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The relationship between blood urea nitrogen levels and metabolic, biochemical, and histopathologic findings of nondiabetic, nonhypertensive patients with nonalcoholic fatty liver disease

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Background/aim: Nonalcoholic fatty liver disease (NAFLD) is known as the most common cause of chronic liver disease. It is accepted that the leading cause of death in patients with NAFLD is from coronary events. Blood urea nitrogen (BUN) was used as a prognostic indicator for cardiovascular disease. We aimed to investigate the relationship between BUN levels and metabolic, biochemical, and histopathologic findings of nondiabetic patients with NAFLD.

Materials and methods: A total of 195 male patients with biopsy proven NAFLD and 82 healthy controls with normal liver and renal function tests and normal abdominal ultrasonography were enrolled in the study. BUN levels were reviewed retrospectively.

Results: The mean BUN levels of patients and controls were 13.07 (11.3–15.41) and 13.31 (10.97–15.87) mg/dL respectively. Patients were grouped as simple steatosis (n = 33, 16.9%), borderline nonalcoholic steatohepatitis (n = 64, 32.8%), and nonalcoholic steatohepatitis (n = 98, 50.3%), and the BUN levels of the histologic subgroups were 13.14 ± 2.89, 14.34 ± 3.04, and 13.71 ± 3.21 mg/dL, respectively. We could not find any differences between the patient group and control group with respect to BUN levels.

Conclusion: Our findings showed that there was no relationship between BUN levels and metabolic, biochemical, and histopathologic findings of patients with NAFLD. Further investigations, including in patients with late stages of NAFLD, are required.

Key words: Nonalcoholic fatty liver disease, blood urea nitrogen, insulin resistance

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is accepted as the most common cause of chronic liver disease. NAFLD represents a spectrum of varying severity of liver disease, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), coexistent inflammation with hepatocyte ballooning and necrosis, variable grades of fibrosis, and ultimately cirrhosis. Also the patients with cirrhosis related to NAFLD have increased risk of hepatocellular carcinoma (1,2).

NAFLD is defined as the liver part of metabolic syndrome (MetS), and insulin resistance (IR), dyslipidemia, and obesity, key features of the MetS, are strongly associated with NAFLD progression (3). Moreover, it is shown that with the development of NASH, the degree and severity of cardiovascular disease (CVD) becomes directly proportional to the amount of inflammation on liver biopsy. NASH carries a higher risk of CVD and mortality than simple steatosis (4,5). In light of the data published in the past several years, it is accepted that the leading cause of death in patients with NAFLD is from coronary events (6–9).

In patients with heart failure (HF), it is shown that increases in blood urea nitrogen (BUN) are associated with increased in-hospital, short-, and intermediate term mortality (10,11). BUN elevation is probably a result of the renal response to systemic hypoperfusion and BUN levels may represent the cumulative effects of several influences, including hemodynamic alterations that result in renal hypoperfusion, neurohormonal activation that is closely associated with altered renal hemodynamics. The main part of this neurohormonal activation is the renin-angiotensin-aldosterone system (RAAS), and BUN may be accepted as a marker of neurohormonal activation in the setting of HF (12).

There are limited data about the relationship between NAFLD and BUN as a prognostic indicator

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for cardiovascular disease. Therefore, in the present study we investigated the BUN levels in nondiabetic and nonhypertensive patients with biopsy proven NAFLD.

2. Materials and methods

We retrospectively analyzed our database between 2007 and 2012 and identified all adult patients diagnosed with histologically proven NAFLD. This study was approved by the Research Ethics Committee of Gulhane School of Medicine in accordance with the Helsinki II Declaration.

2.1. Study population

The study population consisted of 195 male patients who were diagnosed during a periodic health examination and results were obtained from a cohort of young male NAFLD patients. Inclusion criteria were: persistently (at least 6 months) elevated liver enzymes (aminotransferases), liver biopsy confirmed NAFLD, negative test results for hepatitis B and C infection and other causes of liver disease (autoimmune liver disease, Wilson's disease, hemochromatosis, α1-antitrypsin deficiency, etc.), less than 20 g of alcohol intake per day, no medication use known to increase fat deposition in the liver such as nucleoside analogues, methotrexate, and amiodarone. Subjects with hypertension and/or type 2 diabetes mellitus (T2DM) were excluded from the study. Liver biopsies were performed between 2007 and 2012 as part of investigation of abnormal liver function tests, or to stage disease severity, in subjects with radiologically confirmed NAFLD.

The control group consisted of 82 male healthy controls with normal liver and renal function tests and normal abdominal ultrasonography.

2.2. Clinical examination

All attendees underwent a routine standardized medical history and physical examination (including blood pressure measurement), anthropometry, and laboratory assessment of fatty liver risk factors. Height, weight, waist circumference (WC; midway between the lowest rib and the iliac crest at the end of normal expirium), and body mass index (BMI; the weight in kilograms divided by the square of the height in meters, kg/m^2) were measured and calculated by trained research assistants.

2.3. Laboratory assessment

Blood samples were collected into Vacutainer tubes by venipuncture after a fasting period of at least 10 h and serum samples were separated for the analysis of the biochemical parameters without freezing. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), creatinine, and uric acid (UA) levels were measured by the enzymatic colorimetric total bilirubin, indirect bilirubin, urea methods with Olympus AU2700 (Beckman Coulter) auto analyzer by using commercially available reagents. The BUN level as mg/dL was calculated by multiplying the urea level by 0.467**.** Since the direct low-density lipoprotein cholesterol (LDL-C) measurement is expensive in patients with triglycerides under 400 mg/dL, as in our patients, it was estimated using the Friedewald formula (13). Fasting serum insulin concentrations were measured by an ADVIA Centaur assay (Siemens Medical Solutions Diagnostics) with a sensitivity of 0.5 μU/L, and intraassay and interassay CV of 4.6% and 5.9%, respectively. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated as the product of fasting serum insulin (mU/L) and FPG (mmol/L) divided by 22.5 (14).

2.4. Liver histology

A single experienced liver pathologist, blinded to the patients' details, reviewed the histology slides to confirm the diagnosis of NAFLD for all subjects. Histopathological variables were scored according to the NASH Clinical Research Network Scoring System (15). Steatosis was graded as none, mild, moderate, and severe (0–3); lobular inflammation was graded according to the number of inflammatory foci per 200× field (0 is no foci; 1 is <2 foci per 200× field, 2 is 2–4 foci per 200× field, 3 is >4 foci per 200× field); hepatocellular ballooning was graded as none, few balloon cells, and many cells/prominent ballooning (0–2); Mallory's hyaline was graded as none to rare, and many (0–1). The stage of fibrosis was scored on a five-point scale, as follows: stage 0 = no fibrosis, stage 1 = perisinusoidal or periportal fibrosis, stage 2 = perisinusoidal and portal/periportal fibrosis, stage 3 = bridging fibrosis, and stage 4 = cirrhosis. The NAFLD Score (NAS) was calculated as the unweighted sum of steatosis, lobular inflammation, and hepatocellular ballooning scores. According to this, cases with NAS of 0–2 were considered to be simple steatosis (SS), cases with activity scores of 3 and 4 were considered as borderline NASH, and scores of ≥5 were diagnosed as NASH.

2.5. Statistical analysis

All statistical analyses were performed using the SPSS for Windows v. 15. Demographical, biochemical, and histological features were classified as continuous or categorical variables. Kolmogorov–Smirnov analysis was used to test for Gaussian distribution. For Gaussian-distributed variables, the data were expressed as arithmetic means ± standard deviation (SD). For those variables that were not Gaussian distributed, the data were expressed as median (25^{th}–75th interquartile range). Comparisons among groups were performed by using one-way ANOVA with the Bonferroni all-pair-wise multiple comparison or Kruskal–Wallis variance analysis with Mann–Whitney U test comparison, as appropriate. All reported P values were two-tailed, and those less than 0.05 were considered significant.

3. Results

Comparison of anthropometric and laboratory features of patients with NAFLD and controls are shown in Table 1. The mean BUN levels of patients and controls were 13.07 (11.3–15.41) and 13.31 (10.97–15.87) mg/dL respectively, and no difference was found regarding the BUN levels between the two groups.

Histopathological findings of the study participants are shown in Table 2. Patients were grouped as SS, borderline NASH, and NASH. There were 33 patients (16.9%) with SS, 64 patients (32.8%) with borderline NASH, and 98 patients (50.3%) with NASH. Group-wise comparisons showed that NASH, borderline NASH, and SS patients have a significantly higher BMI, WC, FPG, TC, HDL-C, LDL-C, AST, ALT, GGT, HOMA-IR, and insulin levels than the controls ($P < 0.05$). On the other hand, no significant difference was found regarding BUN levels among different histologic subgroups (Table 3).

Comparison of anthropometric and laboratory features of patients with (n = 107) and without (n = 88) fibrosis are shown in Table 4. Both groups were comparable regarding age, BMI, WC, FPG, lipid parameters, and GGT. AST, ALT, and HOMA-IR were significantly higher in patients with fibrosis than in patients without fibrosis ($p < 0.001$, $P = 0.001$, and $P = 0.003$, respectively). On the other hand, no significant difference was found regarding BUN levels among patients with and without fibrosis (Table 4).

We also performed correlation analyses for associations of BUN levels with anthropometric, laboratory, and histopathological findings in NAFLD group. BUN levels were positively associated with TC ($r = 0.127$, $P = 0.039$) and TG ($r = 0.199$, $P = 0.001$) levels.

Table 1. Comparison of anthropometric and laboratory features of patients with non-alcoholic fatty liver disease and controls.

Variable	NAFLD (n = 195)	Controls (n = 82)	P value
Age (years)	32 ± 6	29 ± 5	**<0.001**
BMI (kg/m^2)	28.7 ± 3	23.9 ± 2.7	**<0.001**
WC (cm)	100 (96–104)	86 (82–90)	**<0.001**
FPG (mg/dL)	94 (87–99)	81 (74–90)	**<0.001**
TC (mg/dL)	205 ± 46	177 ± 32	**<0.001**
TG (mg/dL)	160 (122–245)	99 (72–139)	**<0.001**
HDL-C (mg/dL)	40 (37–45)	46 (39–53)	**<0.001**
LDL-C (mg/dL)	128 ± 38	108 ± 30	**<0.001**
AST (IU/L)	48 (37–61)	20 (17–24)	**<0.001**
ALT (IU/L)	102 (73–130)	18 (12–26)	**<0.001**
GGT (IU/L)	57(41–79)	20 (17–26)	**<0.001**
Üre (mg/dL)	28 (24–33)	29 (24–34)	0.419
BUN (mg/dL)	13.07 (11.3–15.41)	13.31 (10.97–15.87)	0.399
Creatinine (mg/dL)	1.05 (0.99–1.12)	1.03 (0.93–1.11)	0.698
GFR (mL/min/1.73 m^2)	89.82 ± 12.31	91.16 ± 11.2	0.414
Albumin (mg/dL)	4.8 ± 0.3	4.7 ± 0.3	0.400
Insulin (μU/mL)	13.76 (9.92–19.41)	6.24 (4.15–9.05)	**<0.001**
HOMA-IR	2.48 (1.41–4.34)	1.02 (0.61–1.61)	**<0.001**

Data are expressed as means ± SD or median (25th–75th interquartile range) as appropriate.
NAFLD: nonalcoholic fatty liver disease, BMI: body mass index, WC: waist circumference, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, BUN: blood urea nitrogen, GFR: glomerular filtration rate, HOMA-IR: homeostasis model of assessment-insulin resistance.
Values in bold are significant.

Table 2. Histological features of patients with non-alcoholic fatty liver disease

Histology (n =195)	
NAS, n (%)	
0–2	33 (16.9 %)
3–4	64 (32.8 %)
5–8	98 (50.3 %)
Lobular inflammation, n (%)	
0	11 (5.6 %)
1	108 (55.4 %)
2	75 (38.5 %)
3	1 (0.5 %)
Steatosis, n (%)	
0	8 (4.1 %)
1	57 (29.2 %)
2	84 (43.1 %)
3	46 (23.6 %)
Hepatocellular ballooning, n (%)	
0	31 (15.9 %)
1	124 (63.6 %)
2	40 (20.5 %)
Fibrosis, n (%)	
0	88 (45.1 %)
1	98 (50.3 %)
2	7 (3.6 %)
3	2 (1.0 %)

Data are expressed as the number of cases (%).
NAFLD: nonalcoholic fatty liver disease, NAS: NAFLD activity score.

4. Discussion

To our knowledge, this is the first study addressing the relationship between BUN and NAFLD in patients diagnosed by liver biopsy. We did not find a significant difference between either in the subgroups of NAFLD or in patients with NAFLD and the control group with respect to the BUN levels. BUN levels were correlated with TC and TG levels.

Urea serves an important role in the metabolism of nitrogen-containing compounds and is the main nitrogen-containing substance in the urine. In the absence of conditions that enhance urea production, such as gastrointestinal bleeding, corticosteroid therapy, or a high-protein diet, elevations in BUN levels are often due to a decrease in glomerular filtration rate (16). It is shown that in chronic cardiovascular diseases, the elevation of BUN is related to mortality; the active RAAS and the nervous system play important roles in this process (17). In a study performed by O'Connor et al. (18), high BUN levels were found to be the strongest predictor of short term mortality in patients with acute heart failure (HF); moreover, lower serum albumin, cholesterol, and systolic blood pressure were other independent predictors of this worst outcome. In another study, higher concentrations of BUN, serum creatinine, and lower serum albumin and TC levels were demonstrated to be a marker for hospital death in older patients with severe, acute HF. Because albumin and TC are accepted as biomarkers of malnutrition-inflammation syndrome, abnormal concentrations of these two biomarkers are common in elderly patients with acute HF (19). In the present study BUN levels were positively correlated with TC and TG levels. We suggest that this positive correlation may make researchers think of BUN as a prognostic indicator for cardiovascular disease.

Insulin resistance (IR) plays a central role in the pathophysiology of NAFLD. We learned from experimental studies that there was a close relationship between insulin signaling and RAAS, resulting in the worsening of IR (20). Angiotensin II induces the generation of reactive oxygen species by activating the nicotinamide adenine dinucleotide phosphate oxidase and regulates the production of proinflammatory mediators, including tumor necrosis factor α, interleukin-6, and PAI-1. This results in impairment of insulin signaling (21,22). It was shown that as the primary effector of the physiologic outcomes of RAAS signaling, Angiotensin II takes part in the development and progression of NAFLD, including increased steatosis, inflammation, insulin resistance, and fibrosis (23). Additionally, data from both animal and human studies indicate that RAAS plays a key role in hepatic fibrosis by activation of hepatic stellate cells, upregulation of proinflammatory/profibrotic cytokines, and induction of oxidative stress (24). We did not find a significant difference between patients with and without fibrosis regarding the BUN levels. However, studies including patients with late stage fibrosis may shed more light on this issue.

There is one previous study in which the value of BUN in patients with NAFLD was investigated (25). In that study, the NAFLD diagnosis was based on blood testing, ultrasound imaging, and liver/spleen ratio of computed tomography values. These imaging modalities can give only information about the steatosis. ALT alone is not an ideal marker for either diagnosis of NAFLD or distinguishing steatosis from NASH (26). Researchers used AST and ALT levels to estimate inflammation. There was no information about the fibrosis level of the patient, which is related to the activation of RAAS. They found that BUN levels in

Table 3. Comparison of anthropometric and laboratory features of patients with SS, borderline NASH, NASH, and controls.

Variable	NASH (n = 98)	Borderline (n = 64)	SS (n = 33)	Controls (n = 82)	P value
Age (years)	33 ± 6	31 ± 6	34 ± 7	29 ± 5[a]	**<0.001**
BMI (kg/m^2)	28.38 ± 2.66	28.58 ± 3.11	29.64 ± 3.12	23.89 ± 2.7[b]	**<0.001**
WC (cm)	101 ± 7	99 ± 12	101 ± 6	87 ± 7[c]	**<0.001**
FPG (mg/dL)	95 ± 11	95 ± 14	92 ± 10	82 ± 11[d]	**<0.001**
TC (mg/dL)	206 ± 44	200 ± 49	210 ± 47	177 ± 32[e]	**<0.001**
TG (mg/dL)	188 ± 108	178 ± 91	231 ± 151	130 ± 126[f]	**<0.001**
HDL-C (mg/dL)	41 ± 7	41 ± 6	41 ± 7	46 ± 8[g]	**<0.001**
LDL-C (mg/dL)	129 ± 36	125 ± 40	130 ± 38	108 ± 30[h]	**0.001**
AST (IU/L)	59 ± 22	50 ± 21	43 ± 15	21 ± 5[i]	**<0.001**
ALT (IU/L)	123 ± 48	102 ± 47	85 ± 29	20 ± 10[j]	**<0.001**
GGT (IU/L)	69 ± 50	69 ± 55	79 ± 77	24 ± 14[k]	**<0.001**
Urea (mg/dL)	29 ± 7	31 ± 7	28 ± 6	29 ± 6	0.196
BUN (mg/dL)	13.71 ± 3.21	14.34 ± 3.04	13.14 ± 2.89	13.40 ± 2.79	0.194
Creatinine (mg/dL)	1.04 ± 0.12	1.05 ± 0.11	1.04 ± 0.14	1.03 ± 0.13	0.826
GFR (mL/min/1.73 m^2)	89.32 ± 11.95	90.64 ± 12.22	89.71 ± 13.82	91.16 ± 12.01	0.770
Albumin (mg/dL)	4.82 ± 0.25	4.73 ± 0.27	4.74 ± 0.37	4.74 ± 0.25	0.239
Insulin (μU/mL)	16.58 ± 8.05	15.74 ± 9.94	16.72 ± 10.43	6.67 ± 2.84[l]	**<0.001**
HOMA-IR	2.81 ± 2.48	2.94 ± 2.51	3.61 ± 2.65	1.12 ± 0.75[m]	**<0.001**

Data are expressed as the means ± SD or median (25th–75th interquartile range) as appropriate. P values were calculated using ANOVA with Bonferroni correction.

NAFLD: nonalcoholic fatty liver disease, BMI: body mass index, WC: waist circumference, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, BUN: blood urea nitrogen, GFR: glomerular filtration rate, HOMA-IR: homeostasis model of assessment-insulin resistance. Values in bold are significant.

[a] P = 0.001 versus NASH, P = 0.003 versus SS; [b] P < 0.001 versus NASH, Borderline NASH and SS; [c] P < 0.001 versus NASH, Borderline NASH and SS;

[d] P < 0.001 versus NASH and Borderline NASH, P = 0.001 versus SS; [e] P < 0.001 versus NASH, P = 0.014 Borderline NASH, P = 0.002 versus SS; [f] P = 0.007 versus NASH, P < 0.001 versus SS.

[g] P < 0.001 versus NASH, P = 0.001 Borderline NASH, P = 0.002 versus SS; [h] P = 0.002 versus NASH, P = 0.033 Borderline NASH, P = 0.031 versus SS.

[i] P < 0.001 versus NASH, Borderline NASH and SS; [j] P < 0.001 versus NASH, Borderline NASH and SS; [k] P < 0.001 versus NASH, Borderline NASH and SS.

[l] P < 0.001 versus NASH, Borderline NASH and SS; [m] P < 0.001 versus NASH, Borderline NASH and SS.

NAFLD patients were significantly higher than those in the control cases and also elevated BUN was negatively correlated with liver/spleen ratio of CT values, ALT, and AST. Previous investigators concluded that elevated BUN was related to the RAAS activity and this may be an early marker in the way of increasing CVD risk in patients with NAFLD.

In the present study we did not observe any significant difference regarding the BUN levels between NAFLD patients and controls. In addition, there was no significant association of BUN levels with either biochemical parameters or histopathologic findings, except positive correlation with TG and TC.

We suggest some possible explanations for the lack of relationship between BUN levels and NAFLD in our study. Firstly, it is shown that one of the pathogenetic mechanisms responsible for the elevation of BUN level is RAAS activation (17). At the same time, RAAS plays

Table 4. Comparison of anthropometric and laboratory features of patients with and without fibrosis

Variable	Fibrosis 0 (n = 88)	Fibrosis 1–3 (n = 107)	P value
Age (years)	31.6 ± 6.3	32.4 ± 6.4	0.270
BMI (kg/m^2)	28.8 ± 2.8	28.3 ± 3.2	0.807
WC (cm)	100 ± 6	101 ± 7	0.892
FPG (mg/dL)	95 (86–99)	94 (88–100)	0.969
TC (mg/dL)	198 ± 38	211 ± 42	0.120
TG (mg/dL)	154 (122–220)	168 (123–250)	0.127
HDL-C (mg/dL)	40 (36–41)	42 (37–47)	0.155
LDL-C (mg/dL)	124 ± 32	131 ± 34	0.283
AST (IU/L)	40 (34–51)	51 (39–68)	**<0.001**
ALT (IU/L)	86 (62–117)	109 (84–135)	**0.001**
GGT (IU/L)	59 (39–92)	57 (44–76)	0.503
Urea (mg/dL)	29.21 ± 6.31	28.94 ± 6.81	0.508
BUN (mg/dL)	13.64 ± 2.95	13.51 ± 3.18	0.508
Creatinine (mg/dL)	1.07 ± 0.12	1.05 ± 0.11	0.456
GFR (mL/min/1.73 m^2)	88.20 ± 11.64	7.20 ± 1.70	0.171
Albumin (mg/dL)	4.7 ± 0.3	4.8 ± 0.3	0.285
Insulin (μU/mL)	12.2 (9.28–17.05)	15.38 (10.14–20.86)	0.147
HOMA-IR	2.34 (1.68–3.94)	2.97 (2.14–4.95)	**0.003**

Data are expressed as means ± SD or median (25th–75th interquartile range) as appropriate.
P values were calculated using Student's t-test and Mann–Whitney U test as appropriate.
BMI: body mass index, WC: waist circumference, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, BUN: blood urea nitrogen, GFR: glomerular filtration rate, HOMA-IR: homeostasis model of assessment-insulin resistance.

a key role in hepatic fibrosis (23). In our group 45.1% of the patients had no fibrosis, while 50.3% had grade 1 fibrosis. Regarding the fibrosis levels, it can be said that our NAFLD cohort contained subjects with early stages of the disease. In the future, progressing fibrosis may cause the elevation of the BUN levels. Secondly, we think that the lack of relationship between BUN levels and NAFLD in our cohort could be dependent on the selection criteria of our study population. Our patients were nondiabetic and nonhypertensive and we know that both T2DM and hypertension can cause renal problems and elevation of BUN levels (27). Thus, NAFLD patients having these comorbid conditions may have high BUN levels.

Nevertheless, the current study needs to be interpreted in the context of certain potential limitations. Firstly, the cross-sectional design of the study makes causal interpretations of associations between BUN levels and NAFLD difficult. Secondly, because of the small number of patients and the strict inclusion criteria, our findings are not representative for all subjects with NAFLD. However, we think that the design of our study was a requirement for the goals we wanted to achieve. Lastly, all participants were men, and it remains to be determined if similar findings would be observed in women.

To summarize, no significant relationship was found between BUN levels and metabolic and histopathologic findings of patients with NAFLD. Further investigations that include patients with late stage NAFLD are required to confirm this finding.

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