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Research Article

The Progression of Carotid Intima-Media Thickness in Subjects of Type 2 Diabetes with an Increased Urine Albumin Excretion - A Two Years Follow-up Study

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Abstract

Background

To observe the two-year progression of mean Carotid intima-media thickness CIMT (mCIMT) in type 2 diabetes with an increased urine albumin excretion (UAE).

Methods

Ninety type 2 diabetic subjects (62 ± 13 years, 58.9% 154 males) with an increase in UAE (urine microalbumin to creatinine ratio [UACR] ≥ 30 mg/g) received follow-up for two years. We recorded clinical and biochemical data as well as mCIMT.

Results

The UACR was not significantly changed (551.6 ± 882.6 mg/g *vs* 580.6 ± 928.8 mg/g, p = 0.583). The mCIMT progressed from 0.70 ± 0.15 mm to 0.74 ± 0.16 mm (p < 0.0001). Compared with those UACR worsened (n = 39), the improved group (n = 51) had lower levels of triglyceride (1.37 ± 0.60 *vs* 1.90 ± 0.97 mmol/L, p = 0.002), HbA1c (7.8 ± 1.3 *vs* 8.9 ± 1.8%, p = 0.001), and UACR (279.4 ± 526.4 *vs* 974.5 ± 1172.7 mg/g, p = 0.001). Subjects with worsened UACR had more progression of mCIMT than those improved (0.053 ± 0.080 *vs* 0.021 ± 0.0592 mm, P = 0.036).

Conclusion

The two years follow-up showed that in subjects of type 2 diabetes with increased UAE, the improvement in UACR is associated with less progression of CIMT. UACR could be considered as an intermediate objective during the follow-up in these patients.

Keywords: CIMT, UACR, UAE.

Introduction

Type 2 diabetes mellitus (DM) is characterized by early development of atherosclerosis resulting in high mortality and morbidity [1]. Moreover, in patients with type 2 DM, the presence of nephropathy is associated with poor renal and cardiovascular outcome. Albuminuria is a characteristic aspect of diabetic nephropathy, while it is also a marker for increased risk of cardiovascular disease (CVD) associated with endothelial dysfunction [2-4]. Therefore patients with albuminuria are at very high risk of vascular injury and should share the same objectives of a vascular risk factor control as patients with overt CVD.

Carotid intima-media thickness (CIMT) is a surrogate marker of subclinical atherosclerosis; increased CIMT had been identified as important markers for prediction of cardiovascular morbidity and mortality [5-7]. The incidence of cardiovascular events is correlated with measurements of CIMT [5]. Furthermore, the association between CVD and CIMT remains significant after adjustment for traditional risk factors [6]. CIMT is reported to be higher in diabetic patients than in healthy subjects [8,9]. CIMT is also significantly higher among newly detected type 2 diabetic patients compared to normal glucose tolerant matched controls [10]. Data on CIMT as a predictor of atherosclerotic disease are scarce in diabetic patients, particularly in patients with an increase in urine albumin excretion (UAE). In addition, whether type 2 diabetic patients with an increased UAE had an increment of CIMT still could not get a conclusion [11-13]. However, most of the studies are only cross-sectional rather than follow-up studies. Our previous cross-sectional study with 239 diabetic patients showed that those with an increase in UAE (urine microalbumin to creatinine ratio [UACR] ≥ 30 mg/g) was not associated with an increase of mean CIMT (mCIMT) [14]. Because of the inconsistent results and the lack of follow-up study, we followed up of these patients for two years. The aim is to observe the progression of mCIMT in type 2 diabetic subjects with an increased UAE.

Methods

Subjects:

The subjects were selected from our previous cross-sectional study of 239 adult (≧18 yr) male and female type 2 diabetic patients. Which was performed in Kaohsiung Veterans General Hospital in 2010. There were 119 subjects with an increase in UAE (UACR ≥ 30 mg/g) [14]. Among these subjects, there were ninety received follow-up for two years. This study was approved by the Medical Ethics and Human Clinical Trial Committee of Kaohsiung Veterans General Hospital.

The clinical and biochemical evaluations included body mass index (BMI), blood pressure (BP), serum concentrations of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglyceride, glucose, blood urea, creatinine, and hemoglobin (Hb) A1c. BMI was calculated as weight in kilograms divided by the square of the height in meters. Estimated glomerular filtration rate (eGFR) was calculated by using Modification of Diet in Renal Disease (MDRD) formula. UACR was analyzed of a spot urine sample. Measurement of UACR was performed only if patients had no concurrent illnesses or conditions capable of interfering with UACR (e.g. urinary infections, stones, menstrual cycle in women). Informed consents were obtained from all after thorough explanation of the procedures. Samples of venous blood were obtained from an antecubital vein after an overnight fast starting at midnight, and sent for assay immediately. The CIMT was performed by the same operator and with the same machine as 2 years ago.

Biochemistry and Hormone Analyses

HbA1c was measured by Cation-exchange HPLC method (Automated Glycohemoglobin Analyzer Tosoh HLC-723G7; Tosoh Co., Tokyo, Japan). The between-lab CV < 5%. Serum concentrations of TC, HDL-C, triglyceride, blood nitrogen, and creatinine were measured by enzymatic colorimetry method (Hitachi 7600-110; Hitachi Ltd., Tokyo, Japan). LDL-C was also measured by same method not by calculation. Plasma glucose concentrations were measured by a hexokinase method using an automatic biochemistry analyzer (Hitachi 7170; Hitachi Ltd., Tokyo, Japan). Urine samples for measuring creatinine and albumin were taken from a spot urine collection at the initial visit. Urine microalbumin concentrations were analyzed by solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000) with a detection limit of 1.0 μg/mL and a measuring range of 2.5–60 μg/mL. Urine concentrations of creatinine were measured by Johnson & Johnson Vitros 950 analyzer (Johnson & Johnson Clinical Diagnostics Inc., Rochester, NY, USA).

Common Carotid Ultrasound

In all subjects, a high-resolution B-mode ultrasound of the common carotid arteries was performed using the HD11 ultrasound system with a frequency 12-3 MHz (Philips Medical systems, Bothell, WA, USA). The CIMT was defined by two parallel echogenic lines (double line pattern), which corresponded to the lumen-intima and the media-adventitia interfaces. The site of CIMT measurement was a perpendicular location relative to the transducer beam, 1 cm far from the bifurcation on the far wall of each common carotid artery (CCA) using the longitudinal axis. A minimum of 10 mm length of the CCA was required for CIMT measurement. Only sites free from discrete plaques were considered for measurement. mCIMT was calculated as the arithmetic mean of bilateral three values.

Statistical Analyses

Values are reported as mean ± SD. Comparisons are made

by student t test. The relations of mCIMT with other variables are made by using Pearson's correlation. Multivariate linear regression analyses are used to assess the relative independence of predictors for mCIMT values. A value of P < 0.05 was considered as statistically significant.

Results

The demographic and clinical characteristics of the study population are shown in Table 1. The mean age was 62 ± 13 years (58.9 % was men). Mean duration of diabetes was 12 ± 8 years. There are 58.9 % combined with hyperlipidemia and 76.7 % combined with hypertension.

Table 1. Characteristics of study population (n = 90)

Age (years)	62 ± 13
Men (n)	53 (58.9 %)
DM duration (years)	12 ± 8
Smokers (n)	17 (18.9 %)
Hyperlipidemia (n)	53 (58.9 %)
Hypertension (n)	69 (76.7 %)
Statin (n)	41 (45.6 %)
RAS blockade (n)	62 (68.9 %)
Insulin (n)	15 (16.7 %)

The comparative profiles of baseline and two years variables are shown in Table 2. The UACR was not significantly changed (551.6 ± 882.6 mg/g vs 580.6 ± 928.8 mg/g, change from baseline = 29.0 mg/g, [95% CI, -75.5 to 133.5 mg/g], p = 0.583). The mCIMT progressed from 0.70 ± 0.15 mm to 0.74 ± 0.16 mm (p < 0.0001). The mean progression of mCIMT in two years was 0.035 mm (95% CI, 0.020 to 0.050 mm).

Table 3 showed the comparisons of variables between subjects with improved UACR (n = 51) and those with worsened (n = 39). The improved group had lower levels of triglyceride (1.37 ± 0.60 vs 1.90 ± 0.97 mmol/L, difference = -0.53 mmol/L, [95% CI, -0.56 to -0.20 mmol/L], p = 0.002), HbA1c (7.8 ± 1.3 *vs* 8.9 ± 1.8 %, difference = -1.12 %, [95% CI, -1.77 to -0.46 %], p = 0.001), and UACR (279.4 ± 526.4 *vs* 974.5 ± 1172.7 mg/g, difference = -695.1 mg/g, [95% CI, -1.61.4 to -328.7 mg/g], p = 0.001).

Table 2. Comparative profiles of baseline and two years variables

Variables	baseline	2 years	change (95% CI)	p
Body mass index (kg/m^2)	26.6 ± 6.4	25.5 ± 4.4	-1.0 (-2.3 to 0.2)	0.105
Systolic BP (mmHg)	139 ± 23	139 ± 23	0.7 (-4.5 to 5.9)	0.791
Diastolic BP (mmHg)	78 ± 11	78 ± 13	-0.5 (-3.1 to 2.1)	0.701
Total cholesterol (mmol/L)	4.67 ± 0.90	4.47 ± 0.77	-0.20 (-0.39 to 0.00)	0.055
LDL-C (mmol/L)	2.52 ± 0.69	2.22 ± 0.57	-0.30 (-0.45 to -0.14)	0.000
HDL-C (mmol/L)	1.08 ± 0.28	1.17 ± 0.34	0.10 (0.05 to 0.15)	0.000
Triglyceride (mmol/L)	1.73 ± 1.008	1.60 ± 0.82	-0.13 (-0.31 to 0.04)	0.135
Blood urea (mmol/L)	7.84 ± 3.88	8.95 ± 6.81	1.11 (0.18 to 2.04)	0.020
Creatinine (μmol/L)	118.8 ± 57.4	152.2 ± 165.8	33.4 (5.6 to 61.2)	0.019
Fasting glucose (mmol/L)	9.26 ± 3.08	7.65 ± 2.327	-1.6 (-2.3 to -0.9)	0.000
HbA1c (%)	8.6 ± 1.8	8.3 ± 1.6	-0.32 (-0.68 to 0.04)	0.077
UACR (mg/g)	551.6 ± 882.6	580.6 ± 928.8	29.0 (-75.5 to 133.5)	0.583
Mean CIMT (mm)	0.70 ± 0.15	0.74 ± 0.16	0.03 (0.02 to 0.05)	0.000

Table 3. Clinical and biochemical characteristics between groups of improved and woresned ACR after two years follow-up

Variables	improved (n = 51)	worsened (n = 39)	Difference (95% CI)	p
Body mass index (kg/m^2)	25.0 ± 5.1	26.2 ± 3.3	-1.2 (-3.1 to 0.6)	0.173
Systolic BP (mmHg)	140 ± 25	138 ± 19	2.2 (-7.4 to 11.8)	0.633
Diastolic BP (mmHg)	77 ± 14	78 ± 12	-0.2 (-5.8 to 5.4)	0.935
Total cholesterol (mmol/L)	4.49 ± 0.75	4.45 ± 0.80	0.04 (-0.29 to 0.36)	0.813
LDL-C (mmol/L)	2.25 ± 0.58	2.19 ± 0.57	0.05 (-0.19 to 0.30)	0.675
HDL-C (mmol/L)	1.23 ± 0.36	1.11 ± 0.31	0.12 (-0.02 to 0.26)	0.098
Triglyceride (mmol/L)	1.37 ± 0.60	1.90 ± 0.97	-0.53 (-0.56 to -0.20)	0.002
Blood urea (mmol/L)	9.52 ± 8.15	8.20 ± 4.48	1.32(-1.56 to 4.20)	0.366
Creatinine (μmol/L)	165.9 ± 186.7	134.3 ± 133.8	31.6 (-35.6 to 101.7)	0.373
Fasting glucose (mmol/L)	7.33 ± 2.01	8.07 ± 2.65	-0.75 (-1.72 to 0.23)	0.147
HbA1c (%)	7.8 ± 1.3	8.9 ± 1.8	-1.12 (-1.77 to -0.46)	0.001
UACR (mg/g)	279.4 ± 526.4	974.5 ± 1172.7	-695.1 (-1.61.4 to -328.7)	0.001
Mean CIMT (mm)	0.74 ± 0.16	0.73 ± 0.16	0.01 (-0.06 to 0.08)	0.794

The figure 1 showed the association of the change of UACR and the progression of mCIMT. We divided the subjects in two groups: one with improvement of UACR (UACR decreased in two years follow-up), and those with worsened UACR (UACR increased). The worsened group had more progression of mCIMT than those with improvement (0.053 ± 0.080 *vs* 0.021 ± 0.059 mm, difference = 0.031 mm, [95% CI,

0.002 to 0.060 mm], p = 0.036).

Figure 1. The progression of CIMT between subjects with improved ACR and those with worsened ACR. The subjects with worsened ACR had more progression of CIMT than those with improved ACR (p = 0.036).

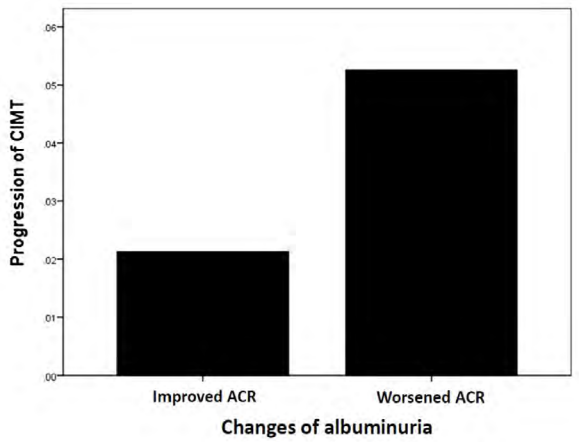

Table 4. Pearson's correlation and multivariate linear regression analysis for determining factors of progression of CIMT

Parameters	Pearson's correlation		multiple linear regression	
	γ	*p*	*β*	*p*
Age (years)	0.325	0.008	0.385	0.019
DM duration (years)	-0.070	0.575	-0.003	0.985
Body mass index (kg/m^2)	-0.165	0.185	-0.091	0.478
Systolic BP (mmHg)	-0.148	0.237	-0.178	0.353
Diastolic BP (mmHg)	-0.145	0.245	0.187	0.381
LDL-C (mg/dL)	0.243	0.050	0.321	0.036
HDL-C (mgl/dL)	0.002	0.988	-0.158	0.318
Triglyceride (mg/dL)	-0.162	0.194	-0.031	0.841
Fasting glucose (mg/dL)	-0.073	0.767	-0.321	0.070
HbA1c (%)	-0.053	0.670	0.324	0.073
eGFR	0.312	0.011	0.007	0.971
ACR	-0.259	0.036	-0.034	0.852

There was no statistic difference in term of progression of mCIMT between subjects who were taking RAS blockade and those not (0.033 ± 0.078 *vs* 0.039 ± 0.050 mm, difference = -0.006 mm, [95% CI, -0.026 to 0.039 mm], p = 0.709). Same result was also observed in those with or without statin (0.048 ± 0.075 *vs* 0.024 ± 0.056 mm, difference = 0.024 mm, [95% CI, -0.006 to 0.053 mm], p = 0.111).

Table 4 showed the Pearson's correlation and multivariate linear regression analysis for determining factors of the progression of mCIMT. In Pearson's correlation, the progression of mCIMT positively correlated with age and eGFR but negatively correlated with UACR levels. In multivariate regression analysis, the progression of mCIMT correlated with age and LDL-C. Neither UACR nor eGFR correlated with the progression of mCIMT.

Discussion

After the studies demonstrating that an increase in UAE is dependent on vascular permeability to albumin and the presence of albuminuria reflects widespread vascular damage [15], the changes in UAE during treatment are also regarded as a marker of cardiovascular risk modification. Both cross-sectional [16] and follow-up[17,18] studies have demonstrated that UAE is associated with a clustering of cardiovascular risk factors.

Whether changes in UAE during management in patients with diabetic nephropathy have CVD prognostic value is a matter of debate. Post hoc analysis from Action in Diabetes Mellitus and Vascular Disease (ADVANCE) [19] have reported positive results with a decrease in UAE being associated with cardiovascular risk reduction. However, a prospective study Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes Mellitus (ROADMAP) [20] reported no association between changes in UAE and CVD. These studies were varied in terms of diabetic duration and risk categories of patients, did not clarify the potential role of change in UAE during management.

Our previous cross-sectional study did not observe an increased mCIMT levels in type 2 diabetic subjects with an increase in UAE [14]. However, in the present 2-year follow-up study we demonstrated the decrease over time of UAE was associated with less progression of mCIMT when compared with those without. Subclinical organ damage, such as left ventricular hypertrophy (LVH), CIMT, pulse wave velocity, or UACR predicted CVD independently of common used risk scores. It seems reasonable to search for asymptomatic organ damage in T2DM patients, both in initial stratification of cardiovascular risk and during follow-up. An assessment of subclinical organ damage is recommended in low to moderate risk patients without evident cardiovascular events. UACR is a test can be reliably quantified and at low cost. Reduction in UACR has been linked with a reduction in other markers of organ damage, such as LVH [21]. The association of UACR change and mCIMT showed in the present study also add information supporting the use during follow-up. However, the regression analysis showed no correlation of mCIMT and UACR. This means that albuminuria might be only a marker of organ damage rather than a direct factor. Nonetheless, the potential role of UACR could not be only a marker of risk but also be a treatment goal to be reduced.

It has been shown that changes in CIMT over time were correlated with future cardiovascular event rates [22,23]. T2DM, a high risk population of cardiovascular events, also increase speed of CIMT progression [24]. However, mCIMT progression rates vary widely in patients with diabetes, from

0.083mm over 6 months to 0.007 mm over 1 year [24,25]. In a review of eleven CIMT intervention trials in diabetes [26], the mCIMT progression rate in the control groups was 0.034 mm per year but varied considerably between trials based on level of control of cardiovascular risk factors. The progression rate in the present study was 0.035 mm in 2 years (0.053 mm in group with worsened UACR, 0.021 mm in those with improved). The low progression rate in the present study might relate to the improvement of blood glucose and LDL-C, HDL-C levels.

The limitation in our study is that the present study is not an intervention study. We just observe the association of change in UACR and the progression of mCIMT, the all management was as usual. The effects of medications on CIMT might be interfered by many confounding factors.

In summary, the two years follow-up showed that in subjects of type 2 diabetes with an increased UAE, the improvement in UACR is associated with less progression of CIMT. UACR could be considered as an intermediate objective during the follow-up in these patients.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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