Increased Urinary Albumin Excretion, Insulin Resistance, and Related Cardiovascular Risk Factors in Patients With Type 2 Diabetes

Evidence of a sex-specific association

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OBJECTIVE — While the relevant role of insulin resistance in the pathogenesis of increased urinary albumin excretion (UAE) is well established in type 1 diabetes, its contribution in type 2 diabetes is controversial. Our aim was to investigate whether insulin resistance was associated with increased UAE in a large cohort of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 363 men and 349 women, aged 61 ± 9 years, with a disease duration of 11 ± 9 years and HbA_{1c} levels of $8.6 \pm 2.0\%$ were included. Insulin resistance was derived from the homeostasis model assessment of insulin resistance ($HOMA_{IR}$), and UAE was derived from the albumin-to-creatinine ratio (ACR) defined as increased if the value was ≥ 2.5 mg/mmol in men and ≥ 3.5 mg/mmol in women. ACR was correlated with $HOMA_{IR}$ ($r = 0.15$, $P = 0.0001$), independently of age, disease duration, blood pressure, HbA_{1c}, triglycerides, waist circumference, and smoking.

RESULTS — When the two sexes were investigated separately, a significant correlation between ACR and $HOMA_{IR}$ was reached in men ($n = 363$; $r = 0.21$, $P = 0.0001$) but not women ($n = 349$; $r = 0.08$, $P = 0.14$), suggesting that insulin resistance and sex may interact (P for interaction = 0.04) in determining UAE. When men were subgrouped into quartiles of $HOMA_{IR}$, those of the third and fourth quartile (i.e., the most insulin resistant) were at higher risk to have increased ACR than patients of the first quartile (third quartile: odds ratio 2.2 [95% CI 1.2–4.2], $P = 0.01$) (fourth quartile: 4.1 [2.2–7.9], $P = 0.00002$). Finally, ACR was significantly higher in men with two or more insulin resistance–related cardiovascular risk factors (i.e., abdominal obesity, dyslipidemia, and arterial hypertension) than in men with fewer than two insulin resistance–related cardiovascular risk factors (0.90 [0.2–115.1] vs. 1.56 [0.1–1367.6], respectively, $P = 0.005$).

CONCLUSIONS — In type 2 diabetic patients, increased UAE is strongly associated with insulin resistance and related cardiovascular risk factors. This association seems to be stronger in men than in women.

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Increased urinary albumin excretion (UAE) is a strong predictor for development of overt diabetic nephropathy and cardiovascular mortality and morbidity in patients with type 1 and type 2 diabetes (1).

Several evidences suggest that insulin resistance precedes and probably contributes to the development of increased UAE in type 1 diabetic patients (2) as well as in nondiabetic subjects (3). At variance, the relationship between insulin resistance and increased UAE in type 2 diabetic patients is less clear. In detail, both negative (4–6) and positive (7–10) results have been reported on the association between the two conditions in these patients. Worth noting, all previous studies have been carried out in small samples, ranging from 20 (4) to 155 (6) patients. Examining the relationship between insulin resistance and increased UAE may help to clarify some of the mechanisms of increased cardiovascular morbidity and mortality in patients with type 2 diabetes, and albuminuria and might be, consequently, useful from a clinical point of view. Insulin resistance is in fact treatable (11,12), and this treatment is effective in reducing cardiovascular mortality in type 2 diabetic patients (13). Therefore, if a pathogenic role of insulin resistance on increased UAE and associated cardiovascular risk in type 2 diabetes is demonstrated, patients with increased UAE might benefit from specific treatments of insulin resistance.

Conflicting results have also been reported for the possibility that the association between insulin resistance and increased UAE in the general population is sex specific, with some investigators reporting the association mostly in men (14–15) and others reporting a similar association in both sexes (16). This latter issue, which may also be of clinical rele-

Table 1—*Clinical features of type 2 diabetic patients with normoalbuminuria or micro- and macroalbuminuria according to sex*

	Men			Women		
	Normoalbuminuria	Micro- and/or macroalbuminuria	P	Normoalbuminuria	Micro- and/or macroalbuminuria	P
Sex	227 (63)	136 (67)		269 (77)	80 (23)	<0.0001
Age (years)	59 ± 9.6	62 ± 9.7	0.004	63 ± 8.8	63 ± 11.1	0.8
Duration of diabetes (years)*	9 ± 8.6	11 ± 8.8	0.4	11 ± 8.9	14 ± 9.2	0.03
BMI (kg/m^2)*	29 ± 4.9	30 ± 4.8	0.005	32 ± 6.3	32 ± 5.9	0.9
Waist circumference (cm)*	100.2 ± 13	102.7 ± 13	0.04	101.9 ± 14	104.7 ± 16	0.1
SBP (mmHg)*	133 ± 17	136 ± 17	0.2	134 ± 16	138 ± 15	0.08
DBP (mmHg)*	79 ± 9	79 ± 8	0.5	79 ± 8	78 ± 10	0.9
Triglycerides (mg/dl)*	142 ± 85	190 ± 50	<0.0001	159 ± 257	186 ± 169	0.005
Total cholesterol (mg/dl)*	194 ± 62	190 ± 50	0.9	206 ± 62	209 ± 53	0.7
HDL cholesterol (mg/dl)*	42 ± 12	40 ± 12	0.06	48 ± 13	46 ± 13	0.4
HbA$_{1c}$ (%)*	8.4 ± 2	9.0 ± 2	0.003	8.5 ± 2	9.2 ± 2	0.002
HOMA$_{IR}$*	2.9 (0.37–72.4)	4.9 (0.66–22.1)	<0.0001	4.1 (0.6–23.9)	4.1 (0.7–36.3)	0.4
ACR (mg/mmol)*	0.75 (0.08–2.37)	6.7 (2.51–1,367.61)	<0.0001	0.93 (0.24–3.48)	8.9 (3.75–157.54)	<0.0001
GFR-d (ml · min^{-1} · 1.73 m^{-2})*	90.4 ± 26	79.6 ± 34	0.04	81.7 ± 26	76.3 ± 30	0.07
Antidiabetic Rx						
Diet alone	25 (11)	17 (13)		32 (12)	8 (10)	
OHA	128 (56)	45 (33)		127 (47)	31 (39)	
Insulin (±OHA)	74 (33)	74 (54)	<0.0001	110 (41)	41 (51)	0.3
Arterial hypertension	171 (75)	121 (89)	0.002	231 (86)	72 (90)	0.3
Antihypertensive treatment	90 (40)	84 (63)	<0.0001	169 (63)	60 (75)	0.04
Treatment with ACE inhibitors/ARBs	68 (30)	53 (39)	0.09	120 (45)	50 (63)	0.007
Dyslipidemia	191 (84)	115 (85)	0.9	247 (92)	72 (90)	0.7
Treatment with hypolipidemic therapy	57 (25)	52 (38)	0.01	89 (33)	31 (39)	0.4
Retinopathy	56 (26)	68 (51)	<0.0001	55 (21)	28 (35)	0.01
Smokers	76 (34)	45 (33)	0.9	16 (6)	10 (13)	0.05

Data are *n* (%), mean ± SD, or median (range). *P adjusted for age. GFR, glomular filtration rate; OHA, oral hypoglycemic agent.

vance, has not been specifically addressed in patients with type 2 diabetes (4–10).

The aim of the present study was to investigate, in a large cohort of type 2 diabetic patients, whether insulin resistance was associated with increased UAE and, if so, if this association was sex specific.

RESEARCH DESIGN AND METHODS — This study was conducted in Caucasian patients with type 2 diabetes who were residents of the Gargano region and surrounding areas, i.e., the center east coast of Italy. A total of 712 type 2 diabetic patients (363 men and 349 women) who met the following criteria were consecutively recruited at the Endocrine Unit of the CSS Scientific Institute in San Giovanni Rotondo: diabetes diagnosed after age 30 years, absence of ketones at diagnosis, and absence of clinically evident autoimmune disease. These criteria were chosen to minimize the risk of including late-onset type 1 di-

abetic patients. In addition, anti-GAD antibodies were determined in 200 randomly selected patients, and only 3 of 200 patients turned out to be anti–GAD antibody positive (>0.9 units/ml), thus indicating that the risk of misdiagnosis is, in fact, trivial in our sample. All patients were interviewed regarding the age of type 2 diabetes diagnosis and ongoing antidiabetic treatments. Duration of diabetes was calculated from the calendar year of data collection minus the calendar year of diabetes diagnosis. Clinical features of patients recruited and subgrouped according to sex and presence or absence of micro- and macroalbuminuria are summarized in Table 1. Among 403 patients who were on antihypertensive treatment, 291 (72%) patients were on either ACE inhibitors or angiotensin II receptor 1 blockers (ARBs); among these, dihydropiridinic calcium antagonists were added in 76 (26%), whereas diuretics and α- or β-blockers were added in 183

(63%) patients. All subjects enrolled in the study underwent physical examination, including measurements of height, weight, waist circumference, and blood pressure (i.e., two measurements rounded to the nearest 2 mmHg in the sitting position after at least 5 min rest, using an appropriate-sized cuff; diastolic blood pressure was recorded at the disappearance of Korotkoff sound, phase V).

Fasting venous blood was sampled from an antecubital vein from all patients for the measurement of serum insulin, total cholesterol, HDL cholesterol, serum triglycerides, and HbA$_{1c}$, as previously described (17). Urinary albumin and creatinine concentration were determined the same morning of the clinical examination on an early morning first void sterile urine sample by the nephelometric method (Behring Nephelometer Analyzer) and the Jaffè reaction-rate method (Hitachi 737 Autoanalyzer), respectively. The urinary albumin-to-creatinine ratio

(ACR) was then calculated. Microalbuminuria was diagnosed if the ACR was ≥2.5 mg/mmol in men and 3.5 mg/mmol in women but <30 mg/mmol. Macroalbuminuria was defined as an ACR >30 mg/mmol, a level that approximates an albumin excretion of 300 mg/24 h, considered as the upper limit of microalbuminuria (18). A total of 179 patients (27%) had microalbuminuria and 37 (5%) had macroalbuminuria. The exclusion of patients with macroalbuminuria from the analysis did not change the results obtained, which were, therefore, presented for the entire cohort. The group of patients with micro- or macroalbuminuria was named the MA group.

Creatinine clearance was calculated with the Cockcroft-Gault formula (19) and was used as a measure of glomerular filtration rate. The homeostasis model assessment of insulin resistance ($HOMA_{IR}$) index was calculated as fasting serum insulin (mU/ml) × fasting plasma glucose (mmol/l)/22.5 (ref. 20).

Patients were considered to have arterial hypertension if systolic blood pressure (SBP) was ≥130 mmHg and diastolic blood pressure (DBP) ≥85 mmHg or were currently receiving antihypertensive treatment. Patients were considered to have dyslipidemia if they were currently receiving lipid-lowering treatment or had total cholesterol ≥200 mg/dl, HDL cholesterol ≤40 mg/dl in men and 50 mg/dl in women, and triglycerides ≥150 mg/dl (21). Presence of retinopathy was defined on funduscopy examination or as a history of laser therapy. Information on smoking habits was obtained by a questionnaire.

The study was performed according to the Helsinki Declaration, and the protocol was approved by the local ethics committee. All subjects provided written informed consent.

Statistical analysis
Data are reported as the mean ± SD or median (range). Mean differences were compared by unpaired Student's *t* test or Mann-Whitney *U* tests, as appropriate. A *P* value <0.05 was considered to be significant.

Univariate and multivariate analyses were performed to correlate independent variables, such as $HOMA_{IR}$, HbA_{1c}, SBP, DBP, waist, duration of disease, sex, age, smoking, lipids, antidiabetic therapy, and use of ACE inhibitors or ARBs with the dependent variable as ACR. Then, in a multivariate logistic regression analysis, we explored the effect of independent variables (i.e., $HOMA_{IR}$) on the binary dependent variable (i.e., micro- or macroalbuminuria: yes or no) and expressed as odds ratio (OR) (95% CI). For these analysis, skewed distributed variables (i.e., $HOMA_{IR}$, ACR, and triglycerides) were logarithmically transformed.

Interaction between HOMA and sex in determining UAE was tested with GLM Univariate analysis, statistical packaged SPSS version 11.5 (SPSS, Chicago, IL). The same statistical package was also used for all other statistical analysis.

RESULTS — In the entire cohort, ACR was significantly correlated with $HOMA_{IR}$ ($r = 0.15$, $P = 0.0001$), age ($r = 0.12$, $P = 0.001$), duration of diabetes ($r = 0.13$, $P = 0.0005$), SBP ($r = 0.15$, $P = 0.0009$), HbA_{1c} ($r = 0.16$, $P = 0.00001$), triglycerides ($r = 0.19$, $P < 0.00001$), and waist circumference ($r = 0.10$, $P = 0.02$). $HOMA_{IR}$ was also correlated with triglycerides ($r = 0.20$, $P < 0.00001$) and HbA_{1c} ($r = 0.24$, $P < 0.00001$). A similar correlation was observed when smoking was also added to this multivariate model ($P = 0.02$).

When the relative contribution of all the above-mentioned variables singly related to ACR was analyzed by multiple regression analysis, $HOMA_{IR}$ ($P = 0.03$), age ($P = 0.009$), SBP ($P = 0.0001$), HbA_{1c} ($P = 0.005$), and triglycerides ($P = 0.0001$) but not duration of diabetes ($P = 0.1$) and waist circumference ($P = 0.6$) were still significantly associated.

The correlation between $HOMA_{IR}$ and ACR was still significant when antidiabetic ($P = 0.02$) or antihypertensive therapy ($P = 0.001$) or only therapy with ACE inhibitors and/or ARBs ($P = 0.03$) were considered as independent variables. To further adjust for the possible confounding effects of antidiabetic and antihypertensive treatments on both ACR and insulin resistance, data were reanalyzed in the subgroup of normotensive patients ($n = 206$) or in the subgroup of patients treated with diet alone ($n = 82$). In both subgroups, the correlation between $HOMA_{IR}$ and ACR was still significant ($r = 0.14$, $P = 0.049$ and $r = 0.3$, $P = 0.009$, respectively).

When the relationship between $HOMA_{IR}$ and ACR was investigated separately in women and men, although a similar trend was observed in the two sexes, a significant correlation was observed in men ($n = 363$; $r = 0.21$, $P = 0.0001$) but not in women ($n = 349$; $r = 0.08$, $P = 0.14$). In fact, a significant interaction ($P = 0.04$) between $HOMA_{IR}$ and sex in determining ACR was observed. The correlation between $HOMA_{IR}$ and ACR in men was still significant ($P = 0.001$) in a multiple regression analysis model after adjusting for age, duration of disease, SBP, HbA_{1c}, triglycerides, waist circumference, and smoking.

ACR measurement reproducibility in our study was calculated in a representative sample of 329 patients (46% of the entire cohort) who collected a second urine sample in a similar fashion. The κ coefficient of ACRs in this subgroup was 0.64, thus indicating a good reproducibility of our ACR measurement. When the second ACR measurement was considered in this subgroup of patients, a significant correlation with $HOMA_{IR}$ was observed in men ($r = 0.18$, $P = 0.024$) but not women ($r = 0.02$, $P = 0.8$).

When patients were stratified according to quartiles of $HOMA_{IR}$ value, there was a progressively increased risk of belonging to the MA group, which became significant for patients of the fourth quartile (i.e., the most insulin resistant) (OR 2.3 [95% CI 1.4–3.7]) (Table 2). Similar to that observed on the linear correlation between the two variables, the association between insulin resistance and micro- and macroalbuminuria was significant among men but not women (Table 2).

We then explored the relationship between UAE and the three specific cardiovascular risk factors that are strictly related to insulin resistance–dependent metabolic syndrome, i.e., waist circumference (>102 cm for men and >88 cm for women), increased blood pressure, and dyslipidemia, as previously defined. Accordingly, patients were subdivided in two groups: group A with fewer than two cardiovascular risk factors ($n = 90$) and group B ($n = 622$) with two or more cardiovascular risk factors. ACR was significantly higher in group B (median 1.33 [range 0.1–1367.6]) than in group A (0.91 [0.2–157.5]) ($P = 0.01$ after adjusting for age and sex). This association was also significant in men (0.90 [0.2–115.1] vs. 1.56 [0.1–1367.6], $P = 0.005$) but not women (1.18 [0.3–157.5] vs. 1.22 [0.2–134.0], $P = 0.9$) patients.

Table 2—*Risk of having micro- or macroalbuminuria according to quartiles of $HOMA_{IR}$ in the whole population, women, and men with type 2 diabetes*

	Whole population	Women	Men
n	712	349	363
Quartiles of $HOMA_{IR}$ (range)			
I (0.37–2.23)	1	1	1
II (2.24–3.80)			
A	0.94 (0.6–1.5) $P = 0.8$	0.7 (0.3–1.4) $P = 0.3$	1.2 (0.6–2.3) $P = 0.5$
B	0.97 (0.6–1.6) $P = 0.9$	0.7 (0.3–1.4) $P = 0.3$	1.2 (0.6–2.3) $P = 0.6$
C	0.91 (0.5–1.5) $P = 0.7$	0.6 (0.3–1.4) $P = 0.2$	1.2 (0.6–2.3) $P = 0.6$
III (3.83–6.34)			
A	1.3 (0.8–2.0) $P = 0.3$	0.6 (0.3–1.3) $P = 0.2$	2.2 (1.2–4.0) $P = 0.01$
B	1.4 (0.9–2.2) $P = 0.2$	0.6 (0.3–1.3) $P = 0.2$	2.2 (1.2–4.2) $P = 0.01$
C	1.1 (0.7–1.9) $P = 0.6$	0.5 (0.2–1.1) $P = 0.07$	1.9 (0.8–3.7) $P = 0.06$
IV (6.35–72.4)			
A	2.0 (1.3–3.1) $P = 0.003$	1.2 (0.6–2.2) $P = 0.8$	3.8 (2.0–7.1) $P = 0.00004$
B	2.3 (1.4–3.7) $P = 0.0005$	1.1 (0.6–2.2) $P = 0.7$	4.1 (2.2–7.9) $P = 0.00002$
C	1.8 (1.1–3.0) $P = 0.02$	0.7 (0.3–1.5) $P = 0.3$	3.7 (1.9–7.5) $P = 0.0002$

Data are OR (95% CI). A, unadjusted values; B, adjusted for age and sex; C, adjusted for age, sex, duration of disease, waist circumference, SBP, and HbA_{1c}.

CONCLUSIONS — The relationship between insulin resistance and UAE in type 2 diabetic patients has been a matter of debate with both positive (7–10) and negative (4–6) results obtained in samples of small to moderate size ranging from 20 (4) to 155 (6) patients; this might have increased the risk of both false-positive and false-negative results. Our present data, obtained in a large sample, clearly indicate that in patients with type 2 diabetes, there is a highly significant association between insulin resistance and UAE. Similarly, insulin resistance was also associated with the presence of micro- and macroalbuminuria. In line with the associations we describe here is a recent report (22) indicating that insulin sensitizer drugs may decrease UAE in type 2 diabetic patients. The association between insulin resistance and UAE is independent of possible confounders affecting both variables, including age, smoking, duration of disease, triglycerides, waist circumference, smoking, metabolic control, blood pressure, and related treatments.

A novel finding of our study is that the correlation between insulin resistance and UAE was significant in male but not female type 2 diabetic patients, although a similar trend was also observed in the latter group. Worth noting, the two groups were of similar magnitude; whether a statistical significance would be reached also in women with a much larger sample size is a possibility that deserves further studies. With the present sample size, sex and insulin resistance seem to interact in modulating UAE in our cohort. It is a matter of debate whether a similar interaction also occurs in the general population (14–16). Why the association between insulin resistance and UAE seems to be stronger in men than women is unknown. Differences in hormonal assessment in the two sexes might be relevant. In our cohort, the vast majority (87%) of women were >50 years of age and, therefore, presumably in the postmenopausal state. Therefore, although it cannot be excluded that hormonal exposition in previous years might be important, estrogens are unlikely to have a major role in this context. At variance, androgens that are known to activate the renin angiotensin system (23) could have played a role in modulating the detrimental effects of insulin resistance and related abnormalities on endothelial cells. Differences in lifestyle between the two sexes, including smoking, diet, and physical activity, might also be implicated in the apparently different results obtained.

Also, the biology of the association between UAE and insulin resistance is not clearly defined. There are several possible explanations. First, it might be based on compensatory hyperinsulinemia characterizing insulin resistance, which may stimulate renal sodium reabsorption, leading to volume expansion, increased adrenergic activity, and hypertension (24–25). Worth noting, insulin resistance could contribute to greater salt sensitivity, increased glomerular pressure, and increased UAE, as recently described in type 2 diabetic patients with microalbuminuria put on a high-salt diet (26). Thus, although in our present series a correlation between insulin resistance and blood pressure was not detectable, likely because of the ongoing antihypertensive treatment, one could speculate that the difference in blood pressure level before treatment was started may have played a significant role in determining the association between UAE and insulin resistance. Second, several reports have suggested that high triglyceride levels, a typical feature of insulin resistance, represents an independent predictor of renal damage in both type 2 diabetes (27) and type 1 diabetes (28). In fact, in our sample, $HOMA_{IR}$ values were significantly correlated with serum triglycerides concentration. Increased formation of small dense LDL, which have increased susceptibility to oxidation, is a likely mechanism through which triglycerides could initiate endothelial damage and eventually induce renal disease (27). Third, patients with insulin resistance are likely to have significantly worse metabolic control (i.e., higher HbA_{1c} levels), which in fact turned out to be the case in the cohort we studied. This difference may have also played a role in determining increased UAE.

It is worth noting that UAE was also associated with the presence of multiple cardiovascular risk factors strictly related

to insulin resistance, namely increased waist circumference, arterial hypertension, and dyslipidemia. This association may partly explain the well-established association between increased UAE and cardiovascular morbidity and mortality (29–30) shown in type 2 diabetes.

We acknowledge that the HOMA$_{IR}$ index used in our present study for measuring insulin resistance is a surrogate of the euglycemic-hyperinsulinemic clamp, the gold standard technique for measuring insulin sensitivity. However, the clamp technique is not applicable to several hundreds of patients. In addition, recent reports have shown a strong correlation between HOMA$_{IR}$ and euglycemic-hyperinsulinemic clamp in both nondiabetic (31) and type 2 diabetic individuals over wide ranges of fasting plasma glucose (31–32), thus validating the use of HOMA$_{IR}$ for large epidemiological studies.

It should be considered that our study was conducted on referred patients; therefore, results obtained cannot be applied to the whole diabetic population. A similar limitation also affects previous results on this issue (4–5,7). In conclusion, because of the large sample analyzed here, we believe our present results add conclusive evidence that in type 2 diabetic patients, UAE is strictly associated with insulin resistance and related cardiovascular risk factors. This association seems to be stronger in men than in women. Because of the possibility to treat insulin resistance with several drugs (11–12) and given the efficacy of this treatment in reducing cardiovascular mortality (13) in diabetic patients, our study suggests that type 2 diabetic patients with increased UAE could particularly benefit from treatment for insulin resistance. In line with this hypothesis, Bakris et al. (22) have recently shown that rosiglitazone, an insulin sensitizer, was effective in reducing UAE in patients with type 2 diabetes. Further prospective studies are needed to better clarify the causative role of insulin resistance on UAE and the possible clinical relevance of this association.

References

1. Viberti GC, Walker JD, Pinto J: Diabetic nephropathy. In *International Textbook of Diabetes Mellitus*. Alberti KGMM, DeFronzo RA, Keen H, Eds. Chichester, New York, Wiley, 1992, p. 1267–1328
2. Orchard TJ, Chang YF, Ferrell RE, Petro N, Ellis DE: Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. *Kidney Int* 62:963–970, 2002
3. Mykkanen DJ, Zaccaro LE, Wagenknecht DC, Robbins M, Gabriel and Haffner SM: Microalbuminuria is associated with insulin resistance in nondiabetic subjects: the Insulin Resistance Atherosclerosis Study. *Diabetes* 47:793–800, 1998
4. Nielsen S, Schmitz O, Orskov H, Mogensen CE: Similar insulin sensitivity in NIDDM patients with normo- and microalbuminuria. *Diabetes Care* 18:834–842, 1995
5. Rizvi A, Varasteh B, Chen YD, Reaven GM: Lack of a relationship between urinary albumin excretion rate and insulin resistance in patients with non-insulin-dependent diabetes mellitus. *Metabolism* 45:1062–1064, 1996
6. Jager A, Kostense PJ, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD: Microalbuminuria is strongly associated with NIDDM and hypertension, but not with the insulin resistance syndrome: the Hoorn Study. *Diabetologia* 41:694–700, 1998
7. Groop L, Ekstrand A, Forsblom C, Widen E, Groop PH, Teppo AM, Eriksson J: Insulin resistance, hypertension and microalbuminuria in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 36:642–647, 1993
8. Pinkney JH, Denver AE, Mohamed-Ali V, Foster C, Yudkin JS: Insulin resistance in non-insulin-dependent diabetes mellitus is associated with microalbuminuria independently of ambulatory blood pressure. *J Diabetes Complications* 9:230–233, 1995
9. Niskanen L, Laakso M: Insulin resistance is related to albuminuria in patients with type II (non-insulin-dependent) diabetes mellitus. *Metabolism* 42:1541–1545, 1993
10. Nosandini R, Manzato E, Solini A, Fioretto P, Brocco E, Zambon S, Morocutti A, Sambataro M, Velussi M, Cipollina MR, Crepaldi G: Peripherial, rather than hepatic, insulin resistance and atherogenic lipoprotein phenotype predict cardiovascular complications in NIDDM. *Eur J Clin Invest* 24:258–266, 1994
11. Widen EIM, Eriksson JG, Groop LC: Metformin normalizes nonoxidative glucose metabolism in insulin-resistant normoglycemic first-degree relatives of patients with NIDDM. *Diabetes* 41:354–358, 1992
12. Yki-Järvinen H: Drug therapy: thiazolidinediones. *N Engl J Med* 351:1106–1118, 2004
13. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
14. Halimini JM, Forhan A, Balkau B, Novak M, Wilpart E, Tichet J, Marre M, the DESIR Study Group: Is microalbuminuria an integrated marker for cardiovascular disease and insulin resistance in both men and women? *J Cardiovasc Risk* 8:139–146, 2001
15. Verhave JC, Hillege HL, Burgerhof JG, Navis G, de Zeeuw D, de Jong PE, PREVEND Study Group: Cardiovascular risk factors are differently associated with urinary albumin excretion in men and women. *J Am Soc Nephrol* 14:1330–5, 2003
16. Palaniappan L, Carnethon M, Fortmann SP: Association between microalbuminuria and the metabolic syndrome: NHANES III. *Am J Hypertens* 16:952–958, 2003
17. De Cosmo S, Margaglione M, Tassi V, Garrubba M, Thomas S, Olivetti C, Piras GP, Trevisan R, Vedovato M, Cavallo Perin P, Bacci S, Colaizzo D, Cisternino C, Zucaro L, Di Minno G, Trischitta V, Viberti GC: ACE, PAI-1, Decorin and Werner helicase genes are not associated with the development of renal disease in European patients with type 1 diabetes. *Diabetes Metab Res Rev* 15:247–253, 1999
18. Gatling W, Knight C, Mullee MA, Hill RD: Microalbuminuria in diabetes: a population study of the prevalence and an assessment of three screening tests. *Diabet Med* 5:343–347, 1988
19. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
21. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
22. Bakris G, Viberti G, Weston WM, Heise

M, Porter LE, Freed MI: Rosiglitazone reduces urinary albumin excretion in type II diabetes. *J Hum Hypertens* 17:7–12, 2003

23. Ritz E: Cardiovascular risk factors and urinary albumin: vive la petite difference. *J Am Soc Nephrol* 14:1415–1416, 2003

24. Abate N: Obesity and cardiovascular disease: pathogenetic role of the metabolic syndrome and therapeutic implications. *J Diabetes Complications* 14:154–174, 2000

25. McFarlane SI, Banerji M, Sowers JR: Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metab* 86:713–718, 2001

26. Vedovato M, Lepore G, Coracina A, Dodesini AR, Jori E, Tiengo A, Del Prato S, Trevisan R: Effect of sodium intake on blood pressure and albuminuria in type 2 diabetic patients: the role of insulin resistance. *Diabetologia* 47:300–3, 2004

27. Colhoun HM, Lee ET, Bennett PH, Lu M, Keen H, Wang SL, Stevens LK, Fuller JH: Risk factors for renal failure: the WHO Mulinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S46–S53, 2001

28. Coonrod BA, Ellis D, Becker DJ, Buncher CH, Kelsey SF, Lloyd CE, Drash AL, Kuller LH, Orchard TJ: Predictors of microalbuminuria in individuals with type 1 diabetes. *Diabetes Care* 16:1376–1383, 1993

29. Jarrett RJ, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murrells TJ: Microalbuminuria predicts mortality in non-insulin dependent diabetics. *Diabet Med* 1:17–19, 1984

30. Mattock MB, Barnes DJ, Viberti GC, Keen H, Burt D, Hughes JM, Fitzgerald AP, Sandhu B, Jackson PG: Microalbuminuria and coronary heart disease in NIDDM an incidence study. *Diabetes* 47:1786–1792, 1998

31. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23:57–63, 2000

32. Yokoyama H, Emoto M, Fujiwara S, Motoyama K, Morioka T, Komatsu M, Tahara H, Koyama H, Shoji T, Inaba M, Nishizawa Y: Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment are useful indexes of insulin resistance in type 2 diabetic patients with wide range of fasting plasma glucose. *J Clin Endocrinol Metab* 89:1481–1484, 2004