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Association between homocysteine status and the risk of nephropathy in type 2 diabetes mellitus

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ABSTRACT

Background: It is well documented that hyperhomocysteinemia induces renal injury. However, the association between homocysteine level and type 2 diabetic nephropathy (T2DN) remains elusive.
Methods: We evaluated the alteration of plasma level of homocysteine in T2DN patients with macroalbuminuria or microalbuminuria compared with type 2 diabetes mellitus (T2DM) controls without albuminuria by performing a meta-analysis. We searched the PubMed, Embase and Cochrane databases from January 1990 to October 2013 to identify studies that met predefined criteria.
Results: Seven studies were included in this investigation. T2DN patients with macroalbuminuria demonstrated a significantly higher level of plasma homocysteine than T2DM without albuminuria (4 studies, random effects SMD: 1.66, 95% CI: 0.46 to 2.87, $P = 0.007$) and T2DN with microalbuminuria (3 studies, random effects SMD: 0.99, 95% CI: 0.62 to 1.36, $P < 0.001$). T2DN patients with microalbuminuria demonstrated significantly higher level of plasma homocysteine than T2DM without albuminuria (6 studies, random effects SMD: 1.29, 95%. CI: 0.59 to 2, $P < 0.001$). Exclusion of any single study had little impact on the pooled SMDs. No evidence of publication bias was observed.
Conclusions: Our findings indicate that the status of plasma homocysteine is associated with both the risk and severity of nephropathy in T2DM. Frequent monitoring and early intervention should be recommended.

1. Introduction

Diabetes mellitus (DM) is an important public health concern affecting life quality and individuals' survival [1]. Type 2 DM (T2DM) accounts for nearly 90% of all DM cases across the world [2]. Diabetic nephropathy (DN), a serious complication of T2DM, is progressive and is characterized by persistent albuminuria, arterial blood pressure elevation, and a decline in glomerular filtration rate (GFR) [3]. The susceptibility to DN varies among T2DM patients, and its etiology is multi-factorial [4]. The main risk factors for DN onset and progression are poor glycemic control and hypertension [5]. Also, interventional studies demonstrated that intensified insulin treatment and antihypertensive therapy could prevent the onset and progression of T2DN [6–8]. However, a number of T2DN cases could not entirely be prevented. It is imperative to search for potential risk factors for T2DN onset and progression.

Homocysteine, a sulfhydryl-containing amino acid, is associated with endothelial damage, smooth muscle proliferation, platelet aggregation, and enhancement of coagulation [9]. Increased concentration of homocysteine has been found in DN [10]. Although the increased status of homocysteine is believed to be secondary to the decreased renal clearance [11], in vivo studies also showed that hyperhomocysteinemia induces glomerulosclerosis and podocyte injury [12–14]. Hyperhomocysteinemia is associated with GFR as well as the albuminuria [15,16]. Hence, we hypothesized that the status of homocysteine was associated with the risk and progression of nephropathy in T2DM.

The past few decades have witnessed a number of studies testing this hypothesis. However, the results remain confusing in the literature due to the facts that thedefinition of T2DN was inconsistent across the studies and the lack of monitoring the level of homocysteine in different stages of T2DN. An improved understanding of this issue may have important implications given the possibility that the status of homocysteine may be a marker of susceptibility or severity of nephropathy in T2DM. Meta-analysis is a good way to summarize the available data to provide more robust results than the individual study.

2. Materials and methods

2.1. Search strategy

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [17], we attempted to search the published

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paper that reported the plasma concentration of homocysteine both in type 2 DN patients and type 2 DM controls without nephropathy from January 1990 to October 2013 using PubMed, Embase and Cochrane databases. No restriction was imposed on search language. The search terms used were as follows: 1) homocysteine, cysteine; 2) serum, urinary, blood, plasma; and 3) risk, concentration, level. Reference lists of retrieved articles were also reviewed. If the same participants were enrolled in more than one study, we recruited the study with the complete analysis.

2.2. Study selection

After a full-text review following a screening of titles or abstracts. Studies were considered eligible if they met the following criteria: 1) case–control, cross-sectional, prospective or cohort study; 2) case: type 2 DN with macroalbuminuria or microalbuminuria; 3) control: type 2 DM without albuminuria; and 4) outcome of interest: plasma level of homocysteine in both cases and controls.

2.3. Data extraction and quality assessment

We extracted any reported mean, median and standard deviation. We also extracted study characteristics from each study. Data were recorded as follows: first author's last name; year of publication; origin of region; characteristics of study population and age at baseline; participant number; diagnosis. We evaluated the quality of each study included using Newcastle–Ottawa Quality Assessment Scale, which included the assessment for participants selection, exposure and comparability. A study can be awarded a maximum of one score for each numbered item within the selection and exposure categories. A maximum of two scores can be given for comparability. Two authors performed the literature search independently, study selection, quality assessment and data extraction with any disagreements resolved by discussion.

2.4. Statistical analyses

Standard mean deviation (SMD) was used to measure the differences in homocysteine level between type 2 DN patients and type 2 DM controls without nephropathy across studies. Heterogeneity of SMDs across studies was tested by using the Q statistic (significance level at $p < 0.05$). The I^2 statistic, a quantitative measure of inconsistency across studies, was also calculated. The SMDs were calculated using either fixed-effects models or, in the presence of heterogeneity, random-effects models. We evaluated the influence of a single study on the pooled SMDs by omitting one study in each turn. Potential publication bias was assessed by Begg's test and Egger's test at the $P < 0.05$ level of significance. All analyses were performed using STATA ver 12.0 (Stata Corp.). A $P < 0.05$ was considered statistically significant, except where otherwise specified.

3. Results

3.1. Literature search

We initially retrieved 163 relevant publications from the PubMed, Embase and Cochrane databases. The majority of these were excluded after the first screening in terms of titles or abstracts, mainly because they were editorials/reviews /case reports or not related to DM or homocysteine. Five articles were excluded because they did not provide the data of homocysteine, 6 studies were excluded because their data was not distributed in Gaussian manner. Finally, 7 studies [5,18–23] were included in our meta-analysis. A flow chart showing the study selection is presented in Fig. 1.

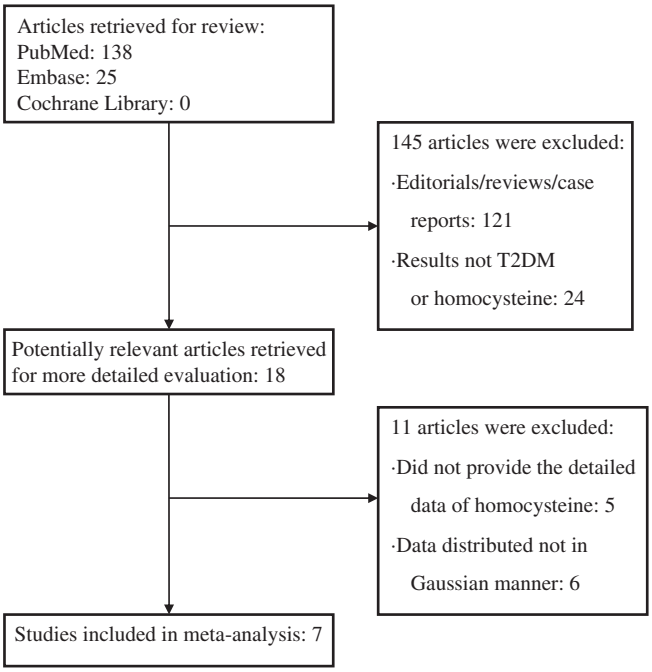

Fig. 1. Flow chart of study selection.

3.2. Study characteristics

The characteristics of the 7 enrolled studies are shown in Table 1. A total of 7 case–control studies were published between 2001 and 2010. Six studies [18–23] were conducted in the Asia, one [5] in Africa. The sizes of studies ranged from 75 to 360. The cases included were type 2 DN with macroalbuminuria or microalbuminuria. The controls were type 2 DM without albuminuria. All the studies adjusted for confounding factors.

3.3. Quality scale

The number of awarded scores of enrolled studies ranged from 4 to 6 (low quality: 1–3, median quality: 4–6, high quality: 7–9). Of the studies included, two studies [19,22] were awarded for 4 scores, 2 [18,23] for 5 scores, 3 [5,20,21] for 6 scores. As shown in Table 1.

3.4. Meta-analysis

Type 2 DN patients with macroalbuminuria demonstrated significantly higher levels of plasma homocysteine than type 2 DM without albuminuria (4 studies, random effects SMD: 1.66, 95% CI: 0.46 to 2.87, $P = 0.007$, as shown in Fig. 2). Substantial heterogeneity was observed among studies ($I^2 = 93.1\%$, $P < 0.001$). Omission of any single study did not change the overall SMDs significantly. The pooled SMDs varied from 0.87 (95% CI: 0.23–1.52) to 1.89 (95% CI: 0.08–3.71). No evidence of publication bias was noted (Begg, $p = 0.089$; Egger, $p = 0.056$). Type 2 DN patients with macroalbuminuria displayed significantly higher levels of plasma homocysteine than type 2 DN with microalbuminuria (three studies, random effects SMD: 0.99, 95% CI: 0.62 to 1.36, $P < 0.001$, as shown in Fig. 3). No marked heterogeneity was observed among studies ($I^2 < 0.1$, $P = 0.448$). Omission of any single study did not change the overall SMDs significantly. The pooled SMDs varied from 0.88 (95% CI: 0.49–1.29) to 1.09 (95% CI: 0.49–1.71). No evidence of publication bias was noted (Begg, $p = 0.296$; Egger, $p = 0.099$). Type 2 DN patients with microalbuminuria demonstrated significantly higher levels of plasma homocysteine than type 2 DM without albuminuria (six studies, random effects SMD: 1.29, 95%