Journal of Vascular Medicine & Surgery
ISSN: 2329-6925

Khaybullina, Vasc Med Surg 2017, 5:1
DOI: 10.4172/2329-6925.1000302

Mini Review Open Access

Inflammation and Oxidative Stress: Critical Role for Metabolic Syndrome

ZR Khaybullina*

Republican Specialized Center of Surgery Named after Academician V Vakhidov, Ministry of Health Republic of Uzbekistan, Tashkent, Uzbekistan

Obesity and Metabolic syndrome (MetS) – is a global health problem. Localization of the excess amount of adipose tissue – visceral adiposity appears to be a key for developing cardiovascular and metabolic diseases [1].

Metabolic syndrome (MetS), according definition of International Diabetes Federation (IDF) consensus (2013) is a cluster of central obesity plus any of 2 of the following factors: raised triglycerides (<150 mg/dL), reduced HDL cholesterol (<40 mg/dL in males, <50 mg/dL in females) or specific treatment of lipid abnormality, raised blood pressure (systolic BP >130 or diastolic BP >85 mm Hg) or treatment of previously diagnosed hypertension, raised fasting glucose >100 mg/dL or previously diagnosed type 2 diabetes [2]. Central obesity, insulin resistance, inflammation and oxidative stress are key factors, that associated with MetS [3], that's why IDF describes "platinum standard" for additional measurements, including pro-inflammatory state (IL-6, TNF-alpha), adipocytokines (leptin, adiponectin), HOMA-IR, elevated free fatty acid, markers of endothelial dysfunction and prothrombotic state (PAI-1, fibrinogen), hormones of pituitary-adrenal axis [4].

Adipose tissue has been shown to express proinflammatory mediators, both by macrophages and adipocytes [5], that lead low intensity inflammation in adipose tissue [6]. Triglycerides deposition in the adipocytes leads macrophageal activation and proinflammatory cytokines overproduction, as well as adipocytokines disregulation [7]. Leptin, PAI-1 and hsCRP showed significant positive association with increased MetS components (P-trend <0.05), while adiponectin was negatively associated with increased MetS components (P-trend <0.0001) [8]. As triggers of inflammation in adipose tissue can be adipocytes hypertrophy, local hypoxia, some of microorganisms such as Cytomegalovirus (CMV), *H. pylori*, *C. Pneumoniae* [9]. Activation of proinflammatory stimuli can be mediated by innate immunity receptors - Toll-like receptors (TLR) after binding of bacterial lipopolysaccharides (LPS) or free fatty acids and derivates of lipids degradation, then nuclear factor (NF)-kB translocation into the nucleus and transcription of IL-6, TNF-a, resistin and different chemokines and adipokines begins [10]. NF-kB regulates activity more 125 genes, most of which are proinflammatory [11]. Monocytes in obesity have significantly increased binding of NF-kB, the key proinflammatory transcriptional factor, leptin and adiponectin secretion are regulated aberrantly.

Recently it has been shown that insulin can suppressed concentration of inflammatory mediators – IL-6, TNF-a, IL-1b and have antiapoptotic effect [12]. Insulin suppresses several proinflammatory transcription factors: NF-kB, Egr-1, activating protein-1 (AP-1) and the corresponding genes regulated by them, such as matrix metalloproteinase-9, PAI-1 [13]. Insulin can suppress reactive oxygen species (ROS) generation and p47 ^{phox} expression, to increase inhibitor (I)-kB expression in mononuclear cells as well as to suppress plasma concentrations of intracellular adhesion molecule-1 and monocyte chemotactic protein-1, and CRP level [14]. The inflammatory events were mainly observed in obese individuals without IR; the absent of inflammatory events and high levels of insulin in obese subjects with IR, suggest a protector role of insulin for developing inflammatory events [15]. Proteasomal dysfunction and impaired proteostasis in adipocytes, resulting from protein oxidation and/or misfolding, constitute major pathogenic mechanisms in the development of IR at obesity [16]. There is the interference of insulin signal transduction by inflammatory mechanisms at obesity. IL-6 and TNF-a can induce serine phosphorilation of the IRS-1, which leads serine phosphorilation in some enzymes and proteins such as insulin receptor, Act-kinase (protein kinase B), NOS. Thus, IL-6 and TNF-a cause inhibition of the insulin receptor, induce ubiquitination and proteosomal degradation of IRS-1, that reduces the activation of Act kinase2 and disturb the translocation of the insulin-responsible glucose transporter GLUT-4 to the plasma membrane. In the absence of Act-kinase2 translocation of Rac-1 increased, it leads translocation of p47 phox from the cytosol to the membrane and full NADFH-oxidase complex formation that begins intensive ROS production [17]. Superoxide radical – is inductor of 2 major proinflammatory transcriptional factors: NF-kB and AP-1, superoxide radical diminished bioavailability of NO, because NO binds to superoxide radical to form peroxynitrite. Thus, TNF a – is strong promoter of insulin resistance, inhibitor of eNOS, activator of ROS overproduction and can disturb endothelium mediated vasodilatation [18]. These data suggests that adipokines and cytokines have been linked to the pathogenesis of MetS and its comorbidities through their effects on vascular function, inflammation and oxidative stress [19]. Recently published and emerging studies now clearly establish that: 1) NADPH oxidases are of critical importance in atherosclerosis and hypertension in animal models; 2) given the tissue-specific expression of key components of NADPH oxidase, it may be possible to target vascular oxidative stress for prevention of CVD [20]. Complex molecular circuits including endothelial nitric oxide synthase, prostacyclin synthase, mitochondrial adaptor p66(Shc), nicotinamide adenine dinucleotide phosphate-oxidase oxidase and nuclear factor kappa-B are involved to the endothelial insulin resistance and oxidative stress; furthermore ruboxistaurin, sildenafil, endothelin receptor antagonists, NO donors are potential compounds for restoring endothelial insulin signaling [21]. Semicarbazide-sensitive amine oxidase (SSAO), an enzyme highly expressed on adipocyte plasma membranes, converts primary amines into aldehydes, ammonium and hydrogen peroxide, and is likely involved in endothelial damage during the course of diabetes and obesity. Hypoxia-induced down-regulation of SSAO activity could represent an adaptive mechanism to lower toxic molecules production, and may thus protect from tissue injury during these harmful conditions [22]. Cytochrome oxidase (COX) dysfunction

***Corresponding author:** ZR Khaybullina, Chief of Biochemistry and Microbiology Department, Auctioneer society "Republican Specialized Center of Surgery Named after Academician V. Vakhidov", Tashkent, Uzbekistan, Tel: +998 71 239-47-95; E-mail: zrkhaybullina1@gmail.com

Received February 04, 2017; **Accepted** February 17, 2017; **Published** February 24, 2017

Citation: Khaybullina ZR (2017) Inflammation and Oxidative Stress: Critical Role for Metabolic Syndrome. J Vasc Med Surg 5: 302. doi: 10.4172/2329-6925.1000302

is associated with mitochondrial oxidative stress. COX4I1 depression is related to insulin resistance and type 2 diabetes in obesity. In peripheral blood monocytes it may be a diagnostically useful biomarker [23].

It has been shown, that four genes involved in inflammation and oxidative stress (IL6, TNFα, mitochondrial transcription factor A (TFAM), and glucose transport 4 (GLUT4) can be aberrant methylated at obesity. Authors believe that aberrant DNA methylation of IL6 gene promoter may play an important role in the etiology and pathogenesis of obesity and IL6 methylation could be used as molecular biomarker for obesity risk assessment because DNA methylation can act as a downstream effector of environmental signals [24]. Among the various nuclear receptors, peroxisome proliferator-activated receptor γ promotes the transcription of adiponectin and antioxidative enzymes, whereas mineralocorticoid receptor mediates the effects of aldosterone and glucocorticoid to induce oxidative stress in adipocytes. It is hypothesized that both play crucial roles in the pathophysiology of obesity-associated insulin resistance and cardiovascular diseases [7].

It has been shown that transcription factor cMYC, TLR2, CXCR4 are overexpressed in monocytes of obese women at high cardiovascular risk and that weight loss was associated with a concomitant decrease of their expression; this suggests that the cMYC has an atherogenic effect by inducing pro-inflammatory genes; paraoxonase, interferon regulatory factor-1, toll-like receptors, CXCR4 and SOD1 as possible targets for intervention [25].

We have been studied interleykin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), C-reactive protein (CRP)) and some markers of cardiometabolic risk such as reactive oxygen species and vasculo-endothelial grows factor (VEGF), as well as lipidomic profile in blood serum of the patients with morbid obesity and after laparoscopic sleeve gasterectomy (LSG). It was established that LSG does not be accompanied by activation of the system inflammation both at early periods and at 3 month after the operation. LSG provides reduction of proinflammatory factors in blood after 3 months in postoperative period, LSG have positive effect on liquidation of the inflammation and metabolic disorders in patients with morbid obesity. LSG causes body mass index and waist circumference decreasing on 25% and 14% after 3 month post operation versus data before treatment that approve visceral fat reduction. LSG reduces cardiometabolic risk by normalizations of lipidomic profile and optimizing the visceral fat tissue metabolism by reduction of inflammation and oxidative stress [26].

One of the most important antioxidants in plasma is uric acid. A recent study of the relationship between uric acid levels and various obesity-related factors found that visceral fat was the factor most strongly related to uric acid levels. Uric acid is itself a potent endogenous antioxidant, but because reactive oxygen species are produced during uric acid generation, it is suggested that uric acid may have opposing effects [27]. Uric acid may have a protective as well as a detrimental role in vascular alterations, thus justifying the multi-directional effects of xantine oxidoreductase (XOR) inhibition. Moreover, XOR products are associated with cell differentiation, leading to adipogenesis and foam cell formation, as well as to the production of monocyte chemoattractant protein-1 from arterial smooth muscle cells, after proliferation and migration; the role of XOR in adipogenesis is also connected with insulin resistance and obesity, two main features of type 2 diabetes [28]. Hyperglycemia-induced oxidative damage in adipocytes and its potential links to diabetes progression when advanced glycation endproducts (AGEs) -especially glycated albumin formation is increased [29]. Elevated AGEs elicit severe downstream consequences via their binding to receptors of AGEs (RAGE), this includes oxidative stress and oxidative modifications of biological compounds together with heightened inflammation [30].

There is conception about macronutrient intake caused oxidative stress and ROS overproduction [13]. Enhancing of the ROS production in hypothalamic neurons exposed to excess lipids promotes metabolic remodeling that reduces local inflammatory and endoplasmatic reticulum (ER) stress responses [31].

Despite these findings, there are metabolically health obese people – this is phenomenon, which first described by Sims [32]. It has been established that in metabolically healthy obese persons CRP level is similar with normal-weight persons are protected from obesity-associated metabolic abnormalities.

These studies contributed to a better understanding of the relationships between metabolic syndrome, insulin signaling, oxidative stress, inflammation and atherosclerosis.

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