Non-alcoholic fatty liver disease in Asian Indians: relationship with insulin resistance, diabetes and cardiovascular risk

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Prevalence of non-alcoholic fatty liver disease (NAFLD) varies in India; up to one-third of the urban population is affected by the disease. In Asian Indians, presence of NAFLD is driven by multiple factors – presence of excess abdominal fat (abdominal subcutaneous and intra-abdominal fat) and lifestyle factors (imbalanced diets and physical inactivity), and it is correlated closely with insulin resistance, the metabolic syndrome and dysglycaemia in the background of genetic predisposition (investigated genes in Asian Indians: *APOC3*, *PNPLA-3*, *PPARγ*, *SREBP-2*, *adiponectin*, *SAMM50*, *PARVB* and *PZP*). Recent studies also show that presence of NAFLD independently correlates with subclinical inflammation and surrogate markers of atherosclerosis (carotid intima-media thickness, impaired flow-mediated vasodilatation) in Asian Indians. A prediction equation (Indian Fatty Liver Index) which includes simple measures has been developed for Asian Indians. On the other hand, increased (more than 15.6 cm) liver span (surrogate marker of fatty liver), in a preliminary study, predicted diabetes in non-obese Asian Indians. Dietary factors are important for the development of NAFLD, and some evidence indicates that regular use of high monounsaturated fatty acid rich oils, and low amount of saturated fat intake are beneficial.

Keywords: Diabetes, insulin resistance, obesity, non-alcoholic fatty liver disease.

Introduction

HEPATIC steatosis (commonly called fatty liver) is an asymptomatic liver disorder associated with many illnesses and diseases. Non-alcoholic fatty liver disease (NAFLD) is accumulation of fat in liver in absence of significant alcohol consumption (less than 20 g/day) and other causes of liver diseases. Mostly, it is on account of lifestyle factors and obesity. It is the most common cause of asymptomatic elevation of liver enzymes worldwide[1]. If fat continues to accumulate in the liver, aggravated by adverse lifestyle factors, hepatic inflammation termed as non-alcoholic steatohepatitis (NASH) may occur, occasionally resulting in cirrhosis and even hepatic carcinoma.

A great deal of research has been done which shows close linkages of adiposity, insulin resistance and liver steatosis[2]. Overall, pathogenesis and treatment of NAFLD is partially similar to obesity and type 2 diabetes mellitus (T2DM). Current evidence indicates that NAFLD represents the hepatic component of a metabolic syndrome characterized by abdominal obesity, hyperinsulinaemia, peripheral insulin resistance, diabetes, hypertriglycaeridemia, and hypertension. Severe hepatic steatosis and insulin resistance were shown associated with the clustering of the five components of metabolic syndrome[3,4].

It is important to note increasing trend of obesity, T2DM and cardiovascular disease (CVD) in Asian Indians, mostly aggravated by lifestyle transition, urbanization and mechanization[5]. When compared to white Caucasians, Asian Indians have higher insulin resistance, greater abdominal adiposity (higher subcutaneous and intra-abdominal fat), and metabolic syndrome[5,6]. These adverse features have implications for the development of NAFLD.

In this review, we shall discuss epidemiology and determinants of NAFLD. While global data have been discussed briefly, most of the article is related to available research on Asian Indians and South Asians.

Search strategy

A literature search was conducted using the terms 'NAFLD and Asian Indians, South Asians, lifestyle, diet, genetics, and treatment' in PubMed (National Library of Medicine, Bethesda, MD, USA) and Google Scholar from 1976 to July 2016. Keywords were selected based on the main thrust of the review article, mainly NAFLD and its comorbities in Asian Indians. A total of 1612 references were extracted and studied. The studies were selected

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Table 1. Prevalence of NAFLD /NASH in India

Reference	n/type of patients	Diagnostic method	Prevalence
55	410 healthy subjects	Liver ultrasonography	28.1%
56	134 morbidly obese subjects	Liver biopsy	65.7%
57	736 T1DM patients	Liver ultrasonography	27.7%
5	645 non-diabetic subjects	Liver ultrasonography	NAFLD in 15.6%, NAFLD and MS 68.5%
58	54 women with PCOS and 55 healthy controls	Liver ultrasonography	67%
59	409 healthy subjects	Liver ultrasonography	24.7%
60	124 T2DM patients	Liver ultrasonography	57.2%
14	204 T2DM patients	Liver biopsy	87%
15	541 healthy subjects	Liver ultrasonography	32%, men: 35.1%, women: 29.1%
16	39, NAFLD; 82, controls	Liver ultrasonography	32.2%
61	1003 subjects	Liver ultrasonography	22.6% Males 164/565 (29%) Females 61/438 (13.9%).
62	100 T2DM patients	Liver ultrasonography	49%
63	341 males 384 females	Liver ultrasonography	18.9%; males 24.6%; females 13.6%
64	41 subjects with NAFLD	Liver biopsy	NASH in 55%, IR in 80%
65	25 subjects with NASH	Evaluation of MS and IR (HOMA)	MS in 17 (68%) IR in 20 (80%)
66	159 healthy subjects	Liver ultrasonography	24.5%; males 26.9%; females 13.8%

NAFLD, Non-alcoholic fatty liver disease; NASH, non-alcoholic steatosis; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IR, insulin resistance; MS, metabolic syndrome; IR (HOMA): insulin resistance (homeostasis model assessment).

based on the following criteria: geographical location in India, study design, adequate sample size, robust trial design (case-control or prospective studies), citations and publication in peer reviewed journals.

Epidemiology

Global

Estimates based on imaging and autopsy studies suggest that about 20–30% of adults in the United States and other Western countries are affected by NAFLD[7–10]. In a study on 3271 Japanese subjects, while the overall prevalence of NAFLD was 24.6%, it was 68.5% in obese and 15.2% in non-obese subjects[7]. In general, the prevalence of NAFLD varies between 14% and 30% in different studies conducted on Asians populations. Specifically, the prevalence of NAFLD in the Chinese population ranged from 5% and 24% (refs 11 and 12).

Asian Indians living in India

The community prevalence of NAFLD in India varies from 5% to 32% depending upon age, gender, area of residence (urban or rural) and socio-economic stratum (Table 1). The prevalence of NAFLD in adults was reported to be 15.6% in non-obese subjects and 68.5% in those with metabolic syndrome[13]. In a study from South India, the overall prevalence of NAFLD was 24.7% (ref. 14). Mohan *et al.*[15] reported the overall prevalence of NAFLD as 32% in the Chennai Urban Rural Epidemiology Study (CURES), and its prevalence was 54.5% in patients with T2DM. According to our data, prevalence of NAFLD was 32% in people residing in New Delhi, North India[16]. In an autopsy data of 1230 adults, NAFLD was reported to be 15.8% (ref. 17).

NAFLD in children

NAFLD is also the most common form of chronic liver disease in children. It is likely that it will continue to rise with increasing obesity, insulin resistance and metabolic syndrome in childhood[18]. The prevalence of NAFLD among children in the United States is 3–10%, rising up to 40–70% among obese children[19]. Taken together, the prevalence of fatty liver in obese children in China, Italy, Japan and the United States has been reported to be between 10% and 77% (refs 20–22). In India, the overall prevalence of fatty liver in children in the age group 4–18 years was 7.4%; however, it increased to 44.4% in children with metabolic syndrome and 61% in obese children[23]. Such high and increasing prevalence of NAFLD in children and adolescents is predominantly due to adverse eating habits and inactive lifestyle.

Correlates of NAFLD in Asian Indians

While there are many correlates of NAFLD, those researched in Asian Indians have been discussed below and summarized in Figure 1.

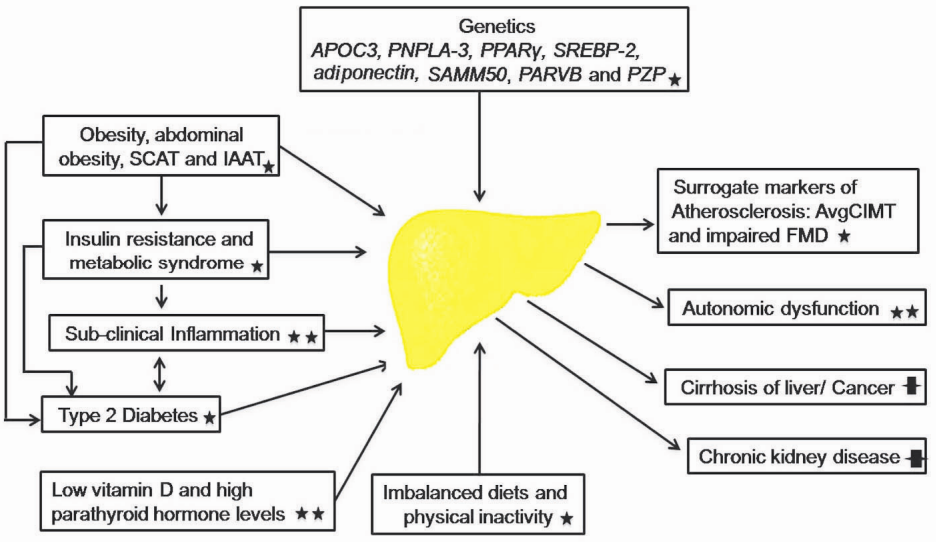

Figure 1. Correlates and consequences of non-alcoholic fatty liver disease in Asian Indians. *APOC3*, Apolipoprotein-C3; *PNPLA-3*, Patatin-like phospholipase domain-containing protein-3; *PPAR-γ*, Peroxisome proliferator-activated receptor gamma, *SREBP-2*, Sterol regulatory element-binding protein-2; *PZP*, Pregnancy zone protein; *SAMM50*, Sorting and assembly machinery of the mitochondria; *PARVB*, Parvin beta; SCAT, Subcutaneous abdominal adipose tissue; IAAT, Intra-abdominal adipose tissue; Avg CIMT, Average carotid intima-media thickness; FMD, Flow-mediated dilatation.

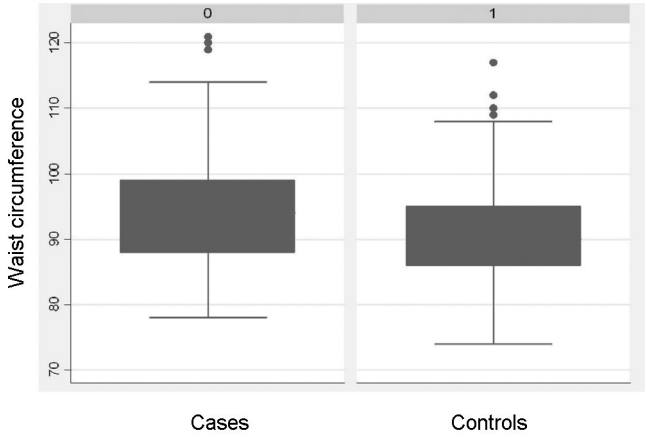

Figure 2. Box plot representation of abdominal obesity by waist circumference (WC) levels in subjects with NAFLD and in controls. Each box comprises values between the 25th and 75th percentiles, and the bold horizontal line is the median value; the whiskers stretch from the 10th and 90th percentiles. *n*; cases, 162; controls, 173. WC cut-offs of ≥90 cm for males and ≥80 cm for females were considered an indicator of abdominal obesity.

Body composition

NAFLD is strongly linked to generalized and abdominal obesity in several populations[16,24,25]. Studies on Asian Indians indicate that various measures of body composition are associated with NAFLD[16,17,24,25]. Our recent data (unpublished) show that people with NAFLD have higher abdominal obesity compared to those without NAFLD (Figure 2). Interestingly, even non-obese Asian Indians with NAFLD had higher subcutaneous skinfold thicknesses and high percentage body fat compared to control subjects[25].

The relationship between abdominal adipose tissue compartments and NAFLD is interesting. The subcutaneous abdominal adipose tissue can be further divided into superficial and deep compartments. The deep abdominal subcutaneous adipose tissue may functionally behave in a manner similar to that of intra-abdominal adipose tissue[26]. Increased flow of non-esterified free fatty acids (FFAs) from excess subcutaneous abdominal and intra-abdominal fat depots could play a contributory role in pathogenesis of insulin resistance and NAFLD. Further, our recent data show that even non-obese patients with T2DM have increased liver span (indicating increased deposition of fat in the liver) correlated well with pancreatic fat (Figure 3)[6].

Predictive equations for NAFLD and prediction of type 2 diabetes using liver span: We have recently published two prediction equations using simple clinical and biochemical measures – Clinical (Indian Fatty Liver Index-Clinical; IFLI-C): 1 (double chin) +15.5 (systolic blood pressure) +13.8 (buffalo hump), and IFLI-Clinical and Biochemical (CB): Serum triglycerides + 12 (insulin) +1 (systolic blood pressure) +18 (buffalo hump). We have further shown the performances of both the prediction equations using receiver operating characteristics (ROC) curve analysis; IFLI performed better than all previously published prediction equations, except one. These prediction scores for NAFLD; IFLI-C and IFLI-CB should useful for clinicians and researchers in India[27].

Further, recently we have reported that non-obese Asian Indian subjects over 30 years of age with serum triglycerides ≥105 mg/dl and liver span ≥15.6 cm have increased risk of T2DM. Specifically, a liver span above

15.6 cm increases the risk of T2DM by nearly four times, especially in males[28]. Liver span can be accurately assessed by ultrasonography, which is available in urban and suburban areas of India at an affordable cost.

Insulin resistance, metabolic syndrome and T2DM

Insulin resistance and metabolic syndrome are closely related to NAFLD[29], and are widely prevalent among Asian Indians[30]. Each component of metabolic syndrome is of higher magnitude in Asian Indians with NAFLD than those without it. Figure 4 *a* and *b* shows higher fasting blood glucose and insulin levels in individuals with NAFLD as compared to those without it[16]. Prashanth *et al.*[14] studied 204 patients with T2DM from Mumbai, India and reported high prevalence of NAFLD and NASH, which increased with multiple components of metabolic syndrome. In a study from north India, 68.5% of subjects with NAFLD had metabolic syndrome associated with hyperinsulinaemia[31]. Petersen *et al.*[32] studied the impact of ethnicity on insulin resistance and hepatic steatosis in young, healthy, body mass index (BMI) and age-matched individuals of Eastern Asian, Asian-Indian, Black, and Caucasian ethnicities in USA. An increased prevalence of insulin resistance was seen in Asian Indian men and was associated with a two-fold increase in hepatic fat content compared with Caucasian men. Sharma *et al.*[33] investigated hepatic gluconeogenesis non-invasively using ^{31}P magnetic resonance spectroscopy (MRS) in 40 non-diabetic subjects with NAFLD and 20 healthy controls in North India, and found that the former showed derangement of hepatic gluconeogenesis metabolites compared with the latter (Figure 5). In particular, even lean subjects with NAFLD exhibited such metabolic derangements.

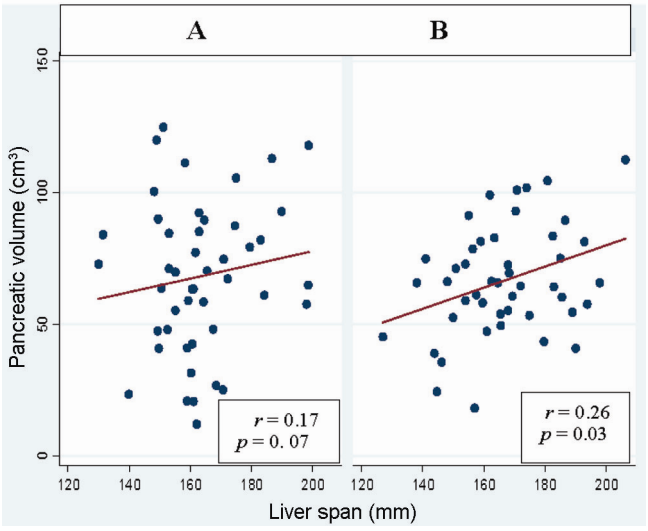

Figure 3. Scatter plots showing correlation of pancreatic volume (surrogate for pancreatic fat) with liver span (surrogate marker of fatty liver) in patients with NAFLD (A) versus those without it (B)[6].

Subclinical inflammation

Elevated levels of inflammation markers, particularly high-sensitivity C-reactive protein (hs-CRP), may play a key role in the development of atherosclerosis. Asian Indians have higher hs-CRP levels compared to the Caucasians[34]. It is speculated that increased risk of atherosclerosis in Asian Indians could be contributed by a combination of high hepatic fat[32] and high magnitude of sub-clinical inflammation depicted by hs-CRP levels. In a case-control study, we showed that hs-CRP (OR (95%CI): 2.1 (1.0–4.4)) was significantly and independently associated with the presence of NAFLD (Figure 6)[35]. Importantly, 1 mg/l increase in hs-CRP was shown to increase the risk of NAFLD by 1.7 times. Increased levels of other pro-inflammatory cytokines in Asian-Indians with NAFLD have been shown in various studies[36,37].

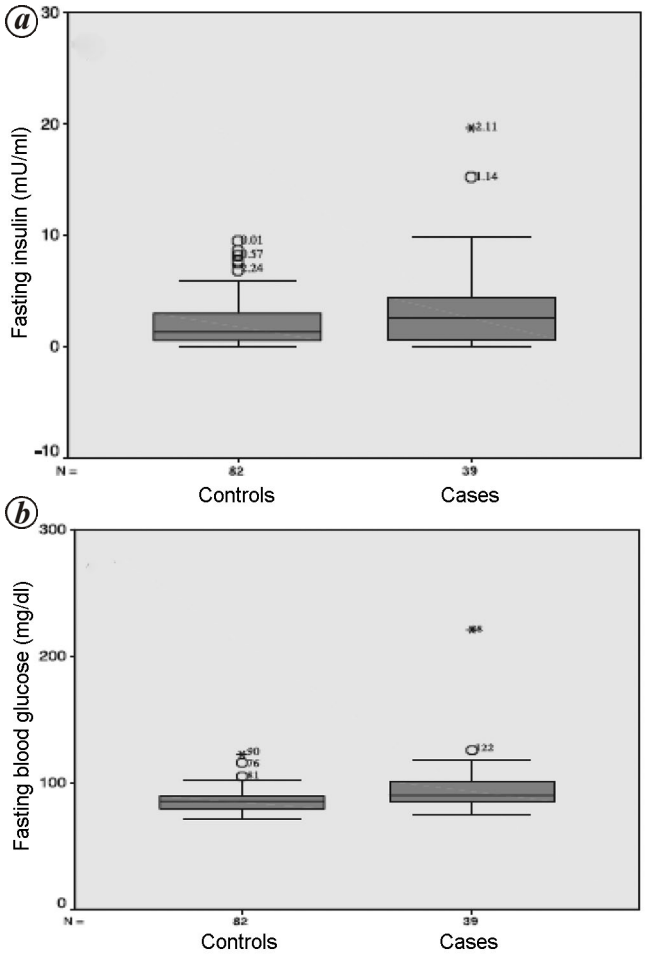

Figure 4. Box plot representation of fasting insulin (***a***) and fasting blood glucose (***b***) levels in subjects with NAFLD (cases) and those without controls. Each box comprises values between the 25th and 75th percentiles; the bold horizontal line is the median value; the whiskers stretch from the 10th and to the 90th percentile. Circles represent individual outlier values. Stars represent extreme value of individuals. Source: Adapted from Bajaj *et al.*[16] with permission.

Atherosclerosis

Recent studies indicate high risk for cardiovascular disease (CVD) in patients with NAFLD, as indicated by surrogate markers (e.g. increased intima-media thickness, etc.)[31,38]. Subjects with NAFLD in North India had markedly greater carotid intima-media thickness (CIMT) and carotid plaque prevalence than those without NAFLD[31]. In another case-control study in North India, the presence of NAFLD was an independent predictor of high average CIMT (OR 4.8; 95% CI: 1.8–12.8), high maximum CIMT (OR 5.4; 95% CI: 2.0–14.4) and impaired flow-mediated dilatation (OR 11.7; 95% CI: 1.4–96.5) after adjusting for obesity, metabolic syndrome, insulin resistance and lipid parameters (Figure 7)[38].

Other determinants/correlates of NAFLD in Asian Indians

Vitamin D deficiency: Low vitamin D levels are believed to play a role in the etiology of metabolic syndrome, either through an association with individual components of the metabolic syndrome or via effects on insulin resistance[39,40]. Targher *et al.*[41] reported that in patients with NAFLD, decreased 25 hydroxy vitamin D (25(OH) vitamin D) concentrations were closely associated with histological severity of hepatic steatosis, necro-inflammation and fibrosis.

Vitamin D deficiency is common in urban as well as rural Asian Indians. In a case-control study (162 cases and 173 age and sex-matched controls), we have shown that low serum 25 (OH) vitamin D (OR (95%CI): 4.46 (2.58–7.72), $P = 0.0001$) and high parathyroid hormone (PTH) (OR (95%CI): 2.21 (1.50–3.30), $P = 0.0001$, Figure 8) levels are independently associated with NAFLD[42]. The mechanism whereby vitamin D deficiency contributes to fat deposition in the liver is not clear at this point. It is possible that vitamin D deficiency may result in increased flow of FFAs in the bloodstream that may promote fat storage into the liver and facilitate the development

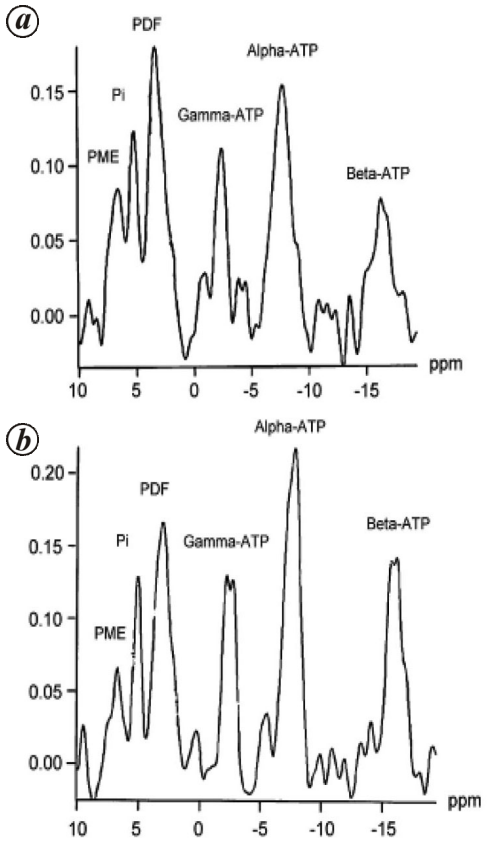

Figure 5. *In vivo* hepatic ^{31}proton MRS spectra from an obese subject (body mass index (BMI) = 30.2 kg/m^2, WC = 104 cm) with NAFLD (***a***) and a non-obese subject (BMI = 22.4 kg/m^2, WC = 78 cm) with NAFLD (***b***) showing resonances from PME, PDE and ATP. Note the higher peak resonance of PME in obese subject compared with non-obese subject with NAFLD. PME: phosphomonoesters, PDE, Phosphodiesters; ATP, Adenosine triphosphate and Pi, Inorganic phosphate. Adapted from Sharma *et al.*[33] with permission.

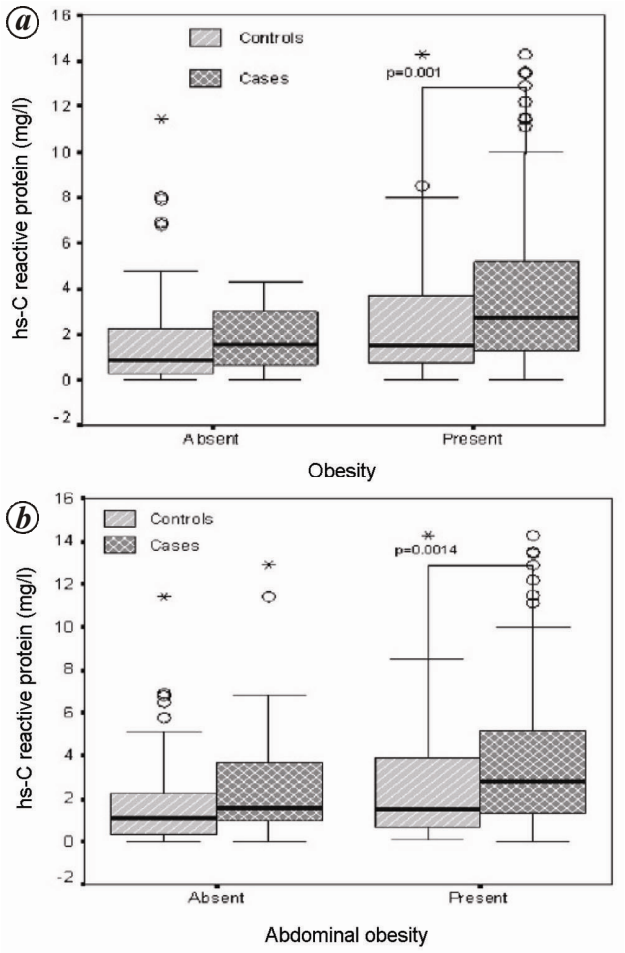

Figure 6. Box plot representation of high-sensitivity C-reactive protein (hs-CRP) levels in subjects with NAFLD (cases) and without NAFLD (controls) having overweight and obesity (***a***), and abdominal obesity (***b***). Each box comprises values between the 25th and 75th percentiles; and the bold horizontal line is the median value; the whiskers stretch from the 10th and to the 90th percentile. Circles represent individual outlier values. Stars represent extreme value of individuals. Reproduced from Nigam *et al.*[35] with permission.

Table 2. Grading of hepatic fat before and after intervention with edible oils containing high monounsaturated fatty acids versus other oils*: a randomized controlled trial in North India

Grades of fatty liver	Pre-intervention			Post-intervention		
	Olive oil (n = 30)	Canola oil (n = 33)	Other oils* (n = 30)	Olive oil (n = 30)	Canola oil (n = 30)	Other oils* (n = 30)
Grade I	22(73.3)	20(60.5)	17(58.62)	7(23.3)	9(20)	19(63.3)
Grade II	6(20)	11(33.4)	9(31.3)	3(10)	1(3.3)	8(26.7)
Grade III	2(6.7)	2(6.1)	4(10.3)	–	–	–
Normal	–	–	–	20(66.7)	20(76.7)	3(10)

*Oils low in monosaturated fatty acids. Adapted from Nigam *et al.*[54].

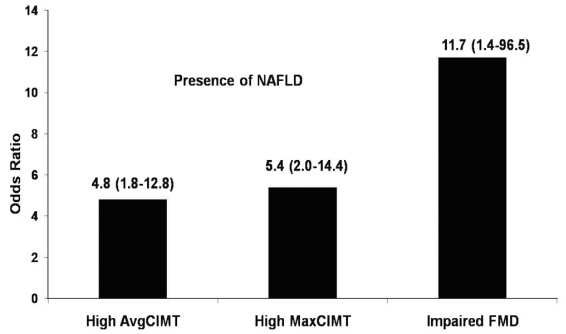

Figure 7. Odds ratio for high Avg carotid intima-media thickness (CIMT), high MaxCIMT and impaired flow-mediated dilatation (FMD) in the presence of NAFLD. Reproduced from Thakur *et al.*[38] with permission.

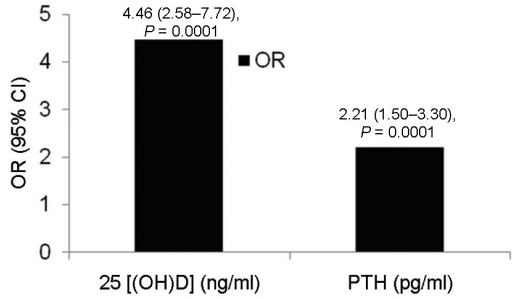

Figure 8. Using multivariable logistic regression model, after adjusting for age, sex, lipid variables, waist circumference, body fat, fasting blood glucose, hepatic transaminases, fasting insulin, homeostasis model assessment insulin resistance (HOMA-IR), independent risk factors associated with a presence of NAFLD were low 25(OH)D (OR (95%CI): 4.46 (2.58–7.72), P = 0.0001) and high parathyroid hormone (PTH) [OR (95%CI): 2.21 (1.50–3.30), P = 0.0001) in Asian Indians from North India[42]. Reproduced from Bhatt *et al.*[42] with permission.

of NAFLD. In this context, it is important to note that Asian Indians have comparatively higher FFA levels post-meal than BMI-matched Caucasians[43].

Autonomic functions: In a recent study, autonomic and vascular functions were compared among NAFLD patients with and without T2DM, and controls (non-diabetic subjects without NAFLD). Patients of NAFLD with and without diabetes were observed to have significantly low baroreflex sensitivity and higher blood pressure variability compared to controls. Heart rate variability was observed to be lower in individuals having NAFLD with and without diabetes compared to controls. These observations suggest that presence of NAFLD may be associated with autonomic dysfunction even in the absence of T2DM in Asian Indians[44].

Genetics: Several genes involved in pathways of fatty acid metabolism in the liver (e.g. uptake, *de novo* synthesis and oxidation of fatty acids) as well as synthesis and secretion of very low-density lipoprotein have been identified as candidates. Few genetic studies have been carried out in obese Asian Indians. Petersen *et al.*[45] showed that the polymorphisms C-482T and T-455C in *apolipoprotein-C3* (*APOC3*) gene were associated with NAFLD and insulin resistance in both Asian Indian (n = 95) and non-Asian men (n = 163) in USA. We have shown that the frequency of G allele of rs738490 polymorphism and GG genotype of *patatin-like phospholipase domain-containing protein 3* (*PNPLA-3*) is significantly associated with NAFLD in Asian Indians from north India[46]; these observations have been corroborated in another study[47]. We have also shown that frequency of Ala allele of Pro12Ala and T allele of C161T polymorphisms of *peroxisome proliferator-activated receptors γ* gene[48], and C allele and the G/C genotype of *sterol regulatory element-binding protein*-2 *1784G>C* (ref. 49) were associated with increased risk of NAFLD in Asian Indians from North India. Further, polymorphisms of *adiponectin* gene have been shown to be associated with severity of liver disease in Asian Indians with NAFLD[50]. In a genome-wide association study from South India, Kanth *et al.*[51] recruited 306 subjects and reported that *sorting and assembly machinery of the mitochondria 50 (SAMM50)*, *parvin beta (PARVB)* and *pregnancy zone protein (PZP)* genes, in addition to *PNPLA3* gene were significantly associated with NAFLD.

Dietary factors: Diet is an important contributor to NAFLD, mainly because excessive energy intake leads to obesity, insulin resistance, T2DM and CVD, and increases the risk for NAFLD. However, not only the amount of energy but also the quality of the diet could play an important role in the development and progression of NAFLD. In an unpublished study (P. Nigam and

A. Misra, unpublished) percentage dietary fat intake, along with three components of the metabolic syndrome (insulin resistance, abdominal obesity and high serum triglycerides) were found to be independent risk factors for the development of NAFLD.

Studies have shown that lifestyle modification, inclusive of dietary changes and physical exercise are beneficial to subjects with NAFLD. Bhat *et al.*[52] reported that regular aerobic exercise by inducing weight loss and increasing of insulin sensitivity result in improvement in ALT (alanine aminotransferase) and liver histology in NAFLD patients from North India[52]. Baba *et al.*[53] investigated 65 persons with NASH from North India and showed that moderate-intensity aerobic exercise improved ALT levels. Previously, we have carried out a six-month intervention study with cooking oil having high monounsaturated fatty acids (canola oil and olive oil) in 93 males with NAFLD, matched for age and BMI, with controls without NAFLD. Intervention led to significant improvements in grading of fatty liver, liver span, measures of insulin resistance and lipids (Table 2)[54].

Conclusion

In Asian Indians, NAFLD is driven by body composition conducive to development of insulin resistance, metabolic syndrome and diabetes, and fuelled by unhealthy lifestyle and genetic predisposition. Presence of NAFLD in Indians may predispose to CVD. Presence of NAFLD could be predicted by the use of simple parameters (Indian Fatty Liver Index). On the other hand, increased liver span (surrogate marker of fatty liver) also predicts diabetes in non-obese individuals. An individualized approach for the lifestyle management of NAFLD should be based on correct dietary choices, particularly edible oils high in mono-unsaturated fatty acids and enhanced physical activity in Asian Indians.

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