

Traditional and Non-Traditional Risk Factors Involved with Endothelial Dysfunction and Arterial Stiffness in Autoimmune Rheumatic Diseases

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Abstract

Autoimmune rheumatic diseases (ARDs) have been closely associated with accelerated plaque progression and the development of atherosclerosis, which lead to high morbidity and mortality rates for cardiovascular diseases. Endothelial dysfunction and arterial stiffness are greatly evidenced in several studies in the early phase of atherosclerosis. In ARDs, endothelial dysfunction and arterial stiffness are related to traditional and non-traditional risk factors. To date, no studies have clearly analyzed the main parameter involved in endothelial dysfunction and arterial stiffness. In this context, the present narrative review's purpose was to describe the main factor in endothelial dysfunction and arterial stiffness in different ARDs. Endothelial dysfunction and arterial stiffness are related to traditional risk factors (*i.e.*, hypertension, diabetes, dyslipidemia, metabolic syndrome, sedentary behavior) and non-traditional risk factors (linked to the immune mechanisms involved in these diseases). Moreover, in the present study, these associations were systemically analyzed in ankylosing spondylitis, antiphospholipid syndrome, rheumatoid arthritis, psoriatic arthritis, systemic autoimmune myopathies, systemic lupus erythematosus and systemic sclerosis. The present review shows that the relationship of traditional risk factors and non-traditional risk factors related to ARDs works in the worsening of function and structural properties of arterial vessels, leading to high cardiovascular morbidity and mortality.

Keywords

Arterial Stiffness, Atherosclerosis, Autoimmune Endothelial Dysfunction, Rheumatic Diseases

1. Introduction

Autoimmune rheumatic diseases (ARDs) are a heterogeneous group of disorders commonly characterized by systemic and chronic inflammatory processes [1]. A high frequency of morbidity and mortality related to cardiovascular diseases (CVD), particularly myocardium infarction, stroke and congestive heart failure has been described in several ARDs [1] [2].

Cardiovascular morbidity and mortality are strongly associated with accelerated atherosclerotic processes, which are preceded by endothelial dysfunction and arterial stiffness [3]. Therefore, the early assessment of endothelial function and arterial stiffness is a useful predictor of CVD risk. It may be accessed via flow-mediated dilatation (FMD) in the former case, and pulse wave velocity (PWV) in the latter [4].

Of note, endothelial dysfunction and increased arterial stiffness have been described in many ARDs, such as ankylosing spondylitis (AS), antiphospholipid syndrome (APS), rheumatoid arthritis (RA), psoriatic arthritis (PsA), systemic autoimmune myopathies (SAM), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) [4]-[9].

Impaired endothelial and arterial functions in ARDs may be explained by traditional risk factors (TRFs) for CVDs, such as systemic arterial hypertension, diabetes mellitus, tobacco habit, obesity and sedentary behavior [10]. In addition, recent data have supported the participation of non-TRFs in CVD, such as cellular and humoral immunity [6] (Figure 1).

No studies have clearly analyzed these ARD factors. In fact, the knowledge of these factors and their impact may contribute to a therapy approach even in the early phase of atherosclerosis [8] [9]. In this context, the present study's purposes were to describe the main parameter involved in endothelial dysfunction and arterial stiffness in ARDs.

1.1. Literature Review

We conducted literature searches on electronic databases (Medline [PubMed]). The selection of the descriptors was carried out from June 2018 to November 2018, according to the Medical Subject Headings, following key-words in English: “ankylosing spondylitis”, “antiphospholipid syndrome”, “arterial stiffness”, “autoimmune diseases”, “dermatomyositis”, “endothelial dysfunction”, “idiopathic inflammatory myopathies”, “myositis”, “polymyositis”, “psoriatic arthritis”, “rheumatic diseases”, “spondyloarthritis”, “systemic autoimmune diseases”, “systemic autoimmune myopathies”, “systemic lupus erythematosus”, “systemic sclerosis”. The keywords were combined with the Boolean operators “AND” and “OR” and adapted for each database as required. In addition, the reference list of each retrieved article was reviewed manually by two reviewers and in case of disagreement a third reviewer was called. The following inclusion criteria were adopted: no chronological limit, original articles, reviews, controlled and randomized clinical trials.

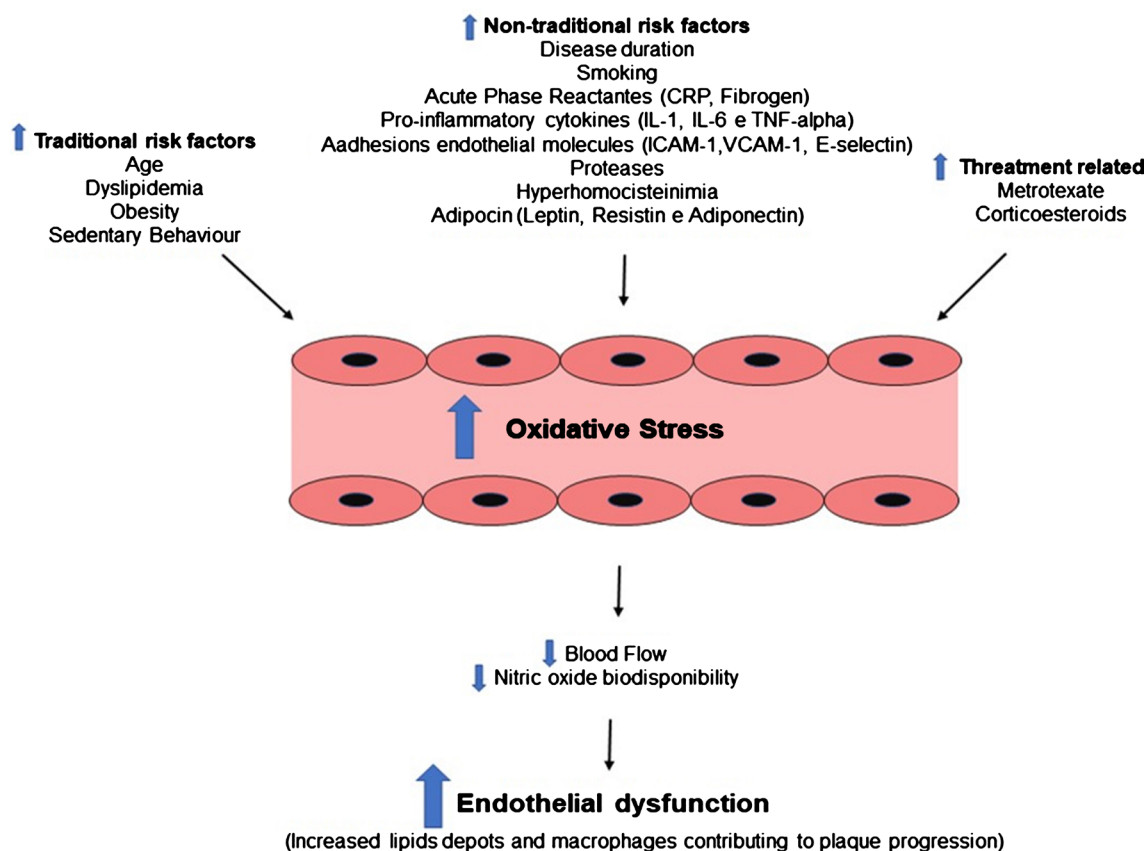


Figure 1. The traditional and non-traditional risk factors to the endothelial dysfunction.

1.1.1. Ankylosing Spondylitis

The literature contains less information about the assessment of endothelial function in AS [11] [12]. Several studies have shown arterial stiffness in patient's large arteries [11] [12]. To our knowledge, the studies have not demonstrated an increase in the common (carotid intima-media thickness) cIMT [11]. Moreover, no studies have evaluated the PWV. Regarding FMD, an important impairment was shown [12]. The possible mechanism involved was related to impairments in the anti-atherogenic factors linked to high density protein [11] [12], but limited studies have elucidated the potential mechanism involved the vascular dysfunction of these patients.

1.1.2. Antiphospholipid Syndrome

APS has often been linked with arterial and thromboembolic events [6]. Unlike in RA and SLE, the TRFs in APS are common among those in the general population, suggesting that TRFs are less important [6].

The non-TRFs in APS are related to auto-antibodies such as anti-oxidized low-density lipoproteins (anti-oxLDL), anti-heat shock protein (HSP), anti-cardiolipin and anti-beta-2-glycoprotein I (anti- β 2GPI) [13] [14]. These autoantibodies can influence the subendothelial lipids retention, leading to accelerated atherosclerosis and other CVDs, such as cerebrovascular events and peripheral artery disease [13].

The presence of anti-oxLDL and β 2GPI complexes and anti-heat shock protein antibodies are described in atherosclerosis [13]. β 2GPI is expressed in adjacent CD4+ T cell infiltrations. During the progression of atherosclerosis, macrophages and endothelial cells bind to β 2GPI [13] [14]. The anti-oxLDL and anti- β 2GPI have the strongest association with the common cIMT and endothelial dysfunction [13] [14]. In the same way, the relationship between anti-cardiolipin and increased common cIMT was observed [13]. These autoantibodies correlate with the frequency of CVD [13]. Similar findings have been founded with the IgA isotype, which was linked to cardiovascular events (stable and unstable angina) [6]. Recently, one study revealed that the activation of the mammalian target of the rapamycin complex rather than the phosphatidylinositol 3 kinase pathway stimulates the intima, promoting chronic vascular disease. However, this association remains unclear, requiring more studies [14]. Moreover, the vascular structure and function in APS-impaired FMD and increased common cIMT [15].

1.1.3. Rheumatoid Arthritis

The most frequently described TRFs for CVD in RA are smoking, sedentary behavior and dyslipidemia [1] [16], whereas mainly non-TRFs are factors in this disease's chronic and systemic inflammatory process [17] [18], as shown in **Table 1**.

Smoking is an independent risk factor for RA [1]. A positive relationship exists between smoking and worse prognoses and disease severity [1] [19]. The probable mechanism is related to the increase of anti-citrullinated protein/peptide antibodies, leading to increased disease severity and a worse prognosis [1] [19].

These factors are related to other TRFs, such as hypertension, dyslipidemia, obesity and sedentary behavior, which contribute to worse prognoses [6] [16] [20] [21]. In the same way, joint deformities can lead to a decrease in muscle function and strength, contributing to increased sedentary behavior [24]. Recently, one study demonstrated that the impairment of microvascular endothelium-dependent vasodilation was correlated with increased sedentary behavior [16].

Table 1. Main risk factors for cardiovascular diseases involved in possible endothelium dysfunction and/or arterial stiffness in rheumatoid arthritis.

Main risk factors for cardiovascular diseases	Relationship	References	
Traditional	Smoking	[1] [6] [16]	
	Obesity	Relation to dyslipidemia. Controversial: protective effect, deleterious effect on the disease's severity.	
	Sedentary behavior	Correlates to the impairment of microvascular endothelium-dependent vasodilation.	
	Dyslipidemia		
Non-traditional	Disease' chronic and systemic inflammatory process	Involving the presence of pro-inflammatory cytokines, chemokines, endothelial adhesion molecules, vascular endothelial growth factors, C-reactive protein, and platelet-derived growth factors. Contributes to insulin resistance, dyslipidemia, obesity, hiperhomocysteinemia.	[17] [23] [25] [26] [27] [28]

Another important TRF is obesity [23] [24]. Considered a paradox, obesity in some studies exerts a potential protective effect through adiponectin, resistin and adipocytokines, but the obesity seems to have a deleterious effect on the disease's severity [23] [24]. However, researchers have reached a consensus on endothelial dysfunction and obesity [24].

Obesity is linked to dyslipidemia in the general population and in RA patients [23] [25]. The prevalence of expressive dyslipidemia in RA is related to abnormalities in lipid profiles [25]. One cross-sectional study identified genes (TRAF1/C5, STAT4 and HLA-DRB1-SE) susceptibility linked to lipid metabolism in RA [26].

The non-TRFs involved in AR mainly feature chronic systemic inflammation, involving the presence of pro-inflammatory cytokines [*i.e.*, tumor necrosis factor (TNF), interleukin (IL)-1, IL-6 and interferon (IFN) α], chemokines, endothelial adhesion molecules, vascular endothelial growth factors (VEGF), C-reactive protein, and platelet-derived growth factors (PDGF) [17] [27].

In relation to the pro-inflammatory cytokines in RA, the involvement of cytokines such as TNF, IL-1 and IL-6 has been shown [9]. High levels of IL-6 and TNF have been positively correlated with some TRFs, insulin resistance, dyslipidemia, and obesity, respectively [9].

It has also been shown that IL-1/TNF can cause alterations in serum concentrations of homocysteine, leading to the production of asymmetric dimethylarginine, which negatively affects the regulating expression of nitric oxide synthase (NOS) [17].

Homocysteinemia seems to be a non-TRF in RA and is linked to folate and B12 metabolism [28]. A deficiency in B12 or folate metabolism can lead to homocysteinemia, causing endothelial damage and contributing to smooth muscle cell proliferation [28].

IL-1/TNF is also related to the expression of homocysteine, which is responsible for regulating paraoxonase, which is closely linked with increased cardiovascular risk and mortality [28]. Moreover, the relationship between these cytokines with higher serum concentrations of endothelial adhesion molecules in RA was shown [27].

From a clinical perspective, decreased endothelial function in RA led to an association between TNF, IL-1 and IL-6 with decreased FMD, similar to disease parameters, which were linked to a decrease in FMD [29]. In agreement with these findings, current evidence demonstrates an important reduction in vascular endothelium-dependent vasodilatation, which is correlated with parameters of clinical disease activity [30]. Caraba *et al.* [31] reported similar findings, demonstrating that disease activity is positively correlated with insulin resistance and endothelial dysfunction [31].

These parameters were identified with disease activity, and after one year, the reduction in disease activity improved the endothelial function, suggesting that chronic inflammation is potentially responsible for impairments in endothelial

function and arterial stiffness [32] [33].

According to the literature, a significant reduction of FMD and cIMT was observed in 87 patients, as well as the irregular expansion of CD4+ and CD28 lymphocytes, similar to patients with CVDs [34].

The emergent association was seen in metalloproteinase and endothelial dysfunction [35]. In RA, metalloproteinases are linked to joint destruction and chronic systemic inflammation. Moreover, metalloproteinases are related to plaque destabilization [35] [36].

In contrast, some studies showed that the prevalence of TRFs is the main determinant of endothelial dysfunction and arterial stiffness in RA patients [37] [38]. These findings are found in a cross-sectional and longitudinal study, which evaluated the connection between inflammatory parameters, TRFs and macro-microvascular function [37]. In the same sense, it was evidenced by the same group in a prospective six-year study [38].

Sandoo *et al.* observed an increase in the common cIMT. This impairment was strongly bound with CVD in patients without a history of vascular disease [37].

Giles *et al.* [39] in a study with mixed ARDs involving 101 patients (including patients with RA) observed the presence of arterial stiffness by angiography, the PWV and FMD [39]. The PWV was correlated with reduced FMD and increased cIMT. According to previous findings, FMD is a strong predictor of atherosclerosis [39].

In agreement with these studies, a recent study that enrolled 5638 patients showed that 70% of cardiovascular events were attributed to TRF, and 40% were attributed to RA [40]. Finally, smoking and systemic arterial hypertension have a greater impact on global CVD risk factors [40].

In RA, the risk factors are associated with the disease, and the traditional risk factors for CVDs together contribute to a significant increase in morbidity and mortality in RA. In addition, chronic inflammatory response results in an important progression of traditional risk factors, ultimately leading to decreased FMD. The potential determinants of these impairments are disease activity or remission, chronic systemic inflammation and traditional risk factors [2] [9] [19] [37] [38].

All of these factors seem to contribute to endothelial dysfunction and arterial stiffness in RA [19] [41]. In RA, endothelial dysfunction can occur in the large vessels (such as the conduit arteries) and the small vessels of the microvasculature, which supply oxygen and nutrients to the tissue and control inflammation, repair and fluid exchange with the surrounding tissues [19]. Moreover, patients with RA show a higher prevalence of arterial stiffness. This alteration correlates with the severity of the inflammatory status and is present even in the disease's early stage [41].

1.1.4. Psoriatic Arthritis

The association between CVDs and PsA was recently described. As with RA and SLE, the presence of TRFs contributes to elevated cardiovascular risk, in the

same way as non-TRFs [42] [43]. TRFs are characterized mainly by hypertriglyceridemia, obesity and smoking [42] [44].

The assessment of subclinical atherosclerosis has been discussed in several studies [43] [44]. The majority agrees that PsA is associated with a higher common cIMT and PWV, as well as decreased FMD [43] [44]. These parameters have been correlated with disease duration and age, as in RA findings [42] [43].

The common cIMT has been strongly correlated with the severity of PsA, age and disease duration [45]. These findings were similar in a large cohort of patients, showing that psoriasis represents independent CVD risk factors [46]. As observed in the study that Balci *et al.* [47] conducted disease duration is associated with increased cIMT [47]. Regarding the PWV, it has been shown that arterial stiffness is related to age and disease duration [42] [46]. These findings were similar after a multivariate regression analysis using the age, gender, smoking, hypertension, and body mass index dependent variables [42] [45].

A functional assessment by FMD revealed a considerable reduction in some studies [42] [45] [46]. However, these observations did not correlate disease duration with the reduction of FMD [42] [45] [46] [47]. In contrast, some studies did not show statistically significant differences between the groups [48]. Further studies are needed to elucidate the functional characteristics of the arterial arteries of patients with PsA.

1.1.5. Systemic Autoimmune Myopathies

To date, only one study evaluated endothelial function and arterial stiffness in patients with SAM [5]. This study demonstrated the presence of arterial stiffness measured by the common cIMT, which was not statistically significant among 38 health controls and 21 patients with dermatomyositis and polymyositis. Regarding endothelial function, a significant reduction of endothelium-dependent vasodilation was observed, suggesting that it could be related to chronic inflammation in the skeletal muscle [5]. However, regarding limitations, this study did not assess clinical, laboratory, or overall CVDs and their risk factors. Therefore, endothelial function and arterial stiffness in systemic autoimmune myopathies remain unclear. More studies are required to elucidate vessel behavior in myopathies and vice versa.

1.1.6. Systemic Lupus Erythematosus

Analogous to other ARDs, SLE is clinically characterized by a high incidence of CVDs [49] [50]. SLE often affects women without previous exposure to atherosclerosis [51]. However, as in other ARDs, a high frequency of CVDs after diagnosis has been observed [49] [50], as shown in **Table 2**.

In SLE, CVD risk is thought to increase as a result of the complex interaction between TRFs: sedentary behavior, dyslipidemia, hypertension, metabolic syndrome and insulin resistance [2] [6].

Immunity deregulation occurs due to disease activity, including the synergic effect of cytokines, chemokines, adipokines, proteases, autoantibodies, adhesion

Table 2. Main risk factors for cardiovascular diseases involved in possible endothelium dysfunction and/or arterial stiffness in systemic lupus erythematosus.

Main risk factors for cardiovascular diseases	Relationship	References
Traditional	Smoking	Worse prognoses and disease severity.
	Obesity	Relation to dyslipidemia. Controversial: protective effect, deleterious effect on the disease's severity.
	Sedentary behavior	Correlates to the impairment of microvascular endothelium-dependent vasodilation.
	Hypertension	
	Insulin resistance	Chronic use of glucocorticoids.
	Metabolic syndrome	Chronic use of glucocorticoids.
	Dyslipidemia	Chronic use of glucocorticoids.
Non-traditional	Disease' activity	Immunity deregulation occurs due to disease activity, including the synergic effect of cytokines, chemokines, adipokines, proteases, autoantibodies, adhesion receptors, oxidative stress and a plethora of intracellular signaling molecules.
	Autoantibodies	Antiphospholipid antibodies, anti-oxidized palmitoyl-arachidonyl-phosphocholine, antibodies to 65 and 70 kDa heat shock proteins (anti-hsp65 and -hsp70), anti-HDL, anti-apolipoprotein A-I and anti-lipoprotein lipase. The release of high numbers of these autoantibodies may increase oxidative stress, leading to endothelial cell damage and apoptosis and helping accelerate the atherosclerotic process.
	Cytokines	Pro-inflammatory mechanism involved is increased by C-reactive protein, adipocytokines and proteases.

receptors, oxidative stress and a plethora of intracellular signaling molecules. These factors together could contribute to the impairment of endothelial function and increased arterial stiffness [20].

Among TRFs, dyslipidemia in SLE has been associated with the chronic use of glucocorticoids [51]. These parameters isolated or combined, corroborate changes in serum high density lipoprotein cholesterol levels and elevated levels of very-low-density lipoprotein cholesterol and triglycerides [51]. It has also been shown that the presence of immunocomplexes may influence endothelium's and macrophages' ability to catalyze and hydrolyze cholesterol [51].

A high frequency of metabolic syndrome has been observed among patients with SLE [20] [52]. The high frequency of metabolic syndrome has been consistently connected to ethnicity and depression [20] [52].

The non-TRFs involved in SLE mainly include by antiphospholipid antibodies (anticardiolipin and anti- β 2GPI), anti-oxLDL, anti-oxidized palmitoyl-arachidonyl-phosphocholine, antibodies to 65 and 70 kDa HSP, anti-high density lipoprotein cholesterol, anti-apolipoprotein A-I and anti-lipoprotein lipase [6]. These antibodies have been linked to the thermogenic process [53] [54]. The release of high numbers of these autoantibodies may increase oxidative stress, thus leading to endothelial cell damage and apoptosis, as well as helping to accelerate the atherosclerotic process [53] [54].

The pro-inflammatory mechanism involved is increased C-reactive protein, adipocytokines and proteases [55]. Particularly, these pro-inflammatory me-

mechanisms influence endothelial permeability and homeostasis, thus leading to further plaque destabilization [55].

C-reactive protein is a pro-atherogenic independent factor that leads to the complementary activation of chemokine and its release into the endothelium contributing to oxLDL and macrophage uptake [56]. The increased levels of oxLDL serum correlate with increased common cIMT, suggesting a strong relationship between these endothelial dysfunction and atherosclerosis factors [57]. Adipocytokines and proteases in SLE are mainly involved with endothelial injury, plaque destabilization and progression [53].

Regarding the evaluation of endothelial function and arterial stiffness in SLE, several studies have investigated vascular behavior and characteristic [2] [6].

Soltesz *et al.* [58] showed vascular abnormalities through the assessment of cIMT, FMD and nitroglycerine mediated dilatation (NMD) in 61 patients with systemic lupus erythematosus with to 26 matched controls. FMD was correlated with arterial hypertension and aging [58]. Similar findings were observed in arterial stiffness evaluated by the PWV and BaPWV [58] [59].

However, unlike in RA, in SLE, the decreased FMD and the increased PWV and common cIMT in SLE correlate strongly with the inflammatory mechanism, which can explain the damage in multiple organs [58] [60].

1.1.7. Systemic Sclerosis

SSc has been reported with inflammatory, vascular and fibrotic events. The mechanisms underlying these factors are mainly associated with macrovascular and microvascular impairments [8] [61].

The microvascular impairments feature histopathological abnormalities in the skin (Raynaud's phenomenon) that influence several molecular and cellular mechanisms [61]. The macrovascular damage is characterized by lumen abnormalities, leading to short-term endothelial injury and apoptosis [62] [63].

The factors involved in macro and microvascular deterioration cannot be explained by TRFs. Several studies have not shown a correlation with the clinical evaluation of cardiovascular risk. In contrast, several cellular and molecular mechanisms have been identified and correlated with the varied clinical evaluation of CVD risk factors [61] [64].

Regarding the relationship with TRFs and SSc, Szamosi *et al.* [65] demonstrated a positive correlation with elevated homocysteine levels and macrovascular diseases in 133 patients with SSc systemic and 21 SSc with diffuse manifestations. In the same study, the authors did not find a relationship between macrovascular disease and TRFs [65]. Other studies strongly support these findings [65] [66].

The cellular and molecular mechanisms are extensively interrelated with the regulation of pro-angiogenic and anti-angiogenic factors, autoantibodies and defective endothelial progenitor cells [19] [63]. The pro-angiogenic factors in SSc are VEGF and their receptors VEGFR, VEGFR-2 and VEGFR-3, PDGF, PDGF-BB, fibroblast growth factor[®], angiotensin-1 and -2 [19] [63] [67].

The anti-angiogenic factors are metalloproteinase 12 and recently VEGF165b antiangiogenic isoform, which correlate with substantial architectural loss and damage in SSc [19].

The increased architectural loss and damage in SSc were explained by a significant increase in specific anti-endothelial antibodies leading to expressive increases in reactive oxygen species' production and oxidative stress [63] [68].

In the same way, the high expression of adhesion cell molecules was shown to increase in hypoxia [63] [68] [69] and was related to the activation of hypoxia inducible factor-1 [8]. In summary, these factors together cause a deleterious effect on micro and microvessels such as defective angiogenesis, hypoxia and defective perfusion [68] [69].

Regarding the assessment of vascular structures and functions, the relationship between FMD and increased serum endothelin-1 was deemed a positive one. It was recently reported that increased common cIMT can be preceded by impaired FMD [2] [68].

Soltész *et al.* [58] observed increased common cIMT and reduced FMD, but FMD was preserved in 29 patients compared with healthy subjects. This study showed a positive relationship among age, disease duration and common cIMT. Similar findings were seen in the PWV [58].

2. Conclusion

The present review shows that the relationship of traditional risk factors and non-traditional risk factors is related to ARDs works in the worsening of function and structural properties of arterial vessels, leading to a high cardiovascular morbidity and mortality.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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