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**Original Article**

# Association of Adiponectin and Oxidized HDL with ABO Blood Groups in Fatty Liver Patients

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## ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a group of liver diseases that are not brought on by alcohol usage and are defined by an excessive buildup of fat in the liver cells. **Objective**: To identify the relationship between the Body Mass Index (BMI) and liver function markers in the study group, as well as Oxidized High-Density Lipoprotein (oxHDL) levels. **Methods:** This study was conducted at the University of Lahore, for the duration of six months from January 2022 to June 2022. For determining the role of adiponectin and oxHDL, (n=200) patients and divided into two group, healthy group (n=100) and disease group (n=100) participants. Biochemical identification, liver function test, lipid profile test and ELISA was done for analyzing the association with NAFLD. SPSS software was used for statistical analysis. **Results:** In this study different parameters were used that's values of parameters mean of cases according to blood group system were varied than normal range, such as adiponectin level, BMI, oxLDL, oxHDL, ALT, AST, ALP, Cholesterol level, d-LDL, Calculated LDL, sdLDL, V-LDL, Triglyceride level, Apolipoprotein-B level was significantly higher and AST/ALT Ratio values, albumin, HDL were slightly less than normal values. O Blood groups was reported very low risk of fatty liver patients due to high adiponectin. **Conclusions:** From analysis it was concluded, that adiponectin and oxHDL associated with high risk of non-alcoholic fatty liver disorder.

## INTRODUCTION

Fatty liver well-defined such as increase of 5% to 10% fat in liver cells. NAFLD include non-alcoholic steatohepatitis, 5% liver fat with inflammation and hepatocellular hyperplasia with or without fibrosis [1]. Several risk factors are elaborated to rise the high risk of NAFLD, high-calorie diets, rise saturated fat level, usage of refined sugar, abnormal metabolism, type 2 diabetes, hypertension, hyperlipidemia, Obesity (overweight) and insulin resistance are the key contributor of develop and growth of NAFLD [2, 3]. The race of NAFLD is frequently higher in Middle East that have 32%, Asia have 27 %, Europe have 23 %, and 9% people affected by NAFLD in India and Pakistan [4, 5]. Genetic variants influence the NAFLD, play very vital role. The first known genetic variation among humans is ABO blood group system which is divided into A, B, AB and O blood groups with respect to RH negative and positive. As such ABO blood system is linked with heart disease and cancer, similarly it is associated with non-alcoholic fatty liver disease (NAFLD) [6]. Lipid profile is effected at very high rate HDL, LDL, VLDL, LDL-C and HDL-C are interlinked [7, 8]. High range of hormone and low adiponectin resistance has been shown to increase the development

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and growth of NAFLD. Adiponectin enhance Fatty Acid Oxidation (FAO) and inhibit De Novo Lipogenesis (DNL) so therefore it increase insulin sensitivity. Increasing the adiponectin level in metabolic syndrome may preventing the serious consequences of NAFLD. HDL (high-density lipoprotein) is often considered "good" cholesterol because it contributes to reverse cholesterol transport. Alternatively, Oxidized HDL (ox-HDL) undergoes structural modifications and might promote atherogenesis instead. HDL can be promoted to oxidation, leading it from protective properties (anti-inflammatory and antioxidant) toward the pathogenic side of the spectrum. Higher levels of ox-HDL have been linked with the development of cardiovascular diseases and metabolic disorders [9, 10].

The main objective of this research was to identify the relationship between the Body Mass Index (BMI) and liver function markers in the study group, as well as Oxidized High-Density Lipoprotein (oxHDL) levels in Lahore population.

## METHODS

The study was cross-sectional. This study was carried out in university of The Lahore. The trial lasted six months, from Dec 2023 to May 2024. A total number of participants N=200 were divided into two group healthy group (100) and fatty liver diseases group consist of 100 participants. The age of participants was 40-65 year old. This study was approved by institutional review board (IRB) IMBB/BBB/21/277, the University of Lahore. Making ensuring the informed consent procedure was understandable and transparent for each and every participant. All patients were resident of Lahore Pakistan. 5ml venous blood was extracted and serum was obtained by centrifugation and stored it at -70oC for biochemical analysis. NAFLD grade III along with following Co-morbidities were included in this study: Diabetes Mellitus, COPD, Due to smoking, Hypertension. The following Co-morbidities were not included in this study: alcohol consumption, viral hepatitis (HBV, HCV) and pregnant women. According to Antigen-Antibody agglutination test by slide method blood group with RH factors were determined. Liver function test includes ALT, AST and ALP was estimated. Statistical software or algorithms are typically used in the sample size calculation process. In order to compare the means of two groups, n= $(Z\alpha^{/2}+Z\beta)2*2\ \sigma 2/d^2$). By calculate the significance level, $\alpha$ = 0.05, which gives $Z\alpha/2$=1.96, Power (1- $\beta$) = 0.80, which gives $Z\beta$=0.84. Statistical analysis (mean and SD) was done by using SPSS v.26. For the continuous variable analysis, a t independent test was applied. P-value <0.001 was consider as significant value.

## RESULTS

Descriptive statistics for Biochemical parameters of patients and controls is tabulated in table 1. Mean age of patients and controls was 58.74 and 52.55 respectively. Values of BMI along with liver enzymes (AST, ALT and ALP) were significantly increased (p<0.001) as compared to controls. Values of AST/ALT ratio and albumin were lower in patients (p<0.001) as compared to controls. Levels of lipid associated parameters such as (c-LDL,d-LDL, Cholesterol, oxHDL, oxLDL, sdLDL, Apolipoprotein-B, triglyceride, V-LDL, adiponectin level) were significantly increased as compared to controls (p<0.001). HDL level was significantly decreased in patients as compared to cases (p<0.001).

**Table 1:** Biochemical Assay of study participants

| S. No. | Variables | Subjects | n | Mean ± SD | Mini-mum | Maxi-mum | P-Value |
|---|---|---|---|---|---|---|---|
| 1 | Age | Normal | 100 | 52.55 ± 5.182 | 45 | 67 | <0.001 |
| | | Patient | 100 | 58.74 ± 4.545 | 45 | 68 | |
| 2 | BMI | Normal | 100 | 21.58 ± 2.40 | 16 | 30 | |
| | | Patient | 100 | 35.67 ± 5.898 | 26 | 48 | |
| 3 | Adiponectin Level | Normal | 100 | 12.360 ± 3.310 | 7.00 | 20.00 | <0.001 |
| | | Patient | 100 | 24.50 ± 4.103 | 17.00 | 35.00 | |
| 4 | V-LDL | Normal | 100 | 25.703 ± 2.386 | 20.60 | 34.50 | |
| | | Patient | 100 | 48.438 ± 5.017 | 38.00 | 56.60 | |
| 5 | Triglyceride | Normal | 100 | 128.170 ± 6.3 | 121.172 | 134.47 | |
| | | Patient | 100 | 242.190 ± 4.92 | 37.27 | 247.11 | |
| 6 | Apolipo protein-B | Normal | 100 | 81.937 ± 5.56 | 76.377 | 87.49 | |
| | | Patient | 100 | 150.624 ± 4.86 | 145.76 | 155.48 | |
| 7 | sdLDL | Normal | 100 | 30.127 ± 4.283 | 22.39 | 42.66 | |
| | | Patient | 100 | 65.294 ± 5.99 | 59.3 | 71.28 | |
| 8 | oxLDL | Normal | 100 | 50.230 ± 5.745 | 37.00 | 60.00 | |
| | | Patient | 100 | 96.940 ± 5.52 | 91.42 | 102.46 | |
| 9 | oxHDL | Normal | 100 | 81.920 ± 4.426 | 73.00 | 91.00 | |
| | | Patient | 100 | 240.680 ± 6.01 | 243.67 | 246.69 | |
| 10 | HDL Level | Normal | 100 | 55.140 ± 5.103 | 45.00 | 67.00 | |
| | | Patient | 100 | 40.266 ± 6.678 | 28.00 | 55.00 | |
| 11 | Cholesterol | Normal | 100 | 174.54 ± 5.23 | 169.31 | 179.77 | |
| | | Patient | 100 | 265.350 ± 4.97 | 260.38 | 270.32 | |
| 12 | d-LDL | Normal | 100 | 98.860 ± 5.86 | 93 | 104.72 | |
| | | Patient | 100 | 182.090 ± 5.94 | 176.15 | 188.03 | |
| 13 | c-LDL | Normal | 100 | 93.766 ± 5.56 | 88.206 | 99.321 | |
| | | Patient | 100 | 177.066 ± 4.48 | 172.58 | 81.54 | |
| 14 | ALT | Normal | 100 | 33.96 ± 4.865 | 22 | 42 | |
| | | Patient | 100 | 65.155 ± 3.3 | 58 | 73 | |
| 15 | AST | Normal | 100 | 29.68 ± 4.86 | 19 | 38 | <0.001 |
| | | Patient | 100 | 50.6 ± 4.29 | 40 | 60 | |
| 16 | ALP | Normal | 100 | 81.33 ± 5.76 | 75.57 | 87.09 | |
| | | Patient | 100 | 95.79 ± 6.482 | 83 | 113 | |
| 17 | Albumin | Normal | 100 | 4.04 ± 0.530 | 2.80 | 5.20 | |
| | | Patient | 100 | 2.803 ± 0.377 | 2 | 3.90 | |
| 18 | AST/ALT Ratio | Normal | 100 | 1.20 ± 0.12 | 57 | 1.15 | |
| | | Patient | 100 | 3.13 ± 1.17 | 62 | 98 | |

According to this study it was found that serum oxHDL and Adiponectin with blood groups of cases and controls is tabulated in table 2. It is observed that the level of oxHDL and Adiponectin was significantly high (p<0.001) in patients

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with blood groups A,B,AB,O with Rh factor +ve compared to same blood groups of controls. The level of oxHDL and Adiponectin was also significantly high ($p<0.001$) in patients with blood groups A,B,AB,O with Rh factor -ve compared to same blood groups of controls.

**Table 2:** Biochemical Assay According to ABO Blood Group

| ABO Blood Groups | | | | oxhdL with Blood Groups Mean ± SD | | Adiponectin with Blood Groups Mean ± SD | |
|---|---|---|---|---|---|---|---|
| Blood Group | Normal | Patients | Total | Patients | Normal | Patients | Normal |
| A+ | 24 | 30 | 54 | 234 ± 4.06 | 86 ± 3.09 | 24 ± 3.62 | 16 ± 2.83 |
| A- | 8 | 2 | 10 | 215 ± 2.82 | 84 ± 3.2 | 26 ± 4.24 | 11 ± 1.85 |
| AB+ | 12 | 16 | 28 | 260 ± 3.03 | 79 ± 3.74 | 29 ± 3.21 | 10 ± 2.25 |
| AB- | 4 | 6 | 10 | 235 ± 4.70 | 80 ± 4.96 | 28 ± 3.74 | 14 ± 3.36 |
| B+ | 20 | 26 | 46 | 244 ± 4.49 | 78 ± 2.4 | 22 ± 3.15 | 10 ± 1.52 |
| B- | 12 | 4 | 16 | 251 ± 4.16 | 82 ± 3.49 | 27 ± 1.63 | 12 ± 2.56 |
| O+ | 16 | 12 | 28 | 224 ± 4.91 | 83 ± 3.79 | 22 ± 2.67 | 13 ± 2.4 |
| O- | 4 | 4 | 8 | 252 ± 3.91 | 81 ± 4.96 | 25 ± 3.16 | 79 ± 1.17 |
| Total | 100 | 100 | 200 | - | | | |

In current reasrch to indicate that for comparison of LDL and oxLDL is tabulated in table 3. The values of LDL and oxLDL was significantly higher in patients ($p<0.001$) as compared to controls.

**Table 3:** Comparison of LDL and oxLDL in Patients and Normals

| Category | Patients (Mean ± SD) | Normals (Mean ± SD) | % increase in patients |
|---|---|---|---|
| LDL | 182.09 ± 5.94 | 98.86 ± 5.86 | 1.89 |
| oxLDL | 96.94 ± 5.52 | 50.23 ± 5.74 | 2.08 |

## DISCUSSION

Various investigations have recognized the higher Adiponectin level as independent risk factor of liver damage and NAFLD [11]. Shabalala *et al.*, highlighted the risk of NAFLD by high level of Adiponectin, according to previous reports in this study Adiponectin level mean was 24.5 ± 4.10346 µg/mL (p-value<0.001), minimum value 17 µg/mL and maximum value was 35 µg/ml. Adiponectin normal level was 12.36 ± 3.31078 µg/mL, minimum value 7 µg/mL and maximum value was 20 µg/mL. Adiponectin level was significantly higher. The association of ABO blood group as developing factor of NAFLD is still unclear. Some previous studies exposed the association of ABO blood group with liver injury and also as NAFLD. Different studies reported different result of ABO blood group association to NAFLD, Non-O Blood group was found to be pointedly association to high risk of NAFLD. In this study A+ blood group have higher NAFLD and at 2nd no B+ blood group was reported in NAFLD, O Blood groups was reported very low risk of NAFLD. The obesity epidemic is closely linked with the rising prevalence and severity of nonalcoholic fatty liver disease (NAFLD). Obesity has been associated not only with the simple steatosis (SS), but also with advanced disease i.e., nonalcoholic steatohepatitis (NASH), NASH-related cirrhosis and hepatocellular carcinoma [12]. Consequently, despite of increasing almost all the mortality causes, obesity tends to increase liver-specific mortality especially in NAFLD patients. However, increased Body Mass Index is not an independent risk factor for the development of in NAFLD patients. The BMI mean of our study 35.67 ± 5.898 kg/m$^2$ (p-value<0.001) verified that obesity was rampant among our subjects weight gaining is the golden indication toward the NAFLD, this result is similar to many previous studies [13]. NAFLD is fairly mutual among elderly population. Intricate process of senescence or aging is complicated in the expansion of a plethora of chronic diseases. Development of senescence includes the pathogenesis and growth of liver steatosis. It includes the development of Nonalcoholic Steatohepatitis (NASH) which is branded by the emergence of inflammation, hepatocyte ballooning, and liver fibrosis. According to Papatheodoridi AM *et al.*, in 2020 the development of Nonalcoholic Fatty Liver Disease (NAFLD) and its progression to NASH are commonly accompanied by several pathological as well as physiological events that include metabolic dysregulation and inflammatory changes occurring within the liver [14]. The average age of cases according to our study was 58.74 ± 4.54 (p-value<0.001), this relatively almost same age is associated with NAFLD which is reported onto several studies [14, 15]. Oxidized High-density lipoprotein (oxHDL) is an emerging biomarker of NAFLD patients. Miura K *et al.*, study reported that Oxidized High-density lipoprotein (oxHDL) level is higher in NAFLD patients similarly in this study Oxidized High-Density Lipoprotein (oxHDL) level in patients was 240.68 ± 6.01 mg/dl (p-value<0.001), minimum value 243.64 mg/dl and maximum value was 246.69 mg/dl. oxHDL normal level was 81.92 ± 4.426 mg/dl, minimum value 73 mg/dl and maximum value was 91 mg/dl. oxHDL level was significantly higher in cases than controls [16]. Increasing oxLDL levels linked to an amplified risk of acute coronary events, metabolic syndrome and hepatocellular damage in clinical cholestasis and fibrosis. oxLDL has been established to increase the production of inflammatory cytokines and chemokines by macrophages and to cause coronary smooth muscle cells to overexpress interleukin, an

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essential gatekeeper of inflammation and tissue damage. oxLDL discovered to increase apoptosis by activating apoptotic signaling pathways like the Fas system [17]. In apoptotic cells, physiologically active oxidized lipids were also discovered. As a result, because oxLDL causes apoptosis, it is not only an inflammatory trigger but also increases cell damage. Furthermore, oxLDL causes inflammation by increasing the production of Reactive Oxygen Species (ROS) and the expression of metalloproteinases. Oxidized Low-Density Lipoprotein (oxLDL) higher value have high risk of NAFLD, similarly in this study Oxidized Low-Density Lipoprotein (oxLDL) level mean in patients was 96.94 ± 5.52 mg/dl (p-value<0.001), minimum value 91.42 mg/dl and maximum value was 102.46 mg/dl . oxLDL level was significantly higher in cases than controls [18]. Dyslipidemia is the most common situation present in NAFLD patients and considered as increasing the level of Small Dense Low-density lipoprotein (sd-LDL) and lower the level of HDL. Hwang HW *et al.*, showed that Small Dense Low-density lipoprotein (sd-LDL) is increased in NAFLD patients, similar to this study in our research sdLDL level mean in patients was 65.294 ± 5.99 mg/dl (p-value<0.001) that is higher than normal range which is less than 40mg/dl (<40 mg/dl) [19]. Apolipoproteins like ApoE, ApoA, ApoC and ApoB are associated with swear diseases of liver especially with NAFLD. In this study Apolipoprotein-B level mean in patients was 150.624 ± 4.86 mg/dl, minimum value 145.76 mg/dl and maximum value was 155.48 mg/dl (p-value<0.001), Apolipoprotein-B level was significantly higher which highlight the high risk of NAFLD [20]. Triglyceride is the independent marker of NAFLD. In this study Triglyceride level was 242.19 ± 4.92 mg/dl (p-value<0.001) and normal value was less than 150 mg/gL (<150 mg/dL) [21]. As earlier reported that maximum patients exhibited the dyslipidemia profile and have abnormal lipid profile which is more frequently in NAFLD patients. Some previous studies reported a significant association of V-LDL with inflammation or liver damages. Mendez-Sanchez N *et al.*, also showed that liver fibrosis (NAFLD) more likely high V-LDL. Similarly, in our study V-LDL was 48.438 ± 5.0174 mg/dl (p-value<0.001), V-LDL level was significantly higher in cases than normal [5]. Earlier studies described the association of low HDL with occurrence of NAFLD. Lower HDL have higher risk of NAFLD and our study HDL mean in cases was 40.266 ± 6.678 mg/dl (p-value<0.001), HDL level was significantly lower [22]. Calculated Low-Density Lipoprotein (c-LDL) is also higher in hepatosytosis and it is the significant reason for the development of NAFLD. In this study the calculated Low-Density Lipoprotein (c-LDL) average level was 177.066 ± 4.48 mg/dl (p-value<0.001). The Desired normal range of this was less than 100 (<100), optimal value was 100-129 and higher than 130 was abnormal condition. This study also verified the previous studies results that Calculated LDL level was significantly higher. Direct Low-density Lipoprotein (d-LDL) Level in NAFLD patients has higher. Normal range of d-LDL was up to 130 mg/dl. Our study stated the d-LDL level mean in patients were 182.09 ± 5.94 mg/dl (p-value<0.001), that was significantly higher than normal [23]. Normal value of cholesterol is less than 200 (<200). In this study Total Cholesterol level mean in patients were 265.35 ± 4.97 mg/dl, minimum value 260.38 mg/dl and maximum value was 270.32 mg/dl. Average result of Cholesterol level was significantly higher (p-value<0.001). Same results were highlighted in Ganjooei NA *et al.*, studies. The concentration of serum albumin reported lower when the intensity of NAFLD increased. The normal level of albumin in serum is 3.5-5 g/dl. In our study Albumin mean in cases was 2.8 ± .377 g/dl, minimum value 2 g/dl and maximum value was 3.9 g/dl (p-Value < 0.001), these results were significantly verified by previous studies [24]. Alkaline Phosphatase (ALP) is also considered as biomarker related to the hepatic fibrosis in the patients. Range of Alkaline Phosphatase is 41 – 133 U/L, 41 U/L is lower and 133 U/L is higher range, in NAFLD patients have higher range and normal people have lower value. In our study ALP average range in cases was 95.79 ± 6.48 U/L, minimum value 83 U/L and maximum value was 113 U/L (p-value <0.001). Other studies also verified our results to describe high range of ALP. AST is also play significant role in diagnosis of liver disorders. The normal value of AST is up to 40 U/L, in our study the mean of AST level was 50.61 ± 4.29 U/L (p-value<0.001) this result show AST values were significantly higher which exposed the high risk of NAFLD. Some NAFLD patients have normal ALT value and some have higher than normal. The normal value of ALT is up to 40 U/L, in our study the mean of ALT level was 65.155 ± 3.316 U/L (p-value<0.001) this result show high level of ALT which shown the high risk of NAFLD. The AST/ALT Ratio mean in patients were 3.13± 1.17 U/L (p-value<0.001), normal valve of AST/ALT ratio is less than 1 (<1 U/L) and in NAFLD this ratio is less than 0.8 U/L (<0.8 U/L). Our study shows AST/ALT value less than 0.8 U/L which is indication of NAFLD [25].

## CONCLUSIONS

This study played a vital role to better understanding the association of adiponectin and oxidizes HDL with ABO blood groups in fatty liver patients. Comparing blood group O to other blood groups, higher adiponectin levels may offer protection against severe non-alcoholic Fatty Liver Disease. Different ABO blood groups were linked to genetic and environmental factors that were associated with variable oxHDL levels. These factors could have an impact on oxidative stress and inflammation in patients with fatty livers.

## Authors Contribution

Conceptualization: NN
Methodology: RA, AR
Formal analysis: SA, AA
Writing, review and editing: RJ

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All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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