndrome and it clearly has a strong correlation with diabetic dyslipidaemia like raised LDL-C and triglycerides with reduced HDL cholesterol.[14,15] Patients with higher UA levels showed elevated systolic blood pressure, BMI, waist circumference and high blood pressure, that are important components of MetS.[16-19] Besides it is also associated with endothelial dysfunction and chronic inflammation.[20] Uric acid is produced from xanthine and hypoxanthine by the action of the enzyme xanthine oxidase which uses molecular oxygen as electron acceptor and generates superoxide anion and other reactive oxygen species (ROS).[21] Under conditions of increased oxidative stress, there is depletion of the local antioxidants.[22] Higher UA levels may be a risk factor for Hypertension and Cardiovascular diseases and lipid abnormalities leading to atherosclerosis,[23,24] endothelial dysfunction and chronic inflammation. UA levels may be elevated in DM and MetS patients as a response to oxidative stress. . UA being a free

radical scavenger is both a pro-oxidant and as an anti-oxidant. [25,26] T2DM is associated with oxidative stress and increased free radical formation.[27] Uric acid was found to be elevated in subjects who were overweight, obese and with increased visceral fat.[28-30] Various studies have shown a strong association between oxidative stress and development of metabolic syndrome.[31,32] The findings of the study by Prabhakar et al., corroborates with a study conducted by Ishizaka N et al., who analysed a cross-sectional data of 8,144 individuals and concluded that the prevalence of metabolic syndrome showed a graded increase along with increasing serum uric acid levels in both sexes. [33] The findings of a uric acid levels in diabetes mellitus and metabolic syndrome by Prabhakar et al.,[20]revealed a positive correlation between serum uric acid levels, Triglycerides and a negative correlation of HDLC, in patients with MetS as compared to controls. These findings also corroborates with an earlier study by Chen L.Y. et al,. that has also reported a negative correlation between HDL-C and insulin resistance [34]. Similarly a study by Narasimman Gurusamy[35] concluded that an elevated serum uric acid level was a contributory factor for an increased risk of MetS. Jae Woong Lee et al., reported a 5 year retrospective cohort study from 2003-2008 that predicted a higher incidence of MetS in those cases with high serum uric acid. [36] Similarly a cross sectional study reported by T P Antony et al also suggested that serum uric acid levels correlated with the prevalence and severity of MetS.

3.3 Role of homocysteine

In the study by Prabhakar et al., on homocysteine levels and MetS it was shown that MetS group had significant increase in serum homocysteine levels which was similar to the findings of Soinio et al., In a study by Santhoshakumari et al.[37] in which 95% of patients with NAFLD were reported to have central obesity, and dyslipidemia (26% had high TGL and 75% had low HDL cholesterol) a common finding in NAFLD and an important risk factor for MetS. In another study, 27% of patients with increased waist circumference (abdominal obesity) had Subclinical Hypothyroidism[38].

3.4 Role of adiponectin

Low serum levels of adiponectin has a strong association with metabolic syndrome, diabetes, CVD, and psoriasis[39]. Leptin, secreted by adipose tissue, activates monocytes and macrophages and increases the release of pro-inflammatory cytokines like IL-6 and TNF and simultaneously suppresses the production of anti-inflammatory Th2 cytokines[40]. Adiponectin exerts opposite effect and protects from the development of hypertension, CVD and psoriasis[41]. Leptin down regulates appetite and food intake by regulating neuropeptides in the hypothalamus [42]. Several studies found significantly higher leptin level (Leptin resistance) in Metabolic Syndrome patients in comparison with controls.[43] In another study significantly increased level of leptin was observed in the psoriatic patients with Metabolic Syndrome compared to the controls.

3.5 Role of resistin

The adipokine, Resistin, is an important factor linking obesity and insulin resistance. It also triggers a proinflammatory state [44] and is expressed in chronic disease conditions like rheumatoid arthritis, atherosclerosis, diabetes, and inflammatory bowel disease. Several studies reported higher levels of Lipoprotein (a)[45], a risk factor for ischemic cardiovascular disease. Lp-PLA2 serves as a biomarker of MS and cardiovascular Disease (CVD)[46] as it is expressed in macrophages of atherosclerotic plaques.

3.6 Role of Malondialdehyde

Malondialdehyde (MDA) [47]is a by-product of polyunsaturated fatty acid peroxidation in cells. Increased production of MDA is caused by an increase in free radicals. Malondialdehyde levels are commonly used to assess oxidative stress and antioxidant status in cancer patients. The levels of MDA an end product of lipid peroxidation was found to be higher in subjects with metabolic syndrome compared with control group.

3.7 Role of leptins

Metabolic syndrome is a major risk to human health, negatively impacting quality of life. Adipose tissue is a vital organ that is responsible for the development of metabolic syndrome. Adipocytokines[48], which are secreted by adipose tissue, are important in storage, food intake, energy expenditure, lipid and glucose metabolism. Leptin regulates food intake, body weight, and energy homeostasis mainly through neuroendocrine functions. According to recent research, leptin impacts insulin sensitivity and lipid metabolism. High leptin levels are linked to obesity as well as the progression of metabolic disease morbidities such as insulin resistance, type 2 diabetes, and cardiovascular disease. Elucidating the method of action of leptin would aid in the development of unique therapeutic approaches for metabolic disorders such as obesity.

3.8 Role of Lipoprotein

An inverse relationship exists between lipoprotein(a) and type 2 diabetes mellitus. However, research on metabolic syndrome (MetS) and Lp(a) is limited[49]. According to some studies, there is no significant association especially in premenopausal women.

3.9 Role of (C Reactive Protein) CRP

Even though the metabolic syndrome is associated with enhanced levels of inflammatory biomarkers like CRP and leucocyte$_{50}$, the increase is usually significant as the the disease becomes more and more severe. See fig 1 for the pathogenesis

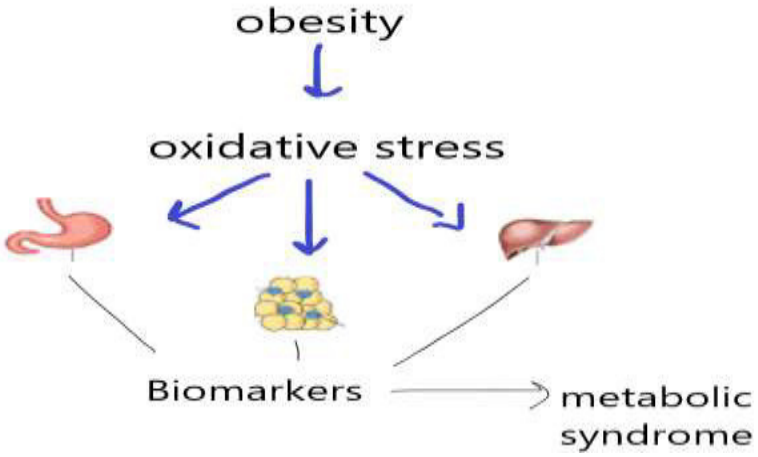


Fig 1 showing the path of metabolic syndrome and biomarkers

3.10 Role of severity of OSA

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repeated episodes of partial or complete upper airway collapse during sleep, leading to reduced oxygen saturation and fragmented sleep. OSA has been linked to metabolic abnormalities, including insulin resistance, oxidative stress, and systemic inflammation, that are hallmarks of metabolic syndrome. Studies have shown that the severity of OSA, as measured by the apnea-hypopnea index (AHI), is positively correlated with the levels of various metabolic markers, such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and others. In individuals with OSA, increased AHI has been associated with increased levels of these markers, indicating a potential link between the severity of OSA and the degree of systemic inflammation. Moreover, studies have demonstrated that effective treatment of OSA, such as continuous positive airway pressure (CPAP) therapy, can reduce levels of these markers and improve metabolic outcomes in individuals with OSA. This highlights the importance of diagnosing and treating OSA, especially in individuals with metabolic syndrome, in order to reduce the risk of cardiovascular disease and type 2 diabetes.[51,52] Overall, the available evidence suggests a link between the severity of OSA and the levels of various metabolic markers, and underscores the importance of addressing OSA in individuals with metabolic syndrome. Further research is needed to fully understand the mechanisms underlying this relationship and to determine the optimal approach for managing OSA in individuals with metabolic syndrome.

3. CONCLUSION

Met S is a global health problem especially among young adults. Since it is more of a lifestyle disease it is very much preventable especially if attended earlier. There is an association various inflammatory markers like uric acid, homocysteine, MDA, lipoprotein and others. More awareness has to be created even at the high school level regarding the ill effects of sedentary lifestyle the likely hood of metabolic syndrome. An early identification of surging biomarker levels in high risk children may find new cases at an earlier stage to prevent upcoming diabetes mellitus and its complications.

4. AUTHOR CONTRIBUTION STATEMENT

T.M.J.Santhoshakumari has done by the concept G.Revathy and Prabha has done the collection

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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