Lipid Profile in children with Rheumatic Diseases

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Abstract:
Close connection between autoimmune inflammation and proatherogenic lipid changes in rheumatoid arthritis has been well established, while for juvenile idiopathic arthritis (JIA) is under discussion. The aim of this review was to study the incidence and intensity of lipid disturbances in patients with JIA.
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The effect of Juvenile Idiopathic arthritis on lipid levels:

Advances in the diagnosis and treatment of JIA over the last few decades have modified outcomes in children and adolescents, resulting in a decrease in mortality due to the better control of disease activity and reduction of secondary infectious complications. However, this group of patients coexists chronically with the disease, and they present early negative outcomes, such as osteoporosis and cardiovascular diseases later on (**1, 2).**

Studies have shown that adult patients with rheumatoid arthritis have an increased risk of atherosclerotic disease. In this group, the risk of cardiovascular diseases is 30 to 60% higher than that in the general population. Long-term JIA adult patients in remission might have subclinical signs of inflammation and cardiovascular risk, showed by an increase in the levels of inflammatory cytokines, endothelial activation, and oxidative stress markers and adipokines, molecules involved in the alteration of the vascular system (**3).**

In adult patients with rheumatoid arthritis, changes in apolipoprotein B (Apo B) concentrations and the Apo B/apolipoprotein A-I (Apo A-I) ratio were compared to those in the classical lipid profile have been independently associated with cardiovascular risk (**3).**

Dyslipidemia affected more than three-quarters of JIA patients, with the predominance of borderline-low HDL-c based on classical lipid profile. Similar results were found in a retrospective study published by other research group. A previous study observed a higher frequency of increased LDL-c, NHDL-c, and Apo B in the systemic subtype than the polyarticular subtype. Systemic-onset JIA and elevated ESR were associated with lower concentrations of Apo A-I, suggesting the involvement, among other factors, of the inflammatory process (**1).**

The identification of cardiovascular risk in the pediatric age group is a major challenge, especially in patients with chronic conditions such as JIA. Measurements of the medial-intimal thickness (MIE) and biomarkers of lipid metabolism have been proposed as mechanisms for achieving this(**4).**

Studies evaluating non-classical biochemical markers related to lipid metabolism in children and adolescents with autoimmune rheumatic diseases are scarce(**3).**

The mechanisms involved in the pathogenesis of dyslipidemia and cardiovascular risk in patients with JIA have not yet been fully elucidated. Inflammation with endothelial dysfunction and increased levels of proinflammatory cytokines have been described. In addition, inadequate food intake, physical inactivity, overweight, and the use of certain medications, such as glucocorticoids, also aggravate dyslipidemia. The use of glucocorticoids seems to play an important role in dyslipidemia, considering that, in previous study, they observed an association between a higher cumulative dose and alterations in total cholesterol TC, low density lipoprotein cholesterol LDL-c, and non-high density lipoprotein cholesterol (NHDL-c (**1).**

In patients with rheumatoid arthritis, the prevalence of dyslipidemia varies between 55 and 65%. The prevalence was 82.3% when they considered changes in Apo A-I and Apo B. Although these apolipoproteins are considered good biomarkers for cardiovascular risk, several studies did not consider them in the evaluation of dyslipidemia (**1).**

Anthropometric markers of adiposity, such as BMI, waist circumference, and intake of fats and carbohydrates, were normal for most patients. This fact could be explained by the role of the multi-professional team in service and suggests important participation of the disease and its treatment in the pathogenesis of dyslipidemia (**3).**

An association between glucocorticoid use and increased levels of LDL-c with the decrease in HDL-c level which was not associated with the use of glucocorticoid medication have been resulted. The progressively increasing use of synthetic DMARDs and biological agents minimizes the harmful effects of glucocorticoids on lipid metabolism **(5).**

It is known that systemic-onset JIA is associated with greater laboratory and

inflammatory alterations, such as anemia, increased platelet count, and acute-phase proteins, and frequent use of corticosteroids. This explains the major changes in LDL-c, apolipoprotein B (Apo B), and NHDL-c found in patients with this JIA subtype. In a longitudinal study, evaluated the lipid profile and atherogenic index of JIA patients after treatment with etanercept and found higher concentrations of HDL-c and lower TG and TC/HDL in the group they called responders (with the inactive disease) compared to non-responders **(6).**

The non-responder group, which consisted of patients with the systemic subtype, did not show improvement in the lipid profile. Other studies addressing dyslipidemia in JIA patients did not individualize the different subtypes and did not evaluate biomarkers such as Apo A-I and Apo B(**3).**

Although an adequate HDL-c level was not associated with demographic and clinical characteristics, nutritional status, or food intake, patients with an adequate HDL-c had a higher value and higher frequency of normal levels of Apo A-I. In the literature, it is well-established that adequate levels of HDL-c, due to its antioxidant (mainly by the presence of Apo A-I), anti-inflammatory, antiatherogenic, antithrombotic functions, and cholesterol transportation, are related to a reduction in cardiovascular risk (**1).**

However, it is worth mentioning that, in the presence of systemic inflammation, there may be a conversion of protective HDL-c to proinflammatory HDL-c, and the reduction in the production of Apo A-I is one of the proposed mechanisms of this transformation (**1).**

Studies have shown an association between disease activity and dyslipidemia. The decrease in the Apo A-I level was more frequent in patients who did not use biological agents (83% versus 16%). This can be explained by the action of these agents inhibiting the production of cytokines and, consequently, inflammation, thus improving the lipid profile (**3).**

The tumor necrosis factor-α (TNF-α) is associated with increased cardiovascular risk, increased hepatic CRP synthesis, and decreased HDL-c levels. Under normal conditions, the major protein fraction of HDL is Apo A-I. However, the literature has shown that, in the presence of inflammation, mainly in increased interleukin-1 and TNF-α conditions, there is an increase in the production of serum amyloid A (SAA) by hepatocytes **(7).**

This protein, on the other hand, has atherogenic action, when released into the bloodstream rapidly, it associates with the third fraction of HDL (HDL3), decreasing serum concentrations of Apo A-I. A study in patients with JIA has shown that anti-TNF-α therapy alters the proatherogenic lipid profile of these patients (**4).**

Interestingly, a negative correlation between the ESR and Apo A-I concentration was observed. Similar results were showed by Bakkaloglu et al., in 1996 that evaluated the lipid biomarkers of 37 patients with JIA,

and found negative correlations between ESR and CRP with APO A-I **(7).**

Although other inflammatory markers, such as proinflammatory cytokines, have been described as present in active JIA, studies show that a high ESR is a good parameter of disease activity, when it is normal, it is one of the variables included in Wallace's inactivity criteria. Based on this, previous findings suggest that, in the presence of high disease activity and/or a high ESR, the investigation of lipid metabolism biomarkers should be expanded(**4).**

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