

DIABETES MELLITUS AND RHEUMATOID ARTHRITIS: FACTS SUPPORTING THEIR POSSIBLE ASSOCIATION

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Introduction

The prevalence of diabetes has been increasing constantly over the last years, becoming an important condition affecting population worldwide. Around 347 million people, corresponding to 7% of the world's population are affected by diabetes and this number is expected to grow to 552 million by 2030, corresponding to approximately 8% of the world's total population [1, 2]. Diabetes caused 4.8 million deaths [2] and is related to several co-morbidities where some of them are considered as its own complications [3]. Arthritis is not yet a comorbid condition recognised with diabetes, although frequent association of these two conditions has been observed. Despite this, up to now their frequent association is still not seen as part of the potential difficulties that patients and medical doctors may experience when managing diabetes [3]. Rheumatoid Arthritis (RA) as a systemic autoimmune disease most common in females and developed countries, affects around 1% of the general population causing long term disability in patients [4]. Regarding Diabetes Mellitus (DM), rates of disability, are reported to be higher than those of the general population [5]. Different studies have reported that more than 50% of patients with DM also have RA [5]. Inflammation and even drugs used for the treatment of RA are thought to have an important role in this regard [6, 7]. On the other hand, evidence has also indicated that DM and RA are equally associated with increased risk of cardiovascular disease which is identified as a major cause of death [8 -10].

RA and DM are both complex multifactorial diseases. The association between these two conditions has not been clearly explored up to now. As indicated by Doran, it is not clear whether there is an increased prevalence of DM in patients with RA or an increased prevalence of RA in patients with DM [11]. Through this study we sought to evaluate elements and that may be relevant in this association.

Systemic Inflammation, Rheumatoid Arthritis and Diabetes Mellitus.

Inflammation is a typical feature of RA. The important role of pro-inflammatory mediators like alfa tumor necrosis factor (α -TNF), interleukine 1 and 6 (IL-1, IL-6) have

been already documented in RA [6]. Beside the important role that α -TNF plays in RA, studies in humans and mice shows that α -TNF mRNA is over expressed in adipocytes of obese individuals [12, 13]. In vitro studies show that this mediator can obstruct the bioactivity of insulin by inhibiting tyrosine phosphorylation and subsequent activation of both insulin receptor and insulin receptor substrate [14]. All this, can predispose the development of insulin resistance (IR) and subsequent diabetes, especially type 2 diabetes mellitus (T2DM). It has also been shown that insulin resistance may help in the development of inflammation instead of being only a consequence of high concentrations of inflammatory mediators [15]. Similar to α -TNF, IL-6 plays an important role in insulin signaling pathways by diminishing the effect of insulin [16]. Moreover it has been observed that IL-6 production is increased in obesity and in females that later develop T2DM [17]. Other inflammatory cytokines seems to be associated with RA, IR and T2DM. Elevated levels of IL-1 and IL-2 have been observed in the serum and synovial tissues, correlating with insulin sensitivity in RA patients [18]. Of note, elevated levels of IL-17 have been observed in synovial tissues of RA patients, inhibiting adipocyte differentiation [19, 20]. In addition to pro-inflammatory cytokines, there are other several proteins produced by the adipose tissue that seems to be related to chronic inflammation. These proteins, named adipokines, can modulate the levels of pro-inflammatory cytokines, contributing like this to inflammation. An independent association has been found between leptin (secreted by adipocytes) and IR in RA patients. In normal conditions, leptin decreases insulin secretion and improves insulin sensitivity while in inflammatory conditions with high levels of circulating C-reactive protein (CRP) there is an leptin resistance enhancing furthermore IR and predisposing the development of diabetes [21]. Resistin is another protein produced by adipocytes in mice while in humans it is produced predominately by monocytes and macrophages. Resistin levels are increased in synovial fluid of RA patients and strongly correlates with inflammatory markers [16, 22]. Resistin increases hepatic IR associated with increased production of IL-6 and α -TNF [16]. Moreover, resistin induces the expression of vascular and intracellular adhesion molecules (ICAM-1, VCAM-1) known to play an important role in the development of atherosclerotic plaques in cardiovascular disease which is the main comorbidity in both RA and DM [9, 10]. Adiponectin is

another group of protein produced by the adipose cells; their levels are inversely associated with the levels of the pro-inflammatory molecules typical for RA, playing like this the role of an anti-inflammatory factor [23]. Adiponectin production is decreased when exposing the adipose cells to α -TNF [24]. There also some reasons for speculating about a possible association between type 1 DM and RA. These include evidence of familial clustering of autoimmune diseases, including RA and type 1 DM, and the common association of the HLA-DR4 allele with both DM and RA [25]. One study found that 13% of 295 RA patients had a first-degree relative with type 1 diabetes [26].

All this facts, gives a new insight to the shared pathogenic pathways between RA and IR involving different mechanisms suggesting that patients with chronic inflammatory conditions are at high risk for developing diabetes. Despite the strong evidence of associations between all these mediators with metabolic and inflammatory effects, the exact pathway of interaction between them has not been fully elucidated.

Drug Therapies in RA and DM

Treatment of both conditions has been investigated in terms of potential positive and negative factors in this association. In this regard, it is well known that treatment of RA with glucocorticoids (GCs) have effects on the function of basic metabolism. The use of high-dose GCs results mostly in hyperglycemia increasing like this the risk of DM, while the effect of daily low-dose GCs used in short term, may improve the glycemic control by enhancing insulin secretion by the pancreas and peripheral insulin sensitivity [7, 27].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as well in the treatment of RA. Considering their effect on inhibiting cyclooxygenase-mediated inflammation, they are supposed to improve IR and reduce the risk for T2DM [28]. On the contrary, in T2DM patients it has been observed that administration of indomethacin decreases the secretion of insulin resulting in increased endogenous intrahepatic glucose production [29].

Regarding traditional Disease Modifying Anti Rheumatic Drugs (DMARDs) and metabolic function there are few data in literature. It has been reported that use of traditional DMARDs like methotrexate (MTX), chloroquine (CQ), hydroxychloroquine (HCQ) or azathioprine reduces IR [27] decreasing like this the probability to develop DM. In particular, hydroxychloroquine used in RA patients has been associated with a reduction in risk for developing DM [30]. In vitro studies showed that both HCQ, CQ inhibit the production of α -TNF [31] contributing like this in the modulation of IR and lowering the risk of T2DM. It has also been demonstrated that HCQ induces autophagic cell death in fibroblastes; this means that HCQ has an antiproliferative effect suggesting its

possible regulatory effect on cellular energy homeostasis [32].

On the other hand, the use of α TNF antagonists for RA treatment has been associated to lipid profile alteration and improved insulin sensitivity in RA patients [33]. In this regard, several studies demonstrated that treatment with etanercept or infliximab are associated to more favorable changes in terms of insulin sensitivity. Treatment with Etanercept showed improvement on IR 24 weeks after the beginning of therapy while treatment with Infliximab improved IR 12 week after administration the first dose of the drug [34, 35].

On the contrary, treatment with Adalimumab was not associated to improvement on IR. Of note, this study evaluated 9 RA patients and the changes in insulin sensitivity were assessed 8 weeks after the beginning of treatment [36]. Considering all this, the lack of effect of Adalimumab on IR in this study may be attributed to the small number of patients included and the insufficient time to detect treatment-related changes in insulin sensitivity. Despite this study, treatment of RA patients with α -TNF antagonists restores the metabolic function and improves IR especially in long-term treatment.

Risk of cardiovascular disease in RA and DM.

The majority of the research focuses on the relationships between both conditions and the risk of CVD. RA patients carry a high risk of morbidity and mortality from CV causes, estimated to be 50 % - 60% higher than that of the general population [37]. The increase in CV events cannot be entirely explained by the traditional CV risk factors; disease-related mechanisms like inflammation and autoimmune pathways plays and important role in this regard [38].

On the other hand, even in diabetes, CVD has been identified as the major complication and primary cause of early death. About 65% of people with diabetes die from heart disease while adults with diabetes are 2 to 4 times more likely to have heart disease when compared to the general population [11].

Several investigations have been performed to compare the potential risk of different elements of CVD in both RA and DM. In this regard, Karanasos et al. investigated the associated of RA with increased cardiovascular morbidity compared to DM. As a result, the authors found that RA patients without previous CVD can develop myocardial ischemia at similar levels as DM patients but higher of that of the healthy population included in this study [39].

Furthermore, in a prospective evaluation it was shown that symptomatic patients with RA exhibited high myocardial ischemic burden which was comparable to patients with DM. It was found that myocardial ischemia was common in patients with no previous CVD [8].

In a similar study, evaluating the presence of silent myocardial ischemia (MI), it was demonstrated that chronic artery disease was more common in DM and controls than in RA patients [40].

Lindhardsen et al. completed a study demonstrating that the overall incidence rate ratio of MI event after developing RA was increased to 1.61 (95% CI 1.42 to 1.83), which was comparable to the risk of MI after developing DM of 1.70 (95% CI 1.59 to 1.83). In accordance with previous findings, this study demonstrated that the risk of MI is especially high among younger patients with RA. Similar to what has been found in DM, this study concluded that RA is an independent risk factor for MI [9].

On the other hand, Yazdanyar et al. concluded that RA was not associated with adverse perioperative CV risk or mortality risk; cases were classified by risk severity as low-risk, intermediate-risk, or high-risk non-cardiac procedure [41]. Results showed that 2.34% of patients with low risk had a composite CV event, and death occurred in the 2.34% of patients. For intermediate and high risk, the numbers were 0.51%, and 2.12% for composite CV event and 0.50%, and 2.59%, for death, respectively [41]. Death was less likely in RA patients than in DM patients for patients undergoing an intermediate-risk procedure, but the difference in mortality rates among those undergoing low-risk versus those with high-risk procedures was not significant [41]. Patients with RA were less likely to have a CV event than patients with DM for procedures of low risk and intermediate risk. After evaluation using adjusted models, RA was not independently associated with an increased risk of perioperative death or a CV event [41].

A 3-year prospective study performed by Peters et al. indicates that the risk of CVD in RA was significantly elevated compared with the general population and comparable with the extent of the risk in T2DM [42]. In this study, the incidence of CVD in patients with RA was 9% in comparison to 4.3% in the general population. The hazard ratio (HR) for patients without diabetes and with

RA (2.16) was comparable with those with T2DM (2.40) [42].

A cross-sectional study evaluating the risk of CVD between DM and RA, concluded that the prevalence of CVD was elevated comparable to T2DM [43]. Prevalence in the population with and without diabetes was 5% versus 12.4% while in RA prevalence was recorded to be 12.9% [43].

Stamatelopoulos et al. demonstrated that atherosclerosis severity and frequency was equal between patients with DM and RA, strengthening the fact that risk factors for CVD should be taken into consideration not only in DM patients but even patients with RA [44].

As described above, there is substantial evidence for increased cardiovascular risk in RA comparable to the risk found in DM. Some researchers have questioned if patients with DM and concomitant RA might have double cardiovascular risk, making this an interesting topic for future studies.

Conclusions

There are several mechanisms that may explain a possible association between DM and RA. It is clear that systemic inflammation as one of the main characteristics of RA predispose the development of insulin resistance and diabetes. On the other hand, drugs used to treat RA contribute widely to the development of insulin resistance increasing like this the risk for developing diabetes. Moreover, both conditions are widely linked to the risk of developing cardiovascular disease as a main co-morbidity and cause of death in these patients. Considering all these results, the next step would consist in designing and implementing a larger and more direct investigation to evaluate the association between diabetes and arthritis and potentially relevant characteristics in Albanian population.

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Biography

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