

Hypertension, Hyperlipidemia, and Abdominal Obesity and the Development of Microalbuminuria in Patients with Non-insulin-dependent Diabetes Mellitus

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Background: The hyperlipidemia syndrome (also called syndrome X or the deadly quartet) is a recognized constellation known to increase cardiovascular mortality, but its effect on renal decline is not well-described. This study examined the differential effects of hypertension, hyperlipidemia, and abdominal obesity on overnight urinary albumin excretion ratios (UAERs) among patients with non-insulin-dependent diabetes mellitus (NIDDM), who by definition possess the remaining component of the syndrome, insulin resistance.

Methods: We conducted a survey of 317 primary care NIDDM patients measuring waist-to-hip ratios, fasting lipid levels and glycemic values, and overnight UAERs. The study was carried out between January 1989 and June 1991.

Results: Using logistic regression controlling for age, race, sex, duration of NIDDM, and smoking status, elevated glycosylated hemoglobin (odds ratio [OR]=1.95, 95 percent confidence interval [CI]=1.16–3.27) or the addition of one component of the deadly quartet to pure diabetes doubled or tripled the odds of an elevated UAER (NIDDM plus obesity OR=2.00, 95 percent CI=1.02–3.93; NIDDM plus hypertension OR=3.45, 95 percent CI=1.38–8.63; NIDDM plus hyperlipidemia OR=1.60, 95 percent CI=0.53–4.81). In a dose-response manner, two additional factors exerted additive effects; all three additional factors combined with pure NIDDM multiplied the effect, with an odds ratio of 9.34 (95 percent CI=2.24–38.9).

Conclusions: These data quantify the incremental effects of abdominal obesity, hypertension, and hyperlipidemia on abnormal UAERs among NIDDM patients and strongly suggest the need for aggressive and simultaneous correction of multiple risk factors to prevent end organ damage in this population. (J Am Board Fam Pract 1996; 9:1–6.)

In 1989, Kaplan¹ coined the term *the deadly quartet* to describe four cardiovascular risk factors that more frequently exist together than chance alone would dictate: upper body obesity as measured by the waist-to-hip ratio, glucose intolerance, hypertriglyceridemia, and hypertension. Also called the hyperinsulinemia syndrome or syndrome X,² these four factors probably share a common pathogenesis, hyperinsulinemia, long recognized as being associated with obesity. Further, Kaplan¹ and others^{3–5} have demonstrated possible ways in which these factors work in

concert to initiate and exacerbate coronary artery disease. These concepts have been supported by epidemiologic evidence:^{6–8} cardiovascular risk increases proportionally as more of these factors are present.

These four factors have been evaluated in relation to renal disease by numerous investigators.^{9–18} Most studies have utilized the measurement of small amounts of albumin in the urine as an early predictor of renal disease. Microalbuminuria, the abnormal urinary excretion of albumin in concentrations between 0.03 and 0.20 g/L, is thought to reflect a widespread increase in transcapillary protein escape and hence is a phenomenon not limited to the renal glomerulus. According to the Steno hypothesis,¹⁹ microalbuminuria denotes vascular damage. Though strictly speaking, microalbuminuria refers to abnormal concentrations of urinary albumin below the level detected by routine dipstick, abnormal urinary albumin excretion

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ratios (UAERs) of albumin to creatinine excretion are usually considered in the range of 0.02 to 0.20 g of albumin per 1 g of creatinine.²⁰

Microalbuminuria and elevated UAERs have also been found to correlate with the development of diabetic nephropathy,²¹ coronary artery heart disease, and increased mortality in general.²² In fact, an elevated UAER might precede the onset of hyperglycemia and other signs in those destined to develop frank diabetes.²³

Obesity,^{9-11,13,15} hyperlipidemia,^{13,16-18} elevated blood pressure,^{10,12,16,17} and poor glycemic control (or elevated insulin levels)^{11,12,15,16} have all been shown to correlate with elevated UAERs in both diabetic and nondiabetic populations. In the United Kingdom, among patients with non-insulin-dependent diabetes mellitus (NIDDM), dietary therapy not only improved body mass index, fasting glucose levels, and systolic blood pressure but also led to a marked reduction in UAERs.¹⁵ None of these studies, however, has investigated the effect of various combinations of the four hyperinsulinemia syndrome factors in predicting elevated UAERs among patients with NIDDM. The purpose of this report is to evaluate the predictive value of these four components, singly and together, in a population of primary care diabetic outpatients for the presence of an elevated UAER.

Methods

After approval by the Institutional Review Board, all diabetic patients older than 16 years who had been seen during 1988 at a large university family practice center and a neighborhood community health center were selected through computerized records and were mailed invitations to participate in a free screening project designed to evaluate predictors of renal decline among patients with NIDDM. Of 424 mailed invitations, 392 individuals were eligible for participation (32 patients had moved or died, or their condition was incorrectly diagnosed as diabetic). Three hundred twenty-three patients agreed to participate, but 6 were subsequently removed from analysis as a result of a previous diagnosis of nephropathy, leaving 317 patients (for a final response rate of 75 percent). These patients met World Health Organization criteria²⁴ for NIDDM as documented in their medical records (ie, fasting glucose ≥ 140 mg/dL or 2-hour glucose tolerance test value ≥ 200 mg/dL). Actual screening of these patients took

place between January 1989 and June 1991.

Patients were interviewed to determine race, sex, duration of diabetes mellitus, and other cardiovascular risk factors; they then underwent a brief but standardized physical examination. Blood pressure was measured by a single observer for patients sitting at rest for 5 minutes using a calibrated mercury sphygmomanometer at the level of the heart. Height, weight, and waist and hip girths were obtained by one trained research assistant. Patients also submitted fasting blood samples for multichannel chemistry evaluation, including fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and calculated low-density lipoprotein (LDL) levels. Glycosylated hemoglobin was measured by the affinity column method (normal values for our population ranged from 2.9 percent to 5.1 percent).

We defined obesity as present if waist-to-hip ratios exceeded 0.85. Hyperlipidemia was defined by fasting triglyceride levels exceeding 200 mg/dL and an LDL cholesterol reading of 130 mg/dL or more. (Although LDL cholesterol is not one of the components of Kaplan's syndrome, its increased level is clearly associated with the three other components¹ and with the development of renal disease.) Hypertension was defined by mean arterial blood pressures exceeding 107 mmHg, equivalent to those whose blood pressures exceeded 140 mmHg systolic and 90 mmHg diastolic. Elevated glycosylated hemoglobin was defined as greater than 8 percent.

Based on these definitions, eight subgroups of patients were then created: (1) those with diabetes alone ($n=36$); (2) those with diabetes and obesity ($n=105$); (3) those with diabetes and hypertension ($n=11$); (4) those with diabetes and hyperlipidemia ($n=12$); (5) those with diabetes, obesity, and hypertension ($n=58$); (6) those with diabetes, obesity, and hyperlipidemia ($n=60$); (7) those with diabetes, hypertension, and hyperlipidemia ($n=5$); and (8) those with diabetes, obesity, hypertension, and hyperlipidemia ($n=30$).

Mean values were compared among subgroups by analysis of variance, or if variances were unequal, by Kruskal-Wallis H. Categorical data were analyzed using chi-square or stepwise logistic regression. The dependent variable in the logistic regression model was a UAER greater than or equal to 0.02 g albumin per gram of creatinine.

Independent predictors included the eight subgroups of patients (the subgroup "diabetes alone" served as the referent category), duration of diabetes mellitus, smoking status, and glycosylated hemoglobin greater than 8 percent. The model simultaneously controlled for age, race, and sex. All calculations were carried out using EpiInfo²⁵ or SPSS-PC.²⁶

Results

Characteristics of the 317 patients included in the analysis are listed in Table 1. More than one half of the patients were women, and the racial balance was nearly equal. Mean arterial pressure was not elevated in this population, but mean fasting glucose values and glycosylated hemoglobin values were. Not listed in Table 1, 199 patients (87 percent) had LDL cholesterol values greater than 130 mg/dL, 68 (21 percent) had HDL cholesterol values less than 35 mg/dL, and 110 (35 percent) had triglyceride values exceeding 200 mg/dL. Additionally, 170 patients (53 percent) had a body mass index of greater than 30 kg/m², and 256 pa-

Table 1. Characteristics of Patients (n=317) with Non-insulin-dependent Diabetes.

Characteristics	Mean $\pm$ SD*
Demographics	
Age (y)	58 $\pm$ 12
African-American (%)	47
Women (%)	58
Blood pressure (mmHg)	
Systolic blood pressure	138 $\pm$ 24
Diastolic blood pressure	81 $\pm$ 14
Mean arterial pressure	100 $\pm$ 15
Glycemic values	
Fasting glucose (mg/dL)	196 $\pm$ 78
Glycosylated hemoglobin (%)	7.3 $\pm$ 2.1
Urinary albumin excretion	
Ratio (gram of albumin per gram of creatinine)	0.698 $\pm$ 0.460
Duration of diabetes (year)	11 $\pm$ 10
Lipid values (mg/dL)	
Total cholesterol	219 $\pm$ 42
LDL cholesterol	137 $\pm$ 37
HDL cholesterol	51 $\pm$ 14
Triglyceride	148 $\pm$ 80
Anthropometric measurements	
Waist-to-hip ratio	0.90 $\pm$ 0.10
Body mass index (kg/m ²)	31 $\pm$ 6

SD=standard deviation, LDL=low-density lipoprotein, HDL=high-density lipoprotein.

*Except for percentages.

Table 2. Urinary Albumin Excretion Ratios (UAERs) of Subgroups of Diabetes Patients.

Patient Group	Number	UAER* Mean $\pm$ SD
Pure diabetes	36	0.006 $\pm$ 0.005
Diabetes and obesity	105	0.055 $\pm$ 0.018
Diabetes and hypertension	11	0.473 $\pm$ 0.235
Diabetes and hyperlipidemia	12	0.458 $\pm$ 0.283
Diabetes, obesity, and hypertension	58	0.195 $\pm$ 0.061
Diabetes, obesity, and hyperlipidemia	60	0.062 $\pm$ 0.027
Diabetes, hypertension, and hyperlipidemia	5	0.120 $\pm$ 0.134
Diabetes, obesity, hypertension, and hyperlipidemia	30	0.267 $\pm$ 0.134

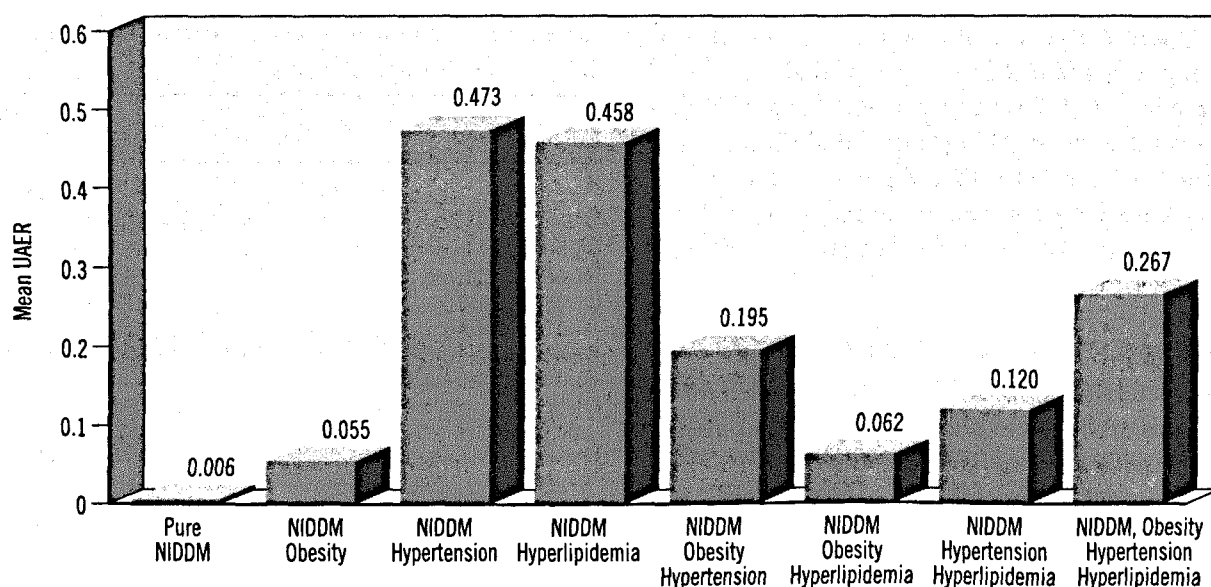
*Urinary albumin excretion ratio, gram of albumin per gram of creatinine.

[†]P < 0.001 by Kruskal-Wallis H.

tients (81 percent) had waist-to-hip ratios greater than 0.85. Only 129 (41 percent) and 65 (20 percent) patients, respectively, had systolic blood pressures greater than 140 mmHg and diastolic blood pressures greater than 90 mmHg.

Mean UAERs within the eight patient subgroups are listed in Table 2, and range from 0.006 $\pm$ 0.005 g of albumin per 1 g of creatinine in patients with pure diabetes to 0.473 $\pm$ 0.283 g of albumin per 1 g of creatinine among diabetic patients with hypertension. These differences were significant at a level of P<0.001 by Kruskal-Wallis H, and are graphically represented in Figure 1. There is a dramatic increase in mean UAERs with the addition of even one risk factor to pure diabetes.

Odds ratios for UAERs greater than or equal to 0.02 g of albumin per 1 g of creatinine are listed in Table 3, and have been controlled for age, race, sex, smoking status, and duration of diabetes. As expected, elevated glycosylated hemoglobin produced an almost twofold increase in risk of an elevated UAER. Looking at patient subgroups, there is a general trend toward a dose-response relation: with each additional risk factor added to pure NIDDM (the referent category), the odds ratio of an elevated UAER increases markedly, and patients with all three additional risk factors (obesity, hypertension, and hyperlipidemia) have the highest odds ratio (OR=9.34, 95 percent CI=2.24-38.9). The two exceptions are diabetic patients with hyperlipidemia and diabetic patients with obesity plus hyperlipidemia, whose increased



NIDDM = non-insulin-dependent diabetes mellitus; UAER = urinary albumin excretion ratio.

Figure 1. Mean UAER (gram of albumin per gram of creatinine) by patient category.

odds ratios are not statistically different from that of patients with diabetes alone. Any two of the three risk factors appear to interact in at least an additive fashion. With all three risk factors present, the model approaches a multiplicative effect.

Table 3. Factors Predicting Urinary Albumin Excretion Ratios > 0.02 g Albumin per 1 g Creatinine in Patients with Non-insulin-dependent Diabetes Mellitus.

Factor	Adjusted Odds Ratio*	95% CI	P Value
Glycosylated hemoglobin	1.95	1.16–3.27	<0.05
Patient groups			
Diabetes only	1.00	Reference	
Diabetes and obesity	2.00	1.02–3.93	<0.05
Diabetes and hypertension	3.45	1.38–8.63	<0.01
Diabetes and hyperlipidemia	1.60	0.53–4.81	NS
Diabetes, obesity, and hypertension	4.53	2.06–9.95	<0.0005
Diabetes, obesity, and hyperlipidemia	1.48	0.42–5.17	NS
Diabetes, hyperlipidemia, and hypertension	7.88	1.38–44.9	<0.05
Diabetes, obesity, hyperlipidemia, and hypertension	9.34	2.24–38.9	<0.005

*Adjusted for age, race, sex, duration of disease, and smoking status.

Note: Obesity: waist-to-hip ratio ≥ 0.85 ; hyperlipidemia: triglycerides ≥ 200 mg/dL and low-density lipoprotein ≥ 130 mg/dL; hypertension: mean arterial pressure ≥ 107 mmHg. CI=confidence interval; NS = not significant.

Discussion

Using three of the four components of the hyperinsulinemia syndrome (upper body obesity, hypertension, and hyperlipidemia) in patients with NIDDM, who by definition possess the fourth component (ie, glucose intolerance), our data have shown an approximate dose-response effect on the development of an elevated UAER. The addition of even one risk factor to patients with diabetes alone markedly increases mean UAERs among patient subgroups and doubles or triples the odds of an elevated UAER. The addition of two factors interacts in additive fashion, while the presence of all three other factors in a diabetic patient exerts a multiplicative effect. Although approaches similar to ours in evaluating the influence of these factors on UAERs have been carried out in various populations of diabetic patients,⁹⁻¹⁸ these are the first data in an American diabetic population showing the incremental effects of these four components on the development of abnormal UAERs.

It makes intuitive sense that, in general, diabetic patients who have more cardiovascular risk factors are more likely to have renal disease. What has not been previously shown is the quantitative effect these factors, singly and in combination, have in the development of microalbuminuria among patients with diabetes.

Mechanistically how do these factors interact to initiate and aggravate renal disease in diabetic patients? It has been shown that abdominal fat

cells are metabolically more active than gluteal or femoral fat cells, with a greater propensity toward adenylate cyclase-mediated lipolysis when stimulated by epinephrine.²⁷ This characteristic would explain the frequently elevated triglyceride levels seen among certain obese individuals,^{1,28} a phenomenon that often acts to reduce levels of HDL cholesterol.²⁹ Furthermore, excess plasma free fatty acids tend to inhibit hepatic extraction of insulin,³⁰ leading to hyperinsulinemia and aggravating the already existing predisposition toward hyperinsulinemia secondary to peripheral insulin resistance from the obesity. Because insulin increases renal sodium resorption,^{31,32} and hyperinsulinemia is associated with increased plasma norepinephrine³³ and vascular hypertrophy,³⁴⁻³⁶ this hormone might be intimately involved in the development of hypertension among patients with NIDDM. Glomerular damage as evidenced by elevated UAER could result, therefore, from the combined renovascular effects of hypertension, glycosylated end products, and atherogenesis associated with obesity and NIDDM.²⁰

Several limitations to the current study deserve comment. First is its cross-sectional design. One could postulate that renal disease predated the development of diabetes, hypertension, obesity, or hyperlipidemia in these patients. Although there is no way to rule out this possibility entirely, preexisting renal disease seems less likely given that our patients with diabetes alone had the lowest mean UAER. A second potential limitation deals with the central role of hyperinsulinemia in the syndrome X or deadly quartet hypothesis. Even though we did not measure insulin levels, virtually all obese patients with NIDDM have hyperinsulinemia.^{1,37} A small proportion of non-obese adults with diabetes are non-insulin dependent but can become insulin dependent in the future,³⁸ so-called type I diabetes in transition. Moreover, almost all of our patients were obese by the body mass index, the usual standard of overweight, even if they lacked abdominal obesity (average body mass index among patients with diabetes alone was 30.5 ± 5 , while their waist-to-hip ratios were less than 0.85). In any case, every patient was by definition glucose intolerant, a surrogate for hyperinsulinemia.¹

One peculiarity of the data should be addressed. In looking at Table 2, the amounts of albumin noted are not consistent. For example, the UAER

for the group with all four factors is less than the UAERs for the two categories of diabetes plus hypertension and diabetes plus hyperlipidemia. Subsequent evaluation of participants' medical records showed that 3 patients with UAERs greater than 2 g of albumin per 1 g of creatinine were found to have diabetic nephropathy soon after this study was completed. Eliminating them from the analysis reduces the average UAER for the group with NIDDM and hypertension ($n=10$) to 0.290 ± 0.163 g of albumin per 1 g of creatinine and for the group with NIDDM and hyperlipidemia ($n=10$) to 0.040 ± 0.022 g of albumin per 1 g of creatinine. This reanalysis did not alter the relative magnitude of the odds ratios in logistic regression or the overall statistical significance of the logistic model.

These results are not only useful in predicting which patients with NIDDM are more likely to develop elevated UAERs, clinical proteinuria, and early mortality²² but are also a useful guide for clinical prevention. Several lines of research have shown that abnormal albumin excretion can be reversed with improved glycemic and blood pressure control, exercise, a reduction in protein intake, smoking cessation, and medications²⁰ (especially angiotensin-converting enzyme inhibitors³⁹ and calcium channel blockers⁴⁰). As clinicians aggressively pursue euglycemia, weight reduction, blood pressure control, and lowered serum lipids in their diabetic patients, they have a favorable impact both on renal disease and also premature death and disability in this high-risk population.

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