Göteborg, 2021

Cardiovascular morbidity and metabolic signature in patients with rheumatoid arthritis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson sal, Academicum, Medicinaregatan 3 , fredagen den 1:a oktober 2021, klockan 9:00

av **Mitra Nadali**

Fakultetsopponent:

Professor Elisabet Svenungsson

Avdelning för reumatologi, Karolinska institutet, Stockholm

Avhandlingen baseras på följande delarbeten:

I. Erlandsson M.C, Lyngfelt L, Åberg N.D, Wasén C, Espino R.A, Töyrä Silfverswärd S, **Nadali M**, Jood K, Andersson K.M.E, Pullerits R, Bokarewa M.I. Low serum IGF1 is associated with hypertension and predicts early cardiovascular events in women with rheumatoid arthritis. *BMC-Biomed Central Medicine (2019) 17:141*

II. **Nadali M,** Pullerits R, Andersson K.M.E, Töyrä Silfverswärd S, Erlandsson M.C, Bokarewa M.I. High expression of STAT3 in subcutaneous adipose tissue associates with cardiovascular risk in women with rheumatoid arthritis. *International Journal of Molecular Sciences, 2017 Nov 13; 18(11):2410*

III. **Nadali M**, Lyngfelt L, Töyrä Silfverswärd S, Erlandsson M.C, Andersson K.M.E, Bokarewa M.I, Pullerits R. Low soluble receptor for advanced glycation end products precedes and predicts cardiometabolic events in women with rheumatoid arthritis. *Frontiers in Medicine (Lausanne). 2020; 7: 594622*

IV. Erlandsson M.C, Töyrä Silfverswärd S, **Nadali M**, Turkkila M, Svensson M.N.D, Jonsson I-M, Andersson K.M.E, Bokarewa M.I. IGF1R signalling contributes to IL6 production and T cell dependent inflammation in rheumatoid arthritis. *Biochimica et Biophysica Acta - Molecular Basis of Disease 1863 (2017) 2158–2170*

SAHLGRENSKA AKADEMIN
INSTITUTION FÖR MEDICIN

GÖTEBORGS UNIVERSITET

Göteborg, 2021

Cardiovascular morbidity and metabolic signature in patients with rheumatoid arthritis

Mitra Nadali

Department of Rheumatology and Inflammation research, Institute of Medicine

Sahlgrenska Academy, University of Gothenburg

Gothenburg, Sweden

Background and objectives: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with excess risk for cardiovascular morbidity and mortality. The treatment of RA by anti-inflammatory drugs has dramatically been improved over the resent decades. Although, articular inflammation and disability burden has been reduced, cardiovascular disease (CVD) still accounts for more than half of all the death in RA population. This cannot entirely be explained by traditional cardiovascular risk factors and inflammatory activity. The general aims of this thesis were to study the role of essential metabolic pathways and their interplay with inflammation and cardiovascular morbidity in RA.

Methods: A cohort of female RA patients was clinically studied and prospectively followed up under 5 years. Cardiovascular risk (CVR) in relation to metabolism regulating molecules in fat tissue and in the peripheral blood was investigated. Blood samples and white fat aspirations were used to study different cytokines and gene expressions. Quantitative PCR was used for transcriptional analysis of proteins. As receptor for insulin-like growth factor 1 (IGF1R) has a key role to connect inflammation and metabolism, the consequences of its inhibition on regulation of T cell balance in experimental RA were explored.

Results: Low serum levels of IGF1 were associated with higher CVR, hypertension and metabolic signature such as adiposity and hyperlipidemia. The levels of IGF1 were constantly low independent to age in IGF1 low group and under 5 years follow-up, the frequency of hypertension and CV events were significantly higher in this group particularly, in younger patients compared to control group. RA patients with hypertension showed unfavorable metabolic profile including higher levels of plasma glucose and insulin followed consequently by higher inflammation and disease activity. Accumulation of signal transducer and activator of transcription 3 (STAT3) in white adipose tissue (WAT) promotes metabolic activity on leucocytes. Interleukin 6 (IL6) and leptin induce metabolic disorders and increased CVR by activating STAT3 in WAT, in RA. Low serum levels of soluble receptor for advanced glycation end products (sRAGE) were associated with both previous and new cardiometabolic events (CME). Younger patients with low sRAGE levels showed higher CVR and adverse metabolic factors. Inhibition of IGF1R on the levels of insulin receptor substrates (IRS1/2) in experimental model resolved the inflammation and arthritis followed by reduced production of IL6 and STAT3 by spleen T cells with consequent up-regulation of the regulatory T cells.

Conclusion: A range of essential metabolic factors interplays with inflammatory pathways and CVR in RA. This underlines the need to apply biomarkers in clinical practice to improve CVD risk factors management in RA female patients. The patients would also benefit of monitoring for hyperglycemia, hypertension, and obesity.

Keywords: Rheumatoid arthritis, cardiovascular risk, cardiometabolic event, IGF1

ISBN: **978-91-8009-436-8** (TRYCK)
ISBN: **978-91-8009-437-5** (PDF)

http://hdl.handle.net/2077/69301