Serum Mannose-Binding Lectin Is a Strong Biomarker of Diabetic Retinopathy in Chinese Patients With Diabetes

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OBJECTIVE

Inflammation and complement activation initiated by mannose-binding lectin (MBL) may be implicated in the pathogenesis of diabetic vascular complications. We investigated serum MBL levels in patients with diabetes with and without diabetic retinopathy (DR).

RESEARCH DESIGN AND METHODS

Serum MBL levels were determined in 348 patients with diabetes and in 100 healthy control subjects. The prediction value of MBL was compared with diabetes duration, hs-CRP, and other known predictors. Multivariate analyses were performed using logistic regression models.

RESULTS

MBL levels on admission were significantly increased in patients with diabetes with DR ($P < 0.0001$) and vision-threatening DR (VTDR; $P < 0.0001$). Multivariate logistic regression analysis adjusted for common indictors showed that serum MBL levels ≥3,385 μg/L were an independent predictor of DR (odds ratio [OR] 3.14, 95% CI 1.77–5.57) and VTDR (OR 7.83, 95% CI 3.35–18.31). The area under the receiver operating characteristic curve of MBL was 0.81 (95% CI 0.76–0.86) for DR and 0.84 (95% CI 0.74–0.93) for VTDR.

CONCLUSIONS

The current study demonstrated that MBL appears to be an independent biomarker for DR in the Chinese population, suggesting a possible role of MBL in the pathogenesis of DR complications in diabetes.

Diabetes has become a major public health problem in China. In 2009, the age-standardized prevalence of diabetes was 9.7%, accounting for 92.4 million adults with diabetes (1). Diabetic retinopathy (DR) is the leading cause of blindness among working-aged adults around the world (2). Approximately 29% of U.S. adults with type 2 diabetes have DR (3), whereas DR will develop in 95% of individuals with type 1 diabetes during their lifetime (4).

The presence of DR was associated with an increased risk of all-cause mortality and cardiovascular events in patients with diabetes (5). However, risk of vision loss due to DR retinopathy can be reduced by effective control of serum glucose and blood pressure (BP). The efficacy and cost-effectiveness of early detection and treatment of DR is well established (6). Although the major risk factors for

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DR (e.g., hyperglycemia, hypertension, and dyslipidemia) have been examined in many epidemiologic studies and clinical trials, the consistency, pattern, and strength of these risk factors varies considerably (3).

Mannose-binding lectin (MBL) is synthesized by hepatocytes and belongs to the family of C-type lectins (7). Its carbohydrate recognition domains bind in a calcium-dependent manner to patterns of carbohydrate residues found on microorganisms. MBL exerts an important role in the innate immune system, and several studies have indicated that low levels of MBL affect the outcome of infectious diseases, critical illness, and kidney graft survival (8–10). Interestingly, high levels of MBL offer protection against invading microorganisms but may confer biological disadvantages in other situations (11). MBL may aggravate local and systemic inflammation through complement activation and modulation of proinflammatory cytokine production (6).

Elawa et al. (12) reported that elevated serum MBL in diabetes indicated possible poor diabetes control and bad progression of the disease, with the possibility of the presence or development of diabetic nephropathy; whereas another study found log MBL levels were not associated with the occurrence of cardiovascular events in South Asians with type 2 diabetes (13). In addition, Hansen et al. (14) found that the median MBL concentration was higher in patients with diabetes than in healthy control subjects, and Bouwman et al. (15) reported that MBL serum concentration were associated with diabetic vascular complications. Currently, no data are available on the relationship between MBL and DR in Chinese patients with diabetes. In this study, we therefore evaluated serum MBL levels in Chinese patients with diabetes with and without DR.

RESEARCH DESIGN AND METHODS

We conducted a prospective case-control study at the endocrinology department of our hospital. We consecutively recruited 348 Chinese with diabetes aged 31–74 years between October 2012 and December 2013. Participants were excluded if they had a history of epilepsy or glaucoma, had undergone previous vitreal surgery, and/or had a cataract on examination. Participants who had no light perception or severe visual impairment in both eyes or had a severe infection in one or both eyes were excluded. Also excluded were patients with systemic infections, cardiocerebrovascular diseases, rheumatic heart disease, chronic obstructive pulmonary disease, and autoimmune disorders. A group of 100 age-matched healthy subjects served as control subjects. To exclude the possibility that the control subjects could have any above concomitant conditions, all control subjects were also clinically examined by one researcher (P.G.). The study followed the tenets of the Declaration of Helsinki and was approved by the Chinese People's Liberation Army (PLA) General Hospital Institute Ethics Committee, with written informed consent obtained from each participant.

The Canon CR6-45NM ophthalmic digital imaging system and the Canon EOS 10D digital camera (Canon, Tokyo, Japan) were used (P.G. and Y.D.) to take two digital images per eye through a nonpharmacologically dilated pupil. Participants (patients and control subjects) were seated in a windowless room with the lights turned off to allow the pupils to dilate naturally in preparation for the retinal imaging examination. One image was centered on the macula and the second on the optic nerve. The digital images were graded by masked photo graders at the Chinese PLA General Hospital Epidemiologic Reading Center, using a modification of the Airlie House classification system (16,17). DR was defined as the presence of one or more retinal microaneurysms or retinal blot hemorrhages with or without more severe lesions (hard exudates, soft exudates, intraretinal microvascular abnormalities, venous beading, retinal new vessels, preretinal and vitreous hemorrhage, and fibroproliferans) using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading standards (18). DR severity was categorized as nonproliferative DR (NPDR) at level 20 through level 53 and as proliferative DR (PDR) at level $\geq$60. Diabetic macular edema (DME) was defined as present or absent and classified as with or without clinically significant macular edema, and vision-threatening DR (VTDR) was defined as the presence of PDR and/or DME (3). Diabetes was defined as self-report of a previous diagnosis of the disease by a clinician (excluding gestational diabetes mellitus) or hemoglobin A_{1c} (HbA_{1c}) of 6.5% (48 mmol/mol) or greater (19).

At baseline, we requested individual participant data regarding presence and severity of DR, DME status, age, sex, ethnicity, diabetes type and duration, HbA_{1c}, systolic and diastolic BP, cigarette smoking status, BMI, and current use of diabetes, antihypertensive, and lipid-lowering medications.

All investigations were performed in the morning after an overnight fast. Venous blood was drawn with minimal stasis from an antecubital vein. Clotted blood was centrifuged within 1 h and serum stored at -80°C. HbA_{1c} was measured by high-performance liquid chromatography (HLC-723 G7; TOSHO, Tokyo, Japan) with a normal range of 4–6% (20–42 mmol/mol). Other biochemical parameters were assessed using Olympus AU2700 (Olympus, Tokyo, Japan).

MBL was measured by time-resolved immune-fluorometric assay on serum samples. Microwells coated with anti-MBL antibody were incubated with dilutions of patient serum and were developed with europium-labeled anti-MBL antibody, and europium was quantified with time-resolved fluorometric assay (Baoman Biological Technology Co., Ltd., Shanghai, China). The detection limit was 1.5 μg/L. The standard concentrations in these kits range from 1.5 to 100 μg/L, providing a range of 150–10,000 μg/L at 1:100 dilution. The coefficients of variation for the intra- and interassay reproducibility are 4.2–5.3% and 6.4–8.9%, respectively. For all measurements, levels that were not detectable were considered to have a value equal to the lower limit of detection of the assay.

Results are expressed as percentages for categorical variables and as medians (interquartile ranges [IQRs]) for the continuous variables. Univariate data on demographic and clinical features were compared by Mann-Whitney *U* test or χ^2 test, as appropriate. Correlations among continuous variables were assessed by the Spearman rank correlation coefficient. Different statistical methods were used to investigate whether MBL allows predicting of both DR and VTDR in diabetes. First, the relation of MBL with the two points was investigated with the use of logistic regression models. We used crude models and multivariate models adjusted for all significant predictors and report

odds ratios (ORs). For multivariate analysis, we included confounders, known risk factors, and other predictors as assessed in univariate analysis. Second, receiver operating characteristic (ROC) curves were used to test the overall predict accuracy of MBL, and results were reported as area under the curve (AUC). All statistical analysis was performed with SPSS 20.0 software (IBM Corp., Armonk, NY) and ROCR 1.0-2 software, which is available from the Comprehensive R Archive Network repository (http://cran.r-project.org/). All testing was two-tailed, and P values of <0.01 were considered to indicate statistical significance depending on the number of statistical variables.

RESULTS

Patient Characteristics

There were 348 people with diabetes (98 with type 1 diabetes and 250 with type 2 diabetes) eligible for the study. The median age of patients included in this study was 56 (IQR 40–67) years, and 56.0% were men. The median time of diabetes duration was 7.5 (IQR 5.5–10) years. DR was found in 107 patients (30.7%). Thirty-nine patients were defined as VTDR; thus the rate was 11.2%. The rates of DR and VTDR were 31.6% and 12.2% in the patients with type 1 diabetes and 30.4% and 10.8% in the group with type 2 diabetes. Baseline characteristics of those patients are provided in Table 1.

Main Results

The results indicated that the serum MBL levels were significantly ($P < 0.0001$) higher in patients with diabetes than in normal subjects (2,892 [IQR 2,321–3,385] μg/L vs. 890 [IQR 675–1,045] μg/L; Fig. 1*A*). Interestingly, the serum levels of MBL in type 1 diabetes were significantly ($P = 0.009$) higher than in type 2 diabetes (3,115 [IQR 2,540–3,652] μg/L vs. 2,764 [IQR 2,114–3,011] μg/L). Serum MBL levels were paralleled with severity of DR (ANOVA $P = 0.006$). Median levels in patients with non-DR, mild DR, and severe DR were 2,560 (IQR 2,100–3,385) μg/L, 2,960 (IQR 2,745–3,560) μg/L, and 3,544 (IQR 3,159–3,955) μg/L, respectively.

Serum MBL levels increased with worse diabetes control, as defined by the HbA_{1c} level (Fig. 2*A*). There was a modest positive correlation between levels of MBL and HbA_{1c} ($r = 0.296$, $P < 0.0001$) and when the groups with DR ($r = 0.315$, $P < 0.0001$) and without DR ($r = 0.289$, $P < 0.0001$) were analyzed separately. Similarly, there was still a modest positive correlation between levels of MBL and HbA_{1c} when the groups with type 1 diabetes ($r = 0.306$, $P < 0.0001$) and type 2 diabetes ($r = 0.292$, $P < 0.0001$) were analyzed separately. In addition, there was a significant,

Table 1—Baseline characteristics of diabetes patients with or without DR

		Retinopathy status		
Characteristics	Diabetes (N = 348)	Yes (n = 107)	No (n = 241)	P
Age at baseline (years)	56 (40–67)	57 (42–68)	55 (39–67)	0.43
Male	56.0	55.1	56.4	0.82
Diabetes duration (years)	7.5 (5.5–10)	9.0 (7.5–12)	6.0 (4.5–8.5)	<0.001
BMI (kg/m^2)	28.6 (26.3–31.2)	29.1 (26.9–31.3)	28.3 (25.7–31.0)	0.26
Systolic BP (mmHg)	132 (125–143)	143 (129–148)	126 (120–145)	<0.001
Smoking status	44.5	42.1	45.6	0.53
Current alcohol intake	39.9	38.3	40.7	0.68
Intensive glucose treatment	45.4	54.2	41.4	0.028
BP treatment	42.2	44.9	41.1	0.34
Use of lipid-lowering medication	39.7	43.9	37.8	0.18
Laboratory findings				
HbA_{1c} (%)	7.8 (7.2–8.6)	8.4 (7.8–9.6)	7.1 (6.5–8.2)	<0.001
HbA_{1c} (mmol/mol)	62 (55–70)	68 (62–81)	54 (48–66)	<0.001
Serum creatinine (μmol/L)	89 (75–98)	90 (77–99)	87 (74–97)	0.22
Total cholesterol (mmol/L)	4.6 (3.8–5.4)	4.8 (4.0–5.5)	4.4 (3.7–5.2)	0.046
Triglycerides (mmol/L)	1.4 (0.9–1.8)	1.5 (1.0–1.9)	1.4 (0.9–1.7)	0.56
LDL cholesterol (mmol/L)	2.5 (1.9–2.9)	2.6 (2.0–2.9)	2.5 (1.9–2.8)	0.67
HDL cholesterol (mmol/L)	1.5 (1.3–1.7)	1.6 (1.4–1.7)	1.5 (1.3–1.7)	0.81
hs-CRP (mg/dL)	0.96 (0.48–2.19)	1.42 (0.66–3.12)	0.76 (0.39–1.78)	<0.001
MBL (μg/L)	2,892 (2,320–3,387)	3,270 (2,950–3,800)	2,560 (2,100–3,110)	<0.0001
Any DR	30.7			
PDR	7.2			
DME	7.5			
VTDR	11.2			
Any DR in type 1 diabetes (n = 98)	31.6			
PDR	8.2			
DME	9.2			
VTDR	12.2			
Any DR in type 2 diabetes (n = 250)	30.4			
PDR	6.8			
DME	6.8			
VTDR	10.8			

Results are expressed as percentages or as medians (IQR).

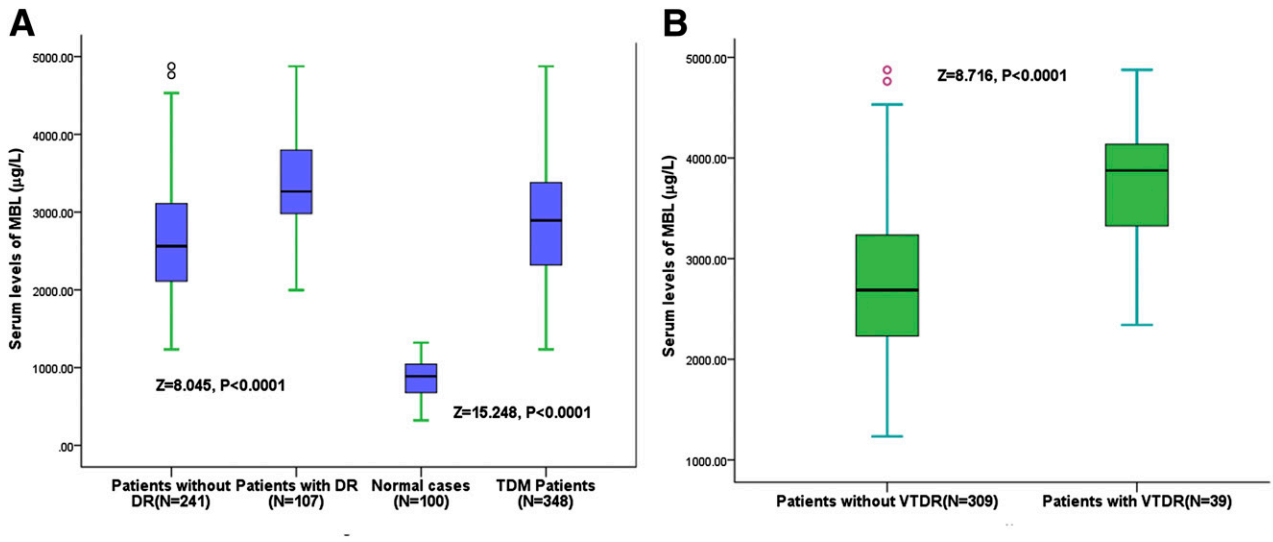

Figure 1—*A*: Distribution of serum MBL levels in patients with type 1 or type 2 diabetes mellitus (TDM), with and without DR, and in normal control subjects. *B*: Distribution of serum MBL levels in patients with and without VTDR. All data are medians (IQR). *P* values refer to Mann-Whitney *U* tests for differences between groups.

albeit weak, positive correlation between MBL levels and hs-CRP (r = 0.198, $P <$ 0.0001; Fig. 2*B*). Again, similar results were found when the groups with DR (r = 0.211, $P <$ 0.0001) and without DR (r = 0.178, P = 0.006) were analyzed separately. There was a positive correlation between levels of MBL and hs-CRP when groups with type 1 diabetes (r = 0.221, $P <$ 0.0001) or type 2 diabetes (r = 0.167, P = 0.009) were analyzed separately. Furthermore, no correlation was found between serum levels of MBL and other factors, such as sex, age, creatinine, triglyceride, cholesterol, LDL and HDL, duration of diabetes, or daily insulin dose, in all the patients or when groups with type 1 or type 2 diabetes were analyzed separately ($P >$ 0.05).

MBL and DR

In the 107 patients with DR, serum MBL levels were higher compared with those in patients without DR (3,270 [IQR 2,950–3,800] μg/L vs. 2,560 [IQR 2,100–3,385] μg/L; $P <$ 0.0001; Fig. 1*A*). In univariate logistic regression analysis, we calculated the OR of per unit MBL level compared with other risk factors, as presented in Table 2. With an unadjusted OR of 1.001 (95% CI 1.001–1.002), MBL had a strong association with DR. After adjusting for all other significant predictors (sex, diabetes duration, hypertension, intensive glucose treatment, HbA_{1c}, and hs-CRP) in univariate analysis, MBL remained an independent DR indictor with an adjusted OR of 1.001 (95% CI 1.001–1.002; $P <$ 0.0001). In multivariate analysis, there was an increased risk of DR associated with MBL levels ≥3,385 μg/L (third quartiles; OR 3.14, 95% CI 1.77–5.57; $P <$ 0.0001) after adjusting for possible confounders. Male sex, diabetes duration, HbA_{1c}, hs-CRP,

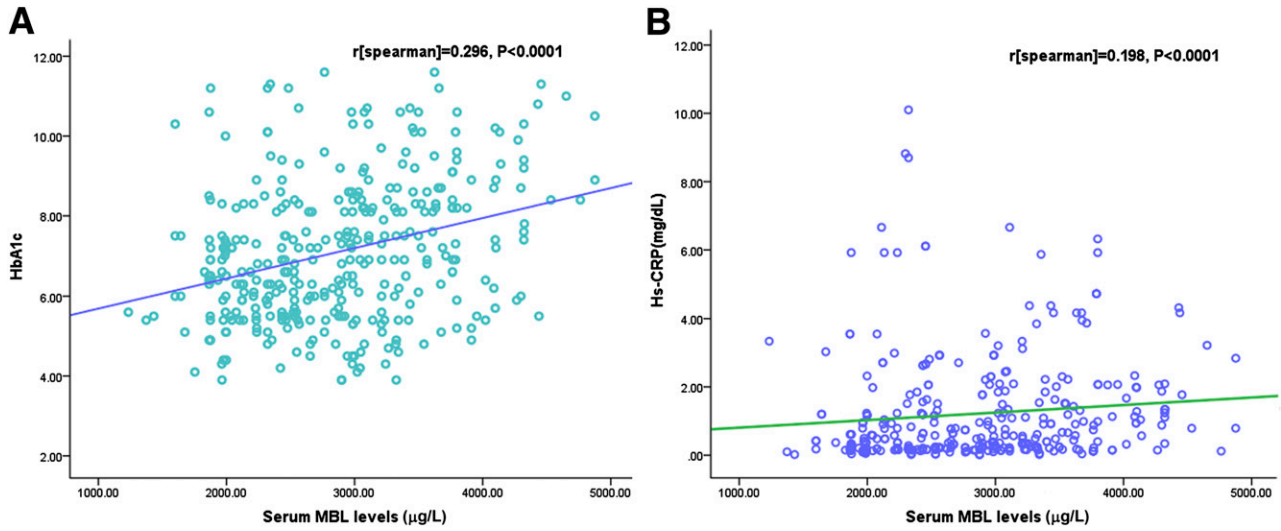

Figure 2—Correlation between the serum MBL levels and HbA_{1c} (*A*) and between MBL levels and hs-CRP (*B*).

Table 2—Univariate and multivariate logistic regression analysis for DR and VTDR

	Univariate analysis			Multivariate analysis		
Parameter	OR[a]	95% CI	*P*	OR[a]	95% CI	*P*
Predictor: DR						
MBL	1.001	1.001–1.002	<0.0001	1.001	1.001–1.002	<0.0001
MBL (≥3rd quartiles)[b]	3.95	2.36–6.56	<0.0001	3.14	1.77–5.57	<0.0001
Male sex	1.25	1.05–1.42	0.006	1.18	1.04–1.30	0.001
HbA_{1c} (%)	1.09	1.03–1.21	<0.001	1.05	1.01–1.16	<0.001
Diabetes duration	1.22	1.11–1.35	0.003	1.15	1.06–1.29	0.009
hs-CRP	1.11	1.05–1.19	<0.001	1.08	1.03–1.18	<0.001
Intensive glucose treatment	2.01	1.24–3.98	0.028	1.95	0.93–3.88	0.236
Hypertension	1.55	1.30–1.76	<0.001	1.31	1.10–1.48	0.003
Predictor: VTDR						
MBL	1.002	1.002–1.003	<0.0001	1.001	1.001–1.002	<0.0001
MBL (≥3rd quartiles)[b]	9.34	4.47–19.50	<0.0001	7.83	3.35–18.31	<0.0001
Male sex	1.18	1.04–1.46	0.022	1.09	1.02–1.37	0.035
HbA_{1c} (%)	1.10	1.03–1.36	<0.001	1.08	1.02–1.20	<0.001
Diabetes duration	1.25	1.05–1.45	0.006	1.12	1.02–1.31	0.009
hs-CRP	1.18	1.10–1.32	0.006	1.16	1.05–1.36	0.009
Intensive glucose treatment	1.21	1.03–1.43	<0.001	1.14	1.06–1.23	0.001
Hypertension	1.70	1.27–3.01	0.009	1.55	1.28–2.34	0.006

[a]The OR corresponds to a unit increase in the explanatory variable. [b]MBL ≥3rd quartiles rather than MBL was a predictor in logistic regression analysis.

and systolic BP were also DR predictors in multivariate analysis (Table 2). Similar results were obtained when the groups with type 1 or type 2 diabetes were analyzed separately. In multivariate analysis, there was an increased risk of DR associated with MBL levels ≥3,385 μg/L (third quartiles; OR 3.35, 95% CI 1.57–6.16; $P < 0.0001$) after adjusting for possible confounders in the group with type 1 diabetes. Again, in the patients with type 2 diabetes, there was also an increased risk of DR associated with MBL levels ≥3,385 μg/L (third quartiles; OR 3.05, 95% CI 1.62–5.36; $P < 0.0001$) after adjusting for possible confounders (Supplementary Tables 1 and 2).

With an AUC of 0.81 (95% CI 0.76–0.86), MBL showed a significantly greater discriminatory ability compared with hs-CRP (AUC 0.67, 95% CI 0.59–0.78; $P < 0.001$), HbA_{1c} (AUC 0.77, 95% CI 0.69–0.83; $P < 0.01$), and male sex (AUC 0.65, 95% CI 0.55–0.76; $P < 0.001$), while MBL was in the range of diabetes duration (AUC 0.79, 95% CI 0.72–0.89; $P = 0.12$). Interestingly, the combined model (MBL and HbA_{1c}) improved the diagnostic value of HbA_{1c}, with an AUC of 0.85 (95% CI 0.78–0.93; $P < 0.01$). This improvement was stable in an internal fivefold cross-validation that resulted in an average AUC (SE) of 0.77 (0.029) for the diabetes duration and 0.85 (0.023) for the combined model, corresponding to a difference of 0.08 (0.006) (Table 3). Similar results were obtained when the groups with type 1 or type 2 diabetes were analyzed separately (Supplementary Table 3).

Table 3—Receiver operating characteristic curve analysis

	DR			VTDR		
Parameter	AUC[a]	95% CI[a]	*P*	AUC[a]	95% CI[a]	*P*
MBL	0.81	0.76–0.86		0.84	0.74–0.93	
Age	0.63	0.52–0.75	<0.0001	0.65	0.51–0.78	<0.0001
Male sex	0.65	0.55–0.76	<0.001	0.62	0.51–0.71	<0.001
Diabetes duration	0.79	0.72–0.89	0.12	0.81	0.71–0.92	<0.01
Systolic BP	0.66	0.60–0.70	<0.001	0.64	0.58–0.70	<0.001
HbA_{1c}	0.77	0.69–0.83	<0.01	0.79	0.70–0.86	<0.01
hs-CRP	0.67	0.59–0.78	<0.001	0.69	0.63–0.75	<0.001
Combined model[a]	0.85	0.78–0.93	<0.01	0.88	0.81–0.95	<0.01

[a]Combined model = HbA_{1c} + MBL.

MBL and VTDR

Serum MBL levels were higher in the 39 patients with VTDR compared with levels in patients without VTDR (3,890 [IQR 3,280–4,145] μg/L vs. 2,690 [IQR 2,230–3,250] μg/L; $P < 0.0001$; Fig. 1*B*). In multivariate analysis, after adjusting for all other significant predictors, MBL remained as an independent VTDR indictor, with an adjusted OR (per unit) of 1.001 (95% CI 1.001–1.002; $P < 0.0001$). In addition, there was an increased risk of VTDR associated with MBL levels ≥3,385 μg/L (third quartiles; OR 7.83, 95% CI 3.35–18.31; $P < 0.0001$) after adjusting for possible confounders. Male sex, diabetes duration, HbA_{1c}, hs-CRP, and systolic BP were also VTDR predictors in multivariate analysis (Table 2). Similar results were obtained when the groups with type 1 or type 2 diabetes were analyzed separately. In multivariate analysis, there was an increased risk of VTDR associated with MBL levels ≥3,385 μg/L (third quartiles; OR 8.18, 95% CI 3.49–20.38; $P < 0.0001$) after adjusting for possible confounders in the group of type 1 diabetes and an OR of 7.17 (95% CI 3.03–16.33; $P < 0.0001$) in the group with type 2 diabetes (Supplementary Tables 1 and 2).

With an AUC of 0.84 (95% CI 0.74–0.93), MBL showed a significantly greater discriminatory ability compared with hs-CRP (AUC 0.69, 95% CI 0.63–0.75; $P < 0.001$), HbA_{1c} (AUC 0.79, 95% CI 0.70–0.86; $P < 0.01$), and age (AUC 0.65, 95% CI 0.51–0.78; $P < 0.0001$), while MBL was in the range of diabetes duration (AUC 0.81, 95% CI 0.71–0.92; $P < 0.01$). Again, the combined model (MBL and HbA_{1c}) improved the diagnostic value of HbA_{1c} (AUC 0.88, 95% CI 0.81–0.95; $P < 0.01$). This improvement was also stable in an internal fivefold cross-validation that resulted in an average AUC (SE) of 0.79 (0.028) for HbA_{1c} and 0.88 (0.017) for the combined model, corresponding to a difference of 0.09 (0.011) (Table 3). Similar results were obtained when the groups with

type 1 or type 2 diabetes were analyzed separately (Supplementary Table 4).

MBL and DME

Serum MBL levels were higher in the 26 patients with DME compared with those in patients without DME (3,940 [IQR 3,150–4,360] μg/L vs. 2,625 [IQR 2,210–3,210] μg/L; $P < 0.0001$). With an AUC of 0.87 (95% CI 0.79–0.95), MBL showed a significantly greater discriminatory ability compared with hs-CRP (AUC 0.72, 95% CI 0.65–0.80; $P < 0.001$), HbA_{1c} (AUC 0.79, 95% CI 0.70–0.88; $P < 0.001$), and diabetes duration (AUC 0.78, 95% CI 0.71–0.87; $P < 0.001$). In multivariate analysis, after adjusting for diabetes duration, hs-CRP, and HbA_{1c}, elevated MBL levels (≥3,385 μg/L) were an independent DME indictor, with an adjusted OR of 9.12 (95% CI 3.11–33.24; $P < 0.0001$). Similar results were obtained when the groups with type 1 or type 2 diabetes were analyzed separately.

CONCLUSIONS

The protein MBL activates the complement system by binding to carbohydrate structures presented by microorganisms and thus could be an important component of the innate immune defense system (20). de Vries et al. (21) indicated that the MBL pathway was involved in ischemia-induced complement activation. Mounting evidence suggests that there may be a link between complement activation and the development of diabetes complications (22,23). One study suggested that MBL and the lectin complement pathway play a significant role in vascular dysfunction and cardiomyopathy after acute hyperglycemia (24). In this study, we first assessed the accuracy of serum MBL levels in diagnosing DR, VTDR, and DME in a sample of Chinese patients with diabetes.

We found that serum MBL levels were significantly higher in patients with diabetes compared with normal subjects ($P < 0.0001$). Importantly, our study has confirmed that elevated MBL is correlated with DR and VTDR and adds significant additional predictive information to the diabetes duration, suggesting a possible role of MBL in the pathogenesis of DR complications in diabetes. Similarly, Hansen et al. (14) demonstrated that circulating MBL concentrations are significantly elevated in patients with type 1 diabetes and suggested a possible role of MBL in the pathogenesis of renovascular complications in diabetes, whereas Hansen et al. (25) reported that measurements of MBL alone or combined with CRP can provide prognostic information on mortality and the development of albuminuria in patients with type 2 diabetes. In another study, Hansen et al. (6) suggested that MBL may be involved in the pathogenesis of micro- and macrovascular complications in type 1 diabetes.

The importance of glycemia, BP, and diabetes duration as risk factors for DR is already well established (26). Male sex has also been reported as a risk factor in other studies (27). Results concerning the relationship between BMI and risk for DR are inconsistent, with both positive (28) and negative associations (29) reported. Importantly, our study found that MBL was a risk factor for DR and, in addition, that male sex, diabetes duration, HbA_{1c}, hs-CRP, and systolic BP were also risk factors.

Usually, in patients with type 1 diabetes, DR symptoms affect 50% of patients after 10 years of the disease and as many as 90% of patients after 20–30 years (30), whereas ~29% of patients with type 2 diabetes have DR (3). Differences in study methodologies, population characteristics, and ascertainment and classification of DR have made direct comparisons between studies difficult. A meta-analysis of 35 studies (1980–2008) provided data from 22,896 individuals with diabetes, and the overall prevalence was 34.6% for any DR (3). Similarly, in our study, 30.7% of the patients with diabetes had DR. Our findings are in line with reports from recent population studies in which the prevalence of DR was 6–23% (25,31,32). Interestingly, DR also occurs in populations without diabetes (33), with estimates ranging from 5.2% in the Pima Indians (32) to 8% in the general U.S. population (34).

DME is the most common cause of visual deterioration in patients affected by diabetes (35). Chronic hyperglycemia is the major risk factor of DME. There are now increasing data on the epidemiology of DME, with studies suggesting DME may affect up to 7% of people with diabetes (36). Approximately half of patients with DME will lose two or more lines of visual acuity within 2 years (37). In our study, we found that an elevated MBL level was as an independent DME indictor, suggesting a possible role of MBL in the pathogenesis of MDE in diabetes.

Despite extensive research, the exact pathogenesis of DR is still unknown. Whether higher serum MBL level is a cause of or merely a marker for DR in diabetes remains uncertain. Firstly, MBL is a slower reacting and much weaker acute-phase reactant than CRP (38), but it is possible that the differences in MBL concentrations between patients with and without DR may reflect differences in inflammatory activity. However, the differences in MBL levels between the groups remained statistically significant after correction for differences in hs-CRP, which indicates that CRP and MBL may carry different types of information as markers of inflammation.

Secondly, MBL may aggravate local and systemic inflammation through complement activation (39) and modulation of proinflammatory cytokine production (40). We can speculate that high levels of MBL and subsequent complement activation will result in a net proinflammatory state, potentiating allograft damage and leading downstream to chronic allograft dysfunction. That high levels of MBL in patients with diabetes may contribute to the development of DR through aggravated complement activation could thus be hypothesized.

Thirdly, oxidative stress leading to changes in cell surface glycosylations may activate the complement system via MBL (39), and MBL binding to fructoselysine and the ensuing complement activation may provide a physiopathological link between enhanced glycation and complement activation in diabetes (41).

A number of issues have to be taken into account when interpreting the results of the current study: Firstly, the relatively small sample size may limit the generalization of the results of this study. Before broad implementation, additional studies (multicenter, large sample) are needed for external validation.

Secondly, without serial measurement of the circulating MBL, this study yielded no data regarding when and how long MBL was elevated in these patients. In addition, whether serial MBL testing further improves the risk stratification of these patients should be investigated.

Thirdly, this was only a preliminary study; further studies should investigate whether MBL can help physicians tailor therapy in view of the relative risk and allocate resources accordingly and whether this strategy might affect DR outcome.

Fourthly, the limited views of the fundus obtained through a nondilated pupil may underestimate the extent of retinopathy and increase the chance of misdiagnosis, despite the increasingly improved capability of modern digital camera systems in capturing the required images. Standard seven-field fundus photography through a dilated pupil should be used in future study.

Lastly, MBL genotypes were not determined. Those results should be useful to explain the differences in MBL concentration between studies.

The current study demonstrated that MBL appears to be an independent biomarker for DR in the Chinese population, suggesting a possible role of MBL in the pathogenesis of DR complications in diabetes. We suggest that further studies should be done with respect to what causes the increased MBL levels and the role of MBL in the pathology of the DR. If it is possible to elucidate this, more intensive efforts could be directed toward the cause and thus, hopefully, improvements in the prognosis of these patients.

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