META-REGRESSION OF RISK FACTORS FOR MICROALBUMINURIA IN TYPE 2 DIABETES

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Abstract. We aimed to determine the risk factors associated with microalbuminuria in type 2 diabetes patients through a systematic review and meta-regression analysis. The analyzed studies were obtained from PubMed, Scopus, British Medical Journal and ProQuest databases. All studies published from 2000 to 2009 were included. The search yielded 1,243 citations, of which 22 studies were analyzed. Pooled odds ratio estimates were obtained using a random effect model. The association of each risk factor with microalbuminuria was examined after adjusting for age and sex using meta-regression analysis. The adjusted odds ratio was 1.26 (95% CI 1.08-1.46) for systolic blood pressure; 1.16 (95% CI 1.03-1.31) for diastolic blood pressure; 1.43 (95% CI 1.14-1.80) for fasting plasma glucose level; 1.37 (95% CI 0.95-1.98) for smoking and 1.49 (95% CI 0.91-2.46) for waist circumference. The risk factors associated with microalbuminuria were found to be poor glycemic control, uncontrolled hypertension, smoking and central obesity. There is an urgent need to launch a health promotion program for changes in individual health behaviors to mitigate these risk factors for microalbuminuria in patients with type 2 diabetes.

Keywords: type 2 diabetes, microalbuminuria, meta-regression

INTRODUCTION

The burdens of chronic diabetic complications are increasing worldwide. The causal association between microalbuminuria and the development of diabetic complications has been well established (Bakris *et al*, 1994; Golan *et al*, 1999; Bakris *et al*, 2002; Poulsen, 2003). Several studies have determined the risk of microalbuminuria depends on several determinants in patients with type 2 diabetes. These determinants include age, gender, body mass index (BMI), duration of diabetes, poor glycemic control, uncontrolled blood pressure and dyslipidemia related to microalbuminuria. However, no systematic reviews have been undertaken to determine risk factors for microalbuminuria in patients with type 2 diabetes. Previous studies of the relationship between various risk factors and microalbuminuria have provided controversial results (Mongkolsomlit and Rawdaree, 2010). Meta-regression is a well-established methodological approach for summarizing research findings. To our knowledge,

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no meta-regression analysis has been performed to estimate the overall effect of a particular factor on the risk of microalbuminuria. To increase our current knowledge of these risk factors, we performed a systematic review and meta-regression analysis of studies to assess the risk factors associated with microalbuminuria in patients with type 2 diabetes.

MATERIALS AND METHODS

Search strategy and data sources

We included both observational studies (analytical cross sectional studies, case-control studies and cohort studies) and randomized control trials (RCTs) published during 2000-2009. The following terms were used for the search: "microalbuminuria AND risk factor," "fasting plasma glucose AND microalbuminuria," "body mass index AND microalbuminuria," "HbA1c AND microalbuminuria," "duration of diabetes AND microalbuminuria," "gender or sex AND microalbuminuria," "age AND microalbuminuria," "smoking AND microalbuminuria," "lipid AND microalbuminuria" and "blood pressure AND microalbuminuria." We performed our searches using the PubMed, Scopus, British Medical Journal and ProQuest databases.

The full articles were retrieved and screened using the following inclusion criteria: 1) study subjects were patients with type 2 diabetes who were more than 18 years old, and 2) microalbuminuria must have been evaluated in the subjects by quantitative or semi-quantitative methods (Micral test). Studies that included participants with end-stage renal disease who were undergoing dialysis or renal transplantation were excluded.

The outcome of interest was microalbuminuria. Our definition of microalbuminuria was based on the American Diabetes Association (ADA) definition (American Diabetes Association, 2009). Microalbuminuria is defined by the ADA as the presence of more than 30 milligrams of albumin per day, more than 20 micrograms of albumin per minute or more than 30-299 micrograms of albumin per milligram of urine. Smoking, blood pressure, blood glucose, lipid profile, BMI and waist circumference were recorded as exposures. Age and gender were recorded as confounding factors.

Study selection and quality assessment

Of the 1,243 identified articles, 1,135 studies were excluded by initial screening by one investigator. Two investigators independently examined the full text of the remaining 108 studies to confirm they met eligibility criteria using a structured eligibility form. We resolved any disagreements by mutual discussion. Finally, we included 22 studies for analysis (Fig 1).

Because no standardized criteria have been established for judging the quality of observational studies, we adapted the meta-analysis of observational studies in epidemiology (MOOSE) group guidelines by selecting as *a priori* several important design characteristics that might affect study quality (Stroup *et al*, 2000). This selection was performed to evaluate possible sources of heterogeneity, including measurement bias, selection bias, selection of cases and controls and clear definitions of exposures and outcomes. To judge the quality of the randomized control trials, we adapted the quality assessment criteria from Jadad's guidelines (Jadad *et al*, 1996), including eligibility criteria for participants, data collection settings and intervention allocations. In both observational studies and RCT

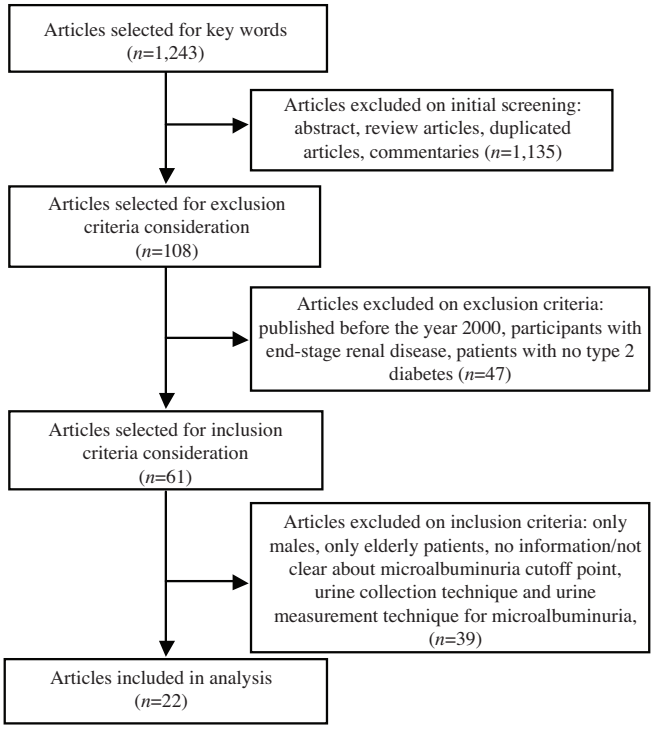

Fig 1–Study flow diagram.

quality assessments, we used the structured quality assessment form for analysis.

Data extraction

The data were extracted using a structured data entry form that categorized the data under the following headings: author, year of publication, population, urine collection method, urine measurements, outcomes and exposures. The units of measurement for the laboratory variables were converted from traditional units into international measurement units (SI units). The standard error of the mean (SEM) was converted to standard deviation (SD) by the following equation: SEM = SD/square root (n). The summarized data were evaluated twice to avoid transcription errors.

Data analysis methods

The relationships between the outcome and risk variables were estimated using the pooled odds ratio and 95% confidence intervals of the pooled odds ratio. For undesirable outcomes, an odds ratio greater than 1 indicated the variable was a risk factor for microalbuminuria. We assessed heterogeneity among the studies using Cochrane Q and I^2 statistics. Heterogeneity significance was an alpha (α) of 0.10. Egger's test was used to assess potential publication bias (Egger *et al*, 1997). We used random effect meta-regression to examine the association of risk factors with microalbuminuria after adjusting for age and sex in the model. All analyses were conducted using STATA software, version 11.0 (Stata Corporation, College Station, TX).

RESULTS

Studies reporting characteristics

A summary of the main characteristics of the 22 studies included in the meta-regression analysis is shown in Table 1. Seventeen studies were cross sectional studies, two were case-control studies, two were cohort studies and one was a RCT. The majority of the studies (*n*=16) were carried out in hospitals. Five studies were conducted at multiple centers and one was population-based. Fourteen studies used the spot morning method for urine collection, five studies used 24-hour urine collection, three studies used a timed urine collection method and one study had an unspecified method of urine collection.

Heterogeneity test and publication bias

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Table 1
Characteristics of the studies reporting associations between risk factors and microalbuminuria (*N*=22).

Author	Publication year	Population	Study design	Study based on	Urine collection	MA positive	MA negative	Factors recorded for exposure[a]
Modebe O	2000	Bahraini	Cross sectional	Hospital based	24-hour	132	180	1, 2, 4, 5, 6, 7, 9, 10, 12, 13
Varghese A	2001	South Indian	Cross sectional	Hospital based	Spot morning	518	907	1, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13
Abdella NA	2002	Kuwaiti	Cross sectional	Hospital based	Spot morning	141	162	2, 8, 9, 10, 11, 12, 13
Bruno G	2003	Italian	Cohort	Hospital based	Timed urine	426	677	1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 13
Hashim R	2004	Pakistani	Cross sectional	Hospital based	Spot morning	70	80	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13
Matsui J	2004	Japanese	Cross sectional	Hospital based	24-hour	11	12	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
Yerong Y	2004	Chinese	Cross sectional	Hospital based	Spot morning	12	12	1, 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 14
Wu AYT	2005	Asian ethnic	Cross sectional	Multicenter	Spot morning	2,211	2,297	1, 2, 3, 4, 5, 6, 8, 9
Ahmedani MY	2005	Pakistani	Cross sectional	Multicenter	Unknown	475	921	2, 7, 9, 10
Buranakitjaroen P	2005	Thai	Cross sectional	Hospital based	Spot morning	42	42	1, 2, 3, 4, 5, 6, 8
Cederholm J	2005	Swedish	Cross sectional	Multicenter	Spot morning	1,151	5,362	1, 2, 3, 4, 5, 6, 7
Baykan M	2006	Turkish	Cross sectional	Hospital based	24-hour	29	39	1, 2, 3, 4, 7, 9, 10, 11, 12, 13
Lutale JJK	2007	Tanzanian	Cross sectional	Hospital based	Timed urine	26	127	1, 4, 5, 6, 9
Amini M	2007	Isfahan	Cohort	Hospital based	24-hour	176	329	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
Helaly MA	2007	Mansoura	RCT	Hospital based	Spot morning	20	20	1, 2, 4, 5, 6, 8, 9, 10, 11, 12, 13
Unnikrishnan R	2007	Indian	Cross sectional	Population based	Spot morning	462	1,163	1, 2, 3, 4, 5, 6, 7, 8, 9, 14
Yokoyama H	2007	Japanese	Cross sectional	Multicenter	Spot morning	2,812	5,152	1, 2, 3, 4, 5, 6, 9
Rossi MC	2008	Italian	Cross sectional	Hospital based	Spot morning	308	1,249	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
Piarulli, F	2009	Italian	Case-control	Hospital based	Timed urine	62	37	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
Esteghamati A	2009	Iranian	Cross sectional	Hospital based	24-hour	237	563	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14
Baris N	2009	Turkish	Case-control	Hospital based	24-hour	45	46	1, 2, 3, 4, 8, 9, 10, 11, 12, 13, 14
Aekplakorn W	2009	Thai	Cross sectional	Multicenter	Spot morning	1,628	2,208	1, 2, 3, 4, 7, 9, 10, 11, 12, 13, 14

[a]1, age; 2, gender; 3, BMI; 4, duration of DM; 5, SBP; 6, DBP; 7, smoke; 8, FBS; 9, HbA1c; 10, total cholesterol; 11, LDL; 12, HDL; 13, triglyceride; 14, waist circumference

Table 2
Heterogeneity statistics and publication bias test.

Factors	MA + (*N*=10,994)	MA - (*N*=21,585)	Heterogeneity statistics		Egger's test	I^2	df	Egger's test
			Q test	*p*-value				
Age (years)	58.7±10.9	57.6±10.5	68.81	<0.001	0.60	72.4	19	0.60
Male	52.6%	51.5%	156.01	<0.001	0.12	87.3	19	0.12
BMI (kg/m^2)	26.7±4.2	26.5±4.0	53.64	<0.001	0.41	70.2	16	0.41
Duration of diabetes (years)	8.8±7.3	7.3±6.4	56.32	<0.001	0.08	68.0	18	0.08
Systolic BP (mmHg)	141.3±22.9	135.2±19.7	70.62	<0.001	0.93	78.8	15	0.93
Diastolic BP (mmHg)	82.7±11.8	80.6±10.8	30.97	0.009	0.18	51.6	15	0.18
Tobacco smoking	10.4%	10.2%	72.06	<0.001	0.75	84.7	11	0.75
FBS (mmol/l)	9.2±2.9	8.2±2.6	72.91	<0.001	0.39	83.5	12	0.39
HbA1c (%)	8.5±2.1	7.9±2.0	194.55	<0.001	0.41	90.2	19	0.41
Total cholesterol (mmol/l)	5.4±1.2	5.2±1.1	243.83	<0.001	0.68	93.8	15	0.68
LDL (mmol/l)	3.3±1.1	3.2±0.9	12.76	0.309	0.14	13.8	11	0.14
HDL (mmol/l)	1.1±0.3	1.2±0.3	58.44	<0.001	0.52	76.0	14	0.52
Triglycerides (mmol/l)	2.0±1.0	1.8±0.9	48.28	<0.001	0.33	71.0	14	0.33
Waist circumference (cm)	93.1±10.4	91.4±10.1	9.84	0.080	0.39	49.2	5	0.39

MA, microalbuminuria

Table 3
Sources of heterogeneity in the analyzed studies.

Source of heterogeneity	Variation in ES attributable to heterogeneity (I^2)						
	Age	Sex	Smoker	FBS	HbA1c	SBP	DBP
Urine collection							
24 hour	33.6	78.6	0.00	19.3	93.2	0.00	0.00
Spot morning	82.6	87.2	37.3	87.8	87.0	86.7	63.3
Timed urine	0.00	0.00	0.00	NA[a]	0.00	0.00	0.00
Study design							
Cross sectional	78.6	88.4	88.4	88.0	82.3	82.4	56.7
Cohort	0.00	93.8	50.3	NA[a]	98.8	84.2	76.6
Case-control	0.00	0.00	NA[a]	0.00	0.00	NA[a]	NA[a]
RCT	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]
Study setting							
Hospital	37.0	76.6	96.7	34.3	88.9	0.1	0.0
Multi-center	93.5	95.9	0.00	NA[a]	89.1	96.0	3.9
Community	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]

[a] NA, not applicable

22 studies included 10,994 cases of microalbuminuric diabetes and 21,585 cases with non-microalbuminuric diabetes. To determine the level of heterogeneity among the studies, we performed the Cochran's Q test. Since we found a statistically significant level of heterogeneity ($p < 0.10$) among the exposure variables except for low-density lipoprotein (LDL) levels, we conducted a random effect model for all the studies to estimate the effect size of each of the exposures. We found no significant evidence of publication bias on any of the factors in our analysis with the Egger's test (Table 2).

Risk factors and microalbuminuria

Table 2 shows the heterogeneity statistics and publication bias test results. All factors showed statistically significant heterogeneity, except for the LDL and waist circumference variables. None of the variables showed significant differences with the publication bias test.

After performing the heterogeneity and publication bias assessments, we performed a meta-regression model analysis using the random effect method to examine the association of each factor with microalbuminuria after adjusting for age and sex (Fig 2). The duration of diabetes, systolic and diastolic blood pressure, fasting plasma glucose and high-density lipoprotein (HDL) values were significantly associated with microalbuminuria (OR 1.16, 95% CI 1.01-1.34; OR 1.26, 95% CI 1.08-1.46; OR 1.16, 95%CI, 1.03-1.31; OR 1.43, 95% CI, 1.14-1.80; OR 0.79, 95% CI, 0.63-0.99, respectively). Smoking and waist circumference were possible risk factors for microalbuminuria, but the differences were not statistically significant (OR 1.37, 95% CI 0.95-1.98; OR 1.49, 95% CI 0.91-2.46, respectively).

DISCUSSION

This meta-regression analysis of 22

Factors	Articles (*n*)	OR (95% CI)
Tobacco smoking	10	1.37 (0.95-1.98)
Body mass index	16	1.08 (0.94-1.23)
Waist circumference	6	1.49 (0.91-2.46)
Duration of diabetes	17	1.16 (1.01-1.34)
Systolic blood pressure	14	1.26 (1.08-1.46)
Diastolic blood pressure	14	1.16 (1.03-1.31)
Fasting plasma glucose	11	1.43 (1.14-1.80)
HbA1c	16	1.20 (1.00-1.45)
Total cholesterol	13	0.97 (0.82-1.16)
Low-density lipoprotein	10	0.99 (0.90-1.10)
High-density lipoprotein	13	0.79 (0.63-0.99)
Triglyceride	13	1.07 (0.82-1.93)

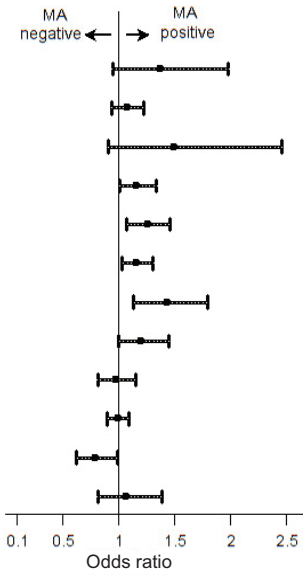

Fig 2–Meta-regression analyses for risk factors and microalbuminuria after adjusting for age and sex.

studies included more than 10,000 cases of microalbuminuric diabetes and a variety of study types, including analytical cross sectional studies, case-control studies, cohort studies and a randomized controlled trial. Estimates of odds ratios (OR) were only appropriate if the data were derived from case-control and cross sectional studies, whereas relative risk (RR) could only be obtained for cohort studies and randomized controlled trials. For this analysis, the majority of the study designs were cross sectional and case-controlled designs (20 studies). We assumed all these studies would give a similar effect estimate, but we also reported the odds ratio in this analysis.

A quality assessment of the included studies was performed because two researchers independently examined the studies, and a structured quality assessment form was used to evaluate the quality of the studies. In theory, when performing a systematic review, a third researcher should consider the quality of the studies when the first two researchers do not agree. However, we were unable to find a third researcher who was available to examine the full text of the analyzed studies. For our structured quality assessment form, we adapted the MOOSE group's guidelines and Jadad's guidelines. For the cross sectional studies, we evaluated the measurement bias, selection bias, confounding control and reporting bias. For the case-control studies, we evaluated the accurate ascertainment of cases, selection of cases/controls, response rate, application of diagnostic testing and appropriate attention to potential confounding factors. We evaluated the quality of cohort study designs by considering the initial assembly of cohort studies, maintenance of comparable groups, attrition rate, assessment of measurements, clear definitions of exposure, inclusion of all important outcomes and adjustment for potential confounding factors. The final design, RCT, was evaluated with regard to the description of the trial design, eligibility criteria for participants, data collection settings, interventions intended for each group, clearly defined primary outcomes for this report, inclusion of all important outcomes, adjustment for potential confounders and important adverse events or side effects.

Most of the studies in this meta-regression analysis were observational

studies, but no significant publication bias was found ($p > 0.05$ for all). Because significant heterogeneity was present, we used the random effects model, since it assumes the true effect estimate for each study does vary. We explored the sources of heterogeneity in the study outcomes among the studies by subgroup analysis. The sources of heterogeneity in the main risk factors were the method of urine collection, study design and study setting. Table 3 shows the variations in effect sizes that are attributable to heterogeneity in the variables of our study. The studies that used the spot morning collection method and a cross sectional study design were affected by high heterogeneity (I^2 of nearly 100%). We cannot explain these heterogeneity effects. The sources of intra-study variability could include differences in study populations, such as age and gender; therefore, we used meta-regression analysis to estimate the effect of each risk factor on microalbuminuria in diabetes type 2 after adjusting for the influences of age and gender.

The findings of this study confirm a substantially higher risk associated with male gender, older age, tobacco smoking, longer duration of diabetes, uncontrolled blood pressure, uncontrolled blood glucose and uncontrolled dyslipidemia associated with microalbuminuria. After adjusting for age and sex by meta-regression analysis, we also found tobacco smoking, longer duration of diabetes, uncontrolled blood pressure and uncontrolled blood glucose are risk factors for microalbuminuria. However, total cholesterol, LDL and triglyceride levels are not associated with microalbuminuria.

The associations between age and sex and microalbuminuria have been confirmed. Age and sex cannot be altered to reduce risk of developing microalbuminuria. However, if greater attention is paid to risk factors among males and older people, this knowledge could help to identify patients in high-risk groups for developing microalbuminuria.

This study confirmed that smoking is a risk factor for microalbuminuric type 2 diabetes. The greater the number of total pack-years smoked the greater the risk of developing proteinuria ($p < 0.05$) (Mattock *et al*, 1992). Duration of diabetes was confirmed as risk factor for microalbuminuria in type 2 diabetes. As a worldwide epidemic, type 2 diabetes has become more common among children and teens. A child with type 2 diabetes will have a long duration of diabetes. However, type 2 diabetes can be reduced or eliminated among younger people by providing health education and health promotion programs. The programs should focus on people who care for children, such as parents, high school teachers and childcare providers; these programs should include students in boarding schools and students attending day schools.

Uncontrolled FBS, HbA1c and elevated blood pressure levels were significantly associated with microalbuminuria. This result was expected because high blood glucose levels are known to result in the thickening of the vascular basement membrane (Cagliego *et al*, 1991). Moreover, elevated blood pressure is documented to be the most significant contributing factor in the pathogenesis and progression of an abnormal urinary albumin excretion rate (AER) and, eventually, in the development of diabetic nephropathy in type 2 diabetic patients (Schmitz *et al*, 1994).

Abnormalities in lipoprotein metabolism, such as elevated triglyceride levels and reduced HDL cholesterol levels, have

been demonstrated in microalbuminuric type 2 diabetic patients (Bonnet *et al*, 2000; Shoji *et al*, 2001). The majority of studies included in this analysis found an association between an abnormal lipid profile and increased urine albumin excretion, but the present study, after adjusting for age and sex by meta-regression analysis, found total cholesterol, LDL and triglyceride levels were not associated with microalbuminuria.

Several studies have found that BMI is associated with microalbuminuria, while others have not. In the past, evidence of an association between basal BMI and increased albumin excretion has been equivocal. This meta-regression analysis shows BMI is not associated with microalbuminuria but waist circumference is possibly associated with microalbuminuria. Waist circumference is an interesting variable. Behan and Mbizo (2007) studied the relationship between waist circumference and biomarkers for diabetes and cardiovascular disease (CVD) among healthy, non-obese women. The results showed waist circumference was correlated with triglyceride, CRP, cholesterol/HDL, non-HDL, LDL and glucose levels and inversely correlated with HDL levels ($r = 0.465$, 0.414, 0.321, 0.299, 0.267, 0.279, -0.266, respectively; $p < 0.001$ for all). It is possible waist circumference depends on the lipid profile of a person and the lipid profile is related to waist circumference. The knowledge analysis of lipid levels is dispensable may enable a reduction in costs to governments and patients when screening for risk factors for microalbuminuria.

Compared to the general population, patients with type 2 diabetes mellitus are at a significantly increased risk for the development of atherosclerotic complications that can lead to cardiovascular morbidity and death; this risk is even greater in diabetic patients who present with microalbuminuria (Friedman *et al*, 2004). Preventing the development of microalbuminuria is a key treatment goal for nephroprotection, retinoprotection and cardioprotection (Turner *et al*, 1998; Ritz, 2003). Several studies have documented microalbuminuria can be reduced by using the angiotensin drug rennin. Early detection of risk factors for microalbuminuria and the early control of diabetes retards the development of structural changes that can lead to early diabetic complications.

Many studies have confirmed microalbuminuria is an early predictor of nephropathic and cardiovascular complications of diabetes (Bennett, 1989; Messent *et al*, 1992; Mattock *et al*, 1998). Nephropathy is a microvascular complication, and cardiovascular problems represent a macrovascular complication. The cause of macrovascular diseases is metabolic syndrome. The criteria for the diagnosis of metabolic syndrome by the International Diabetes Federation (IDF) include central obesity (a waist circumfirance ≥90 cm in males or ≥80 cm in females), elevated TG levels, reduced HDL-C levels, elevated blood pressure and elevated fasting plasma glucose (International Diabetes Federation resourses page). The characteristics of lipid abnormalities in metabolic syndrome are low HDL levels, high triglyceride levels, low LDL levels and high apoprotein B levels. These risk factors are similar to risk factors for microalbuminuria found in this meta-regression analysis. Only LDL level had no significant association with microalbuminuria. At present, we do not know what causes the difference between micro- and macrovascular complications or why some patients with type 2 diabetes present

with microvascular complications, while others present with macrovascular diseases. It is possible the LDL level might be an indicator for this difference.

This study highlights the importance of the early detection of microalbuminuria among patients with type 2 diabetes. With regard to our study limitations, we did not study all of the factors that could influence microalbuminuria. Baris *et al* (2009) found markers of inflammation, including serum hs-CRP and L-arginine, were correlated with microalbuminuria in type 2 diabetes; serum hs-CRP concentrations were significantly elevated in diabetic patients with microalbuminuria ($p = 0.012$). L-arginine concentrations differed significantly between diabetic patients with and without microalbuminuria ($p < 0.001$). This study did not evaluate these factors because it is difficult to include them when screening for microalbuminuria.

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