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Serum TNF-α concentrations in type 2 diabetes mellitus patients and diabetic nephropathy patients: A systematic review and meta-analysis

Yin-ling Chen[a,c,1], Yong-chao Qiao[b,1], Yan Xu[b], Wei Ling[a], Yan-hong Pan[a,c], Yong-cheng Huang[a], Li-jun Geng[a,c], Hai-lu Zhao[a,b,c], Xiao-xi Zhang[a,c,*]

[a] Center of Diabetic Systems Medicine, Guangxi Key Laboratory of Excellence, Guilin Medical University, Guilin 541004, China
[b] Department of Immunology, Xiangya School of Medicine, Central South University, Changsha, Hunan, 410078, China
[c] Department of Immunology, Faculty of Basic Medicine, Guilin Medical University, Guilin 541004, China

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ABSTRACT

Objectives: The aim of this study was to investigate whether the concentrations of serum tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine, increased in type 2 diabetes mellitus (T2DM) and type 2 diabetic nephropathy (T2DN) patients.
Methods: The four databases (PubMed, CNKI, WanFang and Chinese-Cqvip) were searched from Jan 1, 1999 to October 1, 2016 for all clinical case-control studies about the serum TNF-α concentrations in T2DM and T2DN patients. All relevant data were extracted from published reports. The meta-analysis was performed to compare the changes of serum TNF-α concentrations of T2DN and T2DM patients in Eastern and Western with healthy controls. We further evaluated concentrations of serum TNF-α in T2DN patients with mincroalbuminuria or macroalbuminuria. Random-effects models were adopted to assess the pooling data among various variations.
Results: In total of 6 studies (744 patients and 277 healthy controls) were included in this study. Compared with healthy controls (both $p < 0.01$), the groups of different albuminuria levels and ethnicities both showed that the serum TNF-α levels were significantly elevated in T2DN patients as well as in eastern T2DN patients ($p = 0.001$), but not significant changed in western T2DN patients ($p = 0.081$). The results were stable through sensitivity analysis and no significant publications bias existed in this meta-analysis.
Conclusions: Serum TNF-α concentrations are obviously increased in T2DN and T2DM patients, but higher in T2DN patients, suggesting an elevated inflammatory burden in T2DN patients.

1. Introduction

A variety of complications will emerge in patients with type 2 diabetes mellitus (T2DM), especially including diabetic nephropathy (DN) [1]. DN is classified as a microvascular complication of diabetes, which is a principal factor of diabetes-related death [2]. Main form of DN is proteinuria, and epidemiological investigations have reported that 39% diabetes patients around the world are subjected to micro-albuminuria [3]. In the past decade, the incidence of DN had increased by 150 percents in the United States, a trend also seen in Europe [4], which seriously influenced the life quality of patients and imposed a huge economic pressure on the national health care system [5]. Gene and environment are risk factors for the occurrence and development of DN [6,7]. It is considered that the pathogenesis of DN is primarily based on cytokines that form an intricate network [8,9].

Tumor necrosis factor-α (TNF-α) is a cell signaling protein related to systemic inflammation, and as one of the cytokines which institutes the acute phase reaction. The primary role of TNF-α is in regulation of immune cells. TNF-α could accelerate the release and synthesis of inflammatory cytokines, and participate in the progression of DN [10,11]. Though many studies have explored the relationship about the serum concentrations of TNF-α in T2DM and DN patients, no consistent idea is reached [12–14]. Herein, we conduct this meta-analysis to evaluate the change of the serum TNF-α level and hope to provide some evidences for exploring the pathogenic mechanism of this disease in the future.

Abbreviations: TNF-α, tumor necrosis factor-α; T2DM, type 2 diabetes mellitus; T2DN, type 2 diabetic nephropathy

* Corresponding author at: Center of Diabetic Systems Medicine, Guangxi Key Laboratory of Excellence, Department of Immunology, Guilin Medical University, Huan Cheng North 2nd Road 109, Guilin, 541004, China.
E-mail address: mike_527@163.com (X.-x. Zhang).

[1] Equal contribution.

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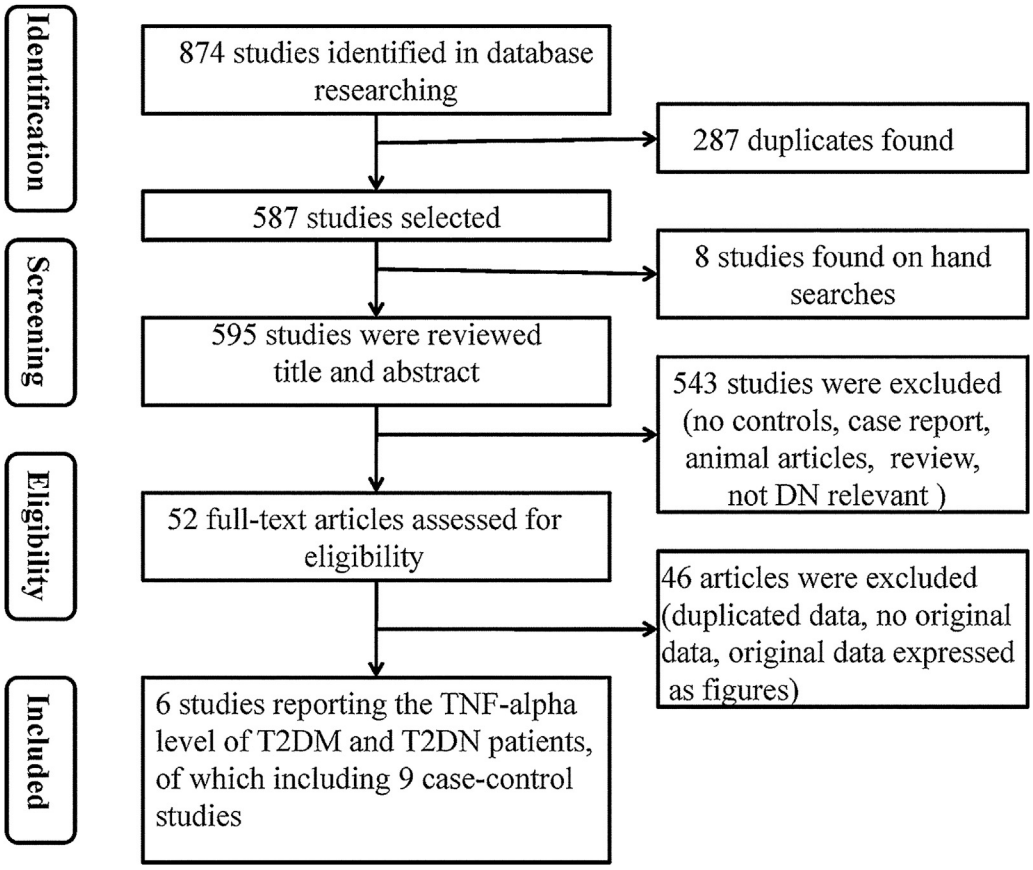

Fig. 1. The flowchart of the study selection process.

2. Methods and materials

2.1. The literature identification and search strategy

We performed this meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and PRISMA guidelines [15] and the Declaration of Helsinki [16], and this study was approved by ethics committee of Guilin Medical University. We searched CNKI, PubMed, Chinese-Cqvip and WanFang databases from Jan 1, 1999 to Oct 30, 2016, using search strategy with terms ("tumor necrosis factor" or "TNF" or "tumor necrosis factor-α" or "TNF-α") and ("diabetic nephropathy" or "DN"). Furthermore, we conducted an extensive search through the references cited in recruited articles.

2.2. Study selection

Relevant researches for determining diabetic nephropathy risk in patients with different TNF-α levels were included if the following criteria were reached in this study: (a) All case-control studies of serum TNF-α concentrations in T2DM and type 2 diabetic nephropathy (T2DN) patients; (b) at least 18 years old and accorded with the WHO diagnosis criteria in 1999; (c) All study data of serum TNF-α concentrations were expressed as or turned into Mean ± SD; (d) For duplicated reports and studies, we only included the latest research. No control group, reviews, animal studies, case reports, and comments were excluded for primary analyses. If the original data displayed as figures, we would exclude the study. Eventually, the articles were inconsistent with the inclusion criteria as described above were also excluded.

2.3. Quality assessment

All abstracts identified in primal search were screened and the studies in violation of the inclusion criteria were excluded by two researchers. Full-text articles were posteriorly reviewed by another two authors, in case of disagreement, a third investigator was invited to assess such studies and the consensus was achieved through discussion. Finally, the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of all included studies [17]. If original data was not shown, the corresponding author of the study was contacted with alone tailored application forms by email.

2.4. Data extraction

We extracted information from the finally included articles that included sample size, mean and standard deviation (SD) of serum TNF-α level in T2DM and T2DN patients. Additional data included first author's name, publication year, country of patients, sexual proportion, study design, statistical analysis, body mass index (BMI), disease duration, level of albuminuria, and the numbers of the cases and controls. Two authors independently extracted the data and searched the bibliographic.

2.5. Statistical analysis

All forest plots and statistical analysis were conducted with Stata 12.0 software (Stata-Corp, College Station, TX). We exhibited the data (sample size, Mean ± SD) to explore the change of serum TNF-α concentrations in patients versus controls, and we used the inverse variance method to verify standardized mean difference with 95% confidence interval for continuous variables. The statistical heterogeneity was estimated by Chi-squared Q test and I^2 statistics. When