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Rheumatoid arthritis (RA) and cardiovascular disease

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A B S T R A C T

Patients with rheumatoid arthritis (RA) suffer cardiovascular events 1.5-2 fold than the general population, and cardiovascular (CV) events are leading cause of death in patients with RA. It is known that patients with RA have endothelial dysfunction, related with impaired function of endothelial progenitor cells (EPCs). The mechanistic pathways leading to endothelial function are complicated, but understanding these mechanisms may open new frontiers of management and therapies to patients suffering from atherosclerosis. Inflammation is a key factor in atherosclerosis, including endothelial function, plaque stabilization and post infarct remodeling; thus, inhibition of TNF-α may affect the inflammatory burden and plaque vulnerability leading to less cardiovascular events and myocardial infarctions. An aggressive management of inflammation may lead to a significant improvement in the clinical cardiovascular outcome of patients with RA. The clinical evidence that showed a reduced risk of CV events following treatment with anti-inflammatory agents may suggest a new approach to treat atherosclerosis, i.e., inhibition of inflammation using biological medications that were primarily aimed to treat the high scale inflammation of RA and other autoimmune-inflammatory diseases, but may be useful also to prevent progression of atherosclerosis.

1. Epidemiology

Patients with rheumatoid arthritis (RA) are at increased risk of mortality, largely attributed to increased cardiovascular (CV) death. The prevalence of cardiovascular disease in autoimmune diseases has been underestimated for decades. The presentation of the cardiovascular involvement is usually insidious without fatal clinical features until the disease is presenting as a full blown disease eventually. The advances in the therapeutic options and the extended life expentancy of patients with rheumatic diseases has changed the drive to look for subclinical atherosclerosis and cardiovascular disease, and to prevent the accumulation of vascular damage, that way to prevent cardiovascular sudden death and other acute vascular events like acute myocardial infarction [1]. Cardiovascular disease is the leading cause of death in RA (10-30% of deaths) [2–4]. Hypertension, smoking and hypercholesterolemia increase the the cardiovascular risk in patients with RA (the same as in the general population) [5,6].

A retrospective study of RA patients in Rochester, MN, found that patients with RA were at increased risk of CV death, ischemic heart disease, and heart failure compared with age- and sex-matched community controls. Evidence of inflammation was found in coronary artery tissue from autopsied RA patients, with increased proportion of unstable plaques. Although traditional CV disease risk factors contribute to the increased risk of mortality in RA patients, they don't fully explain the increased CV mortality in RA. Increased inflammation associated with RA appears to be a dominant key player that contributes to the increased CV mortality. These data suggest that more aggressive management of inflammation may lead to a significant improvement in the clinical cardiovascular outcome of patients with RA [7].

Another study found that women with RA had a 2-3 fold increased risk of myocardial infarction, even in the absence of traditional coronary risk factors [8–10]. The increased CV morbidity and mortality in RA patients raised questions regarding the biologic mechanisms contributing to increased death in RA, the proper approach to identify high risk patients, and the effects of both traditional prevention strategies and RA directed therapies on CV risk in this population [11].

Evidence suggested that the extent of systemic inflammation could predict the poor cardiovascular outcome in patients with RA [12–15], but questions still remain regarding the mechanisms that may link systemic inflammation to increased CV risk. Giles et al. found that higher swollen joints' count and higher average C-reactive protein (CRP) levels were associated with progressive carotid plaques in patients with RA followed for 3 years [16]. Traditional cardiovascular risk factors such as hypertension, hyperlipidemia, smoking, diabetes mellitus and physical inactivity are also highly prevalent among patients with RA and contribute to the CV risk. The impact of traditional risk factors on the CV risk appears to be different in the RA and non-RA population. Screening of these risk factors is suboptimal among patients with RA. Guidelines of the European League against Rheumatism

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(EULAR) recommended aggressive management of traditional risk factors in RA patients. Several CV risk calculators are available for clinical use to stratify patients' risk of developing CV events. Most of these calculators do not take into account RA as a risk factor; thus, a multiplication factor of 1.5 is recommended to predict the CV risk more accurately. In order to reduce CVD in RA patients, national guidelines for the prevention of CV risk should be applied to manage traditional risk factors in addition to aggressive control of inflammatory disease activity [17].

CVD is the leading cause of death even in the general population; however, RA is associated with an increased risk of developing CVD by almost two fold compared to diabetes mellitus [18,19]. RA patients are twice as likely to experience a silent MI and carry a higher burden of coronary plaques even without a clinical history of coronary artery disease [20]. After AMI, patients with RA had a 17.6% 30-day mortality compared to 10.8% in the non-RA population [21]. A meta-analysis of 111,758 patients with 22,927 cardiovascular events that found a 50% increased risk of CV death among patients with RA compared to the general population [22]. Another meta-analysis reported a 60% increase in CV death compared to non-RA subjects [23]. Results from the Nurses' health study found that women with RA had 45% increased CV mortality with a hazard ratio (HR) of 1.5 compared to non-RA women [24]. These studies support the evidence of increased CV mortality in patients with RA [25].

CV mortality had been associated with level of inflammation, HLA–DRB1*0404 [26], use of glucocorticoids [27] and RA autoantibodies [28,29]. A recent (2014) analysis, a United Kingdom (U.K.) based cohort (Norfolk Arthritis Register) included 2517 patients with early inflammatory arthritis with 16,485 person-years of follow-up. In this study, CV mortality decreased with time in the first seven years from recruitment in this register, but was increased among patients who were antibody-positive [28].

The prevalence of atrial fibrillation was found to be 40% higher in RA patients compared with non RA patients [30]. Anti-cytokine therapies have been shown to be effective anti-arrhythmic agents in patients with RA, suggesting that the arrhythmia is associated or induced by the chronic inflammtory condition [31–33]. This suggestion is now gaining popularity in the general population, relating atrial fibrillation with chronic inflammation.

1.1. Autoantibodies in rheumatoid arthritis

Why the immune system is so activated in RA? What is the origin of RA? Studies in the pre-clinical period of RA have provided insights into the evolution of autoimmunity in RA. It has been demonstrated that autoantibody levels rose in the pre-clinical period as time to RA diagnosis decreased [34,35].

The Pima Indians were shown to be carriers of positive rheumatoid factor antibodies, and had a higher risk to develop RA [36], reaching an incidence rate of 48 higher for the highest titer. Another study showed that the development of RA was correlated to rheumatoid factor levels, but these antibodies were also associated with Sjogren Syndrome, Systemic Lupus Erythematosus, and type 1 Diabetes Mellitus [37].

Autoantibodies characteristics are changing during the preclinical stage of RA, including isotypes, avidity, glycosylation and epitope spreading. Doubling of rheumatoid factor (RF)-IgM level was associated with a 3 fold increased risk of developing RA [38], and as the time to diagnosis approaches in the pre-clinical stage of RA, there was increasing aberrant glycosylation, activating complement and Fc receptor engagement [39]. The avidity of antibodies to citrullinated protein antigens (ACPAs) increased over time in pre-clinical RA, but this process was halted once clinically apparent disease was present [40]. Another study evaluated individual ACPAs in preclinical RA samples and demonstrated an increased number of positive ACPAs with a higher specificity to develop RA in the future [41].

Multiple studies discovered abnormalities in levels of biomarkers that reflect systemic inflammation during the preclinical period, including circulating cytokines, chemokines, and other pro inflammatory proteins [42–45]. Elevated inflammatory cytokines were associated with elevations of serum RA-related autoantibodies in unaffected first-degree relatives of patients with RA [43]. The temporal relationship between elevations of autoantibodies and abnormalities of systemic inflammation during the preclinical period was not clear enough. One study found that increasing number of ACPAs preceded the increase in inflammatory cytokines [42].

Overall these findings suggest that there is a period of preclinical RA during which there is an initial restricted immune response that expands over time.

1.2. Where and how RA begins?

Systemic inflammation and autoimmunity precede the onset of RA; however, it is not clear where these processes develop. While plasma cells in the synovia have been shown to generate autoantibodies in patients with established RA [46,47], studies evaluating the joint during the preclinical period have found that the synovia does not appear to be affected in the early stages of RA. No histologic or magnetic resonance imaging (MRI) evidence of synovial inflammation was found in the knees of subjects with serum RA-related autoantibodies without clinically-evident synovitis [48]. Subclinical joint inflammation was reported when ultrasound, MRI and positron emission tomography (PET) imaging were used in a small number of subjects with serum ACPAs, joint symptoms of 'arthralgia's', and no clinically-evident synovitis [49–51].

Overall, these data suggest that the initial inflammation and autoimmunity in RA begins outside of the joints. If RA-related autoimmunity develops outside of the joints, where is that site?

RA-related autoimmunity may originate at a mucosal site, in particular, IgA is the predominant antibody of the mucosal immune system. Data demonstrated that IgA-ACPAs were elevated and are highly specific for RA in the preclinical stage and in the early clinical stage of RA [52–54]. Findings related to specific mucosal sites including the oral cavity, the lungs, and the gut, suggested that environmental factors may affect the mucosa, and appear to play a role in triggering the mucosal site (i.e. the gastrointestinal or genitourinary mucosa) [55].

1.2.1. The oral mucosa

In recent years, the oral mucosa, specifically the gingiva and periodontal regions, have been studied as potential sites for the origins of RA. In patients with RA, there is an increased prevalence and severity of periodontitis in association with RA-related autoantibodies [56–59], and in subjects without RA, severe periodontitis has also been associated with RA-related autoantibodies [60]. In addition, *Porphyromonas gingivalis (P. ging),* a microbe commonly involved in periodontitis, was found to express a peptidyl-arginine deaminize (PAD) enzyme capable of citrullinating human peptides/proteins [61]. In subjects without RA, an association between antibodies to *P. ging* and serum RA-related autoantibodies was found [43], and inflamed gingival tissue has been shown to express elevated levels of PAD and citrullinated proteins [62,63]. Local anti-CCP antibodies were found in gingival fluid associated with gingivitis. It appears that periodontitis and gingivitis are associated as a trigger zone for systemic inflammation, induced by local bacterial infections, but affect the systemic inflammatory systems and the cardiovascular system as well [64]. Longitudinal studies are needed that will evaluate the relationship between oral pathogens, local gingival autoantibodies generation, systemic RA-related autoimmunity, and joint inflammation in order to better understand the role of the oral mucosa in the etiology of RA.

Systemic spread of oral pathogens and their toxins and inlfammatory molecules was defined as the "mobile microbiome" theory [65]. This theory may explain the formation of auto-antibodies in

infections that are located in one place and induce remote phenomena like autoimmune neuropsychiatric disorders that are associated with streptococcal infections, polycystic kidney disease, obesity and daibetes mellitus [66].The molecular basis of the relationship between focal oral infections and systemic diseases is not het clear. Proteomics analysis showed that a wide peptide comminality between bacterial antigens and human cardiovascular autoantigens, potentailly enabling cross-reactions and crossreactivity of bacteria like streptoccocus mutans with human heart tissue [67].

1.2.2. The lungs

Another mucosal surface that is a potential site of autoimmunity in RA is the lung. This possibility is supported by established data that demonstrated increased RA risk with cigarette smoke [68–70], and a high prevalence of lung disease including airways inflammation was found among patients with RA [69,71]. A higher prevalence of inflammatory airways disease was demonstrated by computed tomographic imaging in arthritis-free subjects (by joint examination and in a subset of subjects also by MRI) with serum RA-related autoantibodies compared to autoantibody negative matched controls [71]. This finding was independent of prior or current cigarette smoking. Fischer and colleagues found that 80% of anti-CCP antibodies positive subjects with chronic lung disease (but without joint symptoms) had imaging evidence of airways inflammation [72]. Among these subjects 96% demonstrated histologic evidence of lung inflammation. In these 2 studies, 5 subjects developed synovitis classifiable as RA, and all 5 had evidence of lung inflammation preceding the development of clinically apparent arthritis [72]. In another study arthritis-free subjects had RF antibodies and/or anti-CCP antibodies in their sputum but not present in their serum, suggesting that in this subset, these RA-related autoantibodies are generated in the lung [73].

1.2.3. The gut

To date, much of the data investigating the gastrointestinal mucosa in RA has focused on the gut micro biome. The gut micro biome is known to affect the development of the innate and adaptive immune system, and may trigger the development of autoimmunity [74,75]. In murine studies, specific alterations of gut bacteria can enhance or attenuate susceptibility to experimentally-induced arthritis [76–78]. In humans, studies have identified differences in the gut micro biota in patients with RA compared to controls [79,80]. Still, it is impossible to say whether the differences in gut microbial communities are the cause or the result of an underlying inflammatory environment, or whether the therapies used in RA are responsible for altering the gut microbial composition.

1.3. The coronary bed in RA - vulnerable coronary plaques?

The characteristics of coronary plaques in RA patients was recently studied using cardiac computed tomography angiography (CTA) [81–83]. A study that followed 74 RA patients and 74 matched controls found that asymptomatic RA patients had a higher prevalence, extent, and severity of “vulnerable” non-calcified coronary plaques [83]. Non-calcified plaques in the coronary tree were found in 54% of the patients with RA vs. 21% in the controls ($p = 0.0001$) [83]. Additional clinical study (150 RA patients) found an association between systemic inflammation and vulnerable coronary plaques on CTA [84]. Interestingly, these studies repeat a previous autopsy study, in which RA patients had significantly more “vulnerable” plaques compared to autopsy controls. A vulnerable plaque was defined by the number of inflammatory cells (> 25) per high power field with a thin fibrous cap (< 65 um thick) [85].

A study that evaluated the relative risk of subclinical atherosclerosis in patients with systemic lupus erythematosus, RA and Diabetes Mellitus found a 2-fold increase in atherosclerotic plaques in the carotid and femoral arteries compared to controls. Increased prevalence of subclinical atheroscelrosis in patients with RA was confirmed in several studies [86–88].

1.4. The effect of inflammation on the cardiovascular system in RA

Inflammation is now considered a key mechanistic pathway in atherosclerosis. Active inflammatory processes documented by histopathological and immunochemical observations have been shown to trigger plaque rupture and acute thrombotic events leading to acute vscular occlusion and clinical events like acute myocardial infarction and acute cerebral stroke. Interleukin 1β is a cytokine that has a key role in the infalmmatory response and is triggered by multiple inflammatory pathways like interleukin 6 signaling pathway. It has been suggested that over activation of the innate immunity could be the result of a chronic inflammatory process, that can be induced by endogenous alarm factors (alarmins). It is possible that neutrophil extracellular traps (NETS) are alarmins, actively involved in the chronic inflammatory process underlying the pathogenesis of atherosclerosis [89]. Studies suggested that an imbalance between "NETosis" (a process of NET formation) and NET degradation may be the mechanism of autoimmune diseases. Neutrophils, interleukin 8, ANCA – all play an active role in NET formation, leading eventually to prolonged exposure to NETs related events, and increase the likelihood of systemic organ damage [90]. Premature atherosclerotic coronary artery disease and premature cardiac death were related to interleukin 17A, a cytokine that acts on vessel and myocardial cells, aggravating inflammation, coagulation and thrombosis [91].

Interleukin 1 is a pro-inflammatory cytokine. Members of the IL-1 family regulate recruitment and activation of cells involved in enhancement of the immune response [92]. A randomized trial that examined the inflammatory hypothesis in atherosclerosis was done (the Canakinumab Anti-inflammatory Thrombosis Outcomes Study [CANTOS]) [93]. In that study, patients with a history of myocardial infarction and chronic inflammation (documented by high C reactive protein levels) were eligible to participate, and were randomized to Canakinumab at doses of 50, 150, and 300 mg every 3 months or placebo. Canakinumab is an Interleukin-1 blocker approved by the Food and Drug Administration for treatment of patients with Juvenile Idiopathic Arthritis. It has been used also in patients with adult onset Still's disease [94], hidradenitis suppurativa [95], resistant Familial Mediterranean Fever [96], hyper IfD and periodic fever syndrome [97], amd Bechcet's disease [98]. The mean follow up period was 3.7 years, with a significant decrease in risk of primary end points (nonfatal myocardial infarction, stroke or cardiovascular death) in patients treated with Canakinumab in all doses [93]. Canakinumab also reduced significantly C reactive protein level without any effect on the lipid profile.

1.5. The lipid profile in RA

The function and structure of high-density lipoprotein (HDL) was found to be altered in the setting of systemic inflammation [99–102], also in patients with acute inflammatory response after surgery or during infection [99,102], and in patients with rheumatic diseases, including active RA [103,104]. The anti-atherogenic function of HDL was suspected to be activated through its ability to promote cholesterol efflux from the arterial wall cells [105], and also to protect LDL against oxidation [106–110]. The former function of cholesterol efflux was recently shown to be a strong inverse predictor of both coronary artery disease and carotid intima media thickness (IMT) in non-RA patients [111]. The cholesterol efflux capacity of HDL was also evaluated in patients with RA [112], and found that HDL from RA patients with high disease activity score [measured by a disease activity score using 28 joint count (DAS28)] > 5.1 had significantly decreased ability to promote cholesterol efflux compared to HDL from patients with low disease activity score (DAS28 < 2.6) [112]. In addition, a significant

correlation was found between cholesterol efflux and disease activity in all RA patients (r = -0.39, p = 0.01); the higher the RA disease activity, the lower the HDL efflux [112]. A similar significant correlation was observed with ESR (84). The HDL's protein structure of patients with active RA found 78 different proteins in the HDL complexes [112]. Twelve of these proteins were significantly increased in RA patients with non-protective, pro-inflammatory HDL compared to RA patients with normal anti-oxidant HDL [113]. This data may suggest a potential mechanism by which systemic inflammation can alter HDL's protein cargo with subsequent effects on its protective capacity.

In the general population, the atherogenic lipid profile is considered to be high total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C). Dyslipidemia is commonly seen in patients with RA and is linked to increased cardiovascular disease [114].

A retrospective study of 1078 patients showed that lipid changes (higher TC, lower HDL-C, and higher triglycerides) may be present even before the onset of RA [115]. High levels of lipoprotein(a), which is structurally similar to LDL-C and is atherogenic in nature, have also been reported in patients with RA [116,117]. The relationship of lipids in patients with RA is more complex than in non-RA individuals because of the interplay of cholesterol with inflammation. Cholesterol levels decrease in the presence of active inflammation. The Third National Health and Nutrition Examination Survey (NHANES) compared lipid profiles of 128 patients with RA aged 60 and older to non-RA controls and found that patients with RA who were not on DMARDs or glucocorticoids had significantly low levels of HDL cholesterol [118]. Similarly, low TC and LDL-C levels were seen in patients with active RA while the rate of having a myocardial infarction remained 1.6 times higher than patients without RA [119,120]. This has been defined as the RA 'lipid paradox' [119]. High CRP among patients with RA representing high level of inflammation correlates with lower TC, LDL-C and HDL-C while at the same time that high CRP is associated with increased CVD risk [121,122]. While the exact mechanism for the lipid paradox remains unknown, genetic factors, reduced lipid synthesis, increased clearance as well as cholesterol consumption as an essential substrate to develop an inflammatory response have been implicated as causes for the low cholesterol levels [123–125]. It has also been observed that RA therapies increase the lipid levels while reducing inflammation [126]. These changes gathered special attention during the clinical trials of tocilizumab (TCZ), an interleukin (IL)-6 receptor blocker. A significant increase in lipid levels was observed in patients who received TCZ [127,128]. There are ongoing studies to determine whether these changes are detrimental for CVD risk and if so, to what extent. A similar pattern of lipid changes was also seen with other RA therapies such as DMARDs, and tumor necrosis factor (TNF) alpha inhibitors which suggests that these changes are not only a result of an intrinsic mechanism of action (IL-6 blockade) but also from decreased inflammation.

1.5.1. Effects of statins on endothelial function, inflammation, immunomodulation and thrombogenesis

Statins have been shown to affect the prognosis of patients with cardiovascular risk factors in primary and secondary prevention trials. There is a continuing evidence that the beneficial effects of statins is beyond their effect on the lipid profile per se. Some of the mechanistic pathways that may explain the pleotrophic effects of statins include an effect on vascular inflammation. Inhibition of HMG-CoA reductase reduces the mevalonate pathway (involved in synthesis of isoprenoids like farnesyl pyrophosphate and geranylgeranyl pyrophosphate). Statins have been shown to inihibit production of isoprenylated and geranylderanylated proteins, that way preventing interferance with the mevalonate pathway and blocking the effect of Rho proteins (which downregulate endothelial nitric oxide synthase [eNOS]), thereby increasing eNOS expression. Other effects of statins depend on inhibition of Ras prenylation. This activity downregulates activity of nuclear factor kappa B (NFkB), involved in many inflammatory pathways, with a key role in atherosclerosis [129]. Statins also affect immunomodulation. They inhibit induction of MHC-II expression by interferon γ. It was demonstrated in endothelial cells and in monocyte-macrophages. Statins reduce TH1 responses (CD4+ helper T cells) and promote TH2 cell responses (these cells secrete anti-inflammatory cytokines like interleukin 4, interleukin 10, interleukin 13, and reduce level of transforming growth factor). Statins also induce increase in circulating endothelial progenitor cells (EPCs), which were shown to augment neovascularization of ischemic tissue. Statin treatment of patients with coroanary artery disease was associated with a 1.5 fold increase in the number of endothelial progenitor cells 1 week after initiation of treatment, which was followed by a sustained increased levels of EPCs to 3-fold at week 4 of the treatment. Statin treatment also increased the function of EPCs, demonstrated by their migration ability.

Statins also upregulate endothelial nitric oxide synthase (eNOS). Oxidized low density lipoprotein (LDL) cholesterol downregulates eNOS mRNA. Statins have been demonstrated to upregulate eNOS expression and prevented the negative effect of oxidized LDL on eNOS. This protection is attributed to activation of the PI3K-Akt pathway. Decreased expression of klotho gene is associated with enhanced oxidative stress. Statins prevented L-arginine methyl ester induced decrease of klotho gene expression in rat kidneys, and prevented progression of atherosclerosis. Statins attenuate angiotensin II induced free radical production and downregulate angiotensin AT1-receptor expression [129]. Factor VII and activated tissue factor (TF) form extrinsic complexes on cell membranes and induce rapid and potent thrombosis. Statins induce impaired expression of TF on macrophages, attributed to inhibition of the TF gene induction. Statins also inhibit Rho/Rho-kinase and activation of Akt. They attenuate atherosclerotic plaque thrombogenicity by reducing cell-mediated thrombin generation [129]. A meta-analysis of 15 clinical studies showed that statin therapy in patients with RA increased high density lipoprotein (HDL) cholesterol level, reduced LDL-cholesterol level, total cholesterol and triglyceride levels [130]. Pooled analysis showed that statins decreased C reactive protein and ESR, and 9 studies reported an improvement in disease activity score in RA patients who were treated with statins for 12 weeks, with reduction in the DAS28 score [130].

1.6. Endothelial dysfunction in RA

Endothelial dysfunction has also been linked to systemic inflammation and the development of early atherosclerosis [131,132]. Our group studied the vascular responsiveness of patients with RA and found that most of the patients (86%) had endothelial dysfunction. Those patients who had the highest vascular responsiveness parameters were patients with the lowest clinical scores of RA severity and less inflammation. Those who had the worst vascular parameters had the worst clinical characteristics of RA and severe inflammation [133]. Another study from our group found an impaired function and lower numbers of endothelial progenitor cells (EPCs) in patients with RA, which could explain the endothelial dysfunction observed in patients with RA [134]. Because of the poor regenerative ability (related to the EPCs' inhibition) it is believed that this may explain the high CV death rate and the higher CV events rate among patients with RA. The positive correlation between EPCs and endothelial function and the CV risk assessed by the Framingham score has been demonstrated by Finkel et al. in 2003 [135], where they have demonstrated that healthy subjects with CV risk factors had impaired number and function of their EPCs. The higher the number of risk factors, the less the ability to produce EPCs. Besides, they showed that EPCs' number was inversely correlated with endothelial function. Subjects with lower numbers of EPCs had more significant endothelial dysfunction. The lower the EPCs number the worst the endothelial function [135].

1.7. Endothelial progenitor cells (EPCs) – a key player in atherosclerosis

The value of EPCs as biomarkers for disease severity, prognosis and response to therapy has been the focus of several investigations. In patients at an increased risk of cardiovascular disease, including those who suffer from diabetes mellitus [136], hypertension [137] and chronic kidney disease [138–140], the peripheral EPCs number is reduced and the EPCs function is often impaired. The reduction in EPCs number and function was also observed in patients with coronary artery disease [141] and stroke [142,143]. By contrast, an increased number of EPCs is often observed in patients who present with an acute vascular event like AMI [144] or unstable angina pectoris [145,146], suggesting the mobilization of EPCs during acute ischemic events. Usually EPCs reach a peak at day 5-7 following an acute vascular occlusion, and then start to decline.

1.8. EPCs & atherosclerosis

Hill *et al.* reported that the number of circulating EPCs was associated with the Framingham risk score and endothelial function (measured by flow-mediated brachial artery reactivity) [135]. Those who had impaired ability to grow colonies of EPCs had the worst Framingham score, and the EPCs number correlated with the subjects' endothelial function. The lower the number of EPCs, the worst was the endothelial dysfunction. The relationship between EPCs and cardiovascular outcome was later confirmed by Werner and colleagues, who demonstrated that patients with coronary artery disease and a low baseline number of EPCs experienced a higher death rate from cardiovascular causes [141]. Moreover, EPC levels independently predicted atherosclerotic disease progression even after adjustment for traditional cardiovascular risk factors [147]. Aging was also associated with a decline in the number of circulating EPCs [148].

1.9. EPCs in diabetes mellitus

It is well-known that EPCs of patients with diabetes mellitus are significantly reduced, and the lower number is associated with vascular complications of diabetes mellitus [149]. The macrovasculopathy assessed by ankle brachial index (ABI) or carotid narrowing was reportedly associated with reduced levels of EPCs [150–151], and EPC levels were also found to be reduced in diabetes retinopathy patients [152]. EPC counts were negatively correlated with the albumin excretion in diabetic patients [153]. The reduction of EPCs can already be observed at the onset of diabetes, but a further reduction is seen with longer lasting disease [159].

1.10. EPCs in heart failure

In patients with symptomatic heart failure (New York Heart Association [NYHA] functional class I), level of EPCs were increased compared with matched controls, but then declined progressively with increasing severity of heart failure [154]. EPCs number were an independent predictor of survival along with age and diabetes mellitus in heart failure. Interestingly, exercise was observed to be associated with an increase of peripheral EPCs in patients with NYHA class III heart failure [155], and we have to remember this fact, that tells us that the natural history can be changed and that exercise could have an important role in rehabilitation of patients with heart failure and may improve survival.

1.11. EPCs in rheumatic & chronic inflammatory conditions

Rheumatoid arthritis (RA) is the most common inflammatory joint disease that can lead to joint destruction and disability if insufficiently treated, and it is characterized by an increased cardiovascular mortality and morbidity [164] even after adjustment for traditional risk factors. The increased cardiovascular risk is also seen in other chronic inflammatory conditions, such as systemic lupus erythematosus (SLE), with up to a 50-fold increase in cardiovascular mortality [156–161]. In RA, levels of peripheral EPCs are inhibited compared with matched healthy controls [162,163], and an inverse relationship has been reported between peripheral EPC levels and disease activity. EPCs were also observed to accumulate in the inflamed joints [163], where an increased blood vessel supply is needed, and giving rise to the hypothesis that EPCs are trapped within the highly vascularized inflamed joints [163]. The trapped EPCs are suspected to contribute to disease progression by helping to maintain the inflammatory process through new blood vessels formation, further facilitating the influx of immune cells [163,164].

SLE, a potentially life-threatening disease that can affect multiple organs, was found to be associated with depleted EPC levels [165]. SLE is also associated with impaired EPC differentiation into endothelial cells, depleted adhesion and migration capacity, and increased apoptosis, with reduction of angiogenic growth factors [165–169].

1.12. The effects of inflammation on EPCs mobilization & function

C reactive protein (CRP) is one of the most common acute phase reactants. In 2004, Verma and colleagues had showed that CRP inhibited EPCs differentiation, survival and function [170]. Another observation showed that even in healthy subjects, the colony-forming capacity was negatively correlated with CRP levels [171]. CRP itself may impair EPCs antioxidant defense and may promote EPC sensitivity to oxidant-mediated apoptosis and telomerase inactivation [172]. On the other hand, during an acute inflammation, CRP is released as a consequence of an acute ischemic event or acute endothelial injury, which leads to rapid EPCs mobilization. Together, these findings suggest a dual role of CRP in EPC biology depending on the cause and duration of CRP secretion. We distinguish today between 2 kinds of inflammation – the acute inflammation has a positive role in promotes vasculogenesis and enhanced immunity and defense systems against "intruders", while the long standing, continuous chronic inflammation is considered harmful, since it causes self-destruction, enhanced apoptosis, over expression of reactive oxygen radicals and other free radicals, a cascade of pro-inflammatory events with activation of transcriptional factors like nuclear factor kappa B (NF-k-B), and exhaustion of the immune system and the regenerative system (stem cells) capacity and capability – leading to destruction and eventually to death [170–172]. The production of CRP in the liver is mainly induced and perpetuated by pro-inflammatory cytokines interleukin 6 (IL-6), interleukin 1 (IL-1) and interleukin 17 (IL-17) [173]. IL-6 plays a key role in inflammation of chronic inflammatory disorders. This cytokine is produced by various cells contributing to inflammatory reactions, with the vast majority believed to be secreted from macrophages and lymphocytes [174]. In RA, IL-6 is systemically elevated, and recently its blockade with an IL-6 receptor antagonist was shown to be a successful treatment option [174]. High levels of serum IL-6 levels were associated with low EPCs number in RA patients and in healthy controls [175], suggesting a potential role for this cytokine in EPC homeostasis and biology. An acute increase in IL-6 may lead to EPCs mobilization, whereas chronic IL-6 secretion is associated with a reduction in peripheral EPCs [175].

Exercise-induced EPCs mobilization was linked to IL-6 secretion in healthy individuals [176]. It is likely that IL-6 plays a key role EPCs physiology. Chronically increased systemic IL-6 levels directly and/or indirectly impair EPCs function and number – which could be part of the mechanistic pathway that may explain the devastating effects of long standing chronic inflammation. Tumor necrosis factor Alfa (TNF-α) is a pro-inflammatory cytokine highly up-regulated in RA. In RA, increased TNF-α levels were associated with reduced EPCs number, and patients treated with antibodies blocking TNF-α showed either normal EPC levels (139) or an increased levels of EPCs [177]. Moreover, in

Type 1 diabetes, an inverse relationship was found between EPCs level and TNF-α levels [178]. Addition of TNF-α to EPCs isolated from healthy controls led to a dose-dependent reduction of proliferation, migration, adhesion and tube formation capacity [179]. In addition, TNF increased the EPCs apoptosis rate, and enhanced the expression of pro-inflammatory adhesion molecules and paracrine factors in EPCs. Several medications, like HMG-CoA reductase inhibitors (statins) or resveratrol found in red wine can revert the inhibitory effect of TNF on EPCs and restore the number and function of EPCs in the peripheral blood [180].

1.13. The role of nitric oxide in EPCs biology

Endothelial progenitor cells (EPCs) are essential to blood vessel formation, can differentiate into mature endothelial cells, and promote the repair of damaged endothelium. Nitric oxide (NO) is a short-lived signaling molecule that is produced by vascular endothelial cells and participates in the maintenance of vascular tone. NO is also known to participate in other physiological processes, such as cell survival, proliferation, and migration. Bioavailability of NO is reduced in EPCs from diabetic patients. An inverse relationship exists between the reduction in NO bioavailability in EPCs and the patient's plasma glucose and glicated hemoglobin levels. In addition, NO bioavailability in EPCs correlates with plasma oxidized low-density lipoprotein (LDL) levels in diabetic patients. This reduction in NO bioavailability could be attributed to oxidative stress and it also may be due to impairment of one or more members of the protein signaling cascades that are responsible for NO production. Stimulation of NO production or its signaling cascades in EPCs may increase their number and improve their function, thus attenuating endothelial damage, independent of the vasodilator effects of NO. [181]

Endothelial nitric oxide synthase (e-NOS) is essential for neovascularization. Impaired neovascularization in mice lacking e-NOS is related to a defect in progenitor cell mobilization. Mice deficient in e-NOS (Nos3−/−) showed reduced vascular endothelial growth factor (VEGF)-induced mobilization of EPCs with increased mortality. Intravenous infusion of wild-type progenitor cells, but not bone marrow transplantation, rescued the defective neovascularization of Nos3−/− mice in a model of hind-limb ischemia, suggesting that progenitor mobilization from the bone marrow is impaired in Nos3−/− mice. Mechanistically, matrix metalloproteinase-9 (MMP-9), which is required for stem cells mobilization, was reduced in the bone marrow of Nos3−/− mice. These findings indicated that e-NOS expressed by bone marrow stromal cells influenced recruitment of stem cells and progenitor cells. This may explain the impaired regeneration processes in ischemic heart disease patients, who are characterized by a reduced systemic NO bioactivity [181,182].

2. Management of cardiovascular risk in patients with RA

2.1. Life style modification

2.1.1. Obesity and weight loss

Obesity cause systemic low grade inflammation that may induce autoimmune diseases. Metabolic changes and the enhanced inflammatory state produced by the adipose tissue may aggravate immune diseases and cardiovascular disease. Osteoarthritis (OA) is believed to result from low grade inflammation. Risk factors for OA onset are body mass index (BMI) and fat tissue mass [183]. It can be triggered by mechanical injury, obesity, and type 2 diabetes mellitus. Patienys with elevated BMI have a 3-fold increase in cartilage damage. Obesity has a role in autoimmune diseases, and the incidence of obesity among patients with RA is 27%, compared to 18% in the general population. Pathologic BMI and adipose tissue mass are associated with macrophage activation in the adipose tissue and inflammation. Elevated BMI is associated with RA onset and severity [183–186].

T lymphocytes are significantly increased in adipose tissues of obese subjects. High fat diet suppresses GATA3 (transcription factor of Th2 cells) and FOXP3 (master regulator of Tregs). The number of Th1 cells (producing IFN γ) is incraesed in obese mice [187,188]. RA is a Th-17 mediated disease. In obesity the inflammatory millieu changes Th17 cells [188]. They become polarized in the presence of interleukin 6 and transforming growth factor, however, interleukin 6 and interleukin 23 induce pathogenic Th17 changes, defined by expression of CXCL3, CCL4, CCL5, interleukin 3, interleukin 22, colony stimulating factor 2 and granzyme B [189]. Microbiota may affect RA. Studies have shown that mice under germ free conditions had diminished arthritis [206]. Nutrition may have an effect on inflammation. While the western diet (rich in energy intake, saturated fat, carbohydrates, and low in fiber and antioxidants) may increase RA risk through enhancing inflammation and insulin resistance and obesity, the Mediterranean diet (rich in plant based foods, olive oil, less red meat) may reduce the risk of RA [190].

2.1.2. Physical activity

Physical activity cause a significant increase in T regulatory cells, a decrease in immunoglobulin secretion, and a Th1/Th2 shift, so that there is a decreased Th1 cell production. Exercise releases interleukin 6 from muscles and acts like a myokine, inducing anti-inflammatory response through interleukin 10 secretion and inhibition of interleukin 1 β [191]. Human and animal studies have shown that physcical activity cause a shift in the Th1/Th2 balance towards Th2 predominnance due to upregulation of Th2 genes. The Th1/Th2 ratio affects susceptibility to infections, allergy, and autoimmunity. Th1 cells are related to rheumatoid arthritis, multiple sclerosis and Hashimoto, while Th2 are related with systemic lupus erythematosus. Regulatory T cells are T helper cells that express CD4 and CD 25 markers. It has been shown that intense regular exercise caused a siginificant increase in T-regulatory cells and higher tissue growth factor β (an anti-inflammatory cytokine) [192]. Exercise incraese the number of neutrophils secondary to catecholamine and cortisol secretion during exercise. Exercise intensity affects neutrophils in a different way – moderate intensity increses chemotaxis, phagocytosis and oxidative free radicals activity, while extreme exercise reduces phagocytosis and oxidative stress. During exercise increases levels of interleukin 6, a cytokine that promotes the proliferation and activation of T-cells and the differentiation of B-cells into antibody producing cells. This increase is induced only by exercise and is not involved with tumor necrosis factor α production [192]. Interleukin 6 activates other cytokines like interleukin 1 receptor antagonist and interleukin 10. Both are known to inhibit T cell activation and attenuate inflammation. It has been shown that physical activity decreases the occurance of RA among women who had an active life style, which was more pronounced among women who cycled or walked more than 20 minutes a day and had exercised more than 1 hour per week [193]. Exercise may protect endothelial function through 3 major pathwats – reversal of endothelial dysfunction, antiatherogenic effects, and anti-inflammatory effects. It may also prevent RA related cachexia and fatique [193–197].

2.2. Anti-TNF medications

Atherosclerosis is considered an inflammatory process, and chronic inflammation associated with RA may accelerate this process. Traditional cardiovascular (CV) risk factors do not fully explain the increased risk of MI associated with RA. Drugs inhibiting tumor necrosis factor α (TNF-inhibitors) have been shown to reduce joint inflammation and associated inflammatory markers; thus, they may also influence the future risk of MI in the general population. Some studies found a reduced risk of MI following the use of TNF-inhibitors, compared with treatment with synthetic disease-modifying anti-rheumatic drugs (s-DMARDs). Most of these studies only followed patients for 1–2 years. TNF-inhibitors may influence the incidence of MI in the short

term by stabilizing the vulnerable plaque by inhibition of the inflammatory burden. However, any effect on plaque formation is likely to take much longer, and therefore, the full influence of TNF-inhibitors on future MI risk may take many years to become apparent [198–201].

The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) was a UK-wide prospective observational study that was established in 2001 to monitor the long-term safety of TNF-inhibitors and other biological therapies on many clinical parameters, among them the cardiovascular effects [202]. UK guidelines restricted the prescription of TNF-inhibitors in RA to patients with sustained active disease (28-joint disease activity score (DAS28) > 5.1 on at least two occasions a month apart) and who have failed to respond to therapeutic doses of ≥2 s-DMARDs (including methotrexate) given for ≥6 months. The TNF-inhibitors-treated patients included in this analysis got etanercept, infliximab and adalimumab. Recruitment to each TNF-inhibitors drug continued until the target of 4000 patients per treatment was reached. The control group was a group of biologic-naïve patients with active disease (guide DAS28 > 4.2) that were treated with s-DMARD therapies only [202].

Previous reports of the association between TNF-inhibitor therapy and the risk of MI followed patients up to 1–2 years and did not have consistent findings. The association between TNF-inhibitor therapy and the risk of MI over a longer time period (median 5 years) found a 39% reduction in the risk of MI in patients treated with TNF-inhibitors compared with those on s-DMARD [203].

An important finding was the association between the duration of TNF-inhibitors exposure and a reduction in cardiovascular disease risk in patients with RA. The use of TNF-inhibition for more than a median of 16 months was associated with lower risk of CV events.[228] In a Swedish study, 2 years follow-up on TNF-inhibition was associated with a 32% reduction in the risk of acute coronary syndrome [204].

Inflammation is a key factor in atherosclerosis, including endothelial function, plaque stabilization and post infarct remodeling; thus, inhibition of TNF-α may affect the inflammatory burden and plaque vulnerability leading to less cardiovascular events and MIs. TNF-inhibition may also affect CV risk via changes in lipid profile, decreasing insulin resistance and diabetes risk [205].

It has been observed that a better disease activity control was associated with fewer CV events [206]. Therefore, the current treat-to-target strategy to lower disease activity in RA may improve pain and function, but also reduce CV risk either through using s-DMARDs or biologics or a combination. Blockade of TNF-α may also modify the post MI via post-infarct remodeling and improve the post infarction devastating clinical events. A difference in the relative risk was observed between patients receiving TNF-inhibitors at the time of MI and those who got TNF-inhibitors in the past but stopped the TNF-inhibition therapy 1.3 years prior to the MI (50% reduction vs fivefold increase, respectively) [204–207].

2.3. Is there a cluster effect?

Inflammatory arthritides including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are all associated with increased risk of cardiovascular disease. Data from the Australian Rheumatology Association (4140 patients with RA, PsA and AS, totaling 19,627 patient-years) found that the cardiovascular risk was reduced with anti-TNF medication and other biologic anti-inflammation therapies, but not in those who had ceased biologic therapy. Previous studies have shown that people with any inflammatory arthritis had increased rates of cardiovascular morbidity and mortality compared to the general population [208].

2.4. Other types of anti-inflammatory medications

The pro-inflammatory cytokines interleukin 1 (IL-1) and interleukin 6 (IL-6) were found to be elevated in atherosclerosis, severe congestive heart failure, and in active RA [209]. Both IL-1 and IL-6 have been implicated in inflammatory pathways leading to endothelial dysfunction and atherosclerosis. IL-1 has an important role in atherosclerosis and is associated with plaque destabilization, adverse post-infarction remodelling, and cardiac hypertrophy. High concentrations of IL-6 were found to be associated with increased CV risk and with increased all-cause and CV mortality in hospitalized patients with cardiovascular disease [209–211].

2.4.1. IL-1 inhibition

The inflammatory effects of IL-1 can be neutralized by its physiologic inhibitor, IL-1Ra, or by anakinra which is a recombinant form of human IL-1Ra. In a double-blind, crossover, placebo-controlled study, researchers found that anakinra improved vascular function and left ventricular function in patients with RA. This beneficial effect was much more significant in RA patients who had a documented coronary artery disease.[247] Anakinra prevented adverse post-infarction remodelling in animal models[248] by inhibiting apoptosis of cardiomyocytes. In the Diastolic Heart failure Anakinra Response Trial (D-HART) pilot study (12 patients), showed that anakinra improved peak aerobic capacity in patients with heart failure. Other IL-1 inhibitors, like rilonacept and canakinumab, have yet to be subjected to extensive investigation [212–215].

2.4.2. IL-6 inhibition

Tocilizumab (TCZ) is a humanized monoclonal antibody that targets IL-6 receptor, blocking IL-6-mediated pro-inflammatory signalling. Improvement of endothelial dysfunction and aortic stiffness, assessed through improved FMD and decreased PWV, was found after 6 months of TCZ treatment. TCZ altered HDL particles towards a more anti-inflammatory composition. In a long-term study, the rate of MI was 0.25/100 patient-years and 0.19/100 patient-years for stroke - in patients who got TCZ - versus rates of 0.49/100 person-years for MI and 0.24/100 person-years for stroke in the pooled control groups [216,217].

2.4.3. Rituximab

Studies examining the cardiovascular effects of rituximab, a chimeric anti-CD20 monoclonal antibody, in RA patients are limited. Significant improvements in endothelial dysfunction assessed through increased flow medicated diameter percent change have been noted with rituximab. However, other researchers observed no change in arterial stiffness after 12 months of rituximab therapy despite significant improvements in measures of systemic inflammation. Increased total and LDL-cholesterol with unchanged HDL and triglyceride levels were noted by the same group of researchers, with a non-significant increase in atherogenic lipid profile.[255] A study that assessed the long-term safety of rituximab in 2,578 RA patients found that the rate of MI was 0.56/100 person-years, consistent with rates observed in other epidemiologic studies of RA, with no demonstrable differences in the rate of serious cardiovascular events during placebo-controlled periods [218,219].

2.4.4. Abatacept

Abatacept is a fully human soluble fusion protein consisting of the extracellular domain of human CTLA-4 and the modified Fc portion of human IgG1. After 6 months of abatacept therapy, circulating concentrations of total cholesterol, LDL-cholesterol and HDL-cholesterol levels were increased, with a non-significant decrease in atherogenic index, with worsening of aortic stiffness. More studies examining CV events are needed for this particular biologic agent. When the cardiovascular safety profile of abatacept (ABA) was compared to TNF-inhibitors in RA patients (6102 matched pairs of ABA and TNF-initiators from Medicare and 6934 pairs from MarketScan). Of these, 35.3% in Medicare and 14.0% in MarketScan had baseline CV disease. It was found that the overall CV events rate was 0.67 (Medicare) and 1.08 (MarketScan) for ABA treated RA patients and 0.79 in those treated

with TNF-inhibitors. This study showed that ABA was associated with a 20% reduced risk of CV disease compared with TNF-inhibitors [220].

2.4.5. Tofacitinib

An oral Janus kinase (JAK) inhibitor. As the newest such agent, tofacitinib has perhaps been subject to the least investigation in regards to its potential CV effects. In a systematic review that included data generated from four phase II and four phase III trials, tofacitinib use in approved doses was associated with increases in both LDL and HDL concentrations [221].

3. Summary

Patients with rheumatoid arthritis (RA) are at increased risk of mortality, largely attributed to increased cardiovascular (CV) death. Increased inflammation associated with RA appears to be a dominant key player that contributes to the increased CV mortality.

Inflammation is a key factor in atherosclerosis, including endothelial function, plaque stabilization and post infarct remodeling; thus, inhibition of TNF-α may affect the inflammatory burden and plaque vulnerability leading to less cardiovascular events and MIs. An aggressive management of inflammation may lead to a significant improvement in the clinical cardiovascular outcome of patients with RA.

The clinical evidence that showed a reduced risk of CV events following treatment with anti-inflammatory agents may suggest a new approach to treat atherosclerosis, i.e., inhibition of inflammation using biological medications that were primarily aimed to treat the high scale inflammation of RA and other autoimmune-inflammatory diseases, but may be useful also to prevent progression of atherosclerosis. At that stage we need to plan and conduct large population studies (basic research and clinical trials) in order to consolidate our hypothesis.

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