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Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome

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ABSTRACT

Aim: To estimate prevalence of non-alcoholic fatty liver disease (NAFLD) and its association with glucose intolerance (type 2 diabetes (DM), prediabetes) and metabolic syndrome (MS) in urban south Indians.

Methods: This study was carried out in 541 subjects (response rate 92%) of the original sample of 26,001 subjects in the Chennai Urban Rural Epidemiology Study maintaining the representativeness. Anthropometry and lipid estimations were done in all and oral glucose tolerance test in all, except self-reported diabetic subjects. NAFLD was diagnosed by ultrasonography and MS by modified Adult Treatment Panel III (ATP III) criteria. DM, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were defined using WHO consulting group criteria.

Results: Overall prevalence of NAFLD was 32% (173/541 subjects) (men: 35.1%, women: 29.1%, $p = 0.140$). Prevalence of most cardio-metabolic risk factors was significantly higher in NAFLD subjects. Prevalence of NAFLD (54.5%) was higher in subjects with DM compared to those with prediabetes (IGT or IFG) (33%), isolated IGT (32.4%), isolated IFG (27.3%) and normal glucose tolerance (NGT) (22.5%) (DM vs. prediabetes: $p < 0.05$, DM vs. NGT: $p < 0.001$, prediabetes vs. NGT: $p < 0.05$). Even after adjusting for age, gender and waist circumference, NAFLD was associated with diabetes (OR: 2.9, 95% C.I.: 1.9–4.6, $p < 0.001$) and MS (OR: 2.0, 95% C.I.: 1.3–3.1, $p < 0.001$).

Conclusion: NAFLD is present in a third of urban Asian Indians and its prevalence increases with increasing severity of glucose intolerance and in MS. This is the first population-based prevalence of NAFLD from south Asia which faces the brunt of the diabetes epidemic.

1. Introduction

Non-alcoholic steatohepatitis (NASH) is a type of metabolic liver disease in which fatty change (steatosis) is associated with lobular inflammation, hepatocytic injury and/or hepatic fibrosis and not etiologically associated with alcohol abuse. Non-alcoholic fatty liver disease (NAFLD) is a term used to describe the broader spectrum of the disease that extends

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from steatosis to ''cryptogenic cirrhosis'' [1–4]. The pathophysiological mechanisms underlying NAFLD are poorly understood although a close link with the 'metabolic syndrome' characterized by obesity, glucose intolerance, insulin resistance, hyperlipidemia and hypertension is well recognized [1–5]. Evaluation of liver histology by liver biopsy is undoubtedly the diagnostic test for fatty liver; however due to the attendant risks, expense and uncertain benefit to asymptomatic patients it is not applicable to population-based studies. Serum liver enzymes have been used in some studies although they are neither sensitive nor specific for NAFLD. Ultrasound of the liver although insensitive to pick up steatosis of less than 25–30%, is often used in epidemiological studies due its lower cost and lack of risk.

Although in the general population, the prevalence of NAFLD and NASH are approximately 20% and 3% respectively [6,7], in obese populations, NAFLD may be present in 75% of subjects [8]. Indeed, in the morbidly obese, steatosis (NAFLD) has been found in almost all subjects [9], with NASH being present in 25–70% of these individuals [9,10]. However, these studies were mainly done in western populations. South Asians (people belonging to India, Pakistan, Bangladesh, Nepal, Sri Lanka and Malaysia) in general and Asian Indians in particular, have very high rates of diabetes [11], insulin resistance [12,13] and premature CAD [14]. Moreover, a recent clinic-based study suggests differences in the clinicopathological profile of Indian patients with NAFLD [15]. Thus, the current study was undertaken to establish the prevalence of NAFLD in a representative sample of an urban south Indian population and study its association with glucose intolerance and metabolic syndrome, as there is no population-based data from south Asia on NAFLD.

2. Methodology

The Chennai Urban Rural Epidemiology Study (CURES) is a large cross-sectional study done on a representative population of metropolitan city of Chennai (formerly Madras) in southern India with a population of about 5 million people. The detailed study design of CURES is described elsewhere [16] and the sampling frame is shown in our website http://www.drmohansdiabetes.com/bio/WORLD/pages/pages/chennai.html. Briefly, of the 155 Corporation wards in Chennai, 46 wards were randomly selected across Chennai. Various phases of the study are described below. The institutional ethical committee approval was obtained and informed consent was obtained from all study subjects.

Phase 1 of CURES was conducted in the field, and involved a door-to-door survey of 26,001 individuals $\geq$20 years of age. A detailed questionnaire was administered to all study subjects to collect information regarding demographic, socio-economic, behavioral and health status. A fasting capillary blood sugar, blood pressure and basic anthropometric measures were done in all eligible individuals.

Phase 2 of CURES deals with studies of the prevalence of microvascular and macrovascular complications of diabetes among those identified with diabetes in Phase 1.

In Phase 3 of CURES, every 10th subject recruited in Phase 1 (n = 2600) was invited to our centre for detailed anthropometric measurements and biochemical tests. Of these, 2350 participated in the study (response rate: 90.4%).

In Phase 4 of CURES, every second subject recruited in Phase 3 (n = 1175) was invited to our centre for studies on cognitive function. This is an ongoing study. Phases 1–4 are not discussed further in this article.

This study involves Phase 5 of CURES, where every fourth subject recruited in Phase 3 (n = 588) was invited to our centre to undergo ultrasonography of the abdomen thus maintaining the representativeness of the original CURES sampling frame. Of these, 541 subjects participated in the present study (response rate: 92%).

All the study subjects underwent an oral glucose tolerance test (OGTT) using 75 g glucose load (except self-reported diabetic subjects, for whom fasting venous plasma sample was obtained) after ensuring 8 h of overnight fasting, for estimation of plasma glucose and serum lipids using a Hitachi 912 Autoanalyser (Mannheim, Germany) utilizing kits supplied by Roche Diagnostics GmbH (Mannheim, Germany). Glycated haemoglobin (HbA1c) was measured by the high performance liquid chromatography (HPLC) method using the Variant machine (BIORAD, Hercules, CA). Serum insulin concentration was estimated using Dako kits (Dako, Glostrup, Denmark). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and γ-glutamyltransferase (γGT) were estimated using a Hitachi 912 Autoanalyser (Mannheim, Germany) utilizing kits supplied by Roche Diagnostics GmbH (Mannheim, Germany) using International Federation of Clinical Chemistry (IFCC) standardized methods.

Insulin resistance was calculated using the homeostasis assessment (HOMA) model using the formula: fasting insulin (μIU/ml) $\times$ fasting glucose (mmol/l)/22.5. Subjects whose HOMA insulin resistance values were above the third quartile for the non-diabetic population (i.e. $>$2.58) were considered to have insulin resistance (HOMA-IR) [17].

Anthropometric measurements including weight, height, waist and hip measurements were obtained using standardized techniques [16].

3. Definitions

Body mass index (BMI) was calculated using the formula: weight (kg)/height (m)^2.

Waist circumference: Waist was measured using a non-stretchable fibre measuring tape. The subjects were asked to stand erect in a relaxed position with both feet together on a flat surface. Waist girth was measured as the smallest horizontal girth between the costal margins and the iliac crests at minimal respiration. Two measurements were made and the mean of the two was taken as the waist circumference.

Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mmHg using the mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 min apart and mean of the two was taken as blood pressure. If the difference between the first and the second reading was $>$6 mmHg for systolic and/or $>$4 mmHg for diastolic pressure, then a third measurement