

Fatty Liver Linked to Reduced Frequency of Ocular Complications in T2DM

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Abstract

Purpose: Non-alcoholic fatty liver (NAFL) is comorbid to obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM). It is unclear whether NAFLD constitutes a direct risk factor for macrovascular disease in T2DM. This study aimed at revisiting the cardiometabolic traits linked to NAFL and micro-/macrovascular complications in a biethnic Caucasian and African cohort. **Methods:** Cross-sectional analysis of 568 of T2DM patients (515 Caucasians; 53 Africans) in whom the presence of NAFL was identified by ultrasonography and the cardiometabolic phenotype was exhaustively characterized, including carbohydrate homeostasis, comprehensive lipidogram including Lp(a), cumulative exposure to hyperglycemia, and prevalent micro/macrovascular complications. **Results:** FL was present in 73% of Caucasians and 36% of Africans ($p < 0.0001$). FL+ were more obese, more atherogenic dyslipidemic (Caucasians) and had lower lipoprotein(a) (Africans). All-cause macroangiopathy, ischemic heart disease or stroke did not significantly differ between FL+ and FL- in both groups. A marked reduction in diabetic retinopathy (DR), ocular hypertension and cataracts were found in FL+ of the two ethnicities. In FL+ Caucasians, relative risk of DR was -38%, cataracts -35%, and ocular hypertension -42%. In FL+ Africans, risk of overall microangiopathy was -66% and that of DR -86%. **Conclusions:** An inverse association was observed between NAFL and the presence of diabetic retinopathy, cataract and ocular hypertension. The ophthalmoprotection conferred by liver steatosis was found in Caucasians and

Africans. Among the latter, hepatic steatosis was linked to lower lipoprotein(a) levels. There was no association between hepatic steatosis and prevalent macrovascular complications in neither of the two ethnic groups.

Keywords

Fatty Liver, Type 2 Diabetes, Microangiopathy, Retinopathy, Coronary Artery Disease, Lipoprotein(a)

1. Introduction

Non-alcoholic fatty liver (NAFL) is often comorbid to obesity, metabolic syndrome (MetS) and type 2 diabetes (T2DM). Regardless of glucose homeostasis, NAFL can develop into liver disease (NAFLD), *i.e.* non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, liver failure and hepatocarcinoma. Epidemiologically, NAFL (D) is linked to unhealthy lifestyles and adverse cardiometabolic or cardiovascular (CV) phenotypes, and the presence of FL is predictive of incident CV diseases (CVD). While it is not clear whether NAFLD represents a direct risk factor in the development of macrovascular disease, suggested mechanisms include atherogenic dyslipidemia (AD), insulin resistance (IR), hepatokine and adipokine imbalance, systemic inflammation, hypercoagulation, hypofibrinolysis, and endothelial dysfunction [1] [2] [3] [4].

The link between NAFLD and the joint presence of organ-specific complications is poorly established in T2DM, particularly in terms of microvascular disease. This is compounded by the fact that, as for macrovascular disease, there are many confounding factors associated with diabetic microangiopathy and/or poor glycemic control, including as AD and other MetS components. Besides, considerable ethnic variations exist as regards NAFL prevalence or triglycerides (TG) and TG-rich lipoproteins (TRLs) metabolism, particularly among sub-Saharan Black africans [5]-[10].

We recently performed systematic non-invasive ultrasound research of NAFL for routine characterization of CV risk among outpatient diabetics, to revisit the cardiometabolic traits linked to NAFL and micro-/macrovascular complications. To detect a possible effect of ethno-geographic origin on these interactions, we analyzed a biethnic diabetic cohort composed of Caucasians and sub-Saharan Africans, the latter either 1st generation migrants or expatriates living in Europe, for whom there is little or no relevant metabolic data on NAFL.

2. Patients & Methods

This was a cross-sectional analysis of 578 medical records of T2DM outpatients (Caucasians (n = 525) and sub-Saharan Africans (n = 53)) followed at an academic centre in Brussels. In all patients, a fatty liver screening was performed by ultrasound. A default diagnosis of simple uncomplicated liver steatosis (NAFL)

was made in the presence of ultrasonographic hyper-reflectivity of the hepatic parenchyma (relative to the renal parenchyma), in the absence of dedicated etiologies of hepatic steatosis, such as excessive ethanol consumption and secondary causes of NAFL(D), the latter including inherited disorders of lipid metabolism; glycogen storage diseases; lipodystrophies; drugs (amiodarone; methotrexate; tamoxifen; nontopical corticosteroids; antiretrovirals); hepatitis C infection; celiac disease; Wilson's disease; surgical weight loss [11]. Patients with clinical, radiological or biopsy-proven evidence of liver cirrhosis were excluded, as were those treated with drugs that could affect insulin sensitivity (IS) or β -cell function, other than glucose-lowering drugs (e.g. corticosteroids, antiretrovirals, immune-modulators, anti-psychotics). Patients with chronic inflammatory or infectious diseases, ongoing infections and/or other acute conditions, cancer or major respiratory or cardiac failure were also excluded.

The following variables were recorded: age; gender; diabetes duration; education, as proxy for socio-economic status (dichotomized as lower vs. higher); smoking; ethanol intake; physical activity; weight; height; neck and waist circumference; body mass index (BMI); blood pressure (BP); fat mass, visceral fat and skeletal muscle mass (Omron BF 500, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands). First-degree familial histories for T2DM and/or early-onset coronary heart disease (EOCHD) were also recorded. Hypertension was defined as systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg, and/or ongoing antihypertensive medication(s). Current therapies were recorded, including glucose-lowering drugs, BP-lowering therapies, and lipid-modifying drugs (LMDs: statins; fibrates and/or ezetimibe) and aspirin.

Methods used to define MetS, sleep apnoea, atherogenic dyslipidemia (AD), microangiopathies (diabetic retinopathy (DR); diabetic polyneuropathy (DPN)), and macrovascular complications (coronary artery disease (CAD); cerebrovascular disease [transient ischemic attack (TIA) and/or stroke]; peripheral artery disease (PAD)) were previously described [12] [13] [14] [15] [16]. Briefly, CAD was diagnosed from medical history (myocardial infarction, angioplasty, stenting, revascularization surgery and/or significant coronary stenosis confirmed by angiography), and review of all procedures, and/or screening (exercise testing; echocardiography; magnetic resonance imaging; or other subclinical disease imaging techniques). Cerebrovascular disease was defined as a history of stroke (any neurological deficit ≥ 1 month, without distinction between ischemic, embolic and haemorrhagic events) and/or TIA. PAD was defined by a medical history of lower-limb(s) claudication and/or clinical or imaging evidence for ischemic diabetic foot, angioplasty, stenting, re-vascularization surgery and/or lower-limb artery stenosis at Doppler ultrasonography and/or angiography. The presence of a DR was established from retinal examination by an experienced ophthalmologist and/or fluorescein angiography. The presence of a DPN was diagnosed by clinical examination (knee and ankle reflexes; Semmes-Weinstein plantar and toe monofilament test) and confirmed by lower-limbs electromyography. The

presence of cataracts and glaucoma was also noted. Microalbuminuria was considered for a urine albumin (mg/dL)/creatinine (g/dL) ratio > 30 mg/g. Self-reported prevalence/severity of masculine erectile dysfunction were identified using the 5-items International Index of Erectile Function (IIEF-5) questionnaire.

Fasting lipids and lipoproteins (total cholesterol (C), HDL-C, triglycerides (TG); LDL-C (calculated using Friedewald's formula), non-HDL-C, lipoprotein(a), apolipoproteins A-I and B100 were analysed by routine methods. HbA1c, fasting glucose, insulinemia, CRP, ferritin, sex hormone-binding globulin (SHBG), and liver enzymes aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transferase were determined by routine methods. The aspartate aminotransferase-to-platelet ratio index (APRI) was also calculated, as was the hyperglycemia index (%.year-1), the product of the difference between the annualized HbA1c of patients and the upper limit of normal for HbA1c (6%) and diabetes duration.

β -cell function and insulin sensitivity (IS) were assessed with HOMA-2 modelling. Values of insulin secretion ([B]; normal 100%) were plotted as a function of IS ([S]; normal 100%), defining a hyperbolic product [BxS] (unit: %²; normal: 100%, corresponding to 104 %²), representing residual β -cell function. Secular loss of hyperbolic product ([BxS] loss rate; %.year-1) was obtained by dividing (100%-[BxS]) by patient's age [17] [18] [19] [20].

Each patient gave informed consent, and the study was performed in agreement with the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the Biomedical Hospital-Faculty Ethics Committee of the Catholic University of Louvain (Brussels) B403-2017-16NOV-521. Results are presented as means (\pm 1 standard deviation; SD) or proportions (%). The significance of differences between means was assessed using Student's t test, or Welch's test for data sets with significant differences in SDs, and using Fisher's Exact test for differences in proportions. Results were considered statistically significant or non-significant (NS) for $p < 0.05$ or $p \geq 0.05$, respectively.

3. Results

3.1. Characteristics of the Study Population

Ten patients, all among Caucasians, with NASH diagnosed on the basis of hepatic biopsy and/or pathological fibroscan were excluded from further analysis. NAFL was present in 69% of the remaining patients ($n = 393$). NAFL prevalence was significantly different between Caucasians and Africans, with 73% frequency among Caucasians vs. 36% among Africans ($p < 0.0001$). For all patients ($n = 568$), average age was 70 (12) years; duration of diabetes was 19 (10) years; and gender distribution was predominantly male at 63%. Lower and higher education levels were equally distributed, as was smoking history. Most patients were hypertensive and sedentary. Four-fifths received LMDs, mostly statins (Table 1). A majority of patients had sarcopenic obesity, enlarged waist, IR and a MetS.

Table 1. Patients' characteristics.

		all patients	FL[-] Caucasian	FL[+] Caucasian	P1	FL[-] African	FL[+] African	P2
n		568	141	374	~	34	19	~
age	years	70 (12)	73 (13)	70 (11)	0.0158	62 (16)	59 (12)	NS
diabetes duration	years	19 (10)	20 (10)	19 (9)	NS	20 (12)	14 (6)	0.0190
family history T2DM	%	48	47	48	NS	45	47	NS
family history EOCHD	%	13	14	13	NS	4	6	NS
male - female	%	63 - 37	62 - 38	64 - 36	NS	53 - 47	53 - 47	NS
education*	%	50 - 50	49 - 51	51 - 49	NS	52 - 48	35 - 65	NS
smoking**	%	50 - 50	56 - 44	44 - 56	0.0176	81 - 19	79 - 21	NS
ethanol	U-week ⁻¹	8 (11)	7 (10)	8 (12)	NS	6 (10)	7 (10)	NS
sedentarity	%	62	53	68	0.0020	59	26	NS
physical activity	min-week ⁻¹	58 (111)	74 (125)	47 (99)	0.0221	59 (104)	141 (181)	NS
hypertension	%	89	86	91	NS	85	74	NS
systolic blood pressure	mm Hg	138 (19)	140 (20)	138 (19)	NS	135 (15)	132 (16)	NS
anti-dyslipidemic drug(s)	%	79	75	84	0.0206	53	44	NS
statin - fibrate - ezetimibe	%	70 - 21 - 13	68 - 17 - 17	74 - 26 - 11	NS	50 - 3 - 15	44 - 0 - 6	NS
eGFR	mL·min ⁻¹ . 1.73 m ²	74 (28)	70 (26)	74 (27)	NS	85 (37)	98 (25)	NS

Results are expressed as means (1 SD) or proportions (%) for all patients and according to the presence (FL[+]) or absence (FL[-]) of fatty liver at ultrasonography in patients of Caucasian or African ancestry. *: lower vs. higher; **: never vs. former + current smoking; eGFR: estimated glomerular filtration rate; EOCHD: early-onset coronary heart disease; T2DM: type 2 diabetes mellitus; NS: not significant. P1 and P2 correspond to the statistical significance of the differences between the FL[-] and FL[+] subgroups among Caucasians and Africans, respectively.

One in six patients was diagnosed with sleep apnea. Glycaemic control was, on average, suboptimal with HbA1c 7.5 (1.4) %. A majority of patients were treated with metformin and/or insulin (**Table 2**). Average values of hepatic enzymology were normal, as was mean APRI. Nearly half of patients had AD, the combination of lowHDL-C and high TG, and its prevalence was 52% among Caucasians compared to 21% among Africans, ie a 60% reduction of AD frequency among the latter ($p < 0.0001$) (**Table 3**). Regarding target organ damage, nearly half of patients had microvascular disease from all types, one-third had cataracts, and 13% had ocular hypertonia. Microalbuminuria or proteinuria was present in one-third of patients. More than half of men had erectile dysfunction. Macroangiopathy of all types was found in 37% of patients, including 27% CAD (**Table 4**).

3.2. Caucasians with and without FL

FL[+] were on average 3 years younger than FL[-] patients. They were more likely to be smokers and sedentary, and were more likely to be treated with LMDs. In patients of both groupes on fibrates, the drug was prescribed for atherogenic dyslipidemia, not as a secondary prevention of retinopathy. FL[-] and FL[+] did not differ in terms of family histories, gender distribution, education, alcohol consumption, prevalence of hypertension, and glomerular filtration (**Table 1**).

Table 2. Cardiometabolic characteristics.

		all patients	FL[-] Caucasian	FL[+] Caucasian	P1	FL[-] African	FL[+] African	P2
<i>n</i>		568	141	374	~	34	19	~
body mass index	kg·m ⁻²	29.1 (5.7)	26.1 (5.1)	30.4 (5.6)	<0.0001	26.7 (3.6)	29.6 (4.5)	0.0220
skeletal muscle mass	%	30.5 (4.6)	31.6 (4.9)	30.2 (4.4)	0.0033	30.3 (5.4)	29.5 (5.7)	NS
fat mass	%	32 (9)	29 (9)	33 (9)	<0.0001	32 (10)	34 (10)	NS
visceral fat	0 - 30	13 (5)	11 (5)	14 (4)	<0.0001	11 (3)	11 (4)	NS
waist circumference	cm	104 (14)	97 (14)	107 (13)	<0.0001	93 (10)	101 (11)	0.0130
waist height⁻¹		0.61 (0.08)	0.57 (0.08)	0.63 (0.08)	<0.0001	0.55 (0.06)	0.59 (0.05)	0.0129
neck circumference	cm	40 (4)	38 (4)	41 (3)	<0.0001	38 (3)	39 (3)	NS
sleep apnoea syndrome	%	17	9	22	0.0002	3	6	NS
metabolic syndrome	%	86	70	94	<0.0001	71	74	NS
	score 0 - 5	3.8 (1.1)	3.3 (1.2)	4.1 (1.0)	<0.0001	3.0 (1.0)	3.4 (1.3)	NS
insulin sensitivity	%	51 (37)	74 (48)	41 (27)	<0.0001	71 (45)	43 (17)	0.0022
fasting insulinaemia	pmol·L ⁻¹	123 (84)	87 (66)	139 (89)	<0.0001	93 (61)	124 (52)	NS
hyperbolic product [B × S]	%	27 (18)	32 (20)	24 (15)	<0.0001	40 (26)	39 (19)	NS
[B × S] loss rate	%·year ⁻¹	1.31 (0.50)	1.21 (0.52)	1.37 (0.47)	0.0016	1.19 (0.52)	1.33 (0.61)	NS
HbA_{1c}	%	7.5 (1.4)	7.5 (1.4)	7.6 (1.4)	NS	7.5 (2.0)	7.0 (1.4)	NS
hyperglycemia index	%·year ⁻¹	29 (36)	28 (42)	31 (33)	NS	30 (37)	12 (17)	0.0194
metformin	%	66	55	71	0.0008	61	79	NS
BCS - IBT - SGLT2-i	%	44 - 14 - 5	39 - 14 - 1	47 - 14 - 7	NS - NS - 0.0091	42 - 12 - 0	14 - 7 - 0	NS
insulin	%	52	51	54	NS	36	29	NS
	IU·day ⁻¹	68 (57)	49 (29)	78 (64)	<0.0001	41 (24)	47 (30)	NS

Results are expressed as means (1 SD) or proportions (%) for all patients and according to the presence (FL[+]) or absence (FL[-]) of fatty liver at ultrasonography in patients of Caucasian or African ancestry. BCS: beta-cell stimulant; HbA_{1c}: glycated hemoglobin A1c; IBT: incretin-based therapies; SGLT2-i: sodium-glucose transporter type 2 inhibitors; NS: not significant. P1 and P2 correspond to the statistical significance of the differences between the FL[-] and FL[+] subgroups among Caucasians and Africans, respectively.

Table 3. Laboratory values.

		all patients	FL[-] Caucasian	FL[+] Caucasian	P1	FL[-] African	FL[+] African	P2
<i>n</i>		568	141	374	~	34	19	~
total cholesterol (C)	mg·dL ⁻¹	162 (40)	162 (38)	160 (42)	NS	177 (33)	185 (39)	NS
non-HDL-C	mg·dL ⁻¹	115 (39)	111 (34)	115 (41)	NS	116 (38)	127 (37)	NS
LDL-C	mg·dL ⁻¹	84 (34)	86 (32)	81 (34)	NS	97 (34)	104 (35)	NS
lipoprotein(a)	nmol·L ⁻¹	59 (80)	54 (64)	53 (81)	NS	141 (101)	90 (49)	0.0170
apoB₁₀₀	mg·dL ⁻¹	89 (25)	86 (22)	89 (27)	NS	90 (22)	101 (23)	NS
LDL-C. apoB₁₀₀⁻¹		0.94 (0.26)	1.00 (0.27)	0.90 (0.25)	0.0002	1.07 (0.20)	1.01 (0.17)	NS
HDL-C	mg·dL ⁻¹	47 (16)	51 (19)	44 (14)	<0.0001	60 (18)	58 (21)	NS

Continued

apoA-I	mg·dL ⁻¹	144 (29)	150 (32)	141 (27)	0.0034	159 (24)	159 (46)	NS
triglycerides	mg·dL ⁻¹	163 (130)	129 (68)	184 (149)	<0.0001	91 (44)	116 (52)	NS
atherogenic dyslipidemia	%	49	35	59	<0.0001	15	32	NS
log(TG).HDL-C⁻¹		0.054 (0.053)	0.048 (0.028)	0.059 (0.062)	0.0059	0.035 (0.013)	0.040 (0.015)	NS
CRP	mg·dL ⁻¹	0.35 (0.46)	0.28 (0.37)	0.38 (0.50)	0.0140	0.29 (0.30)	0.39 (0.54)	NS
ferritin	µg·L ⁻¹	157 (163)	130 (171)	168 (163)	0.0236	149 (144)	150 (117)	NS
SHBG	nmol·L ⁻¹	41 (30)	47 (30)	36 (25)	0.0001	63 (67)	48 (29)	NS
AST	IU·L ⁻¹	26 (15)	22 (8)	28 (17)	<0.0001	23 (12)	28 (19)	NS
ALT	IU·L ⁻¹	31 (24)	23 (11)	34 (28)	<0.0001	24 (16)	31 (22)	NS
GGT	IU·L ⁻¹	47 (60)	37 (45)	51 (67)	0.0067	37 (26)	55 (59)	NS
APRI	IU·L ⁻¹ · 10 ⁹⁻¹	0.23 (0.20)	0.19 (0.12)	0.25 (0.22)	<0.0001	0.22 (0.10)	0.30 (0.38)	NS

Results are expressed as means (1 SD) or proportions (%) for all patients and according to the presence (FL[+]) or absence (FL[-]) of fatty liver at ultrasonography in patients of Caucasian or African ancestry. ALT: alanine aminotransferase; apo: apolipoprotein; APRI: AST to platelet ratio index; AST: aspartate aminotransferase; CRP: C-reactive protein; GGT: gamma-glutamyl transpeptidase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; SHBG: sex hormone-binding globulin; NS: not significant. P1 and P2 correspond to the statistical significance of the differences between the FL[-] and FL[+] subgroups among Caucasians and Africans, respectively.

Table 4. Target organ damage.

		all patients	FL[-] Caucasian	FL[+] Caucasian	P1	FL[-] African	FL[+] African	P2
n		568	141	374	~	34	19	~
microangiopathy	%	46	50	46	NS	50	17	0.0185
retinopathy	%	24	32	20	0.0048	42	6	0.0093
polyneuropathy	%	26	29	25	NS	28	17	NS
cataract	%	30	40	26	0.0024	47	22	NS
glaucoma	%	13	19	11	0.0403	13	0	NS
albuminuria	mg·g creatinine ⁻¹	132 (436)	165 (549)	127 (414)	NS	121 (192)	9 (8)	0.0018
(micro) albuminuria	%	32	33	34	NS	34	0	0.0023
erectile dysfunction	%	55	59	55	NS	44	33	NS
IIEF5 score	1 - 25	13 (8)	11 (8)	13 (8)	0.0456	17 (7)	22 (2)	0.0100
macroangiopathy	%	37	40	39	NS	18	11	NS
coronary artery disease	%	27	30	28	NS	9	6	NS
cerebrovascular disease	%	9	11	9	NS	3	6	NS
peripheral artery disease	%	11	13	10	NS	9	0	NS

Results are expressed as means (1 SD) or proportions (%) for all patients and according to the presence (FL[+]) or absence (FL[-]) of fatty liver at ultrasonography in patients of Caucasian or African ancestry. IIEF5: 5-item version of the International Index of Erectile Function questionnaire; NS: not significant. P1 and P2 correspond to the statistical significance of the differences between the FL[-] and FL[+] subgroups among Caucasians and Africans, respectively.

All the anthropophysical and metabolic parameters studied differed considerably and significantly between groups, FL[+] being larger, fatter, more centrally obese and less muscular, and more often suffering from MetS and sleep apnea than FL[-]. FL[+] were significantly more resistant to insulin (+80%). Their fasting insulinemia was increased (+60%), and their residual insulin secretion, estimated by the [BxS] product, was reduced by 25%, with higher annual loss rate of the latter (+13%). FL[+] were more often treated with metformin or SGLT2-i, and their daily insulin doses were higher (+59%). The two groups did not differ in terms of HbA1c and in lifetime glucose exposure, estimated by the hyperglycaemia index (**Table 2**).

Total cholesterol, non-HDL-C, LDL-C, lipoprotein(a) and apoB100 did not differ between FL[-] and FL[+]. On the other hand, all lipid parameters related to AD were significantly different between FL[-] and FL[+], the latter also showing smaller and denser LDLs, as shown by a decreased LDL-C to apoB100 ratio. FL[+] also had increased CRP, ferritin, AST, ALT, GGT, and APRI levels, and decreased SHBG (**Table 3**).

In terms of vascular and avascular complications, FL[+] had markedly and significantly lower rates of DR (-38%) and cataracts (-35%), as well as ocular hypertension (-42%). There was no significant difference between FL[+] and FL[-] regarding albuminuria, whereas erectile dysfunction (ED) was slightly less prevalent, but not significantly so in FL[+], whose mean IIEF5 score was 2 units higher (+18%). However, there was no difference in frequency of macrovascular complications between groups, regarding all-type macroangiopathy or site-specific damage to coronary, cerebrovascular or peripheral vessels (**Table 4**). This lack of difference in macrovascular complications based on FL persisted after adjusting the two groups for age and gender, with all-type macroangiopathy at 39% in FL[-] and 41% in FL[+] (not shown).

Since AD and FL are overlapping comorbidities, we analyzed whether their combined occurrence alters the prevalence of DR. Caucasians were distributed as follows: 42% FL[+] & AD[+]; 30% FL[+] & AD[-]; 18% FL[-] & AD[-]; and 10% FL[-] & AD[+], with DR prevalence of 21%; 17%; 27%; and 42%, respectively. All-type macroangiopathy was 43% in FL[+] & AD[+]; 32% in FL[+] & AD[-]; 37% in FL[-] & AD[-]; and 46% in FL[-] & AD[+]. The presence of AD increased the relative risk of macroangiopathy among FL[+] by 34% (p 0.0308), whereas AD did not modulate macroangiopathy among FL[-] (data not shown).

3.3. Africans with and without FL

African were about 10 years younger than Caucasians and, as for the latter, FL[+] were younger than FL[-]. On the other hand, diabetes duration was much shorter in FL[+], by an average of 6 years compared with FL[-]. All other variables (socio-demographics, BP, LMDs and eGFR) did not differ between FL[-] and FL[+] (**Table 1**). FL[+] had higher BMI, waist circumference and waist/height ratio. Their insulin sensitivity and hyperglycemia index were lower by 39% and 60%, respectively (**Table 2**). AD prevalence was non-significantly higher (by 213%)

among FL[+]. None of the other variables concerning lipids and lipoproteins differed among Africans with or without FL, but for lipoprotein(a), the level of which was much lower among FL[+] ($-36 \text{ nmol}\cdot\text{L}^{-1}$; **Table 3**).

As regards vascular and avascular complications, FL[+] had much lower rates of overall microangiopathy (-66%) and DR (-86%). There was no significant difference between groups regarding ocular hypertony and erectile dysfunction frequency, although as for Caucasians, FL[+] had better IIEF5 score ($+29\%$). FL[+] also showed much lower rates/level values of albuminuria. By contrast, there were no significant differences between FL[-] and FL[+] in overall macroangiopathy and damage to coronary, cerebrovascular or peripheral vessels (**Table 4**).

4. Discussion

This study conducted in a bi-ethnic population with T2DM revealed three highlights. First, there was no difference in prevalence of macrovascular disease between patients with and without FL in either ethnic group. Second, Lp(a) levels were markedly lower among steatotic Africans. Third, there was a marked reduction in prevalence of retinopathy, cataracts and ocular hypertonia in diabetics with steatosis, a lowering found in both ethnicities.

Our characterization of steatotic Caucasians found a series of features which were expected based on published data, including physical inactivity, increased BMI, body fat, central adiposity, and sarcopenia [1] [2] [3] [4]. Caucasians with FL also had reduced insulin sensitivity, less residual insulin secretion, and more B-cell function loss. On the other hand, the prevalence of NAFL in sub-Saharan Africans is barely documented, even less so in diabetics. While data exist from across the Atlantic on African-Americans or Afro-Caribbean people, these minorities do have a certain degree of European, Indian or Latino crossbreeding that can modulate their metabolic features [5]-[10]. The present study, albeit numerically modest, is the first to document in depth the steatotic phenotype of 1st generation African migrants with diabetes.

An increased frequency of macroangiopathies was intuitively expected in steatotic patients, due to many overlaying CV risk factors, such as sedentary, smoking, raised BMI, waist circumference, central adiposity, AD, and subclinical inflammation. It is questionable whether these risk factors are as harmful in case of FL as they are in its absence, or whether the presence of simple steatosis mitigates, through unknown mechanisms, the deleterious exposure to these risk factors. It is not excluded that the longitudinal association observed between NAFL and incident macrovascular disease is more a result of overlapping epidemiological traits than a direct pathological link.

Our data clearly show a marked reduction in prevalence of retinopathy associated with the presence of FL never before described for Caucasians and Africans. This under-prevalence was occasionally noted in Asians, whereas an over-prevalence of retinopathy was reported by Targher *et al.* in Italians [21] [22] [23] [24]. Our data are the first to document an FL-related ophthalmoprotection in

Caucasians and Africans, prevailing beyond the retinal vessels since ocular hypertension and cataracts were also reduced. These two avascular eye disorders are not de facto caused by hyperglycemia, and such multiple organ protection ought to be studied prospectively in different ethnic groups [25]. While lifetime glycaemic exposure could be evoked to account for the lower prevalence of retinopathy among steatotic Africans, whose hyperglycemia index was much lower due to better glycaemic control and a shorter diabetes duration, this was not the case among Caucasians, in whom the 38% reduction in retinopathy related to FL cannot be ascribed to lesser hyperglycemia.

FL-related differences between ethnic groups were most evident at the lipid level, with a strong association between FL and AD among Caucasians, in whom AD prevalence and lipid indices point to more TRLs, small-dense LDLs, and reduced HDLs. These was not the case among steatotic Africans. Although they had more AD, FL+ Africans had still a lower AD prevalence than Caucasians without FL, confirming the marked ethnic dimorphism of TG handling among sub-Saharan Africans [6].

AD is epidemiologically associated with the presence of FL and micro-angiopathy, including DR, and causally associated with macroangiopathy [26] [27]. It would therefore be expected that the combined presence of AD and FL further increases vascular risk. This was indeed the case for all-cause macro-angiopathy. However, the opposite was observed for microangiopathy, with the lowest prevalence of DR observed in FL[+] & AD[+] patients, whereas the highest DR rate was observed in FL[-] & AD[+], twice as high as that of FL[+] & AD[+] patients (p 0.0033; not shown). This shows that AD has a permissive effect on the development of retinal microangiopathy only in the absence of FL. By contrast, FL was associated with a significantly reduced prevalence of DR, regardless of the presence of AD. Due to the low prevalence of both FL and AD in sub-Saharan patients and limited number of patients, it was not feasible to analyze their combined effects in this study.

The presence of FL did not influence Lp(a) levels in Caucasians. While it was expected that Lp(a) would be higher among Africans, a known racial difference, our data show a new and previously unreported feature of this lipoprotein, namely an ethnic dimorphism as a function of FL. Thus, the latter was associated with lower Lp(a) among Blacks but not among Caucasians. One could suggest a possible link between lower Lp(a) level observed in steatotic Africans and reduced frequency of all-type microangiopathy and retinopathy. However, this was not observed among steatotic Caucasians, in whom we previously reported that lower Lp(a) was associated with increased prevalence of microvascular damage [14].

To explain the paradox of ophthalmoprotection related to FL, various hypotheses can be put forward. The least plausible is that having retinopathy would prevent the development of hepatic steatosis. There is nothing in the accepted pathophysiology of DR and FL to substantiate such assumption [28] [29]. Inversely, certain mechanisms promoting hepatic steatosis may be retinoprotective.

The retina is an extension of the brain with a distinct metabolism of cholesterol and lipoproteins. Liver X receptor (LXR) signalling pathways could be involved in such a candidate process. In diabetes, decreased LXR and sirtuin-1 (an LXR agonist) could promote retinopathy while protecting against the development of liver steatosis. Conversely, endogenous or pharmacological activation of LXRs could exert a retinoprotective effect while promoting hepatic steatogenesis [30] [31] [32] [33].

This study has the limitations inherent to its cross-sectional design and small sample size, especially of Africans. This did not allow statistical thresholds to be reached for some differences that were otherwise evident among steatotic Africans. Given the small number of Africans, our results should be interpreted in an exploratory way, pending external confirmation. Patients were dichotomized based on a single ultrasound assessment of steatosis, and we could not distinguish, in the absence of liver biopsy or non-invasive fibrosis tests, patients with simple steatosis from those with frank NAFLD. We excluded cirrhotic patients and those with biopsy-proven NASH and/or overtly pathological fibroses, but we cannot rule out that some patients had steatohepatitis, liver fibrosis, or incipient cirrhosis. However, APRI values show that the vast majority of patients had basic uncomplicated NAFL. One strength of the study is that it used an index of cumulative glucose exposure to better understand the relative microangiopathic risk of the two ethnicities, whose carbohydrate and lipid homeostases determinants are known as distinct.

5. Conclusion

In conclusion, our bi-ethnic analysis of T2DM patients did not show a connection between hepatic steatosis and macrovascular complications. Hepatic steatosis was linked to lower lipoprotein(a) levels only among Africans. In a serendipitous manner, an inverse and unexpected association was observed between diabetic retinopathy and two avascular eye complications, on the one hand, and the presence of hepatic steatosis, on the other hand. The ophthalmoprotection conferred by liver steatosis was found in Caucasians and Africans.

Authors' Contributions

All authors contributed equally to the manuscript; all authors read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

The study protocol was approved by the Biomedical Hospital-Faculty Ethics Committee of the Catholic University of Louvain (Brussels) B403-2017-16NOV-521.

Availability of Data & Material

Data are available at the Division of Endocrinology & Nutrition, Cliniques universitaires St-Luc and the Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain, Brussels (Belgium) (person of contact: Prof. MP Hermans).

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Abbreviations

AD: atherogenic dyslipidemia
Apo: apolipoprotein
APRI: aspartate aminotransferase-to-platelet ratio index
[B × S]: hyperbolic product between β -cell function and IS
BMI: body mass index
BP: blood pressure
CHD: coronary heart disease
CV: cardiovascular
CVD: cardiovascular disease
CRP: C-reactive protein
DM: diabetes mellitus
eGFR: estimated glomerular filtration rate
EOCHD: early-onset CHD
FL: fatty liver
HbA1c: glycated haemoglobin
HDL: high-density lipoprotein
HDL-C: high-density lipoprotein cholesterol
HOMA: homeostasis model assessment
IBT: incretin-based therapies
IIEF5: 5-items International Index of Erectile Function
IS: insulin sensitivity
LDL: low-density lipoprotein
LDL-C: low-density lipoprotein cholesterol
LMD: lipid-modifying drug
MetS: metabolic syndrome
NAFL: non-alcoholic fatty liver
NAFLD: non-alcoholic fatty liver disease
non-HDL-C: non-high-density lipoprotein cholesterol
NS: non-significant
SD: standard deviation
T2DM: type 2 diabetes mellitus
TG: triglycerides (triacylglycerols)
SHBG: sex hormone-binding globulin