



## Review article

# Diabetic nephropathy and endothelial dysfunction: Current and future therapies, and emerging of vascular imaging for preclinical renal-kinetic study



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## ABSTRACT

An explosion in global epidemic of type 2 diabetes mellitus poses major rise in cases with vascular endothelial dysfunction ranging from micro- (retinopathy, nephropathy and neuropathy) to macro-vascular (atherosclerosis and cardiomyopathy) conditions. Functional destruction of endothelium is regarded as an early event that lays the groundwork for the development of renal microangiopathy and subsequent clinical manifestation of nephropathic symptoms. Recent research has shed some light on the molecular mechanisms of type 2 diabetes-associated comorbidity of endothelial dysfunction and nephropathy. Stemming from currently proposed endothelium-centered therapeutic strategies for diabetic nephropathy, this review highlighted some most exploited pathways that involve the intricate coordination of vasodilators, vasoconstrictors and vaso-modulatory molecules in the pathogenesis of diabetic nephropathy. We also emphasized the emerging roles of oxidative and epigenetic modifications of microvasculature as our prospective therapeutics for diabetic renal diseases. Finally, this review in particular addressed the potential use of multispectral optoacoustic tomography in real-time, minimally-invasive vascular imaging of small experimental animals for preclinical renal-kinetic drug trials.

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## 1. Introduction

Before the construction of this review article, we conducted an electronic database search through PubMed access to the MEDLINE database on life sciences and biomedical issues (Fig. 1). This search was inspired by a drastic increase in the number of journal articles on the subject matter of type 2 diabetes (129,504) in the MEDLINE database; approximately two-third of the publications (83,071/129,504) were yielded for the recent 10 years, and more than half of them (49,934/83,071) were found for the recent 5 years by 31 May 2016. Based on our research interest, we searched through PubMed/MEDLINE on the keywords “type 2 diabetes”, “endothelial dysfunction” and “nephropathy” for the recent 5 years, and initially came up with a list of 85 full-text journal articles (Table S1), of which 45 irrelevant articles were excluded based on our contextualized interpretations of the titles and abstracts. The remaining 40 journal articles were used as the framework for constructing this review article, and only research articles (27/40) were summarized in Table S2 (including research type, subject characteristics and significant findings).

The aim of this review was to summarize some common signaling pathways of vasodilators, vasoconstrictors and vaso-modulators from currently proposed endothelium-centered therapies for diabetic nephropathy, and hence highlight some key potential cellular mechanisms for our future therapeutic development. This review also discussed the potential uses of cutting-edge optoacoustic imaging tools in the real-time monitoring of renal cortex/pelvis hemodynamics of small laboratory animals for preclinical drug trials.

## 2. Diabetes mellitus

Diabetes encompasses a spectrum of vascular complications in the micro- (eye, kidney and nerve) and the macro-vasculature (heart and brain) that are considerably responsible for the recently high morbidity and mortality. Epidemiological studies demonstrated the global incidence of diabetes had drastically increased from 108 million in 1980 to 422 million in 2014, which was shown to be obese-associated [1]. Diabetes and higher-than-optimal blood glucose also caused 3.7 million deaths in 2012, of which nearly half of them died before age of 70

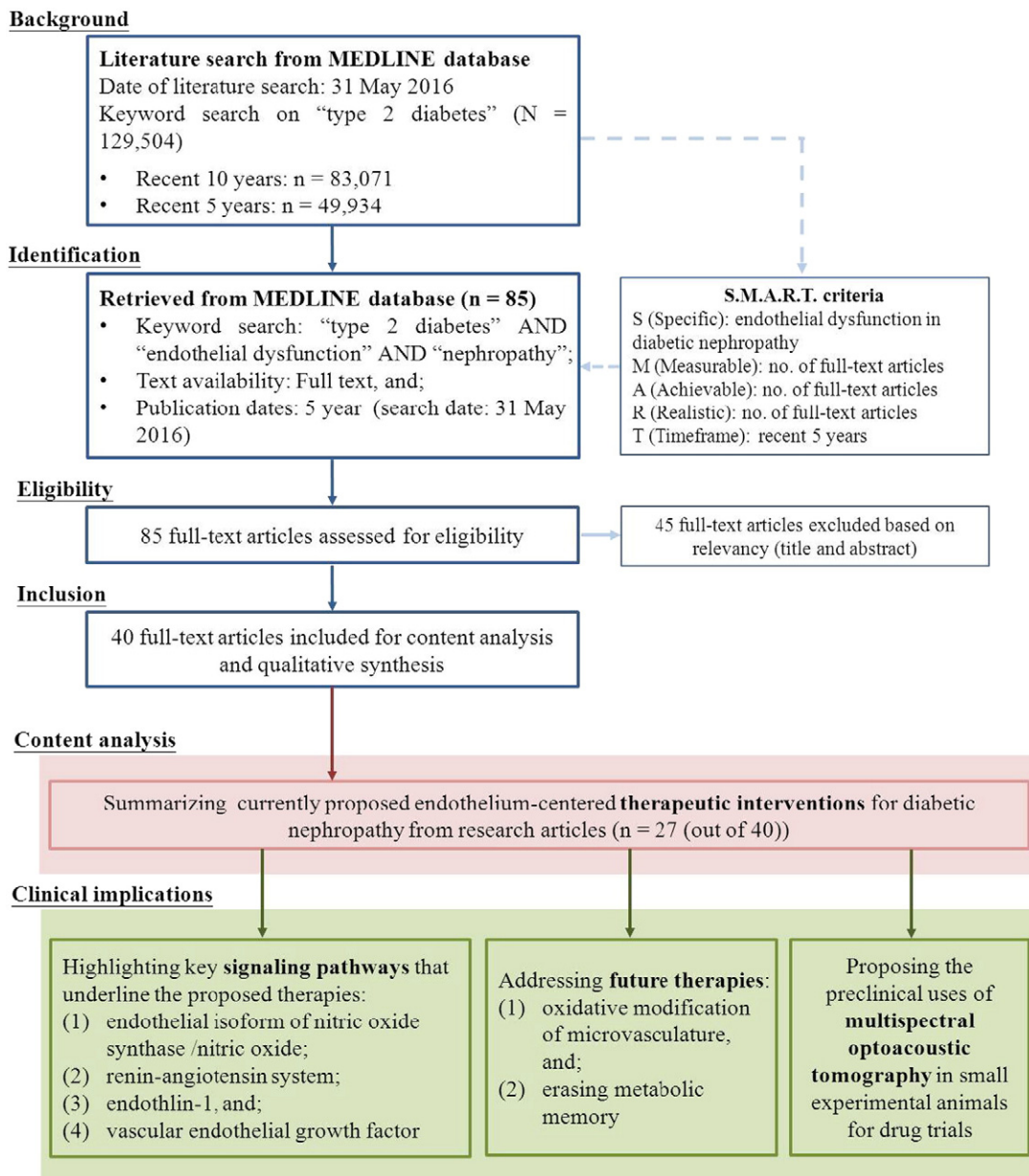


Fig. 1. Schematic workflow outlining the article selection process for the construction of this review article.

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