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Glycated Hemoglobin is Independently Associated with Albuminuria in Young Nondiabetic People with Obesity: A Cross-Sectional Study

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Background: The aim of this study was to explore the association between glycated hemoglobin (HbA1c) level and albuminuria in young nondiabetic people with obesity.

Material/Methods: A total of 537 young nondiabetic people with obesity were enrolled in this cross-sectional study, which was approved by the Rui-jin Hospital Ethics Committee. Albuminuria was defined as a urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g. Multivariate logistic regression was used to analyze the association between HbA1c level and albuminuria.

Results: Urinary ACR progressively increased across the tertiles of HbA1c level (*P* for trend <0.05). HbA1c levels were positively associated with the risk of albuminuria in the logistic regression analysis after adjustment for confounding factors. The adjusted odds ratio (OR) for albuminuria was 3.72 (95% confidence interval [CI], 1.25–11.00; *P*=0.017) when comparing between the highest (≥5.7%) and lowest tertiles of HbA1c level (≤5.3%). Moreover, an increment of 1 SD in HbA1c level increased the risk of albuminuria in a fully adjusted model (OR, 1.73; 95% CI, 1.25–2.46).

Conclusions: These data suggest that HbA1c level was independently associated with albuminuria in young nondiabetic people with obesity.

MeSH Keywords: Albuminuria • Hemoglobin A, Glycosylated • Obesity

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Background

Chronic kidney disease (CKD), which is characterized by reduced estimated glomerular filtration rate (eGFR) and/or albuminuria, is an increasing global concern. Albuminuria, defined as a urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g, is an early marker of CKD and an independent predictor of cardiovascular disease (CVD) [1,2]. Albuminuria has been reported to increase the risk of cardiovascular events, cardiovascular mortality, and all-cause mortality in diabetic and nondiabetic individuals [3–5]. Numerous studies have focused on albuminuria in diabetic patients and the general population [6–9]. However, in people with obesity, the risk factors of albuminuria have not yet been fully elucidated. Only a few studies have revealed that albuminuria is associated with several obesity indicators, including waist circumference, body mass index (BMI), and body fat in obese patients with or without diabetes. In addition, some metabolic parameters, such as random plasma glucose, blood pressure, and triglyceride levels, were also associated with albuminuria in overweight or obese patients with or without diabetes [10,11].

Glycated hemoglobin (HbA1c) level, which is a useful indicator of glycemic control for the previous 3 months, is an independent risk factor of CVD in patients with or without diabetes [12–14] . Recently, high HbA1c level has been shown to increase the risks of cardiovascular adverse outcomes and all-cause mortality in overweight and obese patients with diabetes [15]. Accumulating evidence has revealed that HbA1c level is positively associated with albuminuria and is regarded as a risk factor of albuminuria in normal-weight diabetic patients. However, few studies have examined the relationship between HbA1c level and albuminuria in young nondiabetic people with obesity.

Therefore, the purpose of our cross-sectional study was to evaluate the association between HbA1c level and albuminuria in young nondiabetic people with obesity, after controlling for some potential confounders.

Material and Methods

Study subjects

In accordance with the recommendations of the Working Group on Obesity in China, young nondiabetic people with obesity were enrolled consecutively at the Shanghai Clinical Center for Endocrine and Metabolic Diseases. Young people with obesity were defined as those having a BMI ≥28 kg/m^2 and an age <30 years. According to the Diagnosis and Classification of Diabetes Mellitus in the guidelines established by the American Diabetes Association in 2010 [16], a fasting plasma glucose (FPG) level ≥7.0 mmol/L and a 2-h plasma glucose (2-h PG) level ≥11.1 mmol/L during a 75-g oral glucose tolerance test, or a HbA1c level ≥6.5%, was defined as diabetes. The exclusion criteria were: 1) presence of acute or chronic heart disease, mental disorder, infection, or malignancy; 2) use of any antihypertensive or antidiabetic medication before enrollment; 3) missing HbA1c, urinary albumin, or urinary creatinine data; 4) eGFR <15 mL/(min·1.73 m^2). Finally, 537 young nondiabetic people with obesity were included for further analysis. Informed consent was obtained from each participant. All the protocols were approved by the Rui-jin Hospital Ethics Committee, Shanghai Jiao-Tong University School of Medicine.

Clinical and biochemical measurements

Anthropometric indices, including height, body weight, waist circumference (WC), hip circumference, and neck circumference, were measured. BMI was calculated as weight (kg) divided by height squared (m^2). Using a mercury sphygmomanometer, blood pressure was measured on the right arm with the patients in the seated position after at least a 15-min rest. The patients fasted from 8: 00 p.m. the day before the glucose tolerance test. At 8: 00 a.m. on the test day, a 75-g oral glucose tolerance test was performed, and venous blood samples were collected for measurement of FPG and 2-h PG levels using the glucose oxidase method on an autoanalyzer (Modular P800; Roche, Basel, Switzerland). Triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, and gamma-glutamyl transpeptidase (GGT) levels were measured using an autoanalyzer (Modular E170; Roche, Basel, Switzerland). HbA1c level was measured using high-performance liquid chromatography (BIO-RADD-10, USA). A first-voided, early-morning urine sample was collected to measure urinary albumin and creatinine concentrations. Urinary albumin concentration was determined using an immunoturbidimetric method (Beijing Atom High-Tech, Beijing, China), and urinary creatinine concentration was measured using Jaffe's kinetic method on an autoanalyzer (Hitachi 7600-020, Tokyo, Japan). These laboratory parameters were assessed in the Clinical Laboratory for Endocrinology, Shanghai Institution of Endocrine and Metabolic Diseases, which was certified by the College of American Pathologists.

Definition and calculation

Urinary ACR (mg/g) was calculated by dividing the urinary albumin concentration by the urinary creatinine concentration. Albuminuria was defined as a urinary ACR ≥30 mg/g (microalbuminuria: 30–299 mg/g, macroalbuminuria: ≥300 mg/g). eGFR was calculated using the abbreviated modification of diet in renal disease formula as follows: eGFR=186×(serum creatinine

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level×0.011)$^{-1.154}$ ×(age)$^{-0.203}$ ×(0.742 if female) ×1.233 [17]. The homeostasis model assessment (HOMA) was used to assess insulin resistance (HOMA-IR) and β-cell function (HOMA-β). HOMA-IR was calculated as (fasting insulin [μIU/mL] × FPG [mmol/L])/22.5, and HOMA-β was calculated as (20× fasting insulin [μIU/mL])/(FPG [mmol/L]–3.5) [18].

Statistical analysis

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA). For skewed variables, continuous variables are expressed as mean ±SD and as geometrical means (95% confidence interval [CI]). Categorical variables are presented as numbers or proportions. Owing to the non-normal distribution, TG level, eGFR, urinary ACR, and HOMA-IR were logarithmically transformed before the analyses. The patients were divided into 3 groups according to the tertiles of HbA1c levels, as follows: tertile 1, ≤5.3%; tertile 2, 5.4–5.6%; and tertile 3, ≥5.7%. Differences among the 3 groups were analyzed using one-way analysis of variance for continuous variables and Pearson's χ^2 for categorical variables. Multivariate linear regression and the Cochran-Mantel-Haenszel (CMH) method for continuous and categorical variables, respectively, were used to test the *P* values for trend. The multivariate linear regression model was used to evaluate the association of metabolic characteristics with urinary ACR and to identify the independent determinants of urinary ACR. The risk of elevated urinary ACR in relation to each tertile increment or per 1-SD increment in HbA1c level in the 3 different models was further analyzed using multivariate logistic regression analysis, with or without adjustment for some potential confounding factors. In Model 1, no covariate was adjusted. In Model 2, age, sex, BMI, TG level, TC level, LDL-c level, HDL-c level, systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG level, and 2-h PG level were adjusted. Model 3 was further adjusted for age, sex, BMI, TG level, TC level, LDL-c level, HDL-c level, SBP, DBP, FPG level, 2-h PG level, and eGFR. Odds ratios (ORs) and corresponding 95% CIs were calculated for each tertile or per 1-SD increment of HbA1c level. A *P* value of <0.05 was considered statistically significant.

Results

Clinical characteristics of the study subjects

The study subjects were divided into 3 groups according to tertiles of HbA1c level. The clinical and biochemical characteristics of the 3 groups are summarized in Table 1. Metabolic factors including age, BMI, WC, TG level, TC level, LDL-c level, FPG level, 2-h PG level, and HOMA-IR increased significantly with increase in HbA1c level. Compared with the subjects in the lowest tertile of HbA1c level, those in the second and third tertiles had significantly higher urinary ACRs as follows: 6.13 (4.55–11.19), 6.77 (4.76–11.18), and 8.70 (5.72–16.18) (*P* for trend=0.0064; Table 1). However, no significant differences in HDL-c level, SBP, DBP, eGFR, or HOMA-β were found among the 3 groups.

Prevalence of albuminuria at different HbA1c levels

From the lowest to the highest tertiles of HbA1c level, the prevalence of albuminuria was 6.04, 10.73, and 18.48%, respectively (*P* for trend=0.0003; Figure 1). A significantly increased prevalence of albuminuria was observed in the highest tertile of HbA1c level when compared with the lowest tertile (*P*=0.0006, Figure 1).

Association between HbA1c level and albuminuria

Multivariate linear regression analysis was used to evaluate the possible associations between albuminuria and metabolic parameters, including HbA1c level. We found that age, TG level, LDL-c level, DBP, and HbA1c level were independent determinants of urinary ACR (*P*<0.05; Table 2).

Furthermore, with a HbA1c level ≤5.3% as reference, a higher HbA1c level was significantly associated with albuminuria in the multivariate logistic regression analysis. The multivariate-adjusted ORs for albuminuria for each tertile increment in HbA1c level are presented in Table 3. A similar significant association was found between HbA1c level and albuminuria in the unadjusted, adjusted, and fully adjusted models (*P* for trend=0.0006, 0.021, and 0.017, respectively; Table 3). No significant associations were observed in the second tertile of HbA1c level when compared with the first tertile group in the unadjusted, adjusted, and fully adjusted models. However, by using the subjects with the lowest HbA1c levels as the reference group, those with the highest HbA1c levels were shown to have a significantly higher risk of albuminuria (OR [95% CI], 3.53[1.65–7.53]) in unadjusted Model 1. With adjustment for age, sex, BMI, TG level, HDL-c level, SBP, DBP, FPG level, and 2-h PG level, the OR (95% CI) for albuminuria was 3.52 (1.21–10.26) for the third tertile of HbA1c level. With further adjustment for eGFR in the fully adjusted Model 3, a significant association was still observed (OR [95% CI], 3.72[1.25–11.00]), and this association was not attenuated. More specifically, each 1-SD increase in HbA1c level showed a significant OR for elevated urinary ACR (1.76 (1.39–2.27], 1.69 [1.23–2.39], and 1.73 [1.25–2.46] in the unadjusted, adjusted, and fully adjusted models, respectively].

Discussion

In the present cross-sectional study, we found that HbA1c level was independently associated with albuminuria in young

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Table 1. Characteristics of study subjects by HbA1c level.

	HbA1c level			
	Tertile 1 (≤5.3%) (n=149)	Tertile 2 (5.4–5.6%) (n=177)	Tertile 3 (≥5.7%) (n=211)	*P* for trend
Age (years)	21.5±5.7	21.9±6.9	23.7±7.5	0.0019
Males (%)	65 (43.62)	78 (44.07)	79 (37.44)	0.2093
BMI (kg/m^2)	34.8±5.0	35.7±5.7	37.5±5.7	<0.0001
WC (cm)	107.3±11.0	111.2±12.3	113.0±15.0	<0.0001
TG (mmol/L)	1.43 (1.02–1.95)	1.41 (1.02–1.87)	1.65 (1.24–2.20)	0.0013
TC (mmol/L)	4.35±0.89	4.42±0.86	4.81±3.18	0.034
LDL-c (mmol/L)	2.69±0.76	2.83±0.65	2.91±0.77	0.007
HDL-c (mmol/L)	1.07±0.25	1.06±0.22	1.07±0.26	0.959
SBP (mmHg)	126.6±16.1	127.6±15.1	128.6±17.1	0.2753
DBP (mmHg)	81±9.8	81.8±10.9	82.7±11.9	0.176
FPG (mmol/L)	4.9 (4.63–5.20)	5.0 (4.70–5.34)	5.3 (4.89–5.62)	<0.0001
2-hPG (mmol/L)	6.4 (5.5–7.6)	6.7 (5.8–7.8)	7.7 (6.5–9.2)	<0.0001
HbA1C (%)	5.10±0.21	5.50±0.09	6.04±0.44	<0.0001
Urinary ACR	6.13 (4.55–11.19)	6.77 (4.76–11.18)	8.70 (5.72–16.18)	0.0064
eGFR (ml/min per 1.73 m^2)	139.9 (122.9–160.8)	145.3 (125.9–168.7)	148.2 (127.7–175.3)	0.505
HOMA-IR	4.11 (2.78–5.93)	4.63 (3.32–6.03)	5.76 (4.19–8.34)	<0.0001
HOMA-β	2.80 (1.97–3.84)	2.84 (1.98–3.88)	2.85 (2.00–4.50)	0.141

Data are means ±SD or geometric means (interquartile range) for continuous variables, or percentages for categorical variables. *P* for trend was calculated by linear regression analysis across groups. BMI – body mass index; WC – waist circumference; TG – triglyceride; TC – total cholesterol; LDL-c – low-density lipoprotein cholesterol; HDL-c – high-density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucose; 2-h PG – 2-h postload glucose; eGFR – estimated glomerular filtration rate; Urinary ACR – albumin-to-creatinine ratio; HbA1c – glycated hemoglobin; HOMA-IR – homeostasis model assessment of insulin resistance; HOMA-β – homeostasis model assessment of β cell function.

nondiabetic people with obesity. Our results suggest that HbA1c level is an important risk factor of albuminuria, independent of other anthropometric and metabolic variables such as BMI, blood pressure, FPG level, and TG level, in young nondiabetic people with obesity.

The association between HbA1c level and albuminuria has been previously explored in many studies in subjects with or without diabetes [6,19–22]. In patients with type 1 diabetes, the risk of microalbuminuria was strongly associated with HbA1c level [6]. The UK Prospective Diabetes Study revealed that HbA1c level was an independent risk factor of albuminuria in type 2 diabetes in >15 years of follow-up [22]. Guo et al. also reported that HbA1c level was independently associated with albuminuria in Chinese individuals with type 2 diabetes [23]. Moreover, HbA1c level was reported to be associated with low-grade albuminuria, which is an early marker of CVD in middle-aged and elderly Chinese adults, irrespective of diabetes status [24]. However, these studies mainly focused on diabetic patients and the general population. Few studies have examined the relationship between HbA1c level and albuminuria in nondiabetic people with obesity. In addition, several studies identified some risk factors of albuminuria in people with obesity. Pehlivan et al. showed that blood pressure, random plasma glucose, and other risk factors were determinants of microalbuminuria in people with obesity in primary care units [25]. Lurbe et al. reported that in young people with obesity, albuminuria mainly depends on metabolic factors, including WC and TG level [11]. Intrahepatic triglyceride content was reported to be independently associated with albuminuria in adults with obesity [26]. These studies investigated some determinants of albuminuria in people with obesity, regardless of diabetes

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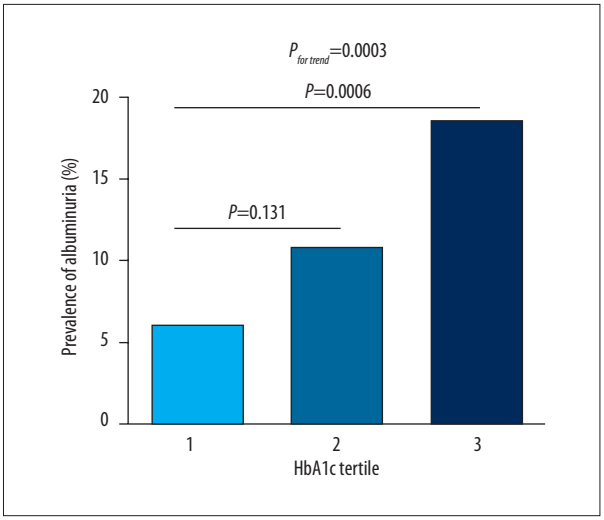

Figure 1. Prevalence of albuminuria at different tertiles of HbA1c level: tertile 1 (T1, n=9), ≤5.3%; tertile 2 (T2, n=19), 5.4–5.6%; tertile 3 (T3, n=39), ≥5.7%.

status. However, the association between HbA1c level and albuminuria in nondiabetic people with obesity, irrespective of some metabolic factors, is not fully understood. Therefore, in this cross-sectional study, we investigated young nondiabetic people with obesity to identify an independent relationship between HbA1c level and albuminuria. These results indicated that HbA1c was positively associated with albuminuria in young nondiabetic people with obesity. However, our cross-sectional study does not establish a cause-effect relationship between HbA1c level and albuminuria in young nondiabetic people with obesity. Whether HbA1c plays a causative role in incident albuminuria young nondiabetic people with obesity remains unknown. Further longitudinal studies aimed at validating the association of HbA1c level with incident albuminuria or incident CKD among young nondiabetic people with obesity are warranted.

Table 2. Multivariate linear regression analysis of risk factors associated with urinary ACR.

	β ±SE	*P* value
Age (years)	0.018±0.008	**0.021**
Sex	0.212±0.109	0.051
BMI (kg/m^2)	–0.007±0.011	0.537
TG (mmol/L)	0.344±0.118	**<0.004**
TC (mmol/L)	0.045±0.024	0.059
LDL-c (mmol/L)	0.156±0.073	**0.033**
HDL-c (mmol/L)	–0.080±0.207	0.699
SBP (mmHg)	0.003±0.004	0.480
DBP (mmHg)	0.014±0.006	**0.025**
HbA1c (%)	0.285±0.117	**0.015**
FPG (mmol/L)	0.092±0.114	0.418
2hPG (mmol/L)	0.019±0.034	0.579
eGFR (ml/min per 1.73 m^2)	0.108±0.163	0.509

BMI – body mass index; TG – triglyceride; TC – total cholesterol; LDL-c – low-density lipoprotein cholesterol; HDL-c – high-density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; HbA1c – glycated hemoglobin; FPG – fasting plasma glucose; 2-h PG – 2-h postload glucose; eGFR – estimated glomerular filtration rate. TG, ACR, eGFR were log-transformed.

However, the pathophysiological mechanisms linking HbA1c level and albuminuria remain unknown. Previous studies speculated that the association between HbA1c level and albuminuria in nondiabetic individuals may be the same as that in diabetic patients [19]. Higher HbA1c levels, which indicate chronic hyperglycemia over the prior 3 months, may contribute

Table 3. Multivariate logistic analysis for the risk of albuminuria by HbA1c level or by each 1-SD increment in HbA1c.

	OR (95%CI)		
	Model 1	**Model 2**	**Model 3**
Tertile 1	1.00	1.00	1.00
Tertile 2	1.87 (0.82–4.27)	2.35 (0.80–6.89)	2.37 (0.80–6.97)
Tertile 3	3.53 (1.65–7.53)	3.52 (1.21–10.26)	3.72 (1.25–11.00)
P for the trend	0.0006	0.021	0.017
1-SD increment of HbA1c	1.76 (1.39–2.27)	1.69 (1.23–2.39)	1.73 (1.25–2.46)

Values are odds ratio (95% confidence interval). Model 1 – Unadjusted. Model 2 – Adjusted for age, sex, BMI, TG, TC, LDL-c, HDL-c, SBP, DBP, FPG, 2-h PG. Model 3 – further adjusted for eGFR, based on Model 2. ACR – albumin-to-creatinine ratio; HbA1c – glycated hemoglobin; BMI – body mass index; TG – triglyceride; HDL-c – high-density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucose; 2-h PG – 2-h postload glucose; eGFR – estimated glomerular filtration rate.

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to glomerular hyperperfusion and hyperfiltration, consequently causing progressive glomerular damage until macroalbuminuria appears [27]. In addition, chronic hyperglycemia may induce greater oxidative stress and endothelial dysfunction in the kidney, which leads to increased leakage of albumin [28].

The present study has several limitations. First, the lack of cross-sectional and observational studies limited our ability to detect causality between HbA1c level and albuminuria. Whether HbA1c concentration and albuminuria are causally associated cannot be concluded from this cross-sectional study alone. Second, the subjects in the study were enrolled at only 1 clinic. Therefore, the ability to generalize our findings may be limited. Caution is also required in interpreting our results due to possible participants bias. Third, due to the missing information for variables such as the duration of obesity, smoking status, alcohol intake, physical activity, and inflammatory factors, these potential risk factors were not included in the analysis. Last, a single morning spot urine sample for measurement of ACR may not reflect the true level of urinary albumin excretion.

In conclusion, our study showed that HbA1c level was independently associated with albuminuria in young nondiabetic people with obesity. This study may support measurement of HbA1c level in young obese patients to detect albuminuria or CKD, even in the absence of diabetes.

Conclusions

HbA1c level was independently associated with albuminuria and might be an indicator of albuminuria in young obese patients without diabetes.

Declaration of interest

The authors declare no conflicts of interest.

Acknowledgments

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