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MAFLD and glomerular hyperfiltration in subjects with prediabetes, visceral obesity and "preserved" kidney function: A cross-sectional study

Aneliya Parvanova [a,1], Manuela Abbate [b,c,d,e,1], Aina Maria Yañez [b,c,e], Miquel Bennasar-Veny [b,c,e,f], Ángel Arturo López-González [g,h], José Ignacio Ramírez-Manent [h,i,j], Ilian Petrov Iliev [k], Sergio Fresneda [b,c,e], Maria Arias-Fernandez [b,c,e], Giuseppe Remuzzi [a], Piero Ruggenenti [a,l]

[a] Department of Renal Medicine, Clinical Research Centre for Rare Diseases "Aldo e Cele Daccò": Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 24020, Ranica, Bergamo, Italy
[b] Research Group on Global Health, University of the Balearic Islands, 07122 Palma, Spain
[c] Research Group on Evidence, Lifestyles and Health Research, Health Research Institute of the Balearic Islands (IdISBa), 07120 Palma, Spain
[d] ADEMA University School, 07009 Palma, Spain
[e] Nursing and Physiotherapy Department, University of the Balearic Islands, 07122 Palma, Spain
[f] CIBER de Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain
[g] Prevention of Occupational Risks in Health Services, Balearic Islands Health Service, 07003 Palma, Spain
[h] ADEMA-HEALTH Group IUNICS, University of the Balearic Islands, 07122 Palma, Spain
[i] Faculty of Medicine, University of the Balearic Islands, 07122 Palma, Spain
[j] Health Research Institute of the Balearic Islands (IdISBa) Foundation, 07120 Palma, Spain
[k] Vaccination Center, Bolognini Hospital of Seriate - ASST Bergamo Est, Italy
[l] Unit of Nephrology and Dialysis, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

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ABSTRACT

Aims: To investigate the prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) in prediabetes, visceral obesity, and preserved kidney function, and explore whether MAFLD is associated with hyperfiltration.

Methods: We analyzed data from 6697 Spanish civil servants, aged 18–65 years, with fasting plasma glucose ≥ 100 and ≤ 125 mg/dL (prediabetes, ADA), waist circumference ≥ 94 cm in men and ≥ 80 cm in women (visceral obesity, IDF) and de-indexed estimated glomerular filtration rate (eGFR) ≥ 60 ml/min, collected during occupational health visits. The association between MAFLD and hyperfiltration (eGFR > age- and sex-specific 95th percentile) was tested by multivariable logistic regression analyses.

Results: Overall, 4213 patients (62.9%) had MAFLD, and 330 (4.9%) were hyperfiltering. MAFLD was more frequent in hyperfiltering than in non-hyperfiltering subjects (86.4% vs 61.7%, P < 0.001). BMI, waist circumference, systolic, diastolic, mean arterial pressure, and prevalence of hypertension were higher in hyperfiltering than in non-hyperfiltering subjects (P < 0.05). MAFLD was independently associated with hyperfiltration, even after adjusting for common confounders [OR (95% CI): 3.36 (2.33–4.84), P < 0.001]. In stratified analyses MAFLD potentiated age-related eGFR decline vs. non-MAFLD (P < 0.001).

Conclusions: More than half of subjects with prediabetes, visceral obesity and eGFR ≥ 60 ml/min presented MAFLD that was associated with hyperfiltration and potentiated the age-related eGFR decline.

1. Introduction

Prediabetes is a condition of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and/or glycosylated hemoglobin (HbA1C) between 5.7 and 6.4%, that often heralds progression to type 2 diabetes mellitus (T2DM) [1]. Its global prevalence varies between 27% and 54% depending on the diagnostic criteria [2], and is increasing steadily in parallel with the increasing prevalence of obesity.

E-mail address: aina.yanez@uib.es (A.M. Yañez).
[1] Co-first authors: Aneliya Parvanova and Manuela Abbate.

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Prediabetes is a highly heterogeneous and often asymptomatic metabolic disorder, and like diabetes, it is associated with an excess risk of cardiovascular disease (CVD), chronic kidney disease (CKD), fatty liver disease, cancer, dementia, as well as all-cause mortality [3–5]. A recent UK study showed that almost 50% of patients are already affected by micro- or macrovascular complications at the time they progress to overt T2DM [6]. Thus, prediabetes represents a time window of opportunity in which modifiable risk factors, such as overweight or obesity, hypercaloric diet, and physical inactivity, can be targeted to prevent or delay the development of T2DM and its chronic complications.

Liver fat accumulation, generally related to obesity and diabetes, is the most common chronic liver disorder and affects about a quarter of the world's adult population [7]. For many years this condition had been identified as "non-alcoholic fatty liver disease" (NAFLD). In 2020, however, an international panel of experts carefully revised the nomenclature and definition of NAFLD and achieved a consensus for the more comprehensive term "metabolic dysfunction-associated fatty liver disease" (MAFLD) [8]. More importantly, it was introduced a simple set of "positive" diagnostic criteria reflecting the dysmetabolic nature of MAFLD and the heterogeneity in its underlying causes, presentation, course, and outcomes. Currently, MAFLD is rapidly emerging as a stronger marker of CVD and CKD than NAFLD [9,10].

Glomerular hyperfiltration—that is an increase in the single-nephron glomerular filtration rate (GFR)—is a functional and potentially reversible hemodynamic change sustained, at least in part, by metabolic abnormalities that are related to severe obesity, in particular visceral obesity, and diabetes, and in most cases of CKD, by congenital or acquired reduction in the number of healthy, functioning nephrons [11–13]. When the number of functioning nephrons is normal or only mildly reduced, single-nephron glomerular hyperfiltration may result in an increase in total kidney GFR (absolute hyperfiltration). When the number of residual functioning nephrons is significantly reduced, single glomerular hyperfiltration may just result in an apparently "normal" or even in a frankly reduced total kidney GFR (relative hyperfiltration) [11]. Absolute hyperfiltration is a risk factor for the onset of nephropathy (heralded in most cases by the appearance of abnormal albuminuria or overt proteinuria) [14], and it may predict all-cause mortality even in healthy populations [15]. Absolute and relative hyperfiltration both contribute to accelerated renal function loss in the average population, in particular in obese patients with diabetes, or patients with CKD [11,16,17]. Glomerular hyperfiltration is often associated with prehypertension and hypertension [18–20], as well as other components of the metabolic syndrome, even in apparently healthy young men [21]. Moreover, cumulating evidence demonstrates an association between hyperfiltration and prediabetes [18,22]. Insulin resistance and hyperinsulinemia are key elements of the aforementioned metabolic disorders and play a central role in the development of glomerular hyperfiltration [23]. Consistently, amelioration of glomerular hyperfiltration (associated with either absolute or relative hyperfiltration) paralleled an improvement in insulin sensitivity in patients with T2DM, abdominal obesity, and "normal" kidney function exposed to 6 months of a calorie-restricted diet [24].

Intriguingly, MAFLD and glomerular hyperfiltration share common metabolic and functional risk factors such as obesity, insulin resistance, prediabetes, diabetes, dyslipidemia, hypertension, and CKD. This evidence can be taken to suggest the possibility of an association between MAFLD and hyperfiltration. Consistently, preliminary data indicate a possible relationship between NAFLD and hyperfiltration in children and adults with metabolic syndrome [25,26]. Furthermore, a very recent longitudinal Korean cohort study showed that glomerular hyperfiltration is associated with an increased risk of NAFLD and the probability of liver fibrosis in the general population [27].

On the basis of this background, we sought to investigate the prevalence of MAFLD in a large sample of subjects at high metabolic risk (i.e., with prediabetes and visceral obesity) and "preserved kidney function" (i.e., estimated GFR (eGFR) $\geq$ 60 ml/min), and whether and to what extent MAFLD *per se* is associated with glomerular hyperfiltration in this population.

2. Subjects, materials and methods

2.1. Study design, participants, and ethics

In this cross-sectional study, we analyzed data from a large database of routine occupational health visits performed between January 2012 and December 2013 in the Spanish communities of the Balearic and Canary Islands. The database included 234,995 civil servants employed either in the public administration, health care, or postal service sectors. The subjects' relevant data, including demographic, clinical, and biochemical variables, and smoking habit (current, former, never), were gathered by well-trained medical examiners. All participants gave written informed consent for use of their personal data for research purposes in accordance with the Declaration of Helsinki. The study protocol was approved (reference number 1887) by the Ethics Committee of Clinical Research of the Balearic Islands (Comitè d'Ètica de la Investigació de les Illes Balears (CEI-IB)).

We selected from the database 18- to 65-year-old subjects who had FPG between 100 and 125 mg/dL—and were therefore considered as having prediabetes according to the American Diabetes Association (ADA) criteria [1]. Participants were also required to have visceral obesity—defined, according to International Diabetes Federation (IDF) criteria as waist circumference $\geq$ 94 cm in men and $\geq$ 80 cm in women [28]—and a de-indexed eGFR $\geq$ 60 ml/min. Individuals with previously diagnosed diabetes (Type 1 and 2), current treatment with antidiabetic drugs or systemic steroids, active cancer, or a history of malignancy in the previous 5 years were excluded, as well as pregnant women.

2.2. Measurements and calculations

Anthropometric measurements were taken by trained staff in compliance with the International Standards for Anthropometric Assessment (ISAK) recommendations [29] and by using the same brand of equipment in all centers involved. Specifically, height was measured to the nearest 0.5 cm using a scale-mounted telescopic stadiometer (Seca 220, Seca GmbH, Hamburg, Germany), with the participant's head maintained in the Frankfort plane; body weight was measured to the nearest 0.1 kg using a mechanical column scale (Seca 700, Seca GmbH, Hamburg, Germany); body mass index (BMI) was calculated by the standard formula (weight in kg divided by squared height in m, kg/m^2). Waist circumference was measured in triplicate using a flexible steel tape (Lufkin Executive Thinline W606, Apex Tool Group, Texas, Unites States) at midway between the last rib and the top of the iliac crest, with the participant standing upright with feet together and arms hanging freely at the sides. The average of the three measurements was recorded and used for statistical analysis.

Blood pressure was measured in triplicate, 1 min apart, after a 10-minute resting period in a sitting position, using an automatic and calibrated sphygmomanometer (OMRON M3, OMRON Healthcare Europe, Spain). The average of the three measurements was recorded and used for statistical analysis. Venous blood samples were collected following a 12-h overnight fast and taken from the antecubital vein in appropriate vacutainers. Samples were centrifuged to obtain serum (15 min, 1,000 g, 4 °C), which was stored at -20 °C and analyzed for FPG, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and uric acid within 3 days in a centralized laboratory and by standard procedures, using an autoanalyzer (SYNCHRON CX®9 PRO, Beckman Coulter, Brea, CA, USA).

The presence of hepatic steatosis was assessed by the validated Fatty Liver Index (FLI) equation proposed by Bedogni G et al. [30]. Estimated GFR was calculated using the 2009 Chronic Kidney Disease

Epidemiology Collaboration (CKD-EPI) equation [31], and de-indexed for body surface area (BSA) to avoid GFR underestimation in patients with obesity by using the following formula: eGFR ml/min = (eGFR ml/min/1.73 m^2 * BSA)/1.73 m^2 [32]. BSA was calculated by the DuBois and DuBois equation [33].

2.3. Definitions

Overweight and obesity were defined according to the World Health Organization (WHO) criteria which consider overweight as a BMI ≥ 25 and < 30 kg/m^2 and obesity as a BMI ≥ 30 kg/m^2.

Hypertension was defined as a systolic blood pressure (SBP) ≥ 130 mmHg and a diastolic blood pressure (DBP) ≥ 85 mmHg or concomitant antihypertensive treatment [9,34].

The presence of MAFLD was defined according to a recently published international expert consensus statement [8] and based on the concomitant presence of hepatic steatosis (hereby defined by a FLI score ≥ 60) [30] and of overweight/obesity.

For the purposes of the study, we defined hyperfiltration as a total eGFR above the age- and sex-specific 95th percentile [18].

2.4. Statistical analysis

The normality distribution of variables was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD), and categorical data as frequencies (percentage, %). Differences between the groups were assessed by independent sample T-test for continuous variables or by Chi-Square for categorical variables. The prevalence of MAFLD and mean eGFR were further evaluated across incremental age categories of 8–10-year intervals. Multivariable logistic regression analysis was used to calculate the odds ratios (ORs) and corresponding 95% confidence intervals (CI) of the risk factors associated with hyperfiltration. The model included all variables which, at univariate logistic regression analyses, were associated with hyperfiltration at a significance level of P < 0.05 and adjusted for age, sex, and smoking status. Finally, to test the possible interaction effect between MAFLD and age on eGFR, a multiple linear regression analysis was carried out including the interaction term.

All statistical tests were two-sided, and P values < 0.05 were considered statistically significant. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 26.0

Table 1
Characteristics of the study population overall and according to the presence or absence of MAFLD and glomerular hyperfiltration.

Characteristics	Overall n = 6697	Non-MAFLD n = 2484 (37.1%)	MAFLD n = 4213 (62.9%)	P *	Non-HF n = 6367 (95.1%)	HF n = 330 (4.9%)	P **
Sex (males), *n* (%)	4804 (71.7)	1207 (48.6)	3597 (85.4)	<0.001	4567 (71.7)	237 (71.8)	0.972
Age (years)	44.9 ± 9.4	43.7 ± 9.9	45.6 ± 9.0	<0.001	45.0 ± 9.4	43.6 ± 9.5	0.010
Age categories, *n* (%)				<0.001			0.998
18–25 years	200 (3.0)	108 (4.3)	92 (2.2)°		191 (3.0)	9 (2.7)	
26–35 years	877 (13.1)	408 (16.4)	469 (11.1)°		834 (13.1)	43 (13)	
36–45 years	2328 (34.8)	878 (35.3)	1450 (34.4)		2212 (34.7)	116 (35.2)	
46–55 years	2379 (35.5)	780 (31.4)	1599 (38.0)°		2261 (35.5)	118 (35.8)	
56–65 years	913 (13.6)	310 (12.5)	603 (14.3)°		869 (13.6)	44 (13.3)	
Smoking status, *n* (%)				<0.001			0.807
Never	3262 (48.7)	1361 (54.8)	1901 (45.1)°		3107 (48.8)	155 (47.0)	
Former	1562 (23.3)	468 (18.8)	1094 (26.0)°		1483 (23.3)	79 (23.9)	
Current	1873 (28.0)	655 (26.4)	1218 (28.9)°		1777 (27.9)	96 (29.1)	
BMI (kg/m^2)	31.6 ± 4.3	29.1 ± 2.9	33.1 ± 4.3	<0.001	31.3 ± 4.0	37.2 ± 6.5	<0.001
Overweight/Obesity, *n* (%)				<0.001			<0.001
BMI ≥ 25 < 30 kg/m^2	2345 (35.0)	1546 (62.2)	799 (19.0)°		2300 (36.1)	45 (13.6)°	
BMI ≥ 30 kg/m^2	4352 (65.0)	938 (37.8)	3414 (81.0)°		4067 (63.9)	285 (86.4)°	
Waist circumference in men (cm)	98.5 ± 5.0	96.4 ± 2.9	99.3 ± 5.4	<0.001	98.2 ± 4.8	104.5 ± 6.7	<0.001
Waist circumference in women (cm)	85.9 ± 4.4	84.6 ± 4.0	88.4 ± 4.2	0.352	85.7 ± 4.4	89.7 ± 4.5	<0.001
SBP (mmHg)	131.5 ± 16.9	125.7 ± 15.2	134.9 ± 16.9	<0.001	131.3 ± 16.8	135.5 ± 17.5	<0.001
DBP (mmHg)	80.7 ± 11.1	77.0 ± 10.1	82.9 ± 11.0	<0.001	80.6 ± 11.1	83.6 ± 10.6	<0.001
MAP (mmHg)	97.6 ± 12.0	93.2 ± 10.7	100.3 ± 12.0	<0.001	97.5 ± 12.0	100.9 ± 11.8	<0.001
Arterial hypertension, *n* (%)	4263 (63.7)	1218 (49.0)	3045 (72.3)	<0.001	4026 (63.2)	237 (71.8)	0.002
FPG (mg/dL)	106.7 ± 6.0	105.7 ± 5.4	107.2 ± 6.3	<0.001	106.6 ± 6.0	107.1 ± 6.6	0.179
Total Cholesterol (mg/dL)	204.9 ± 36.9	196.5 ± 34.7	209.9 ± 37.2	<0.001	205.2 ± 36.8	199.7 ± 38.3	0.009
LDL-C (mg/dL)§	129.5 ± 52.0	123.9 ± 33.3	133.0 ± 60.6	0.001	130.0 ± 51.8	122.4 ± 53.5	0.137
HDL-C (mg/dL)+	51.6 ± 10.5	54.6 ± 10.8	49.6 ± 9.8	<0.001	51.4 ± 10.5	53.1 ± 9.7	0.107
Triglycerides (mg/dL)	155.5 ± 112.1	98.2 ± 38.6	189.4 ± 126.6	<0.001	155.8 ± 112.7	150.9 ± 99.3	0.440
Uric acid (mg/dL)◦	5.6 ± 1.3	4.8 ± 1.1	6.0 ± 1.3	<0.001	5.6 ± 1.3	5.6 ± 1.4	0.903
ALT (IU/L)Δ	24.1 ± 11.5	19.8 ± 7.8	27.0 ± 12.6	<0.001	35.6 ± 22.3	35.6 ± 20.9	0.985
AST (IU/L)¥	35.6 ± 22.2	25.5 ± 12.5	41.5 ± 24.5	<0.001	23.9 ± 10.9	26.1 ± 16.4	0.051
GGT (IU/L)	42.2 ± 54.7	22.5 ± 12.5	53.8 ± 65.6	<0.001	42.2 ± 55.5	41.6 ± 38.2	0.839
FLI	65.1 ± 22.7	40.2 ± 14.0	79.8 ± 10.9	<0.001	64.3 ± 22.6	79.9 ± 18.6	<0.001
MAFLD, *n* (%)	4213 (62.9)				3928 (61.7)	285 (86.4)	<0.001
Serum creatinine (ml/dL)	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	<0.001	0.9 ± 0.2	0.7 ± 0.1	<0.001
eGFR (ml/min)	115. 1 ± 22.1	110.2 ± 20.7	118.0 ± 22.4	<0.001	113.1 ± 20.4	153.3 ± 18.5	<0.001
Hyperfiltering, *n* (%)	330 (4.9)	45 (1.8)	285 (6.8)	<0.001			
Any antihypertensive therapy, *n* (%)	764 (11.4)	183 (7.4)	581 (13.8)	<0.001	721 (11.3)	43 (13.0)	0.342
Any lipid-lowering therapy, *n* (%)	298 (4.4)	67 (2.7)	231 (5.5)	<0.001	284 (4.5)	14 (4.2)	0.851

Data are mean ± SD and number (%); *P-value for comparison between Non-MAFLD and MAFLD; **P-value for comparison between Non-HF and HF; °Significant difference between paired categories. Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; Non-HF, Non-hyperfiltering; HF, hyperfiltering; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FPG, fasting plasma glucose; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; FLI, fatty liver index; eGFR, estimated glomerular filtration rate. §LDL-C available for *n* = 1610 (Non-MAFLD *n* = 621; MAFLD *n* = 989; non-HF *n* = 1499; HF *n* = 111); +HDL-C available for *n* = 1610 (Non-MAFLD *n* = 621; MAFLD *n* = 989; non-HF *n* = 1499; HF *n* = 111); ◦Uric acid available for *n* = 4211 (Non-MAFLD *n* = 1360; MAFLD *n* = 2851; non-HF *n* = 4017; HF *n* = 194); ΔALT available for *n* = 6692 (Non-MAFLD *n* = 2483; MAFLD *n* = 4209; non-HF *n* = 6362; HF *n* = 330); ¥AST available for *n* = 1404 (Non-MAFLD *n* = 571; MAFLD *n* = 833; non-HF *n* = 1293; HF *n* = 111).

(IBM Company, New York, NY, USA).

3. Results

3.1. Demographic and clinical characteristics of the study population considered as a whole

Participants' characteristics are summarized in Table 1. Of the 6697 subjects with prediabetes, visceral obesity and eGFR ≥ 60 ml/min included in the sample, 71.7% were males, and 28% were current smokers. Age averaged 44.9 ± 9.4 years. The prevalence of MAFLD was 62.9%, and, as expected by definition, 330 subjects (4.9%) were hyperfiltering. Mean BMI was 31.6 ± 4.3 kg/m^2: 65% of participants were obese, and 35% were overweight. Overall, 63.7% of subjects had arterial hypertension, and 11.4% were taking antihypertensive therapy. On average, blood pressure was relatively well controlled. Mean total cholesterol and triglycerides levels were slightly higher, and 4.4% of subjects were taking lipid-lowering medications. The mean uric acid value was within the normal range, whereas liver enzymes, and specifically mean AST and GGT values, showed a trend to exceed the upper normal limit.

3.2. Demographic and clinical characteristics of participants according to the presence or absence of MAFLD

Subjects with MAFLD were more frequently males and older (Table 1). The prevalence of MAFLD increased across the 10-year age categories up to 46–55 years. At this stage, the prevalence peaked at 38%. Subjects with MAFLD were more likely to be former and current smokers, to have a higher BMI, and also had a higher frequency of obesity, and a higher mean waist circumference (particularly in men) than subjects without MAFLD. They also had higher levels of SBP, DBP, mean arterial pressure (MAP), FPG, total cholesterol, LDL-C, triglycerides, uric acid, liver enzymes, serum creatinine, lower HDL-C and were more frequently taking antihypertensive and lipid-lowering agents than subjects without MAFLD (P ≤ 0.001 for all comparisons).

Subjects with MAFLD had a higher mean eGFR and higher prevalence of hyperfiltration than those without MAFLD. Mean eGFR declined across age categories in both groups and at any age category was significantly higher in subjects with MAFLD than in those without (Fig. 1). Furthermore, the multiple linear regression model considering MAFLD, age, and their interaction term, adjusted for sex (Table 2, Model 2), revealed that the effect of age on eGFR was modified by the presence of MAFLD (P < 0.001). In stratified data analyses according to the presence or absence of MAFLD, the effect of age on eGFR decline was amplified by the presence of MAFLD (P < 0.001), (Table 2). In other words, the eGFR difference between the two groups tended to decrease for increasing age categories, independently of considered potential confounders (Fig. 1).

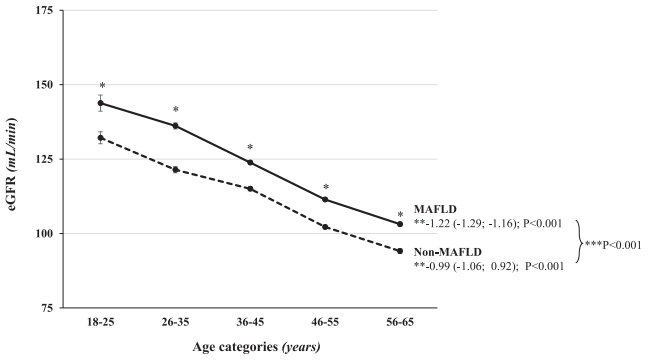

Fig. 1. Distribution of estimated glomerular filtration rate (eGFR) in subjects with and without MAFLD (MAFLD, Non-MAFLD) according to age categories, *P < 0.001. **Stratified analyses according to the presence or absence of MAFLD [β (95% CI)]; ***Multiple linear regression analyses with the effect of interaction term between MAFLD and age on eGFR (P < 0.001).

Table 2
Multiple linear regressions with the effect of the interaction term between MAFLD and age on eGFR and stratified analyses according to the presence or absence of MAFLD.

Variables	Model 1		Model 2	
	β (95% CI)	P-value	β (95% CI)	P-value
MAFLD	6.85 (5.84; 7.86)	<0.001	17.14 (-21.54; -12.74)	<0.001
Age (y)	-1.13 (-1.17; 1.08)	<0.001	-1.22 (-1.29; -1.16)	<0.001
Male vs female	8.43 (7.35; 9.51)	<0.001	8.68 (7.60; 9.76)	<0.001
Interaction MAFLD × Age (y)			-0.23 (-0.33; -0.14)	<0.001
	Stratified analyses			
	MAFLD		**Non-MAFLD**	
	β (95% CI)	P-value	β (95% CI)	P-value
Age (y)	-1.22 (-1.29; -1.16)	<0.001	-0.99 (-1.06; -0.92)	<0.001
Male vs female	7.90 (6.24; 9.55)	<0.001	9.36 (7.98; 10.74)	<0.001

Abbreviations: β, beta; CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; y, years.

3.3. Demographic and clinical characteristics of the study population according to the presence or absence of hyperfiltration

Hyperfiltering subjects were younger than non-hyperfiltering; the prevalence of male sex and smoking status was similar between the two groups (Table 1). The BMI of hyperfiltering subjects was significantly higher and they were more likely to present second- and third-class obesity than non-hyperfiltering subjects. In hyperfiltering subjects, the prevalence of obesity was higher whereas the prevalence of overweight was lower compared to non-hyperfiltering subjects. The waist circumference of hyperfiltering males and females was higher than that of their non-hyperfiltering counterparts. The prevalence of MAFLD was higher in hyperfiltering than in non-hyperfiltering individuals (86.4% vs. 61.7%, P < 0.001). Hyperfiltering participants had a higher SBP, DBP, MAP, and a higher prevalence of arterial hypertension than non-hyperfiltering participants. However, no difference between the groups was observed in the use of antihypertensive therapy. FPG, lipid profile and lipid-lowering therapy use, uric acid, and liver enzymes were similar between the groups with the exception of total cholesterol, that was higher in non-hyperfiltering than hyperfiltering subjects (P = 0.009) and AST that was higher in hyperfiltering than non-hyperfiltering subjects with borderline significance (P = 0.051). Finally, eGFR was significantly higher in subjects with MAFLD than those without MAFLD when considered separately according to the presence or absence of hyperfiltration (Fig. 2).

3.4. Predicting hyperfiltration

The multivariable logistic regression model, including all variables that at univariate logistic regression analyses were associated with hyperfiltration at a significance level of P < 0.05 and adjusted by age, sex, obesity, MAP, and smoking status, showed that MAFLD was independently associated with hyperfiltration, along with severity of obesity, male sex, higher MAP, and younger age (Table 3). Receiving operator characteristic (ROC) curve analysis confirmed the predictive power of MAFLD (area under the curve (AUC) 0.623, 95% CI 0.60–0.65, P < 0.001).

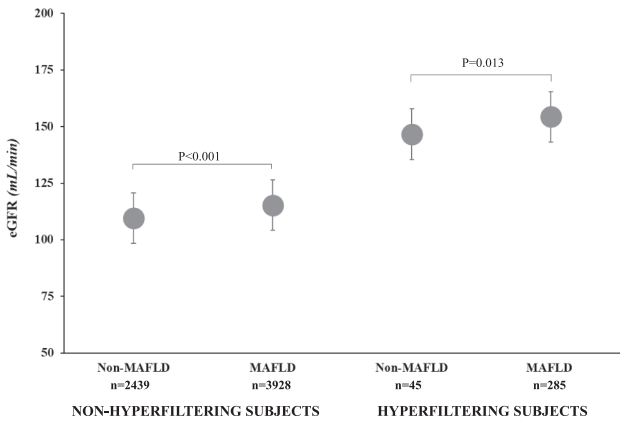

Fig. 2. Distribution of estimated glomerular filtration rate (eGFR) in Non-Hyperfiltering and Hyperfiltering subjects according to the presence or absence of MAFLD (MAFLD, Non-MAFLD).

Table 3
Univariate (crude) and multivariate (adjusted) logistic regression derived odds ratios and 95% confidence intervals for hyperfiltration in prediabetes subjects with visceral obesity and eGFR ≥ 60 ml/min.

Variables	Univariate		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
MAFLD	3.93 (2.86; 5.41)	<0.001	3.36 (2.33; 4.84)	<0.001
Obese vs overweight	3.58 (2.61; 4.93)	<0.001	2.15 (1.52; 3.03)	<0.001
Male vs female	0.97 (0.78; 1.28)	0.972	1.67 (1.27; 2.19)	<0.001
MAP (mmHg)	1.02 (1.01; 1.03)	<0.001	1.02 (1.01; 1.03)	<0.001
Age (y)	0.99 (0.97; 1.00)	0.010	0.97 (0.96; 0.99)	<0.001
Smoking status	1.06 (0.83; 1.35)	0.641	1.05 (0.82; 1.35)	0.676
Arterial hypertension	1.48 (1.16; 1.89)	0.002		
FPG (mg/dL)	1.01 (0.99; 1.03)	0.179		
Triglycerides (mg/dL)	1.00 (0.99; 1.00)	0.440		
HDL-C (mg/dL)	1.02 (1.00; 1.03)	0.107		
Uric acid (mg/dL)	0.99 (0.89; 1.11)	0.903		
GGT (IU/L)	1.00 (1.00; 1.00)	0.839		
Any antihypertensive therapy	1.17 (0.84; 1.63)	0.342		
Any lipid lowering therapy	0.95 (0.55; 1.64)	0.851		

Abbreviations: eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; MAP, mean arterial pressure; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; GGT, gamma-glutamyl transferase.

4. Discussion

In this large population-based study, we found that the prevalence of MAFLD in prediabetes subjects with visceral obesity and an eGFR ≥ 60 ml/min was 62.9%, and that MAFLD was independently associated with glomerular hyperfiltration. Moreover, the age-related eGFR decline could be amplified by presence of MAFLD.

Notably, the observed 63% prevalence of MAFLD in our study population at high metabolic risk exceeded by more than two folds the prevalence (25%) observed in the general adult population [7]. This finding is consistent with the high prevalence of NAFLD observed in people with prediabetes (ranging from 45% in those with IFG, and 48% in those with IGT, to 78% in those with both IFG and IGT) [5], and also exceeded the average 50.7% prevalence of MAFLD reported in overweight/obese adults [35]. This prevalence is even consistent with the prevalence (55–70%) of NAFLD in T2DM [36]. Our finding is not surprising because MAFLD is the liver manifestation of the systemic metabolic disorders related to visceral obesity and IFG that characterize the study population [8].

The cut-off eGFR value to discriminate hyperfiltering from non-hyperfiltering subjects is not univocally identified even because GFR values may physiologically swing according to age and gender [15,37]. Thus, to minimize the confounding effect of the age-related physiological decline of GFR and the GFR differences between sexes, we defined hyperfiltration as an eGFR exceeding age- and sex-adjusted 95th percentile. According to this definition, hyperfiltering study participants were found to be younger than non-hyperfiltering participants—a finding consistent with data in patients with overt T2DM [37]—whereas sex distribution was similar in hyperfiltering and non-hyperfiltering participants. Identifying hyperfiltering subjects is clinically relevant since they appeared to be more frequently affected by second- and third-class obesity as compared to non-hyperfiltering subjects. Notably, the prevalence of obesity was higher in hyperfiltering than non-hyperfiltering subjects whereas the prevalence of overweight was higher in non-hyperfiltering subjects. The hyperfiltering males and females presented greater visceral obesity than their non-hyperfiltering counterparts. The most impressive finding was that 86.4% of hyperfiltering participants presented MAFLD as compared to 61.7% of non-hyperfiltering subjects. This finding was consistent with evidence that at multivariable logistic regression analysis, MAFLD was associated with a three-fold excess prevalence of hyperfiltration independently of the role of obesity, male sex, MAP, and younger age.

Glomerular hyperfiltration is most likely sustained by an imbalance between pre-glomerular vasodilation and post-glomerular vasoconstriction largely related to obesity and diabetes mellitus and possibly by increased sodium reabsorption in the proximal tubule with reduced sodium delivery to the macula densa, inhibition of the tubulo-glomerular feedback and preglomerular vasorelaxation [11–13,16,38,39]. Thus, the association between MAFLD and hyperfiltration could be explained by common mechanisms such as hyperinsulinemia and insulin resistance than can both be sustained by activated inflammatory pathways that originate from the expanded, inflamed, and dysfunctional insulin-resistant visceral adipose tissue. This is a source of free fatty acids (FFAs), different adipokines (such as adiponectin and leptin), cytokines (such as TNF, IL-1β and IL-6), and hormone (Angiotensin II), all involved in the pathogenesis of insulin resistance [38,40]. Thus, on one hand the liver is targeted by the increased influx of FFAs and proinflammatory factors that contribute to liver steatosis, inflammation and oxidative stress leading to liver insulin resistance [41]; on the other hand, the liver produces proinflammatory mediators and “hepatokines” which further increase systemic abnormalities, that in turn mediate the bidirectional interaction between liver and systemic insulin resistance [42]. Thus, the interaction between visceral obesity, insulin resistance and MAFLD is very complex, and it is hard to dissect their specific causal relationships with hyperfiltration.

Consistent with evidence that younger and middle-aged females are somehow protected from metabolic abnormalities [43], in our study we found that male sex was associated with an increased risk of hyperfiltration. This could be explained by the shifting of FFAs towards ketone body production rather than very-low-density lipoprotein (VLDL), and sex-specific browning of white adipose tissue, along with the possible differences in nutritional and physical activity habits between the two sexes [43]. This is in line with the well-known role of sex hormones on energy metabolism, body composition, vascular function, and

inflammatory responses but the exact mechanisms linking estrogens and testosterone to hyperfiltration remain unclear.

Finding that hyperfiltering participants were more frequently hypertensive and tended to have higher SBP and DBP than non-hyperfiltering subjects is consistent with the concept that hypertension may contribute to the pathogenesis of hyperfiltration from the earlier stages of this hemodynamic dysfunction [19–21]. Moreover, in multivariate logistic regression analysis, MAP was independently associated with hyperfiltration. Predominant pre-glomerular vasorelaxation could facilitate the transmission of systemic blood pressure to the glomerular microcirculation, thus enhancing glomerular hydraulic pressure and eventually the GFR [16,38]. Moreover, this seemingly independent link between hypertension and hyperfiltration might also involve pathophysiological mechanisms linking hypertension to insulin resistance that stimulates the sympathetic nervous system (SNS) and/or hyperinsulinemia that increase sodium reabsorption along the nephron tubules [38,44].

Finding that hyperfiltering were younger than non-hyperfiltering subjects also highlights the role of vessel aging in glomerular hyperfiltration. Younger arterioles are less affected by age-related vascular stiffness and being more compliant might more readily react with vasodilation and vasoconstriction to different functional, metabolic, hormonal, and pro-inflammatory factors.

The decline of GFR over time is well-known [37]. It might be associated with an increase in vascular stiffness with glomerular hypoperfusion, and age-related continuous nephron loss (it has been predicted a mean loss of 3676 glomeruli per kidney per year from 18 to 70 years of age) [45]. Within the limit of the cross-sectional design of the analyses, we found that the presence of MAFLD potentiated the age-related eGFR decline, probably because of accelerated vessel aging induced by the MAFLD-functional and metabolic disorders consistent with data for diabetes-associated accelerated arterial aging [46].

This finding highlights the importance of including liver health assessment in the conventional screening approach which currently is predominantly focused on the cardio-metabolic axis. Assessing the presence of MAFLD is practical and simple and this could help primary care providers to timely identify patients that are not only at high risk for cardiovascular disease but also at high risk of hepatic and renal damage. As MAFLD is a reversible state these patients could benefit from early lifestyle modification strategies such as appropriate calorie restricted diets and physical activity programs. There are still no approved therapies for MAFLD, but encouraging data are progressively emerging for some glucose-lowering drugs such as thiazolidinediones, glucagon-like peptide-1 receptor agonists (GLP-1 RA), sodium-glucose co-transporter-2 (SGLT-2) inhibitors, antioxidants (such as vitamin E), statins or other lipid-lowering agents, bile and non-bile acid farnesoid X receptor (FXR) agonists, and very recently Tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA [47,48]. Whether and to what extent reversing MAFLD could result in amelioration of hyperfiltration and, conceivably, long-term nephroprotection, merits further investigation.

We recognize that the present study has some limitations. First, its cross-sectional design does not allow establishing the temporality and causality of the association between MAFLD and hyperfiltration. Secondly, the results might be influenced by the lack of gold standard methods to diagnose liver steatosis such as liver biopsy and/or ultrasound imaging [8], and to directly measure the GFR by iohexol plasma clearance [49]. These are common limitations in large sample studies where it is impossible to apply relatively complex procedures to all participants. However, for the needs of epidemiology studies, the diagnostic and prognostic performance of FLI and eGFR-EPI is recognized [8,50].

The strengths of this study are the large sample size that could be representative of the Spanish working population; moreover, instead of NAFLD we applied the novel definition of MAFLD which helped us to provide robust data on the association between this dysmetabolic disease and hyperfiltration. Furthermore, eGFR was de-indexed for BSA avoiding underestimation of eGFR in patients with obesity [32]. Without general consensus about the definition of hyperfiltration, the assurance of the presence of hyperfiltration was achieved by the selection of participants with an eGFR above the age- and sex-specific 95th percentile.

In conclusion, more than half of subjects with prediabetes with visceral obesity and eGFR $\geq$ 60 ml/min presented MAFLD that was strongly associated with glomerular hyperfiltration. Moreover, the presence of MAFLD could potentiate the age-related eGFR decline.

Longitudinal studies are needed to investigate whether MAFLD is associated with an accelerated decline of GFR in subjects with prediabetes, visceral obesity and still preserved kidney function, and whether long-term improvement of MAFLD can be associated with nephroprotection.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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