REPORT

The Active Role Of Adipose Tissue In Rheumatoid Arthritis

(Targeting Adipose Tissue in Rheumatoid Arthritis – TARA study)

"Begin at the beginning," said the King, "and go on till you come to the end: then stop."

Lewis Carroll, Alice in Wonderland

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes a symmetrical polyarthritis affecting primarily the small joints of the hands and feet without involving the DIP’s, later with the involvement of the shoulders, elbows, knees, and hips. Immunological speaking RA implies an immunological breakdown tolerance towards self. The trigger that initiates the breakdown is still unknown. The environmental factor corroborated with the genetic factor represents one of the possibilities concerning the risk factors.

The white adipose tissue is not longer an inert part of the organism, but it showed lately an active side in inflammation and immunity. Its activity is related with the secretion of the adipokines or the adipose tissue hormones. Those adipokines exhibit similar attitudes/properties as the classical cytokines: pro-inflammatory or anti-inflammatory.

Clinical and experimental studies proved that excessive amounts of adipose tissue are related to increased systemic inflammation.

The ability of adipocytes to produce cytokines (MCP1, IL 6) may be responsible for macrophages infiltration of adipose tissue. Other chemokines may be released (RANTES, CCL-5), leading to the recruitment of T cells that can participate in further production of cytokines.

The adipokines (leptin, adiponectin and resistin) secreted by adipocytes have immune system effects as well as vascular ones.

Leptin and resistin are considered to promote the inflammation and atherosclerosis by increasing the T cell activation and cytokines release proliferation, increase the NK cell activation, macrophages activation, activate NFkB dependent cytokine release, and adhesion molecule expression (including TNF-alpha, IL 6), activate neutrophils and increase their chemotaxis and oxidative burst, induce endothelial dysfunction, increase ICAM, VCAM, VGEF and MMP up regulation. Leptin also acutely releases NO from endothelium; resistin impairs bradykinin dependent vasorelaxation (NO and EDHF) and has no effect on acetylcholine dependent vasorelaxation (NO).

Adiponectin was considered to have an anti-inflammatory role and a vascular protective one by decreasing T cell activation and proliferation, increasing IL 10, inhibiting NFkB dependent cytokine release and adhesion molecule expression, inhibiting phagocytosis and oxidative burst. Adiponectin is decreased in hypertension, is correlated with HDL and inversely with LDL, prevents atherosclerosis (in ApoE knockout mice) and she is able to inhibit Toll-receptor activation and its consequences.

Despite the protective role in metabolic and vascular diseases, adiponectin was found to be involved in key pathways of inflammation and matrix degradation in joints. Its effects appeared to be highly selective by inducing only two mediators of RA pathophysiology: IL 6 and matrix metalloproteinase 1, via the p38MAPK pathway. Along side with adiponectin in promoting inflammation other two cytokines may be involved such as leptin and resistin.

In rheumatoid arthritis the control of the disease activity is the first target of the multidisciplinary team entrusted with the management of the condition. Targeting the possible new molecules involved in the activity of the disease and by such in the outcome of the disease and corroborating the above informations with the few medical data published on the domain of RA and adipokines, the need of a study to emphasize the role of the adipose tissue hormones (leptin, adiponectin and resistin) as biological markers and their correlation with the old biological markers and new non biological markers of the activity in RA was imposed.

So, targeting the adipose tissue by all means in order to reveal new insights in the pathogenesis, the outcome of the disease, the assess of rheumatoid arthritis and the treatment implication became the topic of main field of interest and the TARA (Targeting the Adipose Tissue in Rheumatoid Arthritis) study was designed and applied.

A prospective, observational, case-control study was performed with the following aims: to evaluate the impact of the adipose tissue in the assessment of the RA activity – the main aim. The secondary objectives were:

- To evaluate the impact of the adipose tissue in the outcome of the RA
- To evaluate the impact of the adipose tissue in the management of the RA
- To underline the immunological role of the adipose tissue in RA (dependent or independent factor?)
- To develop strategies concerning the treatment of RA patients, aiming the quality of life
- To evaluate the validity of the ultrasound measurements (Grey scale ultrasound and Colour Doppler ultrasound – semi-quantitative and quantitative assays) in the assessment of the RA activity
Sixty five patients were included in the TARA study. Four sub-studies were performed in order to achieve the objectives.

TARA 1 study – to validate the US measurements
TARA 2 study – A compared study of the variations of the mean values of the adipose tissue’s markers and the ultrasound assays on the RA group patients divided in four groups according with the BMI
TARA 3 study – A correlation study of the old and new presumed biomarkers and non - biological (ultrasound) assay of the disease activity in the groups of the RA patients
TARA 4 study – the control group (healthy subjects) – to observe the adipokines behavior

The main conclusions are enlisted below:

The adipose tissue is an active player in the pathogenesis and outcome of the rheumatoid arthritis patients.

Each of the adipose tissue’s hormones studied proved to have different behavior patterns, thus a pro inflammatory or anti - inflammatory label couldn’t be applied.

The role of each adipose tissue cytokines (leptin, adiponectin, resistin) is to be evaluated in the inflammatory context. Its effects on the inflammatory and the immune response are to be adaptive to the active or the chronic status.

More studies are needed to be performed in order to outline the impact of biologic therapies on the level of the adipose tissue cytokines and thus in modulating the inflammatory response in rheumatoid arthritis.

Genetic mapping may play an important part on the behaviour of the adipose tissue’s products in the outcome of rheumatoid arthritis. The polymorphism of the resistin gene promoter may influence the inflammatory pathways in rheumatoid arthritis. It is warranted to further researches.

The role played by the intra joint adipose tissue may be an active one in rheumatoid arthritis. It is labelled as a potential modulator of local joint inflammation and thus to be part of the sub-clinical activity of rheumatoid arthritis.

The ultrasound examination proved to be a reliable, non-expensive, non-time consumer tool for the evaluation of the intra joint fat pad. It is still warranted (due to lack of data provided by the studies) to further researches in order to be validated.

The Colour Doppler’s ultrasound examination can be used as a non-biological marker for quantifying the local inflammation in RA and thus the sub-clinical activity of rheumatoid arthritis.

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