Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 246–250

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Prevalence and associations of non-alcoholic fatty liver disease (NAFLD) in Sri Lankan patients with type 2 diabetes: A single center study

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ARTICLE INFO

Article history:
Received 16 August 2018
Accepted 7 September 2018

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes for chronic liver disease in Asians. It occurs more commonly in patients with type 2 diabetes mellitus (T2DM). However, data on prevalence and associations of NAFLD among Sri Lankans with diabetes are lacking. The main aim of this study is to investigate the prevalence and factors associated with NAFLD in a cohort of diabetic patients.

Methods: Total of 233 patients with type 2 diabetes mellitus, followed up at a diabetes center in Southern Sri Lanka, were recruited by convenience sampling method. Each of them underwent a detailed medical history, physical examination, laboratory investigations and abdominal ultrasonography(USS). The diagnosis of NAFLD was made according to the established criteria using USS.

Results: The overall prevalence of NAFLD based on USS was 62.6% with no significant gender difference. Compared to USS, elevation in AST and ALT levels, based on NHANES III criteria, occurred only in 42% (98/234). The patients with NAFLD (56.7 ± 8.9) were significantly younger and had higher BMI and waist circumference, and raised AST and ALT than those without NAFLD. Binary logistic regression showed that the use of pioglitazone, higher BMI, and waist circumference were independently and significantly associated with NAFLD.

Conclusions: NAFLD is common in Sri Lankan patients with T2DM and central and global obesity are significant associations. Use of pioglitazone seemed to be protective against the development of NAFLD. These findings underscore the need for weight management as a preventive measure of NAFLD in T2DM patients.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common cause for altered liver function test in western population, and is predicted to be the most common cause of liver transplantation for chronic liver disease in future [1–3]. It's prevalence has risen with the epidemic of obesity and metabolic syndrome [1,2,4,5]. Global prevalence of NAFLD in general population is approximately 15–30%, and higher prevalence of 70–80% has been observed among patients with obesity or type 2 diabetes [1–3,6]. Though there are no national studies, some studies have shown that NAFLD is an important cause for deranged liver enzymes in an urban as well as rural populations in Sri Lanka [7,8].

Majority of patients with NAFLD has simple steatosis with a relatively benign outcome, while 30–40% with NAFLD progress to non alcoholic steatohepatitis (NASH) [1]. Around 25–40% of NASH patients can end up with fibrosis and subsequent liver cirrhosis [9]. NASH related liver cirrhosis has a higher risk of hepatocelluar carcinoma (HCC) compared to its counterparts [2,5,9]. In addition to the progressive liver injury, NAFLD increases overall mortality of

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https://doi.org/10.1016/j.dsx.2018.09.002
1871-4021/

affected individuals by 57% [5]. Not only the severe forms, but merely the presence of NAFLD increases the incidence of cardiovascular and chronic kidney (CKD) disease risk, independently from other cardio-renal risk factors in general population [1,5,10]. Even though, evidence are limited, NAFLD is also recognized as an independent risk factor for diabetic retinopathy and nephropathy [11,12].

Effective treatment to reverse liver fibrosis is yet to be discovered, leaving early diagnosis and prevention of progression as the cornerstones in management of NAFLD [4]. Liver enzymes in particularly aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) have been shown to have a positive correlation with NAFLD [13]. However, they can be typically low in late stages of fibrosis, further complicating the diagnosis and staging of the disease severity. Though the histological assessments is the gold standard in diagnosis of NAFLD, NASH, fibrosis and cirrhosis, It's invasive nature and complications limit its utility as a screening tool [4]. Transabdominal ultrasound scan (USS) is widely used to diagnose hepatic steatosis due its non-invasive nature and free availability. Severe fatty infiltration; more than 30% fat by weight, is detected with sensitivity and specificity of 67–84% and 77–100% respectively [1,4,14]. Sonography is less sensitive for low degrees of fatty infiltrations. Computer tomography (CT) is less sensitive than USS in diagnosis of NAFLD [15]. Magnetic resonance imaging (MRI) has the potential of qualitative and quantitative diagnosing fatty infiltration [15]. However, all three modalities; USS, CT and MRI, are insensitive in detecting liver fibrosis and NASH. MR spectroscopy and US fibro scans are providing some promising results, but their practical values are yet to be evaluated further in future studies [10,15].

Even though, type 2 DM is associated with increased prevalence of NAFLD, the causative factors for increased NAFLD in diabetic patients has not been sufficiently studied. Furthermore, the prevalence of NAFLD and its risk factors could vary depending on factors such as geographical area and ethnicity [1,4,5]. The prevalence of NAFLD in Sri Lankan diabetic population has not been previously evaluated. Therefore, the main objectives of the present study is to investigate the prevalence of NAFLD in a cohort of diabetic population in Sri Lanka and to analyze the associations to ascertain the potential risk factors/predictors with of NAFLD in Sri Lankan setting. Specifically, we aim at studying the risk factors such as age, sex, duration of diabetes, glycemic control, central obesity, global obesity (BMI), blood pressure, medications use such statin and pioglitazone, physical activity, serum creatinine, carotid plaque (as a marker of atherosclerosis) and possible predictors such as liver enzymes.

2. Materials and methods

Total of 233 patients with type 2 diabetes mellitus, who were followed up at a regional diabetes center in Southern Sri Lanka, were recruited by convenience sampling method between October 2017–February 2018.

3. Inclusion criteria

Individuals with aged ≥20 years and clinically determined type 2 DM were qualified to participate in the study.

4. Exclusion criteria

Participants aged <20 years, pregnant women, individuals with past history of acute or chronic liver disease (including acute hepatitis of any cause, viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson disease, alpha 1 antitrypsin deficiency or any illness with jaundice in past), subjects with daily alcohol consumption of more than 20 gm/day (two 30 ml drinks) were excluded from the study. Also patients with other chronic illness including rheumatoid arthritis, severe osteoarthritis, symptomatic heart failure, type 1 DM, myocardial infarction within last 6 months, acromegaly, clinically apparent hypothyroidism, hypogonadism, chronic obstructive airway disease, nephrotic syndrome and chronic kidney disease (stage 3 or more), were also excluded. In addition, patients with malignancies, and extreme body habitus (BMI >40), those on prolong steroid use, and those who were on active drug treatment for obesity were excluded from the study.

5. Data collection, anthropometric measurements, clinical examination and laboratory tests

A pretested interviewer-administered questionnaire was used to obtain demographic and medical information such as age, sex, ethnicity, social background, duration of diabetes, and family history of dyslipidaemia, and diabetes among first degree relatives. Anthropometric measurements including waist circumference (cm), weight (Kg) and height (m) were then measured. Waist circumference (WC) was measured by placing a non-stretchable fibre-glass measuring tape around the waist midway between the last rib and iliac crest with the subject in the standing position. All anthropometric measurements were performed by trained nurses adhering to the WHO guidelines, using calibrated equipment. Blood pressure was recorded using an electronic instrument (Omron Corporation, Tokyo, Japan), as the mean of two readings taken 5 min apart. BMI was calculated as weight (kg)/height [2] (m^2).

All chemical analyses were performed in the laboratory attached to the Regional Diabetic Center mentioned above. Venous blood, drawn in the morning after 8–10 h of fast was used to determine fasting plasma glucose, HbA1c, serum creatinine and aspartate aminotransferase (AST) and alanine aminotransferase (ALT). NHANES III criteria were used to define raised aminotransferase levels (AST >37 IU/L or ALT >40IU/L for men and AST or ALT >31IU/L in women) [16].

Abdominal ultrasonography (USS) was used as the primary method to diagnose NAFLD. An experienced radiologist performed USS with a 3.5 MHz transducer (GE Volusion ultrasound system) in all recruited patients after 8–10 h of fast. Degree of hepatic steatosis (HS) was defined as follows [15,17,18].

6. Definition of fatty liver

Normal liver echogenicity is equals or slightly higher than that of the renal cortical or splenic echogenicities, intra hapatic vasculature is sharply demarcated and the posterior aspect of the liver is well depicted.

Fatty liver was diagnosed when the liver echogenicity was increased compared to renal cortex and the spleen, with evidence of attenuation of the wave, loss of definition of the diaphgram, and poor delineation of the intra hepatic architecture. To avoid false-positive interpretations, one or two of above criteria were fulfilled. Presence or absence and grading of fatty infiltration were recorded.

7. Ultrasound criteria for grading of fatty liver

Normal liver echogenicity – Grade 0.

Slightly increased liver echogenicity with normal visualization of the diaphragm and the intra hepatic.

vascular borders - Grade 01.

Echogenicity was moderately impaired with slight impaired

visualization of the diaphragmatic border and the intra hepatic vasculature – grade 02.

Markedly increased echogenicity with poor visualization of the diaphgram and intrahepatic vasculature and posterior portion of the right lobe – Grade 03.

8. Definition of hepatomegaly

Midclavicular line liver measurement, dome to pole length, more than 15 cm was considered as hepatomegaly [4,15,17].

9. Ethical approval

Ethical clearance for the present study was obtained under the study on "cardiovascular risk assessment in patients with type 2 diabetes in Sri Lanka", from the Institutional Ethics Committee of the Faculty of Medicine, University of Ruhuna. Written informed consent was obtained from all study subjects in the local language.

10. Statistical analysis

All numerical data were expressed as means and standard deviations and categorical data were expressed as frequencies and proportions. Statistical significance was assumed at a p-value of <0.05. The significance of the differences between means and proportions (%) were tested using Student's *t*-test, and the chi square test. To identify independent variables associated with NAFLD, we used multiple linear regression analysis. Then, optimal predictors of NAFLD were identified by performing multiple logistic regression analyses using iterative selection of variables. All analyses were performed using SPSS 17.0.

11. Results

11.1. Study population characteristics

Overall, 233 patents with T2DM enrolled in the study, 110 were males, while 123 were females. The mean (SD) age of the study participants was 58 (9.7) years with mean duration of diabetes of 12.1(6.1). Mean BMI and waist circumference of the study participants were 25 (4.1) and 95(11) respectively. Approximately 67% were overweight or obese (BMI $\geq$ 23 kg/m2), and 87% were centrally obese according to the waist circumference measurements for South Asians (Table 1).

Table 1
Baseline characteristics of the study sample.

Parameters	Mean	SD
Age	58.3	9.7
Height	159.5	9.1
Weight	64.4	10.8
BMI	25.0	4.1
WC	95.5	11.2
Duration of DM	12.1	6.1
ALT	34.1	19.1
AST	33.0	13.3
Serum creatinine	1.3	3.2
Hba1c	8.1	1.6
Parameters	**n**	**%**
Male gender	110	47.0
Overweight of obese	156	66.9
Smoking	37.0	15.7
Use of pioglitazone	72.0	30.6
Use of statin	206.0	87.7
Presence of carotid plague	25.0	10.6

11.2. Prevalence of NAFLD

The overall prevalence of non-alcoholic fatty liver disease (NAFLD) based on USS was 62.6% and almost equal proportions had grade 1 (32%) and grade 2 (30%) fatty liver. In compared to USS, elevation in AST and ALT levels, based on NHANES III criteria, occurred only in 42% (98/234) of the of the study sample (Table 2).

11.3. 93.03

11.3.1. Differences between patients with NAFLD and without NAFLD

The patients with NAFLD were significantly younger than patients without NAFLD (56.7 ± 8.9 vs 60.9 ± 10.4, p 0.002). There were statistical differences in mean BMI, WC, AST and ALT levels, duration of diabetes, weight at the time of the diagnosis of diabetes between the patients with NAFLD and without NAFLD (Table 3). Furthermore, higher proportion of patients with NAFLD were significantly overweight or obese, and had central obesity, and raised AST and ALT. Interesting, significantly lower proportion of patients with NAFLD were on pioglitazone than patients without NAFLD. There was no difference in creatinine, HbA1c, presence of carotid plaque, or use of statin.

Possible risk predictors for NAFLD in patients with T2DM were assessed with binary logistic regression; which revealed that use of pioglitazone, BMI, and waist circumference were independently associated with the occurrence of NAFLD (Table 4). Factors such as age, gender, duration of diabetes, use of statin, smoking history and ALT and AST levels were not shown to be significantly associated with NAFLD.

12. Discussion

Considering the rising incidence of T2DM in Sri Lanka and its close association with NAFLD, studying the prevalence of NAFLD and its associated risk factors among diabetic individuals in Sri Lanka is a timely need. This is further important as NAFLD is now considered as the most common cause for chronic liver disease in diabetic population. However, to best of our knowledge, NAFLD among diabetic population has not been widely studied in Sri Lanka. The main findings of the current study are (1) there is high prevalence (62%) of NAFLD in Sri Lankan patients with type 2 diabetes, (2) raised AST and ALT levels, based on NHANES III criteria is less sensitive than USS in detecting possible NAFLD in diabetic patients in Sri Lanka, (3) higher BMI, and waist circumference were independently associated with the occurrence of NAFLD (4) use of pioglitazone was associated with lower prevalence of NAFLD and (5) factors such as gender, duration of diabetes, and overall glycemic control has no effect on the overall prevalence of NAFLD.

Even though, liver biopsy remains the gold standard test to diagnose NAFLD, it can't be used in day today clinical practice, due to its invasive nature. Considering the high sensitivity, non-invasive nature and low cost, USS is an acceptable alternative to diagnose

Table 2
Prevalence of NAFLD and raised liver enzymes.

Test used			N	%
USS	NAFLD present	Overall	147	62%
		Grade 1	73	31%
		Grade 2	69	29%
		Grade 3	05	2%
	NAFLD absent		86	37%
AST/ALT	NAFLD present (Raised AST/ALT)		97	42%
	NAFLD absent (normal AST/ALT)		136	58%

Table 3
Differences between patients with NAFLD and without NAFLD.

Variables		NAFLD		
		Present 147	Absent 87	p
Age	mean (sd)	56.7 (8.9)	60.9(10.4)	0.002**
BMI	mean (sd)	25.5(3.4)	24.6(3.3)	0.05**
Waist circumference	mean (sd)	96.1(12.7)	94.5(8.1)	0.02**
Gender (male)	No (%)	67(45)	43(50)	.58*
Overweight or obese	No (%)	96(65)	51(59)	0.29*
Central obesity	No (%)	134(91)	69(80)	0.02*
AST	mean (sd)	34.6(13.3)	30.1(12.9)	0.01**
ALT	mean (sd)	37.0(18.6)	29.0(18.8)	0.002**
Raised AST/ALT	No (%)	74 (76)	23 (24)	0.001*
HbA1c	mean (sd)	7.7 (1.1)	7.8 (1.0)	0.75**
Creatinine	mean (sd)	1.3 (1.8)	1.2 (1.6)	0.77**
Duration of diabetes	mean (sd)	11.5(5.8)	13.0(6.2)	0.06**
Weight at present	mean (sd)	65.3(11)	62.7(10.1)	0.06**
Weight at diagnosis	mean (sd)	61.9 (12.9)	60.2(15.2)	0.4**
Use of statin	No (%)	128(87)	77 (89)	0.43*
Use of pioglitazone	No (%)	35 (23)	37 (42.5)	0.003*
Presence of carotid plaque	No (%)	13 (8)	12(13.7)	0.34*

* Chi-Square test **t-test.

Table 4
Possible risk predictors for NAFLD in patients with T2DM.

	B	S.E.	Wald	df	Sig.	Exp(B)
Age	-.044	.023	3.838	1	.084	.957
Gender(1)	.628	.462	1.847	1	.174	1.874
BMI	.082	.071	1.359	1	.044	1.086
WC	.021	.018	.011	1	.047	1.089
Duration of DM	.015	.034	.192	1	.662	1.015
Use of pioglitazone(1)	1.377	.488	7.977	1	.005	3.965
Treated with statin (1)	.278	.761	.133	1	.715	1.320
Smoking	-.436	.565	.597	1	.440	.646
Weight at diagnosis of diabetes	-.006	.016	.160	1	.689	.994
ALT	.017	.018	.938	1	.333	1.017
AST	-.006	.025	.056	1	.812	.994
Mean Hba1C	-.066	.222	.089	1	.765	.936
Serum creatinine (1)	1.721	1.279	1.810	1	.178	5.588
EGFR	-.007	.005	2.065	1	.151	.993
Constant	−1.031	3.359	.094	1	.759	.357

NAFLD. The USS criteria used in this study to diagnose NAFLD have an adequate sensitivity to detect steatosis when more than 33% of hepatocytes contain fat on liver histology [17]. Therefore, we believe that the reported prevalence of NAFLD (61.9%) in our study is accurate.

The reported prevalence of NAFLD in diabetic population varied between 29.6% [19] to 87.1% [20,21], and our study indicated that prevalence of NAFLD in Sri Lankan patients with T2DM was 61.9% (95% CI: 56.1–65.2%). Even though, our study revealed no significant gender difference, contrasting finding of higher prevalence of NAFLD in males were reported in many studies [22,23], while few other studies reported higher prevalence in females as well [23]. There is an assumption that female gender could be an independent protective factor for NAFLD due to the gender differences in hormone levels and lipid levels. However, the protective effect of female hormones is less likely to cause any impact on the prevalence of NAFLD in our study as the cohort of patient that we study are relatively older with a mean age of 58 years. However, due to these contrasting findings, it is unclear whether gender play a significant role in NAFLD, particularly among older individuals with T2DM.

Our study also revealed that raised AST and ALT levels, based on NHANES III criteria is less sensitive than USS in detecting possible NAFLD in diabetic patients in Sri Lanka. Many previous studies have shown that both AST and ALT are associated with NAFLD [1,9,24,25] and therefore, they are sometimes used as a surrogate marker of NAFLD. However, more recent studies have shown that the AST and ALT values do not correlate well with the severity of liver disease and they can be normal in some patients with advanced steatosis [14,25,26]. As previously stated USS is not the gold standard test to diagnose NAFLD; however, considering its higher sensitivity and specificity compared to liver biopsy it can be used reliably in day-today clinical practice. According to our study as well as the previous studies [4,6,10,15], we can confirm that it is not prudent to use AST and ALT as the sole markers of NAFLD in patients with T2DM. Unlike some previous studies involving diabetic patients, our study did not find a significant association of factors such as age, duration of diabetes, and overall glycemic control on the overall prevalence of NAFLD [27].

Many previous studies suggested that central and visceral obesity, and metabolic syndrome in non-diabetic individuals are associated with NAFLD [24,28]. Considering the effect of diabetes on body habitus, we were interested to know whether the same association can be observed in diabetic individuals in Sri Lanka as well. Our finding reliably suggests BMI, and waist circumference were independently associated with the occurrence of NAFLD. Similar association of NAFLD with central and visceral obesity has been reported in previous studies as well [21,29]. Whether this just an association or they have any causative effect on NAFLD is not yet known. However, considering higher prevalence of NAFLD in obese individuals [14], with beneficial effect of weight loss [25], it is sensible to advise obese diabetic individuals to lose weight in order to reduce the future risk of NAFLD.

Our study also revealed that the use of pioglitazone was associated with lower prevalence of NAFLD. In the recent past, few clinical trials have shown the beneficial effect of pioglitazone on NAFLD [4,30]. Cusi et al. showed that treatment with pioglitazone was associated with marked improvements in steatosis, inflammation, and ballooning, with around 60% of patients with NAFLD showing histological improvement after 18 months of treatment [31]. Bril F et al. showed that use pioglitazone is associated with reduction of liver fibrosis and increased adipose tissue insulin sensitivity in patients with T2DM[30]. In our study, unlike two previously mentioned clinical trials, pioglitazone had been used mostly as third line agent after metformin and sulphonylurea. However, use of pioglitazone along with other oral hypoglycemic agents (OHAs) was independently associated with lower prevalence of NAFLD. Therefore, our study may suggest that use of pioglitazone as a useful option in diabetic patients with NAFLD on other OHAs.

While being the first study to report on the prevalence of NAFLD exclusively in a cohort of patients with type 2 diabetes in Sri Lanka, our study has few limitations. Due to non availability of sophisticated diagnostic tools such as the fibro scan, we used conventional USS to diagnose NAFLD. Histological confirmation was not carried out as liver biopsies were not feasible in these asymptomatic, ambulant participants. Moreover, our findings were based on data collected from patients followed up at a single diabetes center and generalization of these findings should be done with caution. Nevertheless we report that nearly two out of three patients with type 2 diabetes in our study has NAFLD based on USS, a figure similar to reported prevalence in most other parts of the world. We also report that obesity, both global and central, are significant associations of NAFLD in these patients with T2DM. In the therapeutic point of view, we conclude that pioglitazone therapy as an oral hypoglycemic agent seems to have a protective effect against NAFLD. Our findings further support the prescription of pioglitazone as an oral hypoglycemic agent for suitable patients with T2DM ensuring the beneficial effects of this drug for NAFLD as recommended by the previous case-control studies. We hope findings

from this single center study would be a timely stimulus for further large scale studies on NAFLD among patients with T2DM in Sri Lankan setting.

Conflicts of interest

Authors declare that there are no conflicts of interest regarding the publication of this paper.

Patient consent

Informed written consent was obtained from all patients.

Ethical approval

Ethical approval for this study was obtained from the institutional research committee, Faculty of Medicine, University of Ruhuna. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee of Faculty of Medicine, University of Ruhuna and with the 1964 Helsinki declaration.

Author's contributions

HMMH designed and wrote the study plan and involved in analysis and writing the manuscript. TPW involved in data collection, and writing the manuscript. IK and GL contributed by writing the manuscript.

Acknowledgements

The authors would like to sincerely thank all the individuals participated in this study. Authors would also like to thank the Regional Diabetes Center, Galle for the assistance given to conduct this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.09.002.

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