Significant Burden of Nonalcoholic Fatty Liver Disease With Advanced Fibrosis in Iranian Population: A Cross-Sectional Analysis

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Abstract- The main cause of chronic liver disease in Iran is Non-alcoholic fatty liver disease (NAFLD). A common pathological feature of chronic liver disease is fibrosis, so particular vigilance against patients with liver fibrosis is necessary to lead healthcare resource planning. The aims of the current study were to determine the prevalence and predictors of significant fibrosis and advanced ones among individuals with NAFLD. In the current cross-sectional study conducted during 2013-2016, the presence of fibrosis among NAFLD patients was assessed using the NAFLD fibrosis score (NFS) and AST to Platelet Ratio Index (APRI) systems. Multivariate logistic regression models were used to predict significant fibrosis or advanced fibrosis among NAFLD patients. Analysis of the results of over 999 patients (569 females and 430 males) with the mean age of 43.28±14.034 years in Iran during 2015-2016 showed that the overall prevalence of NAFLD among Iranian adults was 19.6%. NAFLD prevalence was not significantly higher in males compared to females (51.5% vs. 48.5%, *P*=0.66). On multivariate logistic regression analyses, females were less likely to have NAFLD compared to males (OR 0.32, 95% CI 0.24-0.42, *P*<0.001). The overall prevalence of liver fibrosis among NAFLD patients was 38.8%.20.4% and 6.12% of NAFLD patients had evidence of significant and advanced fibrosis, respectively. Our most recent dataset analysis emphasized the major burden of NAFLD among people of Iranian origin. A high prevalence of individuals with NAFLD and advanced fibrosis was observed.

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Keywords: Non-alcoholic fatty liver disease (NAFLD); Fatty liver; Fibrosis; Chronic liver disease

Introduction

Non-alcoholic fatty liver is a common chronic liver disease that develops in the absence of alcohol abuse and hepatitis B virus or hepatitis C virus infection and is recognized increasingly with excess fat accumulation in hepatocytes (1). Due to ongoing pandemics of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome, The prevalence of NAFLD, including the more aggressive non-alcoholic steatohepatitis (NASH), is increasing rapidly (2). Further, important complications such as liver fibrosis, cirrhosis, and rarely hepatocellular carcinoma (HCC) can appear in consequence of fatty liver disease (1). Fibrosis, a common pathological feature of chronic liver disease, describes the result of the unregulated wound-healing response of the liver to repeated injury and is characterized by the progressive replacement of functional hepatic tissue with highly cross-linked collagen I/III-rich extracellular matrix (2).

Diagnostic work-up should include diagnosing other causes of chronic liver disease and assessing the serum biomarkers to confirm the diagnose of NAFLD imaging-based techniques, such as ultrasonography, computed tomography, and MRI-based that are available, but none are in routine use outside clinical trials (3,4).

So current inadequacies in the field of NAFLD or anti-fibrosis therapeutics make future therapies towards specific subpopulations of patients with F2 and F3 or

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greater disease. Our study focused on the prevalence of both significant and advanced fibrosis predictors among individuals with NAFLD, which may help the development of risk stratification models to identify high-risk patients early. Furthermore, mitigating the long-term risk of disease progression will achieve by implementing preventive care (6).

The aims of the current study were to determine the prevalence and predictors of significant and advanced fibrosis among adults with NAFLD.

Materials and Methods

The current cross-sectional study aimed to provide an updated estimation of the national prevalence of non-alcoholic fatty liver disease (NAFLD) among adults (age ≥18) in the general Iranian population and also to determine the prevalence of significant and advanced fibrosis in NAFLD patients conducted after receiving the ethics approval and patient informed consent in the period of 2013-2016. This study was conducted by the health and nutrition center of the Taleghani Educational Hospital, Tehran, Iran.

A total of 245 patients were initially enrolled in the study. NAFLD was defined based on previous published studies definitions (5-7). They had a fatty liver disease which was diagnosed by the physician meets the following criteria:

1) Elevated Alanine aminotransferase(ALT) (ALT >20 U/L in women, ALT >30 U/L in men) and AST may rise
2) Increased echogenicity on UltraSonography

The subjects meet the following criteria were excluded from the study:

1) Alcohol consumption of more than 210 gr/week for men and more than 140 gr/week for women
2) Any liver disease with other etiology such as Viral Hepatitis, Autoimmune Hepatitis, Drug-Induced Hepatitis and Decompensate cirrhosis

A 10-year-experienced gastroenterologist examined the health status of nationally representative samples with data collected via both self-report questionnaires and physical examinations. Body Mass Index (BMI) with the following categories was calculated for each of participants (Using Formula: BMI=weight (Kg)/Height $(m)^2$): BMI 19-25.0 kg/m2 (normal BMI) and BMI≥ 25.0 kg/m2 (overweight and obesity class I, II and III). The estimated prevalence of significant or advanced fibrosis among NAFLD patients was reported as percentages (%) and frequencies (N).

Before answering the questionnaire, individuals were asked to sign an informed consent. All of the personal information remained anonymous.

NAFLD fibrosis score

The presence of fibrosis among NAFLD patients was assessed by NAFLD fibrosis score (NFS) and AST to Platelet Ratio Index (APRI) systems, which are recommended by the American Association for the Study of Liver Diseases (AASLD), American College of Gastroenterology (ACG), and the American Gastroenterological Association (AGA) (8). The NAFLD Fibrosis score is a non-invasive scoring system based on several laboratory tests, which helps to estimate the amount of scarring in the liver. This score only has been studied in NAFLD. The presence of the score above 0.676 in patients with a NAFLD fibrosis can demonstrate the high accuracy of advanced liver fibrosis diagnosis. In patients with a NAFLD fibrosis score below -1.455, advanced liver fibrosis can be excluded with high accuracy. An APRI score with> 0.7 cut-off point was used to define significant fibrosis (9).

Ethical consideration

This research study followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all patients. The study was approved by our Institutional Review Board.

Statistical analysis

Multivariate logistic regression models were used to predict significant or advanced fibrosis among NAFLD patients. According to our hypotheses, clinical variables expected to affect the prevalence of fibrosis among NAFLD patients were included in the model, and we focused on the variables which were interested in evaluating. The final multivariate model included adjustments for age, gender, Body Mass Index (BMI), and presence of diabetes mellitus. Results are given as odds ratios (OR) and 95% confidence intervals (CI). A *P* of less than 0.05 considered statistically significant.

Results

Results of analyzing over 999 patients (569 females and 430 males) with the mean age of 43.28±14.034 years showed an overall prevalence of 19.6% for NAFLD among Iranian adults.

NAFLD prevalence was none-significantly higher in males compared to females (51.5% vs. 48.5%, *P*=0.66).

On multivariate logistic regression analyses, females were less likely to have NAFLD compared to males (OR 0.32, 95% CI 0.24-0.42, *P*<0.001)

Increasing age was inversely associated with increasing NAFLD prevalence age <40: 47.7% vs. age 40-59: 44.1% vs. age 60 and over: 8.2%, *P*<0.001)

The grade of fatty liver Distribution revealed 59 (30.1%), 75 (38.2%), and 35(17.8%) of patients had the grade I, II, and III respectively (*P*=0.001).

One hundred and one (82.1%) of the NAFLD patients were reported positive for diabetes mellitus. Presence of diabetes (82.1% vs. 16.35%, *P*<0.001) was significantly associated with a higher prevalence of NAFLD.

The majority of NAFLD patients were determined to have a normal BMI (83.1% vs. 15.3%, *P*<0.001). Compared to patients with normal BMI (BMI <25 kg/m^2), those with BMI ≥25 kg/m^2, overweight patients and obesity class I, II and III, had a significantly higher prevalence of NAFLD. The presence of BMI≥ 25 kg/m2 and diabetes were all independently associated with higher odds of having NAFLD.

The mean current body size of participants was 6.93±2.038.

Prevalence of significant and advanced fibrosis in NAFLD patients

The overall prevalence of liver fibrosis among NAFLD patients was 38.8%. The presence of fibrosis among NAFLD patients was determined by NAFLD fibrosis score (NFS) and APRI scoring systems. While assessing for significant (F2 or greater) or advanced fibrosis (F3 or greater) by NFS score and APRI score, 20.4% and 6.12% of NAFLD patients showed evidence of significant and advanced fibrosis, respectively. Males with NAFLD were more likely to have significant and advanced fibrosis compared to females (62.5%% vs. 37.5%%, *P*=0.15).

In patients with significant and advanced fibrosis altogether, 92.5% were with BMI≥ 25 kg/m2 (27.5%, 12.5%, 7.5%, and 45% were overweight, obesity class I, II, and III, respectively). Twenty-seven of total patients with significant and advanced fibrosis were reported. Significant associations with odds of NAFLD-SF were observed based on BMI and presence of diabetes (*P*<0.001 and *P*=0.001 respectively)

Discussion

According to the most recent data, the supposed NAFLD prevalence among Iranian adults is 19.6% which represents about 15.6 million individuals (the recent report of Statistical Center of Iran, presented on Wednesday government meeting, showed that the country's population is 79, 926, 270, with 51 percent men and 49 percent women). Among individuals with NAFLD, we observed an overall prevalence of liver fibrosis 38.8%, representing 6.05 million individuals. 20.4% prevalence of F2 or greater fibrosis (significant fibrosis), representing 3.9 million individuals and 6.12% prevalence of F3 or greater fibrosis (advanced fibrosis), representing 1.1 million individuals were observed.

Our current estimation of NAFLD prevalence in comparison with some systematic reviews and other types of studies -estimating NAFLD prevalence nearly 100 million adults in the US-showed a lower rate of prevalence (10-14). Comparing with national studies also confirmed the lower prevalence of NAFLD in our current study (15-18).

The lower prevalence of NAFLD in our study may partly be due to our intransigent definition of NAFLD. Comparing our methodology definition of NAFLD (the presence of abnormal ALT) to US definition (confirmation after excluding other etiologies of chronic liver disease including viral and autoimmune hepatitis, drug-induced hepatitis, and decompensated cirrhosis) can clarify the prevalence differences. Nevertheless, even without the conservative definition of NAFLD, our recent study demonstrates and presents the considerable burden of NAFLD on the healthcare system.

Nowadays, NAFLD is known as a cause of chronic liver disease. Furthermore, based on recent studies, NAFLD should be considered as a leading cause of hepatocellular carcinoma and end-stage liver disease, which need liver transplantation (6,19-21).

This burden of NAFLD as a public health concern has a remarkable effect on patient quality of life as well as the economic status of the health care system (22,23). According to the results of a recent study in Iran, the total costs for non-alcoholic fatty liver alone exceeded 1 billion PPP$ per year among the Iranian adult urban population (24).

In our recent study, we evaluated fibrosis stages by two commonly employed serology-based scoring systems, including APRI and NFS, which are commonly employed evaluation tools that can be easily applied. All these scoring systems have various performance characteristics. While the mentioned scoring systems were used for fibrosis assessment, APRI predicts the prevalence of significant fibrosis (F2 or greater), whereas NFS predicts the prevalence of advanced fibrosis (F3 or greater). Furthermore, both significant and advanced fibrosis was assessed in the current study to provide a

more accurate evaluation of disease burden.

Individuals with NAFLD-Advanced fibrosis represent a much smaller, howbeit higher risk group that would be prioritized for any therapeutics which becomes available targeting NAFLD or fibrosis pathways and NAFLD-significant fibrosis patients would show a larger group that should be treated to prevent disease progression to advanced fibrosis or cirrhosis.

Liver transplantation is known as the primary curative option for cirrhosis and hepatocellular Carcinoma. Based on observed epidemiological trends, because of death or becoming too ill as a result of the imbalance between the number of liver receivers and the number of donor organs, NAFLD individuals concern about liver transplantation. Therefore, many patients removed from the liver transplant waitlist (25).

Regardless of lacking methods for assessing fibrosis, it's important to highlight the increased risk of NAFLD, significant, and advanced fibrosis with increasing BMI of ≥30 kg/m2 and diabetes. According to these observations, the integrity of the metabolic syndrome and NAFLD associated evidence was confirmed and remarked the importance of optimizing the management of these risk factors in order to reduce the risk of progressing disease among NAFLD patients (11,26-28).

Considering the cross-sectional nature of the recent study design, our current study only provides evidence of NAFLD and NAFLD with advanced fibrosis prevalence and can only establish associations with respect to risk predictions.

Despite the limitations, with the help of the most recently updated dataset, which provides vital epidemiological observations regarding NAFLD in Iran, we deduced the outlook that NAFLD will become the leading etiology of chronic liver disease in the near future in our country.

In conclusion, our most recent dataset analyzing emphasized the major burden of NAFLD among people of Iranian origin. So high prevalence of individuals with NAFLD and also advanced fibrosis is estimating. Lack of facilities to administrate various methods for assessing fibrosis made us represent some risk factors of NAFLD, such as obesity and diabetes, which seemed to increase the risk of NAFLD and fibrosis among patients with NAFLD.

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