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Role of Serum Adiponectin, IL-6 and Hs CRP in Nonalcoholic Fatty Liver Egyptian Patients

Amal Ahmed Mohamed[1*], Wafaa Gh. Shousha[2], Olfat Shaker[3], Mohamed El-Sayed Mahdy[2], Eman M. A. Ibrahim[2], Seham Mohmoud[4] and Ahmed khairalla[5]

[1]Department of Biochemistry, National Hepatology and Tropical Medicine Research Institute, Egypt.
[2]Department of Chemistry, Faculty of Science, Helwan University, Egypt.
[3]Biochemistry Department, Faculty of Medicine, Cairo University, Egypt.
[4]Department of Tropical, El Sahel Teaching Hospital, Egypt.
[5]Department of Microbiology and Immunology, Faculty of Pharmacy, Beni Suif University, Egypt.

Authors' contributions

This whole work was carried out in collaboration between all authors. Authors AAM, OS and EMAI helped in practical and manuscript draft. Authors WGS, AK and MLSM helped in manuscript draft. Author SM helped in selection of patients and manuscript draft.

Original Research Article

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ABSTRACT

Scientific Background: Non alcoholic fatty liver (NAFLD) is accumulation of fat in the liver cells of peoples who drink little or no alcohol causing mild steatosis with mostly no signs, symptoms or complication but this may progress to steatohepatitis (NASH) and may liver cirrhosis then failure. NAFLD is recognized as the most common type of chronic liver disease in Western countries and the leading cause of cryptogenic cirrhosis. Insulin resistance (IR) is a key factor in the pathogenesis of NAFLD, the latter being considered as the hepatic component of IR or metabolic syndrome (MetS). Although the pathogenesis of NAFLD is not fully elucidated, a complex interaction between adipokines and cytokines produced by adipocytes and/or inflammatory cells infiltrating adipose tissue appears to play a crucial role in MetS and NAFLD and its progress. A number of factors are linked with NAFLD such as obesity, type 2 diabetis mellitus (T2DM), hyperlipidemia, gastric

**Corresponding author: Email: amalahmedhcp@yahoo.com;*

bypass, and its progress to NASH correlate with certain cytokines secreted like adiponectin, interlukin-6 (IL-6), and C- reactive protein CRP. Adiponectin is a novel adipocyte-specific protein, which, it has been suggested, plays a role in the development of insulin resistance and atherosclerosis. The role of (IL-6) in liver pathology is very complex, and its participation in the development of NAFLD remains unclear. IL-6 is a key element in the acute phase response, mediating the synthesis of several acute phase proteins (such as CRP and serum amyloid A). Thus, we cannot exclude the possibility that IL-6 might also play an indirect deleterious role in NAFLD pathogenesis. In diet-induced obese mice, treatment with IL-6 antibodies improved sensitivity to insulin.

Objective: This study aim is to evaluate the level of adiponectin, IL-6 and CRP in Egyptian patients with NAFLD.

Methods: This study was conducted on 2 groups 104 NAFLD as diagnosed by ultrasound examination and 21 healthy participants as control group. All the subjects were subjected to an abdominal ultrasonography, liver enzymes ALT & AST, lipid profile (triglycerides, HDL, LDL, cholesterol, CRP, IL-6 & Adiponectin).

Results: Plasma adiponectin levels were significantly lower in NAFLD patients than control gp (3.05±2.65µg/ml vs 10.52±3.35 (µg/ml). IL-6 level was higher in NAFLD than control gp but not significant (114.24±22.32pg/ml vs 104.9±19.98pg/ml). CRP was significantly higher in NAFLD than control gp (17.86±11.59mg/L vs 5.4±3.81mg/L). Adiponectin ROC curve showed an AUROC curve in NAFLD gp (0.918 p=0.0001). IL-6 ROC curve showed an AUROC curve in NAFLD gp (0.703 p=0.0003). CRP ROC curve showed an AUROC curve in NAFLD gp (0.853 p=0.0001).

Conclusion: Patients with NAFLD have lower adiponectin levels and higher IL-6 and CRP levels compared with their control group.

Keywords: MetS; metabolic syndrome; NAFLD; Non alcoholic fatty liver disease; IL-6: interleukin-6.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) describes a range of conditions caused by a build-up of fat within liver cells. It is very common and in many cases is linked to being obese or overweight. Truncal obesity seems to be an important risk factor for NAFLD, even in patients with a normal body mass index (BMI) [1]. NAFLD occurs in 60% ~95% of people with obesity [2]. NAFLD has the potential for major economic impact on healthcare costs because of liver-related morbidity and mortality [3].

NAFLD may lead to NASH, cirrhosis and in some cases, hepatocellular carcinoma [4]. Why some patients develop progressive disease while most do not remains to be determined, although genetic factors may be involved [5,6].

A number of factors are linked with NAFLD such as obesity, type 2DM, hyperlipidemia, gastric bypass, hypothyroidism and others. Adipose tissue is considered an endocrine organ regulating body metabolism [7,8]. The imbalanced production of pro- and anti-inflammatory adipokines secreted from fat contributes to the pathogenesis of NAFLD and its progress.

Adiponectin is the most abundant adipokine synthesized by adipose tissue and has been shown to be a key component in the relationship between adiposity, insulin resistance and inflammation. It circulates in plasma at physiological concentrations that represent 0.05% of all plasma proteins [9]. In the liver, adiponectin acts through the activation of 5-AMP-

activated protein kinase and peroxisome proliferator-activated receptor-α pathways and inhibition of toll-like receptor-4 mediated signalling. There is an evidence that adiponectin decreases hepatic and systematic IR and attenuates liver inflammation and fibrosis. Adiponectin generally predicts steatosis grade and severity of NAFLD, but it remains to be addressed to what extent this is a direct effect or related to the presence of more severe IR [10].

The role of interleukin-6 (IL-6) in liver pathology is very complex, and its participation in the development of NAFLD remains unclear. IL-6 activates several cells, such as immune cells, hepatocytes, hematopoietic stem cells, and osteoclasts [11]. Furthermore, IL-6 has a wide range of biological functions, including induction of inflammation and oncogenesis, regulation of immune response, and support of hematopoiesis [11]. IL-6 was initially considered as a hepatoprotector in liver steatosis, capable of reducing oxidative stress and preventing mitochondrial dysfunction [12]. Furthermore, this potential hepatoprotective effect of IL-6 was confirmed in other models of liver disease, such as ischemic preconditioning models and in liver regeneration after partial hepatectomy in mice [13].

Nevertheless, IL-6 is a key element in the acute phase response, mediating the synthesis of several acute phase proteins (such as C-reactive protein and serum amyloid A) [14] Thus, we cannot exclude the possibility that IL-6 might also play an indirect deleterious role in NAFLD pathogenesis. In diet-induced obese mice, treatment with IL-6 antibodies improved sensitivity to insulin [15]. Furthermore, IL-6 is considered as a predictor marker of insulin resistance and cardiovascular diseases. In patients undergoing bariatric surgery, decreased IL-6 concentrations were associated with weight loss and insulin resistance improvement [16]. Recently, Mas and co-workers showed that diet-induced NASH was reduced in IL-6 knockout mice as compared to controls [17]. In humans with NASH, a positive correlation was found between IL-6 expression in hepatocytes and the severity of NAFLD was observed [18].

C-reactive protein (CRP) is one of the major acute phase proteins and is a marker of systemic inflammation.CRP is synthesized mainly in the liver [19] and is regulated by circulating levels of IL-6 [20]. CRP has short life around 18 hours and the elevation of serum CRP usually reflects its synthesis in response to a pathological process [21]. CRP is therefore considered as a useful nonspecific biochemical marker in chronic inflammation [21].

In contrast to regular CRP assays, a highsensitivity CRP (hs-CRP) assay enables the diagnosis of even low grade inflammation. It has important clinical and prognostic implications in cardiovascular disease hs-CRP level are significantly correlated with liver histology in NAFLD patients, which suggests that NAFLD is associated with low grade inflammation in the liver. However, hs-CRP could be a promising biomarker for screening of NAFLD asymptomatic subjects independently of other metabolic disturbances associated with metabolic syndrome and cardiovascular risk [21,22]. Thus the aim of this study was to investigate the role and correlation of adipocytokines (IL-6 and adiponectin) and hs-CRP in NAFLD patients and correlate them with different anthropometric and clinical variables.

2. MATERIALS AND METHODS

This study was conducted on 104 (43 males and 61 females) patients with NAFLD and 21 healthy subjects as a control. All patients were prospectively recruited from Gastroenterology Out-patients Clinic in El Sahel Teaching Hospital. Their age (Mean±SD) 54.46±10.14 years.

Inclusion criteria were based on ultrasonographic finding of bright liver. We excluded patients with any infections including viral hepatitis, autoimmune diseases, diabetes, hypertension, malignancy, hypothyroid ism, coronary artery disease, Pregnancy, Alcohol consumption, cigarette smoking, use of amiodarone, corticosteroids, tamoxifen, methotrexate, or oral contraceptives. Control group included 21 healthy volunteers, who were gender, age and BMI matched with study group, were enrolled. Informed consent was obtained from all participants before enrollment in the study. The study was carried out in accordance with the principles of the Declaration of Helsinki, and its appendices, and local and national laws.

All participants included in the study were subjected to detailed history taking, complete clinical examination, anthropometric evaluation (height, weight, and BMI were recorded. Overweight and obesity were defined as BMI between 25 and 30kg/m2 and ≥30kg/m2, respectively [7].

NAFLD diagnosis was based according to the standard criteria accepted by the American Gastroenterology Association [23]: The diagnosis was based on ultrasonographic finding of bright liver (the diagnosis of bright liver was based on abnormally intense, high level echoes arising from the hepatic parenchyma, with amplitude similar to that of echoes arising from the diaphragm); In all patients, liver biopsy was not done because the stage and grade of the NAFLD was not of importance in this study and according to Saverymuttu et al., ultrasound examinations can accurately identify steatosis with sensitivity of 94% and a specificity of 84% [24]. Moreover, liver biopsy has several limitations: as it is costly; associated with potentially complications and associated with sampling error [25]. Laboratory evaluations: Venous blood (5 ml) was collected after overnight fasting in vacutainers without additive, allowed to clot for 30 min at room temperature and centrifuged at 3000 c/m for five min. The separated serum was stored into aliquots at-20ºC until biochemical analyses included liver enzymes. Haemolysed samples were excluded. Serum levels of IL-6 were measured with ELISA kit. Serum levels of adiponectin were determined using human adiponectin ELISA kit. The levels of serum hs-CRP were determined by Accu-Bind ELISA Kit (Monobind Inc, USA). Total cholesterol, triglyceride and HDLcholesterol were analyzed enzymatically using kit obtained from Randox Laboratories Limited, Crumlin, UK. Serum LDL cholesterol was determined from the values of total cholesterol and HDL-cholesterol using friedewalds formula [26].

$$\text{LDL-cholesterol} = TC - (TG/5) - \text{HDL-cholesterol (mg/dl)}.$$

3. STATISTICAL ANALYSIS

Data were collected, checked, revised and entered the computer. Data analyzed by SPSS statistical package version 19. Excel computer program was used to tabulate the results, and represent it graphically. For the quantitative variables which are normally distributed, independent t-test used to declare the significant difference between groups at $p<0.05$. Pearson's correlation coefficient used to declare the significant correlation between the quantitative parameters within each group at $p<0.05$. MedCalc creates a list of sensitivity, specificity, likelihood ratios, and positive and negative predictive values for all possible threshold values. MedCalc allows performing Receiver operating characteristic curve ROC curve analysis easily and accurately, the Area under the curve (AUC) with standard error (SE) and 95% confidence interval (CI), with automatic calculation of corresponding sensitivity and specificity.

4. RESULTS

104 patients (43 males and 61 females) with NAFLD were investigated for adiponectin, hs-CRP, IL-6, BMI, liver enzymes and lipid profile. Those patients were compared to 21 healthy controls (12 males and 9 females).NAFLD patients showed significantly higher BMI, serum levels of AST, ALT, GGT, total cholesterol, triglycerides, LDL, hs-CRP levels and significantly lower serum HDL and adiponectin levels in comparison to those of the controls $p<0.05$, But serum AST/ALT and IL-6 levels showed no significant difference between patients and controls (Table 1).

Table 1. Clinical and biochemical characteristics in NAFLD patients and controls

Variables	Controls (n=21)	Patients (n=104)	p- value
Gender M/ F	12/9	43/61	
Age (Years)	40.90±15.52	54.46±10.14	0.000*
BMI (kg/m2)	25.95±4.28	36.03±5.39	0.000*
AST (U/L)	33.86±9.64	58.76±18.98	0.000*
ALT (U/L)	31.43±6.95	66.41±36.57	0.000*
AST/ALT	1.08±0.22	1.04±0.44	.708
GGT(U/L)	35.81±10.15	53.97±21.13	0.000*
Total cholesterol (mg/dl)	168.14±25.39	202.51±27.81	0.000*
Triglycerides (mg/dl)	156.67±31.4	197.24±34.04	0.000*
LDL-C (mg/dl)	108.67±12.5	129.62±21.98	0.000*
HDL-C (mg/dl)	45.24±7.98	41.05±8.92	0.048*
Adiponectin (µg/ml)	10.52±3.35	3.05±2.65	0.000*
IL-6 (pg/ml)	104.9±19.98	114.24±22.32	0.078
CRP (mg/L)	5.4±3.81	17.86±11.59	0.000*

All data expressed as mean±SD, There is a significant difference between control group and patient group by using independent t-test at p< 0.05*

(Table 2) showed significantly higher BMI among females 28.33±4.44 compared to males 24.17±3.29 in control group. While among NAFLD patients; there were no significant difference between male and female according to BMI. According to TG, adiponectin and CRP there was no significant difference between male and female in the two groups.

Table 2. Clinical and biochemical characteristics of the studied NAFLD patients and controls according to gender

Variables	Controls			Patients		
	Male (n=12)	Female (n =9)	p- value	Male (n=43)	Female (n=61)	p- value
BMI (Kg/m2)	24.17±3.29	28.33±4.44	0.023*	35.44±6.25	36.44±4.71	0.354
TG (mg/dl)	145.75±21.61	171.22±37.49	0.064	190.44±22.58	202.03±39.69	0.087
Adiponectin (µg/ml)	11.60±2.19	9.09±4.17	0.089	2.89±1.24	3.16±3.303	0.616
CRP (mg/L)	4.06±2.18	7.19±4.85	0.06	19.25±12.49	16.88±10.91	0.308

*All data expressed as mean±SD, *=There is a significant difference between groups by using independent t-test at p<0.05*

(Table 3) represents correlation coefficient (r) between studied parameters in NAFLD patients. Significant positive correlations were found between BMI and each of TG, HDL,

LDL and cholesterol. There is significant negative correlation between adiponectin and each of TG, LDL and cholesterol while positive not significant regarding HDL. CRP correlated positively with TG, LDL and cholesterol while negatively significantly with HDL. Also there is a significant positive correlation between IL-6 and each TG, LDL and cholesterol and a positive not significant correlation regarding to HDL.

Table 3. Correlation coefficient (r) of the studied variables and lipid profile in NAFLD patients

Parameter	BMI	Adiponectin	IL-6	CRP
Triglycerides	0.156	0.095	.200*	.059
HDL	0.487**	-0.032	0.104	-.203*
LDL	0.331**	0.119	0.142	0.126
Cholesterol	0.13	0.003	.271**	0.1

***Correlation is significant at the 0.01 level, *Correlation is significant at the 0.05 level*

(Table 4) showed there was significant positive correlation between BMI and each ALT and GGT and highly significantly with AST, while regarding to adiponectin the correlation is high significantly negative with all parameters in this table. IL-6 correlates negatively with ALT and positively with AST and GGT. CRP correlates positively only with ALT and GGT and significantly positive only with AST.

Table 4. Correlation coefficient (r) of the studied variables liver enzymes in NAFLD patients

Parameter	ALT	AST	GGT
BMI	-0.05	-0.027	0.02
Adiponectin	-0.083	-0.032	0.046
IL-6	-.201*	-0.091	0.07
CRP	-0.09	-0.027	0.02

**Correlation is significant at the 0.05 level*

Receiver operating characteristic curve for adiponectin showed the following results: area under the curve was 0.918 with confidence interval of (0.855 to 0.960), P=0.0001 (Table 5, Fig. 1) with 96.15% sensitivity, 90.48% specificity, 98.0% PPV and 82.6% NPV.

Table 5. Evaluation of NAFLD parameters in NAFLD patients

Variable	The best cut off	Sensitivity %	Specificity %	P value	AUC	95% confidence interval	
Adiponectin	≤7.3	96.15	90.48	0.0001	0.918	0.855	0.960
IL-6	>106	55.77	85.71	0.0003	0.703	0.615	0.781
CRP	>8	80.77	90.48	0.0001	0.853	0.778	0.910

Receiver operating characteristic curve for IL- 6 showed the following results: area under was 0.703 with (0.615 to 0.781) confidence interval, P=0.0003 (Table 5, Fig. 2) with 55.77% sensitivity, 85.71% specificity, 95.1% PPV and 28.1% NPV while Fig. 3 of CRP showed the following results: area under the curve of 0.853 with confidence interval of (0.778 to 0.910), p=0.0001 with 80.77% sensitivity, 90.48% specificity, 97.7% PPV and 48.7% NPV.

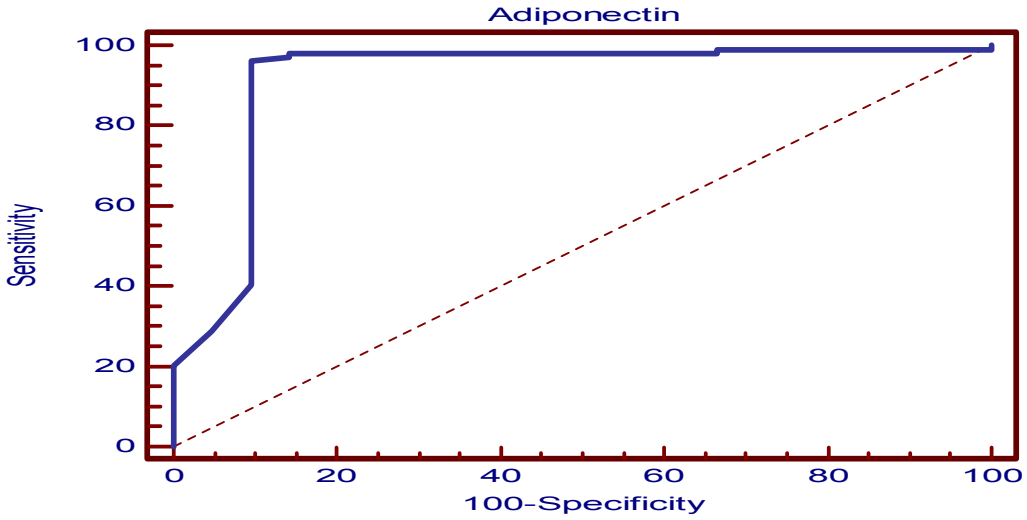

Fig. 1. Receiver operating characteristic curve for adiponectin

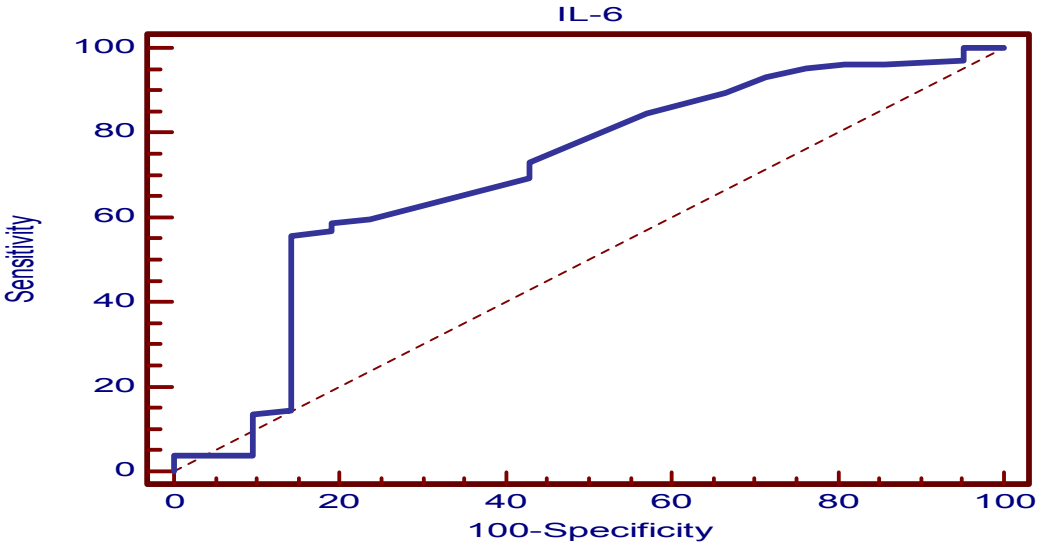

Fig. 2. Receiver operating characteristic curve for IL-6

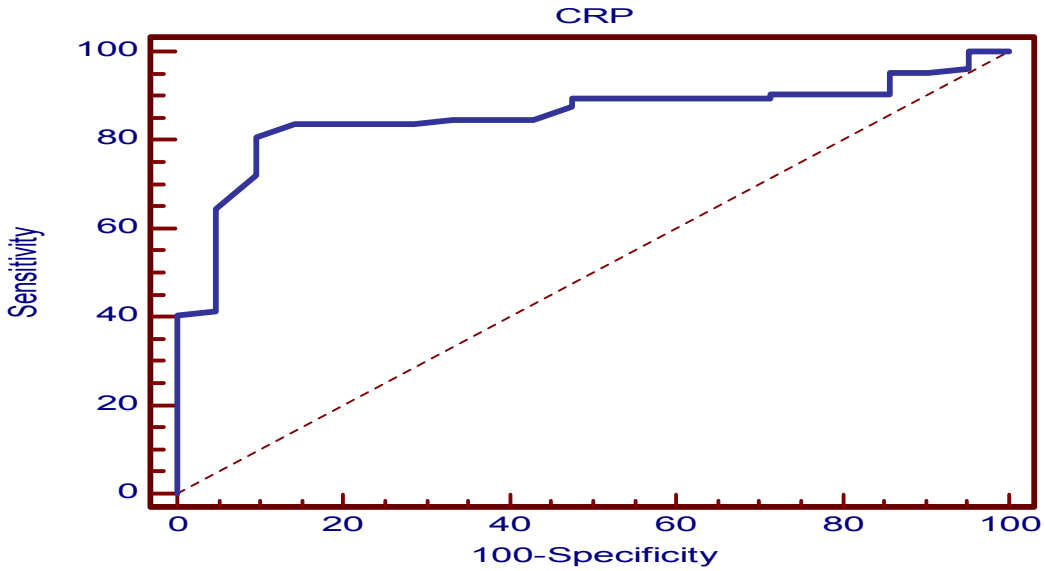

Fig. 3. Receiver operating characteristic curve for CRP

5. DISCUSSION

The pathogenesis of NAFLD/NASH and, in particular, the mechanisms responsible for liver injury and disease progression remain still incompletely understood [27]. Recent studies have focused on the adipokines, bioactive proteins secreted by adipose tissue, including adiponectin and IL-6 [27,28,29]. Adipokines which are central factors in the development and progresion of NAFLD and inflammation have been investigated [30]. Increasing evidence indicates that they might play important roles in the NASH pathogenesis [29]. A number of studies have demonstrated the association between hypoadiponectinemia and NAFLD [29]. In our study we observed significantly lower serum concentration of adiponectin in patients with NAFLD than in healthy subjects, this mean that high levels of adiponectin are associated with a protective effect against fatty liver [31]. Our findings are in accordance with a report by Tsochatzis et al. [3], Bugianesi et al. [32] and Yoon et al. [33] reported that serum adiponectin level was significantly lower in patients with NAFLD than in the control group. Moreover, Hui et al. [34] observed that lower serum adiponectin level in patients was associated with more extensive necroinflammation.

In our study we found that female patients have higher adiponectin levels than males. These findings are agree with those of [32,35]; while others failed to observe a sex difference [36]. They attributed this higher adiponectin expression in women, as compared to men to the fact that women tend to have less visceral fat tissue than subcutaneous fat tissue. Adiponectin levels were determined predominantly by visceral fat, not by subcutaneous fat [37]. Therefore, sexual dimorphism of the body fat distribution might contribute to the difference in plasma adiponectin levels in women and men [33].

The hallmark feature of the pathogenesis of NAFLD, both histologically and metabolically, is the accumulation of triacylglycerol (TAG) in the liver. The plasma non-esterified fatty acid (NEFA) pool contributes the majority of the fatty acids that flow to the liver in the fasted state and thus provides the bulk of the fatty acids secreted by the liver [38].

NAFLD patients of the present study showed a state of dyslipidemia presented by significantly higher levels of serum TG, LDL, total cholesterol and lower not significant serum HDL levels. The prevalence of high cholesterol (P=0.026), and high triglyceride (P<0.001) was significantly higher in patients with NAFLD [39,40]. Also they correlated weakly with adiponectin. On the other hand, Wong et al. [41] and Bugianesi et al. [32] did not find the correlation between serum adiponectin concentration and the disease severity. Also, López-Bermejo et al. [42] reported that adiponectin levels were significantly correlated with ALT, independently of sex, age, BMI and insulin resistance while we observed in our study a weak negative correlation between adiponectin and liver enzymes.

Our study evaluated that the levels of IL-6 were found to be higher in NAFLD patients compared to healthy controls but not significant. This agree with the study of, Polyzos et al. [43] who reported that Adipocytokines and other recognized cytokines produced partially by inflammatory cells infiltrating adipose tissue, play an important role in the pathogenesis of IR and NAFLD, through complex and interactive paracrine and endocrine mechanisms. Some adipocytokines, including adiponectin and leptin decrease IR, while others, including tumor necrosis factor (TNF)-alpha, IL-6 and resistin enhance IR. The multi-hit hypothesis provides a model that summarizes the complex factors and interactions leading from adipocytokines, FFAs metabolism and IR to NAFLD. Also Chu et al. [44] reported that NAFLD patients with abnormal ALT had the highest plasma levels of IL-6 but it did not reach the statistical differences as compared with other group. Another issue in our research is that we have observed a positive significant correlation between the concentration of IL-6 with concentration of TG and cholesterol in NAFLD patient group. These current results agree with those reported by a study of Chu et al. [44] as it demonstrated that patients with NAFLD have a dysregulated cytokine metabolism at baseline and a significant decrease in IL-6 levels after lifestyle changes and vitamin E administration. Also IL-6 correlates significantly with ALT.

The present study also, revealed significant higher levels of serum CRP in NAFLD patients than their controls. These findings agree with those of previous studies of Koruk et al. [45]. reported that increased levels of CRP could be helpful in the diagnostic work-up of patients with fatty liver disease. However, these findings disagree with those of Wieckowska et al. [46] they found no significant difference in levels of CRP among NAFLD patients.

According to gender there was no significant difference between males and females in both groups except for BMI in the control group. These findings disagree with those of previous studies Lizardi-Cervera et al. [22] and Kogios et al. [47]. In our study we observed that CRP correlates positively significantly with HDL and negatively not significantly with ALT and AST.

6. CONCLUSION

Patients with NAFLD have lower adiponectin levels and higher IL-6 and CRP levels compared with their control group in particular; effort is required to improve the consideration of NAFLD as a dangerous condition that should not be underestimated or by-passed.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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