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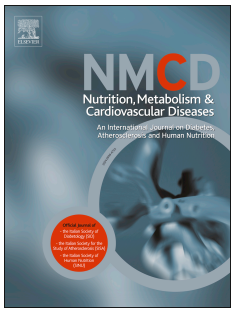

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High glomerular filtration rate is associated with impaired arterial stiffness and subendocardial viability ratio in prediabetic subjects

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Background and aims: High glomerular filtration rate (HGFR) is associated with cardiovascular damage in the setting of various conditions such as obesity and diabetes. Prediabetes was also associated with increased GFR, however, the association between prediabetes, HGFR and cardiovascular damage has not been investigated. In this study, we investigated the association between HGFR and early markers of cardiovascular disease in subjects with prediabetes.

Methods and Results: Augmentation pressure (Aug), augmentation index (AIx), subendocardial viability ratio (SEVR), pulse wave velocity (PWV), intima-media thickness (IMT) and estimated GFR (eGFR) were evaluated in 230 subjects with prediabetes. The eGFR was assessed using the Chronic Kidney Disease Epidemiology Collaboration formula. HGFR was defined as an eGFR above the 75th percentile.

Prediabetic subjects were divided into two groups according to presence/absence of HGFR: 61 subjects with HGFR and 169 subjects without HGFR. Subjects with HGFR showed higher Aug, AIx and lower SEVR compared with prediabetic subjects with lower eGFR (14.1±7.2 vs 10.8±6.2, 32.9±12.7 vs 27.6±11.7, 153.5±27.8 vs 162±30.2, p<0.05). No differences were found in PWV and IMT values between the two groups. Then, we performed multiple regression analysis to test the relationship between Aug, SEVR and several cardiovascular risk factors. In multiple regression analysis Aug was associated with age, systolic blood pressure (BP), HOMA-IR and eGFR; the major determinants of SEVR were systolic BP, HOMA-IR and eGFR.

Conclusion: Subjects with prediabetes and HGFR exhibited an increased Aug, AIx and a reduced SEVR. These alterations are associated with eGFR, insulin resistance and systolic BP.

Introduction

Diabetes-related kidney disease represents the leading cause of end-stage renal disease in the world, being responsible for 40% of the cases requiring renal replacement therapy, and it has been recognized as an important risk factor for cardiovascular morbidity and mortality [1]. The relationship between impaired kidney function and cardiovascular disease has been reported not only in patients with low glomerular filtration rate (GFR), but also in patients with a higher than normal GFR; accordingly, there has been increased interest in patients with high glomerular filtration rate (HGFR), which is a supraphysiological increase in GFR and is well recognized as an early renal alteration in subjects with diabetes mellitus. HGFR may be associated with several medical conditions such as hypertension [2], obesity [3] and lifestyle factors such as smoking [4] and lack of physical activity [5], however, it has only been recently recognized the predictive value of HGFR for clinical outcomes such as increased incidence of coronary calcification [6], left ventricular hypertrophy [7] as well as for eGFR decline [8]. Moreover, HGFR has been reported to be associated with increased cardiovascular risk and higher mortality in several categories of patients including people with diabetes [9,10].

Prediabetes is typically defined as blood glucose concentrations higher than normal but lower than the diabetes threshold, is a high risk state for diabetes and cardiovascular disease development [11]; furthermore, it has also been associated with HGFR [12].

Previous studies have shown that hyperglycemia and insulin resistance, both key features of prediabetic status, are associated with HGFR: Rodriguez-Poncelas *et al.* demonstrated a positive correlation between fasting plasma glucose and estimated GFR, (eGFR) in a study population including 9238 European subjects with prediabetes [12]; Van Bommel *et al.* reported that increased insulin resistance was associated with intrarenal hemodynamic abnormalities in subjects with impaired fasting glucose and/or impaired glucose tolerance [13]. Although HGFR and prediabetes are both associated with increased cardiovascular risk, there is still no evidence in the literature concerning the role of HGFR in enhancing cardiovascular damage in subjects with prediabetes.

In previous reports, we showed that subjects with prediabetes are a heterogeneous population of patients with different levels of cardiometabolic risk, thus, identifying the subjects with higher risk of complications among those with prediabetes might be helpful and clinically relevant to implement preventive and therapeutic strategies [14].

The aim of our study was to investigate the association between HGFR and early markers of cardiovascular disease in subjects with prediabetes. We studied early markers of cardiovascular damage such as arterial stiffness [pulse wave analysis and its central hemodynamic correlates, such as augmentation pressure (Aug), augmentation index (AIx), subendocardial viability ratio (SEVR), and pulse wave velocity (PWV)] and intima-media thickness (IMT).

Methods

Study population: 435 subjects with no previous history of diabetes and cardiovascular disease attending our University Hospital for cardiometabolic risk evaluation were consecutively screened based on inclusion/exclusion criteria. The inclusion criteria were the following: age range between 35 and 65 years; body mass index (BMI) between 18.2-40 kg/m^2.

The exclusion criteria were: diabetes, previous history of overt cardiovascular events (stroke, ischemic heart disease, chronic obstructive peripheral arteriopathy, or heart failure), chronic kidney disease (eGFR <60 ml/min/1.73 m^2), anemia, or hemoglobinopathies, use of medications known to affect glucose metabolism, positivity for antibodies to hepatitis C virus or hepatitis B surface antigen, clinical evidence of advanced liver disease, chronic inflammatory disease or other chronic diseases and/or recent history of acute illness, malignant disease, and drug or alcohol abuse.

All subjects underwent a complete evaluation of glycemic status including fasting glucose, oral glucose tolerance test (OGTT) and glycated haemoglobin A_{1c} (HbA_{1c}). Only subjects with prediabetes participated in the study.

75-g OGTT was performed with basal, 1-h and 2-h sampling for plasma and insulin as previously described [15]. Glucose tolerance status was defined on the basis of fasting glycemia, OGTT and HbA_{1c} according to American Diabetes Association recommendations [16]. Prediabetes was defined as a fasting glycemia between 100-125 mg/dL and/or a 120-min after OGTT glycemia between 140-199 mg/dL and/or a HbA_{1c} between 5.7-6.4%. Homeostatic model assessment for insulin resistance (HOMA-IR) and Matsuda index were calculated as previously described [17]. Body weight and height were measured, and BMI was calculated as weight (kg)/[height (m)]^2. Blood pressure (BP) was measured with a calibrated sphygmomanometer after the subject had rested in the supine position for 10 min. Venous blood samples were drawn from the antecubital vein on the morning after an overnight fast. Baseline venous blood samples were obtained for the measurement of plasma glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and high sensitivity C-reactive protein (hs-CRP). Low density lipoprotein (LDL)

cholesterol concentrations were estimated using the Friedewald formula.

Biochemical Analyses: Plasma glucose, serum creatinine, total cholesterol, triglycerides, HDL cholesterol, and hs-CRP were measured using available enzymatic methods. The eGFR was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [18]. HGFR was defined as an eGFR above the 75th percentile.

HbA_{1c} was measured via high performance liquid chromatography using a National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial assay reference [19]. Chromatography was performed using a certified automated analyzer (HPLC; HLC-723G7 hemoglobin HPLC analyzer; Tosoh Corp.) (normal range 4.25–5.90% [23–41 mmol/mol]).

Pulse wave analysis: Arterial stiffness evaluation was performed with the patients in fasting status and the explicitly expressed recommendation to avoid smoking and coffee intake in the morning of the procedure. All measurements were performed from the right radial artery by applanation tonometry using a Millar tonometer (SPC-301; Millar instruments, Houston, TX.) as previously described [20]. Data were collected directly into a desk-top computer and processed with the SphygmoCor CvMS (Atcor Medical, Sidney, Australia), which allows continuous on-line recording of the radial artery pressure waveform. The integral system software was used to calculate an average radial artery waveform, and generate the corresponding ascending aortic pressure waveform.

The aortic waveform was subjected to further analysis for calculation of aortic pressure, Aug, AIx (calculated by dividing augmentation pressure by pulse pressure) and Buckberg's SEVR (area of diastole divided by area of systole during one cardiac cycle in the aorta). Pulse pressure is the difference between systolic and diastolic blood pressures.

Pulse wave velocity: The SphygmoCor CvMS (AtCor Medical, Sydney, Australia) system was used for the determination of the PWV as previously described [21]. Briefly, this system uses a tonometer and two different pressure waves obtained at the common carotid artery (proximal recording site) and at the femoral artery (distal recording site). The distance between the recording sites and suprasternal notch was measured using a tape measure. An electrocardiogram was used to determine the start of the pulse wave. The PWV was calculated on the mean of 10 consecutive pressure waveforms to cover a complete respiratory cycle as the difference in travel time of the pulse wave between the two different recording sites and the heart, divided by the travel distance of the pulse waveform. The PWV was calculated on the mean of 10 consecutive pressure waveforms to cover a complete respiratory cycle.

Carotid Ultrasound examination: Ultrasound scans were performed using a high-resolution B-mode ultrasound system (MyLab 50 Xvision; Esaote Biomedica SpA, Florence, Italy) equipped with a 7.5-MHz linear array transducer, as previously described [22]. To exclude interobserver variability, a single physician who was blinded to the clinical and laboratory characteristics of the patients performed all ultrasound examinations. The subjects were examined in the supine position. Longitudinal scans were performed, and measurements were conducted at a total of six plaque-free sites 1 cm proximal to the carotid bulb. The obtained values were averaged and are presented as the mean of the IMT of the common carotid artery. Plaques, defined as a clearly isolated focal thickening of the intima-media layer with a thickness of 1.4 mm, were not observed in any individuals. All measurements were obtained in diastole, assessed as the phase in which the lumen diameter is at its smallest and the IMT is at its largest.

Statistical analyses. The sample size was calculated based on Aug using a level of significance (α) set to 5% and power (1- β**)** to 80%. We based the power calculation on previous studies examining Aug among patients with early alteration of glucose homeostasis and controls. The estimated

sample size was 60 patients per group. Statistical comparisons of clinical and biomedical parameters were performed using Stat View 6.0 for Windows. Data are given as means ± SD or median (IQR). Each variable's distributional characteristics including normality were assessed by the Kolmogorov-Smirnov test. Statistical analysis included the unpaired t test for continuous variables and the χ^2 test for non-continuous variables. All analyses were adjusted for age, sex and heart rate. A *p* value less than 0.05 was considered statistically significant. When necessary, numerical variables were logarithmically transformed to reduce skewness, and values were expressed as median and interquartile range.

A multivariate logistic regression analysis was performed to assess the independent correlates of HGFR. Logistic model was adjusted for BMI, smoking status, systolic and diastolic BP, LDL cholesterol, HDL cholesterol, uric acid, fasting glucose, HbA_{1c}, HOMA-IR and Matsuda Index.

In order to identify variables independently associated with variations of Aug, AIx and SEVR, we performed three multivariate regression models: the first model included cardiovascular risk factors (age, sex, BMI, smoking status, systolic and diastolic BP, LDL cholesterol, HDL cholesterol, and uric acid); variables reaching significance in the first model were included in a second model including variables related to glycemic status (fasting glucose, 1-h glucose and 2-h glucose, HbA_{1c}, HOMA-IR and Matsuda Index). Subsequently, variables reaching significance in the first model were inserted into a multiple regression model including HGFR as a dichotomous variable. A confirmatory analysis using a different definition of HGFR was performed; a cut-off of 120 ml/min was used to define the highest eGFR category in confirmatory analysis. The variance inflation factor was used to check for the problem of multi-collinearity among the predictor variables in multiple regression analysis.

The local ethics committee approved the study. Informed consent was obtained from each participant.

Results

In total, 419 individuals referred to our outpatient clinic were evaluated. Of these, 230 subjects satisfied prediabetes diagnostic criteria and were included in the study (**Fig. 1**).

Prediabetic subjects were stratified according to the presence or absence of HGFR (61 prediabetic subjects with HGFR and 169 prediabetic subjects without HGFR). The eGFR was assessed using the CKD-EPI formula. HGFR was defined as an eGFR above the 75th percentile.

The clinical and biochemical characteristics of the study subjects are presented in **Table 1**. Subjects with prediabetes and HGFR exhibited similar characteristics compared with the subjects with a lower eGFR. The two groups differed in triglycerides and HDL cholesterol serum levels. Furthermore, prediabetic subjects with HGFR exhibited a significantly lower Matsuda Index [3.9(2.8-7.4) vs 4.5(3-9), p=0.01] and a higher HOMA-IR without statistical significance [1.87(1.3-2.8) vs 1.75(1.1-2.2), p=0.14)

A univariate regression analysis was performed to test the relationship between eGFR and different clinical variables in prediabetic subjects. eGFR was associated with HDL cholesterol (r= 0.17, p<0.05), triglycerides (r= 0.12, p<0.05), HOMA-IR (r= 0.14, p<0.05), fasting glucose (r= 0.22, p<0.05), 1-h glycemia (0.18, p<0.05) and uric acid (r=0.14, p<0.05).

Multiple logistic regression analysis indicated that the presence of HGFR was associated with systolic BP (p<0.05) and Matsuda Index (p<0.05) **(Table 2)**.

Prediabetes, high glomerular filtration rate and cardiovascular risk

Subjects with prediabetes and HGFR exhibited increased Aug and AIx (14.1±7.2 vs 10.8±6.2 mmHg, p<0.05 and 32.9±12.7 vs 27.6±27.1%, p<0.05) and SEVR was reduced (153.5±27.3 vs 162.1±30.2, p<0.05) compared with subjects with prediabetes without HGFR. No differences were found in PWV and IMT values between the two groups (**Table 3**).

Then, we performed multiple regression analysis to test the relationship between Aug, SEVR and several cardiovascular risk factors. Three multivariate regression models were

performed: the first model included cardiovascular risk factors (age, sex, BMI, smoking status, systolic and diastolic BP, LDL cholesterol, HDL cholesterol and uric acid); the second model included variables related to glycemic status (fasting glucose, 1-h and 2-h glucose, HbA_{1c}, HOMA-IR and Matsuda Index). Subsequently, variables reaching significance were inserted into a multiple regression model including eGFR. The first model exhibited a significant correlation among Aug, age (p=0.001) systolic BP (p=0.001) and HDL cholesterol (p=0.01). The second model exhibited a significant correlation between Aug, age (p=0.001), systolic BP (p=0.01) and HOMA-IR (p=0.02). Finally, the third model showed a significant correlation among Aug, age (p=0.001), systolic BP (p=0.01), HOMA-IR (p=0.01) and HGFR (p=0.02) (**Table 4**). AIx was significantly related with age (p=0.001), HDL cholesterol (P=0.02), and BMI (P=0.01) in the first model. The second model exhibited a significant correlation between AIx, age (p=0.001), and HOMA-IR (p=0.0001). The third model showed a significant correlation among Aug, age (p=0.001), HOMA-IR (p=0.0001) and HGFR (p=0.001) **(Table 4).**

SEVR was associated with systolic BP (p=0.04) and uric acid (p=0.03) in the first model (p<0.05). The second model showed a significant association between SEVR, systolic BP (p=0.03) and HOMA-IR (p=0.02). Finally, the third model showed a significant correlation among SEVR, systolic BP (p=0.003), HOMA-IR (p=0.02) and HGFR (p=0.01) (**Table 4**).

Finally, we performed a confirmatory analysis employing a different definition of HGFR. In particular, we used a cut-off of 120 ml/min to define the highest eGFR category. No significant differences were observed in multiple regression analysis compared with the previous analysis; HGFR was still independently related with Aug, AIx and SEVR (data not shown).

Discussion

Prediabetes is a metabolic stage intermediate between normal glucose homeostasis and diabetes, and it is associated with an increased risk of developing diabetes and cardiovascular disease [23]. Our aim was to investigate the association between HGFR and early markers of cardiovascular disease in subjects with prediabetes.

The main finding of this study is that prediabetic subjects with HGFR exhibited higher Aug and AIx compared with prediabetic subjects without HGFR. HGFR has been reported to be associated with other conditions at high cardiovascular risk such as diabetes, hypertension and obesity [2,3,24]; however, to the best of our knowledge, this is the first study to investigate the association of HGFR with early markers of cardiovascular damage in subjects with prediabetes. The clinical relevance of HGFR in determining cardiovascular risk has been underlined by previous studies: Park *et al*. reported 37% higher risk for all-cause mortality and 66% higher risk of cardiovascular mortality in individuals with HGFR in an apparently healthy population after adjustment for BMI and known risk factors, including smoking [25]. Another study reported that hyperfiltration (eGFR >105 mL/min per 1.73 m^2) was associated with a significant increase risk of death after adjustment for age and exclusion of patients with diagnosed diabetes [10]. Finally, in a study including only patients with clinical cardiovascular disease, van der Sande *et al.* showed an increased risk of all-cause mortality in the highest quartile of eGFR/kidney length ratio, which was presumed to represent hyperfiltration [26]. No one of these studies took into consideration specifically subjects with early alteration of glucose homeostasis.

As reported, we found a significant increase in Aug and AIx in subjects with HGFR compared with subjects without HGFR; in contrast, no difference was observed between PWV and IMT in the same groups. This discordance is not surprising: indeed, wave reflection indices and aortic stiffness do not always change in parallel; other studies reported that Aug, AIx and PWV were differentially affected in subjects with an alteration of glucose homeostasis [27–29]. AIx is

primarily determined by the magnitude and timing of the reflected pressure waves, which depend on the tone and elasticity of the small muscular arteries at the major sites of pressure wave reflection; PWV is a measure of elastic-type large artery stiffness and is inversely related to aortic distensibility and compliance [30]. Therefore, arterial stiffness may be changed independently of PWV due to alterations in vascular smooth muscle tone that do not affect the elastic aorta. Increases in oxidative stress and reduced endothelial nitric oxide availability may impact the peripheral arteries more than the aorta.

Interestingly, in this study, subjects with prediabetes and HGFR exhibited a lower insulin sensitivity (expressed as Matsuda Index); furthermore, the study demonstrated a significant association between high eGFR and insulin resistance (expressed as HOMA index); in the kidney, insulin-resistance/sensitivity may act at multiple levels and modulate different functions such glomerular filtration, gluconeogenesis, renal sodium handling and others [31]. In agreement with our data, van Bommel E *et al.* recently demonstrated that impaired insulin sensitivity is associated with intrarenal hemodynamic dysfunction by gold standard techniques (hyperinsulinemic-euglycemic clamp and urinary inulin) in adults with type 2 diabetes treated with metformin monotherapy [32]. The association between insulin resistance and cardiovascular disease has been previously reported, however, these results suggest that insulin resistance may be associated with hemodynamic renal dysfunction, including hyperfiltration, and raise the possibility that it may represent one factor linking renal function and cardiovascular disease [33]. It is interesting to underline that treatments known to increase insulin sensitivity, such as rosiglitazone or bariatric surgery, were found to reduce glomerular hyperfiltration and renal outcomes in patients with early type 2 diabetes [34].

In this study, SEVR, a non-invasive parameter of coronary perfusion, was reduced in prediabetic subjects with HGFR compared with subjects with prediabetes and lower eGFR. SEVR's relationship with eGFR remained significant in multivariate model. Few studies investigated the

relationship between SEVR and renal hemodynamic parameters. Di Micco L *et al.* analyzed the relationship between SEVR and cardiovascular mortality in patients with chronic kidney disease; they reported that a reduction of SEVR values impacts cardiovascular mortality in this population [35]. Another study explored the hypothesis that arterial stiffness indexes, which predict cardiovascular disease, might have potential for renal risk assessment in patients with childhood-onset type 1 diabetes; SEVR, but not Aug, was independently and negatively related with measures of renal function such as presence of macroalbuminuria and degree of albuminuria and eGFR indicating a potential use of SEVR for early detection of individuals at risk of cardiovascular and renal complications of type 1 diabetes [36].

There were several limitations of this study. First, this was a cross-sectional study, and a longitudinal causal relationship cannot be established between changes in cardiovascular markers and eGFR. Second, as mentioned above, there is not a universal definition of HGFR, therefore, we decided to adopt a relative definition such as an eGFR above the 75th percentile; we choose to adopt the same definition of a prospective cohort study from Van Biesen et al (*Eur Heart J* 2007) conducted on 8913 patients with type 2 diabetes [37]. Third, the data regarding albuminuria in our population are not available for most subjects. Finally, only Caucasian patients were included, it is a single-center study, and no follow-up has been performed; all these study characteristics limit the generalizability of the results.

In conclusion, our data suggest that a high eGFR may be able to identify subjects with higher cardiovascular risk among the prediabetic population. Prospective studies are needed to confirm the real cardiovascular disease and renal dysfunction progression risk of prediabetic patients with HGFR.

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Compenting Interest

The authors declare that they have no competing interests.

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Authors' contribution

A.D. contributed to study design, data acquisition analysis and interpretation and drafted the manuscript; S.M. contributed to study design, data acquisition analysis and interpretation and drafted the manuscript; R.S. contributed to study design, data analysis and interpretation and drafted the manuscript; L.Z. contributed to design, data interpretation, drafted and critically revised the manuscript; V.F. contributed to design, data interpretation, drafted and critically revised the manuscript. F.U. contributed to design, data interpretation, drafted and critically revised the manuscript. A.F. contributed to study conception, drafted and critically revised the manuscript. S.D. contributed to conception, drafted and critically revised the manuscript. A.S. contributed to conception, drafted and critically revised the manuscript. S.P. contributed to conception, drafted and critically revised the manuscript. P.C contributed to conception, drafted and critically revised the manuscript. F.P. contributed to conception, drafted and critically revised the manuscript. A.M.R. contributed to study conception and data interpretation, drafted and critically revised the manuscript.

All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1 – Clinical and metabolic characteristics of the prediabetic population according to presence or absence of high glomerular filtration rate.

	Overall (n=230)	**Prediabetes without HGFR (*n=169*)**	**Prediabetes with HGFR (*n=61*)**	***p* value**
Age (year)	50.4±11.4	50.2±9.6	51.1±11.1	0.56
BMI (Kg/m^2)	30.2±5.3	29.9±4.8	30.7±5.1	0.28
Systolic BP (mmHg)	121.8±13.8	122.1±14.1	120.4±13	0.42
Diastolic BP (mmHg)	74.7±10.8	74.9±10.6	74.2±11.6	0.60
Heart rate (b/min)	72.3±4.3	71.9±5.1	73.4±4.8	0.3
Total cholesterol (mmol/L)	5.25±1.01	5.24±0.99	5.31±1.13	0.68
HDL cholesterol (mmol/L)	1.22±0.35	1.19±0.34	1.35±0.34*	0.02
Triglycerides (mmol/L)	1.15(0.85-1.61)	1.2(0.93-1.64)	0.93(0.77-1.54)*	0.009
LDL cholesterol (mmol/L)	3.14±0.88	3.43±0.9	3.41±0.99	0.9
eGFR (ml/min)	108.2±16.3	100.7±11.3	129.7±6.3*	0.00
Fasting glucose (mmol/L)	5.17±0.62	5.22±0.66	5±0.49	0.63
1-h glucose (mmol/L)	9.01±2.39	9.08±2.46	8.75±2.24	0.31
2-h glucose (mmol/L)	7.1±1.86	7.17±1.8	6.97±2.03	0.16
HbA_{1c} (mmol/mol)	41±4.4	41±4.5	41±4.3	0.43
HOMA-IR	1.8(1.2-2.6)	1.75(1.1-2.2)	1.87(1.3-2.8)	0.14
Matsuda Index	4.2(2.9-6.2)	4.5(3-9)	3.9(2.8-7.4)	0.03

Hs-CRP	0.22(.1-0.44)	0.33(0.1-0.43)	0.35(0.09-0.44)	0.70
Uric acid (mg/dL)	5.1±1.4	5.3±1.5	4.7±0.9	0.06
Active smokers (%)	38%	39%	32%	0.59
Hypertension (%)	30%	30%	30%	0.98
Statin therapy (%)	24%	23%	25%	0.65
Sex (M%)	47%	45%	27%*	0.001
ACEIs or ARBs therapy (%)	13%	14%	12%	0.54

Data are presented as mean ± SD or median (IQR); *p* values refer to results after analysis with adjustment for age and sex.

HGFR, high glomerular filtration rate; BMI, body mass index; BP, Blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high sensitivity C-reactive protein; ACEIs, angiotensin converting enzyme inhibitors; ARBs angiotensin receptor blockers.

Smoking was quantified (number of cigarettes and years smoked) and smoking status was classified in active and nonsmokers.

Hypertension was defined as systolic blood pressure ≥135 mmHg or diastolic blood pressure ≥85 mmHg or taking any hypertension medications.

Table 2 – Multivariate logistic regression analysis evaluating the presence/absence of high glomerular filtration rate as dependent variable.

	Coefficient ß (95%CI)	***p value***
HGFR		
Systolic BP	0.22 (0.51 - 0.02)	0.02
Matsuda Index	-0.21 [-0.075 - (-0.45)]	0.04

Model was adjusted for BMI, smoking status, systolic and diastolic BP, LDL cholesterol, HDL cholesterol, uric acid, fasting glucose, HbA_{1c}, HOMA-IR and Matsuda Index.

Table 3 – Early markers of cardiovascular damage according to presence or absence of high glomerular filtration rate.

	Overall (n=230)	**Prediabetes without HGFR (*n=169*)**	**Prediabetes with HGFR (*n=61*)**	***p* value**
Aug (mmHg)	11.7±6.6	10.8±6.2	14.1±7.2	0.001
AIx (%)	29±12.2	27.6±11.7	32.9±12.7	0.004
PWV (cm/sec)	7.7±1.6	7.7±1.6	7.6±1.4	0.66
IMT (mm)	0.73(0.66-0.82)	0.73(0.66-0.82)	0.73(0.65-0.83)	0.52
SEVR (%)	159.5±29.9	162.5±30.2	153.5±27.8	0.008

Data are presented as mean ± SD; *p* values refer to results after analysis with adjustment for age, sex and heart rate.

HGFR, high glomerular filtration rate; Aug, Augmentation pressure: AIx, Augmentation index; PWV pulse wave velocity; IMT, intima-media thickness; SEVR, subendocardial viability ratio.

Table 4 - Multiple regression analysis evaluating Aug and SEVR as dependent variables.

	Coefficient β	***p value***
Aug		
Model 1*		
Age	0.5	0.001
Systolic BP	0.18	0.001
HDL cholesterol	0.14	0.01
Model 2**		
Age	0.55	0.001
Systolic BP	0.15	0.01
HOMA-IR	0.14	0.02
Model 3***		
Age	0.53	0.001
Systolic BP	0.21	0.01
HOMA-IR	0.17	0.01
HGFR	0.19	0.01
AIx		
Model 1*		
Age	0.54	0.001
BMI	0.14	0.02
HDL cholesterol	0.14	0.01

Model 2**		
Age	0.58	0.001
HOMA-IR	0.24	0.02
Model 3***		
Age	0.6	0.001
HOMA-IR	0.21	0.01
HGFR	0.14	0.002
SEVR		
Model 1*		
Systolic BP	-0.31	0.04
Uric acid	-0.26	0.03
Model 2**		
Systolic BP	-0.15	0.03
HOMA-IR	-0.17	0.02
Model 3***		
Systolic BP	-0.17	0.003
HOMA-IR	-0.16	0.02
HGFR	0.18	0.01

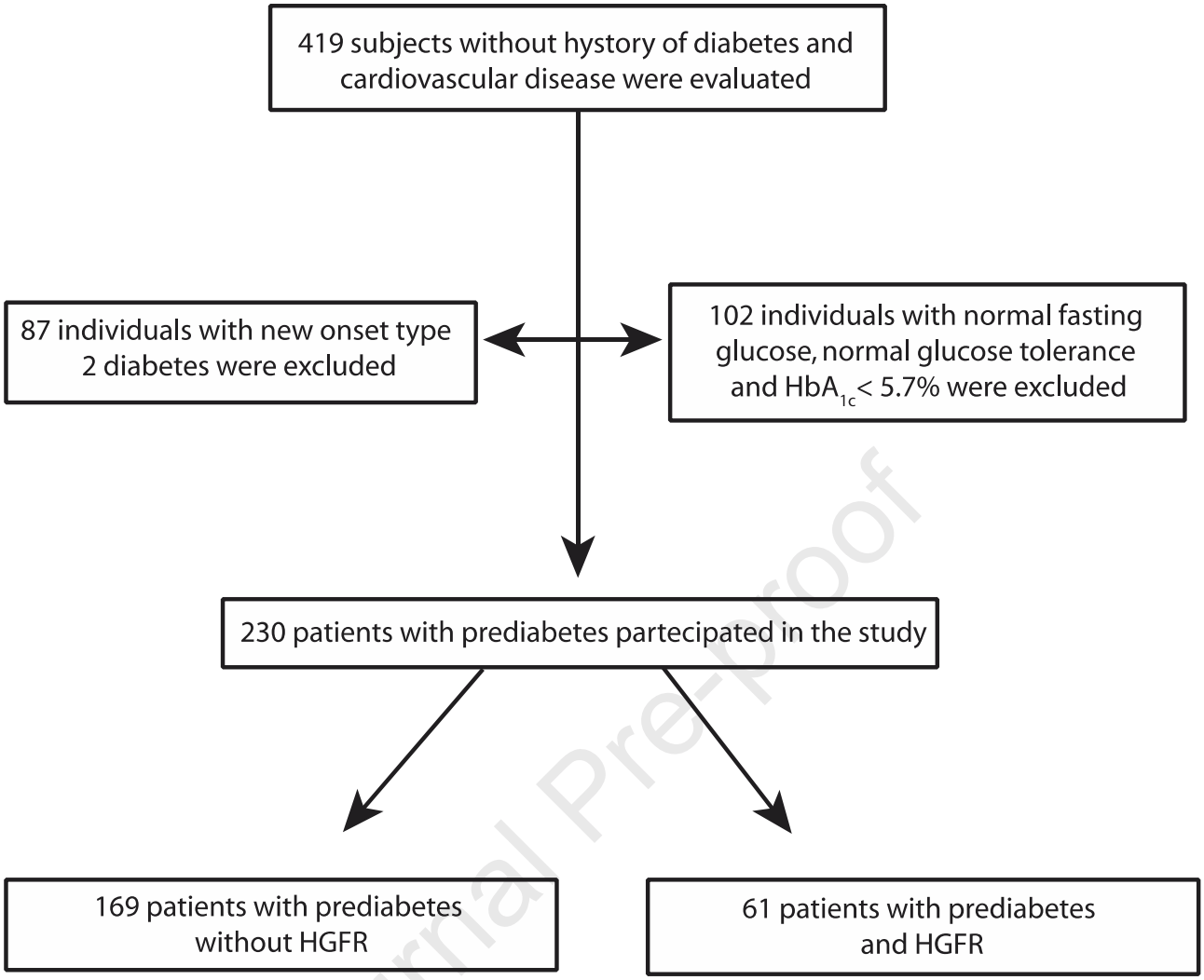
*Model 1 was adjusted for age, sex, BMI, smoking status, systolic BP, diastolic BP, LDL cholesterol, HDL cholesterol, uric acid.

**Model 2 was adjusted for fasting glucose, 1-h glucose, 2-h glucose, HbA_{1c}, HOMA-IR, and Matsuda Index

***Model 3 was adjusted for HGFR

Aug, augmentation pressure; SEVR, subendocardial viability ratio; BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; HGFR, high glomerular filtration rate; $HbA_{1c,}$ glycated haemoglobin.

Figure 1- Enrollment of the study population. HGFR, high glomerular filtration rate.



Highlights

- We studied the relationship between high glomerular filtration rate and vascular damage in prediabetes
- High glomerular filtration rate was associated with increased arterial stiffness
- High glomerular filtration rate was associated with decreased subendocardial viability ratio
- HGFR was one of the major determinants of arterial stiffness
- We showed a significant association between HGFR and insulin resistance