Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2957–2960

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

Original Article

Prevalence and predictors of non-alcoholic fatty liver disease in prediabetes

Rajesh Rajput*, Parul Ahlawat

Department of Endocrinology & Medicine Unit IV, Pt. B D Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India

ARTICLE INFO

Article history:
Received 16 July 2019
Accepted 29 July 2019

Keywords:
Pre-diabetes
NAFLD

ABSTRACT

Backgroud and aims: Various studies have evaluated the prevalence of non-alcoholic fatty liver disease (NAFLD) in patients with diabetes but few studies on prevalence of NAFLD in prediabetes have been performed so far. The present study aimed to evaluate the prevalence and predictors of NAFLD in prediabetics.

Material and methods: In this cross-sectional study, 100 diagnosed cases of Prediabetes were compared with 100 normoglycemic people after random selection from OPD for NAFLD by using various biochemical parameters and ultrasonography.

Results: Among 100 prediabetic cases, IFG was present in 28%, IGT in 26% and both were impaired in 46%. FPG, 2 Hour glucose post OGTT, diastolic blood pressure, weight, BMI, waist circumference, waist hip ratio, waist height ratio was significantly more in prediabetics as compared to controls. On USG, prevalence of NAFLD was more in prediabetics (59%) as compared to controls (26%) with p value =<0.001. Grade 1 fatty liver was present in 37% (n = 37) prediabetics as compare to 22% (n = 22) controls and Grade 2 fatty liver was present in 22% (n = 22) cases as compare to 4% (n = 4) controls with p value < 0.001. SGOT, SGPT, GGT, ALP, UA, TG were significantly higher in prediabetics as compared to controls. GGT and WC are best predictor of NAFLD in pre-diabetes with adjusted odd's ratio of 6.604 and 6.589 respectively.

Conclusion: To conclude with, prevalence of NAFLD is substantially more in prediabetic patients as compared to normoglycemic individuals and elevated WC and GGT were the best predictor of underlying NAFLD among prediabetic individuals.

1. Introduction

Type 2 DM is preceded by a period of abnormal glucose homeostasis called Prediabetes. Glucose intolerance or prediabetes has further two subcategories: impaired fasting glucose (IGF) and impaired glucose tolerance (IGT). Recent studies have shown that, although both IFG and IGT are characterized by β-cell dysfunction, subjects with IGT have impaired late-phase insulin secretion and increased insulin resistance (IR) in skeletal muscle. In contrast, subjects with IFG have impaired early phase insulin secretion and increased IR in liver [1]. Both are also associated with dyslipidaemia, hypertension, abdominal obesity, microalbuminuria, endothelial dysfunction, increased markers of inflammation and hypercoagulability [2].

Hepatic steatosis in the absence of secondary cause of fat accumulation in liver is called non-alcoholic fatty liver disease (NAFLD). It has been shown that insulin resistance can increase the peripheral lipolysis, triglyceride synthesis and hepatic uptake of free fatty acid which ultimately leads to NAFLD. The various risk factors for NAFLD are increased body weight especially abdominal obesity, insulin resistance and metabolic syndrome [3]. Various studies have evaluated the prevalence of NAFLD in patients with diabetes to be 12.5–87.5% [4–6]. NAFLD prevalence is increased in people with type 2 diabetes and has been estimated at around 70% using ultrasound techniques [7]. So far majority of studies have studied the prevalence of diabetes and pre-diabetes among NAFLD patients, but few studies on prevalence of NAFLD in prediabetes have been performed so far [8]. Therefore, the present study was planned to find out the prevalence of NAFLD by ultrasonography and to find out the predictors of development of NAFLD in prediabetic patients.

* Corresponding author. Department of Endocrinology & Medicine Unit IV, PGIMS, Rohtak, 124001, Haryana, India.
E-mail address: drrajeshrajput@outlook.com (R. Rajput).

https://doi.org/10.1016/j.dsx.2019.07.060
1871-4021/

2. Material And Methods

This cross-sectional study was conducted at the Department of Endocrinology and Medicine Unit IV of Pt. B. D. Sharma PGIMS, Rohtak. 100 diagnosed cases of Prediabetes were recruited in the study as cases and 100 normoglycemic people were recruited in the study as control. The study was approved by the institutional ethical committee. Informed consent was obtained after explaining the details of procedure to all subjects. Patients suffering from diabetes mellitus, chronic liver disease, HIV, chronic renal failure, pancreatitis, hemochromatosis, autoimmune hepatitis or other severe illness and patients on steroids/nicotinic acid or other medication likely to cause dysglycemia, consuming alcohol or having history of alcohol consumption with a threshold >20g/day in women, >30 g/day in men were excluded.

Prediabetes was defined as IFG if fasting plasma glucose (FPG) was ≥100 mg/dl and <126 mg/dl and IGT if 2 h post oral glucose tolerance test (OGTT) plasma glucose was ≥140 mg/dl and <200 mg/dl [9]. Abdominal ultrasound examination (USG) was performed in all study participants by a trained radiologist with 3.5 MHz linear transducer in supine and left lateral position during quite inspiration. NAFLD was defined by presence of at least 2 out of 3 of the following findings on USG examination: diffusely increased echogenicity of liver relative to right kidney; attenuation of ultrasound beam; poor visualisation of intrahepatic architectural details [10]. Grading of NAFLD on ultrasound has been used to detect the extent of fatty changes in the liver and defined as Grade 1 if there is increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity, Grade 2 if there is increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm and Grade 3 if there is increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of diaphragm [11]. For diagnosis of metabolic syndrome, IDF criteria are used [12]. This include central obesity defined as waist circumference ≥ 90 cm for males and ≥80 cm for females plus any two of the following criteria i.e. increased triglycerides (≥150 mg/dL), low HDL (<40 mg/dL for males and <50 mg/dL for females), hypertension defined as ≥ 130/85 and fasting plasma glucose ≥100 mg/dL.

Detail demographic profile of the both cases and controls were recorded on a predesigned performa. Anthropometric indices including height (without shoes and socks), weight, waist circumference, and hip circumference were recorded for the subjects. Blood pressure was recorded thrice at 5-minute intervals in a sitting position in the non-dominant arm using a standard adult mercury sphygmomanometer. Serum glutamic oxaloacetic transaminase (SGOT), serum glutathione pyruvic transaminase (SGPT), Alkaline phosphatise (ALP), Gamma glutamyl transpeptidase (GGT), uric acid (UA), triglycerides levels (TG) were assessed for all subjects.

The data collected was analysed using SPSS version of 21.0. For qualitative categorical variables, chi-square test was used and for quantitative normally distributed data, independent sample *t*-test was employed. Logistic regression analysis was to know the predictors of NAFLD in prediabetic patients.

3. Results

100 diagnosed cases of Prediabetics were recruited for the study as cases and compared with 100 matched controls. Baseline demographic and anthropometric profile of study population are summarised in Table 1. There were (37%) males and (63%) females in prediabetics group. Similarly, there were in (34%) males and (66%) females in control group. Among prediabetics, IFG was present in 28%, IGT in 26%, IFG + IGT in 46%. FPG, 2 Hour glucose post OGTT, diastolic blood pressure, weight, BMI, waist circumference, waist hip ratio, waist height ratio was significantly more in prediabetics as compared to controls.

On USG, prevalence of NAFLD was more in prediabetics (59%) as compared to controls (26%) with p value =<0.001. Grade 1 fatty liver was present in 37% (n = 37) prediabetics as compare to 22% (n = 22) controls and Grade 2 fatty liver was present in 22% (n = 22) cases as compare to 4% (n = 4) controls with p value < 0.001 (Table 2). NAFLD was more in prediabetic males (60%) as compared to prediabetic females (40%).

Metabolic syndrome was seen in 31.6% (n = 18/57) of prediabetics with fatty liver as compared to 25.0% (n = 7/28) in control group with significant p value (<0.001) and odd's ratio of 9.46. Among the various parameters of metabolic syndrome, increased WC and triglyceride (TG) levels were significantly associated with prediabetes and NAFLD. Levels of SGOT, SGPT, GGT, ALP, UA, TG were significantly higher in prediabetics as compared to controls (Table 3).

Comparison of various anthropometric and biochemical parameters in prediabetes with NAFLD and without NAFLD is shown in Table 4. Increasing age, Weight, BMI, WC, WHR, waist height ratio, SGOT, GGT, TG, UA, were significantly more in prediabetics with NAFLD as compared to prediabetics without NAFLD. Both univariate and multivariate regression analysis was done to find the association of fatty liver with Prediabetes while adjusting for age,

Table 2
Prevalence of NAFLD in cases and control with Ultrasonography.

Grading on USG	Prediabetics	Controls	P value
1	37 (37%)	22 (22%)	
2	22 (22%)	4 (4%)	
3	0	0	
TOTAL	59%	26%	<0.001

Table 1
Baseline demographic and anthropometric profile of study population.

Variables	Prediabetic (n = 100)	Controls (n = 100)	p-value
Age (yrs)	43.42 ± 11.09	42.06 ± 11.22	0.390
FPG (mg/dl)	108.66 ± 6.96	85.71 ± 6.40	<0.001
2hr Post OGTT Plasma glucose (mg/dl)	156.92 ± 11.51	106.90 ± 12.27	<0.001
Systolic blood pressure (mmHg)	122.51 ± 9.47	122.86 ± 10.51	0.646
Diastolic Blood Pressure (mmHg)	80.36 ± 6.12	77.48 ± 8.40	0.006
Height (cm)	160.83 ± 6.88	166.88 ± 9.09	0.358
Weight (kg)	67.95 ± 9.70	64.37 ± 9.97	0.011
BMI (kg/m^2)	26.21 ± 2.57	24.09 ± 2.82	<0.001
WC (Males) in cm	93.03 ± 7.21	88.20 ± 7.19	0.006
WC (Females) in cm	82.53 ± 6.35	78.83 ± 6.35	0.01
Waist Hip Ratio (Males)	0.90 ± .02	0.89 ± 0.03	0.022
Waist Hip Ratio (Females)	0.89 ± 0.03	0.86 ± 0.03	<0.001
Waist height Ratio	0.54 ± 0.04	0.51 ± 0.04	<0.001

Table 3
Comparison of various biochemical parameters between Prediabetes and controls.

LFT	Prediabetics (n = 100)	Controls (n = 100)	P value
SGOT (Upto 40U/L)	45.38 ± 25.31	37.26 ± 11.28	0.004
SGPT (Upto 40U/L)	46.87 ± 30.80	35.45 ± 9.98	0.001
ALP (39–90 U/L)	92.53 ± 30.87	65.41 ± 15.10	<0.001
GGT (9–48U/L)	40.51 ± 40.40	26.10 ± 7.50	0.001
TG (60–160 mg/dl)	148.16 ± 71.72	130.56 ± 35.45	0.029
UA (3.4–7.0 mg/dl)	5.05 ± 1.52	4.34 ± 1.06	<0.001

BMI, waist circumference, waist hip ratio, systolic blood pressure, diastolic blood pressure and a combination of the mentioned confounders. It was found that out of various biochemical and anthropometric parameter, GGT and WC was found to be best predictor of fatty liver among prediabetes patients with aOR of 6.60 and 6.58 respectively. After adjusting for age, gender, WC, it was found that prediabetes itself was associated with NAFLD with a significant p-value of 0.002 and aOR of 1.82.

4. Discussion

In the present study, prevalence of NAFLD was found to be 59% among prediabetics subjects and was significantly more common as compared to control population. Increasing age, Weight, BMI, WC, WHR, waist height ratio, SGOT, GGT, TG, UA, were significantly more in prediabetics with NAFLD as compared to prediabetics without NAFLD.

Various studies have shown an increased prevalence of NAFLD in T2DM, few studies have addressed the issue of prevalence of NAFLD in pre-diabetes [4–6,8]. As per Indian council of medical research (ICMR) [13], prevalence of Prediabetes in India is around 77.2 million and large number of these individuals with prediabetes will eventually develop diabetes in long-term, therefore, it is very important to find out prevalence of NAFLD in pre-diabetes. Ghannaei et al. [8] in their study involving 181 pre-diabetic patients found that 65.4% were having varying degree of NAFLD. They also observed that increasing age and BMI were associated with presence of NAFLD in pre-diabetes. In the present study, NAFLD was more in prediabetic males (60%) as compared to prediabetic females (40%) and increasing age, BMI, WC, waist/height ratio was associated with presence of NAFLD in pre-diabetic individuals. The average age of cases in our study was much lower in comparison to its western counterparts, since dysglycemia sets in at least a decade earlier among the Indian population than that of western countries. The increased prevalence among pre-diabetic males could be because of fact that premenopausal women are protected from NAFLD due to various sex hormones [14]. The relationship between obesity and NAFLD has been shown in several studies. In a study by Zelber- Sagi et al. [6], the mean BMI of the patient with NAFLD was reported as 29.6+ = 3.8. Ghannaei et al. [8] in their study found that the highest prevalence of NAFLD in prediabetic patient was observed in BMI > 30 kg/m$^{2.}$ patient. In contrast to these studies the mean BMI of pre-diabetic patients in the present study is much lower i.e. 26.21 ± 2.57 kg/m^2 and this could be because of the fact that Indian population develops various metabolic complications of overweight and obesity at much lower BMI as compared to Caucasian counterparts. In the present study, prevalence of metabolic syndrome was significantly more in prediabetic with NAFLD as compared to controls. It is likely that increasing insulin resistance could be a common link between increased prevalence of NAFLD and metabolic syndrome among pre-diabetic individuals. Although we have not calculated insulin resistance in the present study, but significantly increased WC and waist height ratio (clinical surrogate markers of visceral adiposity) among prediabetic population as compared to controls suggests that pre-diabetics are more insulin resistant as compared to controls [15].

37% of the pre-diabetic patients had Grade 1 fatty liver (37%) and 22% has grade 2 fatty liver in the present study. Ghannaei et al. [8] in did not report about severity of NAFLD in their study. In a study from Bangladesh by Israt AH et al. [16] it was seen that out of 74 prediabetics (IGT subjects), grade 0, 1 and 2 fatty liver was present in 51.4%, 33.8% and 9% of the patients respectively. Goh et al. [14] studied that among those T2DM patients who had fatty liver, 36% had grade 1, 33.5% had grade 2 and 28.4% had grade 3 fatty liver. As compared to diabetes patients, prediabetes patients have lesser severity of NAFLD as we have observed the present study where no patient had grade 3 NAFLD. SGOT (AST), SGPT (ALT), ALP and GGT levels were significantly higher in prediabetics as compared to controls in the present study. Similar findings were observed in a study by Ghannaei et al. [8] where these biochemical tests levels were high in prediabetics as compared to controls. The adverse association of liver function enzymes in prediabetes may result from the link between excess central adiposity, NAFLD and hepatic

Table 4
Comparison of various anthropometric and biochemical parameters in prediabetes with NAFLD and prediabetes without NAFLD.

Variables	Prediabetics with NAFLD (n = 59)	Prediabetics without NAFLD (n = 41)	P-value
Age (yrs)	48.80 ± 10.26	42.07 ± 10.94	0.015
FPG (mg/dl)	105.35 ± 5.54	101.98 ± 7.14	0.053
2hr Post OGTT Plasma glucose (mg/dl)	146.80 ± 12.73	146.95 ± 11.27	0.959
SBP (mmHg)	126.00 ± 9.15	121.63 ± 9.40	0.065
DBP (mmHg)	81.00 ± 6.10	80.20 ± 6.15	0.604
Height (cm)	162.70 ± 7.11	160.36 ± 6.78	0.175
Weight (kg)	75.90 ± 10.40	65.95 ± 8.47	0.001
BMI (kg/m^2)	28.52 ± 2.69	25.63 ± 2.20	0.001
WC (male) in cm	97.41 ± 5.56	90.92 ± 7.04	0.008
WC (female)in cm	88.37 ± 5.70	81.69 ± 6.03	0.005
Hip circumference (male) in cm	105.83 ± 5.74	100.68 ± 6.40	0.024
Hip circumference (female) in cm	97.37 ± 4.62	91.49 ± 4.96	0.003
WHR ratio (male)	0.92 ± 0.02	0.90 ± 0.03	0.046
WHR ratio (female)	0.91 ± 0.02	0.89 ± 0.03	0.283
Waist height ratio	0.54 ± 0.03	0.52 ± 0.04	<0.002
SGOT (up to40U/L)	56.70 ± 45.53	42.55 ± 16.22	0.025
SGPT (upto 40 U/L)	57.70 ± 42.37	44.16 ± 26.82	0.079
GGT (9–48 U/L)	79.65 ± 3.95	30.72 ± 15.66	0.001
ALP (39–90 U/L)	99.90 ± 31.75	90.68 ± 30.57	0.234
TG (<150 mg/dl)	220.0 ± 86.60	130.20 ± 54.85	0.001
UA (3.4–7.0 mg/dl)	5.89 ± 1.75	4.83 ± 1.39	0.005

insulin resistance mediated by elevated hepatic free fatty acid flux from visceral fat that induces increased hepatic lipogenesis and triglyceride rich lipoprotein secretion. Out of various anthropometric and biochemical parameters, GGT and WC were found to be best predictor of fatty liver among prediabetes patients with aOR of 6.60 and 6.58 respectively. In present study, it was found that prediabetes itself was associated with NAFLD with aOR of 1.82 with a significant p-value of 0.002.

Various strength of the present study includes inclusion of age and sex matched healthy control group which ensured better matching of unknown confounders, using OGTT for diagnosis making diagnosis of IGT rather than using postprandial glucose as a proxy for OGTT as had been done in some of the previous studies.[22] However because of small sample size of the study population from a limited geographical area results of this study needs to be confirmed in larger studies.

To conclude with, prevalence of NAFLD is substantially more in prediabetic patients as compared to normoglycemic individuals and elevated WC and GGT were the best predictor of underlying NAFLD among prediabetic individuals.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.07.060.

References

[1] Kanat M, Mari A, Norton L, Winnier D, DeFronzo RA, Jenkinson C, et al. Distinct β-cell defects in impaired fasting glucose and impaired glucose tolerance. Diabetes 2012;61(2):447–53.

[2] Petersen JL, McGuire DK. Impaired glucose tolerance and impaired fasting glucose—a review of diagnosis, clinical implications and management. Diabetes Vasc Dis Res 2005;2(1):9–15.

[3] Zelber-Sagi S, Lotan R, Shlomai A, Webb M, Harrari G, Buch A, et al. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. Hepatology 2012;56(5):1145–51.

[4] Ortiz-Lopez C, Lomonaco R, Orsak B, Finch J, Chang Z, Kochunov VG, et al. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). Diabetes Care 2012;35(4):873–8.

[5] Singh SP, Singh A, Pati GK, Misra B, Misra D, Kar SK, et al. A study of prevalence of diabetes and prediabetes in patients of non-alcoholic fatty liver disease and the impact of diabetes on liver histology in coastal eastern India. J Diabetes Mellitus 2014;4(4):290–6.

[6] Zelber-Sagi S, Lotan R, Shibolet O, Webb M, Buch A, Nitzan-Kaluski D, et al. Non-alcoholic fatty liver disease independently predicts prediabetes during a 7-year prospective follow-up. Liver Int 2013;33(9):1406–12.

[7] Musso G, Gambino R, Cassader M, Pagano G. Metaanalysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011;43(8):617–49.

[8] Mansour-Ghanaei F, Jafarinejad A, Roshan ZA, Khosravi H, Hassankhani A, Maaf AA. Non-alcoholic fatty liver disease and prediabetes. J Pioneer Med Sci 2016;6:6–9.

[9] Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl 1). S81–90.

[10] Savermuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in detection of hepatic fibrosis and steatosis. BMJ 1986;292:13–5.

[11] Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg 2004;14:635–7.

[12] Zimmer P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb 2005;12(6). 295-30.

[13] Anjana RM, Ali MK, Pradeepa R, Deepa M, Datta M, Unnikrishnan R, et al. The need for obtaining accurate nationwide estimates of diabetes prevalence in India - rationale for a national study on diabetes. Indian J Med Res 2011;133:369–80.

[14] Goh GB, Pagadala MR, Dasarathy J, Unalp-Arida A, Sargenta R, Hawkins C, et al. Clinical spectrum of non-alcoholic fatty liver disease in diabetic and nondiabetic patients. BBA Clin. 2015;3:141–5.

[15] Mori Y, Hoshino K, Yokota K, Yokose T, Tajima N. Increased visceral fat and impaired glucose tolerance predict the increased risk of metabolic syndrome in Japanese middle-aged men. Exp Clin Endocrinol Diabetes 2005;113:334–9.

[16] Israt AH, Liaquat A. Nonalcohlic fatty liver disease and its association with insulin resistance: a study from Bangladeshi newly diagnosed impaired glucose tolerance subjects. bJ Diabetes Meta 2016;7. 7.