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Endothelial Dysfunction in Cardiovascular Diseases

Indranil Biswas and Gausal A. Khan

Abstract

Endothelium is the inner most cell layer of blood vessels. Endothelial cells make special barrier that separate blood from extravascular tissues. Intact endothelium regulates vascular tone and permeability and maintains non-inflammatory, anti-thrombotic surface. Through its ability to express pro-coagulants, anticoagulants, vasoconstrictors, vasodilators, cell adhesion molecules, and cytokines, the endothelium has emerged as one of the pivotal regulators of vascular homeostasis. Under physiological conditions, endothelial cell sustains a vasodilatory, anticoagulant, and fibrinolytic state in which coagulation, platelet adhesion, as well as leukocyte activation and inflammation are suppressed. In contrast, during endothelial disturbances, a prothrombotic and pro-inflammatory state of vasoconstriction gets support from the endothelial surface. Release of platelet-activating factor (PAF) and endothelin-1 promotes vasoconstriction, whereas production of von Willebrand factor (vWF), tissue factor (TF), and plasminogen activator inhibitor (PAI)-1 shifts the haemostatic balance towards a procoagulant state. Several factors like infection, hyperglycaemia, hyperlipidaemia, malignancy, oxidative stress, and aging can interfere in endothelial function. It is believed that most of the cardiovascular diseases originate from endothelial dysfunction. Endothelial dysfunction has been shown to be involved in atherosclerosis, thrombosis, hypertension, diabetes, and other cardiovascular diseases. In this review we will specifically highlight the role of endothelial dysfunction in development of cardiovascular diseases.

Keywords: endothelial dysfunction, atherosclerosis, hypertension, heart failure, stroke

1. Introduction

Vascular endothelium is considered as a largest endocrinal organ in the body, which has been shown to have a role in homeostasis in the body by exerting various functions [1]. It is made up of simple squamous epithelial cells that line blood vessels, lymphatic vessels, and the heart. The vascular endothelium has a total weight of about 1.5 kg. The endothelium has been recognized as a smart barrier and a key regulator of blood flow in micro- and macro-vascular circulation [2]. Endothelial function is very important, as it interacts with nearly every system in the body and selectively supplies nutrients and growth factors to every organ. On the other hand, endothelium also receives active metabolites and delivers them back to the

circulation. Previously, it was believed that, endothelium is an inactive barrier between blood and extravascular tissues. However, recent research has shown that the vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis.

2. Physiological function of endothelium

When immediate surrounding tissues are at basal conditions, the endothelium functions to maintain the vessel homeostasis, which favors vessel dilatation over vasoconstriction [3]. The endothelium being a dynamic reactive tissue, responds to various intrinsic physical stimuli, that is, shear stress, temperature, and transmural pressure and external stimuli, that is, temperature, mental stress, neurohumoral responses, immune response, and medications [2, 4].

Under normal conditions, endothelial cell maintains basal perfusion, which is determined by cardiac output, systemic, and local vascular resistance. Endothelial metabolism, which is a key regulator of perfusion, is impaired during several disease states like infection, injury, aging, and inflammation [5]. Local blood flow is the result of vascular relaxation and contraction that is balanced by endothelium-derived vaso-dilatative and vaso-constrictive factors. Among these factors, one signal molecule stands out as hub and target of many pathways and mechanisms that is nitric oxide (NO) [6]. It is important to understand the biochemical foundations of NO for endothelial function. NO, a potent vasodilator, is released form the endothelium due to shear stress. This NO is released by endothelial nitric oxide synthase (eNOS) by utilizing L-arginine as a substrate, which leads to the production of intracellular cyclic GMP [7]. However, in an event when the NO-dependent vasodilator mechanism is compromised, then the cytochrome-derived factors, natriuretic peptide [8], and prostacyclin [9]-dependent vasodilator mechanism came in action.

During disease state, there is impaired endothelial function, and this results in the balance shift towards prevailing constrictive factors and/or down-regulation of vaso-dilatative factors. An important counterweight in the vascular balance is cyclooxygenase (COX). This mostly induces COX-1 which is endogenous and may involve COX-2 if it is induced. The COXs have a key role in generating vasoconstrictive factors.

The COX enzymes transform arachidonic acid into endoperoxides and further into thromboxane A_2 (TXA_2) [10], prostaglandins, and prostacyclin [11]. Local presence of thrombin evokes inducible NO release. Platelet release of serotonin and ADP in turn increases NO synthesis and release in healthy endothelium to induce dilatation [12]. When vasodilatory function of endothelium is impaired, then the thrombus formation is mechanically promoted by vasoconstriction via TXA_2 and by the direct effect of serotonin on smooth muscle cells [13].

3. Endothelial dysfunction

Traditionally, endothelial dysfunction has been associated to pathological conditions that have altered anticoagulant function, impaired anti-inflammatory properties of the endothelium, impaired modulation of vascular growth, and dysregulation of vascular remodeling. For instance, a plethora of studies have confirmed the impairment of endothelium-dependent vasorelaxation caused by a loss of NO bioactivity/availability in the vessel wall [4]. The loss of NO bioavailability

is the salient feature of a dysfunctional endothelium, which in turn is the sentinel of systemic or focal vascular disease. A number of previous studies have showed that most of the cardiovascular diseases were initiated from endothelial dysfunction. The decline in NO bioavailability may be caused by decreased expression of the endothelial cell eNOS [14], a lack of substrate or cofactors for eNOS [15], the presence of inhibitor of NOS [16], and alterations of cellular signaling, and finally, accelerated NO degradation by ROS [17]. Another aspect of endothelial dysfunction is impaired endothelial barrier function. Depending on the mode of pathophysiological change, this loss in barrier function may be localized or systemic. Localized loss of the selective barrier function (manifested as edema), coupled with the emigration of leukocytes, has been recognized as cardinal signs of inflammation [18]. From an immunological context, the body's primary reaction to tissue injury or infection is the leukocyte interacting with endothelium. However, from the perspective of hemostasis and thrombosis, endothelial dysfunction is characterized by activation of pro-inflammatory and pro-coagulant molecules, as well as the suppression of anti-inflammatory and anti-coagulant molecules. The intact and normal functioning endothelial lining provides a stable reservoir for blood as its luminal surface does not activate the coagulation cascade or promote leukocyte-platelet adhesion, and it also exhibits anticoagulant and fibrinolytic properties [19]. Systemic endothelial dysfunction may lead to widespread inflammation, vascular leakage, thrombocytopenia, and disseminated intravascular coagulation (DIC). On the other hand, localized endothelial dysfunction and leukocyte adhesion may lead to venous thrombosis. Other than altered endothelial barrier function, localized endothelial dysfunction also leads to tissue factor induction and increased von Willebrand factor (vWF) release that shifts the homeostatic balance towards the pro-coagulant-pro-inflammatory phenotype [20]. Intact endothelium release pro-fibrinolytic molecules like tissue plasminogen activator (TPA) [21]. Endothelial dysfunction suppressed TPA release, thereby impairing fibrinolytic function of endothelium [22]. In contrast to venous endothelial cells and microvascular endothelial cells, arterial endothelial cells are surrounded by a vascular smooth muscle layer and adventitial layer. Arterial endothelial cells physiologically experience high sheer stress and synthesize ample amount of NO that facilitate vascular relaxation. In the context of atherogenesis, endothelial cell dysfunction is mainly characterized by a loss of anatomical integrity of the intima, as described by the seminal *"Response-to-Injury Hypothesis"*. Endothelial cell injury and subsequent sub-endothelial matrix exposure lead to platelet adhesion and activation mediated through sub-endothelial collagen layer [23]. The initiating event in the atherogenic process is some form of overt injury to the intimal endothelial lining that is induced by noxious substances (e.g., oxidized cholesterol, cigarette smoke, hyperlipidemia, hypercholesterolemia, hyperglycemia, etc.) or altered hemodynamic sheer stress (e.g., abnormal blood flow caused by hypertension) [24]. In particular, local endothelial mechanical tearing was seen as the inciting stimulus for platelet adhesion, activation, and the localized release of platelet-derived growth factors. This would then elicit the migration, proliferation, and phenotypic modulation of medial smooth muscle cells and thus generate a fibromuscular plaque [25]. It is of great interest to establish the sequential event that leads to atherogenesis from endothelial injury. But, the direct link between endothelial injury and the genesis of atherosclerotic lesion is still unclear. However, the detailed morphologic examination in diet-induced fatty streak lesions in animal models failed to demonstrate unconcealed intimal injury or platelet adhesion. In this context, it is highly relevant that several molecules including high mobility group protein (HMGB-1) [26] and heat shock proteins (HSPs) [27] are released from injured endothelial cells and facilitate monocyte adhesion, a crucial step for plaque formation.

4. Endothelial dysfunction in atherosclerosis

Endothelial dysfunction of lesion-prone areas of the arterial vasculature leads to atherosclerotic plaque formation [28]. Sequential deterioration of arterial vasculature along with increased sheer stress contributes to lesion formation. Endothelial dysfunction is one of the early events that are responsible for the deterioration of arterial vasculature [29]. Recent insight into the cellular mechanisms involved in atherogenesis shows that deleterious modifications of endothelial physiology or metabolism is the initial event of vascular remodeling that represents a crucial step in the development of atherosclerosis and are also involved in the development of plaque and the occurrence of atherosclerosis [2]. The sequential event including focal permeation, trapping, and physicochemical modification of circulating lipoprotein particles in the sub-endothelial space constructs an inflammatory lesion [30]. This initiates a coordinated cellular signaling, followed by complex pathogenic sequence and endothelial activation. Activated endothelial cells express several cell adhesion molecules, which facilitate selective recruitment of circulating monocytes from the blood, and invade the tunica intima, where they differentiate into macrophages. These macrophages also abnormally take up modified lipoproteins to become foam cells (the hallmark of early fatty streak lesions) [31, 32]. The activated endothelium and macrophages release multiple chemokine and growth factors which act on neighboring smooth muscle cells (or precursors cell) [33] to induce their proliferation and synthesis of extracellular matrix components within the intimal compartment, thus generating a fibromuscular plaque34. This progressive structural remodeling of developing lesions results in the formation of a fibrous cap, overlying a lipid-rich necrotic core that consists of oxidized lipoproteins, cholesterol crystals, and cellular debris. This is also accompanied by varying degrees of matrix remodeling and calcification [34, 35]. The lateral edges of these complicated plaques also contain a rich population of inflammatory cells, that is, activated macrophages, T-lymphocyte, and dendritic cells [36], which secrete several cytokines and chemokines that further activate endothelial pro-inflammatory phenotype and contribute to structural instability of the plaque through release of proteolytic enzymes (matrix metalloproteases) that lead to modification of sub-endothelial matrix components [37]. Another aspect of atherogenesis is governed by lipoproteins, mainly low-density lipoproteins (LDL). This initial arterial remodeling through accumulation of lipids is known as fatty streak formation. The first changes in the arterial wall occur at the branch points of arteries, where adaptive intimal thickening occurs in response to normal hemodynamic stresses [38]. During the early stage of atherogenesis, LDL particles leave the blood and enter the arterial intima, composed of endothelial cells. Fat droplets (LDL) may also accumulate in the cytoplasm of vascular smooth muscle cells (VSMCs) [35]. LDL particles are then modified by enzymes and are oxidized into a highly reactive pro-inflammatory molecule (oxidized LDL), that is recognized by pattern recognition receptors, that is, Toll-like receptors (TLRs) present in endothelial cells as well as pro-inflammatory macrophages [39]. Oxidized LDL incites the reaction of the innate inflammatory system within the intima and contributes to vascular remodeling. Inflammation begins when activated endothelial cells (through TLRs) express cell adhesion molecules and VSMCs secrete chemokines and chemoattractants, which together draw monocytes, lymphocytes, mast cells, and neutrophils into the arterial wall [40]. Once monocytes enter into the arterial wall through the intima, they become activated into macrophages. These macrophages take up lipids as multiple small inclusions and become transferred into foam cells [41]. The degree of lipid accumulation is critical for early stage diagnosis of atherosclerosis. Atherosclerosis is believed to start when the lipid accumulation appears as confluent

extracellular lipid pools and extracellular lipid cores with and decreased cellularity [42]. Endothelial cell dysfunction is also responsible for VSMC proliferation and differentiation to myofibroblast. In an intact vessel, VSMCs never come into contact with plasma proteins and are therefore devoid of growth factor present in plasma. In physiological conditions, VSMCs are always maintained in quiescent states. During early inflammation and endothelial cell activation, VSMCs receive signal from dying cells or growth factors that modify VSMCs to myofibroblast (more proliferative counterpart). Altered VSMCs (myofibroblast) also secrete proteoglycans, collagen, and elastic fibers into the sub-endothelial matrix [43]. This transformation of VSMCs further worsens the histological structure and leads to formation of thin-cap fibroatheroma formation [44]. Fibroatheroma can be of two different types depending on the content and stability of the plaque. Stability of the plaque also determines the fate of the fibroatheroma. Unstable fibroatheroma leads to thrombotic plaque formation, whereas stable fibroatheroma accumulates calcium, becomes stiff, and eventually leads to occlusion [44, 45]. Unstable or vulnerable plaques may lead to a catastrophic transition into atherosclerotic lesion—frank plaque rupture, with luminal release of the highly thrombogenic contents [46, 47]. Else, some significant clinical sequelae can be seen from superficial intimal erosions, without any indication of plaque rupture [48]. Therefore, lately an acute transition appears leading to endothelial cell apoptosis, with localized endothelial denudation and thrombus formation leading to obstruction in regional blood flow [49, 50], whereas the stable lesions, having thick fibrous cap and less lipid as well as inflammatory cell content, can gradually invade on the lumen of the vessel causing ischemic symptoms without atherothrombotic events [51, 52]. Many ruptures of thin fibrous caps are clinically silent in that they heal by forming fibrous tissue matrices of cells, collagen fibers, and extracellular space but may rupture again with thrombus formation of the necrotic core, triggering an atherothrombotic occlusion. These cyclic changes of rupture, thrombosis, and healing may recur as many as four times at a single site in the arterial wall, resulting in multiple layers of healed tissue. In all these steps, calcium deposition in the wall of the vessels forms small aggregates initially, which turns into large nodules at later stage. In later stage, these plaques may rupture and expose the nodules, and it became sites for thrombus formation [47]. Therefore, the increasing number of plaques itself might become adequate to form significant stenosis, which may cause a shattering ischemic event due to flow restriction [53]. Based on its multiple regulatory roles throughout this complex series of events, it is evident that endothelial dysfunction constitutes a well-coordinated multicellular pathogenic sequence that leads to atherosclerosis.

5. Endothelial dysfunction in hypertension

Hypertension affects significantly to worldwide cardiovascular morbidity and mortality and is considered as a diagnostic factor for cardiovascular disease. Hypertension appears to have a complex association with endothelial dysfunction, a phenotypical alteration of the vascular endothelium that precedes the development of adverse cardiovascular events. Endothelial cells along with the vascular smooth muscle cells of resistance vessels (arteries and arterioles) regulate hypertension [54] as they continuously constrict and dilate according to the rhythm of cardiac cycle. In response to the blood flow (perfusion), the quiescent healthy endothelium continuously releases potent vasodilators, which have the potential to lower vascular resistance, thereby regulating the blood pressure [55]. In normal condition, basal perfusion is determined by cardiac output, systemic, and local resistance. In an intact healthy vessel, endothelial cell always maintains a vasodilatory rather than

a vasoconstrictive phenotype. Endothelial dysfunction is a condition comprising not only attenuated endothelium-dependent vasodilatation but also an augmented inflammatory endothelial activation that leads to vasoconstriction. Endothelial dysfunction contributes to hypertension, whereas hypertension also leads to endothelial dysfunction. In healthy endothelial tissues, a balance between endothelium-derived relaxing factors (EDRFs) and endothelium-derived contracting factors (EDCFs) is maintained. Endothelial dysfunction disturbs this balance. Several vasodilatory and vasoconstrictive factors regulate this balance. The endothelium secretes a number of vasodilator factors including NO. Generation of NO can activate guanylate cyclase (cGMP), which causes vasodilation through relaxation of vascular smooth muscle cells [56]. Another vasodilatory factor PGI_2 secreted by the endothelium inhibits platelet aggregation and vascular smooth muscle cell proliferation [57]. Endothelial cells also secrete several vascular contracting factors including angiotensin-II (Ang-II), endothelin-I (ET-I), dinucleotide uridine adenosine tetraphosphate (UP4A), and COX-derived TXA_2 [58]. Endothelins (ETs) are potent vasoconstrictor molecules having a key role in vascular homeostasis. Although there are three types of ET, vascular ECs mainly produce only ET-1, which has prominent roles in vasoconstriction. Active ET molecule is generated by the actions of an ET converting enzyme (ECE) found on the endothelial cell membranes. There are two basic types of ET-1 receptors: ET-A and ET-B, G-protein coupled receptors. Under normal conditions, the ET-A receptor is dominant in blood vessels [59]. ET-1 exerts vasoconstriction through activation of dihydropyridine channel or DHP channel or long lasting Ca^{++} channels (L-type) by binding to ET-A receptors on vascular smooth muscle cells. Smooth muscle cells expressed both ET-A and ET-B receptors. However, endothelial cells express only ET-B receptors, which negatively regulate NO release. Another vasorelaxation factor adenosine released from endothelial cells acts through purinergic receptor and maintains vascular perfusion [60]. Other than these factors, several cytokines and chemokines also play an important role in hypertension. Inflammatory cytokine induces generation of reactive oxygen species (ROS), one of the critical factors that link endothelial dysfunction and hypertension [61]. It is well established that Ang-II induces NADPH oxidases (NOX). But recent finding indicates additional source of ROS generation. In small subcutaneous arteries, a significant portion of Ang-II induced ROS is produced by COX-2. In the mouse aorta, the mitochondrial monoamine oxidase is another mediator of ROS generation and Ang-II or inflammation-induced endothelial dysfunction [62]. Therefore, mitochondrial monoamine oxidase-A and monoamine oxidase-B are also induced due to endothelial dysfunction in the vessels and generate a significant amount of H_2O_2 sufficient to quench endothelial NO. In spite of that, other mitochondrial ROS generating systems, that is, p66Shc, also contribute to hypertension-induced ROS production. ROS production is also regulated by several intracellular signaling, which further attenuate endothelial dysfunction and hypertension.

6. Endothelial dysfunction in heart failure

Heart failure (HF) is the most common cause of hospitalization in cardiovascular disease with a high mortality rate. Despite novel treatment options for patients suffering from HF, morbidity and mortality rates are still high. The impact of the growing HF on global public health is a great concern in health care research. With the advancement of medical management, survival of acute coronary disease and cardiac ischemia has been improved. However, in myocardial infarction, prognosis is still poor, as HF with preserved ejection fraction (HFpEF) has a 65% mortality rate at 5 years. While the heart as the failing "pumping" organ was an initial

focus in research and treatment, neurohumoral activation and subsequently the role of a failing endothelium were recognized and investigated in recent years. Traditionally, HF was recognized as impairment of cardiac muscle activity, known as cardiomyopathy. Later, it was found that altered perfusion in cardiac arteries due to atherogenesis also contributes to cardiac ischemia that leads to cardiomyopathy. Reduced myocardial perfusion due to impaired ventricular function is at least in part a consequence of reduced endothelium-dependent vasodilator capacity of coronary arteries. The prominent regulatory activity of the vascular endothelium in HF was discovered about two decades ago, and its assessment in different cardiovascular disorders, including HF, has been the focus of intense research [63]. On the other hand, declined peripheral vasodilation causes higher systemic and pulmonary vascular resistance and together with stiffness of conductance arteries leads to increased afterload. Elevated afterload further increases cardiac workload and therefore worsens myocardial function. The decreased exercise capability is aggravated by vasomotor dysfunction of the skeletal muscle vessel by increases vascular resistance. Altered endothelial metabolism further contributes to increasing cardiac afterload [13]. Indeed, various aspects of endothelial function are affected in heart failure, including vasomotor, hemostatic, antioxidant, and anti-inflammatory activities [63, 64]. Differences also exist in the pattern of endothelial dysfunction depending on etiology, severity, and stability of HF in individual patients. Endothelial dysfunction also plays a central role in HF. The failing heart is characterized by an altered redox state with overproduction of ROS. The increasing evidence suggests that the abnormal cardiac and vascular phenotypes characterizing the failing heart are caused in large part by imbalances between NO bioavailability and oxidative stress [65]. During initial stages of HF, inflammatory mediators from the myocardium and altered local shear forces modulate gene expression, leukocyte infiltration, increased cytokine production, increased ROS generation, and diminished NO bioavailability. Clinical studies showed significant up-regulation of plasma markers of endothelial activation (e.g. E-selectin) and endothelial damage (e.g. vWF) in HF [22, 63]. However, it is difficult to determine if endothelial dysfunction is the cause or effect of the HF. Therefore, HF is regarded as thrombotic complication. As mentioned earlier, during atherogenesis, decreased lumen of cardiac arteries leads to reduced perfusion to the heart muscle. This phenomenon is coupled with increased sheer stress and impaired blood flow. This reduced perfusion either led to ischemia–reperfusion injury or coronary artery thrombosis [63]. Studies showed that endothelial dysfunction is one of the principle mediators of ischemia–reperfusion injury and thrombosis. This explains the increased endothelial dysfunction markers in coronary artery disease, HF, and thrombosis.

7. Endothelial dysfunction in stroke

The global burden of neurological diseases including cerebrovascular stroke has significantly increased, and development of new treatment modalities for cerebrovascular diseases is an urgent need. Cerebrovascular stroke can be broadly subdivided into acute ischemic stroke and hemorrhagic stroke [66]. Acute ischemic stroke is among the leading causes of death and long-term disability. Cerebrovascular stroke in small vessel has functional (lacunar stroke, cognitive impairment, gait, and movement disorders) and structural (small subcortical infarct, lacunar infarct, lacunes, white matter lesions, and micro bleeds) consequences. In the past few decades, the immense development of neuro-radiological methods enabled better imaging of cerebral blood vessels. From the clinical point of view, it is very important to identify the location of vascular lesion. However,

the treatment strategies do not depend on the location of vascular impairment. It is now well recognized that endothelial dysfunction represents a systemic syndrome involving multiple vascular beds, including the cerebral vasculature [67]. Endothelial function is not uniform throughout the arterial system. It differs between organs and potentially also between different vascular beds within the same organ. Cerebral endothelium is probably one of the most specific types since it is the crucial element of the well-known blood-brain barrier (BBB). The BBB is a term used to describe the unique properties of the microvasculature of the central nervous system that protects the brain from harmful agents and pathogens [68]. CNS vessels are continuous non-fenestrated vessels, but also contain a series of additional properties that allow them to tightly regulate the movement of molecules, ions, and cells between the blood and the CNS. This heavily restricting barrier capacity allows BBB ECs to tightly regulate CNS homeostasis, which is critical to allow for proper neuronal function, as well as protect the CNS from toxins, pathogens, inflammation, injury, and disease. The cell-to-cell interaction with astrocytes, microglia, and neurons mainly played an important role for maintenance of BBB controlled by endothelial cells and pericytes [69].

However, the integrity of BBB is mainly disrupted due to decrease in endothelial cell-cell junction proteins and the detachment of pericytes from the endothelial membrane in homorganic condition [70]. Cerebral autoregulation maintains constant blood flow (CBF) through the brain in spite of changing mean arterial pressure. Autoregulation of cerebral blood flow consists of mechano- and chemo-regulation. The serum level of carbon dioxide (CO_2) is directly controlled by the chemo-regulation independent of changes in mean arterial pressure [71]. However, mechano-regulation depends on transmural pressure gradient and endothelial vasodilatation.

8. Conclusion

From the above discussion, it is evident that CVDs and cardiovascular morbidity are associated with endothelial dysfunction, but the mechanistic links between inflammatory diseases, endothelial dysfunction, and CVDs have not been fully elucidated. The role of traditional cardiovascular risk factors in patients with inflammation, especially sterile inflammation, has received considerable attention, though traditional factors alone are insufficient to explain the excess burden of CVDs. It seems likely that sterile inflammation, a shared feature of CVDs, is involved in the pathogenesis of accelerated endothelial dysfunction.

Patients with chronic inflammatory/and or sterile inflammatory diseases are at high risk for cardiovascular morbidity and mortality. In many inflammatory diseases, this heightened risk of CVDs is reflected in early endothelial dysfunction, even in the absence of any other detectable diseases. Several others mechanisms, that is, auto-antibodies, oxidative stress, and interactions with traditional risk factors like dyslipidemia and insulin resistance might be involved. Therefore, further research in future is required to delineate the importance of these processes. So, the current approaches to diminish cardiovascular morbidity and mortality are focused on controlling traditional modifiable cardiovascular risk factors and reduction of disease risk. Therefore, the precise mechanisms leading to development of CVDs due to inflammation/or sterile inflammation need to explore. These studies might help to identify unique therapeutic targets to combat these diseases.

The endothelium therefore represents an integrator of vascular risk, and the study of its dysfunction may help elucidate mechanisms driving accelerated CVDs in future, which could help to develop therapeutic targets for control of CVDs.

Acknowledgements

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