Microalbuminuria Precedes the Development of NIDDM

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Several studies have indicated that insulin resistance, elevated blood pressure (BP), and dyslipidemia precede the onset of non-insulin-dependent diabetes mellitus (NIDDM). Little data, however, exist on the presence of renal disease in prediabetic subjects. We measured albumin excretion in a cross-sectional population study in subjects 65–74 years of age living in eastern Finland in relation to the risk of developing diabetes 3.5 years later. The prevalence of microalbuminuria (urinary albumin-to-urinary creatinine ratio ≥2 mg/mmol) was 1.3-, 1.8-, and 2.0-fold higher among subjects with impaired glucose tolerance ($n = 242$), newly diagnosed NIDDM subjects ($n = 92$), and previously diagnosed NIDDM subjects ($n = 136$), respectively, compared with subjects with normal glucose tolerance ($n = 826$). Nondiabetic subjects with microalbuminuria had multiple abnormalities in cardiovascular risk factors including elevated BP, high triglyceride concentration, high insulin concentration, and a low high-density lipoprotein cholesterol concentration, a cluster of risk factors typical for prediabetic individuals. The relationship between microalbuminuria and the incidence of NIDDM over the 3.5-year follow-up was studied in 891 subjects who were free of diabetes at baseline. Converters to diabetes ($n = 69$) had a higher prevalence of hypertension (68.1 vs. 54.4%, $P < 0.05$) and a higher prevalence of microalbuminuria (43.5 vs. 30.4%, $P < 0.05$) than nonconverters ($n = 822$). In logistic regression analysis, microalbuminuria predicted the development of NIDDM independently of BP level. However, after adjustment for plasma glucose and insulin levels at baseline, the difference in the prevalence of microalbuminuria between converters and nonconverters was not statistically significant. These results suggest that microalbuminuria may be a feature of the prediabetic state and that the increase in albumin excretion rate may be related to increases in glucose and insulin concentrations. *Diabetes* 43:552–57, 1994

Slightly increased urinary albumin excretion (UAE) rate, microalbuminuria, is predictive of clinical proteinuria in non-insulin-dependent diabetes mellitus (NIDDM) (1). Moreover, in NIDDM, microalbuminuria is associated more with early mortality, especially cardiovascular mortality, than with future end-stage renal failure (1–4). Microalbuminuria also predicts and aggravates abnormalities in lipoproteins in NIDDM patients (5).

Several reports have shown that microalbuminuria already is present early in the course of NIDDM. Newly diagnosed NIDDM patients had an elevated albumin excretion rate (6,7). Subjects with an impaired glucose tolerance (IGT) (8–11) and nondiabetic subjects with a parental history of diabetes (11), who are at an increased risk for developing NIDDM, had an excess prevalence of microalbuminuria compared with control subjects. Three studies (12–14) in NIDDM subjects showed that microalbuminuria is associated with insulin resistance. Moreover, microalbuminuria was shown previously to be associated with hyperinsulinemia in nondiabetic subjects (15). Hyperinsulinemia (16–19) and insulin resistance (18) are risk factors for the development of NIDDM in numerous prospective studies. Thus, microalbuminuria in subjects at an increased risk for developing NIDDM could be a feature of the prediabetic state (11).

All previous information suggesting that microalbuminuria might be a feature of the prediabetic state is based on cross-sectional data. Therefore, we investigated in a prospective population-based study in nondiabetic elderly subjects living in eastern Finland whether microalbuminuria precedes the development of NIDDM. Furthermore, we examined whether microalbuminuria is cross-sectionally associated with adverse changes in cardiovascular risk factors.

RESEARCH DESIGN AND METHODS

The baseline cross-sectional study was conducted in Kuopio in eastern Finland from 1986 to 1988. The formation (20) and representativeness (21) of the study population have been described in detail previously. The 1,300 subjects who participated in the study at baseline were selected randomly from the Kuopio population and were 65–74 years of age. The follow-up was performed in 1990–1991, on average 3.5 years (42 ± 4 mo) after the baseline cross-sectional study. After the baseline study, 108 subjects died leaving 1,192 subjects eligible for follow-up. Eventually, 1,054 subjects participated in the follow-up giving an overall participation rate of 88%. At baseline, 1 subject had insulin-dependent diabetes mellitus (IDDM) (20), and 3 subjects were missing urine samples; they were excluded from the cross-sectional analyses in this study, which left 1,296 subjects. Subjects with NIDDM at baseline were excluded from the follow-up analyses of microalbuminuria and the incidence of NIDDM, leaving 891 subjects.

Weight and height were measured in light clothing without shoes. Body mass index (BMI) (kg/m^2) was used as an index of overall adiposity. Waist circumference was measured at the level of the

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; BMI, body mass index; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; RIA, radioimmunoassay; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; TG, triglyceride; UAE, urinary albumin excretion; ACR, urinary albumin-to-urinary creatinine ratio; ANOVA, analysis of variance, ANCOVA, analysis of covariance; FPG, fasting plasma glucose.

umbilicus with the subject standing and breathing normally. Hip circumference was measured at the level of the greatest hip girth. The waist-to-hip ratio was used as a measure of body fat distribution. Blood pressure (BP) was measured in the supine position with a mercury sphygmomanometer after a 5-min rest. Two readings were taken (interval 1.5 min), and the latter one was used in statistical analyses. A subject was defined as having hypertension if systolic blood pressure (sBP) was ≥160 mmHg, diastolic blood pressure (dBP) was ≥95 mmHg, or if the subject was receiving drug treatment for hypertension. Smoking was defined if the subject was a current smoker. Family history of diabetes was regarded positive if one parent or sibling had NIDDM.

Previously known diabetes was considered to be present if diabetes was diagnosed previously by a physician (20). The World Health Organization plasma glucose criteria for diabetes were used in the classification of subjects without a previous diagnosis of diabetes (22). Insulin-treated diabetic subjects whose C-peptide level 6 min after intravenous glucagon (1 mg) stimulation (23) was <0.20 nM were regarded as having IDDM (24).

Blood samples were taken between 0730 and 0930 after a 12-h fast. All subjects underwent an oral glucose tolerance test (75 g of glucose). Venous blood samples for glucose and insulin determinations were taken before and 2 h after the glucose load and placed in chilled tubes, and plasma was separated immediately. Plasma glucose was determined by the glucose oxidase method (Glucose Auto and Stat HGA-1120 analyzer; Daiichi, Kyoto, Japan). Plasma insulin was determined from samples stored at −70°C by a commercial double-antibody solid-phase radioimmunoassay (RIA) (25; Phadeseph Insulin RIA 100; Pharmacia, Uppsala, Sweden). Serum high-density lipoprotein (HDL) cholesterol was determined after the precipitation of low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) with dextran sulfate and magnesium chloride (26). Commercial enzymatic methods were used in the determination of serum cholesterol (26,27) (Monotest; Boehringer Mannheim, Mannheim, Germany) and triglycerides (TG) (28; Peridocrome; Boehringer Mannheim). Commercial control sera were used to standardize the measurements of cholesterol and TGs (Seronorm, Seronorm Lipids; Nycomed, Oslo, Norway).

Urinary albumin concentration was assessed in a morning spot urine sample. Urinary albumin was measured from samples stored at −20°C by a commercial immunoturbidimetry assay with a sensitivity of 4 mg/L and intra- and interassay coefficient of variations ≤7.1% (Orion, Espoo, Finland). Urinary albumin concentrations <4 mg/L were set to 0. Urinary creatinine was determined by a modified Jaffe method (29). The urinary albumin (milligram per liter)-to-urinary creatinine (millimole per liter) ratio (ACR) was used as a measure of albumin excretion. Overnight ACR correlates well with albumin excretion rate (30,31), and ACR measured in a single untimed urine specimen has been shown to be an effective means for identifying diabetic patients who are at risk of developing overt nephropathy (32). An overnight ACR ≥2 mg/mmol predicts an albumin excretion rate >30 μg/min with a high sensitivity and specificity (30).

Statistical analysis. Data analyses were performed with the SPSS/PC+ statistical software (33). The results for continuous variables are means ± SE. The two-tailed Student's t test for independent samples, analysis of variance (ANOVA), and analysis of covariance (ANCOVA) were used in assessment of the significance of difference between group means. The χ^2 test was used for evaluating differences in proportions between groups. Age and sex adjustment of continuous variables was done by ANCOVA. Age and sex adjustment of prevalence rates was done by logistic regression analysis. The risk of developing diabetes associated with various risk factors was assessed by logistic regression analyses and calculating odds ratios. To improve skeweness and kurtosis of the distributions urinary albumin, ACR, total TGs, and insulin values were log-transformed for statistical analyses and then back-transformed to their natural units for presentation in the tables.

RESULTS

Of the 1,296 subjects who participated in the baseline examination, 312 men and 514 women had normal glucose tolerance (NGT), 84 men and 158 women had IGT, 33 men and 59 women had newly diagnosed NIDDM detected at the survey, and 40 men and 96 women had previously diagnosed NIDDM (Table 1). Subjects with IGT, newly diagnosed NIDDM, and previously diagnosed NIDDM had a higher sBP, a higher prevalence of hypertension, and took medication for hypertension more often than NGT subjects. However, no differences were noted in the level of dBP between the glucose tolerance groups. Urinary albumin concentration was significantly higher in subjects with IGT, newly diagnosed NIDDM, and previously diagnosed NIDDM compared with subjects with NGT. Albumin excretion as measured by ACR also was higher in subjects with IGT, newly diagnosed NIDDM, and previously diagnosed NIDDM than in subjects with NGT. The prevalence of microalbuminuria (ACR ≥ 2 mg/mmol) was 1.3-, 1.8-, and 2.0-fold higher among subjects with IGT, newly diagnosed NIDDM, and previously diagnosed NIDDM, respectively, compared with subjects with NGT. The prevalence of clinical proteinuria (ACR > 20 mg/mmol) was 3.0, 2.9, 7.6, and 15.4% in subjects with NGT, IGT, newly diagnosed NIDDM, and previously diagnosed NIDDM, respectively. Because the main focus of this study is microalbuminuria and associated factors in prediabetic subjects, those with NIDDM at baseline were excluded from the rest of the analyses.

Table 2 shows baseline characteristics in nondiabetic subjects according to the presence of microalbuminuria (ACR > 2 mg/mmol). IGT was 1.4-fold more common among subjects with microalbuminuria than among those without microalbuminuria. Subjects with microalbuminuria more often were hypertensive and on medication for hypertension, had lower waist-to-hip ratio, and higher levels of total TGs, sBP and dBP, fasting and 2-h plasma glucose, and fasting and 2-h plasma insulin than subjects without microalbuminuria. No difference was found in BMI, total or LDL cholesterol level, the proportion of current smokers, or subjects with a positive family history of diabetes between subjects with microalbuminuria and subjects without microalbuminuria. All these differences between subjects with microalbuminuria and subjects without microalbuminuria were independent of age and sex, except for the difference in waist-to-hip ratio, which disappeared after adjustment for these variables (data not shown). Differences in total TG, HDL cholesterol, and fasting and 2-h insulin levels between subjects with microalbuminuria and those without microalbuminuria also remained statistically significant after further adjustment for BMI, waist-to-hip ratio, fasting glucose or glucose tolerance status (NGT vs. IGT), and sBP (data not shown).

During the 3.5-year follow-up, 69 of 891 nondiabetic subjects (7.7%) developed NIDDM. These subjects had higher dBP and hypertension more often at baseline than subjects who remained healthy during the follow-up (Table 3). Subjects who developed diabetes had higher ACR and microalbuminuria more often (ACR ≥ 2 mg/mmol) at baseline than those who remained healthy. No statistically significant differences were noted in sBP or urinary albumin level between subjects who developed diabetes and subjects who remained healthy. All the differences between subjects who developed diabetes and those who remained healthy were independent of age and sex.

Table 4 shows results of logistic regression analyses for the incidence of diabetes. Subjects who had microalbuminuria (ACR > 2 mg/mmol) at baseline had a 1.76-fold risk of developing diabetes during the 3.5-year follow-up compared with subjects without microalbuminuria. The association between microalbuminuria and the risk of diabetes was independent of age, sex, and dBP (model 2). However, microalbuminuria was not significantly related to the risk of

TABLE 1
Clinical characteristics of the study population at baseline by glucose tolerance status

	Glucose tolerance status				
	NGT	IGT	Newly diagnosed NIDDM	Previously diagnosed NIDDM	*P* value
n	826	242	92	136	
Sex (M/F)	312/514	84/158	33/59	40/96	
Age (years)	69.0 ± 0.1	68.8 ± 0.2	69.5 ± 0.3	69.6 ± 0.2	0.074
BP (mmHg)					
sBP	156 ± 1	160 ± 1*	160 ± 2	166 ± 2†	<0.001
dBP	81 ± 1	82 ± 1	84 ± 1	81 ± 1	0.120
Hypertensive (%)	52.7	67.4†	75.0†	70.6†	<0.001
Medication for hypertension (%)	23.2	31.0*	48.9†	55.9†	<0.001
Urinary albumin (mg/L)	23.7 ± 2.5	26.4 ± 3.3‡	49.2 ± 8.8†	67.1 ± 12.1†	<0.001
ACR (mg/mmol)	3.29 ± 0.48	3.59 ± 0.75*	5.44 ± 0.94†	11.61 ± 2.11†	<0.001
Microalbuminuria (%)	29.8	38.8‡	54.3†	61.0†	<0.001

Data are means ± SE. *P* value for ANOVA or χ^2 test over glucose tolerance status groups. Microalbuminuria, ACR ≥ 2 mg/mmol. * $P < 0.05$; IGT, newly diagnosed NIDDM, or previously diagnosed NIDDM vs. NGT. † $P < 0.001$; IGT, newly diagnosed NIDDM, or previously diagnosed NIDDM vs. NGT. ‡ $P < 0.01$; IGT, newly diagnosed NIDDM, or previously diagnosed NIDDM vs. NGT.

diabetes after adjustment for baseline fasting plasma glucose (FPG) and insulin levels (model 3).

DISCUSSION

This study provides the first prospective results showing that microalbuminuria precedes the development of NIDDM. The association between microalbuminuria and the development of NIDDM was statistically independent of BP level at baseline. This novel finding supports the hypothesis of Haffner et al. (11) that microalbuminuria may be a feature of the prediabetic state. We also showed that the UAE rate is increased in elderly subjects with IGT and newly diagnosed NIDDM, confirming previous findings in middle-aged (7–11) and elderly (6) subjects. In addition, nondiabetic subjects with microalbuminuria had multiple abnormalities in cardiovascular risk factors including elevated BP, high TG concentration, high insulin concentration, and low HDL-cholesterol concentration, which are a cluster of risk factors typical for prediabetic individuals (34–37).

In elderly subjects, an increased albumin excretion rate also may occur because of diseases other than NIDDM (38). Accordingly, as many as 30% of normoglycemic subjects in the study population had microalbuminuria (ACR ≥ 2 mg/mmol). However, IGT, newly diagnosed NIDDM, and previously diagnosed NIDDM were associated with an additional increase in the albumin excretion rate in elderly subjects, confirming results of Damsgaard and Mogensen (6). The prevalence of microalbuminuria in subjects with IGT was intermediate of that in normoglycemic subjects and those with newly diagnosed NIDDM. Albumin excretion as measured by ACR was fourfold higher in subjects with previously diagnosed NIDDM than in normoglycemic subjects. The prevalence of microalbuminuria was about twofold higher among subjects with NGT in our population compared with elderly nondiabetic (6) and elderly newly diagnosed diabetic subjects (39) from Denmark. This could partly be the result of the higher prevalence of hypertension in our population than in the Danish population (39).

Although microalbuminuria was common in nondiabetic subjects, it was not a benign phenomenon but associated

TABLE 2
Clinical characteristics of nondiabetic subjects at baseline according to the presence of microalbuminuria

	Microalbuminuria	No microalbuminuria	*P* value
n	340	728	
IGT (%)	27.6	20.3	0.008
Age (years)	69.2 ± 0.2	68.8 ± 0.1	0.018
BMI (kg/m^2)	27.4 ± 0.2	27.0 ± 0.1	0.136
Waist-to-hip ratio	0.91 ± 0.01	0.92 ± 0.01	0.030
Total TGs (mM)	1.78 ± 0.04	1.66 ± 0.03	0.010
Total cholesterol (mM)	6.49 ± 0.07	6.60 ± 0.05	0.175
LDL cholesterol (mM)	4.42 ± 0.06	4.53 ± 0.04	0.136
HDL cholesterol (mM)	1.26 ± 0.02	1.31 ± 0.01	0.022
BP (mmHg)			
sBP	164 ± 1	154 ± 1	<0.001
dBP	84 ± 1	81 ± 1	<0.001
Hypertensive (%)	69.4	49.7	<0.001
Medication for hypertension (%)	28.9	22.3	0.031
FPG (mM)	5.8 ± 0.1	5.7 ± 0.1	0.002
2-h plasma glucose (mM)	6.8 ± 0.1	6.5 ± 0.1	0.014
Fasting plasma insulin (pM)	97 ± 3	86 ± 1	<0.001
2-h plasma insulin (pM)	490 ± 21	415 ± 14	<0.001
Current smokers (%)	9.7	10.0	0.870
Family history of diabetes	26.8	30.8	0.181

Data are means ± SE. Microalbuminuria, ACR ≥ 2 mg/mmol. *P* values for Student's *t* test or χ^2 test.

TABLE 3
Age- and sex-adjusted baseline characteristics of nondiabetic subjects according to diabetes status at 3.5-year follow-up

	Developed diabetes	Remained healthy	*P* value
n	69	822	
BP (mmHg)			
sBP	160	156	0.157
dBP	84	81	0.032
Hypertensive (%)	69.9	54.4	0.014
Urinary albumin (mg/L)	43.7	22.3	0.105
ACR (mg/mmol)	5.81	2.97	0.037
Microalbuminuria (%)	44.4	30.4	0.017

Microalbuminuria, ACR ≥ 2 mg/mmol.

with multiple cardiovascular risk factors. IGT was more common in subjects with microalbuminuria than in those without microalbuminuria. Subjects with microalbuminuria in this study also had elevated BP, TG level, insulin level, and higher prevalence of hypertension confirming previous studies (15). In our population microalbuminuria was associated with decreased HDL-cholesterol level. This risk factor profile was independent of age and sex. In addition, elevated TG and insulin levels and decreased HDL-cholesterol levels associated with microalbuminuria also were independent of obesity, body fat distribution, hypertension, and glucose levels. Niskanen et al. (5) have shown that persistent microalbuminuria predicts and aggravates abnormalities in lipoprotein composition and a decrease in HDL cholesterol in NIDDM patients.

Microalbuminuria preceded the development of NIDDM. Subjects who developed NIDDM during the 3.5-year follow-up had higher prevalence of microalbuminuria as well as higher dBP and prevalence of hypertension at baseline than subjects who remained healthy. A relationship between an excessive albumin excretion rate and BP has been described previously in nondiabetic subjects (6,15,40) and in patients with NIDDM (8,10,41), although some studies (1–4) have found no association between microalbuminuria and hypertension in NIDDM. In this study, nondiabetic subjects with microalbuminuria had higher BP levels than subjects without microalbuminuria. Thus, the association between microalbuminuria and a prediabetic state could have been the result of elevated BP. However, our prospective study showed that the association of microalbuminuria and the development of NIDDM was statistically independent of the BP level at baseline. Previous cross-sectional studies also have reported that the increased prevalence of microalbuminuria in subjects with IGT (10,11) and in subjects with a parental history of diabetes (11) was not accounted for by differences in the BP level.

TABLE 4
Multiple logistic regression analyses for the incidence of diabetes during 3.5-year follow-up

	Odds ratio	95% confidence interval	*P* value
Model 1	1.76	1.07–2.90	0.026
Microalbuminuria (yes/no)			
Model 2			
Age (10-year change)	0.64	0.26–1.54	0.321
Sex (M/F)	0.73	0.44–1.22	0.232
dBP (10 mmHg change)	1.23	0.97–1.56	0.084
Microalbuminuria (yes/no)	1.71	1.02–2.86	0.040
Model 3			
Age (10-year change)	0.62	0.25–1.55	0.306
Sex (M/F)	0.86	0.50–1.48	0.585
dBP (10 mmHg change)	1.24	0.97–1.58	0.085
FPG (0.5 mM change)	1.91	1.55–2.35	<0.001
Fasting plasma insulin (60 pM change)	1.35	0.98–1.86	0.068
Microalbuminuria (yes/no)	1.40	0.82–2.39	0.219

Microalbuminuria, ACR ≥ 2 mg/mmol.

IGT is an important risk factor for developing NIDDM. In this population, nearly 70% of subjects developing NIDDM during the 3.5-year follow-up had IGT at baseline (37). Because subjects with IGT had an increased prevalence of microalbuminuria, it might be anticipated that microalbuminuria would predict the incidence of NIDDM. Indeed, the prevalence of microalbuminuria was higher in IGT subjects who developed NIDDM over 3.5 years than in those who remained in the IGT category or reverted to NGT (50.0% [24 of 48] vs. 35.5% [55 of 155], $P = 0.071$), but the difference between these groups was not statistically significant.

Increased urinary albumin loss has been postulated to be a marker of a generalized increase in vascular permeability, which might predispose to greater penetration of atherogenic lipoprotein particles into arterial wall (42). Several studies have indicated that microalbuminuria is associated with cardiovascular disease both in nondiabetic (15,43,44) and NIDDM subjects (1–4). Widespread vascular damage could be one cause of microalbuminuria in this study because the participants were elderly subjects who had a high prevalence of cardiovascular disease as reported previously (45).

Microalbuminuria in newly diagnosed NIDDM (6,7) and in nondiabetic subjects with essential hypertension (40) is probably of glomerular origin. Possibly, localized increased pressure in the glomerular vessels is involved in increased albumin excretion (46). Insulin has hemodynamic effects on kidneys. Acute hyperinsulinemia caused renal vasodilatation resulting in increased plasma flow and increased glomerular hydrostatic pressure gradient in normal rats (47) and renal vasodilation and increased glomerular filtration rate in the isolated perfused rat kidney (48). The long-term effects hyperinsulinemia has on glomerular hemodynamics are not known. In this study, subjects with microalbuminuria had elevated plasma insulin levels compared with subjects without microalbuminuria suggesting that they were more insulin resistant. Moreover, in the follow-up study a marked proportion of the association between microalbuminuria and the incidence of NIDDM was explained by baseline insulin and glucose levels. Thus, a common denominator for microalbuminuria and the risk of developing diabetes may be hyperinsulinemia.

One limitation of our study is that we used only a single spot urine sample to assess microalbuminuria instead of timed collections that would have been preferable. However, we calculated UAE as a ratio of urinary albumin and urinary creatinine that enhances markedly the accuracy of the single spot urine sample in the assessment of microalbuminuria (30–32). Another limitation of this study is that the urine was not cultured to detect bacterial infections, which are possible candidates for a cause of increased UAE in some of the elderly subjects we studied. Diabetic subjects may have had more urinary tract infections than nondiabetic subjects. However, subjects with IGT are not known to be more prone

to urinary tract infections than normoglycemic subjects. Moreover, our follow-up study included only nondiabetic subjects. Thus, inclusion of subjects with urinary tract infection would have been likely to add random variation in UAE and bias results toward the null hypothesis, i.e., finding no difference in the risk of NIDDM between subjects with and without microalbuminuria. However, we found that subjects with microalbuminuria developed NIDDM more often than those without microalbuminuria. Finally, antihypertensive therapy was common in our study population and is a possible confounding factor in this study. However, diuretics and β-blockers were the most commonly used antihypertensive agents in our study population, and only 21 of 388 subjects were taking other antihypertensive medications. Diuretics and β-blockers are not known to effect UAE beyond their antihypertensive property.

In conclusion, microalbuminuria predicted the development of NIDDM independently of the BP level. The UAE rate was increased in subjects with IGT and newly diagnosed NIDDM. In nondiabetic subjects, microalbuminuria was associated with multiple adverse changes in cardiovascular risk factors and hyperinsulinemia. Although the role of microalbuminuria in nondiabetic subjects needs to be explored more fully, together these results support the hypothesis that microalbuminuria is an hyperinsulinemic condition and possibly a feature of the prediabetic state (11) or a marker for hyperinsulinemia and raised glucose levels.

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REFERENCES

1. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–60, 1984
2. Jarrett JR, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murrells TJ: Microalbuminuria predicts mortality in non-insulin-dependent diabetes. *Diabetic Med* 1:17–19, 1984
3. Schmitz A, Vaeth M: Microalbuminuria: a major risk factor in non-insulin-dependent diabetes: a 10-year follow-up study of 503 patients. *Diabetic Med* 5:126–134, 1988
4. Mattock MB, Morrish NJ, Viberti GC, Keen H, Fitzgerald AP, Jackson G: Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes* 41:735–41, 1992
5. Niskanen L, Uusitupa M, Sarlund H, Siitonen O, Voutilainen E, Penttilä I, Pyörälä K: Microalbuminuria predicts the development of serum lipoprotein abnormalities favouring atherogenesis in newly diagnosed type II (non-insulin-dependent) diabetic patients. *Diabetologia* 33:237–243, 1990
6. Damsgaard EM, Mogensen CE: Microalbuminuria in elderly hyperglycaemic patients and controls. *Diabetic Med* 3:430–35, 1986
7. Uusitupa M, Siitonen O, Penttilä I, Aro A, Pyörälä K: Proteinuria in newly diagnosed Type II diabetic patients. *Diabetes Care* 10:191–94, 1987
8. Keen H, Chlouverakis C, Fuller J, Jarrett RJ: The concomitants of raised blood sugar: studies in newly-detected hyperglycaemics. II. Urinary albumin excretion, blood pressure and their relation to blood sugar levels. *Guy's Hosp Rep* 118:247–54, 1969
9. Collins VR, Dowse GK, Finch CF, Zimmet PZ, Linnane AW: Prevalence and risk factors for micro- and macroalbuminuria in diabetic subjects and entire population of Nauru. *Diabetes* 38:1602–10, 1989
10. Nelson RG, Kunzelman CL, Pettitt DJ, Saad MF, Bennett PH, Knowler WC: Albuminuria in type II (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in Pima Indians. *Diabetologia* 32:870–876, 1989
11. Haffner SM, Gonzáles C, Valdez RA, Mykkänen L, Hazuda HP, Mitchell BD, Monterrosa A, Stern MP: Is microalbuminuria part of the prediabetic state? The Mexico City Diabetes Study. *Diabetologia* 36:1002–1006, 1993
12. Groop L, Ekstrand A, Forsblom C, Widen E, Groop P-H, Teppo A-M, Eriksson J: Insulin resistance, hypertension and microalbuminuria in patients with type II (non-insulin-dependent) diabetes mellitus. *Diabetologia* 36:642–47, 1993
13. Nosadini R, Solini A, Sambataro M, Cipollina MR, Trevisan R, Duner E, Strazzabosco M, Barzon I, Brocco E, Velussi M, Crepaldi G: Relationships among insulin resistance, hypertension and microalbuminuria in non-insulin-dependent diabetes: role of cell ion handling (Abstract). *Diabetes* 41 (Suppl. 1):62A, 1992
14. Niskanen L, Laakso M: Insulin resistance is related to microalbuminuria in patients with type II (non-insulin-dependent) diabetes mellitus. *Metabolism* 42:1541–45, 1993
15. Haffner SM, Stern MP, Gruber KK, Hazuda HP, Mitchell BD, Patterson JK: Microalbuminuria: potential marker for increased cardiovascular risk factors in nondiabetic subjects? *Arteriosclerosis* 10:727–31, 1990
16. Lillioja S, Mott DM, Howard BV, Bennett PH, Yki-Järvinen H, Freymond D, Nyomba BL, Zurlo F, Swinburn B, Bogardus C: Impaired glucose tolerance as a disorder of insulin action: longitudinal and cross-sectional studies in Pima Indians. *N Engl J Med* 318:1217–25, 1988
17. Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK: Incidence of type II diabetes in Mexican-Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes* 39:283–88, 1990
18. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn R: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 113:909–15, 1990
19. Charles MA, Fontbonne A, Thibult N, Warnet J-M, Rosselin GE, Eschwege E: Risk factors for NIDDM in white population: Paris Prospective Study. *Diabetes* 40:796–99, 1991
20. Mykkänen L, Laakso M, Uusitupa M, Pyörälä K: Prevalence of diabetes and impaired glucose tolerance in elderly subjects and their association with obesity and family history of diabetes. *Diabetes Care* 13:1099–1105, 1990
21. Mykkänen L, Laakso M, Penttilä I, Pyörälä K: Asymptomatic hyperglycemia and cardiovascular risk factors in the elderly. *Atherosclerosis* 88:153–61, 1991
22. World Health Organization: *Diabetes Mellitus. Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser. no. 727)
23. Faber OK, Binder C: C-peptide response to glucagon: a test for the residual beta-cell function in diabetes mellitus. *Diabetes* 26:605–10, 1977
24. Madsbad S, Alberti KGMM, Binder C, Burrin JM, Faber OK, Krarup T, Regeur L: Role of residual insulin secretion in protecting against ketoacidosis in insulin-dependent diabetes. *Br Med J* 2:1257–59, 1979
25. Hales CN, Randle PJ: Imunoassay of insulin with insulin antibody precipitate. *Biochem J* 88:137–46, 1963
26. Penttilä IM, Voutilainen E, Laitinen P, Juutilainen P: Comparison of different analytic and precipitation methods for direct estimation of serum high-density lipoprotein cholesterol. *Scand J Clin Lab Invest* 41:353–60, 1981
27. Siedel J, Hägele EO, Ziegenhorn J, Wahlefeld AW: Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. *Clin Chem* 29:1075–80, 1983
28. Wahlefeld AW: Triglycerides determination after enzymatic hydrolysis. In *Methods of Enzymatic Analysis*. 2nd ed. Bergmeyer HV, Ed. New York, Academic, 1974, p. 1831–35
29. Kroll MH, Chesler R, Hagengruber C, Blank DW, Kestner J, Rawe M: Automated determination of urinary creatinine without sample dilution: theory and practice. *Clin Chem* 32:446–52, 1986
30. Gatling W, Knight C, Mullee MA, Hill RD: Microalbuminuria in diabetes: a population study of the prevalence and an assessment of three screening tests. *Diabetic Med* 5:343–47, 1988
31. Hutchison AS, O'Reilly DSJ, McCuish AC: Albumin excretion rate, albumin concentration, and albumin/creatinine ratio compared for screening diabetics for slight albuminuria. *Clin Chem* 34:2019–21, 1988
32. Nelson RG, Knowler WC, Pettitt DJ, Saad MF, Charles MA, Bennett PH: Assessment of risk of overt nephropathy in diabetic patients from albumin excretion in untimed urine specimens. *Arch Intern Med* 151: 1761–65, 1991
33. Norušis MJ: *SPSS/PC+4.0 Base Manual for the IBM PC/XT/AT and PS/2*. Chicago, SPSS, 1990
34. Ohlson L-O, Larsson B, Björntorp P, Eriksson H, Svärdsudd K, Welin L, Tibblin G, Wilhelmsen L: Risk factors for type II (non-insulin-dependent) diabetes mellitus: thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 31:798–805, 1988
35. Haffner SM, Stern M, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–98, 1990
36. McPhillips JB, Barrett-Connor E, Wingard DL: Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a community of older adults. *Am J Epidemiol* 131:443–53, 1990
37. Mykkänen L, Kuusisto J, Pyörälä K, Laakso M: Cardiovascular disease risk factors as predictors of type II (non-insulin- dependent) diabetes mellitus in elderly subjects. *Diabetologia* 36:553–59, 1993
38. Pelz KS, Gottfried SP, Paz E: Kidney function studies in old men and women. *Geriatrics* 20:145–49, 1965

39. Olivarius N de F, Andreasen AH, Keiding N, Mogensen CE: Epidemiology of renal involvement in newly-diagnosed middle-aged and elderly diabetic patients: cross-sectional data from the population-based study "Diabetes Care in General Practice", Denmark. *Diabetologia* 36:1007–16, 1993
40. Parving H-H, Jensen Æ, Mogensen CE, Evrin P-E: Increased urinary albumin-excretion rate in benign essential hypertension. *Lancet* 1:1190–92, 1974
41. Gatling W, Mullee MA, Knight C, Hill RD: Microalbuminuria in diabetes: relationships between urinary albumin excretion and diabetes-related variables. *Diabetic Med* 5:348–51, 1988
42. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage: the Steno hypothesis. *Diabetologia* 32:219–26, 1989
43. Yudkin JS, Forrest RD, Jackson CA: Microalbuminuria as predictor of vascular disease in nondiabetic subjects. *Lancet* 2:530–33, 1988
44. Kannel WB, Stampfer MJ, Castelli WP, Verter J: The prognostic significance of proteinuria: the Framingham study. *Am Heart J* 108:1347–52, 1984
45. Mykkänen L, Laakso M, Pyörälä K: Asymptomatic hyperglycemia and atherosclerotic vascular disease in the elderly. *Diabetes Care* 15:1020–30, 1992
46. Brenner BM: Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. *Kidney Int* 23:647–55, 1983
47. Tucker BJ, Anderson CM, Thies RS, Collins RC, Blantz RC: Glomerular hemodynamic alterations during acute hyperinsulinemia in normal and diabetic rats. *Kidney Int* 42:1160–68, 1992
48. Cohen AJ, McCarthy DM, Stoff JS: Direct hemodynamic effect of insulin in the isolated perfused kidney. *Am J Physiol* 257:F580–85, 1989