Epidemiological, clinical, and biochemical characteristics of Saudi patients with nonalcoholic fatty liver disease: a hospital-based study

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Ann Saudi Med 2012; 32(3): 288-292
DOI: 10.5144/0256-4947.2012.288

BACKGROUND: The estimated prevalence of nonalcoholic fatty liver disease (NAFLD) in Saudi Arabia is 7% to 10%. Despite the high prevalence of risk factors including diabetes, obesity, and hyperlipidemia, no recent epidemiological studies have measured the disease burden. We aimed to determine the characteristics of Saudi NAFLD patients attending a university hospital, and study factors affecting alanine aminotransferase (ALT) levels.

DESIGN AND SETTING: A prospective study among patients referred for ultrasonography in King Khalid University Hospital in Riyadh, Saudi Arabia from February to May 2009.

PATIENTS AND METHODS: NAFLD was defined as an appearance of fatty liver on routine abdominal ultrasound in the absence of coexisting liver disease and alcohol consumption. Patients were classified into normal and high ALT (ALT >60 U/L) level groups for analysis.

RESULTS: The prevalence of NAFLD was 16.6% (218/1312). Patients with normal ALT had the mean (SD) age of 45.9 (10.6) years and the mean body mass index of 34.5 (7.9) kg/m². Forty percent of the 151 patients with normal ALT had diabetes, 66.2% were obese, and 29.1% had hypertension. Forty-three patients (23%) had high ALT levels. These patients had significantly lower age (P=0.003) and fasting blood sugar (P=0.03) than the normal ALT group. Non-diabetic patients (odds ratio 0.30, 95% CI 0.1-0.8), men (female OR 0.23, 95% CI 0.1-0.5), lower cholesterol (P=0.001), high-density lipoprotein (P=0.006), and low-density lipoprotein (P=0.008) levels were more likely to be observed among patients with high ALT levels. In a multivariate analysis, younger age (OR 0.96, 95% CI 0.93-0.99), being male (OR 0.23, 95% CI 0.09-0.57), and a lower cholesterol level (OR 0.55, 95% CI 0.37-0.82) were significant predictors of high ALT levels.

CONCLUSION: Based on the high prevalence of obesity and diabetes, the prevalence of NAFLD will continue to be high, unless awareness is inculcated among the local population.
on NAFLD in Saudi Arabia, and this did not study contributing risk factors. We, therefore, undertook this study to determine the clinical, epidemiological, and biochemical characteristics of Saudi patients with NAFLD. Since the presence of an elevated alanine aminotransferase (ALT) level is often the first clue in the diagnosis of NAFLD, we evaluated ALT levels as well as levels of other biochemical liver markers. Further, we explored potential predictors of high ALT levels in patients whom we categorized as having NASH.

**PATIENTS AND METHODS**

For the purpose of this study, NAFLD was defined as an appearance of fatty liver on routine abdominal ultrasound in the absence of coexisting liver disease and alcohol consumption. All patients having an ultrasound in King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, from February to May 2009 were screened for fatty liver as part of the study, regardless of the primary ultrasound indication. Any patient with an appearance of fatty liver on ultrasound was referred from the ultrasound department to the hepatology clinic for recruitment into the study. Patients who were found to have normal liver enzymes and no other evidence of liver disease were given lifestyle modification advice, published studies on weight loss, and healthy diet and were discharged. Patients who were found to have high liver enzymes were followed routinely in the hepatology clinic with standard conventional medical care.

All ultrasonography images were read by a single experienced radiologist. Patients were included if they were above 18 years old, had a fatty liver detected by routine ultrasound, and were willing to give an informed consent. Patients were excluded if they had other liver diseases (manifested by hepatitis B surface antigen [HBsAg] or hepatitis C virus antibody [HCV Ab] positivity, antinuclear antibodies [ANA], antismooth muscle antibodies [ASMA] titer equal or above 1/160, abnormal iron studies, or a low serum ceruloplasmin), consumed any alcohol, were on medications that may cause steatosis, or if the patient refused to be enrolled. Other exclusion criteria included secondary causes of NAFLD such as bowel bypass or recent weight loss of more than 10 kg in 6 months.

All patients had laboratory investigations including complete blood count, ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, albumin, ANA, ASMA, anti-mitochondrial antibodies, serum iron (Fe), transferrin saturation, serum ceruloplasmin, lipid profile, and fasting blood sugar. Direct enzyme-linked immuno-

**RESULTS**

A total of 1312 upper abdominal ultrasounds were performed within the 4-month-study period. A total of 218 patients were labeled as having fatty liver on imaging, giving a prevalence rate of 16.6%. Of these, 6 refused to give blood samples, 6 had hepatitis B, and 4 had hepatitis C, leaving a remaining of 202 patients in the study. The mean age for the 202 patients was 44.7 (11.5) years, including 102 (51.0%) men and 100 (49.0%) women. The mean body mass index (BMI) and waist circumference were 34.5 (8.1) kg/m2 and 113.5 (15.5) cm, respectively. Sixty-nine patients (34.2%) had abnormal iron studies, or a low serum ceruloplasmin, while the mean BMI and waist circumference were 34.5 (8.1) kg/m2 and 112.9 (15.4) cm, respectively. Sixty-nine patients (34.2%) had hypertension. Details of patient demographics and basic laboratory results are summarized in Table 1.

Of the 202 patients, 43 (21.3%) had abnormally high ALT levels (defined as any reading above our laboratory’s upper limit of normal, i.e., > 60 U/L) and were labeled as having NASH. This group was analyzed separately in comparison to the group with normal ALT levels. After removing outlying data points, we were left with a final sample of 151 patients in the normal ALT group, including 68 (45.0%) men and 83 (55.0%) women (Table 2). The mean age was 45.9 (10.6) years, while the mean BMI and waist circumference were 34.5 (7.9) kg/m2 and 113.5 (15.5) cm, respectively. Sixty
patients (40.0%) had diabetes, 100 (66.2%) were obese (BMI ≥30 kg/m²), and 44 (29.1%) had hypertension. Women were more obese (OR 2.8, 95% CI 1.5-5.2).

When we looked at the family history for risk factors of NAFLD, we found that 95 (62.9%) patients had a family history of diabetes, 83 (55.0%) had a family history of hypertension, 48 (31.8%) had a family history of obesity, and 24 (15.9%) had a family history of liver disease. Thirteen (8.6%) patients smoked. Physical activity, which was defined as walking for 30 minutes at least 5 days per week, was found in 32 (21.2%) of the patients. Forty-eight (32.8%) patients had hyperlipidemia, and mean cholesterol, triglycerides, and albumin levels were 4.9 (1.0) mmol/L, 1.7 (0.9) mmol/L, and 39.1 (3.7) g/L, respectively. The mean ALT level was 39.2 (9.5) U/L. Mean AST, ALP, and GGT levels were 19.8 (7.2) U/L, 95.2 (27.0) U/L, and 44.4 (25.6) U/L, respectively. The mean serum Fe level was 13.1 (5.8) µmol/L, while mean fasting blood sugar level was 6.7 (3.4) mmol/L.

We compared various parameters between those with normal ALT levels and high ALT levels (Table 2). The high ALT group had significantly lower age (P=.003) and fasting blood sugar (P=.03) than the normal ALT group. Non-diabetic patients (OR 0.30, 95% CI 0.1-0.8) and men (female OR 0.23, 95% CI 0.1-0.5) were more likely to be observed among the high ALT level group though no differences were seen with regard

Table 1. General characteristics of nonalcoholic fatty liver disease patient population of Saudi Arabia under study (n=202).

| Variable                   | Mean (SD), median (range), or frequency (%) |
|----------------------------|--------------------------------------------|
| Age (years)                | 44.7 (11.5)                                |
| Gender                     |                                            |
| Male                       | 102 (51.0)                                 |
| Female                     | 100 (49.0)                                 |
| BMI (kg/m²)                | 34.5 (8.1)                                 |
| ALT (U/L)                  | 42 (16-672)                                |
| ALP (U/L)                  | 93 (15-352)                                |
| Triglycerides (mg/dL)      | 1.7 (1.0)                                  |
| Cholesterol (mg/dL)        | 4.8 (1.1)                                  |
| Serum ferritin (µmol/L)    | 13.7 (6.2)                                 |
| Fasting blood sugar (mmol/L)| 6.5 (3.2)                                  |
| Ferritin (ng/mL)           | 95.8 (1.5-238)                             |
| TIBC (µmol/L)              | 72.6 (13.8)                                |
| Diabetes                   |                                            |
| No                         | 133 (65.8)                                 |
| Yes                        | 69 (34.2)                                  |
| Hypertension               |                                            |
| No                         | 148 (73.3)                                 |
| Yes                        | 54 (26.7)                                  |
| Hyperlipidemia             |                                            |
| No                         | 142 (70.3)                                 |
| Yes                        | 60 (29.7)                                  |

SD: Standard deviation, BMI: body mass index, ALT: alanine aminotransferase, ALP: Alkaline phosphatase, TIBC: total iron–binding capacity.

Table 2. Univariate analysis of predictors of high alanine aminotransferase levels and different parameters.

| Variable                | Normal alanine aminotransferase (n=151) (mean (SD) or frequency [%]) | High alanine aminotransferase (n=43) (mean (SD) or frequency [%]) | P value or OR, 95% CI |
|-------------------------|------------------------------------------------------------------------|------------------------------------------------------------------|-----------------------|
| Age (years)             | 45.9 (10.6)                                                            | 39.6 (13.5)                                                      | .003b                 |
| Gender                  |                                                                        |                                                                  |                       |
| Male                    | 68 (45.0)                                                              | 31 (72.1)                                                       | .23, .1-.5*           |
| Female                  | 83 (55.0)                                                              | 12 (27.9)                                                       |                       |
| BMI (kg/m²)             | 34.5 (7.9)                                                             | 34.4 (8.7)                                                      | .96*                  |
| Obese                   | 51 (33.8)                                                              | 14 (32.6)                                                       |                       |
| No                      | 100 (66.2)                                                             | 29 (67.4)                                                       |                       |
| Diabetes                |                                                                        |                                                                  |                       |
| No                      | 91 (60.3)                                                              | 34 (79.1)                                                       | .30, .1-.8*           |
| Yes                     | 60 (39.7)                                                              | 9 (20.9)                                                        |                       |
| Fasting blood sugar (mmol/L) | 6.7 (3.4)                                                               | 5.4 (1.6)                                                      | .03*                  |
| Cholesterol (mg/dL)     | 4.9 (1.0)                                                              | 4.2 (1.2)                                                       | .001b                 |
| HDL (mmol/L)            | 1.2 (0.3)                                                              | 1.1 (0.3)                                                      | .006b                 |
| LDL (mmol/L)            | 3.0 (0.9)                                                              | 2.6 (0.8)                                                      | .008b                 |
| Triglycerides (mg/dL)   | 1.7 (0.9)                                                              | 1.8 (1.2)                                                      | .54*                  |
| Hypertension            |                                                                        |                                                                  |                       |
| No                      | 107 (70.9)                                                             | 33 (76.7)                                                       | .94, .4-2.1*          |
| Yes                     | 44 (29.1)                                                              | 10 (23.3)                                                      |                       |

*OR: Odds ratio (OR) and 95% confidence interval (CI); †t test. SD: standard deviation, BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

Table 3. Multivariate analysis of showing statistically significant predictors of high alanine aminotransferase levels.

| Predictor       | Multivariate analysis          |
|-----------------|-------------------------------|
| Age (years)     | OR (95% CI)                   |
| Gender (female) | 0.96 (0.93-0.99)              |
| Cholesterol (mg/dL) | 0.55 (0.37-0.82)            |

Logistic regression with odds ratio (OR) and 95% confidence interval (CI).
to triglycerides level ($P=0.54$), obesity (OR 1.16, 95% CI 0.5-2.5), BMI ($P=0.96$), or hypertension (OR 95% CI 0.94, 0.4-2.1). Slightly lower cholesterol ($P=0.001$), HDL ($P=0.006$), and LDL ($P=0.008$) levels were found in those with high ALT levels. In the multivariate analyses (Table 3), younger age (OR 0.96, 95% CI 0.93-0.99), being male (OR 0.23, 95% CI 0.09-0.57), and having a lower cholesterol level (OR 0.55, 95% CI 0.37-0.82) were significant predictors of high ALT levels. Keeping other variables constant, for each 1 year increase in age, there is about a 4% decrease in the odds of being in the high ALT level group. Similarly, the odds of being in the high ALT level group decreases by 77% for women and every 1 unit increase in cholesterol level decreases the odds of being in the high ALT level group by 45%.

**DISCUSSION**

The estimated prevalence of NAFLD in our study was found to be 16.6%, which is slightly higher than the rates found in previous studies in Saudi populations.\(^4\) A retrospective study conducted by El-Hassan et al in 1992 looked at the radiological prevalence of NAFLD. In their study, 138 (9.7%) of 1425 computed tomography (CT) scans revealed fatty infiltration of the liver. Of these, 39% had abnormal liver enzymes.\(^4\) Another study by Al-Quorain et al examined the liver biopsies of 544 patients, and 7.2% of these patients were labeled as having fatty liver disease.\(^3\) The difference in prevalence of NAFLD in our study compared to Al-Quorain and colleagues may be attributed to differences in diagnostic methods and case definitions. Our study used ultrasound to diagnose fatty livers, whereas their study used a more specific one, i.e., liver biopsy. In a study by Akbar and Kawther aiming to find the prevalence and characteristics of NAFLD in Saudi type 2 diabetic patients, NAFLD was diagnosed in 55% of the 116 patients.\(^2\) However, this study was targeted at diabetic patients and hence is not comparable to our population. Our study found prevalence rates closer to those found in Europe and Japan where the prevalence has been reported to be around 14% to 21%.\(^7,8\) Similarly, the prevalence in the United States from the National Health and Nutrition Examination Study (NHANES III) was 24%.\(^9\)

Our study is not an accurate representation of the Saudi population since patients were recruited from a population of people who were sent for upper abdominal ultrasounds and as such selection bias is very probable. However, we believe that our figure is close to that of the actual population because ultrasounds were requested by general practitioners in patients not known to have primary liver disease. Moreover, the true prevalence of NAFLD is difficult to study because many people with early stages of the disease are relatively asymptomatic and the gold standard for diagnosing and staging NAFLD is via a liver biopsy.\(^10\)

Our study population had more women than men with NAFLD (55% vs. 45%, respectively), which is in contrast to that found in the NHANES III study in which men had higher prevalence rates than women (33% vs. 17%). NAFLD was previously thought to be more common in women.\(^11,12\) A significant relationship was also found between the presence of NAFLD and female gender in the study by Akbar and Kawther.\(^2\) However, these series of patients were obtained from gastrointestinal clinics, and more recent population-based studies have concluded that NAFLD could be more common in men.\(^8,11,14\) The higher number of women in our study could be due to female gender being a surrogate factor for obesity, since women were more likely to be obese compared to men (OR 2.8, 95% CI 1.5-5.2), a finding that echoes results found by Al-Nozha et al., in the Saudi population previously.\(^6\) Unfortunately, this study has the major limitation of not having a control group; thus we are unable to conclude that females are more likely to have NAFLD. Nonetheless, obesity has been shown in many studies to be a determinant in causing NAFLD.\(^13-16\) The mean BMI in our population was alarmingly higher at 34.5 (7.9) kg/m\(^2\) compared to that found in the NHANES III study that was only 25.6 kg/m\(^2\) (10th percentile 20.5 kg/m\(^2\), 90th percentile 33.5 kg/m\(^2\)). This is a worrying trend especially considering that the lack of physical activity is a common phenomenon in Saudi Arabia, being as high as 79% in the population we studied and 96% in the Saudi Coronary Artery Disease registry.\(^17\)

NAFLD has been shown in various studies to be independently associated with type 2 diabetes, low HDL cholesterol, high triglycerides, and insulin resistance.\(^5,13,15,16\) These factors were also reflected in our study. Forty percent of patients had diabetes and 32.8% had hyperlipidemia. Comparing our NASH patients with those with normal ALT levels, lower age ($P=0.003$), being male (female OR 0.23, 95% CI 0.1-0.5), and lower fasting blood sugar (6.7 (3.4) vs. 5.4 (1.6) mmol/L, $P=0.003$) were independently associated with elevated ALT levels. This is similar to the NHANES III study where lower age and male gender were associated with elevated ALT levels. However, that study had a higher proportion of people with high fasting blood sugar in the group with elevated ALT levels unlike ours. The higher fasting blood sugar in the normal ALT group could reflect the impaired blood glucose in the high number of diabetic patients found in this group. Non-
diabetic patients (OR 0.30, 95% CI 0.1-0.8) were more likely to be observed among the high ALT-level group in our population, similar to that in the NHANES III study. Lower cholesterol (P = .001), HDL (P = .006), and LDL (P = .008) levels were also found in those with high ALT levels. Unlike the NHANES III study, we did not find any significant correlation between elevated ALT levels and higher BMI or triglycerides. Our multivariate analysis for predictors of high ALT levels revealed that younger age, male gender, and low cholesterol levels were associated with elevated ALT levels. This is similar to previous studies that showed association between elevated ALT levels and younger age and male gender.13,14

Our study used ultrasound in the diagnosis of NAFLD even though liver biopsy is the gold standard for diagnosing NAFLD after exclusion of other liver diseases. However, liver biopsy is costly and involves a moderate risk of complications. Apart from helping to exclude other possible liver disease etiologies and staging the progression of NAFLD, there are some arguments against liver biopsy given the absence of effective treatment approaches. The histologic interpretation of possible uneven lipid distribution varies from one pathologist to another, increasing the likelihood of sampling variability of liver biopsies.18 A population-based cohort study found that NAFLD patients who did not undergo a liver biopsy had a significantly higher survival than patients selected for biopsy; thus, making it difficult to justify the benefit of biopsy in the general population with NAFLD.20 Ultrasound is more sensitive but less specific than CT in fatty liver detection. However with a sensitivity greater than 80% and specificity greater than 90%, ultrasound represents the most convenient and least expensive modality for diagnosing fatty liver.20-23 For these reasons, ultrasound is widely used in surveying the prevalence of NAFLD.

In conclusion, to our knowledge, this is currently the most up-to-date report on the prevalence of NAFLD in a hospital-based study in Saudi. Among this cohort of patients seen at the ultrasound unit in KKUH, the prevalence was found to be 16.6%. Based on the high prevalence of obesity and Type 2 diabetes, it is safe to assume that the prevalence of NAFLD will continue to be high unless awareness is inculcated among the local population. Further studies should be conducted to study the change in prevalence of NAFLD within the population over time to closely monitor the epidemiology of this disease.

REFERENCES

1. Rector RS, Thyfault JP, Wei Y, Ibda J. Nonalcoholic fatty liver disease and the metabolic syndrome An update. World J Gastroenterol 2008;14:185-92.
2. Akbar DH, Kawther AH. Nonalcoholic Fatty Liver Disease in Saudi Type 2 Diabetic Subjects Attending a Medical Outpatient Clinic. Diabetes Care 2003;26:351-2.
3. al-Quorain A, Satti MB, al-Hamdan AR, al-Gindan Y, Ibrahim E, Khatib R, et al. Pattern of care 2003;263:351-2. Attending a Medical outpatient clinic. diabetes
4. Arafah MR, Khalil MZ, Khan NB, et al. obesity in diabetes mellitus in Saudi Arabia. Saudi Med J 1988;27:142-9.
5. al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, Al-Harthi SS, Arafah MR, Khalil MZ, et al. Diabetes mellitus in Saudi Arabia. Saudi Med J 2004;25:1603-10.
6. Al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, Al-Harthi SS, Arafah MR, Khalil MZ, et al. The prevalence of obesity and Type 2 diabetes, it is safe to assume that the prevalence of NAFLD will continue to be high unless awareness is inculcated among the local population. Further studies should be conducted to study the change in prevalence of NAFLD within the population over time to closely monitor the epidemiology of this disease.

NOMENKLATUR

1. Rector RS, Thyfault JP, Wei Y, Ibda J. Nonalcoholic fatty liver disease and the metabolic syndrome An update. World J Gastroenterol 2008;14:185-92.
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3. al-Quorain A, Satti MB, al-Hamdan AR, al-Gindan Y, Ibrahim E, Khatib R, et al. Pattern of care 2003;263:351-2. Attending a Medical outpatient clinic. diabetes
4. Arafah MR, Khalil MZ, Khan NB, et al. obesity in diabetes mellitus in Saudi Arabia. Saudi Med J 1988;27:142-9.
5. al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, Al-Harthi SS, Arafah MR, Khalil MZ, et al. Diabetes mellitus in Saudi Arabia. Saudi Med J 2004;25:1603-10.
6. Al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, Al-Harthi SS, Arafah MR, Khalil MZ, et al. The prevalence of obesity and Type 2 diabetes, it is safe to assume that the prevalence of NAFLD will continue to be high unless awareness is inculcated among the local population. Further studies should be conducted to study the change in prevalence of NAFLD within the population over time to closely monitor the epidemiology of this disease.