Prevalence and Risk Factors of Taiwanese Microalbuminuric Type 2 Diabetic Mellitus with and without Diabetic Retinopathy

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Abstract

BACKGROUND: Although microalbuminuria in diabetic patients is a well-known manifestation of diabetic nephropathy, it does not necessarily indicate the presence of other microvascular complications such as diabetic retinopathy (DR). This study aims at determining the prevalence and clinical characteristics of diabetic retinopathy in microalbuminuric patients with type 2 diabetes.

METHODS: A total of 417 microalbuminuric type 2 diabetic patients were enrolled in this cross-sectional study. Demographic characteristics of patients, serum biochemistry [i.e., HbA1c, serum total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, uric acid, albumin, creatinine, high sensitive C-reactive protein (hsCRP)] and hematological parameters (i.e., complete blood count, and differential white count) were recorded and analyzed. The presence of retinopathy including background diabetic retinopathy, non-proliferative retinopathy, or proliferative retinopathy, was determined by an experienced ophthalmologist by dilated fundus examination (indirect ophthalmoscopy). Logistic regression analysis was performed to identify the independent risk factors of DR.

RESULTS: The prevalence of DR was 46.2%. Independent risk factors included use of insulin (OR: 3.437, P = 0.001), presence of hypertension (OR: 2.671, P = 0.015), DM duration (OR: 1.063, P = 0.013), age at DM diagnosis (OR: 0.970, P = 0.029), triglyceride (OR: 0.995, P = 0.017), hsCRP (OR: 0.773, P = 0.006), and hemoglobin (OR: 0.713, P < 0.001).

CONCLUSIONS: Our results suggest that nephropathy and retinopathy may not be concurrent. Moreover, the etiologies of microalbuminuria in type 2 diabetes may be variable. Moreover, frequent ophthalmologic examinations may be indicated for microalbuminuric type 2 diabetic patients with risk factors of diabetic retinopathy. (Acta Nephrologica 2011; 25: 43-49)

KEY WORDS: type 2 diabetes, microalbuminuria, diabetic retinopathy, risk factor

Introduction

Microalbuminuria in type 2 diabetes may be an early clinical manifestation of diabetic nephropathy, even though it can also result from other clinical situations such as hypertension or waist circumference (1). In type 1 diabetes, microalbuminuria is closely associated with microangiopathy, such as diabetic retinopathy.
years, and > 15 years) was also analyzed.

Although the prevalence and risk factors for DR in type 2 diabetes have been extensively investigated (4-7), there are few data addressing the issue of clinical characteristics for distinguishing microalbuminuric type 2 diabetic patients with DR from those without. This cross-sectional study aims at determining the prevalence and characteristics of DR in patients with type 2 diabetes who have microalbuminuria for early intervention in these patients.

Methods

Study Setting, Inclusion and Exclusion Criteria

A cross-sectional study was conducted among 1,715 diabetic patients attending a single outpatient diabetic clinic managed by one diabetologist (Rue-Tsuan Liu) for more than one year at Chang Gung Memorial Hospital-Kaohsiung Medical Center between April 2008 and November 2008. Of all patients, 46 were diagnosed as type 1 diabetes and excluded from this study. Thirteen patients with prolonged indwelling Foley catheter, repeated urinary tract infection, or receiving chemotherapy for malignant diseases were also excluded.

Study Parameters and Definitions

Urinary albumin concentration was measured by random daytime urine samples. Albumin excretion rate (AER) was defined entirely by calculation of albumin-to-creatinine ratio (ACR) in urine specimen. The definitions of normoalbuminuria (NA), microalbuminuria (MA), and macroalbuminuria (MAA) were an ACR < 0.03 mg/mg once, 0.03-0.3 mg/mg, and > 0.3 mg/mg in two urine samples collected, respectively. Retinopathy was determined through dilated fundus examination by an experienced ophthalmologist blinded to the study. Dilated fundus examination was using binocular indirect ophthalmoscopy and +20 D lens. Diabetic retinopathy (DR) was graded as background diabetic retinopathy (BDR), non-proliferative retinopathy (NPDR), or proliferative retinopathy (PDR) by the diabetic retinopathy disease severity scale (8). In our study, BDR was defined as mild or moderate; while nonproliferative DR and NPDR was defined as severe nonproliferative DR. Finally, a total of 417 microalbuminuric patients with (n = 193) or without (n = 224) retinopathy were recruited in the study. Prevalence of DR in different DM duration groups (< 5 years, 5-10 years, 11-15 years, and > 15 years) was also analyzed.

Each patient participated in a detailed interview regarding his or her personal disease, smoking and drinking history by two trained interviewers. The data compiled for this study included age, age at DM diagnosis, gender, duration of diabetes, body height and weight (for the calculation of BMI), drinking and smoking (defined as current smoker and ex-smoker who had quit smoking irrespective of the duration). Neuropathy was defined as abnormal vibration perception of the tuning fork (9).

Coronary heart disease (CHD) was defined as acute myocardial infarction, coronary artery disease confirmed by coronary angiography, and presentations of typical angina pectoris. Blood pressure was obtained from the upper limbs with the patients in supine position, using an automated device which simultaneously measured bilateral brachial and ankle blood pressure using the modified oscillometric pressure sensor method (BP-203RPE; Colin, Komaki, Japan). Hypertension was defined as a systolic blood pressure of > 140 mmHg and/or a diastolic blood pressure > 90 mmHg, or if the patients were receiving antihypertensive treatment. Use of insulin was defined as any insulin treatment alone or in combination with oral antidiabetic agents.

Metabolic syndrome was defined as the fulfillment of at least three of the following criteria: [1] waist circumference > 90 cm for men and > 80 cm for women, [2] serum triglyceride ≥ 150 mg/dL or drug treatment for elevated triglycerides, [3] serum high-density lipoprotein (HDL) level < 40 mg/dL in men and < 50 mg/dL in women or drug treatment for low HDL-C, [4] elevated blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or previous diagnosis of hypertension) and [5] increased fasting plasma glucose (≥ 100 mg/dL) or previous diagnosis of DM.

Venous blood samples were collected for measurements of total cholesterol, triglycerides, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, uric acid, albumin after 12-hour fasting, serum creatinine, HbA1c, hsCRP, complete blood count, and differential count. Two blood samples were obtained for serum hsCRP analysis. Data were discarded when a hsCRP level > 10 mg/L (10). The average hsCRP level was chosen for each patient. HsCRP was measured with the cardiophase high-sensitivity nephelometric method (Dade Behring, Marburg, Germany) via a Behring Nephelometer II Analyzer. The lowest detection limit was < 0.15 mg/L. Mean intra-assay coefficients of variance were less than 3.5% in our laboratory. Creatinine concentrations in plasma and urine were determined with a Wako Creatinine-Test kit by the Jaffe method (Wako Pure Chemicals, Osaka, Japan). Albumin concentrations were determined by immunonephelometry (Dade-Behring, Marburg, Germany).

The absolute count of a leukocyte subtype was calculated as the product of the percentage of each
subtype and the total leukocyte count. To eliminate the confounding effect of infection or bone marrow hematopoietic problems, patients with WBC > 10 × 10^{12}/L or WBC < 4 × 10^{12}/L and/or those with red blood cell of MCV > 100 fl or MCV < 80 fl as well as those with platelet < 150 × 10^{12}/L or > 400 × 10^{12}/L were also excluded. Hemoglobin level was compared among the three different DR groups (Non-DR, BDR + NPDR, and PDR). Estimated glomerular filtration rate (eGFR) was calculated by the modified Diet and Renal Disease (MDRD) equation. [\text{eGFR (mL/min/1.73 m^2)} = 186 \times \text{(Serum creatinine)}^{-1.154} \times \text{(age)}^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})] \ (11). The Human Research Ethics Committee of our hospital approved this study and informed consent was obtained from each patient.

**Statistics**

Data are shown as means ± SD or percentage and as median with range for values that are not normally distributed. The Statistical Package for Social Science program (SPSS for Windows, version 13.0; SPSS) was employed to perform the statistical analysis. The independent t-test or ANOVA was used for comparing normally distributed continuous variables between different groups. The between-group differences in data for variables that are not normally distributed were analyzed with the Mann-Whitney U test. The Chi-square test was used for examining categorical variables. All parameters with significant differences between groups with or without retinopathy were enrolled in logistic regression analysis, the results of which were shown as odds ratio (OR) and 95% confidence interval (CI). \( P \) values less than 0.05 are considered statistically significant.

**Results**

**Characteristics of Study Subjects**

A total of 417 type 2 diabetic patients were included in this cross-sectional study. The mean age of the study subjects was 64.9 ± 10.8 years (range, 25-94), and the mean duration of diabetes was 11.4 ± 6.5 years (range, 1-39). The prevalence of background diabetic nephropathy, non-proliferative retinopathy or proliferative retinopathy was 29.0%, 5.0%, and 12.2%, respectively (Table 1). The DR prevalence was 21.6, 29.8, 58.7 and 74.0% in the four DM duration groups (i.e. < 5 years, 5-10 years, 11-15 years, and > 15 years) \( P = 0.000 \) (Fig. 1).

**Univariate Analysis of Diabetic Retinopathy**

The patients’ demographic characteristics and relevant laboratory parameters between groups with or without retinopathy are shown in Table 2. Retinopathy in microalbuminuric type 2 diabetic patients was found to be positively associated with female gender, habit of drinking, use of insulin, age at DM diagnosis, DM duration, presence of hypertension, neuropathy, and stroke. Negative correlation was noted in the level of total cholesterol, triglyceride, HDL-cholesterol, total cholesterol to HDL-cholesterol ratio, albumin and hemoglobin. Hemoglobin concentration

**Table 1. Characteristics of study subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male, %)</td>
<td>54.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.9 ± 10.8</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>11.4 ± 6.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.4 ± 3.9</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>84.3</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>84.8</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>134.6 ± 17.2</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>74.9 ± 10.1</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>46.3</td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>38.5</td>
</tr>
<tr>
<td>CHD (%)</td>
<td>5.0</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>5.3</td>
</tr>
<tr>
<td>Use of insulin (%)</td>
<td>21.1</td>
</tr>
<tr>
<td>HBA1c (%)</td>
<td>7.5 ± 1.4</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>64.3 ± 24.1</td>
</tr>
</tbody>
</table>

**Diabetic retinopathy (%)**

BDR: 29.0, NPDR: 5.0, PDR: 12.2

Abbreviations: BP, blood pressure; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; BDR, background diabetic retinopathy; NPDR, nonproliferative retinopathy; PDR, proliferative diabetic retinopathy.
of the three DR groups (i.e. Non-DR, BDR + NPDR, and PDR) was 13.5 ± 1.7, 12.8 ± 1.9, and 12.3 ± 1.7 mg/dL, respectively, and there was significant difference among the three DR groups (P < 0.001, followed by LSD test to compare group means) (Fig. 2).

Multivariate Analysis of Diabetic Retinopathy

Independent risk factors included use of insulin (OR: 3.437, 95% CI: 1.629-7.653, P = 0.001), presence of hypertension (OR: 2.671, 95% CI: 1.206-5.917, P = 0.015), DM duration (OR: 1.063, 95% CI: 1.013-1.115, P = 0.013), age at DM diagnosis (OR: 0.970, 95% CI: 0.944-0.997, P = 0.029), triglyceride (OR: 0.995, 95% CI: 0.992-0.999, P = 0.017), hsCRP (OR: 0.773, 95% CI: 0.644-0.930, P = 0.006), and hemoglobin (OR: 0.713, 95% CI: 0.603-0.843, P < 0.001) (Table 3).

Discussion

In this hospital-based cross-sectional study, DR
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was noted in 46.2% of type 2 diabetic patients with microalbuminuria. The prevalence of diabetic retinopathy in the present study was similar to that found in two previous cross-sectional hospital-based studies with figures of 43.4% and 40.3%, respectively (4, 12). Thus, our results and those of other studies suggest that longer duration of DM may be required for the development of DR in comparison to the development of diabetic nephropathy in type 2 diabetic patients. Alternatively, these results confirm the heterogeneity of microalbuminuria in type 2 diabetes. In this study, use of insulin, hypertension, earlier age at DM diagnosis, longer DM duration, lower serum level of triglyceride and hsCRP and reduced hemoglobin were all independently associated with the occurrence of DR in type 2 diabetic patients with microalbuminuria.

Of the risk factors identified in our cohort, hypertension and longer DM duration have been the most consistently reported in other studies. In the United Kingdom Prospective Diabetes Study (UKPDS), longer duration of diabetes and hypertension have been shown to contribute to the development of DR in type 2 diabetes (13). In this cross-sectional study, we demonstrated that longer duration of diabetes was significantly associated with DR in type 2 diabetes with microalbuminuria (Table 3) with the odds ratio of 1.063. It must be noted, however, that the prevalence of DR was reported to be rapidly increasing when DM duration was longer than 10 years (4, 13, 14). Similar findings were observed in this study (Fig. 1), which was in agreement with a comparable series described previously in Korean type 2 diabetes with microalbuminuria (12).

Our study and those of other investigators (15, 16) found that use of insulin was independently associated with DR in type 2 diabetes. In line with our previous studies of peripheral arterial disease and diabetic nephropathy in type 2 diabetes (17, 18), we consistently demonstrated that use of insulin was an independent risk factor for diabetic chronic complications. Use of insulin for glycemic control has been recommended in type 2 diabetic patients with varying degree of loss of β cell function (19). In the clinical practice of the author (R-T Liu) and perhaps of most diabetologists in Taiwan, insulin treatment begins when type 2 diabetic patients experience oral antidiabetic drug failure. At this point, most of patients might already have developed microvascular complications. Therefore, it would not be surprising that use of insulin was an independent factor for DR.

Many studies report an independent association between either higher HbA1c or higher systolic blood pressure and DR in type 2 diabetic patients upon multivariate analysis (4, 5, 7). In this cross-sectional cohort analysis, we observed a tendency for higher HbA1c and higher systolic blood pressure among those with retinopathy than those without, albeit short of significance. Failure to replicate the results of previous studies could be due to the intensification of glycemic and blood pressure control in our patients.

The impact of age at diagnosis of type 2 diabetes on the risk of developing retinopathy is unclear. In this cross-sectional analysis, earlier age at DM diagnosis is an independent risk factor for DR. This observation is compatible with a previous finding of an

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of insulin</td>
<td>3.437</td>
<td>1.629 – 7.253</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at DM Diagnosis</td>
<td>0.970</td>
<td>0.944 – 0.997</td>
<td>0.029</td>
</tr>
<tr>
<td>DM duration</td>
<td>1.063</td>
<td>1.013 – 1.115</td>
<td>0.013</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.671</td>
<td>1.206 – 5.917</td>
<td>0.015</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.713</td>
<td>0.603 – 0.843</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.773</td>
<td>0.644 – 0.930</td>
<td>0.006</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.995</td>
<td>0.992 – 0.997</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; hsCRP, high sensitive C-reactive protein.
association between earlier age at DM diagnosis and DR in Non-Chinese population (20).

Anemia is associated with an increased risk of the vascular complications of diabetes including nephropathy (21-23) and retinopathy (24-26). Here, we show that the degree of anemia was proportional to the severity of DR in type 2 diabetic patients with microalbuminuria (Fig. 2). Our results confirm previous observation of the relationship between reduced hemoglobin level and DR (27). These findings lend support to the hypothesis that anemia may modulate the activity of pathways that lead to progressive end-organ damage in diabetes (26).

Recent developments indicate that the classical pathophysiological determinants of diabetic microangiopathy, namely hyperglycemia, and hypertension are accompanied with heightened inflammatory activity, endothelial dysfunction, and disturbed coagulation; and these processes may constitute final common pathways to the vascular complications of diabetes (28). It is noteworthy that both serum levels of triglyceride and hsCRP were negatively and independently associated with DR in this study. Elevated triglyceride levels have been shown to independently increase the likelihood of albuminuria in type 2 diabetes in several studies including ours (1, 18, 29, 30). Recent reports also demonstrated an independent association of higher hsCRP levels with albuminuria in subjects with type 2 diabetes (30, 31). The significant association of hsCRP with albuminuria supports the role of inflammation in diabetic nephropathy. However, the relationship between triglyceride or hsCRP with DR was controversial (5-7, 24, 25, 32-36). Most, but not all, studies found no significant association between higher triglyceride or higher hsCRP levels and DR in type 2 diabetic subjects. These results suggest different pathogenesis between DN and DR in type 2 diabetes.

The results presented for the current study need to be interpreted in the context of the study’s limitations. First, the cross-sectional nature of the present study limits assessment of the causal relationship between the independent risk factors we identified and occurrence of diabetic retinopathy in type 2 diabetic patients with microalbuminuria. A prospective study should be undertaken to confirm its causality. Second, since our study cohort was hospital-based and from a single diabetologist, selection bias was a potential confounding factor. Thus, the generalizability of our study findings to the general diabetic population requires further investigation. Despite these limitations, there are several strengths involved in the current study. This study involved a well characterized and sufficient sample size, a cohort design and a comprehensive risk factor analysis. Furthermore, all patients were treated by a single physician, which minimized potential bias during treatment and follow-up.

In conclusion, use of insulin, presence of hypertension, earlier age at DM diagnosis, longer DM duration, lower serum level of triglyceride and hsCRP, and reduced hemoglobin are independently associated with an increased prevalence of diabetic retinopathy in type 2 diabetes with microalbuminuria. Microalbuminuric type 2 diabetic patients with risk factors of diabetic retinopathy may need more frequent ophthalmologic examinations. However, further studies are required to confirm the reproducibility of these results and its causal relationship.

References

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