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REVIEW ARTICLE

Recent advances in molecular biology of metabolic syndrome pathophysiology: endothelial dysfunction as a potential therapeutic target

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Abstract
Current advances in molecular pathobiology of endotheliocytes dysfunctions are promising in finding the pathogenetic links to the emergence of insulin resistance syndrome. Physiologically, human organism homeostasis is strictly controlled to maintain metabolic processes at the acquainted level. Many factors are involved in maintaining these physiological processes in the organism and any deviation is undoubtedly accompanied by specific pathologies related to the affected process. Fortunately, the body's defense system can solve and compensate for the impaired function through its multi-level defense mechanisms. The endothelium is essential in maintaining this homeostasis through its ability to modulate the metabolic processes of the organism. Pathological activity or impairment of physiological endothelium function seems directly correlated to the emergence of metabolic syndrome. The most accepted hypothesis is that endothelium distribution is due to endoplasmic reticulum stress and unfolded protein response development, which includes inhibition of long non-coding RNAs expression, cytokines disbalance, Apelin dysregulation, glycocalyx degradation, and specific microparticles. Clinically, the enhancement or restoration of normal endothelial cells can be a target for novel therapeutic strategies since the distribution of its physiological activity impairs homeostasis and results in the progression of metabolic syndrome, and induction of its physiological activity can ameliorate insulin resistance syndrome. Novel insights on the molecular mechanisms of endothelial cell dysfunction are concisely represented in this paper to enhance the present therapeutic tactics and advance the research forward to find new therapeutic targets.

Keywords Pathogenesis · Insulin resistance · Endothelial cells · COVID-19 · Metabolic syndrome · Oxidative stress · Lipid peroxidation · Nitric oxide

Introduction/background

The interest in studying metabolic syndrome dramatically increased in the few previous decades due to the urbanization and enhancement of the socio-economic state of the population accordingly promoted metabolic syndrome expansion. Therefore, it is extremely important to highlight the pathogenetic mechanisms that underlie metabolic syndrome emergence. Several underlying pathological pathways stand behind insulin resistance syndrome. The remarkable advances in molecular biology lead to uncovering a wide diversity of pathophysiologic alterations related to the metabolic syndrome development; primarily, endothelial dysfunction initiates homeostatic disorders and atherosclerotic events that eventually lead to cardiovascular events and insulin resistance and usually characterized by hypercoagulability due to dysbalance between the hemostatic factors and fibrinolysis proteins including plasminogen activator inhibitor-1(PAI-1).[1] Metabolic syndrome is multifactorial pathology that is defined as a cluster of systematic metabolic homeostatic abnormalities that work synergistically and leads to the appearance of insulin resistance and cardiovascular pathologies.[2–5] Dyslipidemia, hyperglycemia, and hypertension are three classical signs of

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metabolic syndrome, which arise as cumulative homeostatic disorders.[6] Different lipid fractions have a different role in metabolic syndrome pathogenesis.[7] Pathophysiology of metabolic syndrome is extremely complex and has many factors attribute to that; firstly it's the heterogeneity of the possible mechanisms and secondly is the limitation of present data where there is a lack in grasping of the complete molecular pathological chain of development of the metabolic syndrome.[8–10] Consequently, serious limitations are present in the current therapeutic targets of metabolic syndrome. Since there is a combination of etiologies that collectively works to give rise to the dyslipidemic syndrome, therefore, the management mandatory must eliminate these risk factors separately or once. Neurohormonal disorders, dyslipidemia; especially hypercholesterolemia, protein and carbohydrate metabolism, endothelial dysfunction, oxidative stress, chronic inflammation, and even gut microbiota dysbiosis are involved in the pathogenesis of the metabolic syndrome as well as vitamin D deficiency.[7, 11–21] Late events of insulin resistance syndrome are the dysfunction of endothelial cells, probably associated with hyperhomocysteinemia and hyperuricemia, which is directly connected to cardiovascular diseases' appearance, indicated by the high serum level of von Willebrand factor.[22–26] A key regulatory role is played by the endothelium through its capacity to release several physiological mediators that regulate vascular tone, immune response modulation, hemostasis, and control vascular cell growth. The endothelium is contributing to maintaining the vascular tone by releasing nitric oxide and as a metabolic regulator by vascular endothelial growth factor B (VEGF-B) releasing.[27] The VEGF-B bioavailability is crucial in insulin resistance and hypertension development, and endothelial cell health state, therefore, VEGF-B elevation is an indicator of a high risk of metabolic syndrome development. Moreover, the disturbance of the physiologic balance between VEGF and NO was shown to be related to endothelial cell dysfunction.[28] The topography of endothelial cells gives them anatomical and physiological significance, while their function is regulated by neurohormonal signals and from the underlying basement membrane or vascular smooth muscle cells.[29].

Recently, the study of metabolic syndrome dramatically increased in the few previous years since the number of affected and candidates of metabolic syndrome exponentially increased, and this was finally culminated by the lockdown of most countries which also contributed to the lack of physical activity and increase in obese people and metabolic syndrome emergence.[30, 31].

New insights into the possible mechanism of endothelial cells dysfunction

Physiological regeneration of endothelial cells is sufficient for maintaining a healthy vascular lining layer and keeping the endothelium-secreted agents at the required level. However, due to specific niche factors, the endothelium can be damaged to an irreversible level that leads to the loss of its normal function. Consequently, disturbance in the endothelial protection role, permeability regulation, and secretion function are extremely important in controlling vasoactivity and releasing anticoagulant factors such as protein c, s, and calmodulin in addition to presenting on the endothelial surface antithrombin III. The primary signs of endothelial cell dysfunction are fluctuation in the serum level of adhesion molecules (sVCAM-1, sICAM-1, E-selectin), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), von Willebrand factor, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), circulating mature endothelial cells, endothelial progenitor cells, vasoconstrictor agent endothelin-1 (ET1), microalbuminuria as well as endothelial microparticles.[32–35] Indeed, only the PAI-1, LOX-1, ET1, and tPA are specific for endothelial dysfunction which was directly related to metabolic syndrome appearance.[36] Pathological changes in the previously mentioned markers can be translated to clinical practice as an early sign of the metabolic syndrome.

Endothelial cells are insulin-independent, in healthy endothelial cells insulin enhances nitro oxide synthesis, thereby vasorelaxation. However, in a state of insulin resistance, the dysfunction of the endothelial cells will be by high energy intake and not due to insulin resistance because endothelial cells are insulin-independent. Accordingly, vascular complications of endothelial dysfunction appear, but these complications are not only due to the damage of the inner lining layer of blood vessels but also due to disturbance of tunica media by insulin resistance, impairment of the barrier function of endothelial cells as well as permeability-increasing.[37] Usually, increasing in the endothelin-1 secretion is accompanied by the activation of Erk1 / 2 and MAP kinase cascade which promotes vasoconstriction.[38] While in the physiological condition, endothelin-1 secretion is controlled by phosphatidylinositol 3-kinase (PI3K)-Akt-eNOS axis and mitogen-activated protein kinase (MAPK) axis of the insulin signaling pathways.

MALAT1 is a long non-coding RNA (lncRNA) involved in endothelial dysfunction possibly through the miR-181b-5p-MEF2A-ET-1 pathway and modulation of MEF2A expression by miR-181b-5p.[39] Clinical research by Cuiting and his colleagues was performed on patients with persistent coronary slow flow, their data were indicating that MALAT1 overexpression was probably responsible

for endothelial dysfunction, and MALAT1 depletion has enhanced endothelial cell function and normalize nitric oxide levels.[40] Several indicators were used to confirm the improvement in the endothelial cell activity including; decreasing ET-1 and MALAT1 serum level, and increasing the miR-181b-5p expression.[41] These changes in serum level are of clinical importance to predict and detect early endothelial cell dysfunction.

Undeniably, membrane lipids play an extremely significant role in the physiology and pathology of each cell separately depending on its lipid content mixture.[42] Disruption of the physiological membrane lipid content undoubtedly results in subclinical or even clinical pathology. Herein, endoplasmic reticulum stress of the endothelial cells has been shown directly related to endothelial dysfunction. On the molecular level, specific microparticles have been found circulating in vesicles; extravascular that induce endothelial cell dysfunction.[43–46] Interestingly, these in vitro findings were correlated with significant impairment in the physiological releasing of nitric oxide and induced inflammation mediators secretion, cytotoxicity, and oxidative stress, besides impaired autophagy and apoptosis mechanism regulation of the endothelial cells.[47] A single study has shown that coronary microvascular dysfunctions are induced by endoplasmic reticulum stress which is promoted by the activation of the PERK/CaN/NFATc4 signaling axis.[48] Recent findings have indicated that hypoglycemic drugs in particular exendin-4, empagliflozin, metformin alleviated endoplasmic reticulum stress and enhanced protein folding activity by AMPK-dependent ERO1α upregulation of the endothelial cells as well as arteries, indicated by lowering expression endothelial dysfunction markers.[49, 50] However, the classical pathophysiological pathway of endothelial dysfunction is lipid peroxidation of the cell lipid membrane and organelles lipid membrane, especially the mitochondrion and endoplasmic reticulum lipid membrane, where unfolded protein response occurs after high energy uptake by the cells after uncontrollable hyperglycemia.[51] This illustrates the role of hyperglycemia in the pathophysiological cascade of metabolic syndrome. Primary responsibility for the elimination of the misfolded proteins by inducing the release of small heat shock proteins (sHSP), particularly, HspB1, HspB5, and HspB6.[52] Where elevation in the HspB6 level is significantly enhanced insulin signaling and endothelial cell survival by its antiapoptotic features.[53, 54] The elimination of mitochondrial peroxidation products, particularly, mitochondrial superoxide, is affected by the activation of HXK2, which is mediated by the Wnt/β-catenin/c-Myc axis.[55] Physiologically, the antioxidant defense system is enough to eliminate lipid peroxidation products, but in a state when the free radicals levels exceed the limit of the antioxidant defense system of the cell this leads to the progression of endothelial cell dysfunction.[42, 56].

Endothelial cell dysfunction is strongly related to visceral obesity and dyslipidemia where there is an elevation in low-density lipoprotein (bad lipoprotein) and or decrease in the amount of healthy lipoprotein.[57, 58] Usually, the bad lipoprotein binds to a specific receptor on the endothelial cell surface and activates a secondary signaling cascade and reducing nitric oxide formation and releasing in addition to induction of intracellular oxidative stress and inflammatory reaction. The high concentration of specific free fatty acids serum concentration has been shown related to metabolic syndrome development.[7, 59–62] Collectively, each pathological process has its role in endothelial cell dysfunction and later apoptosis. Therefore, dyslipidemia is considered the initiator of the pathological chain, and endothelial dysfunction is only one link that due to its damage arises atherosclerotic diseases and their sequelae. Effective management of endothelial cell dysfunction can cut the pathological chain and is sufficient to promote the life expectancy of patients with atheromatic coronary artery disease and reduce insulin resistance. The fluctuation of vitamin D serum level can be used as a sign of uncontrolled hyperglycemia.[21].

The glycocalyx degradation by the heparanase, matrix metalloproteinase, hyaluronidase, hyaluronic acid synthase, and neuraminidase were shown to be related to endothelial dysfunction too.[63, 64] This endorses the hypothesis of synergistic work of metabolic syndrome components.

Impairment of nitric oxide releases by the endothelial cells, catalyzed by nitric oxide synthetase (eNOS) from L-arginine, is the initiator for endothelial dysfunction since nitric oxide absence leads to persistent vasoconstriction and accordingly hyperplasia of vascular smooth muscle cells and later its dysfunction.[65, 66] Furthermore, endothelial dysfunction stimulates lipid peroxidation, oxidative stress: increases reactive oxygen species in the endotheliocytes which later forms oxidant peroxynitrites ($ONOO^-$), vascular smooth muscles, and macrophages as well as inhibits endothelial cells proliferation.[67–69] Besides, endothelial dysfunction decrease glutathione and endogenous antioxidant system activity as well as decreases releasing of hydrogen sulfide by endothelial cells.[70, 71] The current advances in molecular biology have identified a group of interactions between lncRNAs, microRNAs (miRNAs or miRs), and the Ser/Thr kinase AKT that synergistically act to impair endothelial cell function.[72, 73] In sustained hyperglycemic and uncontrolled glucose state, the lncRNA MIR181A2 is downregulated with reducing the ability to sponge miR68325p, miR68425p, and miR8056 which consequently leads to elevation of the miR68325p, miR68425p, and miR8056 concentration. It is known that human umbilical vein endothelial cell proliferation and migration is regulated by AKT2

expression, and elevation of the miR68325p, miR68425p, and miR8056 targets the 3'UTR of AKT2 mRNA, subsequently leads to decrease AKT2 expression, accordingly reducing proliferation and migration of the endotheliocytes. [72].

In vitro and in vivo findings were showing that hyperglycemia has downregulated insulin receptor substrate p53 (IRSp53) and upregulated the gal-3 that consequently activates the NF-κB which finally impairs endothelial cell migration.[74] Therefore, Hyperglycemia is involved in the pathogenesis of endothelial cell dysfunction too. Moreover, hyperglycemia currently is a well-known inducer for cellular hypoxia including endothelial cells.[75] Mechanically, the abnormal flow pattern of the blood in diabetic patients results in the damaging of the endothelial layer and triggering atherosclerosis formation and its complications(e.g. hypertension and peripheral neuropathy).[76] Probably the calcium-dependent phospholipase C signaling pathway is disrupted in dysfunctional endothelial cells since this pathway is involved in the phosphorylation of eNOS at Ser-1179 and de-phosphorylation at Thr-497 which maintains nitric oxide level.[77] Besides, inhibition of miR-19b by fibrinogen was sufficient to protect endothelial cells from destruction. The miR-19b performs anti-endotheliopathy activity via stabilizing syndecan-1.[78].

Cytokines include IL-1β also engaged in endothelial cell dysfunction, particularly through reducing eNOS expression. Moreover, NLRP3 inhibition by melatonin has rescued eNOS expression and improved endothelial-dependent nitric oxide release.[79, 80] Significant elevation of IL-33 serum level was found in obese individuals, which indicates a higher risk of developing metabolic syndrome as well as can be used as a marker of risk score.[81].

Apelin dysregulation is another possible mechanism for endothelial dysfunction in metabolic syndrome, clinical data founded that increasing Apelin adipokine in diabetic patients was sufficient to induce endothelial cell dysfunction by APJ activated NFκB pathways.[82] The favorable effects of Apelin on endothelial cells are suspected to be through decreasing the expression of sVCAM-1, sICAM-1, and E-selectin, in addition to reducing apoptosis and angiogenesis, as well as by increasing proliferation, and expression of E-cadherin, VEGFR 2, and Tie-2.[83].

Recent data were showing that in a state when the metabolic syndrome is persistent it acts differently on organs of the same system and this leading us, how to predict the future changes going to be and at what stage the metabolic syndrome.[84] According to these findings, the therapeutic strategies are probably variable following the stage of metabolic syndrome even in the same individual. Enhancement in the present therapies can be achieved by a triage of the patients into homogenous groups according to the present changes in their organs.

Furthermore, Current investigations have shown that dysregulated erythrocytes programmed cell death is directly correlated with endothelial dysfunction which is involved in the metabolic syndrome emergence.[85] Eryptosis is probably due to hyperglycemia that leads to high energy uptake by erythrocytes also the metabolic products of active glucose (glyoxal and methylglyoxal) and glycated proteins of the vascular endothelium have a damaging effect on blood cells which later leads to initiate the intrinsic pathway of apoptosis, and or the direct effect of vasoconstriction on the viscosity and motion of the erythrocytes that leads to activation of the extrinsic pathway of eryptosis.[57, 86] Moreover, a recent study has shown that erythrocytes can directly cause endothelial dysfunction by A1R and P2 × 7R targeting, purinergic signaling, in diabetic patients.[87].

The molecular mechanism of endothelial dysfunction probably includes the formation of endothelial cell metabolic memory which involved several signaling pathways of nuclear factor-κB (NF-κB)/miR-27a-3p/ erythroid-2 related factor 2 (NRF2)/ROS/ transforming growth factor-β (TGF-β)/ endothelial-to-mesenchymal transition (EndMT). The targeting of endothelial cell metabolic memory by NRF2 activator or miR-27a-3p inhibitor is sufficient to prevent cardiovascular complications of diabetic patients by impairment of endothelial cell metabolic memory.[88, 89].

Interestingly, recent clinical analyses were shown that not only hyperglycemia can induce endothelial dysfunction but low glucose level too.[90] This is probably related to the decrease in the fuel of endotheliocytes which is required for maintaining their homeostasis. Energy depletion is directly connected to the activation of specific apoptotic genes that leads to endothelial cell death.

Conclusions

To date, little is explored about molecular mechanisms of endothelial dysfunction and its sequelae role in insulin-resistant and cardiovascular disease development. The recent advances in the molecular mechanisms of endothelial role in the appearance of insulin resistance and cardiovascular still need elucidation since endothelial dysfunction is the most common component of metabolic syndrome. Defining the complete pathogenetic link of endothelial cells' role in metabolic syndrome is sufficient to introduce a novel therapeutic strategy for future therapeutic possibilities in people with diabetes type II and coronary artery disease. Indeed, endothelial dysfunction and its siblings participate not only in the appearance or progression of metabolic syndrome but

they contribute in the appearance of almost all pathologies in all the organs.[91–93].

Current studies emphasized the role of insulin resistance syndrome in the emergence of non-related metabolic syndrome diseases, recent evidence was with COVID-19. [94–98] Were many patients were suffering from metabolic syndrome have a severe form of infection and even there was a piece of clear evidence on their mortality and morbidity rate. Particularly, endothelial dysfunction and procoagulant state induced in the obese and hypertensive individual were found higher expression of ACE2 receptors on the pneumocytes type two which supports viral entrance. Therefore, metabolic syndrome affects not limited to specific diseases and its non-specific effects are on the whole organism.[99–103].

Currently, endothelial dysfunction is staged into structural and functional changes of the endothelocytes.[104] Hypothetically, functional changes are reversible by the elimination or controlling of the risk factors from hyperglycemia, inflammation, hypoglycemia, specific denervation syndrome, and enhance endothelial cells antioxidant defense system as well as the promotion of their physiological activity by inhibitors of endothelium-derived contracting factors (ACE), smoking cessation, statins, diet, and physical exercise.[105] However, the structural changes are widely irreversible and require regeneration from endothelocytes progenitor cells. But, unfortunately, regeneration not always occurs without induction of progenitor cells or transdifferentiation of another cell lineage to endothelial cells. Due to the global shortage of treatment for metabolic syndrome, it is important to find a surrogate strategy to defense against dyslipidemic syndrome. Currently, most of the used drugs in metabolic syndrome patients don't eliminate the etiologies rather than control for the outcomes since no clear etiologies are known.

Endothelial dysfunction has been progressively studied in the last year because of the direct association between COVID-19 mortality rate and endothelial dysfunction.[106] As we have shown in this paper that endothelial dysfunction increases the rate of thrombosis formation and impairs hemodynamic state which is both used as an indicator of the severity of the infection.

Currently, metabolic syndrome is the leading cause of cardiovascular and diabetes mellitus type II development. Metabolic syndrome is an accumulative metabolic disorder that usually starts from the childhood period. A cluster of heterogeneous disorders collectively contributes to insulin resistance syndrome emergence. Physiologically, endothelial cells control vascular tone and possibly improve insulin receptors sensitivity through vasodilation. Clinically, metabolic syndrome candidates are individuals with hypertension, dyslipidemia, central obesity, and glucose metabolism impairment. Usually, central obesity and dyslipidemia are considered the frontline in the endothelial cells pathophysiology. The paper emphasizes the pathophysiological role of endothelial cells in the pathogenesis of metabolic syndrome. Whereas, the recent clinical data emphasize the role of an early healthy lifestyle in the prevention of metabolic syndrome.[107].

Abbreviations

ACE2	angiotensin-converting enzyme 2
PAI-1	plasminogen activator inhibitor-1
tPA	tissue plasminogen activator
VEGF-B	vascular endothelial growth factor B
sHSP	small heat shock proteins
ET1	endothelin-1
LOX-1	lectin-like oxidized low-density lipoprotein receptor-1
IRSp53	insulin receptor substrate p53

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