Relationship between transforming growth factor-β1 and type 2 diabetic nephropathy risk in Chinese population

Tianbiao Zhou1*, Hong-Yan Li2*, Hongzhen Zhong1* and Zhiqing Zhong1

Abstract

Background: Diabetes mellitus (DM) is divided into four different etiological categories: type 1 DM (T1DM), type 2 DM (T2DM), other specific types, and gestational DM. One severe complication of T2DM is type 2 diabetic nephropathy (T2DN). The possible association of serum transforming growth factor-β1 (TGF-β1) levels and the TGF-β1 T869C gene polymorphism with patient susceptibility to T2DN in Chinese population is unclear at present. This study was conducted to assess these relationships in Chinese population by a meta-analysis.

Methods: Association reports were searched and pulled from the Cochrane Library, the China Biological Medicine Database (CBM), and PubMed on March 1, 2018, and eligible studies were selected and used for calculations. The results were expressed as weighted mean differences (MD) for continuous data. Odds ratios (OR) were used to express the results for dichotomous data. Additionally, 95% confidence intervals (CI) were calculated.

Results: Forty-eight reports for the relationship between serum TGF-β1 levels and the risk of T2DN and 13 studies on the association of the TGF-β1 T869C gene polymorphism with susceptibility to T2DN in Chinese population were retrieved from this study. Serum TGF-β1 levels in the T2DM group were higher than those in the normal control group (MD = 17.30, 95% CI: 12.69–21.92, P < 0.00001). The serum TGF-β1 level in the T2DN group was significantly higher than that in the normal control group (MD = 70.03, 95% CI: 60.81–79.26, P < 0.00001). The serum TGF-β1 level in the T2DN group was significantly higher than that in the T2DM group (MD = 56.18, 95% CI: 46.96–65.39, P < 0.00001). Serum TGF-β1 levels in T2DM patients with microalbuminuria were increased when compared with those in T2DM patients with normoalbuminuria. Furthermore, serum TGF-β1 levels in T2DM patients with macroalbuminuria were increased when compared with those in T2DM patients with microalbuminuria. The TGF-β1 T allele, TT allele and CC genotype were associated with T2DN susceptibility in Chinese population (T: OR = 0.74, 95% CI: 0.59–0.92, P = 0.007; TT: OR = 0.55, 95% CI: 0.31–0.96, P = 0.04; CC: OR = 1.38, 95% CI: 1.14–1.67, P = 0.001).

Conclusions: High levels of TGF-β1 are associated with susceptibility to T2DM, T2DN and the progression of proteinuria in T2DN patients in Chinese population. Further, the TGF-β1 T allele, and TT genotype were protective factors against the onset of T2DN and CC genotype was a risk factor for the susceptibility of T2DN in Chinese populations.

Keywords: Type 2 diabetic nephropathy (T2DN), Diabetes mellitus (DM), Transforming growth factor-β1, T869C, Gene polymorphism, Meta-analysis

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Background
Transforming growth factor beta1 (TGF-β1) is one of the pro-fibrotic cytokines and is thought to be the primary mediator driving the progression of fibrosis, glomerulosclerosis and especially mesangial cell phenotype transformation in diabetic nephropathy (DN) [1, 2]. TGF-β1 directly stimulates the transcription of extracellular matrix (ECM). Increased TGF-β1 is reported to be associated with DN disease [3–5]. Gene polymorphisms of TGF-β1 can affect the activity of TGF-β1. The TGF-β1 T869C gene polymorphism is one of the most important gene polymorphisms that affects the protein expression of TGF-β1 [6]. Gene polymorphisms have been reported to be associated with some diseases [7–9]. However, there are conflicting reports on the association of the TGF-β1 T869C polymorphism with T2DN susceptibility [10–13].

Diabetes mellitus (DM), characterized by elevated levels of blood glucose, is a complex and heterogeneous, chronic metabolic disease [14]. DM is the leading cause of morbidity and mortality worldwide and is a major global health problem [15, 16]. DM is divided into four different etiological categories: type 1 DM (T1DM), type 2 DM (T2DM), other specific types, and gestational DM. The main characteristic of T2DM is insulin resistance, often followed by the failure of pancreatic β-cells. Recent data indicate that morbidity and mortality among diabetic patients are increased [14]. One severe complication of T2DM is type 2 diabetic nephropathy (T2DN), which is characterized by hypertension, albuminuria, and a progressive decline in glomerular filtration rate, developing into end-stage renal disease [17, 18]. There is increasing evidence showing that TGF-β1 takes part in the pathogenesis of T2DN [19–21].

In this study, we assessed the association between TGF-β1 levels and T2DN risk, and the association of the TGF-β1 T869C gene polymorphism with the susceptibility to T2DN in Chinese population, by a meta-analysis method.

Methods
Search strategy
The electronic databases of the Cochrane Library, the China Biological Medicine Database (CBM), and PubMed were searched on March 1, 2018, and relevant studies were retrieved. The retrieval strategy of the electronic database was "transforming growth factor-β1 OR TGF-β1" AND (diabetic nephropathy OR diabetic kidney disease)" was entered and searched in these databases. Additional investigations were extracted from the references cited in articles retrieved in this search.

Inclusion and exclusion criteria
Inclusion criteria
(1) Each study had at least two comparison groups (case group vs. control group); (2) The outcome in patients had to be T2DN; (3) Each study should show data on the TGF-β1 level and/or the TGF-β1 T869C genotype distribution.

Exclusion criteria
(1) Editorials, review articles, case reports; (2) Study results not showing the TGF-β1 level or the TGF-β1 T869C gene polymorphism to disease; (3) Multiple publications from the same study group; (4) Study not conducted in Chinese population.

Data extraction and synthesis
The information was extracted from each eligible report by two authors independently: the surname of the first author, the publication year, the country of the study or ethnicity, the TGF-β1 levels, the number of patients or controls, and the number of subjects in case groups and control groups for TGF-β1 genotypes.

Statistical analysis
Cochrane Review Manager Version 5 software (Cochrane Library, UK) was used to calculate the available data from each investigation. The fixed effects model was used to calculate the pooled statistic. However, a random effects model was used to assess the relationship when the P value of the heterogeneity test was less than 0.1. The results were expressed as weighted mean differences (MD) for continuous data, and odds ratios (OR) were used to express the results for dichotomous data. Additionally, 95% confidence intervals (CI) were also counted. P < 0.05 was required for statistical significance for the pooled OR. I² was used to test the heterogeneity among the included investigations. The Egger regression asymmetry test [22] and the Begg adjusted-rank correlation test [23] were used to test the publication bias, and P < 0.10 was considered significant.

Results
Study characteristics
Forty-five reports [24–68] were included for the meta-analysis of the relationship between TGF-β1 level and T2DN risk in Chinese population (Table 1). One report [67] was published in English and other reports were published in Chinese.

Eight studies [12, 32, 69–74] reporting the association of the TGF-β1 T869C gene polymorphism with susceptibility to T2DN were included in this study. Two report [69, 74] were published using the English language and the other reports were published using Chinese. The data for the pooled OR were extracted (Table 2). Those 8 investigations contained 1018 patients with T2DN and 941 controls. The average distribution frequency of the TGF-β1 T allele in the T2DN group in Chinese patients was 38.15% and the average frequency in the control group was 44.72%. The average distribution frequency of the TGF-β1 T allele in the case group was lower than that in the control group in Chinese population (Case/Control = 0.85).
Table 1: General characteristics of the included studies for TGF-β1 levels in T2DN in this meta-analysis

| First author, year | Country | According to | Case | Control |
|--------------------|---------|--------------|------|---------|
|                     |         | UAER or UACR | Mean  | SD  | N  | Mean  | SD  | N  |
| Ju HB 2000          | China   | Normoalbuminuria | 35.02 | 6.7 | 14 | 23.95 | 8.01 | 15 |
|                     |         | Microalbuminuria | 39.31 | 5.35 | 18 | 23.95 | 8.01 | 15 |
|                     |         | Macroalbuminuria | 58.58 | 9.56 | 13 | 23.95 | 8.01 | 15 |
| Wang YJ 2002        | China   | Normoalbuminuria | 147.03 | 22.57 | 34 | 136.97 | 37.96 | 35 |
|                     |         | Macroalbuminuria | 170.65 | 18.74 | 31 | 136.97 | 37.96 | 35 |
| Li WM 2004          | China   | Normoalbuminuria | 58.91 | 11.03 | 46 | 47.25 | 6.22 | 48 |
|                     |         | Microalbuminuria | 387.45 | 82.06 | 48 | 47.25 | 6.22 | 48 |
| Li ZJ 2004          | China   | Normoalbuminuria | 146.0 | 22.0 | 36 | 131.0 | 36.0 | 40 |
|                     |         | Macroalbuminuria | 172.0 | 19.0 | 44 | 131.0 | 36.0 | 40 |
| Jiang ZL 2005       | China   | Normoalbuminuria | 428.3 | 43.7 | 29 | 412.5 | 58.4 | 35 |
|                     |         | Microalbuminuria | 578.5 | 69.4 | 27 | 412.5 | 58.4 | 35 |
|                     |         | Macroalbuminuria | 683.4 | 84.3 | 28 | 412.5 | 58.4 | 35 |
| Li ZZ 2005          | China   | Normoalbuminuria | 41.5 | 15.57 | 27 | 10.04 | 5.33 | 18 |
|                     |         | Microalbuminuria | 66.35 | 18.04 | 12 | 10.04 | 5.33 | 18 |
|                     |         | Macroalbuminuria | 53.31 | 15.64 | 18 | 10.04 | 5.33 | 18 |
| Zhou Y 2005         | China   | Normoalbuminuria | 31.12 | 12.39 | 30 | 29.4 | 10.62 | 30 |
|                     |         | Microalbuminuria | 79.63 | 15.96 | 30 | 29.4 | 10.62 | 30 |
|                     |         | Macroalbuminuria | 136.6 | 21.45 | 30 | 29.4 | 10.62 | 30 |
| Jing CY 2005        | China   | Normoalbuminuria | 31.16 | 14.23 | 31 | 24.58 | 12.61 | 20 |
|                     |         | Microalbuminuria | 48.2 | 18.3 | 25 | 24.58 | 12.61 | 20 |
|                     |         | Macroalbuminuria | 62.12 | 21.3 | 23 | 24.58 | 12.61 | 20 |
| Wei YS 2005         | China   | NR | 41.57 | 10.55 | 91 | 25.46 | 7.88 | 105 |
| Li HP 2006          | China   | Normoalbuminuria | 147.02 | 20.57 | 108 | 131.96 | 3.84 | 120 |
|                     |         | Macroalbuminuria | 170.64 | 17.72 | 132 | 131.96 | 3.84 | 120 |
| Tao SP 2006         | China   | Normoalbuminuria | 147.0 | 23.0 | 28 | 132.0 | 36.0 | 25 |
|                     |         | Macroalbuminuria | 172.0 | 18.0 | 34 | 132.0 | 36.0 | 25 |
| Meng T 2006         | China   | Normoalbuminuria | 217.7 | 12.6 | 28 | 84.5 | 23.4 | 30 |
|                     |         | Microalbuminuria | 288.2 | 109.4 | 24 | 84.5 | 23.4 | 30 |
|                     |         | Macroalbuminuria | 345.5 | 118.2 | 22 | 84.5 | 23.4 | 30 |
| Xie HF 2006         | China   | Normoalbuminuria | 42.1 | 9.3 | 60 | 35.9 | 8.1 | 30 |
|                     |         | Macroalbuminuria | 61.8 | 11.2 | 45 | 35.9 | 8.1 | 30 |
| Qian YX 2006        | China   | Normoalbuminuria | 146.0 | 22.0 | 48 | 131.0 | 36.0 | 60 |
|                     |         | Macroalbuminuria | 172.0 | 19.0 | 23 | 131.0 | 36.0 | 60 |
| Fu CX 2007          | China   | Normoalbuminuria | 36.2 | 8.8 | 34 | 34.4 | 8.2 | 35 |
|                     |         | Microalbuminuria | 69.4 | 12.8 | 31 | 34.4 | 8.2 | 35 |
| Du JW 2007          | China   | Normoalbuminuria | 179.16 | 13.13 | 20 | 68.47 | 31.75 | 19 |
|                     |         | Microalbuminuria | 192.66 | 57.25 | 21 | 68.47 | 31.75 | 19 |
|                     |         | Macroalbuminuria | 582.04 | 211.25 | 20 | 68.47 | 31.75 | 19 |
| Zhang WJ 2007       | China   | Normoalbuminuria | 23.35 | 3.7 | 36 | 20.35 | 3.7 | 40 |
|                     |         | Microalbuminuria | 41.31 | 4.3 | 45 | 20.35 | 3.7 | 40 |
|                     |         | Macroalbuminuria | 55.28 | 6.8 | 45 | 20.35 | 3.7 | 40 |
| First author, year | Country | According to | Case | Control |
|-------------------|---------|--------------|------|---------|
| Lai X 2007        | China   | Normoalbuminuria | 89.65, 28.33, 27 | 31.46, 9.07, 43 |
|                   |         | Microalbuminuria  | 121.02, 32.36, 21 | 31.46, 9.07, 43 |
|                   |         | Macroalbuminuria  | 211.69, 69.83, 17 | 31.46, 9.07, 43 |
| Lin YH 2007       | China   | Normoalbuminuria  | 97.24, 18.6, 19 | 58.36, 13.72, 23 |
|                   |         | Macroalbuminuria  | 136.75, 23.48, 24 | 58.36, 13.72, 23 |
| Zhang SF 2007     | China   | Microalbuminuria | 21.188, 20.87, 15 | 6.99, 18.57, 18 |
|                   |         | Macroalbuminuria  | 13.64, 19.44, 16 | 6.99, 18.57, 18 |
| Zhang WK 2008     | China   | Normoalbuminuria  | 23.3, 10.1, 30 | 20.3, 3.7, 26 |
|                   |         | Microalbuminuria  | 41.3, 4.2, 38 | 20.3, 3.7, 26 |
|                   |         | Macroalbuminuria  | 88.2, 6.8, 32 | 20.3, 3.7, 26 |
| Wang YP 2008      | China   | Normoalbuminuria  | 35.4, 7.1, 44 | 32.5, 6.8, 35 |
|                   |         | Macroalbuminuria  | 68.2, 12.5, 32 | 32.5, 6.8, 35 |
| Zhang SB 2008     | China   | NR             | 121.5, 37.2, 36 | 55.2, 16.8, 30 |
| Li QX 2008        | China   | Normoalbuminuria  | 31.9, 9.72, 26 | 21.5, 6.89, 20 |
|                   |         | Microalbuminuria  | 49.6, 14.78, 23 | 21.5, 6.89, 20 |
|                   |         | Macroalbuminuria  | 70.3, 26.48, 18 | 21.5, 6.89, 20 |
| Feng SJ 2008      | China   | Normoalbuminuria  | 208.2, 110, 25 | 80.62, 3.4, 38 |
|                   |         | Microalbuminuria  | 293.3, 118.5, 23 | 80.62, 3.4, 38 |
|                   |         | Macroalbuminuria  | 263.5, 108.2, 18 | 80.62, 3.4, 38 |
| Zhang HM 2008     | China   | Normoalbuminuria  | 32.52, 12.24, 40 |  |
|                   |         | Microalbuminuria  | 43.61, 20.37, 48 |  |
| Cao B 2009        | China   | Normoalbuminuria  | 31.2, 5.6, 31 | 17.4, 3.4, 30 |
|                   |         | Microalbuminuria  | 54.9, 7.8, 34 | 17.4, 3.4, 30 |
|                   |         | Macroalbuminuria  | 78.2, 10.3, 30 | 17.4, 3.4, 30 |
| Li QX 2009        | China   | Normoalbuminuria  | 31.9, 9.72, 26 | 21.5, 6.89, 20 |
|                   |         | Microalbuminuria  | 49.6, 14.78, 23 | 21.5, 6.89, 20 |
|                   |         | Macroalbuminuria  | 70.3, 26.48, 18 | 21.5, 6.89, 20 |
| Yang YZ 2010      | China   | Normoalbuminuria  | 28.59, 3.64, 25 | 21.07, 3.48, 30 |
|                   |         | Macroalbuminuria  | 43.12, 4.62, 25 | 21.07, 3.48, 30 |
| Feng LM 2010      | China   | Normoalbuminuria  | 34.2, 7.1, 40 | 32.8, 6.4, 35 |
|                   |         | Microalbuminuria  | 69.4, 12.4, 32 | 32.8, 6.4, 35 |
| Wu YJ 2010        | China   | NG             | 172.5, 20.4, 30 | 125.4, 14.6, 28 |
| Ye CF 2010        | China   | Normoalbuminuria  | 31.36, 5.75, 37 | 26.54, 5.78, 32 |
|                   |         | Macroalbuminuria  | 58.69, 9.87, 37 | 26.54, 5.78, 32 |
| Huang JW 2010     | China   | Normoalbuminuria  | 41.85, 10.38, 29 | 22.5, 5.75, 30 |
|                   |         | Microalbuminuria  | 79.51, 44.95, 32 | 22.5, 5.75, 30 |
|                   |         | Macroalbuminuria  | 118.15, 59.38, 28 | 22.5, 5.75, 30 |
| Chen D 2011       | China   | Normoalbuminuria  | 129.16, 27.08, 30 | 83.32, 30.55, 60 |
|                   |         | Microalbuminuria  | 162.97, 98.58, 30 | 83.32, 30.55, 60 |
|                   |         | Macroalbuminuria  | 563.46, 122.67, 30 | 83.32, 30.55, 60 |
| Li QX 2011        | China   | Normoalbuminuria  | 31.9, 9.72, 26 | 21.5, 6.89, 20 |
|                   |         | Microalbuminuria  | 49.6, 14.78, 23 | 21.5, 6.89, 20 |
|                   |         | Macroalbuminuria  | 70.3, 26.48, 18 | 21.5, 6.89, 20 |
Association of the TGF-β1 level with T2DN risk

In this study, we found that the serum TGF-β1 level in the T2DM group was higher than in the normal control group (MD = 17.30, 95% CI: 12.69–21.92, P < 0.00001; Table 3 and Fig. 1). The serum TGF-β1 level in the T2DN group was higher than that in the normal control group (MD = 70.03, 95% CI: 60.81–79.26, P < 0.00001; Table 3 and Fig. 2). The serum TGF-β1 level in the T2DM group was higher than in the T2DN group (MD = 56.18, 95% CI: 46.96–65.39, P < 0.00001; Table 3 and Fig. 3). The serum TGF-β1 level in T2DM patients with microalbuminuria was increased compared to that in T2DM patients with normoalbuminuria (MD = 22.78, 95% CI: 16.88–28.68, P < 0.00001; Table 3). Furthermore, the serum TGF-β1 level in T2DM patients with macroalbuminuria was increased compared to that in T2DM patients with microalbuminuria (MD = 28.47, 95% CI: 21.28–35.66, P < 0.00001; Table 3).

Table 1 General characteristics of the included studies for TGF-β1 levels in T2DN in this meta-analysis (Continued)

Table 2 General characteristics of the included studies on TGF-β1 T869C gene polymorphism with T2DN risk in Chinese population

Association between the TGF-β1 T869C gene polymorphism and T2DN susceptibility in Chinese population

In this meta-analysis, the TGF-β1 T allele, TT allele and CC genotype were associated with T2DN susceptibility in Chinese population (T: OR = 0.74, 95% CI: 0.59–0.92, P = 0.007; TT: OR = 0.55, 95% CI: 0.31–0.96, P = 0.04; CC: OR = 1.38, 95% CI: 1.14–1.67, P = 0.001; Fig. 4 and Table 4).
Evaluation of publication bias

There were publication biases for DM vs. control (Egger $P = 0.001$, Begg $P = 0$; Fig. 5a), DN vs. control (Egger $P = 0$, Begg $P = 0$; Fig. 5b), DN vs. DM (Egger $P = 0$, Begg $P = 0$; Fig. 5c), microalbuminuria vs. normoalbuminuria (Egger $P = 0.021$, Begg $P = 0$; Fig. 5d), macroalbuminuria vs. microalbuminuria in Chinese population (Egger $P = 0.051$, Begg $P = 0.042$; Fig. 5e). Interestingly, there was no publication bias for the association of the TGF-β1 T869C gene polymorphism with T2DN susceptibility in Chinese population (Egger $P = 0.627$, Begg $P = 1.000$; Fig. 5f).

Discussion

TGF-β1 can stimulate the transcription of extracellular matrix (ECM) proteins, and high levels of TGF-β1 are associated with ECM accumulation, fibrosis, and
glomerulosclerosis. Glomerulosclerosis is one of most important characteristics of patients with T2DN. In this study, we performed the meta-analysis in Chinese population and found that serum levels of TGF-\(\beta_1\) in the T2DM group were higher than those in the normal control group. The serum TGF-\(\beta_1\) level in the T2DN group was higher than that in the normal control group or the T2DM group. Indeed, the levels of TGF-\(\beta_1\) in the T2DM group and the T2DN group were higher than those in the normal control group. The level of TGF-\(\beta_1\) in T2DN was higher than that in the other two groups. We also performed a subgroup analysis according to albuminuria levels. The serum TGF-\(\beta_1\) level in T2DM patients with microalbuminuria was increased over that in T2DM patients with normoalbuminuria, and the serum TGF-\(\beta_1\) level in T2DM patients with macroalbuminuria was increased over that in T2DM patients with microalbuminuria. This indicated that the more urine protein is, the more severe the kidney disease becomes.

Qiao et al. [75] conducted a meta-analysis based on 26 studies with 1968 cases and 2100 controls to evaluate the association between the levels of serum TGF-\(\beta_1\), and urinary TGF-\(\beta_1\) in patients with DM or diabetic nephropathy (DN). They reported that the levels of serum and urinary TGF-\(\beta_1\) were significantly increased in T2DM and T2DN. Mou et al. [76] assessed 9 reports that included 264 patients and 227
healthy controls in a meta-analysis to study the relationship between serum TGF-β1 levels and the risk of diabetic nephropathy. Their study indicated that increased serum TGF-β1 levels in DM patients were associated with a high risk of renal involvement. The results from Qiao et al. and Mou et al. indicated that serum and urinary TGF-β1 were significantly increased in DM and DN. Our meta-analysis included 45 reports to study the relationship between TGF-β1 level and T2DN risk in Chinese population. Our study concludes that high levels of TGF-β1 are associated with the susceptibility to T2DM, T2DN, and the progression of proteinuria in T2DN patients in Chinese population.

The association of the TGF-β1 T869C gene polymorphism with the risk of T2DN in Chinese population was also assessed. In this meta-analysis, we found that TGF-β1 T allele, and TT genotype were protective factors against the onset of T2DN in Chinese population and CC genotype was a risk factor for the susceptibility of T2DN in Chinese populations. There was no publication bias for this meta-analysis. The results might be robust to some extent. However, there were only eight studies included into for this meta-analysis in Chinese population and more number of studies should be conducted to confirm the validity of these conclusions in the future.

In a previous study, Jia et al. [77] conducted a meta-analysis to evaluate the impact of the TGF-β1 T869C gene polymorphism on DN, and reported that the TGF-β1 T869C gene polymorphism was associated with an elevated risk of DN disease. However, this notable association was observed only in T2DM patients. Zhou et al. [78] conducted a meta-analysis and indicated that the TGF-β1 CC genotype was associated with T2DN risk, and that the TGF-β1 T allele and the CC genotype were associated with the susceptibility to T2DN. In this meta-analysis, we firstly conducted the meta-analysis in Chinese population and observed that
**Fig. 4** Association of TGF-β1 T869C CC genotype with DN susceptibility

| Genetic contrasts | Studies number | Q test P value | Model selected | OR (95% CI) | P     |
|-------------------|----------------|---------------|----------------|-------------|-------|
| CC vs. CT + TT    | 8              | 0.74          | Fixed          | 1.38 (1.14, 1.67) | 0.001 |
| TT vs. CT + CC    | 8              | <0.00001      | Random         | 0.55 (0.31, 0.96) | 0.04  |
| T vs. C           | 8              | 0.01          | Random         | 0.74 (0.59, 0.92) | 0.007 |
the TGF-β1 T allele, TT genotype and CC genotype are associated with the susceptibility to T2DN in Chinese population. However, more studies are also needed to confirm this in the future.

The conclusions of our meta-analysis are limited because of the nature of the studies we analyzed. The studies themselves had several limitations, such as publication bias (most of the included studies from Chinese populations), heterogeneity of enrolled cases, small sample sizes, varying levels of plasma protein in different studies and different samples, and different timelines. In this meta-analysis, we conducted a subgroup analysis to delete any study with small sample size (less than 100), and we found that in the meta-analysis of only the larger sample studies, the CC genotype was

Fig. 5 Publication bias. a DM vs. control. b DN vs. control. c DN vs. DM. d microalbuminuria vs. normoalbuminuria. e macroalbuminuria vs. microalbuminuria. f the association of the TGF-β1 T869C gene polymorphism with T2DN susceptibility in Chinese population.
associated with T2DN susceptibility (data not shown). However, the TGF-β1 T869C gene polymorphism was not associated with T2DN susceptibility in the meta-analysis that included small sample size studies (data not shown). In this study, we also found that there were publication biases among the recruited investigations for the relationship between serum TGF-β1 levels and the risk of T2DN, and for the relationship between the TGF-β1 T869C gene polymorphism and the risk of T2DN.

Conclusions
In conclusion, this study indicated that the serum TGF-β1 level in T2DM patients with microalbuminuria was significantly increased over that in T2DM patients with normoalbuminuria in Chinese population. The serum TGF-β1 level in T2DM patients with microalbuminuria was significantly increased over that in T2DM patients with microalbuminuria in Chinese population. Furthermore, the TGF-β1 T allele, TT genotype and CC genotype are associated with the susceptibility to T2DN in Chinese population. However, more association studies are required to confirm the relationships.

Abbreviations
DM: Diabetes mellitus; DN: diabetic nephropathy; ECM: extracellular matrix; T2DN: type 2 diabetic nephropathy; TGF-β1: transforming growth factor-β1

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
TBZ was in charge of conceiving and designing the study. HYL and HZZ were responsible for the collection of data and performing the statistical analysis and manuscript preparation. HZZ and ZQZ were responsible for checking the data. All authors were responsible for drafting the manuscript, analysis and manuscript preparation. HZZ and ZQZ were responsible for the collection of data and performing the statistical analysis studies are required to confirm the relationships.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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