Review

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Abstract: Inflammation has a critical role in the development and progression of atherosclerosis. On the molecular level, inflammatory pathways negatively impact endothelial barrier properties and thus tissue homeostasis. Conformational changes and destruction of the glycocalyx further promote proinflammatory pathways also contributing to procoagulability and a prothrombotic state. In addition, changes in the extracellular matrix composition lead to (peri-)vascular remodelling and alterations of the vessel wall, e.g., aneurysm formation. Moreover, progressive fibrosis leads to reduced tissue perfusion due to loss of functional capillaries. The present review aims at discussing molecular and clinical effects of inflammatory processes on the micro- and microvasculature with a focus on peripheral artery disease.

Keywords: atherosclerosis; inflammation; peripheral artery disease; glycocalyx; endothelial dysfunction;

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality world-wide and accounts for millions of deaths globally [1]. CVD is associated with a significant impairment of quality of life and the prevalence of main manifestations, such as coronary artery disease (CAD), cerebrovascular disease and peripheral artery disease (PAD) has been increasing steadily over the last two decades [1, 2].

Atherosclerosis is considered the major driver of CVD. Formerly, atherosclerosis was thought of as a process primarily related to dyslipidaemia and the deposition of triglycerides and cholesterol [3]. However, besides lipid accumulation, more recent insights into the pathogenesis of atherosclerosis increasingly emphasise the role of inflammation and endothelial dysfunction as major drivers of atherogenesis [3–8]. Moreover, the mentioned pathomechanisms depend on each other and amplify their response. Indeed, a central element initiating prothrombotic processes and herein atherogenesis remains glycocalyx destruction due to inflammatory processes [9]. In PAD, inflammation is also

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triggered by ischaemia-reperfusion (I/R) injury promoting increased production of reactive oxygen species (ROS) [10], which contribute to endothelial dysfunction and microvascular pathology [11].

Chronic autoimmune diseases, which are associated with significantly elevated levels of systemic inflammation, e.g., rheumatoid arthritis, systemic lupus erythematosus, anti-phospholipid syndrome and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), are associated with markedly increased prevalence of CVD [12–14]. Conversely, there is accumulating evidence that some agents with anti-inflammatory characteristics reduce cardiovascular risk significantly [15, 16]. Canakinumab, a monoclonal antibody targeting interleukin (IL)-1β [15], and colchicine, which attenuates leukocyte responsiveness by inhibition of tubulin polymerisation [16, 17] have been shown to improve outcome in CAD in randomized controlled trials [15, 16]. While not yet implemented in regular clinical practice, there is increasing awareness for anti-inflammatory therapy in secondary prevention of CVD in the current guidelines [18].

The single most effective prevention of CVD, smoking cessation, lowers levels of systemic inflammation as assessed utilising biomarkers of inflammation and oxidative damage [19, 20]. Statins, which are the most widely established agents for lipid control, also have been shown to exert significant immuno-modulatory influence by inhibiting the nuclear factor kappa B (NF-κB) pathway and decreasing the expression of toll-like receptors (TLR) [21]. Smoking cessation and statins are both recommended in all patients with CVD [22].

Formation of aneurysms is also discussed to be linked to atherosclerosis. Recently, the role of leukocytes and especially neutrophils for development of aneurysms has been revisited [23, 24]. Activation of matrix metalloproteinases (MMP), degradation of extracellular matrix (ECM), smooth muscle apoptosis and oxidative stress all contribute to aneurysm formation and are mediated by cytokines secreted by leukocytes [23, 25]. Interestingly, atherosclerosis and aneurysm formation do not always occur at the same locations. While the abdominal aorta, an area of predilection for aneurysm formation, is also prone to atherosclerosis, the external iliac artery, a common location for significant atherosclerosis, is very seldomly involved in the formation of aneurysms. Which cellular and non-cellular processes discern these two locations is currently unclear, however, the different embryologic origin of these vessels may be responsible for varying susceptibility to atherosclerosis and aneurysm formation, respectively [24].

This review aims to describe inflammatory pathomechanisms implicated in atherosclerotic processes of the macro- and microvasculature, their determinants and implications for interactions with the endothelium, leukocytes and non-cellular components involved in vascular homeostasis. In addition, therapeutic applications of anti-inflammatory concepts for the management of PAD are discussed.

2. Pathophysiology

2.1. Inflammation and endothelial dysfunction

Endothelial and vessel homeostasis is to a wide extent ensured by an intact glycocalyx coverage [26]. The endothelial glycocalyx is located at the luminal side of the cells and consists of membrane-bound proteoglycans and, together with adsorbed proteins, forms the endothelial surface layer [27]. Its components exert significant influence on the interactions between the blood and the endothelium, including rolling and diapedesis of leukocytes [28], platelet adhesion and activation [29], interaction with pro-coagulatory proteins [27], endothelial permeability [30], and the regulation of vascular tone [31].

Dysfunction and degradation of the endothelial glycocalyx allows low-density lipoprotein (LDL) to accumulate in the endothelial wall [32]. Following aggregation, LDL is oxidised (oxLDL) and subsequently phagocytosed by macrophages, which transform into foam cells and thereby initiate the progressive process of atherogenesis [32]. In turn, the integrity of the endothelial glycocalyx is disturbed by vascular inflammation, therefore creating a vicious cycle of endothelial dysfunction, inflammation and progression of atherosclerosis [33].

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The components of the glycocalyx also play a major role in the modulation of thromboinflammatory pathways [9, 34]. Importantly, the glycocalyx barrier does not only cover endothelial cells, but functions as a protective barrier exhibiting steric and charge hindrance on blood components such as macrophages, erythrocytes, microspheres, tumour cells, and microbes [35, 36]. Similarly, neutrophils have been demonstrated to express syndecan-1 and syndecan-4, hyaluronan, serglycin and cluster of differentiation (CD) 44 in their surface layer [37]. These molecules are essential components of both the endothelial as well as the neutrophil surface layer and are thought to regulate neutrophil rolling and recruitment [37]. Modifications to the neutrophil surface layer, including shedding of the glycocalyx and formation of microvilli, are though to regulate leukocyte behaviour by exposing receptor proteins and promoting leukocyte activation [36, 38]. However, the exact interactions of the endothelial and the neutrophil surface layers remain to be completely elucidated [37].

Macrophage activation after phagocytosis may lead to macrophage extracellular trap (MET) formation, but the process might be dependent on the recognized pathogen [39, 40]. On the other hand, inflammation triggers leukocyte activation, promoting neutrophil- and monocyte- platelet aggregate formation [41, 42]. The process is perpetuated by ETosis and enhanced oxidative stress [43–45].

Moreover, activated platelets lead to a thrombin burst, and further platelet activation through alternative signalling pathways [9]. The latter also include damage-associated signalling through TLRs [34].

Some risk factors commonly associated with atherosclerosis and thromboembolic events are also thought to impair the integrity of the glycocalyx [33]. Chronic diseases, such as diabetes mellitus (DM) and chronic kidney disease, are often linked to inflammatory processes, and promote glycocalyx disturbance [33, 46–52].

Several pathophysiologic properties link atherosclerosis and DM [53]. First, DM-associated dyslipidaemia leads to increased triglyceride-rich lipoproteins (TLP) in serum [53]. Under physiologic circumstances, insulin regulates hepatic lipoprotein and triglyceride production, however, in DM, these regulatory properties are diminished due to hepatic insulin resistance [53]. It has been demonstrated that not only the prevalence of lipoproteins, but also their modifications can be considered essential for atherogenesis [54]. In a murine model of DM, the injection of LDL from diabetic patients resulted in a fourfold increase in arterial wall LDL retention compared to injected LDL from clinically healthy, non-diabetic control subjects [54].

Advanced glycation end-products (AGEs) are formed in patients with prolonged hyperglycaemia by non-enzymatic post-translational modification of proteins, lipids and nucleic acids [55]. AGEs promote inflammation by facilitating the activation of the endothelium, increasing cytokine release from macrophages, and ultimately enhancing ROS production [10]. The latter are also key in I/R injury in PAD and contribute to inflammatory processes and endothelial dysfunction [10]. During I/R injury NO bioavailability is decreased and ROS activate the nucleotide oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 (NLRP3) inflammasomes, promote mitochondrial fission and endothelial microvesicle release as well as change connexin/pannexin signalling [56]. As a result of the oxidative stress, I/R impairs capillary perfusion [56].

CVD including PAD is further linked to a reduced endothelial progenitor cell (EPC) number [57]. The inflammatory processes induced by uncontrolled oxidative stress also modify EPC function and thus impair endothelial regenerative potential [58]. EPCs have been shown to express gene transcripts coding for TLR 1-6, including the TLR-4 co-receptor CD14, TLR 8-10 and the TLR adaptor molecule myeloid differentiation factor 88 (MyD88) [59]. Hence, during inflammation, EPCs might also be modulated by TLR signalling pathways such as TLR-4 mediated caspase 3 signalling promoting EPC apoptosis [58, 60]. In addition, ROS formation triggers extracellular trap formation by different cells of the immune system such as neutrophils, eosinophiles, macrophages and mast cells, hereby influencing coagulability and vascular perfusion [34, 61].

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Corona virus disease 2019 (COVID-19), which increases the risk of thromboembolic events during and after the infection [62], is also thought to impair the regular functioning of the glycocalyx [9, 63, 64]. The degeneration of the glycocalyx is mediated by a complex interaction of cellular and non-cellular factors, but is mainly driven by infection of endothelial cells by severe acute respiratory distress syndrome coronavirus type 2 (SARS-CoV-2) [65]. Subsequent endothelial inflammation and damage leads to disintegration of the glycocalyx, collagen exposure and, thereupon, activation of leukocytes and platelets [66]. These processes are thought to lead to an environment of thromboinflammation, which may ultimately trigger atherogenic processes and promote organ dysfunction [9, 64].

2.2. Microparticles

Microparticles (MP) are cell-membrane derived vesicles which are shed by, among others, endothelial cells, leukocytes, monocytes and platelets [67] at an increased rate upon cell activation due to oxidative injury, shear stress and apoptosis [68]. MPs can carry a plethora of cell-specific proteins and molecules such as receptors, lipids and both mitochondrial desoxyribonucleic acid (DNA) and messenger ribonucleic acid (mRNA) [67]. MPs are thought to contribute to cell-cell communication as their surface is representative of the originator cell [67, 69, 70]. Novel diagnostic and therapeutic applications are currently under investigation and first results seem promising [71]. MP composition has been demonstrated to be altered in inflammatory conditions, where endothelial cells stimulated with tumour necrosis factor (TNF)-α secrete MPs rich in pro-inflammatory cytokines and chemokines [72] Intercellular signalling via MPs is therefore considered to exert a significant regulatory role in vascular homeostasis [73, 74].

Under physiologic conditions, endothelial nitric oxide (NO) synthetase maintains vascular homeostasis by regulation of vascular tone and inhibition of platelet function through NO [75]. In conditions associated with CVD e.g., hypertension, tobacco abuse and dyslipidaemia, the endothelial production of NO is drastically reduced leading to increased platelet activation and leukocyte diapedesis [75–77].

As described above, endothelial dysfunction is generally considered the earliest stage of atherogenesis [78]. ROS are associated with inflammatory conditions [79] and are considered one of the most significant causes of endothelial dysfunction [80]. MPs aggravate ROS production [81, 82], but ROS in turn stimulate MP formation [83], potentially creating a vicious cycle of self-sustained pro-atherogenic stimuli. Importantly, MPs can not only induce the release of pro-inflammatory cytokines and ROS, but in fact act as a vehicle of transfer between donor and recipient cells thus potentiating pro-inflammatory effects [84].

Especially MPs derived from endothelial cells (EMP) and platelets (PMP) disrupt endothelial function and impair endothelium-induced vasodilation [81, 82]. Formation of EMPs has been shown to correlate with carotid artery atherosclerotic plaque size in patients recovering from stroke [85] and promote inflammation [86]. Via regulation of macrophage function, adipose tissue derived MPs facilitate foam cell formation, herein being central in the progression of atherosclerosis [87].

2.3. Neutrophil extracellular traps

Neutrophil extracellular traps (NETs) - web-like structures consisting of cell-free DNA - are extruded from neutrophils upon activation during inflammatory processes and consist of chromatin, histones and neutrophil granule proteins [88, 89]. Previously, NETosis, which describes the process of neutrophils releasing NETs, was primarily regarded as a mechanism of the innate immune system to engulf and neutralise a wide range of extracellular pathogens including bacteria [88], viruses [90] and fungi [90]. However, NETosis is suggested to play a crucial role in inflammatory diseases including vasculitis [91], atherosclerosis and thrombosis [92].

There is increasing evidence that NETs contribute to endothelial dysfunction [93, 94], glycocalyx degradation [9] and atherosclerosis [92] by generation of ROS and concomitant release of neutrophil granule proteins associated with atherogenesis including neutrophil elastase and myeloperoxidase

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[95, 96]. Vice versa, both enzymes also play a crucial role in the induction of NETosis [97, 98]. Moreover, ROS stimulate the formation of pro-inflammatory MPs [83], Figure 1.

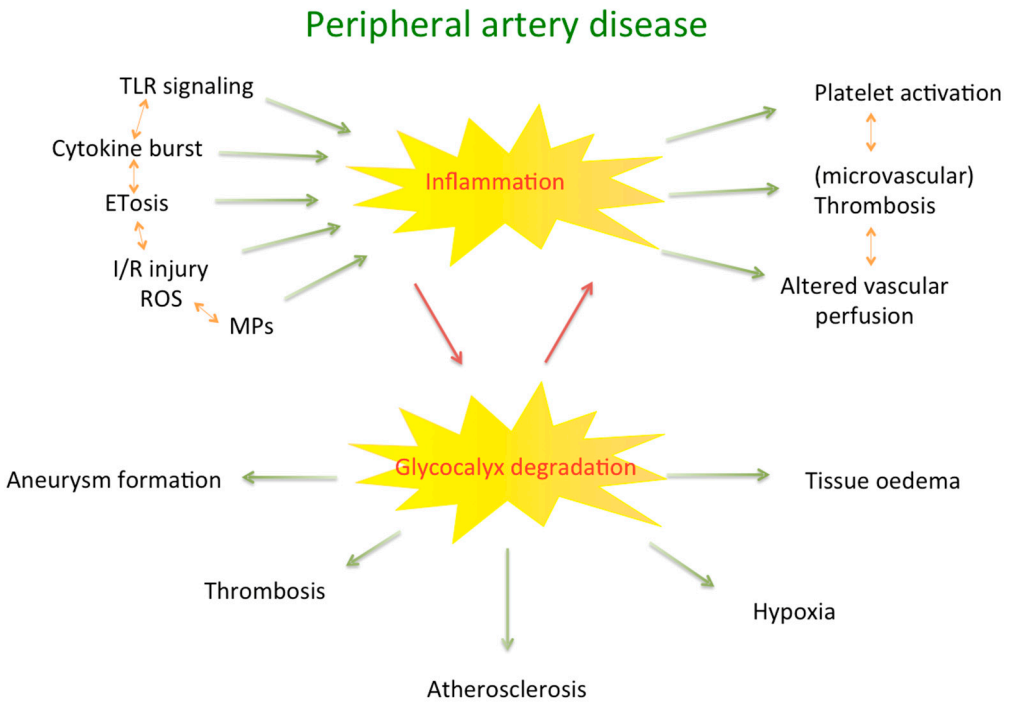

Figure 1. Pathophysiologic consequences of inflammation on the vasculature and adjacent tissue: Inflammatory processes promotes endothelial dysfunction by glycocalyx degradation, leading to altered vascular homeostasis [9]. The pathological processes influence each other perpetuating disease progression. ETosis, extracellular trap formation; I/R, ischaemia reperfusion injury; MPs, microparticles; ROS, reactive oxygen species; TLR, toll-like receptor.

In atherosclerosis, oxLDL is also a potent stimulus for NET formation. Awasthi et al. have shown that incubation of neutrophils with oxLDL leads to NETosis in a time- and concentration-dependent manner [99] oxLDL is likely to induce NETosis via TLR-2 and TLR-6 as their blockade resulted in significantly reduced NETosis [99]. Furthermore, the recognition of NETs promotes the production of an IL-1β precursor in macrophages and the subsequent release of mature IL-1β upon phagocytosis of oxLDL [100]. This in turn causes IL-17 production from T-cells [100]; IL-17 is a potent chemokine perpetuating the pro-atherogenic inflammatory environment [100]. In addition, oxidative stress induced by NET-associated enzymes including myeloperoxidase and NO synthetase is considered to promote oxidation of high-density lipoprotein (HDL), therefore rendering this inherently anti-atherosclerotic protein dysfunctional [101].

From a clinical perspective, NETs also offer relevant insight into the mechanisms of atherothrombosis [102, 103]. Activated neutrophils and NETs were detected in about 90% of thrombi from patients with acute myocardial infarction and NET load correlated with infarct size and resolution of ST-segment elevation [103].

2.4. The role of inflammation in aneurysm formation

The most common location of aortic aneurysms is the infrarenal segment of the abdominal aorta [104]. While often asymptomatic, abdominal aortic aneurysms (AAA) are associated with significant mortality. In the UK, ruptured AAAs account for 7.5 and 3.7 deaths per 100.000 for men and women, respectively, while in the Mediterranean, these numbers are closer to 1.0 – 2.8 per 100.000 per year [105].

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The presence of leukocytes [106, 107], enzymes degrading ECM in the aortic wall [108, 109] and excessive levels of inflammatory parameters [25] have been reported hallmarks of aneurysm formation. The risk factors associated with aneurysm formation are similar to those for atherosclerosis, namely, among others, male sex, dyslipidaemia and tobacco use [110, 111].

While DM is a common risk factor for atherogenesis [22], it is associated with a reduction of morbidity due to AAA by almost a third [112]. DM enhances atherosclerosis progression and vascular calcification [113, 114]. The latter accounts for a higher cardiovascular risk and higher mortality in diabetic patients and those with chronic kidney disease [115, 116].

The observed survival benefit in diabetic patients with AAA is not yet fully elucidated and may be attributed towards DM itself or concomitant metformin therapy [117] as randomised placebo-controlled trials investigating metformin-repurposing for the prevention of AAA formation and enlargement are still ongoing [118–120]. Furthermore, increased vascular calcification is linked to aortic aneurysmal wall stabilization and slower AAA progression [121].

The estimated rate of comorbidity of atherosclerosis and aneurysm formation is about 27% - 53% [122, 123]. Atherosclerosis and aneurysm formation are both increasingly regarded as inflammatory diseases, as leukocyte and platelet activation is a key factor for the pathogenesis of both disease entities [124–126]. AAA pathogenesis is characterised by infiltration of the aortic wall by neutrophils, macrophages and lymphocytes [127]. Subsequently, secreted enzymes, proteases and cytokines lead to ECM degradation, e.g., of collagen and elastin fibres, and an increased rate of apoptosis of smooth muscle cells promoting destruction and dilation of the vessel wall [128].

Macrophages are thought to play a decisive role in AAA formation [126]. Accumulation of macrophages during aneurysm formation can be observed in all three layers of the vessel wall, but is particularly pronounced in the adventitia and the intraluminal thrombus (ILT) [129, 130]. While the role of different subsets of macrophages in the stages of AAA development is not yet fully elucidated, it is hypothesised that bone-marrow derived macrophages extravasate into the aortic wall and contribute to inflammatory processes and early stages of AAA formation [126].

The recruitment of monocytes into the aortic wall has been shown to be largely dependent on monocyte chemotactic protein 1 (MCP-1) and IL-6 produced by aortic adventitial fibroblasts [131]. Tieu et al. have shown that recruited monocytes locally mature into macrophages, which in turn stimulate the activation of adjacent fibroblasts and the release of further pro-inflammatory cytokines, forming a vicious circle of macrophage-fibroblast activation [131, 132].

The pathways involved in AAA monocyte recruitment are also thought to play a decisive role in atherogenesis [133]. The infusion of angiotensin 2 in an apolipoprotein-E-deficient mouse model prone to atherosclerosis was not only shown to increase the severity of atherosclerotic lesions, but also promote AAA formation [134]. Upon stimulation by angiotensin 2, aortic adventitial fibroblasts release MCP-1 and IL-6, which cause monocyte recruitment, differentiation, and cytokine release [131, 132].

The chemokine receptor 2 (CCR-2) signal, which is induced by MCP-1, plays a central role in various inflammatory diseases including cancer and CVD [135]. Tieu et al. have demonstrated that the knock-out of CCR-2 resulted in significantly reduced adventitial fibroblast proliferation in a murine model of AAA formation [131]. Conversely, the transfer of CCR-2 positive monocytes resulted in restored proliferation and restored AAA formation [131]. The MCP-1/CCR-2 axis is thought to be crucial to the initiation of atherogenesis by promoting monocyte accumulation in atherosclerotic lesions [131, 132]. In addition, levels of MCP-1/CCR-2 expression are associated with plaque vulnerability [136].

The activation of TLR-2 and TLR-4 and their downstream signalling pathways including among others MyD88, NF-κB, and mitogen-activated protein kinase is also considered a relevant driver of both, aneurysm formation and atherosclerosis [34, 137, 138]. As a consequence, inhibition of the TLR-4/MyD88/NF-κB pathway by statins conveys anti-inflammatory and anti-atherosclerotic properties [21].

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Neutrophils are considered to be both regulators and effector cells of inflammation [139]. In the context of AAA formation, activated neutrophils contribute to chronic inflammation mainly by releasing ROS, NETs, histones and neutrophil granule proteins [140–142].

The formation of an ILT is frequently observed in progressive AAA and a risk factor for AAA rupture [143, 144]. An ILT with concomitant platelet activation contributes to inflammation, vessel remodelling, and ECM degradation [145]. Platelets activated in the context of ILT formation secrete pro-inflammatory cytokines and chemokines, which in turn stimulate leukocyte recruitment, activation and, ultimately, AAA progression [144–147].

Klopf et al. have reviewed various parameters including neutrophil-derived markers of inflammation, e.g., gelatinase-associated lipocalin [148, 149], neutrophil elastase [150], myeloperoxidase [151, 152], MMP [153] and NETs [154] as potential biomarkers for prognosis in AAA [25]. While the exact mechanisms, which lead to aortic wall inflammation and leukocyte recruitment are not yet fully elucidated, these findings illustrate the involved processes and may help establish a better understanding of both factors determining prognosis and potential new therapeutic targets in AAA [25].

Importantly, inflammatory processes evoked by different infections, e.g., those with Porphyromonas gingivalis, Epstein-Barr virus, cytomegalovirus or papillomavirus are also being discussed as potential promoter of local inflammation and risk factor for aneurysm formation [155, 156]. In fact, the presence of periodontal disease, with mainly Porphyromonas gingivalis [157], and the occurrence of periodontal bacteria in the bloodstream or in the vascular lesion is associated with AAA formation [158–160]. In patients with AAA, cytomegalovirus was detected about five times as often as in healthy volunteers and was associated with increased levels of pro-inflammatory TNF-α and higher rates of arterial hypertension and CAD [156, 161].

In addition to inflammatory conditions, aneurysms may also occur on the basis of pathogenic gene variants [162]. The variants best established generally concern structural proteins, e.g., procollagen type III α1, transforming growth factor β and fibrillin 1 as seen in Marfan syndrome [162].

2.5. Vasculitis

Vasculitides are a group of rare diseases characterised by auto-immune inflammation of blood vessels of various sizes [163]. The introduction of targeted immuno-modulatory agents has improved prognosis and reduced mortality due to exacerbated vasculitis or infection drastically [164]. In patients with vasculitis, CVD is now the most common cause of death [165, 166]. In addition, a chronic inflammatory state is independently associated with long-term mortality in patients with Raynaud's phenomenon [167].

Surrogate markers of endothelial dysfunction, e.g., endothelium-dependent dilation of the brachial artery or pulse-wave velocity, are increased in the context of AAV [168].

An acceleration of atherogenesis in patients with predominantly AAV has been previously demonstrated [169]. One study evaluated atherosclerotic plaque burden by means of ultrasound and found that, compared to a healthy control cohort, AAV patients had a significantly higher plaque burden in the abdominal aorta and the carotid and the femoral arteries [169]. It may be hypothesised that a continuous sub-clinical inflammatory state contributes to the acceleration of atherogenesis in these patients [170]. The shedding of the endothelial glycocalyx, endothelial dysfunction [171] with enhanced expression of leukocyte adhesion factors and leukocyte-diapedesis into the vessel wall promotes a pro-inflammatory and pro-coagulatory state [172, 173]. Furthermore, risk factors commonly associated with atherosclerosis are more prevalent in patients with AAV [171, 174].

Despite advances in immune-modulatory therapy, glucocorticoids, which are frequently used for induction therapy, are also associated with significant toxicity. Traditional risk factors for atherosclerosis, i.e., hypertension, hyperglycaemia and dyslipidaemia, are exacerbated in patients with frequent glucocorticoid intake [175]. Risk factor management for the prevention of cardiovascular events in these high-risk patients has been shown to be insufficient in many patients [14, 176].

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However, it must be noted that solid evidence of accelerated atherosclerosis has thus far only been established for Kawasaki's disease, Takayasu's arteritis, and, most prominently, AAV [170].

3. Current and novel therapeutic targets and strategies

Current guidelines in PAD emphasise on metabolic risk management including reduction of LDL levels, antiplatelet therapy, management of hypertension, glycaemic control, smoking cessation, and physical activity [177–181]. While some of these interventions also exert a positive influence on systemic and local levels of inflammation [20, 182, 183], therapeutic strategies, which directly intercept pro-inflammatory signalling pathways may be promising and are only beginning to be established [18]. In the following, we highlight some of the anti-inflammatory drugs and concepts.

3.1. Statins

The management of dyslipidaemia and specifically reduction of elevated levels of LDL has been a cornerstone of preventive cardiovascular medicine for many years. Statins, which inhibit the hepatic 3-hydroxy-3-methylglutaryl-coenzyme-A reductase and therefore impair cholesterol synthesis [184], are first line agents in treatment of CVD [18, 177].

However, there is accumulating evidence that the positive effects of statins on atherosclerosis go beyond LDL reduction [185]. In fact, statin therapy has been demonstrated to result in increased endothelial biosynthesis of NO with a positive effect on the vascular tone and platelet aggregation, and even plaque stabilisation or regression [185]. It has been suggested that statins also interfere with various endothelial adhesion molecules and therefore reduce leukocyte transmigration [186]. In patients with AAA, anti-inflammatory properties of simvastatin treatment were shown by reduced TNF-α as well as cyclosporine A levels and decreased amount of phosphorylated extracellular-signal regulated kinases (ERK) 1/2 [187, 188]. Furthermore, a significant difference in the concentration of MMPs and their inhibitors was observed in aneurysmal wall tissue and ILT [189]. In addition, simvastatin reduced monocyte tissue factor expression in response to LPS treatment in healthy volunteers [190].

Anti-inflammatory effects of statins also include the reduction c-reactive protein (CRP) concentration regardless of LDL levels.[191] Utilising fluorodeoxyglucose-positron emission tomography and computed tomography imaging, Tawakol et al. demonstrated a dose dependent anti-inflammatory effect of atorvastatin in patients with suspected or proven atherosclerosis [192]. In a recent meta-analysis of three randomised controlled trials in patients receiving statins, inflammation as assessed by CRP was a stronger predictor than LDL for cardiovascular events and death [193].

Beyond CVD, anti-inflammatory effects of statin therapy have also been demonstrated in other diseases. In chronic kidney disease, statins have resulted in levels of CRP [194] and in asthma, statins reduced both symptoms and biomarkers of inflammation [195].

3.2. Colchicine

Colchicine has been used for centuries for the treatment of inflammatory diseases including gout and familial Mediterranean fever [17]. The pharmacodynamics of colchicine are complex and they exert multiple effects on cellular signal transduction [17]. Colchicine has been demonstrated to reduce neutrophil chemotaxis by inhibition of the polymerisation of tubulin [196], reduced the expression of TNF-α [17, 197], and attenuated the exocytosis of neutrophil granules [17, 198]. Though less well elucidated, inhibitory effects of colchicine on the NLRP3 inflammasome have been observed and may inhibit the proliferation of smooth muscle cells as seen in the context of atherosclerosis [199].

The discovery of colchicine's pleiotropic effects on inflammation and atherosclerosis [200, 201] have led to the initiation of the phase III randomised placebo-controlled Colchicine Cardiovascular Outcomes Trial (COLCOT) trial [202]. Therein, 4745 patients who have suffered from myocardial infarction within the previous 30 months were randomised to receive either 0.5mg of colchicine or

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placebo. The risk for the primary end-point of cardiovascular death and serious cardiovascular events was reduced significantly in the colchicine group with a hazard ratio (HR) of 0.77 [202].

Based on these findings, the 2021 guidelines on CVD prevention by the European Society of Cardiology have now included a class IIb, level A recommendation to consider low-dose colchicine in secondary prevention of CVD [18].

In the future, colchicine may also be applied in the context of acute myocardial infarction. A recent study by Wang et al. showed that an infusion of colchicine-loaded nanoparticles subsequent to myocardial infarction reduced inflammation and myocardial infarct size by 45% on average [203]. These findings highlight the potential of colchicine as a promising anti-inflammatory agent in CVD, both in the acute as well as the chronic setting [204].

3.3. Eicosapentaenoic acid ethyl ester

Eicosapentaenoic acid ethyl ester and its purified prescription form icosapent ethyl (IPE) is an omega-3 fatty acid and has demonstrated several anti-inflammatory and anti-atherosclerotic properties [205]. In a large randomised placebo-controlled trial in patients with established CVD or several risk factors for the development of CVD and elevated triglyceride levels, the addition of IPE to standard statin treatment resulted in a highly significant risk reduction (HR 0.75) for ischaemic events and cardiovascular death when compared to placebo [206]. Furthermore, Budoff et al. documented a significant reduction in plaque size in patients with established CAD who received IPE when compared to a control group [207].

The exact mechanisms leading to these results remain to be established, especially as allocation to the IPE cohort in the Reduction of Cardiovascular Events with EPA - Intervention Trial (REDUCE-IT) trial did not result in a relevant reduction of inflammatory parameters [206]. In other trials, however, a high-sensitivity CRP and lipoprotein-associated phospholipase A2 lowering effect has been documented [205].

It is hypothesised that protective effects with regard to CVD may be attributed to the production of the bioactive IPE metabolites thromboxane A3 and prostacyclin, which exert antithrombotic influence on platelets and promote endothelial vasodilation [208]. In addition, IPE integration in cellular membranes also seems to have a biophysical anti-atherogenic effect [208].

The reduction in TLP, which is observed under large doses of IPE is also considered to have protective effects in CVD [209]. As these predominantly transport saturated fatty acids, which are thought to promote activation of the NLRP3 inflammasome, the reduction of TLP levels may also attenuate atherogenesis [208, 210].

3.4. Canakinumab and anakinra

The NLRP3 inflammasome is a pro-inflammatory signalling complex with pleotropic effects on cytokine release and cleavage of pro-interleukins [211]. Its activation is mediated by pathogen- and damage associated molecular patterns including, among others, TLR-2 and TLR-4 and results in activation of the IL-1 pathway [211]. In the context of atherogenesis, the NLRP3 inflammasome is activated by the recognition of oxLDL and cholesterol crystals via various receptors in macrophages. The subsequent release and formation of, among others, IL-1β results in activation of endothelial cells, promotes the expression of adhesion molecules and the proliferation of smooth muscle cells, and increases the production of MCP-1 [211].

The monoclonal antibody canakinumab, which targets IL-1β, and anakinra, an IL-1β receptor antagonist, are applied in various immune-mediated disorders [212], and were also considered potential therapeutics in atherosclerosis [213–216]. The pivotal Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease (CANTOS) trial has demonstrated a dose-dependent effect of canakinumab on systemic levels of inflammation in patients with previous myocardial infarction [15]. In this trial, 150mg of canakinumab every three months reduced the risk of adverse cardiovascular events (HR: 0.85) compared to placebo independently of lipid level lowering [15].

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3.5. Glucocorticoids

Glucocorticoids are analogues of endogenous cortisone and constitute a cornerstone of the treatment of various chronic inflammatory conditions [217]. Glucocorticoids exert their pleiotropic effects by binding to intracellular steroid-receptor proteins and regulate gene expression and cellular signalling [218].

However, long-term glucocorticoid excess is also associated with significant undesirable effects including hyperglycaemia [219], arterial hypertension [220], obesity [221], dyslipidaemia [222], and dysregulation of the coagulation cascade [223], all of which are considered well-established risk factors for atherogenesis and adverse cardiovascular events [218]. In patients diagnosed with Cushing's disease, which is characterised by endogenous overproduction of cortisone, a thickened intimal-medial layer and a lower systolic carotid artery lumen diameter [224] have been observed [225]. Furthermore, the ankle-brachial pressure index is elevated in Cushing's disease [226]. In large register studies, glucocorticoid prescription has been associated with significant and dose-dependent increases in the risk for CVD [225, 227–229].

3.6. Antidiabetic drugs

Several antidiabetic drugs have been proposed to promote anti-inflammatory pathways or inhibit pathways associated with inflammation [230].

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors and Glucagon-like peptide 1 (GLP-1) receptor agonists have originally been developed for the control of hyperglycaemia in patients with DM type 2. However, recent studies have proposed potential concomitant anti-inflammatory effects of these substances [230].

SGLT-2 inhibitors prevent glucose reabsorption in the proximal tubule and cause glucosuria, therefore lowering glucose levels in serum [231]. Large-scale clinical trials have demonstrated that SGLT-2 inhibitors significantly reduce the risk for hospitalisation and cardiovascular death in patients with heart failure [232–235]. Today, SGLT-2 inhibitors constitute an integral component of heart failure therapy and are recommended in the most recent heart failure guidelines [236].

In addition to pleiotropic metabolic and cardiovascular effects of SGLT-2 inhibitors, which have been described in detail by Hou et al., anti-inflammatory and anti-atherogenic properties going beyond metabolic risk reduction were observed [237, 238]. In murine models, SGLT-2 inhibitors were demonstrated to reduce the expression of MCP-1 and IL-1β [239–241]. A reduction of inflammasome activation and the subsequent release of IL-1β was also found in patients with DM [242]. Furthermore, macrophage behaviour seems to be influenced by SGLT-2 inhibitors as increased autophagy and cholesterol efflux were observed in a murine model. Therein, the modulation of an adenosine-monophosphate-kinase (AMP-K)-dependent pathway resulted in attenuated atherosclerosis [243].

Among a plethora of metabolic effects, GLP-1 receptor agonists were also found to exert a robust anti-inflammatory effect by lowering the levels of ROS generation and reducing NF-κB activation as well as expression of mRNA coding for, among others, TNF-α, IL-1β, TLR-2 and TLR-4 [244, 245]. In apolipoprotein E and LDL receptor deficient mice, the application of liraglutide or semaglutide resulted in decreased aortic intima thickening, and inhibited plaque progression compared to a control group [246]. Semaglutide was also demonstrated to alter the expression of genes associated with inflammation and atherogenesis including IL-6, chemokine ligand 2, MMPs and proteins relevant for cholesterol metabolism [246]. In-vitro, GLP-1 receptor agonists have been shown to modulate macrophage behaviour and reduce the secretion of pro-inflammatory cytokines (e.g., interferon γ, TNF-β, IL-1β, IL-2, IL-6), and promote the release of anti-inflammatory IL-10 [247].

Clinical trials in patients with DM type 2 showed a consistent reduction in CRP, TNF-α and malondialdehyde [248]. Cardiovascular outcome was also improved in patients with DM type 2 receiving GLP-1 receptor agonists treatment in some, but not all clinical trials [249].

Metformin used to be considered the established first-line therapy for patients with DM type 2 for decades [250]. In recent years, the attention has been increasingly focused on the effects of metformin beyond control of hyperglycaemia [251].

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Though the exact pharmacodynamic properties of metformin have yet to be fully elucidated, there is some mechanistic evidence that metformin may attenuate atherogenesis [252, 253]. In vitro studies have demonstrated that metformin attenuates foam cell formation and phagocytosis of oxLDL [254]. On a molecular level, metformin administration resulted in reduced expression of the macrophage scavenger receptor A and CD36, both of which are involved oxLDL uptake [254–256]. The expression of inflammatory markers, including IL-1β, IL-18, cysteinyl aspartate specific proteinase-1, NLRP3 and ROS was reduced in macrophages treated with metformin [254]. In a rabbit model of atherosclerosis, treatment with metformin resulted in significantly decreased burden of atherosclerotic lesions with lower macrophage content [257]. In addition to reducing plasma levels of MCP-1, CRP and TNF-α, metformin also reduced the expression of mRNA coding for vascular adhesion molecule 1 and intercellular adhesion molecule 1, therefore ameliorating adhesion of monocytes to endothelial cells [257]. Furthermore, the activation of AMP-K, the inhibition of NF-κB expression, and NET formation are also considered potentially anti-atherogenic properties of metformin [252, 258, 259].

Though there is some evidence that metformin therapy has a positive effect on cardiovascular outcomes in patients with DM type 2 [252, 253, 260], data is hitherto contradictory for non-diabetic patients [261–264]. The ongoing Glucose Lowering in Non-diabetic hyperglycaemia trial (GLINT) [265, 266] may help to determine the role of metformin in prevention of CVD in these patients [264].

Dipeptidyl peptidase 4 (DPP4) inhibitors or gliptins are established second-line anti-diabetic agents, which exert their effect by inhibition of proteolysis of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide [267, 268].

DPP4 is involved in the cleavage of chemokines and cytokines, therefore potentially exhibiting a role in cell-cell communication [269]. Furthermore, it is suggested that DPP4 induces endothelial dysfunction, promotes the expression of TLR-2 and TLR-4 and subsequent activation of inflammatory pathways [269–271]. The inhibition of DPP4 is therefore considered to attenuate inflammation and improve endothelial function, potentially by stimulation of NO synthesis and reduction of endothelin 1 expression [269, 272–274]. Gliptins have also been demonstrated to reduce the expression of vascular adhesion molecules and MCP-1, TNF-α, IL-1β, and IL-6, as well as LDL- or lipopolysaccharide-induced foam cell formation, most likely due to attenuation of NF-κB and c-Jun N-terminal kinase signalling and AMP-K phosphorylation [269, 272]. There is evidence that DPP4 inhibitors can increase the number of circulating EPC [274–276] and repress the activation of the NLRP3 inflammasome [274, 277]. On a systemic level, reduced hepatic production of TLP [278] and an accelerated postprandial lipid metabolism [279] have been observed under DPP4 therapy [269].

While pre-clinical data may look promising and gliptins have demonstrated to reduce established risk factors for CVD in patients with DM type 2 including dyslipidaemia and hypertension [269], randomised controlled trials have thus far failed to demonstrate a beneficial effect beyond glycaemic control with regard to cardiovascular outcomes [268, 280–283].

Table 1. Potential novel applications of established therapeutic agents.

	Standard Application	**Proposed mechanism**	**Clinical effect**	**Selected evidence**
Statins	LDL reduction secondary prevention of CVD	NO synthesis ↑ leukocyte adhesion ↓	cardiovascular events & death ↓	Tawakol et al. [192] Ridker et al. [193]
Colchicine	gout familial Mediterranean fever	leukocyte chemotaxis ↓ TNF-α ↓	cardiovascular events and death following MI ↓	Tardif et al. [202] Chen et al. [204]

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		exocytosis of neutrophil granules ↓ NLRP3 activation ↓		
Icosapent ethyl	no previous application	active metabolites (thromboxane A3, prostacyclin) ↑ biophysical effect on cell membranes TLP ↓	cardiovascular events & death in established CVD or risk for CVD & hypertriglyceridemia plaque progression ↓	Bhatt et al. [206] Budoff et al. [207]
Glucocorticoids	various inflammatory conditions	modulation of gene transcription	risk of CVD including CAD, PAD ↑	Pujades-Rodriguez et al. [229] Macleod et al. [225]
IL-1β antagonists	cryopyrin-associated periodic syndromes gout familial Mediterranean fever macrophage activation syndrome recurrent pericarditis rheumatoid arthritis systemic juvenile idiopathic arthritis	endothelial activation ↓ adhesion molecule expression ↓ smooth muscle cell proliferation ↓ MCP-1 ↓	cardiovascular events and death in patients with elevated CRP and MI	Ridker et al. [15]
SGLT-2 inhibitors	DM type 2	NLRP3/IL-1β/MCP-1 pathway ↓ AMP-K pathway ↑ cholesterol efflux and autophagy in macrophages ↑	hospitalization and cardiovascular death in heart failure	McMurray et al. [232] Solomon et al. [284] Packer et al. [285] Anker et al. [235]

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GLP-1 receptor agonists	DM type 2	ROS generation ↓ NF-κB activation ↓ INF-γ, MMP, TNF-β, IL-1β, IL-2, IL-6 from macrophages ↓ IL-10 ↑	CRP, TNF-α ↓ Trials inconclusive	Bethel et al. [249]
Metformin	DM type 2	oxLDL phagocytosis ↓ scavenger receptor A, CD36 ↓ NLRP3, ROS, MCP-1, CRP, TNF-α NET formation ↓ NF-κB activation ↓ AMP-K pathway ↑	all-cause death in DM type 2 & atherothrombosis ↓	Roussel et al. [260] GLINT (ongoing) [265, 266]
DDP4 inhibitors	DM type 2	NO synthesis ↑ endothelin 1 ↓ MCP-1, TNF-α, IL-1β, IL-6 ↓ NF-κB activation ↓ AMP-K & c-Jun N-terminal kinase pathway ↑ NLRP3 activation ↓ TLP ↓	dyslipidaemia & hypertension in patients with DM type 2 ↓ cardiovascular death, MI, stroke in patients with DM type 2 ~	Rosenstock et al. [280] Green et al. [281] Scirica et al. [282] White et al. [283]

Abbreviations: AMP-K, adenosine-monophosphate-kinase; CAD, coronary artery disease; CD, cluster of differentiation; CRP, c-reactive protein; CVD, cardiovascular disease; IL, interleukin; INF, interferon; LDL, low-density lipoprotein; MCP-1, monocyte chemotactic protein 1; MI, myocardial infarction; NF-κB, nuclear factor kappa B; NLRP3, nucleotide oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3; NO, nitric oxide; oxLDL, oxidised low-density lipoprotein; PAD, peripheral artery disease; ROS, reactive oxygen species; TLP, triglyceride-rich lipoprotein; TNF, tumour necrosis factor.

3.7. Antiplatelet therapy

Current antiplatelet regimes interfere with thromboinflammatory pathways; however, platelet reactivity is to a wide extent also determined by alternative platelet activation pathways despite adequate guideline-driven platelet inhibition [178, 286–289]. Platelet activation and the formation of platelet-leukocyte aggregates is a hallmark of inflammatory atherosclerotic processes [290].

Recently, there is increasing evidence, that platelet-to-lymphocyte ratio (PLR) - a simple marker calculated from the blood count - is related to platelet activation and ischemic events in CVD [290–293]. Moreover, a high PLR is also related to target vessel restenosis after revascularization in PAD [294].

Platelet reactivity can be modulated by various conditions such as age [295], sex [296], HDL levels [297, 298], cytochrome P450 2C9/2C19 polymorphism [299, 300], but also anaemia [301, 302]. The latter is often associated with chronic inflammation and implicated in both, thrombotic and

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bleeding events [303, 304]. Moreover, iron deficiency is associated with major adverse cardiovascular and leg events in PAD, suggesting anemia as possible therapeutic target [305].

Another aspect relevant for pain management of PAD patients with critical ischaemia is the drug interaction of morphine or fentanyl, as a decrease in plasma levels and/or antiplatelet effects of $P2Y_{12}$ inhibitors can occur [306–310]. In contrast, morphine did not exert a significant effect on aspirin-mediated platelet inhibition [311].

Platelet activation has furthermore a high impact on platelet metabolism and redox balance [312], hence attenuation of platelet reactivity may have beneficial effects on redox processes.

3.8. Attenuation of ischaemia-reperfusion injury

The counter regulation of the decrease in NO bioavailability due to I/R injury is one possible therapeutic approach to minimize endothelial dysfunction. Herein, dietary supplementation of NO donors, enhancers of NO availability, NO synthase inducers and antioxidants has been studied [313, 314].

Interestingly, pleiotropic effects of statins include the increase in endothelial NO synthase expression and function [315]. In patients with AAAs, simvastatin reduced lipid peroxidation level as demonstrated by lower 4-hydroxy-trans-2-nonenal concentration [316].

Moreover, simvastatin has been shown to induce heme oxygenase 1 (HO-1), an enzyme with antiinflammatory, antioxidant, antithrombotic, pro-angiogenetic and antiapoptotic properties [317–320]. Induction of HO-1 can also be achieved by heme arginate infusion, which improves reperfusion patterns during I/R injury [321–323].

Further concepts to ameliorate I/R injury include a plethora of therapies such as blocking of intercellular adhesion molecule 1, administration of polymerised albumin, colchicine, tocilizumab, anakinra, and revacept as well as pre-, per- and postconditioning [324–329]. Another important cornerstone in the therapy of risk factors in PAD patients are angiotensin converting enzyme inhibitors, which ameliorate (micro-)vessel perfusion by increasing nitrite production [330]. In addition, ROS formation is amongst others reduced by SGLT-2 inhibitors and GLP-1 receptor agonists [331–333].

3.9. Physical exercise

Regular physical exercise is a cornerstone in the prevention of CVD [18]. Besides improving endothelial function by increasing circulating EPC numbers [334], low intensity aerobic training also increases capillary density in skeletal muscle [335]. Furthermore, significant positive effects on established cardiovascular risk factors, e.g., hyperglycaemia [336], hypertension [337], and dyslipidaemia [335] have been demonstrated and a reduction in systemic markers of inflammation can be observed with physical exercise [338]. These include, among others, TNF-α and CRP as well as the expression of vascular adhesion molecules; all of which are considered to be of crucial importance in the pathogenesis of atherosclerosis [338]. In addition, protective effects of previous physical activity may also improve outcome following cardiovascular events [339, 340].

4. Discussion

PAD is increasingly regarded as an inflammatory process affecting not only the macro- but also the microvasculature [10, 178, 181]. Herein, modification of glycocalyx conformation, charges and density leads to endothelial dysfunction [341]. Thromboinflammatory processes involving leukocyte and platelet activation as well as ETosis are central pathomechanisms in plaque formation [44, 342].

Altered flow conditions due to plaque formation promote further disease progression by modulation of endothelial cell metabolism [343]. Upregulated 6-phosphofructokinase/2,6-bisphosphatase 3 (PFKFB3), which is a key enzyme in endothelial glycolysis, gives an impulse for angiogenesis with immature vessel formation, thus enhancing plaque vulnerability [343–345]. Moreover, rupture of the atheroma followed by atherothrombosis may also be triggered by (N)ETosis,

as neutrophil, macrophage and mast cell activation play a critical role in atherosclerotic lesions [342, 346, 347].

In addition, NETs were shown to contribute to fibrous vascular occlusion [102]. This may also contribute to systemic microvessel rarefication, which was observed in PAD and other CVD [348–351].

NET release promoting subsequent microvascular thrombosis is regarded as hallmark of atherosclerotic processes. The interplay of platelet activation, platelet- leukocyte aggregate formation, ETosis and ROS formation perpetuates thromboinflammation, resulting in altered microvascular fluid filtration, microthrombosis and finally tissue necrosis (compare Fig. 1) [9, 352].

Capillary perfusion is also impaired by ROS formation during I/R injury, as it occurs during ischemic vascular diseases [352]. I/R injury also contributes to postischemic capillary no-reflow after successful arterial recanalization [353]. Attenuation of I/R injury to preserve microvascular hemodynamics [354] will be of importance for refinement of interventional PAD treatment.

In the context of the recent SARS-CoV-2 pandemic and the long-term consequences it should be noted, that viral persistence promoting (subclinical) inflammation will have an impact on the vasculature and atherosclerosis [9, 355–357].

Despite all pharmacotherapeutic progress modulation of the fragile glycocalyx and in consequence preservation of endothelial cell function is demanding. Concepts to reduce endothelial dysfunction by interference with redox processes could hitherto only marginally been integrated into clinical practice [358]. However, different pharmacotherapies such as statins, angiotensin converting enzyme inhibitors, GLP-1 receptor agonists or SGLT-2 inhibitors may ameliorate inflammatory pathways [185, 238, 245, 359]. The reduction of fibrosis and arterial stiffness may directly influence long-term pathogenesis [360].

In addition to pharmacotherapy, exercise training should remain a cornerstone in patients with stable PAD [18]. In particular aerobic exercise training has been shown to upregulate microvessel perfusion [361]. Moreover, the number of circulating EPCs increases in patients with regular endurance training being associated with improved endothelial function [334, 362]. Therefore, future concepts should emphasize on preventive strategies [18] including governmental- promoted exercise training and programs to raise awareness for cardiovascular risk factors.

5. Conclusions

Inflammatory pathways have a critical role in the development, disease perpetuation and complications of atherosclerosis. Novel research results regarding disease pathophysiology imply the need for a paradigm shift in the therapeutic approach to atherosclerotic diseases. In the future, the attenuation of (subclinical) inflammatory processes will become equally important to other risk factor management in the therapy of PAD. However, further studies regarding long- lasting outcome of PAD patients are warranted.

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