Original Article

Level of Serum C-Reactive Protein (CRP) and Procalcitonin in Non-Alcoholic Fatty Liver Disease Patients

Humaira Achakzai[1], Fahim Ullah[2], Rizwan Kundi[1], Haiqa Khan[4], Naseer Ahmed[3] and Shahzada Imran[1]

ABSTRACT

Objective: To compare the CRP and PCT serum levels in patients with non-alcoholic fatty liver disease (NAFLD) and determine the discriminative and diagnostic role of CRP and PCT.

Study Design: Comparative study

Place and Duration of Study: This study was conducted at the Department of Medicine, Rehman Medical Institute, Peshawar, Pakistan from 1st January 2021 to 31st November 2021.

Materials and Methods: Fifty-five patients were taken as study group and fifty-five healthy individuals were taken as control. Body mass index, liver function tests along with insulin resistance was determined. Ultrasound evaluations followed by measuring serum CRP levels with nephelometric method and PCT level measurement by Kryptor based system.

Results: There was no difference in the levels of serum PCT in steatohepatitis and simple steatosis patients. CRP levels were found to be higher in steatohepatitis groups as compared with the control group.

Conclusion: Serum PCT levels have no diagnostic value and levels of CRP in NAFLD patients were elevated as compared to the control healthy patients' group. Hence, C-reactive protein can be used as a diagnosing marker for NAFLD but cannot differentiate between simple steatosis and steatohepatitis.

Key Words: C-reactive protein, Serum level, Proclactitonin, Non-alcoholic fatty liver disease.

Citation of article: Achakzai H, Ullah F, Kundi R, Khan H, Ahmed N, Imran S. Level of Serum C-Reactive Protein (CRP) and Procalcitonin in Non-Alcoholic Fatty Liver Disease Patients. Med Forum 2023;34(7): 95-98. doi:10.60110/medforum.340722.

INTRODUCTION

The non-alcoholic fatty liver disease (NAFLD) occurrence in population is on the rise, particularly in western nations.[1,2] Co-morbidities like metabolic syndrome, hyperlipidemia, and diabetes are frequently linked to it.[3] Although at first it was thought to be a benign ailment, it is now recognized that the disease's spectrum includes everything from steatosis leading to steatohepatitis and worsening to cirrhosis.[4] At present, no non-invasive serum markers have been identified to indicate or reflect the stage of the disease.

C-reactive protein and procalcitonin are widely utilized for the diagnostic purposes and follow-up of numerous morbidities because they are accessible, frequently used, trustworthy, affordable serum indicators.[5]

1. Department of Medicine / Endocrine / Pharmacology[3], Rehman Medical Institute, Peshawar.
4. Department of ORIC, Prime Foundation, Peshawar

Correspondence: Dr. Fahim Ullah, Assistant Professor of Endocrinology, Rehman Medical Institute, Peshawar.
Contact No: 0332-9142021
Email: drfaheemullah@gmail.com

Received: February, 2023
Accepted: April, 2023
Printed: July, 2023

Most CRP is produced in the liver. Diabetes and the metabolic syndrome have both been linked to elevated blood CRP levels.[6] In patients diagnosed with metabolic syndrome, serum c-reactive protein levels have been associated with the prediction of cardiovascular events.[6,7]

Procalcitonin which is a 116-amino acid pro-calcitonin hormone, is produced in the thyroid gland. The detection of PCT response during acute inflammation in thyroidectomy patients indicates the increased production of PCT in inflammatory cells. Serum procalcitonin was discovered to be elevated in cases of sepsis and bacterial infections.[8] Cirrhosis and chronic liver disorders have also been linked to similarly changed serum PCT levels. However, viral or autoimmune liver disorders showed no change in serum PCT levels.[9]

Liver is the major source of serum CRP and PCT. As, in the past serum PCT levels are not examined in NAFLD, therefore, we set out to determine the diagnostic value of serum CRP and PCT level in NAFLD.

MATERIALS AND METHODS

This study was conducted at Department of Medicine, Rehman Medical Institute, Peshawar, Pakistan from 1st January 2021 to 31st November 2021 having abnormal

LFTs (liver function tests), history of no drug or alcohol, negative hepatitis detection tests and negative auto-immune serology were then tested for NAFLD. The patients who had undergone gastric bypass surgery, chronic liver disease that are suspected, cholestatic liver disorders, obstructive jaundice, which were earlier confirmed Wilson illnesses, systemic disorders, hemochomatosis, or infections were exempted from the study. These patients were not taking any medications known to alter serum CRP levels, such as statins, corticosteroids, or other medications. Fifty-five patients were included in the study out of the 262 patients that were evaluated in total.

Patients underwent a general physical examination as well as standard laboratory tests. White blood cell counts and urine analyses were both normal in all patients. There were no infections found during a physical examination. Each individual had an ultrasonography evaluation and their body mass index (BMI) was calculated. A liver biopsy was carried out when necessary. An expert pathologist performed histopathological examinations in accordance with the classification established by Brunt et al. According to a classification system, steatosis was divided into four categories: no steatosis as S0, macrovesicular steatosis in 30% hepatocytes biopsies as S1, macrovesicular steatosis in 30-60% hepatocytes as S2 and macrovesicular steatosis in more than 60% of the hepatic cells as S3.

Consecutive 55 individuals with liver biopsy-confirmed NAFLD (35 men and 20 women) were included in the study. To compare the results, 55 healthy volunteers were used as control group. An ultrasound examination of the control subjects revealed no NAFLD. Tests of liver function in controls were normal.

The blood samples were taken after the conclusive diagnosis on the same day. To measure glycemia, cholesterol, cholesterol (HDL and LDL), and perform liver function tests, fasting blood samples were collected. A homeostasis model assessment of insulin resistance (HOMAIR) was used for quantification of insulin resistance.[11] Nephalometric analysis was used to measure serum CRP. As advised by the firm, serum procalcitonin was assessed in plasma samples using a Kryptor-based device. The smallest detection threshold was 0.01 ng/ml. Values > 0.5 ng/ml was regarded as abnormal as per the protocol. The study was approved by the Rehman Medical Institute ethical committee. All participants provided their informed written consent. The results are shown as mean.

The statistical analysis was done using the SPSS-20. The nonparametric Kruskall-Wallis test and the paired Student's t-test served as the foundation for the statistical study. To determine the markers' specificity and sensitivity, ROC analysis was used. Significance value was defined as P 0.05.

RESULTS

The distribution of gender (male/female) and age (Years) between the NAFLD group and the healthy controls was similar. Twenty-two patients had steatohepatitis confirmed by liver biopsy, whereas 25 had widespread steatosis and eight had localized fatty infiltration. BMI and serum AST and ALT concentrations were all noticeably elevated in the NAFLD patient group in comparison to controls (Table 1). Serum procalcitonin levels in the NAFLD group and control groups were both within normal limits. The PCT levels in the steatohepatitis, steatosis, and control groups were similar to one another. When compared to controls, individuals with steatosis and steatohepatitis had considerably higher CRP levels. However, blood CRP levels were not significantly differed between patients with steatohepatitis and those with steatosis. Insulin resistance had no effect on the levels of PCT and CRP in NAFLD patients as they were split into two groups steatosis and steatohepatitis. procalcitonin had no association with the Liver function tests, BMI, or the existence of insulin resistance. Serum C-reactive protein levels that are more than 3 have sensitivity about 73% and specificity about 68% for NAFLD (Tables 1-3).

Table No. 1: General Characteristics of Patients with NAFLD

Variable	Steatohepatitis (n=22)	Diffuse Steatosis (n=25)	Focal Fatty Liver (n08)	Control (n55)
Age (Y)	53.1	44.1	55.1	42.8
BMI (kg/m2)	29.6	33.7	25.7	27.1
AST (U/I)	53.1	44.2	67.0	26.3
ALT (U/I)	67.0	68.6	41.0	27.5
GGT	61.8	52.2	47.0	48.3
Cholesterol (mg/dl)	202.8	173.0	166.0	170.0
Triglycerides (mg/dl)	213.0	133.8	72.0	90.0

Table No. 2: Level of CRP and PCT levels in study groups.

Level of CRP & PCT	Controls (n=50)	NAFLD			P value
		Focal fatty liver (n=8)	Steatohepatitis (n=22)	Steatosis (n=25)	
CRP	2.80	1.65	5.40	7.70	<0.01
PCT	0.05	0.02	0.05	0.03	NS

Table No. 3: Effect on serum CRP and PCT levels by insulin resistance

Variable	Steatosis			Steatohepatitis		
	Insulin resistance -ve	Insulin resistance +ve	P value	Insulin resistance -ve	Insulin Resistance +ve	P value
PCT	0.04	0.05	0.75	0.05	0.03	0.14
CRP	7.10	5.70	0.58	5.87	5.10	0.65

DISCUSSION

Levels of serum PCT have been examined for their diagnostic and prognostic usefulness in liver problems in certain investigations, with mixed results.[10] High PCT levels were a sensitive and specific method for the early detection of bacterial infection in patients diagnosed with decompensated liver cirrhosis.[11] On the other hand, moderate elevations in serum PCT levels are caused by acute alcoholic hepatitis, acute viral hepatitis on cirrhotic backgrounds, and acute viral hepatitis.[12,13] Our study found that patients with steatohepatitis and steatosis had serum procalcitonin levels within normal ranges.

The liver may not be the primary source of PCT production, despite the fact that we did not assess the pattern of PCT expression. PCT did not correspond with measurements of liver function, body mass index, or the existence of insulin resistance. We also assessed CRP's clinical utility in the NAFLD diagnosis. A small number of studies[14-16] suggested that NAFLD was associated with higher blood CRP. CRP has 18 hours short half-life, and an increase in serum CRP typically signifies that more of it is being produced in pathological process response.[17]

As a result, C-reactive protein is regarded as a helpful non-specific biochemical measure of high level inflammation.[17] Our research proved that the elevation in CRP levels in the bloodstream could serve as a standalone indicator for diagnosing NAFLD. Nevertheless, the C reactive protein reaction by itself lacks diagnostic specificity. CRP readings can only properly be understood when all other laboratory and clinical data is available due to its low specificity. As a result, we recommend serial CRP readings for the clinical management and NAFLD patient's follow-up.

Elevated CRP was linked to the metabolic disorders and its elements in clinical trials. Although the liver is the primary source of CRP synthesis, adipose tissue also makes a major contribution. However, there is no proof that adipose tissue produces PCT. It is also widely documented that patients who were extremely obese had moderately higher CRP concentrations; however, these elevations were unrelated to steatohepatitis.[18] In line with this, our investigation was unable to detect any link between both levels and the occurrence of insulin resistance. Since the study's steatohepatitis and steatosis groups were both obese, an association between obesity and equally elevated CRP was likely present.

The increase in acute phase cytokines is one more suggested mechanism for CRP response in NAFLD. For instance, IL-6 is a powerful activator of CRP production. According to Haukeland et al., IL-6 levels in the serum of patients with simple steatosis and steatohepatitis were considerably higher than those of healthy controls.[14] The equally high serum C-reactive protein levels in the steatosis and steatohepatitis groups in our study, despite the fact that we did not examine the amount of inflammatory cytokines in the serum. Unfortunately, the discriminative function of CRP for steatohepatitis is diminished by this common aetiology. Experimental investigations have already shown that these cytokines have immediate effects on PCT levels, but this effect is definitely less pronounced in NAFLD.

CONCLUSION

In individuals with simple steatosis or steatohepatitis, serum PCT was within normal levels, however it is useless as a diagnostic tool for NAFLD. CRP is a further marker that can be used to diagnose NAFLD, however it is useless in separating steatohepatitis from simple steatosis. Insulin resistance is not a decisive factor for blood CRP levels; obesity is. Serial CRP measures in obese patients have the potential to improve the diagnosis accuracy for NAFLD and should be included in future research.

Author's Contribution:

Concept & Design of Study:	Humaira Achakzai
Drafting:	Fahim Ullah, Rizwan Kundi
Data Analysis:	Haiqa Khan, Naseer Ahmed, Shahzada Imran
Revisiting Critically:	Humaira Achakzai, Fahim Ullah
Final Approval of version:	Humaira Achakzai

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Farrell GC. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? J Gastroenterol Hepatol 2003, 18:124-38.
2. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;18:1221-31.
3. Chitturi S, Abeygunasakera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, et al. NASH and insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatol 2002;35: 373-9.
4. Björnsson E. The clinical aspects of non-alcoholic fatty liver disease. Minerva Gastroenterol Dietol 2008;54(1):7-18.
5. Massaro KS, Costa SF, Leone C, Chamone DA. Procalcitonin (PCT) and C-reactive protein (CRP) as severe systemic infection markers in febrile neutropenic adults. BMC Infect Dis 2007;22:137.
6. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000; 321:199-204.
7. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.
8. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 2004;39:206-17.
9. Maruna P, Nedelnikova K, Gurlich R: Physiology and genetics of procalcitonin. Physiol Res 2000;49 Suppl 1:S57-61.
10. Connert S, Stremmel W, Elsing C. Procalcitonin is a valid marker of infection in decompensated cirrhosis. Z Gastroenterol 2003;41:165-70.
11. Viallon A, Zeni F, Pouzet V, Lambert C, Quenet S, Aubert G, et al. Serum and ascitic procalcitonin levels in cirrhotic patients with spontaneous bacterial peritonitis: diagnostic value and relationship to pro-inflammatory cytokines. Intensive Care Med 2000; 26:1082-1088.
12. Elefsiniotis IS, Skounakis M, Vezali E, Pantazis KD, Petrocheilou A, Pirounaki M, et al. Clinical significance of serum procalcitonin levels in patients with acute or chronic liver disease. Eur J Gastroenterol Hepatol 2006;18:525-30.
13. Spahr L, Morard I, Hadengue A, Vadas L, Pugin J. Procalcitonin is not an accurate marker of spontaneous bacterial peritonitis in patients with cirrhosis. Hepatogastroenterol 2001;48:502-5.
14. Haukeland JW, Damås JK, Konopski Z, Løberg EM, Haaland T, Goverud I, et al. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. J Hepatol 2006;44:1167-74.
15. Yoneda M, Mawatari H, Fujita K, Iida H, Yonemitsu K, Kato S, et al. High-sensitivity C-reactive protein is an independent clinical feature of nonalcoholic steatohepatitis (NASH) and also of the severity of fibrosis in NASH. J Gastroenterol 2007;42:573-82.
16. Riquelme A, Arrese M, Soza A, Morales A, Baudrand R, Pérez-Ayuso RM, et al. Non-alcoholic fatty liver disease and its association with obesity, insulin resistance and increased serum levels of C-reactive protein in Hispanics. Liver Int 2009;29: 82-8.
17. Kao PC, Shiesh SC, Wu TJ. Serum C-reactive protein as a marker for wellness assessment. Ann Clin Lab Sci 2006;36:163-9.
18. Anty R, Bekri S, Luciani N, Saint-Paul MC, Dahman M, Iannelli A, et al. The inflammatory C-reactive protein is increased in both liver and adipose tissue in severely obese patients independently from metabolic syndrome, Type 2 diabetes, and NASH. Am J Gastroenterol 2006;101:1824-33.