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Review Article

Biochemistry Section

Obesity, Cardiovascular Diseases and COVID-19

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ABSTRACT

Obesity is a metabolic disorder which is emerging as a worldwide epidemic. It is often associated with diabetes, hypertension and Cardiovascular Diseases (CVDs). High calorie intake/nutrition causes excess deposition of Free Fatty Acids (FFA) in adipose tissue, which later transports those FFA to the liver for further metabolic activities, resulting in dyslipidemia. However, altered secretion of adipokines plays an important role in the pathophysiology of obesity related complications via low grade chronic inflammation. Adipokine like Interleukin-6 (IL-6) favour endothelial dysfunction by stimulating monocyte to macrophage differentiation using adhesion molecules. Secretion of the Renin Angiotensin System (RAS) components and angiotensin-II activity promotion are considered the additional functions of adipose tissue. Indeed, all these aspects of adipose tissues have been evidenced for the development and the progression of CVDs. Coronavirus Disease (COVID-19) is a worldwide pandemic affecting millions of people. Pre-existing obesity and CVDs have been suggested as a potential risk factor for increased severity of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in patients. Therefore, this review focuses on the possible role of obesity related CVDs as a significant risk factor for COVID-19 severity.

Keywords: Adipose tissue, Free fatty acid, Severe acute respiratory syndrome coronavirus 2 severity

INTRODUCTION

The World Health Organisation (WHO) has declared the COVID-19 as a global pandemic. The International Committee on Taxonomy of Viruses renamed the virus as SARS-CoV-2 due to the aetiology and the symptoms. The SARS-CoV-2 is a positive-sense single stranded Ribonucleic Acid (RNA) (30 kb) enveloped virus which belongs to the β coronavirus family with a diameter of 50-220 nm. The spike glycoprotein (S1 and S2 heterodimers) is a key structural protein of this virus, which make it more pathogenic [1,2]. However, this is not the first time when coronavirus has infected humans. With common cold like symptoms, coronavirus was first reported in the year 1966 by Tyrell and Bynoe. Later in the year 2003, SARS-CoV-1 and the year 2012, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) had infected people of many countries [3]. Interestingly, the genome of SARS-CoV-2 reported being associated with the genome of SARS-CoV-1 and MERS-CoV [1]. Worldwide, more than 3,000,000 people were infected and more than 2,00,000 people were killed by COVID-19, suggesting the severity of SARS-CoV-2 [4].

Meta-analysis on patients with COVID-19 elucidated CVDs as a major risk factor for severe COVID-19 infection. A meta-analysis of 76993 patients with COVID-19 reported that the prevalence of CVD was 12.11%, and hypertension was 16.37% [5]. Another study on 44672 patients reported that the prevalence of CVD was 10.5%, and hypertension was 6% [6]. Other studies show similar findings suggesting that pre-existing CVDs may be a risk factor for elevated mortality rate in COVID-19 disease [7-10]. Moreover, obesity has been considered as a prominent risk factor for the development and the progression of cardiovascular complications clustering myocardial infarction, dysrhythmias, carditis, heart failure venous thrombosis and thromboembolic disease [11]. Therefore, this review focuses on the functional, biochemical and pathophysiological aspects of the obesity mediated CVDs and their effects on the COVID-19 severity.

ADIPOSE TISSUE PHYSIOLOGY AND COVID-19

Adipose tissue is a vital organ typically involved in energy homeostasis of the body. In mammals, adipose tissues are classified as Brown Adipose Tissue (BAT) and White Adipose Tissue (WAT). BAT is enriched with mitochondria and active uncoupling proteins, hence appear brown and generate heat via non-shivering thermogenesis respectively. Conversely, WAT is subdivided as visceral and subcutaneous fat depots and is principally involved in altered lipid metabolism (dyslipidemia) and obesity [12]. However, to store excess energy preadipocytes potentially differentiate in mature adipocyte, under the strict control of CCAAT/Enhancer-Binding Proteins (C/EBPs) and Peroxisome Proliferator Activated Receptor gamma (PPARγ) transcription factors. This leads to adipose tissue expansion through hyperplasia (increase in adipocyte number) and hypertrophy (increase in adipocyte volume/size), responsible for obesity and its associated co-morbidities [13]. Further, adipose tissue acts as an endocrine organ that secretes various hormones/adipocytokines/enzymes called “adipokines”. Elevated dyslipidemia and altered secretion of adipokines such as adiponectin, leptin, Plasminogen Activator Inhibitor-1 (PAI-1), IL-6 and visfatin have been reported as a major risk of CVDs in patients with obesity [14] and thus might be involved in the severity of COVID-19.

At present, there is no direct evidence explaining SARS-CoV-2 infection in adipose tissue, except Angiotensin Converting Enzyme-2 (ACE-2) receptor expression on several cells within this tissue, including mature adipocyte, macrophages, stromal vascular cells and endothelial cells [15,16]. Thus, the analysis of these cells may provide a possible interlinked mechanism between adipose tissue and the severity of COVID-19. Visceral adipose tissue is distributed specifically throughout the body. Hence, adipose tissue associated with lung might act as a SARS-CoV-2 reservoir and can modulate inflammatory responses, vascular wall dysfunction (atherosclerosis), CVDs and thereby, the severity of COVID-19 disease [17].

DISLIPIDEMIA, CVDs AND COVID-19

Excess dietary FFA deposit in adipose tissue which is later transported to the liver. The Triglyceride (TG) rich lipoproteins (chylomicrons) derived from dietary FFA and cholesterol promotes fat storage in the adipose tissue, while catabolism of TG promotes mobilisation of FFA as a fuel to the tissues and organs; therefore,

lipogenesis and the lipolysis are considered as the chief functions of the adipose tissue [18]. In the liver, FFA generates Very Low Density Lipoproteins (VLDL) consist of TG, cholesterol and apolipoprotein, suggesting hypertriglyceridemia. This lowers the amount of High Density Lipoproteins cholesterol (HDL-c) and increases the amount of Low Density Lipoproteins cholesterol (LDL-c) in serum, leading to dyslipidemia [19]. Conventionally, this altered lipid status has been reported for the diagnosis and the prognosis of the CVDs, atherosclerosis and hypertension [20]. Thus, determining dyslipidemia in patients with COVID-19 might give a link between CVDs and severity of this disease.

Almost all studies performed to determine dyslipidemia in patients with COVID-19 have shown the decreased levels of Total Cholesterol (TC), HDL-c and LDL-c [21-24]. These levels further decrease in critical and severe patients compared to mild patients, while putatively increases with the recovery of patients [25]. Also, higher monocyte/HDL-c ratio and the lower HDL-c levels in the primary infection cases than the secondary infection cases have also been reported [21]. Decreased LDL-c, HDL-c, and TC have been reported in many viral infections, including Hepatitis B Virus (HBV) and chronic illness such as cancer [26]. However, the role of cholesterol in the progression of viral infections has been well studied in Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV). The mechanism of the disease involves Scavenger Receptor B type 1 (SR-B1) binding site, HDL-c, free cholesterol and TG [27]. Further, membrane bound cholesterol has been reported to facilitate the entry of the virus in the host cell [28]. As far as SARS-Cov-2 is concerned, cholesterol facilitates the binding of SARS "S" protein with ACE-2, which allow the entry of the virus into the target cell (tongue/bronchi/lung). Also, a recent study showed that cholesterol metabolism regulating protein/enzyme decrease in human colon epithelial carcinoma cells infected with the SARS-CoV-2, which suggests the cholesterol modulatory effects of this virus [26]. Hence, a cholesterol lowering and ACE-2 upregulating drug like statin could be recommended as a therapeutic to prevent host cell infection and lung injury in patients with COVID-19 [29]. Conversely, Shrestha SK argued that the use of statin causes very low or no synthesis of endogenous cholesterol, resulting in the upregulation of LDL-c in the cell membrane [30]. Thus, the use of statin may increase the risk of COVID-19 by promoting host cell infection.

As per the standard lipid profile, decreased HDL-c and increased LDL-c is responsible for CVDs. However, in contrast to this, the patients with COVID-19 exhibit hypolipidemia. Decreased HDL-c favours CVD, while decreased LDL-c creates an enigma as it correlates with the increased severity of COVID-19 [26,31]. Further, as decreased level of cholesterol reduces the severity of host cell infection by SARS-CoV-2; however, patients with COVID-19 shows hypolipidemia, which warrants further investigations about the COVID-19 disease progression.

ADIPOKINES, CVDs AND COVID-19

Adipokines secreted by adipose tissue are reported for the pathophysiology of diabetes mellitus, non-alcoholic fatty liver diseases and CVDs [32]. Among various adipokines leptin, PAI-1, resistin, visfatin, hepcidin and chemerin have been reported for increased risk of CVDs via peripheral and central mechanisms, whereas adiponectin, omentin and IL-10 have been reported for their cardioprotective roles [33,34]. Therefore, altered secretion of adipokines during obesity could be used to correlate CVDs with the severity of COVID-19 and their possible pathophysiological mechanisms, of which adiponectin and leptin have received more importance [35]. Adiponectin exhibit an anti-inflammatory role by promoting secretion of anti-inflammatory cytokines like IL-10 and IL-1 receptor antagonist and by regulating pro-inflammatory cytokines like IL-6 and Tumour Necosis Factor alpha (TNF-α). On the contrary, leptin acts as a pro-inflammatory cytokine and thus modulates cellular immune responses by favouring synthesis of pro-inflammatory cytokines like TNFα, IL-2 as well as interferon-γ and by attenuating the synthesis of anti-inflammatory cytokines like IL-4 and IL-5 [36,37]. Hence, low grade chronic inflammation is a typical characteristic of obesity that affects the vessel wall and cardiovascular homeostasis. Also, leptin/adiponectin ratio has been proposed for adipose tissue dysfunction, lung injury and the progression of CVD [38]. Adiponectin helps in determining the mortality of patients with COVID-19 [39]. Thus, it could be predicted that CVD related COVID-19 severity may be due to the abnormal secretion of adipokines.

ADHESION MOLECULES, CVDs AND COVID-19

Elevated expression of adhesion molecules like Vascular Cell Adhesion Molecule (VCAM), Intracellular Cell Adhesion Molecule (ICAM) and E-selectin are evidenced for progression and diagnosis of CVDs [40]. During chronic inflammation, adhesion molecules and pro-inflammatory cytokines guide circulating monocytes for their endothelial migration and differentiation into the macrophages [41]. Accumulation of macrophages increases the further burden of inflammation in endothelial cells leading to CVDs and atherosclerosis lesions [42]. As stated before, obesity exhibit low grade chronic inflammation and contribute to the pro-inflammatory cytokines like IL-6 as well as TNF-α, and, therefore, promote atherosclerosis, hypertension and CVDs via aforesaid adhesion molecule mediated mechanism [43]. However, the severity of obesity mediated endothelial dysfunction and CVDs are significantly increased by IL-6 and an adipocytokine Monocyte Chemoattractant Protein-1 (MCP-1). IL-6 stimulates monocyte to macrophage differentiation [43,44], while MCP-1 regulates cytokine and adhesion molecule expression [45]. IL-1 and IL-6 blockers may reduce inflammation [46].

Adipokines are also reported for their effects on adhesion molecule targeted vascular wall disease and CVDs. Among them, adiponectin has been documented for the decreased production of adhesion molecules, while resistin and ghrelin stimulate VCAM-1 expression and ghrelin alone can increase the ICAM expression [47,48]. Also, Lung marginated monocytes have been reported for acute lung injury [49]. This discussion suggests that obesity induced altered expression of cell adhesion molecules are responsible for chronic endothelial dysfunction, CVDs and lung injury. Interestingly, it has been revealed that the Influenza virus infection in alveolar epithelial cells facilitates monocyte migration and macrophagic differentiation. This transepithelial migration of monocyte is favoured by binding of monocyte β1, and β2 integrins and integrin associated protein with adhesion molecules (VCAM-1, ICAM-1, Cluster of Differentiation (CD47) and junctional adhesion molecule-c) expressed on the epithelial cells. The severity of this transepithelial monocyte infiltration is further accelerated by TNF-α [50,51]. Recently, Tong M et al., reported the elevated levels of VCAM-1, ICAM-1 and Vascular Adhesion Protein-1 (VAP-1) in patients with COVID-19 signifies the role of CVDs as a major risk of COVID-19 [52]. Although the authors did not explain the leading cause of higher adhesion molecules or inclusion/exclusion criteria related to obesity in the study, hence, a predicted cause associated with obesity might be postulated based on the above arguments.

RAS MEDIATED CVDs AND COVID-19

The Rennin Angiotensin System (RAS) is a crucial mechanism operating in the body that regulates cardiovascular functions and contributes to a series of CVDs [53]. As ACE-1 works actively with the RAS system and a potent source for cellular SARS-CoV-2 invasion, discussing it could be another pathway that can contribute to the high COVID-19 severity via CVDs [54]. Usually, the RAS system is composed of Angiotensinogen (AGT), rennin, angiotensin-I (Ang-I), angiotensin-II (Ang-II), ACE I and II (ACE-I and ACE-II) and two Ang II receptors namely angiotensin type 1 receptor (AT-1) and Angiotensin Type 2 receptor (AT-2) [55,56]. The rennin is an enzyme which acts on a 1,2 AGT (a 452 amino

acid-containing protein) to produce Ang-I. Ang-I (a decapeptide) acts as a substrate for ACE and produce Ang-II. Ang-II (an octapeptide) plays a pivotal role in distinct pathophysiological functions via AT-1 and AT-2 receptors [57,58].

Among these two receptors, binding of Ang-II to AT-1 receptor promotes vascular proliferation, growth, endothelial dysfunction and vasoconstriction, which are responsible for hypertension and atherosclerotic CVDs [59]. AT-2 acts reversely and favour tissue growth and repair mechanisms [60]. ACE-II inhibitors prevent the conversion of Ang-I into Ang-II and therefore can suppress the deleterious effects of Ang-II. Also, Ang-II inhibition stimulates the release of bradykinin, which shows vasodilatory and tissue protective effects [61,62]. Thus, attenuation of AT-1 and use of ACE inhibitors are considered as a potential therapeutic line for the treatment of RAS related disorders [60]. Further, both AT-I and AT-II receptors have been located in adipose tissue; suggesting local RAS [61]. Adipocytes are reported as a source for the synthesis of RAS components; however, synthesis is regulated with respect to the status of obesity and hypertension [62]. Ang-II exerts a crucial role in adipose tissue, including adipocyte growth and differentiation, adipokine release, lipid metabolism and different local RAS component production in the visceral and subcutaneous fat depot [63]. Hence, targetting a RAS might provide a link between obesity-related CVDs and severe SARS CoV-2 infection in patients.

CONCLUSION(S)

In summary, obesity is a chronic metabolic disorder responsible for CVDs via low state chronic inflammation. Studies on current COVID-19 pandemic shows various major risk factors that are associated with increased severity of SARS-CoV-2 infection in patients. Obesity makes favourable conditions for the development of the CVDs, however, these favourable conditions may contribute in the progression of COVID-19 severity through dyslipidemia, altered secretion of adipokines and adhesion molecules, endothelial dysfunction and the RAS. Therefore, targeting these aspects might provide new opportunities for developing novel therapeutic approaches to decrease the severity of SARS-CoV-2 infection in patients.

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