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# Association of urinary albumin excretion with central foveal thickness and intravitreal conbercept treatment frequency in patients with diabetic macular edema

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## Abstract

**● AIM: To investigate the effect of albuminuria on diabetic macular edema (DME) and the possible association between baseline urinary albumin excretion (UAE) and intravitreal conbercept (IVC) treatment frequency in DME patients.**

**● METHODS: In this hospital-based retrospective study, a total of 350 in-patients with type 2 diabetes mellitus were recruited and their clinical records were reviewed. Thereafter, 52 patients identified with severe non-proliferative diabetic retinopathy (NPDR) combined with albuminuria were divided into the microalbuminuria (UAE 30-300 mg/24h) and macroalbuminuria (UAE>300 mg/24h) groups, which were compared and analyzed by both independent sample *t*-test and Chi-square test. Correlations between the systemic variables and the central foveal thickness (CFT) were evaluated using Spearman's correlation and linear regression analyses. Of the 52 patients with center-involved DME, 43 received an initial combined injection of conbercept (0.5 mg/0.05 mL) and triamcinolone acetonide (1 mg/0.05 mL), followed by an IVC injection, as needed. The relationship between baseline UAE and number of IVC injections during the first year of treatment was analyzed using Spearman's partial correlation.**

**● RESULTS: Of 350 patients, a higher incidence of DME was observed in severe non-proliferative retinopathy (NPDR) patients than that observed in other groups. By dividing the 52 patients with severe NPDR into the micro- and macro-albuminuria subgroups, significant differences in CFT, systolic blood pressure, total cholesterol and serum creatinine levels, and UAE were revealed. Furthermore, a positive liner correlation between the UAE and CFT was found. Finally, the partial correlation coefficient adjusted for either the CFT or UAE indicated that both parameters directly correlated with the number of IVC injections administered during the 12mo of follow-up.**

**● CONCLUSION: Generally, macular edema occurred in patients with severe NPDR, for whom the UAE is an independent risk predictor of DME. The baseline UAE and CFT predicted the treatment frequency of IVC injections administered in the first year for eyes with DME.**

**● KEYWORDS:** diabetic macular edema; urinary albumin excretion; intravitreal conbercept injection; treatment frequency

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## INTRODUCTION

While diabetic retinopathy (DR) and diabetic kidney disease (DKD) manifest similar pathological features[1-2], it is generally accepted that kidney dysfunction is associated with the presence and severity of DR[3-4]. Furthermore, diabetic macular edema (DME) represents the most prevalent retinopathy threatening the eye sight and it may occur at any stage of DR[5-6]. Although the relationship between DKD and DME is expected to be similar to that between DKD and DR, controversial results from the same ethnic groups exist[7-10]. While the differences in sample size and characteristics between studies may be the reason underlying the contrasting results, a possible explanation is also provided by the

dissociation of albuminuria with reduced estimated glomerular filtration rate (eGFR) in some diabetic patients[11-12]. It is widely recognized that DKD is caused by progressive microvascular alterations and can be diagnosed early through albuminuria [urinary albumin excretion (UAE)>30 mg/24h or albumin to creatinine ratio (ACR)>30 mg/g] or defective renal function manifested as eGFR<60 mL/min/1.73 $m^2$[2,13]. Clinically, diabetic patients may present albuminuria, decreased eGFR, or both[11-12]. Although decreased eGFR is associated with the presence and severity of DR, a relation with DME is not present[3,14]. Given that DME is caused by the hyperpermeability of damaged retinal blood vessels[1,15] and that microalbuminuria indicates generalized vascular dysfunction[16], it is reasonable to speculate that the level of albuminuria might reflect the severity of DME. However, the role of albuminuria in the development of DME is yet to be defined.

Although anti-vascular endothelial growth factor (anti-VEGF) agents have recently been the mainstay treatment for DME, defective baseline kidney function may slow the resolution of DME after anti-VEGF injections[17]. Several studies identified the humanized, soluble, VEGF receptor (VEGFR) protein conbercept to be effective and safe in treating DME[18-19]. Furthermore, considering that the intravitreal conbercept (IVC) treatment for DME is produced locally, it has gradually become common in China. Therefore, the present study both investigates the association between albuminuria and DME in a group of in-hospital type 2 diabetes mellitus (DM2) patients in northern China and discusses the impact of albuminuria on IVC treatment frequency during the first year of follow-up.

## SUBJECTS AND METHODS

**Ethical Approval** This hospital-based retrospective study was approved by the ethics committee of the hospital and followed the tenets of the Declaration of Helsinki. All the patients signed a medical informed consent document prior to the performance of the surgery.

**Patients Selection** A total of 350 eligible in-patients with a known diagnosis of DM2 and who met our inclusion criteria between September 2016 and 2017 were enrolled in the current study at the 2nd Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. This center is a Xi'an comprehensive institute including ophthalmology, endocrinology and nephrology. The data related to patients' age, gender, diabetes duration, systemic variables and detailed ophthalmic evaluation at their first visit were retrieved from both the electronic medical records and case files. Furthermore, standard fundus photographs of each eye were taken and assessed by two experienced ophthalmologists blind to the patients' demographic data and medical history. More specifically, each individual's fundus photograph was graded lesion by lesion and their final retinopathy grading was provided according to their worst eye. When inconsistencies occurred between readers, the images were again reviewed and a final agreement was reached. The DR severity was classified according to the Early Treatment of Diabetic Retinopathy Study Researched Group (ETDRS) in 1991[20] as follows: 1) no retinopathy; 2) mild non-proliferative diabetic retinopathy (mild NPDR); 3) moderate non-proliferative retinopathy (moderate NPDR); 4) severe non-proliferative retinopathy (severe NPDR); and 5) proliferative retinopathy (PDR). In addition, macular retinal thickness was measured using the spectral domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany). In contrast, the urine protein concentration was initially measured through the dipstick test and the results were reported semi-quantitatively as negative, positive grade I, II and III. Thereafter, 156 patients were found to have positive proteinuria and a quantitative measurement using a 24-hour urine collection was attained, with microalbuminuria defined as a UAE of 30-300 mg/24h and macroalbuminuria as a UAE>300 mg/24h.

For a further analysis of DME and albuminuria, only those patients with severe NPDR ($n$=52) were assessed. Additional exclusion criteria included: 1) coexisting ocular disorders (*i.e.*, vitreous hemorrhage, ischemia, epiretinal membrane, and uveitis); 2) suboptimal fundus image quality possibly caused by severe opaque media and poor focus; 3) coexisting disorders other than diabetes causing renal inadequacy; 4) subjects who received certain relevant interventions [*e.g.*, panretinal photocoagulation (PRP), intravitreal anti-VEGF injection and intravitreal injections of triamcinolone acetonide (IVTA)] within 6mo. As a result, 52 patients met all the criteria. Therefore, one eye of each patient was analyzed, *i.e.*, the eye with thicker fovea for patients with bilateral macular edema.

**Other Non-ophthalmic Parameters** Other non-ophthalmic parameters included: systolic/diastolic blood pressure (mm Hg), glycated hemoglobin A1c (%), total cholesterol (mmol/L), triglyceride (TG) (mmol/L), and serum creatinine (CREA) (mmol/L).

**Intervention** The initial treatment consisted in the intravitreal injection of conbercept (KH902; Chengdu Kanghong Biotech Co., Ltd., Sichuan, China) combined with triamcinolone acetonide (IVC+IVTA) in 46 eyes of the above 52 patients with center-involved DME. More specifically, triamcinolone acetonide (TA) (40 mg in 1 mL vial) was first filtered through a 0.22-mm porous filter to remove the preservative and then resuspended in a 1-mL balanced salt solution. After disinfection, conbercept (0.5 mg/0.05 mL) and TA (1 mg/0.05 mL) were injected posteriorly to the limbus (4.0 mm), which was followed by an instillation of antibiotics. Patients were assessed monthly during a year of follow-up for additional IVC

injections if required (PRN strategy). Re-treatment criteria were defined as: 1) increased central foveal thickness (CFT) (≥50 mm) compared to the lowest previous measurement; 2) new or persistent cystoid macular edema or subretinal fluid on OCT; 3) loss of ≥5 letters from the best previous best corrected visual acuity (BCVA) measurement as well as any increase in the CFT. In addition to the conbercept injections, all the patients received a PRP or supplemental PRP in their third week following the first injection given that, during this time, the macular edema subsided and the IVTA powder dissipated (most suitable for laser treatment). Finally, 43 patients completed the 12-month follow-up.

**Statistical Analysis** All the data of the current study were presented as mean±SD and analyzed by SPSS 20.0 (SPSS, Inc., Chicago, IL, USA). Pairs of groups were compared through both the independent samples *t*-test and the Chi-square test. The relationship between the systemic variables and CFT was evaluated *via* the Spearman's rank correlation analysis and significant factors were further examined through a linear regression. Similarly, the scatter diagrams were graphed to determine whether a linear trend existed. Finally, Spearman's partial correlations were applied to assess the relationships between the UAE, CFT and treatment frequency of IVC injections after the adjustment for either CFT or UAE. A *P*-value <0.05 was considered as statistically significant.

## RESULTS

**The Distribution of Diabetic Macular Edema in Patients with Various Diabetic Retinopathy** Of the 350 patients diagnosed with DM2, 244 presented clinical DR, encompassing 32 mild NPDR (4 positive *vs* 28 negative for DME), 29 moderate NPDR (7 positive *vs* 22 negative for DME), 123 severe NPDR (107 positive *vs* 16 negative for DME) and 60 PDR (46 positive *vs* 14 negative for DME) (Table 1). Overall, a higher incidence of DME was noted in severe NPDR patients compared to the other DR categories (Table 1). Furthermore, the Chi-square test demonstrated statistically significant differences in DME positivity between severe NPDR patients and those with absent DR, mild NPDR, and moderate NPDR ($P<0.001$). However, a difference between severe NPDR and PDR patients was not identified ($P>0.05$).

**Demographic and Clinical Features of Patients with Severe Non-proliferative Diabetic Retinopathy Complicated by Albuminuria** Of the 52 patients with severe NPDR complicated by quantitative albuminuria, 23 and 29 presented microalbuminuria and macroalbuminuria, respectively. The demographic and clinical features, as well as the non-ophthalmic parameters, are summarized in Table 2. Significant differences in systolic blood pressure, cholesterol, CREA, UAE and CFT were found between the two groups. In contrast, the same was not valid for other variables, including diastolic blood pressure, glycated hemoglobin and TG. The two groups were similar in age ($P=0.710$), gender ($P=0.051$), and diabetes duration ($P=0.699$).

**Table 1 DME distribution in patients with various grades of DR**

*n* (%)

| Status of DR | DME | | Total |
|---|---|---|---|
| | Positive (+) | Negative (-) | |
| No DR | 5 (1.4) | 101 (28.9) | 106 (30.3) |
| Mild NPDR | 4 (1.1) | 28 (8.0) | 32 (9.1) |
| Moderate NPDR | 7 (2.0) | 22 (6.3) | 29 (8.3) |
| Severe NPDR | 107 (30.6) | 16 (4.6) | 123 (35.2) |
| PDR | 46 (13.1) | 14 (4.0) | 60 (17.1) |
| Total | 169 (48.3) | 181 (51.7) | 350 (100) |

DME: Diabetic macular edema; DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

**Table 2 Demographics and clinical features of patients with severe NPDR complicated by either microalbuminuria or macroalbuminuria**

*n* (%)

| Items | Microalbuminuria (*n*=23) | Macroalbuminuria (*n*=29) | $t/\chi^2$ | *P* |
|---|---|---|---|---|
| Age (y) | 54.65±11.10 | 53.62±8.18 | 2.909 | 0.710[a] |
| Gender | | | | |
| Female | 9 (39) | 14 (48) | 0.435 | 0.051[b] |
| Male | 14 (61) | 15 (52) | | |
| Duration (y) | 10.76±7.58 | 10.02±5.07 | 0.039 | 0.699[a] |
| SBP (mm Hg) | 122.67±19.04 | 136.03±19.10 | -0.180 | 0.018[a] |
| DBP (mm Hg) | 78.95±11.11 | 83.14±11.07 | -1.317 | 0.194[a] |
| HbA1c (%) | 8.76±1.97 | 8.81±2.16 | -0.063 | 0.951[a] |
| TC (mmol/L) | 4.51±1.06 | 5.70±1.62 | -3.190 | 0.020[a] |
| TG (mmol/L) | 1.38±0.64 | 2.35±2.53 | -2.004 | 0.053[a] |
| CREA (mmol/L) | 69.78±22.96 | 139.45±158.63 | -2.082 | 0.027[a] |
| UAE (mg/24h) | 184.61±94.11 | 4018.83±2550.14 | -7.192 | 0.000[a] |
| CFT (mm) | 348.35±101.79 | 413.48±104.08 | -2.264 | 0.028[a] |

Values are means±SD. NPDR: Non-proliferative diabetic retinopathy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Hemoglobin A1c; TC: Total cholesterol; TG: Triglyceride; CREA: Serum creatinine; UAE: 24-hours urinary albumin excretion rate; CFT: Central foveal thickness; $t/\chi^2$, *t* value or $\chi^2$ value. [a]Independent *t*-test; [b]$\chi^2$ test.

**Correlation Analysis of Central Foveal Thickness with Various Systemic Factors** Following an inspection of the Spearman's rank correlation coefficient, a significant positive correlation between CFT with CREA and UAE was observed ($r>0$, $P<0.05$). However, the same was not found for systolic blood pressure and total cholesterol ($P>0.05$; Table 3).

As opposed to CREA ($t=0.466$, $P=0.643$), further linear regression analyses were employed to disclose a linear correlation between CFT and UAE ($t=3.177$, $P=0.003$; Figure 1). UAE was thus discovered as an independent risk factor for DME in patients with severe NPDR.

**Table 3 Correlation analysis of the central foveal thickness with various systemic factors**

| Parameters | *r*-value | *P*-value |
|---|---|---|
| SBP (mm Hg) | 0.120 | 0.406 |
| TC (mmol/L) | 0.222 | 0.113 |
| CREA (mmol/L) | 0.387 | 0.005 |
| UAE (mg/24h) | 0.338 | 0.014 |

SBP: Systolic blood pressure; TC: Total cholesterol; CREA: Serum creatinine; UAE: 24-hours urinary albumin excretion rate.

**Association Between Baseline Urinary Albumin Excretion and Treatment Frequency of Intravitreal Conbercept Injections** As an initial treatment, a total of 46 eyes received IVC+IVTA, which was then followed by PRN IVC injections. In addition, 43 patients completed the 12-month follow-up. Specifically, the average number of IVC injections was 3.1±1.1 (range 1-5).

Several studies have reported the baseline CFT as a predictor of treatment frequency of anti-VEGF therapy for DME[21-23]. To exclude the confounding effect of CFT, a partial correlation analysis adjusted for CFT was conducted and a positive correlation between the baseline UAE and the number of IVC injections during the 12-month follow-up was found ($r$=0.623, $P$=0.000; Figure 2).

**Association Between the Baseline Central Foveal Thickness and the Treatment Frequency of Intravitreal Conbercept Injections** The individual effect of CFT on treatment frequency of IVC injections was also analyzed by partial correlation analysis after adjusting for UAE. A positive correlation between CFT and the number of IVC injections during the 12-month follow-up was found ($r$=0.413, $P$=0.007; Figure 3).

## DISCUSSION

A review of the literature from the past decade on albuminuria and DME displayed controversial results (Table 4)[3,7-10,24-28], likely due to patient selection, ethnic characteristics of samples and measurement methodology.

In concordance with previous studies, our data indicated a significant correlation between DME and severe NPDR[29-30]. To minimize the effects of confounding factors, patients at the same stage of DR severity, *i.e.*, severe NPDR, were selected for further analysis of the relationship between albuminuria and DME. In fact, the other patients would have presented either a negative urinary protein concentration (in absent, mild or moderate NPDR) or a complication of the epiretinal membrane at the posterior retina (in PDR) causing a tractive effect on the macula and thus preventing an accurate evaluation. A positive linkage between CFT and the level of albuminuria was here found. As a marker of widespread vascular endothelial damage, microalbuminuria indicates increased permeability of small blood vessels. The close

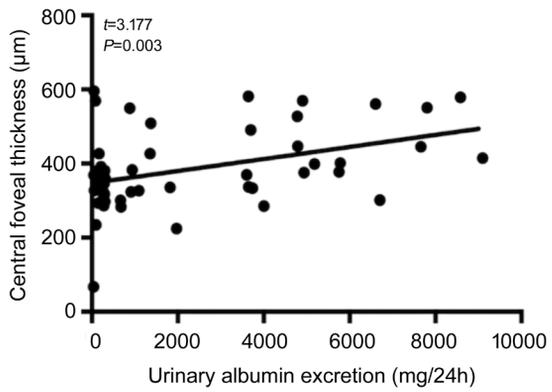


**Figure 1 The scatter diagram of central foveal thickness and UAE**
A positive linear correlation between central foveal thickness and UAE was observed in patients with severe NPDR.

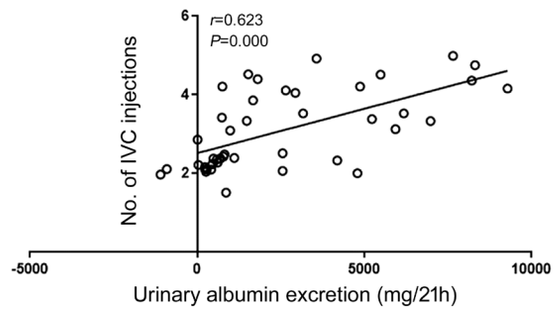


**Figure 2 Relationship between the UAE and the number of IVC injections during the 12-month follow-up.**

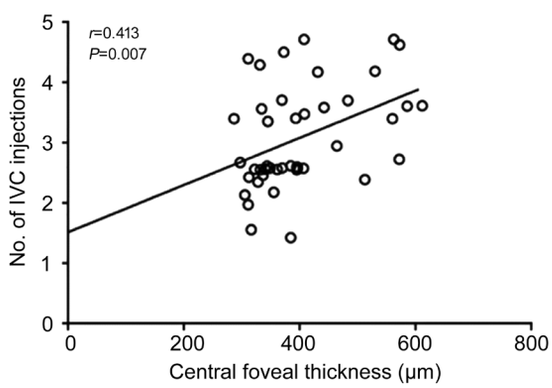


**Figure 3 Relationship between CFT and the number of IVC injections during the 12-month follow-up.**

relationship between DME and heavy albuminuria observed in the present study suggests that a thicker macula might be an ocular manifestation of a generalized vascular impairment rather than an isolated retinal event in DM2 patients with kidney disease. At the same time, an absence of significant correlation between CREA and DME was seen, even though patients with macroalbuminuria exhibited a higher level of CREA than those in the microalbuminuria group. The association between CFT and albuminuria, but not with CREA, advocates the overlapping, yet distinctive, pathophysiologic mechanisms underlying DME and DKD. In fact, the severity of DME, represented by an increased CFT, corresponds to a generalized vascular hyperpermeability in diabetic patients, which does not fully reflect renal status.

**Table 4 Summary of the literature on albuminuria & DME**

| Study | Study location and sample source | Sample size and category | Comments | Correlation between DME and micro/ macroalbuminuria |
|---|---|---|---|---|
| Romero P[7] (2007) | Spain, hospital-based | 102, type 1 | Microalbuminuria was not significant for DME in type 1 diabetic patients | None |
| Knudsen LL[24] (2007) | Denmark, population-based | 656, type 1<br>328, type 2 | Increased UAE was significantly associated with CSME in type 2 diabetic patients | Positive with macroalbuminuria |
| Asensio -Sánchez VM[8] (2008) | Spain, hospital-based | 208, no division between diabetes types | High levels of proteinuria and microalbuminuria are risk factors of DME for both type 1 and type 2 diabetic patients | Positive with both micro and macroalbuminuria |
| Ajoy Mohan VK[25] (2011) | India, hospital-based | 306, type 2 | Microalbuminuria is a strong predictor for CSME in type 2 diabetic patients | Positive with microalbuminuria |
| Kamoi K[26] (2013) | Japan, hospital-based | 131, type 2 | UAE is not significantly correlated with CSME | None |
| Burgess PI[27] (2014) | Malawi, hospital-based | 126, type 1<br>231, type 2 | ACR was not associated with sight-threatening retinopathy (including DME) | None |
| Park YH[3] (2015) | South Korea, population-based | 15409, no division of diabetes types | Proteinuria, as opposed to decreased eGFR, is more significantly associated with either DR or vision-threatening DR | Positive with macroalbuminuria |
| Hammes HP[28] (2015) | German/Austrian, population-based | 64784, type 2 | Presence of macroalbuminuria increased the risk of DME by 177% | Positive with macroalbuminuria |
| Jeng CJ[9] (2016) | Taiwan, population-based | 53453, no division of diabetes types | DKD was an independent risk factor for DR, but it did not markedly affect DME development | None |
| Hsieh YT[10] (2018) | Taiwan, hospital-based | 2135, type 2 | A high-baseline ACR was associated with DME | Positive with macroalbuminuria |

DME: Diabetic macular edema; UAE: Urinary albumin excretion; CSME: Clinically significant macular edema; ACR: albumin to creatinine ratio; eGFR: estimated glomerular filtration rate; DR: Diabetic retinopathy.

Contrary to the general belief, significant differences in HbA1c level and disease duration between micro- and macro-albuminuria groups were not detected. Similarly, further Spearman's coefficient analysis failed to reveal a meaningful association between DME severity and either blood pressure or TG, which are both known risk factors for DME and DKD[1-2]. These perplexing findings might originate from the specific sample selection of this study, as cases of severe NPDR hospitalized patients with similar disease durations may be included, and systemic variables clinically controlled.

Therapeutically, both intravitreal anti-VEGF agents and IVTA are common modalities for DME. Although the anti-VEGF therapy is most effective to improve the visual acuity of DME patients, this treatment is expensive and requires frequent injections. In contrast, the IVTA is economically accessible, however, its usage is restricted due to the secondary increase in intraocular pressure (IOP) and cataract[31]. In our study, the patients received an initial IVC combined with IVTA (1 mg), which was then followed by an IVC injection if needed (PRN strategy). The rationale behind using the combined regimen in the current study encompasses the following: 1) the combination of an anti-VEGF agent and TA was found to reduce the number of additional injections when compared to mono-therapy, even though synergistic effects were not observed[32]; 2) patients who received the 1-mg TA dosage were reported to have less complications[33]; and 3) DME patients with hypoalbuminuria were noted to be less responsive to the anti-VEGF therapy[17]. In this study, an IOP elevation was observed in one patient only who did not require any surgical intervention. The average number of necessary IVC injections was 3.1±1.1 during the first year, which was a significantly lower number compared to the previously published results (6.7±0.9)[18] and (5.6±0.8)[19] using IVC monotherapy. Furthermore, our analyses indicated the baseline UAE level to predict the treatment frequency of IVC injections during the first 12-month follow-up. Therefore, the impact of systemic conditions should be taken into consideration when assessing patients' responses to the anti-VEGF treatment.

The limitations of the current study include the retrospective nature of its research design, the relatively small number of cases enrolled, and the random analyses of the baseline clinical parameters which may fluctuate over time. Nonetheless, our results indicate the UAE to be an independent risk predictor of DME for patients with severe NPDR. In addition, the levels of baseline UAE and CFT were found to predict the treatment frequency of IVC injections in the first year of follow-up.

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