Impaired Fasting Glucose Is Associated With Renal Hyperfiltration in the General Population

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OBJECTIVE—Increased glomerular filtration rate (GFR), also called hyperfiltration, is a proposed mechanism for renal injury in diabetes. The causes of hyperfiltration in individuals without diabetes are largely unknown, including the possible role of borderline hyperglycemia. We assessed whether impaired fasting glucose (IFG; 5.6–6.9 mmol/L), elevated HbA_{1c}, or hyperinsulinemia are associated with hyperfiltration in the general middle-aged population.

RESEARCH DESIGN AND METHODS—A total of 1,560 individuals, aged 50–62 years without diabetes, were included in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6). GFR was measured as single-sample plasma iohexol clearance. Hyperfiltration was defined as GFR >90th percentile, adjusted for sex, age, weight, height, and use of renin-angiotensin system inhibitors.

RESULTS—Participants with IFG had a multivariable-adjusted odds ratio of 1.56 (95% CI 1.07–2.25) for hyperfiltration compared with individuals with normal fasting glucose. Odds ratios (95% CI) of hyperfiltration calculated for a 1-unit increase in fasting plasma glucose (FPG) and HbA_{1c}, after multivariable-adjustment, were 1.97 (1.36–2.85) and 2.23 (1.30–3.86). There was no association between fasting insulin levels and hyperfiltration. A nonlinear association between FPG and GFR was observed (df = 3, $P < 0.0001$). GFR increased with higher glucose levels, with a steeper slope beginning at FPG ≥5.4 mmol/L.

CONCLUSIONS—Borderline hyperglycemia was associated with hyperfiltration, whereas hyperinsulinemia was not. Longitudinal studies are needed to investigate whether the hyperfiltration associated with IFG is a risk factor for renal injury in the general population.

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Chronic kidney disease (CKD) is recognized as a global health problem. The prevalence of CKD is estimated to exceed 10% in Western societies and in many Asian countries (1). Concurrently, the incidence of obesity and prediabetes, defined as impaired fasting glucose (IFG) or impaired glucose tolerance, has reached epidemic proportions worldwide (2). Growing evidence links prediabetes and insulin resistance to microalbuminuria and CKD, but the pathophysiologic mechanisms for renal injury have not been elucidated (3,4). However, studies in animals and humans indicate that an abnormally elevated glomerular filtration rate (GFR), or hyperfiltration, may increase the susceptibility to renal injury in obesity and in diabetes (5,6).

At the single-nephron level, hyperfiltration is hypothesized to be an early link in the chain of events that lead from intraglomerular hypertension to albuminuria and, subsequently, to reduced GFR (7). This paradigm has received attention in experimental research, but is difficult to study at the population level because obtaining accurate measurements of GFR is complicated and time-consuming. GFR estimated from creatinine or cystatin C levels is imprecise in the normal or upper range of GFR and is biased in individuals with atypical body composition or creatinine production (8). Accordingly, although hyperglycemia is known to mediate hyperfiltration in diabetes, the causes of hyperfiltration in the general population are largely unknown; particularly, whether prediabetes or insulin resistance is associated with hyperfiltration is unknown.

The current study investigated whether IFG, elevated HbA_{1c}, hyperinsulinemia, or insulin resistance are associated with hyperfiltration in a general middle-aged population. To avoid the problems of estimating GFR from creatinine or cystatin C values, we measured GFR as iohexol clearance, which is recognized as an accurate method (9).

RESEARCH DESIGN AND METHODS

—The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) is a part of the population-based sixth Tromsø study (Tromsø 6) in the municipality of Tromsø, Northern Norway. Tromsø 6 was conducted in 2007 through 2008 and included an age-stratified representative sample of 12,984 inhabitants of Tromsø. Among the 5,464 invited persons in the group aged 50 to 62 years, 3,564 (65%) met and completed the main part of Tromsø 6, which included a self-administered questionnaire on health status, a physical examination, and collection of three separate morning spot urine samples. From this group, the 2,825 subjects without previous myocardial infarction, angina pectoris, stroke, diabetes, or renal disease were invited to participate in RENIS-T6 (Supplementary Fig. 1).

The age-group of 50 to 62 years was chosen to study a relatively healthy

population, but with a sufficient risk of CKD and cardiovascular disease for a later end point study. A detailed description of RENIS-T6 has been published elsewhere (10). Briefly, 2,107 (75%) responded positively and 72 were excluded. A total of 1,632 subjects were included according to a predetermined target size. The characteristics of the RENIS-T6 cohort were comparable with the 2,825 eligible recruits, as previously reported (10). For the present analyses, subjects with fasting plasma glucose (FPG) $\geq$7.0 mmol/L or HbA$_{1c}$ $\geq$6.5% were considered to have diabetes and were excluded. We also excluded subjects with an iohexol clearance <60 mL/min/1.73 m^2 according to the definition of CKD.

Study participants met in the morning after an overnight fast, including abstinence from tobacco. Blood pressure (BP) was measured three times with an automatic device (model UA-799, A&D Medical, San Jose, CA), and the last two readings were averaged. A Teflon catheter was placed in an antecubital vein and fasting plasma samples were drawn for biochemical analyses. Iohexol (5 mL) was injected, and the syringe was weighed before and after injection. The venous catheter was flushed with 30 mL of isotonic saline. The iohexol blood sample was drawn from the same catheter and the iohexol concentration was measured by high-performance liquid chromatography.

GFR was calculated as described by Jacobsson (11). Details about the iohexol clearance measurements were published previously (10). Plasma creatinine levels were analyzed by the enzymatic method that was standardized against isotope dilution mass spectroscopy. Cystatin C was measured by particle-enhanced turbidimetric immunoassay (Gentian, Moss, Norway). We estimated GFR (eGFR) from creatinine or cystatin C by using the recalibrated four-variable Modification of Diet in Renal Disease (MDRD) equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and Rule's equation of 2006 (12,13). Values for FPG, triglycerides, and cholesterol were measured on the Modular model P800 (Roche Diagnostics Corp., Indianapolis, IN). IFG was defined according to the American Diabetes Association criteria of 5.6–6.9 mmol/L for FPG.

The insulin samples were measured with an ELISA kit (DRG Instruments, Marburg, Germany). The intraassay and interassay coefficients of variation were 4.7 and 6.3%. Insulin resistance (IR) was expressed by homeostasis model assessment (HOMA)-IR: [FPG (mmol/L) × fasting insulin (µU/L)]/22.5.

HbA$_{1c}$, urinary albumin excretion (UAE), and urinary creatinine were measured in the main part of Tromsø 6. HbA$_{1c}$ was measured with a liquid chromatographic method. UAE and urinary creatinine were measured with commercial kits, as described in a previous study (14). The albumin/creatinine ratio (ACR) was calculated for each urine specimen, and the mean ACR value was used in the analyses (14).

We estimated age- and sex-adjusted means or median values across two groups: those with normal FPG and those with IFG. Differences across groups were tested by linear regression for mean values, quantile regression for median values, and multiple logistic regression for dichotomous variables. The associations between GFR expressed in mL/min/1.73 m^2 and FPG, HbA$_{1c}$, fasting insulin, and HOMA-IR were assessed by multiple linear regression analysis, adjusting for the following known or possible determinants of GFR: age, sex, height, weight, current smoking, diastolic BP, and current use of ACE inhibitors or angiotensin receptor blockers (ARB). The same analyses were repeated for the absolute GFR expressed in mL/min.

To investigate a possible nonlinear association between FPG and GFR, we used local regression smoothing in a generalized additive model, adjusting for the same variables as in the linear regression analyses. Renal hyperfiltration was defined as an absolute GFR >90th percentile after adjusting for sex, age, weight, height, and the use of ACE inhibitors or ARB. This was done by selecting all subjects >90th percentile in the distribution of residuals from a multiple linear regression analysis where we used the logarithm of absolute GFR as a dependent variable and sex, use of ACE inhibitors or ARB, and the logarithm of age, weight, and height as independent variables.

Multiple logistic regression analyses were performed to determine the odds ratios of hyperfiltration associated with the same independent variables, and adjusted for age, sex, height, weight, current smoking, diastolic BP, and use of ACE inhibitors or ARB. The same linear and logistic regression analyses were repeated with adjustment for BMI instead of for height and weight. We tested for interactions between the independent variables and sex, age, and BMI in all analyses.

Stata 11 software (Stata Corp., College Station, TX) was used for the statistical analysis. Generalized additive models were analyzed using PROC GAM in SAS 9.2 software (SAS Institute, Cary, NC). Statistical significance was set at $P < 0.05$. The study was approved by the regional ethics committee of Northern Norway. All subjects provided informed written consent.

RESULTS—The study excluded 33 individuals with diabetes according to their FPG or HbA$_{1c}$ results, 34 with measured GFR <60 mL/min/1.73 m^2, and 5 with a failure in the iohexol measurement (Supplementary Fig. A1).

IFG was present in 311 men (40%) and 141 women (18%). Table 1 reports the characteristics of the study population divided by glucose status, adjusted for age and sex. Individuals with IFG had higher BMI, insulin levels, and BP, but not higher ACR compared with those with normal FPG. Measured GFR, but not creatinine- or cystatin C–based eGFR, was higher in individuals with IFG ($P = 0.002$).

Multiple linear regression analyses with measured GFR as a dependent variable are reported in Table 2. FPG, HbA$_{1c}$, fasting insulin, and HOMA-IR were positively associated with GFR in separate models when adjusted for age, sex, weight, height, diastolic BP, current smoking, and use of ACE inhibitors or ARB. Because of collinearity, HOMA-IR and insulin were analyzed in separate models. Regression diagnostics did not indicate problems with collinearity between FPG and insulin or HOMA-IR. The effect estimates of insulin and HOMA-IR were no longer significant in models including FPG. There were no significant interactions among age, sex, or BMI and the predictor variables listed in Table 2. The pattern of statistically significant estimates was similar when we used the logarithm of absolute GFR as the dependent variable and the same independent variables but with log-transformed age, weight, and height (not shown). A nonlinear association between FPG and GFR was observed by using local regression smoothing in a generalized additive model, after multivariable adjustment (df = 3, $P < 0.0001$; Fig. 1). GFR increased with higher glucose levels, with a steeper slope beginning at FPG $\geq$5.4 mmol/L.

The 79 women and 77 men with hyperfiltration had mean GFRs of 110.1 (range 98.7–138.6) and 118.2 (107.5–137.3) mL/min/1.73 m^2, compared with

Table 1—General characteristics of the study population grouped by glycemic category*

	Fasting glucose		
	Normal†	Impaired‡	
Variable	$n = 1,108$	$n = 452$	P
Male sex	42	69	<0.001
Age (years)	57.8 ± 3.7	58.5 ± 3.9	0.001
BMI (kg/m^2)	26.7 ± 3.8	28.4 ± 3.9	<0.001
Overweight	48	48	0.86
Obese	18	32	<0.001
Current daily smoking	23	18	0.02
Systolic BP (mmHg)	128.6 ± 16.6	131.4 ± 16.9	0.003
Diastolic BP (mmHg)	83.0 ± 9.4	84.5 ± 9.6	0.005
Triglyceride level (mmol/L)	0.9 (0.7–1.4)	1.1 (0.8–1.6)	<0.001
HDL cholesterol level (mmol/L)	1.55 ± 0.40	1.50 ± 0.40	0.03
Fasting glucose (mmol/L)	5.1 ± 0.3	5.9 ± 0.3	
HbA$_{1c}$ level (% unit)	5.5 ± 0.3	5.7 ± 0.3	<0.001
Fasting insulin level (μU/mL)	7.7 (5.4–10.6)	10.8 (7.8–14.7)	<0.001
HOMA-IR (index)	1.7 (1.2–2.4)	2.9 (2.1–3.9)	<0.001
ACR (mg/mmol)	0.33 (0.19–0.59)	0.31 (0.18–0.58)	0.18
Measured GFR§	100.7 ± 15.0	106.1 ± 15.2	<0.001
Adjusted for BSA	91.8 ± 12.4	94.0 ± 12.6	0.002
eGFR			
MDRD‖	94.4 ± 16.2	94.2 ± 16.4	0.8
CKD-EPI¶	95.2 ± 8.8	95.0 ± 8.9	0.69
Cystatin C#	92.6 ± 16.4	92.7 ± 16.7	0.91

Values are expressed as means ± SD, percentages, or medians (interquartile range). BSA, body surface area. *Values are adjusted by age and sex. †Normal fasting glucose: <5.6 mmol/L (<100 mg/dL). ‡IFG: 5.6–6.9 mmol/L (100–125 mg/dL). §GFR (mL/min/1.73 m^2) measured by single-sample iohexol clearance. ‖GFR (mL/min/1.73 m^2) estimated by the MDRD equation (12). #GFR (mL/min/1.73 m^2) estimated by Rule's cystatin C–based equation of 2006 (13). ¶GFR (mL/min/1.73 m^2) estimated by the CKD-EPI equation (12).

86.5 and 93.6 mL/min/1.73 m^2 for women and men with normal filtration. Multivariable-adjusted odds ratios for hyperfiltration in relation to metabolic factors are reported in Table 3. Higher levels of FPG, HbA$_{1c}$, and HOMA-IR, and having IFG, were significantly associated with an increased odds ratio of

Table 2—Multiple linear regression analyses with measured GFR as the dependent variable

| Independent variable	β Coefficient	95% CI	P
Model 1			
BMI, per unit	0.04	−0.12 to 0.21	0.64
Model 2			
Fasting glucose, per mmol/L (18 mg/dL)	3.67	2.29–5.06	<0.001
Model 3			
HbA$_{1c}$, per % unit	2.38	0.46–4.31	0.015
Model 4			
Fasting insulin, per μU/mL	0.16	0.03–0.29	0.015
Model 5			
HOMA-IR, per unit	0.80	0.31–1.29	0.001
Model 6			
Fasting glucose, per mmol/L (18 mg/dL)	3.46	2.02–4.89	<0.001
Fasting insulin, per μU/mL	0.08	−0.05 to 0.21	0.230
Model 7			
Fasting glucose, per mmol/L (18 mg/dL)	3.28	1.78–4.78	<0.001
HOMA-IR, per unit	0.36	−0.16 to 0.89	0.177

All models except model 1 were adjusted for age, sex, weight, height, diastolic BP, current smoking, and the use of ACE inhibitors or ARB. Model 1 was adjusted for the same variables except for weight and height. GFR was measured by iohexol clearance and expressed as mL/min/1.73 m^2.

hyperfiltration. Fasting insulin level was not associated with hyperfiltration. The effect of FPG and IFG remained strong and significant after additional adjustment for HDL cholesterol, triglycerides, insulin, ACR, and BMI (not shown). HOMA-IR, however, was not associated with hyperfiltration after adjusting for FPG (model 8). All the logistic regression models were repeated with a stricter definition of hyperfiltration by defining only those with adjusted absolute GFR >95th percentile as having hyperfiltration. These analyses yielded similar findings. Some degree of hemolysis was found in 180 serum samples (11%), and this significantly influenced the mean insulin levels but not the mean glucose levels. However, both the linear and logistic regression estimates remained essentially the same after excluding individuals with hemolysis in serum samples.

CONCLUSIONS—In this middle-aged population without diabetes, we found that IFG was associated with hyperfiltration independent of age, sex, BMI, BP, smoking status, and insulin levels. A similar association was found between HbA$_{1c}$ and hyperfiltration, which indicates not only an acute effect but also an effect of chronically elevated glucose levels on GFR. Furthermore, we observed a nonlinear association between FPG and GFR, with steepening of the regression curve at FPG ≥5.4 mmol/L.

Experimental studies in healthy subjects have shown increased GFR was induced by acute glucose infusion, but plasma glucose in these experiments was increased to >7.0 mmol/L (15). In dogs, a continuous glucose infusion for 6 days, producing a modest rise in serum glucose from 6.5 to 7.1 mmol/L, increased GFR significantly (16). To our knowledge, no previous human studies have found that glucose levels in the nondiabetic range significantly and independently influence GFR. A few studies found that FPG in the nondiabetic range was associated with increased GFR, but these studies did not adjust GFR for sex, body size, or body weight (17). FPG was not associated with hyperfiltration in two previous hyperfiltration studies in nondiabetic individuals (18,19). However, these studies used creatinine clearance or creatinine-based eGFR, which are limited by low precision and bias, especially in the upper GFR range (8).

The estimating formulas are also influenced by non-GFR factors such as
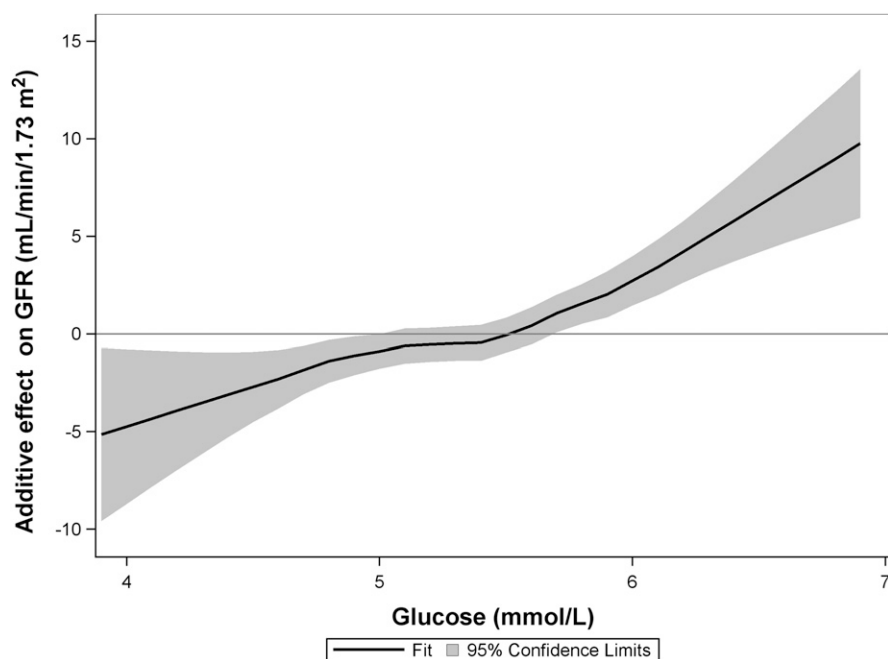
Figure 1—*A nonlinear effect of fasting glucose on measured GFR, calculated by local regression smoothing in a generalized additive model (df = 3, P < 0.0001), and adjusted for age, sex, height, weight, current smoking, diastolic BP, and the use of ACE inhibitors or ARB.*

body composition and glycemic status (20). In the current study, we found a significantly higher measured GFR but not higher creatinine- or cystatin C–based eGFR in persons with IFG. This demonstrates the difficulty of studying hyperfiltration with eGFR. Cystatin C was recently proposed as a new and better marker of renal function in the normal GFR range. However, cystatin C is also influenced by non-GFR factors. We recently showed that cystatin C–based eGFR did not perform better than creatinine-based eGFR when validated against iohexol clearance in the

general population (10). We are aware of only one previous study that measured GFR to assess the association between IFG and hyperfiltration. In a study that included 363 participants of African descent with a positive family history of hypertension, individuals with IFG had an increased risk of hyperfiltration, although not statistically significant (21). Hyperfiltration in this study was defined as GFR >140 mL/min/1.73 m², without adjusting for age and sex.

In the current study, fasting insulin levels and HOMA-IR were associated with increased GFR in the linear regression analysis, but not after adjusting for FPG. Furthermore, insulin levels were not associated with hyperfiltration. Previous population studies of insulin levels and GFR are scarce, none included an exact method to measure GFR, and the results are divergent (22). Nevertheless, hyperinsulinemia and insulin resistance are both proposed as mediators of hyperfiltration and subsequent renal injury in obesity (22). Our results are inconsistent with the hypothesis that hyperinsulinemia causes hyperfiltration in the general population where overweight and obesity is prevalent. Thus as previously suggested, mechanisms other than hyperfiltration, such as inflammatory cytokines or lipotoxicity, may link insulin resistance to kidney damage (5).

Unlike most previous hyperfiltration studies (18,19,21), we adjusted for age, sex, height, and body weight when defining hyperfiltration. There is no consensus on how to define hyperfiltration. The clinical relevance of hyperfiltration is based on a proposed pathologic effect of increased single-nephron GFR, which cannot be measured in humans. Instead, whole-kidney hyperfiltration, with a threshold arbitrarily set in different studies from 125 to 140 mL/min/1.73 m², was assumed to reflect hyperfiltration at the glomerular level (6). However, because the number of nephrons varies significantly between individuals, whole-kidney GFR will reflect variation in nephron number as well as in single-nephron GFR. Moreover, GFR and nephron number both decrease with age and are lower in women than in men (23). A noncorrected threshold for hyperfiltration would mask hyperfiltration at older ages and in women. Because body weight could confound the association between IR or prediabetes and hyperfiltration, we chose to adjust GFR not only for age, sex, and height but also for body weight, in the definition of hyperfiltration.

Table 3—*Multiple logistic regression analyses of odds ratio for hyperfiltration*

Independent variable	Odds ratio* (95% CI)	P
Model 1		
BMI, per unit	1.02 (0.98–1.06)	0.38
Model 2		
Fasting glucose, per mmol/L (18 mg/dL)	1.97 (1.36–2.85)	<0.001
Model 3		
HbA$_{1c}$, per % unit	2.23 (1.30–3.86)	0.004
Model 4		
IFG†, yes/no	1.56 (1.07–2.25)	0.019
Model 5		
Insulin, per μU/mL	1.03 (1.00–1.06)	0.08
Model 6		
IFG†, yes/no	1.48 (1.01–2.25)	0.04
Insulin, per μU/mL	1.02 (0.99–1.05)	0.20
Model 7		
HOMA-IR, per unit	1.14 (1.01–1.28)	0.033
Model 8		
Fasting glucose, per mmol/L (18 mg/dL)	1.86 (1.25–2.76)	0.002
HOMA-IR, per unit	1.06 (0.93–1.20)	0.41

*All models except model 1 were adjusted for age, sex, weight, height, diastolic BP, current smoking, and the use of ACE inhibitors or ARB. Model 1 was adjusted for the same variables except weight and height. Models 6 and 8 were also adjusted for the other variable in the same model. †IFG: 5.6–6.9 mmol/L (100–125 mg/dL).

The mechanism behind hyperfiltration in hyperglycemia is not fully understood, but studies in diabetic animals indicate a key role of increased sodium reabsorption through sodium-glucose cotransport in the proximal renal tubules (24). Raised proximal sodium reabsorption is also found in individuals with IFG compared with subjects with normal FPG (21). Furthermore, other factors associated with hyperglycemia, such as nitric oxide, vascular inflammation, oxidative stress, or activation of the renin-angiotensin system, could alter renal vascular tone, and consequently, increase GFR (24).

There is solid evidence that increased glomerular pressure causes kidney damage, but there is less evidence that glomerular hyperfiltration per se is harmful (5). For example, the long-term risk of proteinuria and end-stage renal disease after kidney donation, a state that implies hyperfiltration in the remaining kidney, is similar to that in the general population. However, transplant donors are carefully selected individuals without other CKD risk factors; therefore, their risk of renal failure should be low. In contrast, a high risk of developing proteinuria was found after unilateral nephrectomy for reasons other than kidney donation, particularly in overweight individuals (25). We are aware of only one prospective study of hyperfiltration in nondiabetic individuals. In a study of subjects with stage 1 hypertension, the risk of developing microalbuminuria was increased in those with hyperfiltration at baseline (19). These findings are consistent with the "multi-hit hypothesis" of CKD, where hyperfiltration in concert with other CKD risk factors causes kidney injury. In diabetes, some but not all studies showed an association between hyperfiltration and the subsequent development of nephropathy (6).

IFG is present in approximately 30% of the adult U.S. population, and CKD was recently found in 17% of individuals with IFG compared with 12% of those with normal FPG (2,4). Moreover, an increase in FPG within the normal range, or increased HbA_{1c}, were both associated with progression of UAE in the general nondiabetic population (3,14). In the current study, which included a relatively healthy population, IFG was not associated with ACR. Longitudinal studies with an exact method of measuring GFR are needed to explore the temporal relationship between IFG, hyperfiltration, UAE, and CKD.

Some limitations in our study should be noted. The cross-sectional design limits inferences on causality. The study population consisted of middle-aged Caucasians only, thus the results cannot automatically be generalized to other age-groups or populations. In addition, IR was not measured with the gold standard euglycemic clamp method. However, the HOMA-IR correlates well with values obtained with the euglycemic clamp technique and remains the preferred method in epidemiologic studies.

The strength of this study includes the use of an exact method to measure GFR in a large sample of the general population. We conclude that IFG is associated with an increased risk of hyperfiltration in the middle-aged nondiabetic population. Hyperfiltration caused by IFG may be one of several mechanisms for renal injury in the general population. Longitudinal studies are needed to explore whether hyperfiltration increases the risk of CKD in nondiabetic individuals.

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