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Review Article

OBESITY, ADIPOSE TISSUE DYSFUNCTION AND ATHEROSCLEROSIS

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ABSTRACT

Obesity is becoming a major health problem around the globe and reported as a severe risk factor for insulin resistance, diabetes, hypertension and atherosclerosis. Organ-specific distribution and the pattern of gene expression make visceral fat more atherogenic than subcutaneous fat. Adipose tissue expansion due to a high-calorie diet adversely affects the vessel wall by modulating blood pressure, systemic inflammation and glucose as well as lipid metabolism (dyslipidemia). Adipose tissue acts as an endocrine and paracrine organ that secretes various adipokines. In patients with obesity, altered secretion of adipokines leads to a chronic low-grade inflammatory state, which exerts detrimental effects on vascular endothelial cells, trigger atherosclerosis. This review focuses on the role of obesity in the pathophysiology of atherosclerosis. In the current scenario, obesity has been considered as a potential risk factor for the progression of Coronavirus disease-2019 (COVID-19). Thus, this review gives a brief idea about a possible link between obesity, atherosclerosis and COVID-19.

Keywords: Obesity, Adipose tissue, Atherosclerosis, Adipokines, Dyslipidaemia, COVID-19

1. INTRODUCTION

Obesity is often considered as a lifestyle disease and emerging as a worldwide pandemic. As per the recent statistics, in the United States, among adult men and women, the prevalence of obesity was 42.4%; however, adults aged 40 to 59 years showed severe obesity [1]. It is estimated that one in every two people by the year 2030 would have obesity and associated complications [2]. In a developing country like India, the situation will be worst if early preventive measures not taken. It is forecasted that up to the year 2040, the prevalence of overweight and obesity in Indian adults will increase to 30.5% from the prevailing percentage [3]. These statistics suggest the upcoming burden of obesity and its related diseases.

Obesity pathogenesis is mainly governed by organ-specific white adipose tissues (WAT), which originated from mesoderm and mesenchymal stem cells during embryonic development. Adipose tissue comprises of progenitor adipocyte (pre-adipocyte) cells, which have differentiation and de-differentiation potentials, therefore, maintain adipocyte pool within the body [4]. During metabolic disturbances, progenitor cells differentiate into mature adipocytes and store extra energy, which triggers obesity-related comorbidities. Further, adipose tissue secretes many bioactive factors/ hormones termed as "adipokines" which not only regulate metabolic pathways but also involve in the pathogenesis of cardiovascular disease like atherosclerosis [5]. This is a concise review of the current update on the functional and the pathophysiological aspects of obesity mediated dysfunctional adipose tissue in atherosclerosis.

2. ADIPOSE TISSUE, DYSLIPIDAEMIA AND ATHEROSCLEROSIS

2.1. Adipose tissue physiology

Adipose tissue is a vital organ not only involved in lipolysis and lipogenesis but also modulates various physiological functions including body weight, food intake, inflammation, vascular functions and insulin sensitivity [6]. Adipose tissue comprises of various cells such as preadipocyte, mature adipocyte, stromal vascular cells, macrophages and endothelial cells, which facilitates modulation of other tissue growth, innate immunity (bacteria sensing, phagocytosis, antimicrobial peptides), shock absorbance, sonar (echolocation) and nutritional support during energy deprivation. In mammals, adipose tissues are classified as brown adipose tissue (BAT) and white adipose tissue. During embryonic development, Myf5 and Pax7 expressing precursor cells from the mesoderm develop BAT, which contains a prodigious amount of mitochondria, hence brown in appearance. Due to high mitochondria and active uncoupling proteins

BAT predominantly produces heat [7].

Conversely, WAT is mostly distributed throughout the body, including visceral depot (omental, retroperitoneal, pericardial and mesenteric) and subcutaneous depot (beneath the skin) and thus associated with overweight and severe obesity [8]. In lean subjects, adipose tissue exhibit preadipocytes howbeit to store excess energy these preadipocytes can differentiate into mature adipocyte through strict transcriptional regulation of CCAAT/enhancer-binding proteins (C/EBPs), peroxisome proliferator-activated receptor-gamma (PPARγ) and sterol regulatory element-binding protein-1C (SREBP-1C) [9].

2.2. Adipose tissue expansion and obesity

C/EBPs and PPARγ arbitrate transcriptional regulation of gene expression in adipocytes, which determines the adipose tissue mass expansion in response to excess calorie intake. This event plays a pivotal role in metabolic syndrome and cardiovascular disease like atherosclerosis [10]. Both visceral and subcutaneous WAT expands and contracts dynamically to satisfy an organism's metabolic demand. The expansion of WAT evokes through a rise in adipocyte number (hyperplasia) and/or by increasing adipocyte size/volume (hypertrophy) [11]. Hyperplasia is related to severe obesity, while hypertrophy is related to overweight, obesity and might diabetes. Maintenance of adipocyte numbers depends on a pool of progenitor cells; therefore, hyperplasia maintains a healthy expansion of adipose tissue. To the contrary, hypertrophy results in necrosis like adipocyte death and releases cellular debris in the extracellular space, triggering inflammatory responses (macrophages surrounds adipocyte). In adults, adipocyte number stays constant; however, weight alterations are related to adipocyte size; thus, hypertrophy may cause serious complications [12].

Studies on rodent showed the various origins of preadipocyte and so contribute differently to adipose tissue expansion. Visceral adipose tissues exhibit greater expandability as compared to subcutaneous adipose tissues. Another crucial factor that expands WAT and favours energy storage is hypoxia, which induces hypoxia-inducible factor 1 (HIF1) liable to inflammation, insulin resistance and adipocyte hypertrophy [11]. Differentiation of pre-adipocyte into mature adipocyte and de-differentiation of mature adipocyte back to pre-adipocyte is additionally significant for fat mass expansion. A recent study on mice and 3T3L1 preadipocyte cell line highlighted adipocyte expansion capacity. This study reported that repeated exposure of the high-fat diet to epididymal WAT of formerly obese mice halt WAT expansion, at the same time, immune cells like macrophages and T cells are retained. The weight loss cycle studied for six months in mice reported long lasting changes in the physiological response to regain weight [13].

2.3. Dyslipidemia in adipose tissue

In mammals, a rise in adipocyte number and volume due to altered metabolic activities promotes obesity. Primary dyslipidemia in obese patients is associated with modified lipid storage and mobilisation, which favour atherosclerosis. In adipose tissue, fat storage is promoted by chylomicrons (triglyceride-rich lipoprotein) derived from dietary fatty acids and cholesterol and are stored in adipose tissue as triglyceride (TG), while fat mobilisation is promoted by lipolysis of TG which supplies free fatty acid as fuel to tissues and organs [14]. In the presence of insulin, the liver plays a significant role in the processing of those free fatty acids and generate very-low-density lipoproteins (VLDL). Both visceral and subcutaneous fat depots transport a pool of free fatty acids to the liver. Hence, during obesity, dyslipidemia is characterised by hypertriglyceridemia, a well-known risk factor of atherosclerosis. Of note, the visceral fat depot is highly associated with hypertriglyceridemia than subcutaneous fat depot. Further, VLDL consists of TG, cholesterol and apolipoproteins, which suggests hypertriglyceridemia elevation. Hypertriglyceridemia promotes the TG enrichment of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein (LDL), resulting in a lower concentration of HDL and a higher level of LDL. This dyslipidemic condition in obesity promotes atherosclerotic plaque formation [15]. As per the early studies decrease of 5mg/dL in HDL cholesterol increases cardiovascular diseases (CVD) risk by 14%, whereas an increase of 1mg/dL HDL cholesterol decreases CVD risk by 3%. Besides this, reverse cholesterol transport (RCT) has been reported for anti-atherogenic effects and thus reduces CVD risk [16, 17] (Fig. 1).

Apopliproteins facilitate the transport of lipids (TG) throughout the body and maintain the amount of LDL, VLDL and chylomicron remnants, which have been reported as potential markers for atherosclerosis. It has been reported that angiopoietin-like 3 (ANGPTL3) regulates LDL, VLDL and TG and hence considered as a target to decrease atherosclerosis risk. Higher plasma levels of ANGPTL3, apoC-III and apoB48 and decreased LPL activity have been reported for dysfunctional visceral fat in adolescents obesity. Decreased LPL activity

debilitates chylomicron and VLDL catabolism leading to atherogenic remnants [18]. Further, various exchangeable apolipoprotein such as apolipoprotein A1 (ApoA1), apolipoprotein A5 (ApoA5), apolipoprotein C3 (ApoC3) and apolipoprotein E (ApoE) have been reported for altered lipid metabolism in both plasma and adipocytic as well as hepatocytic cells, resulting in dyslipidemia [19]. Activated microRNA-378a-3p modulates ApoB100-sortilin-1, while the patatin-like phospholipase domain containing protein 7 (PNPLA7) modulates ApoE stability, which stimulates hepatic VLDL synthesis and thereby promote hyperlipidemia [20, 21]. Stabilisation of the LDL receptor and statin lowers the plasma TG rich lipoproteins and LDL subclasses respectively and reduces the risk of atherosclerosis [22, 23]. Also, there is evidenced that fatty liver index (FLI) detects nuclear magnetic resonance atherogenic changes in patients with obesity, a breakthrough to standard lipid profile, as VLDL particle number and size elevate with FLI, while HDL particles and size are inversely related with FLI [24, 25].

3. ADIPOSE TISSUE WORKS AS AN ENDOCRINE ORGAN

Adipose tissue secretes many adipokines, which work as hormones, enzymes, cytokines as well as growth factors and modulates metabolic energy homeostasis. Adipokines act in an autocrine, paracrine and endocrine ways that not only maintain adipose tissue development and enlargement but also modulate many functions of metabolism, reproduction, CVDs and immunity [26]. To explore the endocrinology of adipose tissue, colossal work has been done in the last two decades. During this time not only varieties of adipokines have been discovered, but also their biochemical and physiological functions have been studied extensively. Amid them, the critical adipokines include: leptin, which is one of the first discoveries of an adipocyte-derived adipokine, regulates food intake capacity and energy expenditure [27], adiponectin imparts its crucial role in the regulation of obesity and its consequences [28], resistin and TNF-α modulates insulin resistance [29], complement factor-D (adipsin) and acylation stimulation protein (ASP) promotes TG storage [30], apelin promote fatty acid oxidation and glucose uptake in skeletal muscles [31], visfatin and omentin helpsin glucose homeostasis [32,33], monobutyrin acts as a vasodilator [34], macrophage inflammatory protein-1α (MIP1-α) and monocyte chemoattractant protein-1 (MCP-1) promote inflammation,transforming growth factor-β (TGF-β), hepatic growth factor (HGF) and insulin-like growth factor-1 (IGF-1) stimulates adipocyte differentiation and development [35,36], while vaspin is employed as a biomarker of inflammation [37] (Fig.1).

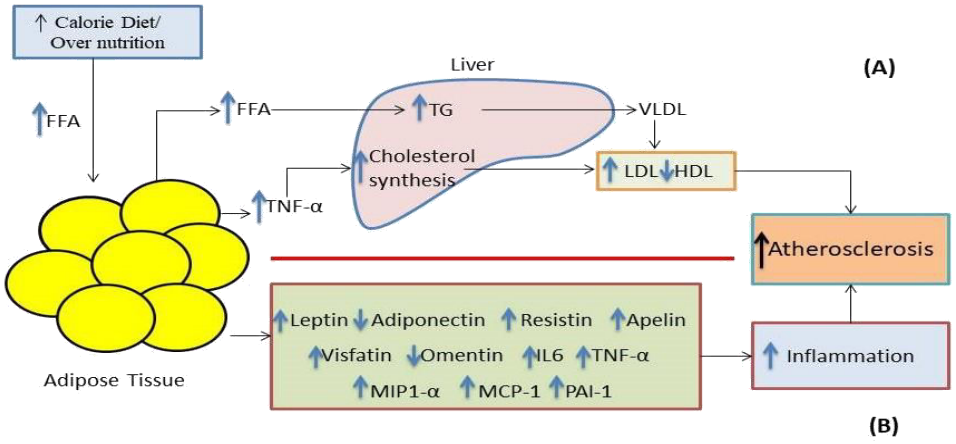

Fig. 1: (A) Dyslipidemia in adipose tissue: *High-calorie diet leads to adipose tissue dysfunction, resulting in higher TNF-α expression and FFA mobilisation to the liver. Elevated FFA synthesis increases TG concentration (hypertriglyceridemia) and later converts into VLDL, while TNF-α increases the cholesterol synthesis. Finally, both FFA and TNF-α increases the amount of LDL, while decreases the amount of HDL. This altered lipid metabolism promotes atherosclerosis.* **(B) Adipokines and cytokines in atherosclerosis:** *Dysfunctional adipose tissue secretes various adipokines/cytokines, which modulates inflammatory responses in vascular endothelial cells via macrophages and thus contribute to atherosclerosis. Of note, adiponectin reverses the effect of dysfunctional adipocytes. FFA: Free fatty acid, TG: Triglyceride, VLDL: Very low-density lipoprotein, TNF-α: Tumour necrosis factor-α, LDL: Low-density lipoproteins, HDL: High-density lipoproteins, IL: Interleukin, MIP1-α: Macrophage inflammatory protein-1α, MCP-1: Monocyte chemoattractant protein-1 (MCP-1), PAI-1: Plasminogen activator inhibitor-1.*

4. ROLE OF ADIPOKINES IN ATHEROSCLEROSIS

Moreover, leptin, plasminogen activator inhibitor -1 (PAI-1), resistin, visfatin, hepcidin, TNF-α, and IL-6 promote atherosclerosis, whereas adiponectin, omentin and IL10 exhibit anti-atherosclerotic properties [26]. Due to space limitations, two atherogenic and two anti-atherogenic adipokines have been discussed, whereas other adipokines involved in atherosclerosis have been mentioned in table 1.

Table 1: Role of adipokines in the pathophysiology of atherosclerosis

Adipokine	Study model	Action	References
Leptin	ApoE-/-mice	↓ Hypercholesterolemia ↓Atherosclerosis	[46]
PAI-1	Human/Mouse	PAI-1 inhibitor ↓Thrombus formation	[47]
Resistin	HUVECs	↑ICAM-1,↑VCAM-1,↑Monocyte adhesion	[48]
	Mice	↑Cardiac homing	[49]
Visfatin	Human cells	↑ICAM-1,↑VCAM-1,↑Monocyte adhesion	[50]
	Human	↑miR21↑Inflammation and ACS	[51]
Hepcidine	ApoE-/-mice	↓Atherosclerosis after erythrophagocytosis	[52]
TNF-α	Human cells	↑Oxidative stress and endothelial dysfunction	[53]
	Human cells	KLF-4 regulates NOS expression	[54]
IL-6	Mouse	↑Endothelial dysfunction in diabetes	[55]
Adiponectin	HUVECs	↓Endothelial inflammation ↓Insulin resistance	[56]
Omentin	HUVECs	↓Adhesion molecule expression	[57]
IL-10	Mice	↓Arterial lesion formation	[58]
	Human/HAECs	↓mtROS mediated innate immune activation	[59]

ApoE: Apolipoprotein-E, PAI-1: Plasminogen Activator Inhibitor-1, HUVEC: Human Umbilical Vein Endothelial Cells, ICAM: Intracellular Adhesion Molecule-1, VCAM: Vascular Adhesion Molecule-1, miR21: Micro-RNA21, ACS: Acute Coronary Syndrome, TNF-α: Tumour Nechrosis Factor-α, KLF-4: Kruppel Like Factor, NOS: Nitric Oxide Synthase, IL: Interleukine, HAEC: Human Aortic Endothelial Cells, mtROS: Mitochondrial Reactive Oxygen Species.

4.1. Leptin

Leptin (16 kDa) is a 167 amino acid containing nonglycosylated hormone, encoded by the "ob" gene, which is the murine homologue of the human gene LEP. Mutational studies on leptin in the animal model (ob/ob mice) revealed hyperphagia and morbid obesity. Leptin composed of four alpha-helices and belongs to a class-I cytokine superfamily [38]. It regulates adipose tissue mass by energy expenditure, food intake and hormones under the strict control of the hypothalamus [27]. Leptin has six different isoform receptors; however, only the long isoform is functional and expressed in many cells and organs, including the CVD system. It has been reported that hyperleptinemia in obesity is associated with atherosclerosis [38]. Apart from this, leptin exerts many atherogenic effects such as hypertrophy, the proliferation of vascular smooth muscle cells, platelets aggregation and migration, oxidative stress, the release of monocyte colony-stimulating factor from macrophages, cholesterol accumulation in macrophage, stimulate angiogenesis, hypertension and most importantly the induction of endothelial dysfunctions [26, 39].

Notwithstanding, leptin stimulates initial phages of atheroma formation by activating inflammatory factors like TNFα, IL-6, monocyte chemoattractant protein (MCP-1) and adhesion molecules like vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and E-selectin. This causes circulating monocyte attraction and migration through endothelial cells, leading to plaque formation [40,41]. In women with obesity, the elevated leptin levels are positively associated with C-reactive protein, white blood cells (WBCs), neutrophils and monocytes [42], while in women with polycystic ovary syndrome (PCOS) adiposity, leptin increases by body fat percentage [43]. In-vivo study on dose dependant effect of leptin in leptin-deficient low-density lipoprotein receptor (LDLR-/-;ob/ob) female knockout mice demonstrate decreased mRNA expression of IL-6 and MCP-1, resulting in decrease macrophage infiltration in adipose tissue and thus regulates atherosclerotic plaque

formation [44]. The role of matrix metallo-proteinases (MMPs) in rupturing the atherosclerotic plaque through the extracellular matrix (ECM) protein degradation is documented. Leptin increases the pro-duction of MMP-9 and lowers atherosclerotic plaque by the leptin receptor/MAPK/ERK signalling pathways which facilitate the binding of activator protein-1 transcription factor (AP-1) to the MMP-9 promoter, in-vivo and in-vitro [45].

4.2. Plasminogen activator inhibitor-1

Plasmin is an enzyme act on fibrin, which eliminates blood clot. Plasmin is synthesised from its inactive precursor called plasminogen. Plasminogen activator inhibitor -1 (PAI-1) is a physiological inhibitor of plasminogen activator in plasma, thereby, promote vascular thrombosis and atherosclerosis [60]. Moreover, in human endothelial cells, leptin upregulatesthe expression of PAI-1 [61]. Due to inflammatory factors and loss of cellular replicative capacity, cell senescence is responsible for atherosclerosis. In vivo study demonstrated that PAI-1 promotes cell senescence in smooth muscle, while its inhibition attenuates vascular senescence and atherogenesis [62]. The TGF-β1/p53/ PAI-1 and caveolin-1 signalling pathways also regulate vascular senescence and modulates atherosclerosis [63]. Tiplaxtinin, an inhibitor of PAI-1, reveals its role in smooth muscle cell migration (*in-vitro*) and fibrosis (*in-vivo*) [64].

It has been shown that in familial combined hyperlipidemia PAI-1 is elevated with insulin resistance and carotid atherosclerosis [65], of note, serum bilirubin level shows the inverse relation with PAI-1 [66]. Using Apo-/- and LDLR-/- double knockout mice, it has been evidenced that a decrease in thrombolytic activity increases the risk of atherosclerosis progression [67]. In contrast, PAI-1-knockout mice exhibit reduced adhesion of monocytes to aortic intima and thus, atherosclerosis prevention [68]. Further, PAI-1 target anti-atherogenic therapeutic approaches include hesperetin sulfate and glucuronide metabolites [69], mitochondria-targeted esculetin [70] and crocin [71].

4.3. Adiponectin

Adiponectin is a 30 kDa protein highly expressed in subcutaneous adipose tissue than visceral adipose tissue. Decreased level of adiponectin is associated with obesity, type 2 diabetes mellitus and atherosclerosis [72]. Albeit, the exact mechanism of action by which adiponectin acts on vascular endothelial cells is still not fully resolved. Recent in-vivo studies have been evidenced that adiponectin reverses vascular injuries. T-cadherin (a cell-cell adhesion molecule) triggers the accumulation of adiponectin in the tunica intima where proliferation and migration of the vascular smooth muscle cells occur (neointima). This association of T-cadherin and adiponectin prevents vascular injury and thereby neointima and atherosclerotic plaque formation [73]. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is an essential transcription factor that modulates inflammatory gene expression responsible for vascular injury and atherosclerosis. Adiponectin inhibits the synthesis of "nuclear protein p65" a necessary subunit of NF-kB and avert its effect [74]. Fibroblast growth factor 21 (FGF-21) is another protein that suppresses atherosclerotic plaque formation via inhibiting SREBP-2 and by promoting adiponectin expression [75]. Nitric oxide synthase and oxidised LDL (ox-LDL) induce vascular endothelial cell proliferation (in-vitro) [76] and carotid atherosclerotic plaque formation (in-vivo) [77], is regulated by adiponectin. However, elevated macrophage autophagy by perivascular adipose tissue-derived adiponectin suppresses carotid atherosclerosis, suggesting an anti-inflammatory role of adiponectin [78]. Further anti-inflammatory and anti-atherogenic role of adiponectin include decreased inflammation and vascular calcification in human vascular smooth muscle cells [79], promote reverse cholesterol transport (RCT) and cholesterol efflux [80], modulation of NLRP3 inflammasome via Foxo-4 [81] and suppression of glucolipotoxicity-induced inflammation [82].

4.4. Omentin-1

Omentin is 313 amino acid containing (35 kDa) hydrophilic adipokine. It is also called as intellectin-1 and highly expressed in visceral adipose tissue than subcutaneous adipose tissue. Similar to adiponectin omentin-1 regulates insulin resistance, obesity, diabetes mellitus and metabolic syndromes. Omentin-1 increases glucose uptake and transport; however, its lower concentration is positively related to arterial stiffness and atherosclerosis in diabetic patients [83]. In mouse, omentin is a key adipokine which regulates high glucose-induced endothelial dysfunction by increasing AMP-activated protein kinase (AMPK) phosphorylation and PPAR-δ expression [84]. In patients with the atherosclerotic lesion, the concentration of omentin-1 has

reported 7.53 ng/ml, while in healthy individuals, the reported concentration is 12.56ng/ml. Thus, decreased omentin level in diseased condition establishes a link between atherosclerosis and this adipokine [85]. Elevated oxidative stress causes oxidation of LDL, resulting in overexpression of VCAM-1 and E-selectin stimulated endothelial dysfunction. Omentin-1 attenuates this effect by increasing glutathione peroxidase (GPX) activity [86,87]. Further, Ox-LDL reduces kruppel like factor-2 (KLF-2) dependant gene expression, which promotes adipocyte maturation by upregulating C/EBPα and PPARγ. Omentin -1 reverses this effect, thereby reduces obesity arbitrate atherosclerosis [86,88]. Omentin-1 suppresses athero-sclerosis by modulating inflammatory effects, including tanshinone IIA action on macrophages in apoE-/- mice [89], inhibition of TLR4/MyD88/NF-κB signalling pathway as well as macrophages [90] and TXNIP/ NLRP3 signalling pathway [91].

5. OBESITY, ATHEROSCLEROSIS AND COVID-19

Obesity, atherosclerosisand other CVDs have been reported as a major risk factor for the development and the progression of Coronavirus disease-2019 (COVID-19); a worldwide pandemic as per the World Health Organisation (WHO). Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), a positive sense RNA enveloped virus is responsible for this disease, preferentially affects the human respiratory tract and characterised by mild to lethal clinical complications [92,93]. Besides this, a robust association between obesity-related atherosclerosis and influenza/ previous coronaviruses have also been demonstrated, suggesting a crucial link between obesity-related complications and viral load development. Interestingly, adiponectin helps in predicting the mortality rate in patients with COVID-19 [94], while elevated leptin can regulate inflammation via "Treg" cells [95]. Thus, targeting adipose tissue can be essential to determine the progression of COVID-19 in patients with obesity. Adipose tissue secretes many inflammatory cytokines that modulate the immune response via chemotaxis and monocyte differentiation, which may increase the severity of SARS-COv-2 in patients. Moreover, previously the role of IL6 (a pro-inflammatory cytokine) is reported for influenza-related respiratory disorders. Adipokines secreted form thoracic visceral adipose tissue (epicardial and mediastinal) are thought to be essential in the pathophysiology of this disease [94,96-98]. However, adipose tissue imparts its direct role in the COVID-19 through the angiotensin-converting enzyme 2 (ACE2). The SARS-COv-2 spike protein binds with the ACE-2 and infects the cells of the tongue, bronchi, and lungs [99]. Moreover, ACE-2 expression increases in obesity, diabetes and athero-sclerosis and actively involved in the renin-angiotensin-aldosterone system (RAAS). Thus, suppression of RAAS might be a potential therapeutic for COVID-19 in patients with obesity [100].

6. CONCLUSION

In conclusion, obesity-associated adipose tissue dysfunction promotes dyslipidaemia, hypertension, inflammatory responses and impaired glucose meta-bolism, which provokes atherosclerosis. Obesity-induced dyslipidaemia is regulated by angiopoietin-like 3 factors suggesting its therapeutic role. Various adipokines have been reported for direct impact on the atherogenic micro-environment of the vascular wall by regulating gene expression, functions of endothelial cell, higher expression of adhesion molecules, arterial smooth muscles and monocyte to macrophage conver-sion. Moreover, adiponectin governs the progre-ssion of atherosclerosis. Obesity-related adipose tissue dysfunction and cardiovascular diseases have been reported as a serious risk factor for increased clinical complications of COVID-19 patients, which suggest more studies about the role of adipokines in COVID-19 disease progression. Succinctly, obesity-induced dyslipidaemia and adipokines might provide new opportunities for developing novel therapeutic approa-ches for atherosclerosis and COVID-19.

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