

**The clinical value of anti – cyclic citrullinated peptide (anti-CCP) antibodies and insulin resistance (IR) in detection of early and subclinical atherosclerosis in Rheumatoid arthritis**

Thesis

Submitted by

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## **Summary**

Rheumatoid arthritis is a systemic autoimmune disease of unknown etiology. Cardiovascular disease is a leading cause of mortality in rheumatoid arthritis (RA).

Endothelial dysfunction often precedes manifest atherosclerosis. Both traditional, risk factors and inflammation-associated factors are involved in RA-associated atherosclerosis. Among imaging techniques, the early determination of common carotid intima-media thickness (ccIMT), flow-mediated vasodilation (FMD), and nitroglycerine-mediated vasodilation (NMD) may be useful to determine atherosclerosis and endothelial dysfunction.

We and others found increased ccIMT and impaired FMD in RA patients. Among immunological and metabolic laboratory markers, anticyclic citrullinated peptide (anti-CCP) antibodies, insulin resistance (IR) may be involved in the development of vascular disease in RA.

The present study was performed to assess the prevalence of atherosclerosis in RA patient and to determine if it is associated with anti-CCP as immunological marker and insulin resistance as metabolic laboratory marker.

We studied fifty six (56) RA patients compared to nineteen (19) age and sex matched healthy controls. The diagnosis was based on the American College of Rheumatology (ACR) 1987 revised criteria for the classification of rheumatoid arthritis. Control and RA patients with known atherosclerotic complications such as stroke and MI, those undergoing hemodialysis, patients with peripheral vascular disease, malignancy or infections, hypertensive and diabetic patients were excluded.

Demographic and risk factor data were collected from both patients and controls. All patients underwent a complete history review, clinical examination according to the standard protocol and

routine laboratory investigation in addition to serum levels of anti-CCP and US-CRP were assessed using ELISA, also we calculated IR according to the HOMA2-IR model [serum insulin ( $\mu$ U/ml)  $\times$  plasma glucose (mmol/L)/22.5].

In patients group the disease activity were assessed by DAS28 and anteroposterior radiographs of both hands and feet were done and Simple Erosion Narrowing Score (SENS) was used for x-ray scoring of Joint space narrowing (JSN) and Erosions.

In both patients and controls, and by using high- resolution ultrasound, right and left carotid arteries were evaluated for intima-media thickness and for presence of plaque. Endothelial function was also assessed by flow-mediated dilatation (FMD) in brachial artery in response to reactive hyperemia and after glyceryl trinitrate (GTN) to detect early atherosclerosis.

There was a significant difference between patients and controls as regarding the mean, maximum and left IMT which was

significantly higher in the first group ( $P < 0.05$ ). The overall prevalence of atherosclerosis in the studied patients was 30.37% all of them had thickened intima and only of them three (3) patients (5.4%) had atherosclerotic plaque. Meanwhile, one (5.3%) of the controls had thickened intima with no detected plaque formation.

The flow-mediated dilatation (endothelial dependent dilatation) in our study was significantly impaired in RA patients when compared to controls. However, GTN responses did not differ between RA and controls.

A significant difference was found in HOMA-2 IR values ( $P < 0.05$ ) between patient and control, whereas no significant difference emerged in the prevalence of metabolic syndrome or one or more of its factors. Meanwhile, a statistically significant correlation was observed between thickened intima and flow mediated dilatation HOMA-2 IR values and a negative correlation between insulin resistance and post FMD, FMD dilatation percent

and dilatation ratio as parameters which assess the endothelial function in RA patients.

Anti-CCP positively correlated with ultrasonographic duplex findings of IMT of carotid arteries left IMT, mean IMT, and maximum IMT ( $P = 0.005$ ,  $0.009$  and  $0.009$  respectively), but negative correlation was found with parameters which assess the endothelial function of RA patients; post FMD, FMD dilatation percent and dilatation ratio ( $P = 0.02$ ,  $0.005$  and  $0.001$  respectively).

There was no significant correlation between US-CRP with ultrasonographic duplex findings of carotid arteries and parameters of endothelial function in RA patients.

There is association between Das28 and thickened intima media thickness and presence of plaques with a significant negative correlation between Das28 score and endothelial function

parameters in RA patients; FMD dilatation percent and dilatation ratio (0.005 and 0.007 respectively) and also it has a significant correlation with ultrasonographic duplex findings of carotid arteries significant correlation with ultrasonographic duplex findings of IMT of carotid arteries; left IMT, mean IMT, and maximum IMT (P= 0.01, 0.001 and 0.01 respectively).

As regarding the sensitivity of anti-CCP; it was less (94.12 %) than that of insulin resistance (100%) and its specificity was higher (46.15%) than that of IR (12.82%). And the positive predictive values of both of them were nearly equal, while the negative predictive value of IR was slightly greater.

