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# Lipid and liver abnormalities in haemoglobin A1c-defined prediabetes and type 2 diabetes

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**Abstract** *Background and aims:* We aimed to investigate lipid abnormalities and liver steatosis in patients with HbA1c-defined prediabetes and type 2 diabetes compared to individuals with HbA1c-defined normoglycaemia.
*Methods and results:* Ninety-one subjects with prediabetes according to HbA1c, i.e. from 5.7 to 6.4% (39–46 mmol/mol), 50 newly diagnosed patients with HbA1c-defined type 2 diabetes (HbA1c ≥6.5% [≥48 mmol/mol]), and 67 controls with HbA1c lower than 5.7% (<39 mmol/mol), were studied. Fasting blood samples for lipid profiles, fatty liver index (FLI), bioimpedance analysis, ultrasound scan of the liver, and BARD (body mass index, aspartate aminotransferase/alanine aminotransferase ratio, diabetes) score for evaluation of liver fibrosis, were performed in all subjects. In comparison to controls, subjects with prediabetes were characterised by: lower apolipoprotein AI and HDL cholesterol levels, higher blood pressure, triglycerides levels and apolipoprotein B/apolipoprotein AI ratio, higher FLI, increased prevalence of and more severe hepatic steatosis, similar BARD score, and higher total body fat mass. In comparison to subjects with diabetes, subjects with prediabetes exhibited: similar blood pressure and apolipoprotein B/apolipoprotein AI ratio, similar FLI, reduced prevalence of and less severe hepatic steatosis, lower BARD score, increased percent fat and lower total body muscle mass. In comparison to controls, subjects with diabetes showed: lower apolipoprotein AI and HDL cholesterol levels, higher blood pressure and triglycerides levels, higher FLI, increased prevalence of and more severe hepatic steatosis, higher BARD score, and higher total body muscle mass. Moreover, HbA1c was correlated with BMI, HOMA-IR, triglycerides, HDL cholesterol, AST, and ALT.
*Conclusions:* Subjects with HbA1c-defined prediabetes and type 2 diabetes, respectively, are characterised by abnormalities in lipid profile and liver steatosis, thus exhibiting a severe risk profile for cardiovascular and liver diseases.


## Introduction

New recommendations for the use of glycated haemoglobin A1c (HbA1c) to diagnose prediabetes and type 2 diabetes say that subjects with HbA1c levels above 6.5% (48 mmol/mol) are classified as type 2 diabetes, and subjects with HbA1c levels of 5.7–6.4% (39–46 mmol/mol), are classified as having prediabetes [1]. Furthermore, prediabetes

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encompass subjects with a fasting blood sugar level from 5.6 to 6.9 mmol/L (impaired fasting glucose [IFG]) and/or a 2 h-blood sugar level from 7.8 to 11.0 mmol/L after 75 g-oral glucose tolerance test (OGTT) (impaired glucose tolerance [IGT]). In individuals with HbA1c-defined prediabetes, the risk of developing diabetes is more than ten times that of people with normal HbA1c levels [2]. The pathophysiology of prediabetes defined as IFG and IGT have been extensively characterised in regard to lipid and apolipoprotein changes [3]. In type 2 diabetes – defined from fasting plasma or post-OGTT glucose – abnormal lipid profile (i.e. elevated triglyceride and triglyceride-rich lipoproteins, decreased HDL cholesterol, and small dense LDL particles) and increased risk of cardiovascular diseases have been extensively described [4]. Among lipid parameters, the apolipoprotein B/apolipoprotein AI ratio has been shown to be a strong indicator of cardiovascular risk [5]. Moreover, non-alcoholic fatty liver disease (NAFLD) has been shown to be markedly increased in type 2 diabetes [6] – and to a lower extent in prediabetes [7] – diagnosed from plasma glucose measurements. NAFLD is promoted by overweight [6], dyslipidaemia [8], and diabetes [9], and is considered the hepatic expression of the metabolic dysfunctions induced by insulin resistance. The overall mortality in patients with NAFLD is significantly higher than the background population [10].

An important question is whether individuals with HbA1c-defined prediabetes and type 2 diabetes, respectively, have similar physiological deficiencies as those identified by fasting plasma glucose and/or post-OGTT plasma glucose measurements. Indeed, it is unknown whether the current recommendations for the management of prediabetes and type 2 diabetes (that rely on fasting or post-OGTT plasma glucose [11,12]) are effective when applied to individuals with HbA1c-defined prediabetes and type 2 diabetes, respectively [13]. Therefore, in the present study we aimed to evaluate whether lipid abnormalities and liver steatosis are present in HbA1c-defined prediabetes and type 2 diabetes, respectively.

## Methods

### *Study population*

A total of 208 Caucasian subjects volunteered for the study. They were recruited among patients attending our outpatient clinic for cardiovascular risk evaluation. None of them had lost weight or changed dietary habits during the three months preceding the study. Subject characteristics are shown in Table 1. Group 1 consisted of 67 subjects with normal HbA1c levels (lower than 5.7% [39 mmol/mol]). Nine subjects were receiving statin treatment (13%). Group 2 consisted of 91 subjects with prediabetes according to HbA1c (5.7–6.4% [39–46 mmol/mol]). Twelve subjects were receiving statin treatment (13%). Group 3 consisted of 50 patients with newly diagnosed type 2 diabetes (defined from HbA1c higher than 6.5% [48 mmol/mol]). Thirteen were receiving statin treatment (26%). Diabetic patients were, without any glucose-lowering medications and did not have diabetic retinopathy, nephropathy or neuropathy (as evaluated from normal ocular fundus examination, absence of microalbuminuria in a 24-h urine collection and normal reflex, light touch perception, superficial pain and vibration testing). None of the participants had anaemia or haemoglobinopathies, impaired renal function (normal plasma creatinine levels <130 μmol/l and no albuminuria), previous history of overt cardiovascular events, liver disease (viral hepatitis, hereditary haemochromatosis, autoimmune liver disease, alpha-1 trypsin deficiency, Wilson disease, drug induced liver injury were excluded on the basis of biochemical and immune-serological analyses), recent history of acute illness, and/or was treated within the last 3 months with pioglitazone, orlistat, insulin, any other drugs associated with hepatic steatosis (including glucocorticoids, tamoxifen, amiodarone or methotrexate). Weekly alcohol intake was <14 units for women and <21 units for men [14]. All subjects agreed to participate

**Table 1** Characteristics of the subjects.

| | Group 1: controls | Group 2: subjects with prediabetes | Group 3: patients with type 2 diabetes |
|---|---|---|---|
| *N* (F/M) | 67 (42/25) | 91 (45/46) | 50 (23/27) |
| Age (years) | 46.9 ± 1 | 46.7 ± 1 | 49.5 ± 0.9 |
| BMI (kg/m$^2$) | 29.7 ± 0.7 | 31.7 ± 0.7 | 32.5 ± 1.8 |
| HbA1c (%) | 5.3 ± 0.03 | 5.9 ± 0.02*[1] | 7.5 ± 0.2 *[1,2] |
| HbA1c (mmol/mol) | 34 | 41*[1] | 58*[1,2] |
| Systolic blood pressure (mmHg) | 117.4 ± 2.1 | 124.5 ± 1.5*[1] | 125 ± 2.3*[1] |
| Diastolic blood pressure (mmHg) | 71.6 ± 1.4 | 76.1 ± 1,2*[1] | 77 ± 1.7*[1] |
| Fasting glucose (mmol/l) | 4.8 ± 0.1 | 5.1 ± 0.1 | 6.8 ± 0.3*[1,2] |
| Fasting plasma insulin (pmol/l) | 52.1 ± 4.1 | 66 ± 3.5*[1] | 78.5 ± 10.4*[1] |
| Waist circumference (cm) | 99.3 ± 1.6 | 103.4 ± 1.3 | 104.1 ± 1.9 |
| Smoke (No/Yes) | 43/24 | 43/48*[1] | 19/31*[1] |
| HsCRP (mg/dl) | 0.2 ± 0.02 | 0.5 ± 0.1*[1] | 1.3 ± 0.6*[1] |
| HOMA-IR | 1.6 ± 0.1 | 2.2 ± 0.1*[1] | 3.3 ± 0.5*[1,2] |

Group 1, controls with normal glycated haemoglobin A1c (HbA1c) levels (<5.7% [39 mmol/mol]); group 2, subjects with HbA1c-defined prediabetes (5.7–6.4% [39–46 mmol/mol]); group 3, patients with HbA1c-defined type 2 diabetes (≥6.5% [48 mmol/mol]). Data are means ± SE. HsCRP, high-sensitive C reactive protein. *Significant differences between the groups using one-way ANOVA (followed by the number of the group compared with).