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REVIEW PAPER

Molecular Insights into the Relationship Between Platelet Activation and Endothelial Dysfunction: Molecular Approaches and Clinical Practice

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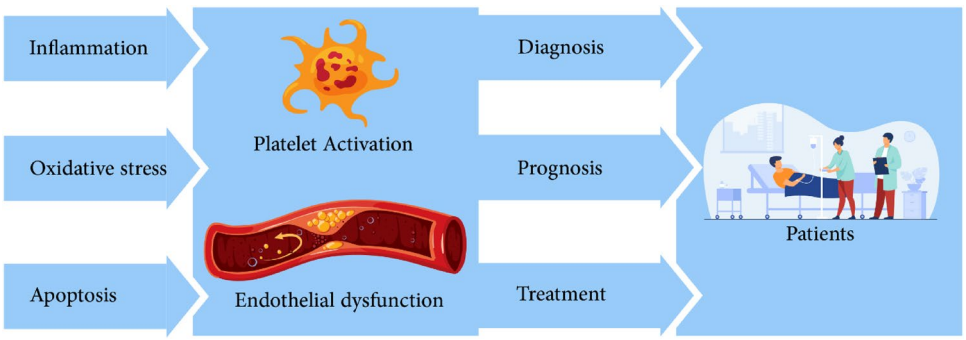
Abstract

Platelets are one of the coagulation cells. When platelet activation occurs, many mediators are released and affect endothelial cells (ECs) and lead to endothelial dysfunction (ED). ED plays an important role in the pathogenesis of many diseases, including cardiovascular disease (CVD). Platelet are of important factors in ED. The release of mediators by platelets causes the stimulation of inflammatory pathways, oxidative stress, and apoptosis, which ultimately result in ED.

On the other hand, platelet activation in CVD patients can be associated with a bad prognosis. Platelet activation can increase the level of markers such as p-selectin in the serum. Also, in this study, we have discussed the role of platelet as a diagnostic factor, as well as its use as a treatment option. In addition, we discussed some of the molecular pathways that are used to target platelet activation.

Graphical Abstract



Keywords Platelet · Endothelial Dysfunction · Diagnostic · Molecular Pathway · Prognostic

Introduction

Endothelial cells (ECs) are ubiquitous tissues found between the lumen and the walls of blood vessels, lining the inner surfaces of the vessels. ECs primarily are effective in the regulation of vascular tone, vascular integrity, and homeostasis. Endothelial dysfunction (ED) can be an onset to diseases such as thrombosis, cardiovascular disease (CVD), and other diseases; which can affect physiological and mental symptoms [1–4]. Various factors can contribute to the development of ED; oxidative stress, inflammation, and damage to ECs due to platelet activation can lead to the onset of ED [1, 5].

Platelets are small, disc-shaped, anucleate cells derived from the cytoplasm of megakaryocytes and have a lifespan of 7 to 10 days. They are key element in regulating hemostasis and wound healing. Evidence suggest that platelets may

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also be involved in various immunological pathways, inflammation, and chemotaxis [6, 7]. Chronic inflammation and infection can activate platelets and produce pro-thrombotic states. Also, platelets play a role in CVD through the regulation of genes and microRNAs (miRs) (Table 1).

It is said that one of the main reasons for the activation of platelets and their interaction with the endothelium is ED. In addition, damaged endothelium itself can further activate platelets. The connection between endothelium and activated platelets forms the basis for atherosclerosis and thrombosis [8, 9].

Most recent studies have investigated the pathogenesis of ED by drugs, coagulation system, and inflammatory factors in CVD patients. In addition, other studies have shown that platelet activation affects ED and CVD incidence in patients. However, the molecular mechanisms that cause platelet interaction with ECs and the occurrence of ED have not been fully identified. Understanding these molecular pathways help to introduce diagnostic methods to identify high-risk patients, as well as designing therapeutic strategies for the treatment of CVD. Therefore, we have investigated the molecular activation of platelets and its relationship with ED.

Platelet Activation and Aggregation in Endothelial Dysfunction

ED stands as a significant predisposing factor for the onset of CVD. The endothelium, a pivotal component in the regulation of platelet activation and aggregation pathways, normally exhibits antithrombotic characteristics. Maintenance of the antithrombotic properties of the endothelial environment is accomplished through the release of nitric oxide (NO) and prostacyclin under normal conditions. However, the balance is disrupted in injury, leading to the release of von Willebrand factor (VWF) and collagen from the damaged endothelium. The phenomenon, in turn, activates platelets and initiates a cascade wherein platelet activation is facilitated by adenosine diphosphate (ADP) and Thromboxane A2 (TXA2) [10–12].

Consequently, granular alterations occur and the glycoprotein IIb/IIIa receptors undergo activation process on the platelet surface. These modifications result in an increased affinity of fibrinogen for platelets and ultimately leading to platelet aggregation. On the other hand, the production of inflammatory mediators by platelet aggregation can lead to NO production decrement and prevent the expansion of ECs, which finally causes ED. The intricate interplay between ED and the activated platelets significantly contributes to the pathogenesis of thrombotic disorders within the realm of CVD. Consequently, a thorough investigation into the molecular mechanisms governing platelet activation and aggregation in the context of ED is imperative for the development of effective treatment strategies [10, 13, 14].

Impact of Platelet-Derived Mediators on the Endothelial Health

The role of platelet-derived mediators is pivotal in maintaining endothelial health and ensuring vascular homeostasis. Following activation, platelets engage in the release of a diverse array of mediators, including growth factors, cytokines, and chemokines through various processes. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) assume a critical role in fostering the proliferation and angiogenesis of ECs. Additionally, TXA2 and Serotonin contribute to vasoconstriction and platelet aggregation. Nevertheless, in pathological conditions such as atherosclerosis or inflammation, the delicate balance and homeostasis of these molecules may be disrupted and ED occurs [15–17].

Under pathological circumstances, platelet-derived mediators have the potential to induce endothelial inflammation, oxidative stress, and in severe cases apoptosis of ECs. The production of cytokines by platelets leads to the interaction of ECs with leukocytes. In addition, interaction can cause

Table 1 Evaluation of miRs-related platelets in pathogenesis of CVD

miRs	Disease	Mechanism	Ref.
MicroRNA 365-3p	CAD	Increased expression of miR-365-3p correlated with CAD and use of antiplatelet therapy decreased it	[126]
miR-223	Kawasaki disease	Expression of miR-223 through targeting of PDGFRβ leads to prevent vascular injury and CVD	[127]
miR-25-3p	Atherosclerosis	Expression of miR-25-3p inhibit NF-kB pathway and reduce inflammatory mediators lead to prevent Atherosclerosis	[128]
miR-4306	Coronary disease	Through inhibition of VEGFA/ERK1/2/NF-κB pathway reduce inflammation	[129]
miR-513a-5p	Atherosclerosis	circ_0004872 through targeting miR-513a-5p/TXNIP cause proliferation of VSMCs	[130]
miR-200a-3p	AIS	Through inhibition MAPK pathway reduce expression of VEGF and ET-1	[131]

CAD coronary artery disease, *CVD* cardiovascular disease, *PDGFRβ* platelet-derived growth factor receptor-β, *VEGF* vascular endothelial growth factor, *VSMCs* vascular smooth muscle cells, *TXNIP* thioredoxin-interacting protein, *AIS* acute ischemic stroke, *ET-1* endothelins -1

chemotaxis of monocytes, neutrophils, and other leukocytes towards ECs, which ultimately causes ED. A nuanced comprehension of the dual effects exerted by platelet-derived mediators on platelet and endothelial homeostasis, both in normal and pathological conditions, stands as a crucial avenue for developing targeted therapies aimed at susceptible patient populations [15, 18].

Signaling Pathways Involved in Platelet-Endothelial Crosstalk

Following vascular injury or endothelial activation, a series of events is set into motion as platelets adhere to the exposed subendothelial matrix. This initiation prompts a cascade of diverse signaling pathways, with a pivotal role played by the interaction between platelet surface receptors like glycoprotein Ib and IIb/IIIa and VWF and fibrinogen. Platelet activation triggers the release of TXA2 and ADP, activating various signaling pathways. This, in turn, leads to the activation and recruitment of additional platelets to the injury site. Concurrently, the endothelium acts to impede platelet activation and aggregation by releasing NO and prostacyclin. This intricate interplay involves crosstalk mediated by intracellular signaling pathways, including phosphoinositide 3-kinase (PI3K) and protein kinase C (PKC), exerting influence over platelet adhesion, activation, and aggregation [19].

On the other hand, the activation of some other signaling pathways such as protein kinase G (PKG) and phospholipase C (PLC) can cause ED due to the release of calcium in platelets. Also, the activation of the NF-kB signaling pathway can cause the production of inflammatory mediators and the occurrence of ED. Any disturbance in the balance of homeostasis and signaling pathways precipitates the formation of a thrombus, contributing to the development of CVD [19, 20].

Genetic and Epigenetic Factors Influencing Platelet Function in Endothelial Dysfunction

In the situation of ED, the interplay of genetic and epigenetic factors introduces a nuanced complexity to the functioning of platelets. Genetic alterations in platelet receptors, particularly glycoproteins IIb/IIIa and the P2Y12 receptor, wield a notable influence on platelet aggregation. Polymorphisms within these genetic domains can give rise to divergent responses to antiplatelet treatments and variations in susceptibility to thrombus formation [21]. On the epigenetic front, aberrant changes in DNA, encompassing methylation, and histone acetylation are linked to changes in platelet and vascular function. Such epigenetic modifications not only elevate the risk of CVD but also disrupt the intricate interplay between platelets and the endothelium. This multifaceted interplay of genetic and epigenetic factors contributes significantly to the intricate landscape of platelet dynamics in ED [22, 23].

Inflammatory Biomarkers and Endothelial Dysfunction

In the event of oxidative stress, inflammatory mediators are released from various cells. Oxidized Low-Density Lipoprotein (OX-LDL), Advanced Glycation End Products (AGEs), c-reactive protein (CRP), and High Mobility Group Protein Box 1 (HMGB1) are among the inflammatory mediators [24, 25]. HMGB1 triggers the production of cytokines such as IL-1B, TNF-α, and IL-6 via the TLR4/MYD88/TRAF6/NF-kB pathway and results to the recruitment of inflammatory cells, particularly neutrophils; consequently, this process induces pyroptosis and netosis. HMGB1 binds to the surface of other platelets and ECs via receptors such as advanced glycation end products (RAGE) and TLRs [6, 26–28]. In addition, under conditions of oxidative stress, the amount of reactive oxygen species (ROS) increases and the MAPK/P38/NF-kB pathway activated, leading to the production and secretion of HMGB1 from monocytes and causing inflammation. In LPS-induced inflammatory responses, the NOTCH/JNK/JAGGED1 pathway is activated, resulting in the secretion of inflammatory cytokines (Table 2) [29, 30].

TNF-α triggers the inflammation by recruiting TRADD, receptor-interacting protein (RIP), and TRAF2, leading to the activation of NF-kB. Another signaling pathway activated by this cytokine includes AP-1/MAPK, factors such as cJUN/JNK, cJUN/ATF2, and cJUN/cFos. Activation via these pathways affects ECs and increases the expression of ICAM-1, VCAM-1, and E-SELECTIN on their surfaces [5, 31, 32]. Consequently, inflammatory cells and platelets bind to ECs surface molecules via p-selectin and CD40L. In the case of systemic increment of TNF-α, MCP1 is produced and secreted via the Rho/Rho-kinase and P38MAPK pathway. Activation of ERK/Rho/Rho kinase is said to cause smooth muscle cell proliferation, which can lead to vascular disorders [33, 34].

Platelets recruit and increase the adhesion of monocytes and other circulating leukocytes to ECs through the secretion of MCP-1 and CCL5. Recruited monocytes take up OX-LDL with the help of the scavenger receptors of CD36 and the macrophage scavenger receptor (SR-A) and activation of the ERK/AMPK/SREBP1 signaling pathway and transform into the foam cells. It is also suggested that miR-33a is involved in the conversion of monocytes/macrophages into foam cells by inhibiting the expression of ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) [19, 35–39].

Table 2 Role of inflammation in pathogenesis of ED

Type of disease	Sample	Mechanism	Ref.
coronary heart disease	Mice	Increases the expression of adhesion molecules through cJUN/ATF2/JNK/cFos	[5, 31, 66]
Atherosclerosis	Mice	Leads to the secretion of pro-inflammatory cytokines (IL-6, TNF-α) and adhesion molecules (ICAM-1, VCAM-1) through NF-KB/AP-1 and MAPK/ERK/JNK/P38	[132, 104]
Hypertension	Human	Increases oxidative stress, and inflammation; activates the renin–angiotensin–aldosterone system; dysregulates production of vasoconstrictor NO and causes platelet aggregation through PI3K/AKT/MAPK and NO-cGMP-PKG signaling pathways	[5, 133]
Thrombosis	Mice	Dysregulates the expression of VWF, Enhances platelet adhesion and activation through SYK/FYN/PI3K/PKC and PLCɣ/DAG-IP3/PKC	[105, 134]
Stroke	Rat/human platelets/human	Interrupts the blood flow; leads to platelet activation through PI3K/AKT/MAPK; induces the secretion of inflammation through NF-KB signaling Activates oxidative stress and brain damage through AKT/FOXO3	[135, 136, 100]
Diabetes mellitus	Mice	Induces oxidative stress and AGEs formation; activates NADPH oxidase and PKC, affects ca2 + levels	[106, 137]
Pulmonary arterial hypertension	Mice	Aberrant TGF-β/ALK/smad and TGFB/BMP signaling contributes to ED, proliferation of smooth muscle cells, and vascular remodeling Overexpression of Endothelin-1/caveolin-1 by ECs promotes vasoconstriction	[138–140]

NF-KB nuclear factor kappa-light-chain-enhancer of activated B cells, *VCAM-1* vascular cell adhesion molecule 1, *NO* nitric oxide, *TGF-β* transforming growth factor-β, *NADPH* nicotinamide adenine dinucleotide phosphate, *ECs* endothelial cells, *ICAM-1* intercellular adhesion molecule 1, *TNF-α* tumor necrosis factor-α, *ED* endothelial dysfunction

Platelet glycoproteins are impressive in the adhesion, activation, and aggregation of platelets when they come into contact with various active factors. Platelets use these glycoproteins to attach themselves to ECs, other cells, and also other platelets. For example, platelets are associated with thrombin and VWF in high-flux shear using GPIb/IX. Activation of these glycoproteins activates members of the SRC and Rac1 kinase family, leading to the activation of PI3K/AKT, MAPK (ERK1/2/P38), and LIM kinase 1 (LIMK1); this process finally leads to platelet granule release and production of thromboxane. In addition to the above factors, Bruton's tyrosine kinase (Btk) and ADAP are also involved in this process. During platelet adhesion to collagen by GPVI, the ITAM/SFK/PI3K/Tec/Btk/PKC signaling pathway is activated, which also plays an important role in granule secretion. Besides activating platelets, ITAM is also involved in activating the leukocytes [40].

Inflammation-related pathways are initiated following the release of endogenous and exogenous mediators and result in platelet activation via various receptors, including TLRs and NLRs. TLR2, TLR4/MD-2, TLR4/MYD88, TLR9, and TIM3 play the most important role in the pathway of pro-inflammatory cytokines production. In addition, various replication factors within this signaling pathway, such as ERK1,2 and P38 MAPK are affected and alter gene expression [41]. NF-kB and interferon regulatory factor 3 (IRF-3) are of the important pathways. The binding of the ligand to TLR4 triggers the recruitment of various adapter proteins including TRIF/MYD88/TIRAP/TRAM/SARM and stimulates signaling pathways such as TBK-1/IRAK-1/JNKs/MAPK/TRAF/IRF3/NF-kB, leading to the induction of different inflammatory responses. Inflammatory pathways, cytokine production, and CD62P expression are regulated by the HMGB1/RAGE/NF-kB axis and the inflammation-related cGMP-cGKI/TLR4 pathways. Inflammatory mediators activate the NF-kB by inhibiting the IKB-alpha [13, 26, 35, 42–45].

In contrast to the HMGB1-RAGE NF-kB axis, the SIRT1/HMGB1/NF-kB axis represses pathways that lead to inflammation and SIRT1 blocks the HMGB1 to prevent inflammation. Controlling this pathway can be considered a therapeutic target to reduce inflammation and prevent ED [46–48]. NOD2 facilitates aggregation and thrombus formation by activating the MYD88/MAPK and NO-cGMP-PKG pathways [40].

In addition to the mediators mentioned, several miRNAs are also involved in ED. The expression of miR-92a under atheropronous conditions is regulated by STAT3/CMYC and targets the SIRT1/ITGA5/KLF2/KLF4/NF-kB genes, resulting in the recruitment of monocytes into ECs [49, 50]. miR-126 regulated by ETS1/2 affects the regulation of adhesion molecule expression and vascular integrity. It inhibits the production of VCAM1 on ECs by targeting the SPRED1/PIK3R2/pak1/SDF1. As levels of this miRNA decrease, VCAM1 expression increases on ECs in the presence of high levels of TNF-α [51]. In contrast to the above cases, miRNA-10a negatively regulates the MAP3K7 and ß-TRC pathways leading to NF-kB. In the atherothrombotic environment,

miRNA-10a expression decreases while MAP3K7 and β-TRC expression increases (Fig. 1) [52].

In general, the activation of ECs and platelets, the production of inflammatory cytokines, the recruitment of inflammatory cells to the site of inflammation, and increased expression of adhesion molecules on ECs and other inflammatory cells contribute to the development of ED. The interplay of these factors can lead to microvascular disturbances; if the process continues, the production of arterial thrombi and the risk of CVD increase (Table 2).

Oxidative Stress and Endothelial Dysfunction

ROS are produced in response to endogenous and exogenous stimuli and are involved in inflammatory responses, vascular tone, platelet activation, and ED. They are generated in response to various mediators by activating different signaling pathways. For example, LPS induces an increase in ROS production through the LPS/TLR/NOX/MYD88/Rac signaling pathway. Cytokines such as TNF-α, IL-1ß, and growth factor like EGF activate the TNF-α/TNF-αR/TRADD/TRAF2/RIP, IL-1ß/IL-1ßr/NOX/MYD88/Rac, and EGF/EGFR/Grb2/SOC/ERK pathways, respectively; ultimately, it leads to the activation of the MAPK/ERK1/2, cPLA2, and PKC pathways [53–55]. Following this activation, the activity of the key enzyme NOX, which is crucial for ROS production increases.

LPS plays an important role in platelet activation and ED through the Akt/ERK1/2/PLA2 pathway upon binding to TLR. Inhibitors of PI3K, Akt, and ERK1/2 decrease during LPS stimulation, leading to increased ROS production and platelet activity. ROS, along with TNF-αfurther stimulates platelets and promotes the production of pro-inflammatory cytokines; it causes vascular damage and multi-organ damage [53, 54, 56, 57].

Different platelet agonists induce ROS production.. Platelet binding of GPVI/FCRɣ to collagen through SYK-dependent and SYK-independent pathways leads to ROS generation. Activation of NOX following the activation of TRAF4/LYN/SYK/Src/PKC/PLCɣ pathways increases ROS expression and TXA2 production. TXA2 upon binding to its receptors on the cell surface activates the SYK/Src/PKC/PLCɣ pathway and increases intracellular calcium levels and induces ROS production [58, 59]. The TRAF/P47PHOX/Hic5/Pyk2/NOX pathway, which is independent of SYK is responsible for ROS generation. Collagen binding to GPVI on platelets increases affinity and expression of GPIIb/IIIa. Along the PLCɣ2/B/CalDAG-GEFI/GTPase/rap1 axis, the expression of GPIIb/IIIa increases. Activation of PI3KC2α also activates the NOX complex and promotes $O^0_{2^-}$ production. This pathway is potentiated by PKC, MAPK, and ligand (agonists) interaction with GPαIIbß3, establishing a bridge between platelets.

Through outside-in signaling and activation of the PI3K/PDK1/AKT/GSK3 axis, it maintains clot stability and integrity. Thrombin binding to PAR1/4 (mainly PAR4) and GPIbα on the platelet surface activates FAK/P47PHOX, leading to NOX1 activation and increased ROS production. However, the activation of different pathways depends on the concentration of ROS generated; low ROS level activates the AKT/PKB in the short term, indicating an antioxidant role in this pathway [56, 58–65].

In addition to agonists and cytokines, various inflammatory mediators can induce the production of ROS. OX-LDL binding to CD36 on macrophages activates the SYK and SRC/PI3K/PKC/Ca2 + /PLA2 pathway, resulting in

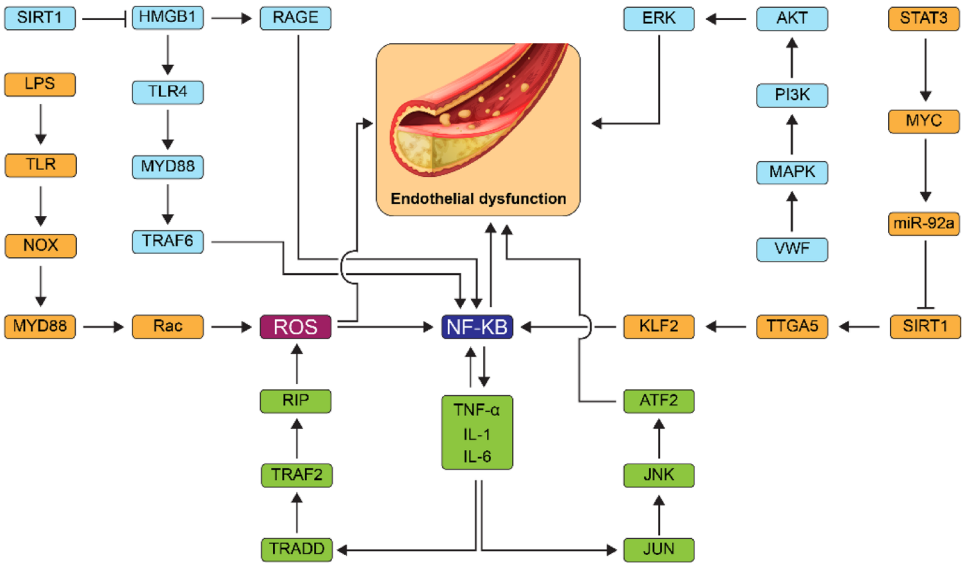

Fig. 1 The role of inflammation in ED. The main pathway in inflammation is NF-kB, which causes the production of inflammatory cytokines. In addition, the production of HMGB1 also affects NF-kB and causes inflammation. On the other hand, SIRT1 inhibits HMGB1. LPS: Lipopolysaccharide; TLR: Toll Like Receptor; ROS: Reactive Oxygen Species; TNFR1-Associated Death Domain Protein; Signal Transducer And Activator Of Transcription 3; HMGB1: High Mobility Group Box 1

increased ROS and TXA2 production. sCD40L/CD40 induces ROS production through the Akt/p38 MAPK axis with an effect on NOX [1, 53, 66, 67]. ROS activates NF-kB through various pathways. In one pathway, under stress conditions and in response to infectious agents, it is activated through the MEKK1/TAK1/IKBα/RelA/P50 pathway. In another pathway it is activated through the NIK/IKKα/RelB/P52 pathway, in response to CD40, lymphotoxin, and BAFF. Increased ROS inhibits IKß phosphorylation and disrupts the ubiquitination of factors in these pathways, ultimately leading to increased expression of NF-kB, ELK1, ATF2, vascular inflammation, increased production and secretion of pro-inflammatory cytokines, and ED [60, 68, 69].

ROS production during oxidative stress leads to changes in vascular tone and vascular function. Vascular changes, increased platelet activity, platelet aggregation, and ultimately inhibition of antioxidant pathways induce inflammation, apoptosis, increased vascular leakage, and ED [1, 45, 70].

Apoptosis and Endothelial Dysfunction

Apoptosis is a programmed cellular death that occurs through internal and external pathways. The internal pathway (mitochondrial) is triggered by cellular stress, while the external one is induced by ligand binding to cell surface receptors known as death receptors. Apoptosis in ECs can contribute to ED [71].

The main pathway initiated by ligand binding to receptors involves the production of ceramide by sphingomyelinase, formation of the DISC (Death-Inducing Signaling Complex), and the activation of caspase 8. In this pathway, ligands such as TNF-α, APO-1L, APO-3L, LT-α, FasL, and TRAIL bind to their respective receptors on the cell surface, leading to the recruitment of TRAF2/C-IAP/RIP-1/TRADD/FADD/CYLD and subsequently activating the TAK1 and NIK. This activation results in the activation of NF-kB, caspase 8, and effector caspases 3, 7, and 9 [72–74]. FasL and APO-1L upon binding to FAS and APO-1 receptors respectively, initiate apoptosis in ECs through the FADD/Cas-8 pathway, followed by DXX/JNK and ultimately RIP/RAIDD/Cas-2 induction. By binding to its receptor and influencing canonical and non-canonical NF-kB pathways, TNF-α plays an important role in apoptosis.

In the canonical pathway, after the inhibition of cIAPs by smac, cIAPs dissociate from the TRADD/FADD/TRAF2/RIPK1/PRO-Cas-8/cIAPs complex, and the FADD/RIPK1/Cas-8 complex activates Cas-3, leading to apoptosis. If the FADD/RIPK1/RIPK3/Cas-8 complex is formed, the pathway proceeds toward necroptosis. In the non-canonical pathway, upon TNF-α binding to its receptor and recruitment of TRAF2/TRADD/RIPK1, the formation of the FADD/RIPK1/Cas-8 complex occurs, leading to the activation of Cas-3 and apoptosis. In this pathway, NIK is separated from the TRAF2/TRAF3/cIAPs/NIK complex through ubiquitination and the inhibitory effect of SMAC on cIAPs. NIK then activates the NF-kB through the IKKa/RelB/P52 pathway, resulting in TNF-α secretion and amplification of the pathway by the produced TNF-α.

Additionally, TNF-α, FAS, and TRAIL activate ASK1 and JNK/CJUN, leading to the activation of P53 and increased production of BIM. P53 has various effects on ECs. It also activates caspase-2 by influencing the RIP/RAIDD/PIDD/Cas-2 complex. Furthermore, it leads to an increase in the expression of NUXA and PUMA. SEPT4/ATR serves as a major and important target of the P53 gene, primarily involved in the mitochondrial pathway of apoptosis. APO-3L by binding to DR3/WSL/TRAMP/LARD plays a role in apoptosis similar to TNF-α [75–80]. Under in vitro conditions, the interaction between LPS/TLR4 induces signaling through TRAF6/IRAK1/MYD88/TIRAP/JNK/cJUN and apoptosis [81].

The mitochondrial pathway is regulated by pro-apoptotic proteins of the BCL2 family, such as PUMA, BAD, BID, BIK, BIM, BMF, HRK, and NOXA (Fig. 2). These proteins bind to the mitochondrial membrane under stress conditions and induce the opening of the Permeability Transition Pore (PTP) in the mitochondrial membrane. The continuation of the mitochondrial apoptosis pathway involves pro-apoptotic proteins such as AIF, Smac/DIABLO, Omi/HtrA2, and cytochrome C. The release of cytochrome C from the pores formed in the mitochondria and its interaction with APAF-1 leads to the activation of procaspase 9 and the formation of the apoptosome complex. At the end of this process apoptosis happens in ECs and platelets [82, 83].

DNA damage activates ATM/ATR/Chk1/2 and leads to the activation of p53/PUMA and increased production of Bak/BAX. BAK and BAX contribute to the production of MOMP, resulting in the release of cytochrome C and Smac/DIABLO. In addition to the effector caspases, DNA damage activates P53 and the formation of the PIDD/RAID/Pro-Cas2 complex (PIDDosome) happens. It also activates caspase 2, Bid/tBid, and BAK/BAX, thereby activating the mitochondrial apoptosis pathway (Fig. 2) [77, 80, 84, 85].

In response to TGF-β, ATR is activated. ATR leads to the localization of P53 and induces the interaction between P53 and BCL-XL in the mitochondria. ATR induces apoptosis by promoting the degradation of the pro-survival protein BCL2 and inhibiting the XIAP. Additionally, TGF-β activates SMAD6/SMAD7 and directly affects signaling pathways such as ERK/P38 kinases and SAPK/JNKMAP, leading to the induction of apoptosis and regulation of BCL2 family proteins such as BID, BAK, and BAX in ECs. TGF-β also plays a role in the

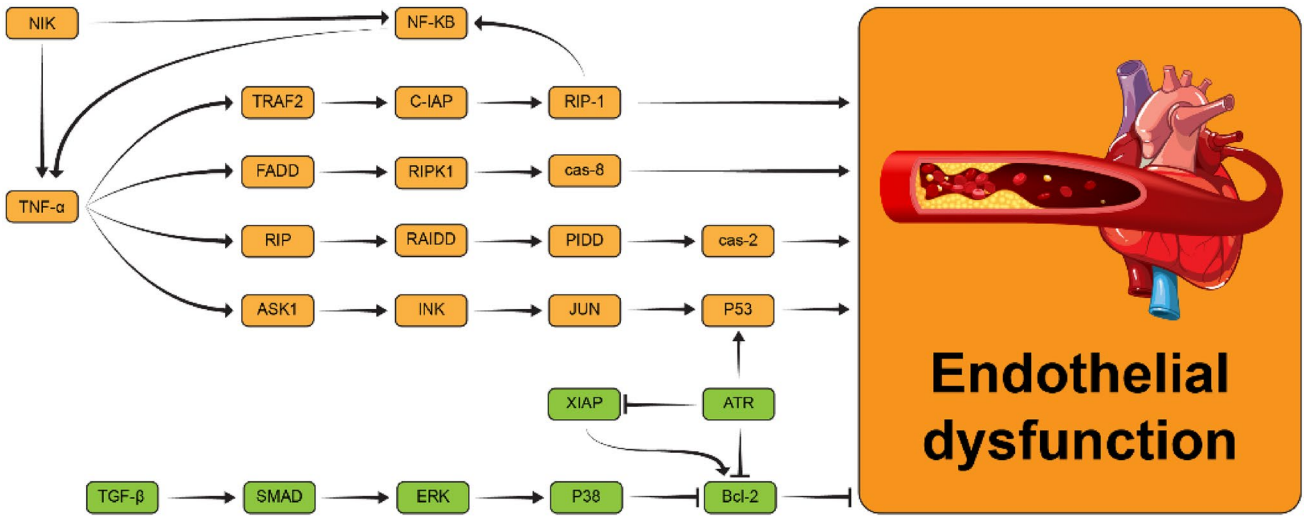

Fig. 2 The role of apoptosis in ED. The production of TNF-α leads to the activation of caspase 2 and 8 and leads to apoptosis. On the other hand, the production of TGF-β through the SMAD pathway leads to the expression of BCL-2 and inhibition of apoptosis. TGF-β: Tumor Growth Factor-β; TNF-α: Tumor Necrosis Factor-α; NF-kB: Nuclear Factor kappa-light-chain-enhancer of activated B; FADD: FAS-associated Death Domain Protein; PIDD: P53-induced protein with a death domain

inhibition of the AKT/PKB pathway and cell survival by increasing the expression of SHIP mRNA [76, 86, 87].

Oxidative stress induces apoptosis in cells. ROS production in the mitochondria leads to the recruitment of the apoptosome complex (AIF/CYTOCHROME C/APAF) and the activation of initiator caspases. ROS causes protein damage and facilitates apoptosis by activating the transcription factors such as FOXO/MAPK/NF-kB [54, 88]. In the presence of intracellular calcium levels increment and endoplasmic reticulum stress the JNK pathway is activated. It inhibits iTCH and c-FLIP, leading to the activation of caspase 8 and increased expression of tBid [85]. In addition to IAPs and FLIP, apoptosis regulators contribute to the inhibition of apoptosis in cells. For example, nitrosylated NO and the inactivation of caspases 1, 3, and 8 prevent apoptosis in ECs. Activation of cGMP signaling protein kinase leads to an increase in anti-apoptotic proteins and inhibits apoptosis. Up regulation of BCL2, BCL-XL, and HSP70 proteins also contributes to the inhibition of apoptosis in ECs [54].

In conditions of ED, due to endothelial damage, there is a decrease in NO, an increase in OX-LDL, and elevated production of inflammatory cytokines and AngII; these factors drive ECs into the apoptotic cycle. Lipid accumulation in vascular cells, particularly due to plaque rupture, pushes ECs toward apoptosis. During apoptosis, the vesicles produced contribute to further endothelial damages, leading to the progression of atherosclerosis along the pathway [1].

Non-invasive Diagnostic Techniques for Detection of Endothelial Dysfunction

Non-invasive diagnostic techniques, including flow-mediated dilation, imaging techniques (magnetic resonance angiography), and circulating biomarkers (NO, endothelin-1, ADMA, galectin-3, ghrelin, miRs) are integral for assessing vascular health and detecting early signs of ED and cardiovascular disease [89]. Flow-mediated dilation is a non-invasive ultrasound-based method that gauges the brachial artery's responsiveness to increased blood flow, and is indicative of endothelial function. Furthermore, pulse wave analysis or digital photoplethysmography are used for measurement of changes in vascular function especially in inflammations [90, 91]. The incorporation of circulating biomarkers provides a comprehensive view of biochemical changes in vessels and the endothelium. Non-invasive tests enable timely identification of ED and facilitate prompt interventions and therapeutic strategies for optimal vascular health outcomes [92].

Platelet-Related Biomarkers for Early Detection of Endothelial Dysfunction

Exploring platelet-related biomarkers offers a dual advantage by potentially identifying early signs of ED and deepening our understanding of endothelial health. Platelets, central to their dynamic interplay with the endothelium, exhibit functional changes that can serve as markers for the onset of ED. Key biomarkers associated with platelet activation, such as CD40L, P-selectin, and platelet-derived microparticles coupled with platelet reactivity tests and emerge as valuable tools for early ED detection. The secretion of anti- or pro-inflammatory factors such as IL-1β and RANTES (CD150) by platelets can be used as biomarkers [93, 94]. Elevated levels of these biomarkers act as potential signals, indicating not only underlying ED but also an elevated risk of CVD. Ongoing research in the field of platelet-related biomarkers not only sharpens our ability to detect platelet disorders and ED early on but also holds the potential to improve their effective management [94].

Platelet Function as a Predictor of Disease Progression and Potential Integration of Platelet Assessments in Clinical Practice

Platelet function, traditionally pivotal in hemostasis, assumes a prognostic role in diverse pathologies. Beyond their hemostatic function, platelets are increasingly recognized for their involvement in CVD, cancer, and inflammation. Emerging evidence underscores platelet activation and aggregation as the valuable prognostic markers in clinical settings. Elevated platelet activation correlates with an augmented risk of thrombosis in CVD, predicting adverse events such as myocardial infarction and stroke [66, 95]. Similarly, platelet activation in cancer is linked to tumor progression and reduced survival rates, impacting proliferation, invasion, and drug resistance [96, 97].

Assessing platelet function provides non-invasive, cost-effective insights into disease risk, with dynamic responsiveness to therapeutic interventions, facilitating treatment monitoring and individualized therapy. The examination of platelet function not only serves as a valuable prognostic tool, shedding light on potential disease risks, but also facilitates personalized treatment strategies; ultimately, it contributes improving patient outcomes across a spectrum of clinical scenarios [98, 99].

ED occurs in various forms of cardiovascular diseases. Factors such as inflammation, platelet activation, oxidative stress, and different diseases contribute to the ECs damage, creating a foundation for CVD. Prevention and treatment of ED aim to promote endothelial regeneration and prevent further damages (Table 3) [1].

Prognostic Significance in Cardiovascular Events and Complications

Prognostication in cardiovascular medicine is vital for optimal patient care. Exploring novel biomarkers like platelet function, ECs progenitor, and genetic risk markers are

Table 3 Summary of the drugs for treating ED

Drug	Platelet factors	Mechanism	Ref.
Cangrelor (Kengreal)	ADP receptor inhibitor/blocks the P2Y12 signaling pathway PI3K/Rab1b/AKT and PKA	Activates adenylyl cyclase by upregulating GαS protein levels and regulates PI3K/Rab1b/AKT and PKA signaling pathway	[141–143]
Tirofiban (Aggrastat)	Glycoprotein IIB/IIIA inhibitor	Blocks Platelet Adhesion to Fibrin through PI3K/PDK1/AKT/GSK3 axis	[144]
Kaempferol	anti-thrombotic and anti-platelet activation	Inhibits thrombin and factor X activation, formation of fibrin and blood clots, and collagen and epinephrine-induced platelet activation by activation of (ERK) 1/2, p38, JNK 1/2, and PI3K/PKB (AKT)	[145]
Cilostazol	Inhibits the platelet aggregation and P2Y12 signaling both in vitro and ex vivo/inhibits phosphodiesterase III in platelets	inhibits the platelet aggregation induced by collagen, ADP, epinephrine, and arachidonic acid by regulating cAMP/PKA/VASP	[146, 114]
NSAIDs	inhibit platelet cyclooxygenase, block the formation of thromboxane A2 in platelets	Impairs platelet aggregation induced by thromboxane A2/anti-inflammatory and anti-thrombotic role	[147]
Vorapaxar (Zontivity)	inhibitor of PAR-1 (thrombin receptor) and granule release and integrin activation	Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation through regulation of PI3K/AKT/ERK1/2block platelet activation and clot formation	[148]

ADP adenosine diphosphate, *PI3K* phosphoinositide 3-kinase, *JNK* c-Jun N-terminal kinase, *NSAIDs* non-steroidal anti-inflammatory drugs, *PAR-1* protease-activated receptor-1

of prognostic factors. Elevated platelet activation signals heighten CVD risk and propose its utility as a valuable prognostic marker. Techniques for platelet function assessment include aggregation assays and flow cytometry. Integrating these markers into clinical practice holds the potential to identify high-risk individuals early, enabling personalized treatment. Ongoing research is essential to validate their prognostic value and develop effective interventions for those at elevated CVD risk [100–103].

Targeting Platelet-Related Pathways for Endothelial Dysfunction Management

Platelets, not only crucial in hemostasis and thrombosis but contributors to ED. They initiate thrombus formation and inflict endothelial damage through adhesion and aggregation mechanisms mediated by surface receptors and adhesion molecules. Targeting platelet-related pathways emerges as a promising strategy for managing ED and reducing CVD risk. The judicious use of antiplatelet agents and anti-inflammatory therapies can effectively modulate platelet-endothelium interactions, foster vascular repair, and improve overall cardiovascular health [104–106].

Antiplatelet agents like aspirin, P2Y12 inhibitors, and direct thrombin inhibitors offer a promising therapeutic avenue by effectively curbing platelet activation and aggregation. They alleviate endothelial injury and enhance endothelial function [106–108]. Furthermore, platelets release inflammatory mediators exacerbating endothelial inflammation and dysfunction. Anti-inflammatory therapies such as Statins and Colchicine demonstrate efficacy in modulating platelet-derived inflammatory mediators, fostering endothelial repair, and enhancing vascular function [104, 109, 110].

Anti-Platelet Therapy

Platelets are axial cells in ED. By inhibiting various receptors and signaling pathways within platelets, the activation and aggregation of platelets can be prevented. One important receptor is the thrombin-activated protease-activated receptors (PARs). By inhibiting the binding of thrombin and blocking the signaling through PAR1 and PAR4 receptors, such as the PI3K/AKT/NO/cGMP axis, PLCB/IP3/DAG axis, and the Ras/Raf/P38/IKKB/PKA/ERK/PLA2/TXA2 axis with drugs like SCH 530348 platelet activation and aggregation and granule release can be inhibited [111, 112].

Inhibitors of ADP receptors (P2Y1 and P2Y12) such as Ticagrelor, Elinogrel, Ticlopidine, Clopidogrel, and Prasugrel inhibit the activation of GPIIB/IIIa integrin and platelet aggregation. They achieve this by affecting the Giα/Adenylate cyclases/cAMP/PKA/VASP axis and Giβγ/PI3K/Rab1b/PKB/AKT axis. These drugs also prevent platelet activation, aggregation, and shape change by inhibiting the Gq/PLC/IP3-DAG/PKC/Ca2 + axis. Glycoprotein inhibitors, particularly GPIIb/IIIa inhibitors like Abciximab and Eptifibatide prevent platelet aggregation [111–113]. It is said that GPIb/IX/V inhibitors like Caplacizumab inhibits the receptor through the SFK/Rac1/PI3K/AKT/PKG/MAPK pathway by binding to the A1 domain of VWF,, thereby preventing granule release and TXA2 production [107, 108].

Dipyridamole inhibits phosphodiesterase (PDE) and increases adenosine and cAMP levels in platelets. It prevents platelet activation via the mentioned mechanism. It also inhibits PDE in ECs, resulting in increased production of PGI2 and cGMP; ultimately, it leads to increased NO production and vasodilation in blood vessels [111, 114, 115]. Cilostazol by inhibiting the PDEIII and increasing the cAMP/PKA/VASP also prevents platelet activation [111, 114].

Anti-inflammatory and Anti-oxidant Therapy

Aspirin and Ibuprofen prevent the production of prostaglandin H2 and TXA2 by inhibiting the COX1 [26]. Inhibition pathways leading to the production of pro-inflammatory cytokines such as TNF, IL-6, and IL-1 can also prevent inflammation and ED. Tocilizumab, an inhibitor of IL-6 production, inhibits the IL-6R and gp130 and leads to the production of complexes such as SOCS1/JAK and SOCS3/gp130. They prevent the activation of JAK/STAT3 and JAK/SHP2/MAPK [66, 116]. Drugs such as Infliximab, Etanercept, Adalimumab, and Golimumab inhibit signaling pathways like RIP1/RIP3/AKT induced by TNF-α, preventing platelet activation, aggregation, and ultimately inflammation [79, 117, 118].

Antioxidant drugs by reducing the production of ROS particularly in platelets can prevent platelet activation and ED. Cinnamtannin B1 inhibits ROS production in platelets, thereby preventing platelet activation. Z-Lig, acting as an inducer for Nrf2 signaling, reduces lipid peroxidation and OX-LDL-induced elevation of ROS levels, thus preventing atherosclerosis and ED in individuals with hyperlipidemia [109].

Colchicine, known as an anti-inflammatory drug, inhibits the activation of NLRP3, caspase 1, inflammasome, and the NF-kB/IKB axis, thereby preventing the production of pro-inflammatory cytokines such as IL-1 and IL-18. It is said that cholesterol crystals and OX-LDL are involved in the activation of the inflammasome complex and contribute to ED and atherosclerosis. Colchicine prevents cytoskeleton rearrangement, shape change, and platelet aggregation by binding to B-Tubulin [66, 119].

Lipid-Lowering Therapy

Statins are considered lipid-lowering drugs. By inhibiting the AKT/mTOR/4E-BP1, they lead to a decrease in the expression of AP-1, NF-KB, and HMG-CoA reductase enzyme, and an increase in the expression of KLF2, thereby preventing cell migration, proliferation, and survival. Statins have an indirect inhibitory effect on the KRAS/MAPK/RAC/RHO pathway. They also have various effects on platelets [119]. By downregulating PPAR alpha and PPAR gamma, as well as PAR1, which is essential for platelet aggregation and activation, a reduction happens in the expression of AKT/ERK/MAPK/P38/PKC and cytosolic calcium; also an increase in cAMP as a function of Statins leads to decreased platelet activity and platelet adhesion.

Statins, through their effects on platelet phospholipase A2, TXA2, and the MAPK pathway, reduce intracellular calcium in platelets, COX1 activity, and prostaglandin production. By affecting NADPH oxidase, particularly the NOX2 subunit, they decrease the expression of PKC/P47phox, the production of ROS, isoprostanes, and glycoprotein IIb/IIIa, while increasing the production of NO.

Platelet recruitment and adhesion, which are influenced by the expression of CD40L and CD62L are reduced by Statins. They cause upregulation of endothelial nitric oxide synthase (eNOS) activity and downregulation of cyclooxygenase-1 (COX1) activity, as well as receptors for OX-LDL such as CD36 and LOX1. Statins also induce apoptosis in platelets through modulation of BCL2, caspases, and the TNF pathway [1, 66, 120–122].

Personalized Medicine Approaches Based on Platelet Function

In healthcare, personalized medicine transforms treatment by tailoring it to an individual's unique characteristics. In cardiovascular care, platelet function, pivotal in blood clot formation, emerges as a promising focus for personalized approaches. Variability in platelet function significantly influences cardiovascular event risk [123]. Personalized medicine seeks to identify high platelet reactivity as a notable risk factor. Assessments, such as platelet aggregation assays and flow cytometry, alongside genetic testing inform tailored antiplatelet therapy regimens. This individualized approach optimizes treatment efficacy while minimizing adverse effects. Furthermore, data-driven tools and novel technologies in addressing the shortcomings of healthcare systems, patient-centric care, preventive measures, and healthcare accessibility lead to advances in personalized medicine. Ongoing research into novel antiplatelet therapies, targeting specific platelet signaling pathways holds the potential for further advancements in personalized cardiovascular care [124, 125].

Case Studies and Clinical Trials Assessing Platelet-Related Markers in Patients

The role of platelets in ED and the interaction with ECs are not fully defined, however, treatments based on the interaction between them have been designed. On the other hand, it is known that platelets release a series of markers during activation and aggregation. Recent evidence has shown that these markers can be used to evaluate and manage patients. On the other hand, the use of some drugs can decrease the

Table 4 Summary of some studies related platelet markers in disease

Type of study	Disease	Results	Ref.
Case control	ACS	Results showed that level of Platelet factor 4, beta-thromboglobulin, platelet/endothelial cell adhesion molecule-1, P-selectin, thromboxane, prostacyclin, vascular cell adhesion molecule-1, and E-selectin increased in ACS patients compare with control group	[149]
Clinical trial	Coronary disease	Results showed that increased of MRP-8/14 and soluble P-selectin markers associated with MACE in patients under PCI	[150]
Clinical trial	CAD	Results showed that P-selectin expression reduce in patients treatment with clopidogrel	[151]
Case control	T2DM	Results showed that increased ADP related active platelet and cause CVD in T2DM patients	[152]
Case series	spontaneous venous thromboembolism	There is a connection between the levels of soluble P-selectin and vWF with ED and venous thromboembolism that was statistically significant	[153]
Clinical trial	STEMI	Atorvastatin is linked to enhanced endothelial function and inhibition of platelet activation and aggregation with ADP	[154]

ACS acute coronary syndromes, *MRP-8/14* myeloid-related protein-8/14, *MACE* major adverse cardiovascular events, *PCI* percutaneous coronary intervention, *CAD* coronary artery disease, *T2DM* type 2 diabetes mellitus, *CVD* cardiovascular disease, *ADP* adenosine diphosphate, *vWF* von Willebrand factor, *STEMI* ST segment elevated myocardial infarction

level of platelet markers in patients after treatment. The effect of drugs on the level of platelet markers in various diseases especially CVD are also studied\. For example, it has been shown that the use of platelet antagonists such as Aspirin reduces the level of p-selectin (Table 4).

Conclusion and Future Perspective

ED is one of the impressive disorders in the pathogenesis of CVD. Platelet activation is known as the main factor in ED. Platelet is activated due to interaction with ECs and causes the production of inflammatory mediators. In addition to activating the inflammatory pathways, these mediators cause apoptosis and oxidative stress. In addition, some genes and molecular pathways have a dual role and impress the occurrence or inhibition of ED by platelets.

Platelet evaluation in CVD patients as a diagnostic factor can be effective and economical. Increased level of markers related to platelet activation including p-selectin in CVD patients can help in identifying high risk patients. An increase in markers in patients can be associated with a poor prognosis and exacerbation of clinical symptoms. In addition to diagnosis, treatment design based on platelets can also be considered. Actually, personalization medicine and target therapy can be used to treat patients in order to prevent ED. Measuring the level of platelet markers and checking their activation by related markers is suitable for cost-effectiveness in responding to the treatment.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent Form This study does not use animal or human samples.

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