Insulin Sensitivity Measured With Euglycemic Clamp Is Independently Associated With Glomerular Filtration Rate in a Community-Based Cohort

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OBJECTIVE — To investigate the association between insulin sensitivity and glomerular filtration rate (GFR) in the community, with prespecified subgroup analyses in normoglycemic individuals with normal GFR.

RESEARCH DESIGN AND METHODS — We investigated the cross-sectional association between insulin sensitivity (*M/I*, assessed using euglycemic clamp) and cystatin C–based GFR in a community-based cohort of elderly men (Uppsala Longitudinal Study of Adult Men [ULSAM], $n = 1{,}070$). We also investigated whether insulin sensitivity predicted the incidence of renal dysfunction at a follow-up examination after 7 years.

RESULTS — Insulin sensitivity was directly related to GFR (multivariable-adjusted regression coefficient for 1-unit higher *M/I* 1.19 [95% CI 0.69–1.68]; $P < 0.001$) after adjusting for age, glucometabolic variables (fasting plasma glucose, fasting plasma insulin, and 2-h glucose after an oral glucose tolerance test), cardiovascular risk factors (hypertension, dyslipidemia, and smoking), and lifestyle factors (BMI, physical activity, and consumption of tea, coffee, and alcohol). The positive multivariable-adjusted association between insulin sensitivity and GFR also remained statistically significant in participants with normal fasting plasma glucose, normal glucose tolerance, and normal GFR ($n = 443$; $P < 0.02$). In longitudinal analyses, higher insulin sensitivity at baseline was associated with lower risk of impaired renal function (GFR <50 ml/min per 1.73 m^2) during follow-up independently of glucometabolic variables (multivariable-adjusted odds ratio for 1-unit higher of *M/I* 0.58 [95% CI 0.40–0.84]; $P < 0.004$).

CONCLUSIONS — Our data suggest that impaired insulin sensitivity may be involved in the development of renal dysfunction at an early stage, before the onset of diabetes or prediabetic glucose elevations. Further studies are needed in order to establish causality.

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Reduced insulin sensitivity is a key component in the pathogenesis of diabetes, and diabetic nephropathy is a leading cause of end-stage renal disease (ESRD) (1). However, lower insulin sensitivity has also been suggested to be associated with impaired renal function in individuals without overt diabetes (2). For instance, insulin resistance has been shown to predict ESRD in patients with mild renal impairment due to IgA nephritis (3). Furthermore, the opposite chain of events has also been observed; patients with ESRD without diabetes have been shown to develop insulin resistance in the later stage of the disease (3,4). Based on previous data, we hypothesized that reduced insulin sensitivity could be involved in the development of renal dysfunction via pathways that are not primarily mediated via increased glucose levels.

We are aware of a few previous community-based studies that have reported the association of reduced insulin sensitivity to diminished renal function (2,5,6). These studies, however, have been limited by the use of surrogate markers of insulin sensitivity or by the use of creatinine-based glomerular filtration rate (GFR). Furthermore, all previous studies have included patients with impaired fasting glucose and impaired glucose tolerance, making it difficult to fully evaluate whether the association between insulin sensitivity and GFR is independent of elevated fasting and postload glucose levels. Moreover, most previous studies (2,5) have included patients with impaired renal function at baseline, and our knowledge of the relationship between insulin sensitivity and GFR within the normal range in the community is limited.

Thus, we investigated the association between insulin sensitivity, evaluated by euglycemic clamp, and cystatin C–based GFR in a community-based cohort of elderly men with prespecified subgroup analyses in individuals with normal fasting glucose, normal glucose tolerance, and normal GFR. We also investigated the longitudinal association between insulin sensitivity and renal dysfunction during follow-up and evaluated whether this association was independent of other glucometabolic factors.

RESEARCH DESIGN AND METHODS

Study sample

The design and selection criteria of the Uppsala Longitudinal Study of Adult Men (ULSAM) have been previously described (7), and further details can be found on the Internet (http://www.pubcare.uu.se/

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ULSAM/). At the third examination cycle (1991–1995), 1,221 men (mean age 71 years) were investigated. We excluded 151 men for the following reasons: unavailable clamp data ($n = 61$), unavailable cystatin C data ($n = 26$), hospitalization for kidney failure before the baseline ($n = 4$), and use of diabetes medicine ($n = 60$). Thus, the present study sample was comprised of 1,070 individuals. We also performed analyses in participants with normal fasting glucose and glucose tolerance ($n = 517$) and in participants with normal fasting glucose, normal glucose tolerance, and normal GFR (>50 ml/min per 1.73 m^2, $n = 433$). Follow-up data at the fourth examination cycle (1998–2002; mean age 77) was available in 694 participants. All participants gave written informed consent, and the ethics committee of Uppsala University approved the study protocol.

Clinical and biochemical evaluation at baseline

Serum cystatin C was measured by latex enhanced reagent (N Latex Cystatin C; Siemens) using a BN ProSpec analyzer (Siemens). GFR was calculated from serum cystatin C levels, which have been shown to be closely correlated with iohexol clearance (8) in milligrams per liter by the formula $y = 77.24x^{-1.2623}$.

The euglycemic-hyperinsulinemic clamp technique according to DeFronzo (9) was used, with a slight modification to suppress hepatic glucose production (10), for estimation of in vivo sensitivity to insulin. Insulin (Actrapid Human; Novo, Copenhagen, Denmark) was infused in a primary dose for the first 10 min and then as a continuous infusion (56 mU/min per body surface area in meters squared), during which DeFronzo (9) used 40 mU/min per body surface area in meters squared, for 2 h to maintain steady-state hyperinsulinemia. The target plasma glucose level was 5.1 mmol/l, maintained by measuring plasma glucose every 5 min. The glucose infusion rate during the last hour was used as a measure of insulin sensitivity (*M* value). The insulin sensitivity index (*M/I* ratio) was calculated by dividing *M* by the mean insulin concentration during the same period of the clamp. *M/I* thus represents the amount of glucose metabolized per unit of plasma insulin.

An oral glucose tolerance test (OGTT) was performed; subjects ingested 75 g glucose dissolved in 300 ml of water, and blood samples for plasma glucose and insulin were drawn immediately before and 30, 60, 90, and 120 min after ingestion of glucose. Plasma glucose was measured by the glucose dehydrogenase method (Gluc-DH; Merck, Darmstadt, Germany). Plasma insulin was assayed using an enzymatic-immunological assay (Enzymmun; Boehringer Mannheim, Germany) performed in an ES300 automatic analyzer (Boehringer Mannheim).

Urinary albumin excretion rate was calculated using the amount of albumin in urine collected during the night. The subjects were instructed to void immediately before going to bed and to record the time. All samples during the night and the first sample of urine after rising were collected and used for the analysis (Albumin RIA 100; Pharmacia, Uppsala, Sweden).

Coffee, tea, and alcohol consumption were recorded using a 7-day precoded food diary, based on instructions of a dietitian. Daily intakes were calculated using a computer program and the Swedish National Food Administration Database (SLV Database, 1990). Participants reported leisure-time physical activity on a standardized questionnaire (7). Smoking status was based on interviews performed by a nurse.

Diabetes was diagnosed as fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl) or 2-h postload glucose level >11.1 mmol/l (>200 mg/dl) or by the use of oral hypoglycaemic agents or insulin. Impaired glucose tolerance was defined as a 2-h postload glucose value of 7.8–11 mmol/l (140–199 mg/dl). Impaired fasting glucose was defined as fasting plasma glucose of 5.6–6.9 mmol/l (100–125 mg/dl). BMI was calculated as weight in kilograms divided by the square of height in meters. Hypertension was defined as use of antihypertensive medication or having a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Dyslipidemia was defined as total cholesterol ≥5 mmol/l (>200 mg/dl) or HDL cholesterol ≤1.0 mmol/l (<40 mg/dl) or the use of lipid-lowering medication.

Follow-up and outcome

Renal impairment during follow-up was defined as having a GFR <50 ml/min per 1.73 m^2 at the fourth examination cycle (after ~7 years) or as being hospitalized for renal failure during follow-up. We defined renal dysfunction as GFR <50 ml/min per 1.73 m^2, according to the current definition used in clinical practice in Sweden for individuals older than 50 years. Subjects who were hospitalized for renal failure were identified by the Swedish hospital discharge register using the following ICD codes: renal failure; 584–588 (ICD-9) and N17–N19 (ICD-10).

Statistical analysis

If necessary, logarithmic transformation was performed to achieve normal distribution (fasting plasma glucose, 2-h plasma glucose, fasting plasma insulin, and 2-h plasma insulin). Linear regression analyses were used to assess the cross-sectional associations between insulin sensitivity index (*M/I*; independent variable) and cystatin C–based GFR (dependent variable). The following models were used:

- Model A: age adjusted
- Model B (glucometabolic model): adjusted for age, fasting plasma glucose, fasting plasma insulin, and 2-h glucose
- Model C (cardiovascular risk factor model): adjusted for age, hypertension, dyslipidemia, and smoking
- Model D (lifestyle model): adjusted for age, BMI, physical activity, and consumption of tea, coffee, and alcohol
- Model E (combined model): adjusted for covariates in models A–D

We also performed the above analyses in the following prespecified subgroups: *1*) normal fasting glucose and normal glucose tolerance ($n = 517$) and *2*) normal fasting glucose, normal glucose tolerance, and normal GFR (>50 ml/min per 1.73 m^2, $n = 433$). In secondary analyses, the separate addition of urinary albumin excretion rate (modeled as normoalbuminuria [<20 μg/min], microalbuminuria [20–200 μg/min], or macroalbuminuria [>200 μg/min]), serum triglycerides, and 2-h plasma insulin at the OGTT to multivariable model E were also investigated. We exchanged the hypertension variable in model C for systolic and diastolic blood pressure and use of α-blockers, β-blockers, ACE inhibitors, diuretics, and calcium antagonist; we also exchanged the dyslipidemia variable in model C for total cholesterol, HDL cholesterol, and use of lipid-lowering medication. Moreover, we investigated the association of insulin sensitivity to creatinine-based GFR (calculated with the Modification of Diet in Renal Disease [MDRD]) formula (11). Also, we investigated the association between the glucose disposal rate (*M*) and GFR and the association between 2-h plasma insulin (as a

Table 1—*Baseline characteristics of the whole study population and different subsamples*

Variable	Total cohort	Normal fasting glucose and normal glucose tolerance	Normal fasting glucose, normal glucose tolerance, and GFR >50 ml/min per 1.73m^2
n	1,070	517	433
Age (years)	71.0 ± 0.59	71.0 ± 0.58	71.0 ± 0.56
Glomerular filtration rate (ml/min per 1.73m^2)	61.5 ± 13.7	61.5 ± 13.0	65.3 ± 10.4
Urinary albumin excretion rate (μg/min)	21.9 ± 84.0	19.0 ± 86.6	11.9 ± 33.0
Fasting plasma glucose (mmol/l)	5.5 ± 0.9	5.1 ± 0.3	5.1 ± 0.3
Insulin sensitivity (*M/I*) (100 × mg · kg^{-1} · body weight^{-1} · min^{-1} · mU^{-1} · l^{-1})	5.2 ± 2.5	6.2 ± 2.4	6.3 ± 2.4
OGTT 2-h glucose (mmol/l)	7.7 ± 3.0	5.8 ± 1.2	5.7 ± 1.2
Fasting plasma insulin (mu/l)	12.5 ± 7.2	10.6 ± 5.3	10.3 ± 4.9
Systolic blood pressure (mmHg)	146.7 ± 18.5	143.9 ± 18.3	143.3 ± 17.3
Diastolic blood pressure (mmHg)	83.9 ± 9.4	82.7 ± 9.3	82.5 ± 8.9
BMI (kg/m^2)	26.2 ± 3.4	25.2 ± 3.0	25.1 ± 2.9
Coffee (cups per day)	3.4 ± 1.6	3.4 ± 1.7	3.5 ± 1.6
Tea (cups per day)	0.67 ± 1.0	0.73 ± 1.2	0.73 ± 1.2
Alcohol (g/day)	6.4 ± 7.0	6.4 ± 7.0	6.6 ± 7.1
Diabetes	61 (5.7)	—	—
Impaired fasting glucose	365 (34.0)	—	—
Impaired glucose tolerance	410 (38.3)	—	—
Smoking	221 (20.7)	125 (24.2)	100 (23.1)
Dyslipidemia	938 (87.7)	446 (86.3)	372 (85.9)
Hypertension	789 (73.7)	351 (67.9)	289 (66.7)
Physical activity level			
Sedentary	36 (3.7)	15 (3.2)	12 (3.0)
Moderate	324 (33.4)	151 (31.8)	124 (31.2)
Regular	551 (56.8)	276 (58.2)	229 (57.8)
Athletic	60 (6.2)	32 (6.8)	31 (7.8)

Date are means ± SD for continuous variables and *n* (%) for dichotomous variables.

marker for daylong hyperinsulinemia) and GFR. The potential nonlinearity of the association between *M/I* and GFR was investigated using penalized regression splines.

Logistic regression was used to relate insulin sensitivity to renal dysfunction during follow-up. In these analyses, 108 participants with impaired GFR at baseline (<50 ml/min per 1.73 m^2) were excluded, which leaves 586 participants with longitudinal data. Given the moderate sample size and the low number of participants that developed renal dysfunction during follow-up ($n = 32$), we limited the multivariable modeling to models A and B, described above. We also performed these longitudinal analyses in participants with normal fasting glucose and normal glucose tolerance. In secondary analyses, we added baseline GFR to the longitudinal multivariable logistic regression models. A two-sided *P* value <0.05 was regarded as significant in all analyses. The statistical software package STATA 10.0 (Stata Corp, College Station, TX) was used for all analyses.

RESULTS

Baseline characteristics

Baseline characteristics of the study population and the different subsamples are presented in Table 1.

Cross-sectional association between insulin sensitivity and GFR

In the whole cohort, 1 unit higher of *M/I* was significantly associated with 0.85–1.19 ml/min per 1.73 m^2 higher GFR adjusting for age (model A), glucometabolic variables (model B), cardiovascular risk factors (model C), lifestyle factors (model D), and the combination of all covariates in models A–D (model E, Table 2). In participants with normal fasting glucose and normal glucose tolerance, the positive association between insulin sensitivity and GFR remained essentially the same in all models (models A–E; Table 2). After further exclusion of participants with impaired GFR (<50 ml/min per 1.73 m^2) the association between insulin sensitivity and GFR remained statistically significant in all models but with lower regression coefficients (Table 2).

In secondary analyses, the association between insulin sensitivity and GFR was not substantially altered after further adjustment for urinary albumin excretion rate, serum triglycerides, or 2-h plasma insulin at an OGTT; when exchanging the hypertension variable in model C for systolic and diastolic blood pressure and use of α-blockers, β-blockers, ACE-inhibitors, diuretics, and calcium antagonist; or when exchanging the dyslipidemia variable in model C for total cholesterol, HDL cholesterol, and use of lipid-lowering medication (data not shown). The association of insulin sensitivity with creatinine-based GFR was essentially similar to the association of insulin sensitivity with cystatin C–based GFR (model E, β coefficient 1.05 [95% CI 0.61–1.50]; $P < 0.001$). The association between *M* and GFR was similar to the association between *M/I* and GFR (model E, 1.09 [0.44–1.75]; $P < 0.001$). No deviation from linearity was detected in the association

Table 2—*The association of insulin sensitivity index (M/I) and GFR: multivariable linear regression*

Model	Total cohort (n = 1,070)		Normal fasting glucose and normal glucose tolerance (n = 517)		Normal fasting glucose, normal glucose tolerance, and GFR>50 ml/min per 1.73m^2 (n = 433)	
	β coefficient (95% CI)	*P*	β coefficient (95% CI)	*P*	β coefficient (95% CI)	*P*
A	0.86 (0.53–1.19)	<0.001	1.03 (0.57–1.50)	<0.001	0.52 (0.11–0.93)	0.01
B	1.10 (0.67–1.53)	<0.001	0.79 (0.25–1.33)	0.004	0.54 (0.07–1.00)	0.02
C	0.85 (0.52–1.19)	<0.001	1.03 (0.56–1.56)	<0.001	0.55 (0.14–0.97)	0.01
D	0.88 (0.45–1.31)	<0.001	1.09 (0.51–1.67)	<0.001	0.61 (0.11–1.10)	0.02
E	1.19 (0.69–1.68)	<0.001	0.86 (0.23–1.49)	0.007	0.66 (0.12–1.19)	0.02

Data are regression coefficients for a 1-unit higher *M/I*. Model A is adjusted for age, model B is adjusted for age and glucometabolic factors (fasting plasma glucose, fasting plasma insulin, and 2-h plasma glucose at OGTT), model C is adjusted for age and cardiovascular risk factors (hypertension, dyslipidemia, and smoking), model D is adjusted for age and lifestyle factors (BMI, physical activity, and consumption of tea, coffee and alcohol), and model E is adjusted for all covariates in models A–D.

of *M/I* and GFR, as evaluated by regression splines. Moreover, 2-h plasma insulin was inversely associated with GFR in all multivariable models (A–E; $P < 0.001$ for all) and after adding *M/I* to multivariable model E (−2.07 [−3.95 to −0.19]); $P = 0.03$).

Insulin sensitivity and the development of renal dysfunction

Of the participants with normal GFR (>50 ml/min per 1.73 m^2) at baseline, 32 developed renal dysfunction during follow-up. Of these, none underwent dialysis or renal transplantation, suggesting that the renal impairment during follow-up was not severe. Moreover, only six of these participants were diagnosed with diabetes, indicating that diabetic nephropathy was not the main underlying cause for the renal dysfunction.

Higher insulin sensitivity was borderline significantly associated with lower risk of developing renal dysfunction in the age-adjusted models (model A) and after adjustment for glucometabolic variables (model B). Interestingly, the association between insulin sensitivity and renal dysfunction appeared stronger in the subsample with normal fasting glucose and normal glucose tolerance (Table 3). Further addition of baseline GFR to multivariable model B attenuated this association in the whole sample (odds ratio [OR] 0.86, [95% CI 0.68–1.08]; $P = 0.19$). Still, the association between insulin sensitivity and impaired renal function remained statistically significant in the participants with normal glucose after the addition of baseline GFR to multivariable model B (0.61 [0.42–0.91]; $P = 0.01$).

CONCLUSIONS

— We identified a significant positive association between insulin sensitivity and GFR in a community-based sample of elderly men. This association was also consistent in participants with normal fasting glucose, normal glucose tolerance, and normal renal function and after taking glucometabolic variables, cardiovascular risk factors, and lifestyle factors into account in multivariable analyses. Moreover, in longitudinal analyses, insulin sensitivity at baseline predicted subsequent renal dysfunction independently of other glucometabolic variables. Our data suggest that the association between impaired insulin sensitivity and lower GFR is not primarily mediated via elevated glucose levels and that this association is evident already in individuals without any clinical signs of kidney dysfunction or glucose dysregulation.

Comparison with the literature

Our findings are in accordance with previous community-based studies that have investigated the cross-sectional association of insulin sensitivity and GFR (2,5,6). In these studies, decreased insulin sensitivity (assessed by serum insulin levels or homeostasis model assessment [HOMA] insulin sensitivity) was associated with impaired renal function. However, both fasting insulin and HOMA insulin sensitivity are limited as indicators of insulin sensitivity because they are also highly influenced by the individual's β-cell function, i.e., insulin secretion. The association between insulin sensitivity, as evaluated by the gold standard euglycemic clamp technique, and GFR has not been previously reported. Furthermore, no previous studies have analyzed this association in individuals with normal glucose levels and normal GFR.

We are aware of one previous study that has evaluated the longitudinal association between insulin sensitivity and incidence of renal dysfunction. In contrast to the present study, Fox et al. (12) reported that HOMA insulin resistance did not significantly predict renal dysfunction

Table 3—*The association of insulin sensitivity index (M/I) and the incidence of renal dysfunction in participants with GFR >50 ml/min per 1.73 m^2 at baseline: multivariable logistic regression*

Model	Total cohort*		Normal fasting glucose and normal glucose tolerance†	
	OR (95% CI)	*P*	OR (95% CI)	*P*
A	0.85 (0.72–1.00)	0.055	0.67 (0.51–0.89)	0.006
B	0.82 (0.65–1.02)	0.071	0.58 (0.40–0.84)	0.004

Data are ORs for a 1-unit higher *M/I*. Model A is adjusted for age, and model B is adjusted for age, fasting plasma glucose, fasting plasma insulin, and 2-h glucose at an OGTT. *Number of events per number at risk: 32 of 586. †Number of events per number at risk: 16 of 295.

in participants with normal glucose levels. The discrepant results could perhaps be explained by differences between the studies in the assessment of insulin sensitivity or that our study sample consisted exclusively of elderly men. However, no firm conclusions should be drawn from the present study with regard to the longitudinal association between insulin sensitivity and incident renal impairment due to the moderate number of events during follow-up, particularly in the subsample with normal glucose levels. Further studies are needed in order to shed further light on this issue.

Possible mechanisms for observed associations

Impaired insulin sensitivity and compensatory hyperinsulinemia have been suggested to contribute to development of renal injury via a number of different pathophysiologic pathways: insulin per se stimulates the expression and activation of IGF-1, transforming growth factor-β, endothelin-1, and components of the renin-angiotensin-aldosterone system (13). These factors have been shown to promote mitogenic and fibrotic processes in the kidney, such as proliferation of mesangial cells and extracellular matrix expansion (13). Moreover, insulin resistance and hyperinsulinemia are closely associated with oxidative stress (14), which could promote renal injury via decreased production and availability of nitric oxide (15) and accelerated formation of glycoxidation and lipid peroxidation products (16–18). Also, insulin resistance is linked to increased activity of proinflammatory cytokines and adipokines, factors that have been suggested to contribute to the progression of renal disease (19). There are also data suggesting that renal insufficiency suppresses renal clearance of insulin, leading to higher circulating levels of insulin and thus further stimulation of the deleterious effect of insulin on the kidney, i.e., leading to a vicious circle (20). We are not able to fully evaluate the potential influence of reduced renal clearance of insulin in our study, but the strong positive association between the glucose disposal rate (*M*) and GFR and the similar results in individuals with normal renal function indicate that the potential impact of a reduced renal clearance of insulin on the present results is not likely to be major.

The fact that the association between insulin sensitivity and GFR remained robust after adjustment for both fasting and 2-h postload insulin would argue against hyperinsulinemia as the sole explanation of our findings. Also, as 2-h postload insulin was associated with GFR independently of insulin sensitivity and all potential confounders in model E, it is possible that daylong hyperinsulinemia per se independently contributes to a reduced GFR. Since these two conditions are so closely interrelated, it is not possible to fully disentangle the individual contributions of hyperinsulinemia and insulin resistance to GFR in the present study.

There are also some other potential mechanisms that merit discussion: reduced insulin sensitivity may lead to diabetes, which is one of the leading causes of renal failure. However, as insulin sensitivity was associated with GFR in individuals with otherwise normal glucose metabolism after adjustment for both fasting and postload glucose levels, higher glucose levels are not a likely explanation for the results in the present study. Also, insulin sensitivity is associated with several glucometabolic, cardiovascular risk, and lifestyle factors that have been shown to be associated with a reduced GFR and the development of chronic kidney disease (2,12,21–23). The fact that insulin sensitivity remained significantly associated with GFR in all multivariable models suggests that confounding by these factors does not explain our findings.

Clinical implementations

While the cross-sectional regression coefficients suggest that the magnitude of the association between insulin sensitivity and GFR could be modest, the ORs from the longitudinal logistic regression analyses imply that the potential impact of lower insulin sensitivity on the development of renal dysfunction over time could be substantial. Since no firm conclusions regarding causality and effect size should be drawn from observational data, intervention trials are needed to properly investigate these issues.

Strengths and limitations

The strengths of our investigation include the large, homogenous, community-based study sample with detailed characterization of glucometabolic variables, cardiovascular risk factors, and lifestyle factors. Moreover, the ULSAM cohort is the largest cohort in the world examined with the euglycemic clamp technique. Furthermore, serum levels of cystatin C were used to estimate GFR; this method is considered to be a more reliable indicator of kidney function than estimation via creatinine-based GFR, particularly in the elderly (24).

Limitations include the unknown generalizability to women and other age- and ethnic groups. Also, multiple statistical analyses in several different subgroups were performed. Yet, because of multiple testing, the consistency of results across all models and subsamples makes it unlikely that the observed associations arose by chance. Moreover, we have not used the gold standard method to measure GFR (isotope clearance measurements). However, isotope clearance measurement is seldom used in epidemiological research, as it is a very time consuming and costly procedure. Importantly, cystatin C–based GFRs have been shown to be closely correlated with GFR assessed by isotope clearance measurements (8).

In summary, in a community-based sample of elderly men, lower insulin sensitivity was associated with lower renal function, even in individuals with normal glucose levels and normal GFR. Our data suggest that impaired insulin sensitivity may be involved in the development of renal dysfunction at an early stage, before the onset of diabetes or pre-diabetes glucose elevations. Further studies are needed to establish causality and to evaluate the clinical implications of our findings.

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