MARKERS OF SYSTEMIC INFLAMMATION IN NONALCOHOLIC FATTY LIVER DISEASE

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Cuvinte cheie: *ficat gras non-alcoolic, inflamaţie, fibroză hepatică*

Keywords: *non-alcoholic fatty liver, inflammation, liver fibrosis*

Abstract: *This paper evaluates a group of patients with non-alcoholic fatty liver compared with a group of healthy subjects in terms of serological markers of inflammation. I studied correlations between markers of inflammation and various biological or anthropometric values.*

Rezumat: *Lucrarea evaluează un lot de pacienţi cu ficat gras non-alcoolic comparativ cu un lot de subiecţi sănătoşi din perspectiva markerilor serologici de inflamaţie prezenţi în această afecţiune. Sunt studiate corelaţii între markerii de inflamaţie şi diferite valori biologice sau antropometrice.*

INTRODUCTION

Interleukin 6 (IL6), C-reactive protein (CRP) and TNF-alpha are markers of inflammation, involved in inflammatory processes of metabolic syndrome and non-alcoholic liver disease.

It has been suggested in several clinical studies that the level of erythropoietin (EPO) would increase with the level of endogenous IL6. Other studies found that with elevated transaminases, the EPO values decreases.

THE PURPOSE OF THE STUDY

We aimed to study if there is any correlation between IL6, TNF, CRP and liver biochemical tests. Also, we plan to study whether EPO level correlates with other markers of inflammation or liver biochemical tests in patients with non-alcoholic fatty liver disease.

MATERIAL AND METHOD

We measured IL6, IL8, TNFα, EPO and PCR in 43 patients with non-alcoholic fatty liver (group A) and 34 healthy subjects considered the control group.

RESULTS

We obtained the following average values:

Tabel no. 1. Group A vs. control group comparison

Plot A	Control group	Normal values
IL6-5.212791	**IL6**-3.22	0-3.4pg/ml
IL8-199.7116	**IL8**-4.99	0-62pg/ml
TNFα-9.669767	**TNFα**-21.6	0-8.1pg/ml
EPO-12.17674	**EPO**-7.36	3.7-29.5μu/ml
CRP- 15.03921569	**CRP**- 10.2	1.4-11mg/l

As shown in Table 2, in group A we found a tight linear correlation between levels of inflammatory markers IL6-TNF, IL6- CRP, TNF-CRP.

At the same time we see an acceptable degree of association between TNF levels- waist circumference, CRP-waist circumference, waist circumference -IL6, CRP-GGT, GGT-IL6.

I also found a significant linear correlation between markers of inflammation and fibrosis Forns index (IL6-Forns - r = 0.47, TNF-Forns - r = 0.32; EPO-Forns - r = 0.25).

Table no. 2. Correlation between inflammatory markers and anthropometric / biochemical values

IL6-TNF- r = 0.7 **IL6-CRP - r = 0.9** IL6-Age - r = 0.24 **IL6-Forns - r = 0.47** IL6-ASPRI - r =0.2 IL6-Waist- r = 0.34 IL6-Glycemia - r = 0.21 IL6-GGT- r = 0.33
TNF-Forns - r = 0.32 **TNF-CRP- r =0.68** TNF-Waist - r = 0.33 TNF-Body mass index (BMI) - r = 0.2
CRP-Waist - r = 0.37 CRP –GGT - r =0.3
EPO-Forns- r = 0.25 EPO-ALAT- r = -0.11

Close linear correlations between markers of inflammation found in NAFLD patients sustain synergistic participation of these proinflammatory cytokines in pre-development processes of liver fibrosis. (1), (2).

The correlation between IL6 and Forns index of liver fibrosis demonstrates involvement of this cytokine in the pathogenesis of fibrosis process.

TNF expression is induced among other enteral endotoxin, being stimulated by leptin deficiency and thus aggravating insulin resistance. Leptin deficiency occurs in the context of rapid weight loss or fatting. Leptin is synthesized in the spinal cord. These cytokines (TNFα, TGF-β, IL-8, IL-10) induce and maintain the process of inflammation and fibrosis .Fig. 4. (1)

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Article received on 25.02.2010 and accepted for publication on 17.09.2010
ACTA MEDICA TRANSILVANICA December 2010; 2(4)pagina pagina

Figure no. 1. The correlation between IL6-PCR

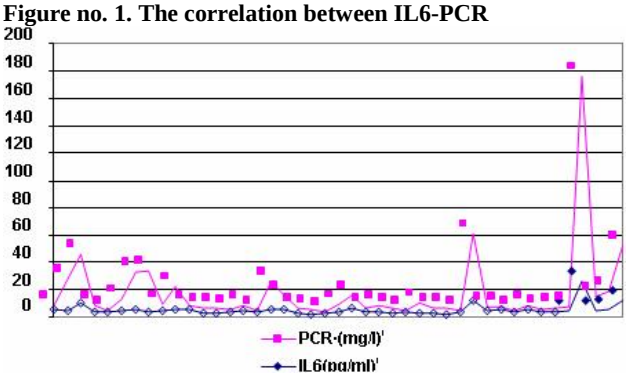


Figure no. 2. The correlation between TNF- IL6

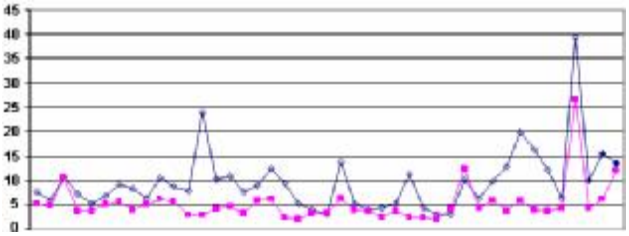


Figure no. 3. The correlation between IL6 - Index Forns

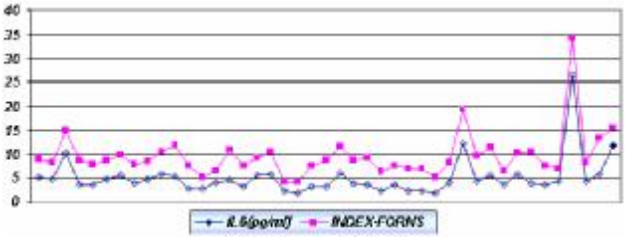
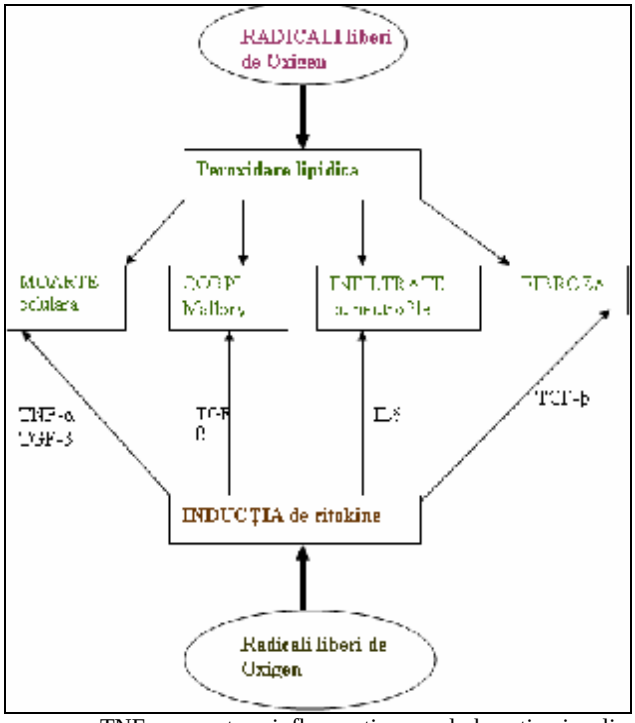


Figure no. 4. The influence of the free radicals and cytokines in developing the non-alcoholic steatohepatitis; after Brunt, 2001



TNF promotes inflammation and hepatic insulin resistance, elevated levels of TNF being more likely in patients with NAFLD and overcrowding due to bacterial endotoxin derived from the digestive tract or TNF polymorphism. (1), (2), (3), (4).

It not only increases ROS formation but also a variety of key effects in intracellular processes such as activation of nuclear transcription factor NFκβ. Additionally, increased TNF initiates fibrosis both by direct activation of stellate cells and by stimulating production of a very potent profibrotic cytokine - growth factor TGF-β (Transforming growth factor-beta). Fatty liver is associated with increased expression of TNF receptor polymorphism but also with promoting it. (5)

We know that while TNF production in response to endotoxin is increased in animal models of obesity and fatty liver, there is still a growth gene expression in TNF sensible at gamma interferon which may lead to susceptibility of animals in trace amounts low endotoxin. (6)

DISCUSSIONS

- Close linear correlations between the level of inflammation markers TNF-IL6, IL6, CRP, TNF-CRP confirmed the involvement of these mediators of inflammation in the pathogenesis of non-alcoholic fatty hepatopathy.
- Also, the association between levels of TNF-waist circumference, CRP-waist circumference, waist circumference - IL6, confirms the importance of involvement in the promotion of abdominal obesity and metabolic disorders, including inflammatory syndrome. There are studies that mention the abdominal obesity to be the most important predictor of undiagnosed diabetes (7). The result of our studies confirm that patients with elevated IL6 have an increased risk of metabolic syndrome, most likely due to the role of adipose tissue to generate these proinflammatory cytokines. We have demonstrated strong and independent correlation between plasma levels of IL6 and other markers of inflammation, endothelial dysfunction and cardiovascular risk factors (8).
- Other studies confirm the association between elevated markers of inflammation and obesity, demonstrating reduced levels of CRP along with weight loss, lifestyle changes and medications (low doses of aspirin, statins) (9)
- Studies have shown elevated plasma TNF in diabetic men and have not found the same increase in women, while administration of anti-TNF agents are not followed by a decline in insulin sensitivity. At the same time, were demonstrated in all patients, regardless of sex, increased levels of IL6, cytokine secreted by many cell types, including adipocytes, especially after meals and in much larger quantities in diabetic patients compared with patients without diabetes mellitus.
- The highest values of these cytokines were found in patients with moderate obesity (BMI> 30) studies showing that increased expression of TNF and IL 6 is highly significantly correlated with obesity associated insulinresistance. (10).
- Our study confirmed the existence of higher values for IL6, IL8, CRP and EPO in group A compared with controls, and also such results were obtained in larger studies. However, TNF levels were lower than those of control group, probably due to the higher number of women with fatty liver and obesity.
- Comparative study confirmed in the group of patients with fatty liver that there are positive correlations between CRP-GGT, GGT-IL6, once again stressing GGT participation in maintaining the inflammatory process. Moreover, several studies have confirmed the involvement of GGT in the oxidative stress mechanisms being considered even an

early marker of it.

- We also found significant linear correlations between the existence of markers of inflammation and fibrosis Forns index (IL6 - Forns - r = 0.47, TNF - Forns - r = 0.32; EPO-Forns - r = 0.25).

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