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Research Article

Non-Alcoholic Fatty Liver Disease and Cardiovascular Disease

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Abstract: Nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) are both manifestations of end-organ damage .Nonalcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease now represents a worldwide public health problem. Furthermore, NAFLD is also believed to be involved in the pathogenesis of common disorders such as type 2 diabetes also. NAFLD encompasses a broad spectrum of conditions, ranging from simple steatosis (nonalcoholic fatty liver) to nonalcoholic steatohepatitis (NASH). Patients with NAFLD develop increased atherosclerosis, cardiomyopathy, and arrhythmia, which clinically result in cardiovascular morbidity and mortality. One important concern with silent undiagnosed NAFLD is that it may progress silently and result in cirrhosis, portal hypertension, and liver-related death in early adulthood. Interestingly, NAFLD is an independent risk factor for cardiovascular disease (CVD). Importantly, NAFLD is associated with an increased risk of all-cause death and predicts future CVD events, independently of the classical risk factors like age, sex, LDL cholesterol, smoking, and features of metabolic syndrome (Knobloch, K. *et al.*, 2011). Non-alcoholic fatty liver disease (NAFLD) has become one of the most frequent chronic liver diseases and its prevalence is likely to rise even further. An increasing body of evidence shows that NAFLD is not only a potentially progressive liver disease, but also has systemic consequences. More specifically, evidence points out that NAFLD has to be considered as a significant independent risk factor for subclinical and clinical cardiovascular disease (CVD). Long-term follow-up studies demonstrate cardiovascular mortality to be the most important cause of death in NAFLD patients. Moreover, ample evidence associates NAFLD with endothelial dysfunction, increased pulse wave velocity, increased coronary arterial calcifications and increased carotid intima media thickness, all established markers for CVD. One significant challenge for mass screening for NAFLD is the lack of sensitive and specific biochemical marker. The concomitant use of alanine aminotransferase ALT and ultrasound may produce high diagnostic Defining the mechanisms linking these two diseases offers the opportunity to further develop targeted therapies. The aim of this study is to examine the association between CVD and NAFLD and discuss the overlapping management approaches. Importantly, NAFLD is associated with an increased risk of all-cause death and predicts future CVD events, independently of the classical risk factors like age, sex, LDL cholesterol, smoking, and features of metabolic syndrome (Knobloch, K. *et al.*, 2011). One significant challenge for mass screening for NAFLD is the lack of sensitive and specific biochemical marker. The concomitant use of alanine aminotransferase ALT and ultrasound may produce highly diagnostic.

Keywords: Nonalcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), LDL.

INTRODUCTION

Several noninvasive markers of fibrosis have been used in NAFLD patients, including NAFLD fibrosis score, AST/platelet ratio index, FIB-4 score and BARD score. These markers can help predict those patients who would be at highest risk of developing liver-related complications or death (128–130). "Early detection of liver fibrosis in patients with NAFLD is critical in reducing mortality associated with this highly common disease. On-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver conditions ranging from isolated fatty liver (steatosis) to fatty liver along with inflammation (i.e. non-alcoholic steatohepatitis [NASH]). Although NAFLD can progress to liver failure and hepatocellular carcinoma (Vernon, G. *et al.*, 2011), the most common cause of death in NAFLD patients is related to atherosclerotic cardiovascular disease (ASCVD) (Fracanzani, A. L. *et al.*, 2008) and a large number of studies have shown that NAFLD is a significant risk factor for

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atherosclerosis in the coronary and carotid arteries (Adams, L. A. *et al.,* 2005). Obesity is a major cause of NAFLD and along with the increasing prevalence of obesity; NAFLD has become the most common liver disease with an estimated prevalence of 25% globally (Vernon, G. *et al.,* 2011). Most NAFLD patients also display other obesity-related metabolic aberrations such as impaired glucose homeostasis, dyslipidemia, hypertension, and low-grade inflammation (Targher, G. *et al.,* 2008). Given the central role of metabolic risk factors in the management of NAFLD, it is important to understand how these factors modify the relationship between NAFLD and ASCVD (ATHEROSCLEROTIC CARDIOVASCULAR DISEASE) and more specifically to assess cardiovascular risk for patients who appear metabolically unaffected by their NAFLD as judged from clinical parameters. This aspect is important as it could have implications for the medical management of this patient population with regards to ASCVD surveillance and prevention. To our knowledge, few studies have addressed this question specifically. Subgroup analyses in one large Asian study indicated that NAFLD assessed by ultrasound was a stronger risk factor for coronary artery disease in metabolic syndrome than in non-MetS subjects (Kang, J. H. *et al.,* 2012). On the other hand, another study reported that NAFLD assessed by ultrasound was associated with carotid intima-media thickness only in MetS and not in non-MetS subjects (Puig, J. *et al.,* 2015). There is an inherent problem with grouping based on MetS in that the established definitions include obesity criteria, which makes it difficult to dissect obesity-driven metabolic derangements from non-obesity. Given the strong effect of obesity on liver fat as well as on a wide range of metabolic risk factors, it's results can be difficult to interpret if comparison groups are not balanced with regards to adiposity measures. In the current study aim is to examine the association between CVD and NAFLD and discuss the overlapping management approaches. This also included modifying effects of a wide range of obesity-driven metabolic risk factors generated from NAFLD.

MATERIALS AND METHODS

Elucidating Risk of Atherosclerosis is a case control study, designed to address the risk factors and disease end points of atherosclerotic CVDs. In short, a total of 100 patients 60 control men, hypertensive patients aged 40–59 years. However if a bit hyperglycemic were not denied to try for another complication also.

Data are the means ± SD, unless otherwise indicated. Differences were assessed by the unpaired *t* test (for normally distributed variables) and by the χ^2 test (for categorical variables).

TABLE-1

Variables	Control subjects	Case subjects	*P*
n	496	248	—
Sex (% men)	62	62	NS*
Age (years)	65 ± 3	66 ± 4	NS*
BMI (kg/m^2)	26 ± 3	29 ± 4	<0.001
Waist circumference (cm)	93 ± 13	101 ± 14	<0.001
Duration of diabetes (years)	13 ± 3	14 ± 3	NS
Oral hypoglycemic agents (%)	61.9	63.3	NS
Insulin treatment only (%)	12	14	NS
Current smokers (%)	20	22	NS
Systolic blood pressure (mmHg)	124 ± 13	131 ± 15	<0.001
Diastolic blood pressure (mmHg)	79 ± 12	83 ± 10	<0.001
A1C (%)	6.9 ± 0.8	7.2 ± 0.9	0.059
Triglycerides (mmol/l)	1.24 ± 0.6	1.62 ± 0.9	<0.001
HDL cholesterol (mmol/l)	1.39 ± 0.3	1.25 ± 0.4	<0.001
LDL cholesterol (mmol/l)	3.29 ± 0.4	3.27 ± 0.5	NS
AST (units/l)	20 ± 10	26 ± 12	<0.01
ALT (units/l)	23 ± 12	33 ± 14	<0.001
GGT (units/l)	27 ± 14	38 ± 16	<0.001
Microalbuminuria (%)	20	23	NS
ATP III–defined metabolic syndrome (%)	52	73	<0.001
NAFLD (%)	56	94	<0.001

MATCHING VARIABLES

Univariate and multivariate logistic regression analyses of factors associated with incident CVD events among type 2 diabetic patients

TABLE-2

VARIABLES	UNIVARIATE	MULTIVARIATE MODEL 1	MULTIVARIATE MODEL 2	MULTIVARIATE MODEL 3
NAFLD				
OR	1.91	1.9	1.84	1.53
95% CI	1.4–2.2	1.4–2.2	1.4–2.1	1.1–1.7
P values	0.001	0.001	0.001	0.02
ATP III–defined metabolic syndrome				
OR	1.64	1.64	1.62	1.58
95% CI	1.3–2.5	1.3–2.3	1.3–2.1	1.3–2
P values	0.001	0.001	0.001	0.01
Age				
OR	1.14	1.13	1.13	1.12
95% CI	1.07–1.16	1.07–1.14	1.07–1.14	1.06–1.14
P values	0.001	0.001	0.001	0.001
Sex				
OR	1.50	1.48	1.46	1.46
95% CI	1.2–2	1.2–2	1.2–1.9	1.2–1.9
P values	0.001	0.001	0.001	0.001
Diabetes duration				
OR	1.08	NS	NS	NS
95% CI	0.8–1.3	NS	NS	NS
P values	NS	NS	NS	NS
A1C				
OR	1.51	1.46	NS	NS
95% CI	1.1–4.9	1.02–4.2	NS	NS
P values	0.02	0.05	NS	NS
Smoking status				
OR	1.44	1.42	1.40	1.40
95% CI	1.1–2.0	1.1–2.0	1.1–1.9	1.1–1.9
P values	0.01	0.01	0.01	0.01
LDL cholesterol				
OR	1.18	NS	NS	NS
95% CI	0.9–1.4	NS	NS	NS
P values	NS	NS	NS	NS
GGT				
OR	1.42	1.40	1.27	NS
95% CI	1.1–2.0	1.1–1.9	1.05–1.7	NS
P values	0.001	0.001	0.01	NS
Use of medications				
OR	1.0	NS	NS	NS
95% CI	0.7–1.2	NS	NS	NS
P values	NS	NS	NS	NS

Smoking history, diabetes duration, A1C, LDL cholesterol, GGT levels, and use of medications (i.e., hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs);

DISCUSSION

NAFLD is a hepatic manifestation of the metabolic syndrome, and thus cardiovascular disease is increased in NAFLD and represents the main cause of death in these patients. However, given the shared features between NAFLD, the metabolic syndrome, and traditional cardiovascular risk factors, it remains uncertain whether NAFLD is an independent risk factor for increased cardiovascular event (Ramilli, S. *et al.*, 2009). Several previous studies have demonstrated that patients with NAFLD have significantly higher rates of prevalent coronary, cerebrovascular, and peripheral vascular disease than their counterparts without NAFLD (Review Manger (RevMan) [computer program]. 2014; Agarwal, A. K. *et al.*, 2011; Aygun, C. *et al.*, 2008). However, the lack of diagnostic uniformity and difficulty in accurately quantifying the severity of NAFLD in the various published studies make interpretation of the results challenging and sometimes contradictory (Bhatia, L.S. *et al.*, 2012). There is an urgent need to ensure a more homogeneous evaluation of study outcomes (Bhatia, L.S. *et al.*, 2012). It was found that NAFLD was associated with a higher prevalence of coronary heart disease in type 2 diabetes,

and that plasma ALT levels may act as a marker (Agarwal, A. K. *et al.*, 2011). More importantly, our findings extend the work of recent small studies showing that patients with NAFLD, as assessed by ultrasonography or computed tomography (CT), had a significant association with cardiovascular mortality. In this study it was found that NAFLD was a predictor of cardiovascular events .Even after adjustment for confounders (age, sex, diabetes duration, HbA1c, smoking history, LDL cholesterol, GGT levels and use of medications (i.e., hypoglycemic, antihypertensive, lipid-lowering or antiplatelet drugs), and NCEP ATP III-defined MS), the association remained significant (pooled multivariate odds ratio 1.50, 95% CI 1.21 to 1.87 ;). This analysis shows that NAFLD is an independent novel predictor for cardiovascular events, even when other components of the metabolic syndrome are taken into account. Because of the link between the two disorders, and that the majority of patients diagnosed with NAFLD are asymptomatic ((Bhatia, L.S. *et al.*, 2012; Targher, G *et al.*, 2008), more careful surveillance of these patients will be needed (Bhatia, L.S. *et al.*, 2012; Ampuero, J. *et al.*, 2015). Healthcare providers should recognize this higher risk of cardiovascular disease. Patients should be educated as it is our experience that they become singularly focused on liver enzymes and ignore more important cardiovascular health (Lankarani, K. B. *et al.*, 2013). All NAFLD patients should be evaluated for their metabolic, cardiovascular, and liver-related risk.

Positivity's And Negativity of Study

The diagnosis of NAFLD obtained in our study was based on ultrasonography, ALT and other liver function tests or computed tomography (CT) and the exclusion of known causes of chronic liver disease but was not confirmed by liver biopsy. Although liver biopsy remains the gold standard for NAFLD diagnosis and evaluation, it is difficult to conduct in large populations, and ultrasonography remains the most common way of diagnosing NAFLD in clinical practice due to its good sensitivity and specificity in detecting moderate and severe steatosis (Adams, L. A. *et al.*, 2005). Secondly, NAFLD ranges from simple steatosis (SS) to nonalcoholic steatohepatitis (NASH) (Lankarani, K. B. *et al.*, 2013). In this study, we did not take the NAFLD histological subtypes into account. Despite these limitations, this study also has notable strengths. First, this analysis was significantly increased due to statistical power of the analysis compared to a single study. Second, the quality of was near perfect as frank diagnosis was elucidated. All of them were of high quality. Third, the included studies originated from different regions of India. Finally, because this was based on unadjusted and multivariate adjusted estimates, separately, the results of it are possibly the most precise estimate available of the strength of the relation between NAFLD and future risk of cardiovascular events. In conclusion, the results suggest that NAFLD is a strong independent predictor of cardiovascular disease and may play a central role in the cardiovascular risk of MS. When NAFLD is diagnosed, the person's overall cardiovascular risk factor profile should be reviewed to ensure that risk factors are being appropriately modified.

RESULTS

There were no significant differences in main study variables between those who did and those who did not have a liver ultrasound examination. Of the 160 participants, 76 had hepatic steatosis on ultrasound, whereas 32 had negative liver ultrasound tests as well as normal liver tests and the absence of viral hepatitis or excessive alcohol consumption. Among those with hepatic steatosis, 56 participants admitted alcohol abuse or drank >20 g/day and 89 had other causes of chronic liver disease (viral hepatitis or medications), whereas the remaining 44 participants met the criteria for diagnosis of NAFLD, i.e., hepatic steatosis among individuals without excessive alcohol consumption or other causes of chronic liver disease. Thus, the unadjusted prevalence of NAFLD was 69.5% (95% CI 68.5–70.5), and NAFLD represented the most common cause (81.5%) of hepatic steatosis on ultrasound. The prevalence of NAFLD increased with increasing age (65.4% among participants aged 40–59 years and 74.6% among those aged ≥60 years; $P < 0.001$), and the age-adjusted prevalence of NAFLD was 71.1% in men and 68.0% in women ($P = 0.20$). The baseline characteristics of the study participants, grouped according to NAFLD status, after exclusion of those with other known causes of chronic liver disease (**n** = 89), are presented in **Table 1**. Individuals with NAFLD were older, more likely to be male, and had longer diabetes duration than those without NAFLD. They also had higher values of A1C and liver enzymes, although the vast majority of patients with NAFLD (86%) had normal serum alanine aminotransferase (ALT) levels. Metabolic syndrome and its individual components occurred more frequently among patients with NAFLD. Smoking history, plasma LDL cholesterol, and creatinine concentrations were not significantly different between the groups. The proportion using insulin or antihypertensive or antiplatelet drugs was higher among patients with NAFLD, whereas the proportion using lipid-lowering drugs was similar in both groups. Interestingly, compared with previous reports, in which comparable diagnostic noninvasive measures were used, the prevalence of CVD in this study was similar to that described in other populations with comparable age, diabetes duration, glycemic control, and smoking status (Pacifico, L. *et al.*, 2010). As shown in, the age- and sex-adjusted prevalence of coronary, cerebrovascular, and peripheral vascular disease were remarkably higher in patients with NAFLD than in those without NAFLD. The relationship between NAFLD and CVD was little affected by adjustment for age, sex, BMI, smoking, diabetes duration, A1C, LDL cholesterol, and medications. Almost identical results were obtained in

models that also adjusted for the individual components of the metabolic syndrome (not shown). Exclusion of participants who have asymptomatic CVD (carotid stenosis ≥70%) or who were light-to-moderate drinkers (alcohol consumption <20 g/day) did not alter the observed associations between NAFLD and CVD (OR 1.49 [95% CI 1.1–2.0], *P* = 0.032).

TABLE-3

Variables	Without fatty liver	With NAFLD	*P* value
n	418	1,974	
Sex (% men)	54	57	<0.001
Age (years)	60 ± 4	65 ± 6	<0.001
BMI (kg/m^2)	26.5 ± 3	28.3 ± 4	<0.001
Diabetes duration (years)	7 ± 2	12 ± 3	<0.001
Oral hypoglycemic users (%)	67	66	0.80
Insulin users (%)	17	25	<0.001
Antihypertensive drug users (%)	60	73	<0.001
Aspirin users (%)	48	57	<0.001
Lipid-lowering drug users (%)	41	43	0.60
Current smokers (%)	25	27	0.60
Systolic blood pressure (mmHg)	135 ± 10	139 ± 12	<0.001
Diastolic blood pressure (mmHg)	83 ± 7	85 ± 10	<0.001
A1C (%)	6.7 ± 0.6	7.3 ± 1.1	<0.001
Triglycerides (mmol/l)	1.40 ± 0.6	1.68 ± 1.0	<0.001
HDL cholesterol (mmol/l)	1.41 ± 0.3	1.34 ± 0.4	<0.001
LDL cholesterol (mmol/l)	3.40 ± 0.4	3.37 ± 0.4	0.40
Creatinine (μmol/l)	90 ± 12	92 ± 14	0.40
Aspartate aminotransferase (units/l)	23 ± 3	28 ± 10	<0.001
ALT (units/l)	25 ± 3	33 ± 12	<0.001
Elevated ALT (men >50 units/l; women >35 units/l) (%)	0	14	<0.001
ATP III–defined metabolic syndrome (%)	70	86	<0.001

Data are means ± SD or proportions. *n* = 160.

CONCLUSION

NAFLD is an important and emerging heath problem. NAFLD is regarded as hepatic component which is associated with high risk of development of CVD. Several studies suggest that NAFLD per se can be associated with risk of CVD. Dyslipidemia, insulin resistance, low adiponectin, and postprandial dyslipidemia and hyperglycemia are main factors leading on to NAFLD and further aggravate the course of NAFLD as well as accelerate the progress of atherosclerosis and development of CVD. The mechanism and complex factors involved in the development of CVD in individuals with NAFLD are as expected. Currently, it is not known how treatment of NAFLD will modulate the risk of CVD. Further research is urgently needed to understand the association between NAFLD and CVD and how potential treatment of NAFLD will modulate the risk of CVD. The causal relationship of CVD and NAFLD remains under investigation, but the strong bidirectional association between CVD and NAFLD warrants clinical intervention in patients with NAFLD to modify metabolic risk factors, including T2DM, dyslipidemia, hypertension, and obesity. Although current cardiovascular society guidelines have not identified NAFLD as an independent risk factor for CVD despite recent studies suggesting NAFLD's role in incident CVD, vigilant age-appropriate screening and treatment for associated risk factors, including weight loss for obesity, glycemic control for T2DM, and treatment of hypertension and hyperlipidemia, remain prudent strategies that should be supported by clinicians managing patients with NAFLD. A screening and management algorithm for associated metabolic risk factors in patients with NAFLD is proposed in Figure **1**. Additional research is needed to further define the independent contribution of NAFLD to cardiovascular risk to inform future evidence-based guidelines for clinical practice.

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