

Obesity Induced Metaflammation: Pathophysiology and Mitigation

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Abstract

Obesity is dramatically increasing worldwide and there exists a significant association of its prevalence with Type 2 Diabetes Mellitus, hypertension, cardiovascular diseases etc. The altered homeostasis of nutritionally overloaded metabolic cells marks the development of obesity induced inflammation. It is marked by elevated expression of the genes encoding for cytokines, chemokines and other inflammatory mediators through activated transcription factors-nuclear factor- κ B, activator protein-1, nuclear factor of activated T cells and signal transducer and activator of transcription 3 and; execution of a macromolecular innate immune cell sensor- inflammasome to activate caspase-1 pathway resulting in photolytic maturation. In brief, there occurs an evidential increase in pro-inflammatory cytokines released from the M1 macrophages of white adipose tissue including TNF- α , IL-6, CRP, IL-1 β , etc. on contrary an observable decrease in anti-inflammatory cytokines like IL-10, IL-1Ra, adiponectin etc. released from M2 macrophages. Along with adipose tissue, immune cells, liver, brain, muscles and pancreas also suffers undergoes inflammatory damage. The inflammatory kinases like JNK and IKK apart from inhibiting insulin action and glucose uptake, also down-regulate transcriptional process resulting in increased expression of pro-inflammatory cytokines. The inflammatory process is initiated by Macrophage-like Kupffer cells following the transducer signals produced by the white adipose tissues further leading to necro-inflammation. Muscle fibre is said to suffer from decreased glycogen synthesis. Obesity also triggers the hypothalamic-pituitary adrenal axis. Pancreas modulating the insulin homeostasis and glucose tolerance is also exaggeratedly affected. Multi-dimensional interventions so as to check obesity induced metaflammation have been undertaken that includes therapeutic intervention and administration of synthetic drugs to target the actual inflammatory. Thus, by proper weight management and diet inflammatory responses in obesity can be controlled to a large extent.

Keywords Cytokines; Chemokines; Macrophage infiltration; Free fatty acid; White adipose tissue; Inflammatory cascade

Introduction

Obesity, being a grave problem and one of the profoundly discussed metabolic disorders is given immense of research concern to re-evaluate its pathophysiology [1]. It is one of the most escalating health hazard stretched all over the world population with a BMI >30 Kg/m² and; an approximate statistical prevalence of ~ 500 million people suffering with its synergistic morbidities [2-4]. Obesity aggravates broad spectrum of metabolic complications as all of these are inter-related through the vital bio-chemical pathways undertaken by the tissue system mainly adipose tissue, liver, pancreas, brain etc [5]. Metabolic homeostasis is hampered following excess nutrient intake during obesity that renders initiation of inflammatory phenomenon triggered by the specialized metabolic cells [6,7].

Obesity alters expression intracellular signalling molecules

The genes encoding for the inflammatory mediators like- cytokines, chemokines etc are up-regulated via activation of transcription factor-nuclear factor- κ B (NF- κ B), activator protein-1 (AP-1), nuclear factor of activated T cells (NFAT) and signal transducer and activator of transcription 3 (STAT 3) [8,9]. Increased sequestration of free fatty acid during obese condition signals inflammasome- a macromolecular innate immune cell sensor to activate caspase-1 pathway that results in proteolytic maturation and elevated secretion of pro-inflammatory

cytokines [10-14]. Later to the up-regulated genes encoding for adipocytokines, there occurs fluctuation in the prominent intracellular factors like C-Junction N terminal Kinase (JNK), Inhibitors of K Kinase (IKK) and Protein Kinase R (PKR) that further induces inflammatory pathway in the metabolic tissues [15,16]. Researches on genetic analysis have rendered an inevitable association between obesity, its synergistic effects with varied phenotypes of metabolic complications and the gene induced inflammatory cascade [17-20].

Obesity induced metaflammation

Adipose tissue: The adipose tissue acts as an endocrine gland initiating metabolic phenomenon of cytokine and chemokine secretion; hypoxia or cell death and infiltration of immune cells [21]. The distinctive M1 and M2 types of macrophages secreted from the white adipose tissue (WAT) are classically altered showing greater phenotypic coding of M1 macrophages as characterized by CD11+ surface marker and production of enzymes of nitric oxide synthase (iNOS) [22]. These further results in release of cytokines like TNF- α , CRP, IL-1 β , complement C (C3) and IL-6 [23-26]. Contradictorily, the anti-inflammatory cytokines like IL-10, IL-1Ra and iNOS inhibited by arginase are found to be diminishingly produced by the macrophages [27,28]. These alterations later stimulate the hypothalamic-pituitary-adrenal axis [29-31]. Hence, such obesity related biomarkers may contribute vitally through regulating other metabolic complications like insulin sensitivity, diabetes, impaired glucose tolerance and altered lipid metabolism [26]. Aberrant lipid metabolism marked by fatty acyl CoA and diacyl glycerols production further results in altered insulin

signalling as a result of serine/threonine kinase cascade mediated phosphorylation of insulin receptor substrate (IRS)-1. Similar mechanism occurs in the liver where increased hepatocellular diacylglycerol activating protein kinase C hinders tyrosine phosphorylation of IRS-2 [32]. Downregulation of transcription factors including activator protein-1 (AP-1), NF- κ B, interferon regulatory factor (IRF) and peroxisome-proliferator-activated receptor (PPAR γ) eventually renders decline in adiponectin specified cytokines [33].

Immune cells: Along with macrophage levels which are mentioned to be elevated among obese mice as noted by researchers, an observable modulation of T cells, mast cells and natural killer cells (NK) are also noticed during obesity [34-37]. Obesity increases CD8+ to CD4+ T cell counts and decreases immunosuppressive T regulatory cell number that further promotes macrophage recruitment and aggravates kinase activity [38-42]. Adipose tissue over-expressing chemoattractant CCL2 leads to macrophage infiltration, insulin resistance and hepatosteatosis [43,44].

Liver: Macrophage like Kupffer cells in the liver gets over-activated for inflammatory phenomenon among obese individuals as compared to controls [45,46]. Experimental studies on mice have shown liver specific activation of IKK β resulting in reduced insulin sensitivity, glucose tolerance [46] and; increased cytokines like CRP, PAI-1 and serum amyloid A. A significant relation has been chalked out between WAT secreted products (leptin, adiponectin, TNF- α) and hepatic damage [47]. There is a reciprocal relationship between adiponectin and hepatic necro-inflammation [48,49]. The mechanisms underlying the deleterious association between accumulation of macrophages in WAT and liver pathology could involve increased free fatty acid (FFA) flux and/or delivery of proinflammatory factors to the liver through the portal circulation. Portal vein of obese subjects has marked increased IL-6 level that may end up in liver damage [50]. A significant worsening effect has been noted between omental WAT-secreted products (leptin, adiponectin, TNF- α) and hepatic damage associated with necroinflammation [51-53].

Muscle: The inflammatory phenomenon in the muscle tissues and insulin sensitivity are said to be influenced by the inflammatory mediators like TNF- α , IL-6, CCL-2, retinol binding protein etc. Released from the liver and adipose tissue, although no such obesity induced macrophage infiltration is observed [54, 55]. Muscle wasting phenotype in the muscle tissues of mice via the activation of IKK/NF κ B pathway have been revealed without any evidential cytokine mediated inflammation [56].

Brain: Convincing evidence submitted by Souza et al. revealed that obesity marks activation of inflammatory pathways in the hypothalamus that eventually modulates the expression of TNF- α , IL-1 β and IL-6 resulting in hypothalamic apoptosis [57-59].

Pancreas: Increased macrophage infiltration results in steep increase of inflammatory cytokines and recruitment of neutrophils, monocytes, and lymphocytes to the pancreas during obesity thus paving way to glucose intolerance [60-63]. Activation of NF- κ B pathways is influenced by IL-1 β and IFN γ that can be downregulated by using non-degradable inhibitor for NF- κ B which signals IKK α thus resulting in curing of islets from NO $_2$ production and IL-1 β induced apoptosis [64]. Obesity and pancreatitis together creates more proneness to higher circulating inflammatory cytokines among patients [65,66].

Mitigation of inflammatory responses in obesity: Multidimensional approaches including targeted inflammatory molecule or therapeutic

interventions are being undertaken so as to check obesity induced metaflammation with an objective of hindering inflammatory response by neutralizing the cytokines, chemokines, adhesion molecules/ other mediators [67-71]. Available research evidence has revealed improved insulin action in animal models by blocking specific inflammatory kinases pathway [72,73]. Checking the plasma concentration of TNF- α using its antagonist have shown to down regulate blood glucose level and elevate adiponectin levels [74]. Recombinant IL-1 receptor antagonist, synthetic/peptide JNK inhibitors and interfering RNAs have shown to result in insulin sensitivity and glucose tolerance [75-79]. Significant reduction in cholesterol level, diminished proneness towards CVD and depressed cell adhesion/ migration associated with metaflammatory phenomenon have been achieved by statin therapy which henceforth checks TNF- α and IL-6 concentration [80-86]. Statin therapy has shown to act via different immune-mechanism in obesity induced inflammatory cascade [86-90]. Cell-based immunotherapy have proved beneficial thus by eliminating T cell and mast cell population, CD11+ cells [91-93]. Introduction to chemical chaperons, thiazolidenes exhibit positive effects as the former reduces ER stress and the later possess agonistic properties to PARP γ which altogether enhances insulin sensitivity and glucose tolerance [94-98]. Recombinant protein has shown to curtail TNF- α production, blood sugar and fatty liver synthesis [99-101]. Diet restricted with excess fat and empty calories can prove beneficial. Omega-3 and omega-6 fatty acid; linolenic fatty acid and PUFA constituting of metabolites-EPA and DHA renders anti-inflammatory function can prevent CVD, atherosclerosis along with depressing cytokine expression and macrophage infiltration [102-106]. Dietary consumption of Mediterranean foods, use of mustard oil/soya bean oil, increased intake of fruits, vegetables, nuts and whole gram can curb the complication [107,108]. Coffee, cocoa, vitamin E and green tea also help in the mitigation of inflammatory responses in obesity [109-111]. Regular physical activity also deliver better and positive results with mitigated inflammation among obese patients [112,113]; also improvement in endothelial function, liver and tissue angiogenesis [114,115]. Thus, by proper weight management and diet inflammatory responses in obesity can be controlled to a large extent [116].

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