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Antioxidant for treatment of diabetic nephropathy: A systematic review and meta-analysis

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ABSTRACT

Background: Diabetic nephropathy (DN) is one of the leading causes of morbidity and mortality amongst the diabetes mellitus patients. Oxidative stress played a major role in the pathogenesis of DN. Many studies reported that therapies with antioxidant potential have a beneficial effect on DN but there is conflicting evidence amongst them.

Objective: To elucidate the association between antioxidant and DN and to develop a robust evidence for clinical decisions by conducting systematic reviews and meta-analysis.

Patient and methods: A comprehensive systematic literature search was conducted in PubMed, EMBASE, Cochrane Library, CPCI-S, ICTRP, and Google Scholar till February 2017 by two independent researchers. Various outcomes were included and statistical analyses were performed using RevMan V.5.3.

Results: There were total 1461 participants identified from twelve studies, of which 882 (60.37%) were monitored on antioxidant treatment. Results indicated that antioxidant treatment was associated with significantly change in Blood Urea Nitrogen (SMD = 1.11, 95% CI: 0.38 to 1.85, p = 0.003), urinary Transforming Growth Factor-β (SMD = 2.16, 95% CI: -0.01 to 4.33; p = 0.05) and estimated Glomerular filtration Rate (SMD = 0.30, 95% CI: 0.06 to 0.55; p = 0.02) than control group. There was no association of change in urine albumin-to-creatinine ratio, serum creatinine, adverse events and rate of death with antioxidant treatment.

Conclusion: The findings of this investigation indicate that antioxidant treatment is effective clinically for DN treatment in T2DM patient. However, there is a need of high degree of caution for interpreting the outcomes of the studies with a short duration of antioxidant treatment.

1. Introduction

Diabetes mellitus (DM), as one of the most common metabolic disorder which levies considerable humanistic and economic burden to the society [55]. As per estimates from the International Diabetes Federation, the global prevalence of diabetes was 382 million and it has been predicted to reach 592 million by 2035 [24]. Moreover, it has well been documented that DM is associated with long-term vascular complications including diabetic nephropathy (DN) [55]. DN accounts for about 15% of end-stage renal disease (ESRD) and thus a leading cause of ESRD worldwide [57].

Unfortunately, the pathogenesis of DN is not yet fully understood, however, several genetic and environmental factors that can conspicuously impaired health-related quality of life (HRQoL) of patients [12]. Hyperglycemia in DM leads to the development of an array of metabolic, biochemical and hemodynamic alteration in renal tissues. These alterations includes intracellular activation of polyol pathway and protein kinase C, increased advanced glycation end products (AGEs), elevated oxidative stress via influx of reactive oxygen species (ROS), alteration in glomerular filtration rate, shear stress and mechanical stretch due to hypertension which leading to DN [64]. Moreover, it has been documented that production of Angiotensin II (Ang II) via elevated blood glucose level exerts inflammatory and profibrogenic effects on renal tissue [58]. A compelling body of evidence supports that activation of inflammatory pathways via release of pro-inflammatory cytokines (tumor necrosis factor (TNF) and interleukin 1 (IL 1)) [58], Transcription factor (nuclear factor κ of activated B cells (NF-κB)) [46], toll-like receptors 4 (TLR4) [45] responsible for development and maintenance of DN.

In spite of tremendous advances in the pharmaceutical drug industry over the past 20 years, the availability of drugs capable that reduce the rate of progression of DN is still limited [56]. Furthermore, more innovative strategies should be employed beyond glycemic and hypertensive control to prevent and treat DN [56]. Numerous scientific studies have been carried out for the treatment of DN however, several of them are disappointing [18,50].

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Novel emerging therapies, accompanied with the sophisticated mechanism of action can help reduce the incidence of DN and increase the quality of life (QoL) for patients. Reliable information on a patients' with DN including high glucose levels, microalbuminuria, estimated glomerular filtration rate (eGFR), serum creatinine level is essential in care and management of DN. Healthcare professionals use this information to determine the effectiveness of treatment and lifestyle regimens and identify adjustments needed to treat DN. In this context, a comprehensive systematic review may provide a more significant evaluation of the effects of various treatment against DN. An array of antioxidants such as Bardoxolone methyl [17,60], green tea [6,7], *Nigella sativa (N. sativa)* oil [11], pyridoxamine [21,40], Pyridoxine in combination with ascorbic acid [41], turmeric [42], D-α-tocopherol [44], vitamin C [52,53,61] and Vitamins E [52,65] have been used clinically as a treatment option for DN. However, conflicting evidence amongst these reports limits the implication of therapeutic benefit of antioxidant therapy in DN. Hence, it is necessary to evaluate the effects of antioxidant therapy on DN to provide more significant information about the clinical evidence with the help of systematic review. To our knowledge, at present, there is no comprehensive assessment of the relation between antioxidant therapy and DN. Therefore, the aim of present study was to develop a robust evidence for clinical decisions by conducting systematic reviews and meta-analysis for the association between antioxidant and DN via pooling the results from cross-sectional studies and clinical trials.

2. Methods

2.1. Data sources and selection criteria

This systematic review and meta-analysis were conducted as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [60]. The following electronic databases were searched: PubMed, EMBASE, the Cochrane Library, CPCI-S (Conference Proceedings Citation Index-Science), ICTRP (International Clinical Trials Registry Platform), and Google Scholar were searched in February 2017. Two independent reviewers (ADK and AAM) conducted an abstract review of all records. The following keywords were used in the search strategy: Diverse anti-oxidative substances, such as vitamin C, vitamin E, allopurinol, b-carotene, selenium, and methionine, acetylcysteine, *N*-acetylcysteine, NAC, diabetes mellitus, nephropathy, and diabetic nephropathies. Additional papers were found through a manual search of reference lists of review articles.

2.1.1. Inclusion criteria

The outcome of interest was the urine albumin-to-creatinine ratio (UACR) because proteinuria is considered the main manifestation of nephropathy (defined as UACR > 30 mg/g). However, all studies of type 2 diabetic patients with nephropathy that reported at least one of the following outcome measures; UACR, serum creatinine, Estimated Glomerular filtration Rate (eGFR), Blood Urea Nitrogen (BUN), Transforming Growth Factor-β (TGF-β), rates of adverse events, and rates of death were considered for inclusion and filtered by articles published in English and Humans.

2.1.2. Exclusion criteria

Studies with patients with diabetes other than Type 2, pregnant females, or patients with underlying debilitating conditions, experimental studies, mechanistic (association) studies, Letters/reviews/editorials, commentary, animal studies, in-vitro studies, Case series (sample size < 10 patients), case reports, pharmacodynamic/pharmacokinetic studies and studies with full-text published in a language other than English were excluded.

2.2. Quality assessment of the articles

The quality of each study included in the analysis was assessed using the Cochrane Risk of Bias Tool for systematic reviews of interventions (version 5.0.1) [17] and also using the Downs and Black critical appraisal tool. This validated Cochrane Risk of Bias tool consisted of the following six categories: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants; (4) incomplete outcome data; (5) selective outcome reporting; and (6) other bias. Each category was scored as high, uncertain, or low ROB. Two independent reviewers performed the quality assessment and disagreements on scores were resolved through discussion.

2.3. Data analysis

The standard mean difference (SMD) was used with 95% confidence intervals (CI) and standard deviation (SD). A meta-analysis was conducted with simultaneous use of random-effect models. All statistical analyses were performed using RevMan V.5.3 (Cochrane Collaboration, Oxford, UK) software. The meta-analysis included data from parallel-group design studies. Since the data used for the meta-analysis were continuous variables such as BUN, eGFR, serum creatinine (SCr) and Transforming Growth Factor-β (TGF-β), the standardized mean difference (SMD) and 95% CI were used for meta-analysis. Statistical analysis for dichotomized outcomes (rates of adverse events, and rates of death) was performed using odds ratio (OR) and 95% CI. Heterogeneity of the included studies was tested with the Higgins I^2 test, and meaningful heterogeneity was determined by 50% of the I^2 value. When the I^2 value was > 50, a random-effect model was used for the meta-analysis.

3. Results

3.1. Summary of included studies

As shown in Fig. 1 (PRISMA flow chart), the database searches initially yielded 2534 results. After duplicates were removed and reports screened by title, keywords and abstract, they were screened for inclusion and exclusion. After screening, 2513 of these (study design (784), not relevant disease/indication (639), review/editorial (287), copy (2), cost study (16), patient population (298) and animal/in vitro study (487)) were excluded. Further, none more studies were deemed irrelevant, based on the title or abstract, and were also excluded. Of the remaining twelve studies [6,7,11,21,40–42,44,52,53,61,65] were included for qualitative and quantitative analysis.

The primary findings from the included studies are summarized in Table 1. Participants were selected from different countries. Three studies were conducted in the United States [52,53,65], three in India [7,41,42] and each one in Brazil [11], Denmark [21], Iran [40], Iraq [6], Muti-country [44] and Republic of Mauritius [61]. Studies have used various antioxidant including bardoxolone methyl by two studies [52,53], two studies used green tea as a treatment option for diabetic nephropathy [11,61], one study used *Nigella sativa* (*N. sativa*) oil [7], pyridoxamine was used in two studies [44,65], pyridoxine or ascorbic acid by one study [6], one study used turmeric [40], D-α-tocopherol by one study [21], vitamin C in combination by three studies [21,41,42] and Vitamins E were reported by two studies [41,42].

3.2. Characteristics of the studies

3.2.1. Included studies

Table 1 shows the study characteristics. There was a total of 1461 enrolled patients, of which 882 (60.37%) patients received antioxidant treatment, whereas remaining were on placebo or conventional treatment. Ten studies were randomized controlled trials [6,11,21,40–42,44,53,61,65] out of which six were double blinded [11,21,40,44,53,65], three were open controlled [41,42,61] and one