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A NOVEL INSIGHT ON THE ROLE OF HMGB1 AS A POTENTIAL BIOMARKER OF METABOLIC SYNDROME

Endocrinology

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ABSTRACT

The metabolic syndrome is a collection of conditions that increase your risk of coronary heart disease, diabetes, stroke, and other major health issues. In India, the prevalence of MetS in adults would be 20% to 25%. The factors responsible for these difficulties have not all yet been identified, despite the fact that several processes have been explored. Various international organisations have suggested multiple MetS categories with different focuses and diagnostic threshold values, including NCEP (National Cholesterol Education Program), ATP3 2005, WHO 1999, IDF (International Diabetes Federation), and AHA/ NHLBI (2009). Finding a suitable indication and the corresponding appropriate cut-off values is crucial for the early detection and prevention of MetS. HMGB1 is a multifunctional, non-histone nuclear protein that has been connected to a variety of clinical conditions, from sepsis to ischemia, as a DNA chaperone and a damage-associated molecular pattern (DAMP) with immune-stimulating capabilities. This review's purpose is to summarize the most recent information on HMGB1's role in METS problems.

KEYWORDS

Metabolic syndrome, Biomarker, HMGB1.

INTRODUCTION

Non-communicable diseases (NCDs) are the leading cause of morbidity & mortality in the globe. The main global health threat among the NCDs is metabolic syndrome (MetS). MetS, a clinical condition is characterized by a collection of significant risk factors for cardiovascular disease (CVD), type 2 diabetes, dyslipidemia, hypertension and abdominal obesity [1]. The MetS global prevalence varied from 12.5% to 31.4% [2]. Adults in India would have a prevalence of 20%-25% for MetS, with a substantially higher prevalence in females [3]. In this review article, we provide a general overview of fundamental role of HMGB1 & its relationship metabolic risk factors.

Background of MetS:

Numerous international organizations, including those listed below, have proposed multiple MetS classifications with varying foci and diagnostic threshold values [4].

NCEP (National Cholesterol Education Program) ATP3 2005 [5]:
A minimum of three of the following conditions must be met:

I. A blood sugar level that is higher than 5.6 mmol/L (100 mg/dl) or medication for an increased blood sugar level
ii. Low HDL cholesterol or medication therapy (HDL cholesterol 1.0 mmol/L [40 mg/dl] in males, 1.3 mmol/L [50 mg/dl] in women).
iii. Having blood triglyceride levels that are greater than 1.7 mmol/L (150 mg/dl) or taking medication to lower them
iv. Waist > 88 cm or > 102 cm (for males) (women)
v. Hypertension or a blood pressure reading of 130/85 mmHg or above. WHO 1999[6]:

Insulin resistance or high blood sugar present 6.1 mmol/L (110 mg/dl), 2 h glucose > 7.8 mmol (140 mg/dl), and two or more of the following:

i. For males, HDL cholesterol levels should be 0.9 mmol/L (35 mg/dl) and for women, 1.0 mmol/L (40 mg/dl).
ii. Triglycerides more than 1. 7 mmol/L (150 mg/dl)
iii. Men's or women's waist-to-hip ratios of greater than 0.9 or 0.85, or a BMI of greater than 30 kg/m2, respectively
iv. Blood pressure above 140/90 mmHg.

IDF (International Diabetes Federation) 2006[7]:
Male or female waist measurements of 94 cm or greater, as well as two or more of the following conditions:

i. Diagnosis of diabetes or blood glucose levels higher than 5.6 mmol/L (100 mg/dl)
ii. Low HDL cholesterol treated with medication or HDL cholesterol below 1.0 mmol/L (40 mg/dl) in males and 1.3 mmol/L (50 mg/dl) in women
iii. Blood triglyceride levels that are more than 1.7 mmol/L (150 mg/dl) or medication for triglyceride elevation
iv. High blood pressure of greater than 130/85 mmHg or medication for hypertension.

AHA/ NHLBI (2009) [8] :
The metabolic syndrome must meet at least three of the following requirements to be diagnosed:

i. At the apex of the iliac crest at the conclusion of a typical expiration, the waist must be at least 40 inches (102 cm) in circumference for males and 35 inches (89 cm) in circumference for women.
ii. A triglyceride level of at least 150 mg/dL (1.70 mmol/L), or being treated with medication for high triglycerides
iii. Having an HDL cholesterol level of less than 40 mg/dL (1.05 mmol/L) in males or 50 mg/dL (1.30 mmol/L) in women, or using medication to treat low HDL cholesterol
iv. At least 130 mm Hg in the systolic or 85 mm in the diastolic blood pressure.

A biomarker, often known as a biological marker, is an objective indication of a particular biological state or condition. It is utilised to assess or gauge how a therapeutic intervention affects pathogenic processes, typical biological processes, and pharmacologic responses. As a result, a variety of biomarkers are utilised in MetS to identify individuals at risk for cardiovascular illnesses early on and to stratify their risk. Interleukin-6, leptin, tumour necrosis factor-alpha, uric acid, interleukin-10, ghrelin, adiponectin, paraoxonase, oxidised LDL, plasminogen activator inhibitor, C-reactive protein (CRP), and other substances are included in it [9,10,11].

Structure of HMGB1:

A group of nonhistone proteins were isolated from the chromatin of the calf thymus in 1973 by Ernest Johns, Graham Goodwin, and colleagues. Because of their great mobility in polyacrylamide gel electrophoresis methods and lack of aggregation, these proteins were subsequently referred to as "high mobility group" (HMG) proteins [12,13]. The human HMGB1 protein has 215 amino acid residues, which are organised into two successive DNA binding domains called the HMG A box domain and the HMG B box domain, respectively. A C-terminal acidic tail (186-215 amino acids) and a brief but crucial N-terminal area follow. Three alpha helices and two loops, organised in a "L" form, make up the structural components of each of HMGB1's two HMG boxes [14]. The distribution of HmgB1 between the nucleus and cytoplasm relies on the tissue type, the redox state of HmgB1, and the stage of cell development. For instance, this protein is found in high concentrations in the thymus, testis, and spleen, both in the nucleus and cytoplasm, whereas HmgB1 is mostly localized in the cytoplasm of brain and liver tissue. The active involvement of HmgB1 in the control of transcription, replication, recombination, and DNA repair is well established [15].

Mechanism of action of HMGB1:

As a DNA chaperone and a damage-associated molecular pattern

(DAMP) with immune-stimulating properties, HMGB1 is a multifunctional protein. Toll-like receptors (TLRs), TLR2, TLR4, TLR9, and the receptor for advanced glycation end products are just a few of the pattern recognition receptors that may be activated by extracellular HMGB1 in order to affect immune cells as a DAMP molecule (RAGE). Through stimulating the mitogen-activated protein kinase (MAPK)/cJun N-terminal kinase (JNK)/p38 and nuclear factor kappa light-chain enhancer of activated B cells (NF-jB) pathways, the binding of HMGB1 to these cell surface receptors can trigger inflammatory reactions. Extracellular HMGB1 has been shown to have a strong affinity for the TLR2, TLR4, and RAGE [16, 17].

Secretion of HMGB1:

HMGB1 can be secreted from various cells both actively and passively. The endotoxin lipopolysaccharide (LPS) can cause cultured macrophages to produce substantial amounts of HMGB1 into the extracellular space, in accordance with a 1999 study by Wang and colleagues [18]. There have been put forth and extensively referenced two models of HMGB1 active release. One includes the release of HMGB1 into the extracellular space as a result of stimulating target cells to become active. The second method involves the packing of HMGB1 into intracellular vesicles (like lysosomes or autophagosomes) and the subsequent release of HMGB1 outside the cell following the fusion of the vesicles with the cell plasma membrane. The modulators (proteins or organelles) that better regulate the active secretion of HMGB1 are oxygen atom-containing free radicals, Reactive nitrogen species (RNS), calcium ions, tumor necrosis factor (TNF), mitogen-activated protein kinase (MAPK), tumor protein P53 (TP53, best known as p53), Peroxisome proliferator-activated receptors (PPARs), Inflammasomes etc. In response to various stressors or damage, HMGB1 can be passively released following many forms of cell death (such as necrosis, necroptosis, apoptosis, NETosis, lysosome-mediated cell death, pyroptosis, autophagy-dependent cell death, and ferroptosis). Some of the key regulators of HMGB1 passive release are Receptor-interacting serine-threonine kinase (RIPK), Poly (ADP.ribose) polymerase (PARP), Cathepsin, deoxyribonucleases, caspase, autophagy-related (ATG) proteins, etc [19].

HMGB1 & blood glucose levels:

Diabetes mellitus (DM), a chronic metabolic condition, is the ninth leading cause of mortality worldwide. It affects 10% of the global population and is distinguished by hyperglycemia brought on by impaired insulin secretion or insulin resistance [20, 21]. The involvement of inflammation in the aetiology of diabetes mellitus was the subject of several researches. Advanced glycation end products (AGEs), protein C kinase (PCK), and the polyol pathway are all activated in a hyperglycemic milieu, in addition to increased reactive oxygen species (ROS) production . TNF-, IL-1, IL-6, IL-8, and HMGB1 are among the pro-inflammatory cytokines that are promoted by all of these variables [22]. A research has shown a novel function of HMGB1 in the presence of IL-2, which modifies the production of several cytokines and leptin, mostly from NK (Natural Killer) cells through activating the Toll-like Receptors (TLR) systems in peripheral blood mononuclear cells (PBMCs). This could boost the pro-inflammatory response and cause monocytes to secrete more IL-1. Moreover, leptin secretion was elevated and PBMCs, namely the NK and NK-T subpopulations, may be activated in the presence of high insulin and glucose concentrations. These findings revealed that PBMCs may become activated in response to "metainflammation," and leptin release may reveal the degree of the dysmetabolism [23]. A biomarker for cell injury and ischemia is extracellular HMGB1. Elevated levels of HMGB1 have been seen in diabetics with diabetic nephropathy, retinopathy, and insulin resistance. In both animal models and humans with type 2 diabetes, a link between HMGB1 levels and diabetes complications has been discovered. This research revealed that glucose infusion-induced hyperglycemia in rats was related with higher blood HMGB1 levels [24]. In a research using an experimental model of diabetic rats, a decrease in HMGB1 was seen at a dosage of 10 mg/kg metformin, demonstrating its relationship with inflammatory management and blood sugar levels [25]. Also, a research revealed a substantial, linear connection between HMGB1 and maternal age that was only seen in Gestational diabetes mellitus patients [26]. It has been proposed that insulin can lower blood HMGB1 levels in infected mice, suggesting that glucose metabolism may have an influence in controlling HMGB1 release [27]. A disease that promotes glycation, such as diabetes, may cause an increase in the levels of extracellular HMGB1, suggesting that glycation promotes HMGB1 secretion [28]. HMGB1 is a type of delayed inflammatory factor that can increase insulin resistance, lead to impaired glucose tolerance, promote tumor metastasis, and affect the blood-brain barrier permeability [29, 30].

HMGB1 & Hypertension:

A major concern facing the world's health care systems is the increased prevalence of cardiovascular disease (CVD). The development and occurrence of CVD are intimately tied to inflammation. As HMGB1 affects tissue regeneration and tissue healing in a pro-inflammatory and restorative manner, it has received particular interest in the field of cardiovascular disease (CVD). The main factor causing the sustained rise in pulmonary blood pressure, also known as pulmonary hypertension, is remodelling and vasoconstriction of the tiny pulmonary arteries, which results in pulmonary vascular resistance, right ventricular (RV) failure, and finally mortality. An essential peptide for vasoconstriction is angiotensin II (Ang II), which regulates blood pressure and homeostasis. According to studies, TLR-4 and HMGB1 expression is increased by Ang II-induced inflammation in rat tubular epithelial cells on both the mRNA and protein levels, which increases the production of pro-inflammatory cytokines. Moreover, TLR-4 knockdown and HMGB1 blockage have an anti-inflammatory impact, which is demonstrated by reduced nuclear factor kappa B (NF-B) signalling and ROS production. Our findings imply that HMGB1-TLR4 interference can reduce Ang II-induced inflammation and that Ang II-mediated signaling is a possible therapeutic target for pulmonary hypertension [31, 32]. Research has revealed that HMGB1 is up-regulated in essential hypertension, which influences how smooth muscle cells change phenotypically from contractile to synthetic under the stimulation of the renin-angiotensin system, resulting in vascular remodeling [33]. Studies on animals have shown that HMGB1 is essential for the development of pulmonary hypertension brought on by exposure to hypoxia and monocrotaline treatment [34]. A successful rat model of hypoxic pulmonary hypertension (HPH) was developed, offering a new paradigm for preclinical research on HPH and shedding light on the function of HMGB1.Moreover, it was shown that HMGB1 promotes inflammation in the model via RAGE, which severely impairs lung function in HPH [35]. The importance of HMGB1 in pulmonary arterial hypertension (PAH) has been highlighted. Studies have shown that HMGB1 stimulates the extracellular signal-regulated kinase 1/2, bone morphogenetic protein receptor 2, and dynamin-related protein 1 (ERK1/2/ Drp1/Autophagy/BMPR2/Id1) axis, which in turn promotes pulmonary arterial smooth muscle cell proliferation and migration. The HMGB1 signalling pathway may be a useful target for PAH therapeutic intervention [36]. According to clinical research, HMGB1 levels in the serum are positively correlated with inflammatory factor levels and significantly elevated early after the onset of pulmonary hypertension of the newborn (PPHN) in newborns with the condition. These levels then significantly decrease after remission. Even while there was no discernible pulmonary vasculature remodelling in PPHN rats, animal studies on HMGB1 levels in peripheral blood and lung tissue supported this finding. HMGB1 is a key player in the early stages of hypoxia-induced PPHN and acts as an inflammatory mediator, which raises the possibility that it might serve as an early marker for the diagnosis of PPHN [37]. According to a research, the immunological checkpoint regulator hypoxia-induced mitogenic factor (HIMF) and the HIMF/HMGB1 signalling axis are key players in Pulmonary Hypertension [38]. A study also presents a novel viewpoint on the expression and functioning of HMGB1. Moreover, it corroborates the critical role necrotic cell death plays in the release of HMGB1, activation of TLR4, and the emergence of sex differences in pulmonary arterial hypertension severity [39].

HMGB1, Obesity & Dyslipidemia:

In both developed and developing nations, obesity is a growing public health concern. Obesity is a condition that is connected to a persistent low-grade inflammatory state. This disorder has grown to be a serious threat to public health. The development of obesity-related metabolic problems is strongly influenced by metabolic inflammation, often known as "meta-inflammation". The major underlying causes of nonalcoholic fatty liver disease (NAFLD), which is strongly related to insulin resistance, include obesity and the metabolic syndrome [40]. Several studies have shown that HMGB1 protein expression levels are elevated in adipose tissues of obese patients as well as obese mice [41, 42]. In comparison to the levels of expression seen in the control groups, HMGB1 and toll-like receptor-4 (TLR4) were both strongly expressed in the serum and peripheral blood mononuclear cells

(PBMCs) of patients with obesity and T2DM, respectively. Certain factors connected to obesity and glycolipid metabolism were favorably linked with the expression levels of HMGB1 and TLR4 [43]. According to research, the DNA methylation of the histone variation 2AX (H2AX) and HMGB1 may play a crucial role in the regulation of the genes in adipose tissue and inflammation [44]. In a Chinese research, patients with pure T2DM had higher plasma HMGB1 levels, which may have been brought on by IR. With its proinflammatory action, serum HMGB1 contributed to the pathological development of obesity and T2DM [45]. In a research, it was shown that mice fed a high-fat diet had more HMGB1-labeled nuclei, which is related to greater levels of HMGB1 and inflammatory cytokines expressed in adipose tissue [46]. While inflammation and inflammatory illnesses are prominent in the adipose tissue of obese people, targeting HMGB1 may represent a promising therapeutic approach. Antagonists of HMGB1 active release might interfere with its cytoplasmic exporting and diminish its pro-inflammatory effects. To modulate the HMGB1 response, further techniques focused at various HMGB1 isoforms may be of relevance [47]. It has been observed that ablation of Hmgb1 in intestinal epithelial cells results in increased expression of scavenger receptor class B type 1 and decreased expression of apolipoprotein B48, lipid accumulation in jejunal intestinal epithelial cells, decreased chylomicron packaging and/or release, decreased serum triglyceride, and decreased liver steatosis [48]. The findings suggest that through maintaining -oxidation and preventing endoplasmic reticulum stress, hepatocyte HMGB1 protects against aberrant lipid metabolism. This suggests a distinct mechanism for HMGB1-regulation of hepatic steatosis and suggests that HMGB1 stabilisation in hepatocytes may be a therapeutic strategy for treating and preventing non-alcoholic fatty liver disease [49]. A composite population's circulating HMGB1 levels are described by age, sex, and race in the study. The findings show that circulating HMGB1 levels are greater in Blacks than Whites, in females than males, and that circulating HMGB1 levels rise with age [50].

CONCLUSIONS

Metabolic Syndrome is a heterogeneous entity, with age and sex variation in component clusters, might have significant effects on how the metabolic syndrome and cardiovascular risk are related over the course of human life. It is essential to determine an adequate indicator and the related ideal cut-off levels for the early prediction and prevention of MetS. HMGB1 is a non-histone nuclear protein which is a highly conserved, ubiquitous & position-dependent multifunctional protein. Whereas cytoplasmic HMGB1 supports autophagy, nuclear HMGB1 controls the shape and operation of chromosomes inside the cell. HMGB1 mediates inflammatory, immune, and metabolic reactions outside of the cell. The degree of HMGB1 release can be altered and is connected to active or passive processes. Thus, HMGB1 can serve as a novel & potential biomarker in the prognosis & diagnosis of Metabolic syndrome.

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