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Commentary

Chronic Kidney Disease and Diabetes–A Potential Causal Link

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Over the past decades, the incidence and prevalence of type 2 diabetes (T2D) have increased spectacularly throughout the world, especially in developing countries (Chen et al., 2011). T2D is associated with many complications, however, the chronic kidney disease, may be one of the most devastating complications with respect to patient survival and quality of life. The underlying mechanisms by which T2D may lead to kidney damage are unclear. The prevalence of chronic kidney disease (CKD) varies across populations with diabetes. For example, in the US, according to the data from the 1999 through 2006 National Health and Nutrition Examination Survey, in a representative sample of the civilian, noninstitutionalized US population, nearly 40% of people with diagnosed and 41.7% with undiagnosed diabetes had CKD; 17.7% with prediabetes and 10.6% without diabetes had CKD (Plantinga et al., 2010), while in a primary care setting in Finland, approximately 70% of patients with T2D have some sign of CKD and about half of all T2D patients have a significant CKD (Metsärinne et al., 2015). Clearly, diabetic kidney disease is now becoming a global public health concern.

In this issue of *EBioMedicine*, Xu et al. explored the causal association between T2D and CKD in 11,502 participants, Shanghai, China. The authors concluded that the relation between T2D and CKD may be causal (Xu et al., 2016). Observational epidemiological studies have already identified T2D as a risk factor for CKD. Why is it important to establish a causal relationship between T2D and CKD? The answer is that there is a critical distinction between a risk actor and a causal factor in the prevention of a disease: a risk factor can be identified from observational studies, while a causal factor usually has to be established in a randomized clinical trial (RCT).

Observational studies usually suffer from selection bias since randomization is not implemented. Not all findings derived from observational studies can be verified and confirmed by RCT. In one meta-analysis, up to one fourth of observational studies gave different results than randomized trials (Shikata et al., 2006). For example, observational studies have suggested both low vitamin E and selenium levels may be risk factors for prostate cancer. However, a randomized, placebo-controlled trial (Selenium and Vitamin E Cancer Prevention Trial [SELECT]) of 35,533 men not only did not show any beneficial effect of selenium or vitamin E, alone or in combination on prevention of prostate cancer in this population of relatively healthy men, but also suggested that there were marginally statistically increased risks of prostate cancer in the vitamin E group (Lippman et al., 2009).

Randomized clinical trials could be successfully used to examine whether an environmental factor is causally associated with a disease. However, if examined genetic factors, RCT approach cannot simply be utilized since it is impossible to perform randomization.

Xu et al. employed Mendelian randomization approach to conduct a "pseudo" randomized trial to examine the causal association between T2D and CKD (Xu et al., 2016). Mendelian randomization analysis has major advantages in minimizing confounding and reverse causation.

In theory, this study should be almost identical to a RCT to test efficacy of a drug, except that the randomization in the drug trial is done by investigators, while the "randomization" for studying an allele is done by the random "assignment" of genes from parents to offspring, thus, this randomization is called Mendelian randomization. In Xu et al.'s study, a genetic risk score, GRS, summing up 34 established T2D common variates in East Asia was used in this investigation (Xu et al., 2016). The GRS is a single variable summarizing multiple genetic variants associated with T2D. In Xu et al.'s study, the GRS (as an instrumental variable) was used to derive estimates of the causal effect of T2D on CKD (Davey Smith and Ebrahim, 2003).

The findings of Xu et al.'s study demonstrated for the first time that the relationship between T2D and CKD was potentially causal (Xu et al., 2016). The strengths of this well-designed and painstakingly performed investigation included a large sample size (N = 11,502), and an ethnically homogenous study population. The Mendelian randomization approach not only controlled for potential confounding factors by employing GRS as proxies, but also excludes the possibility of reverse causation (Lawlor et al., 2008).

Several limitations deserve attention. First, GRS is similar to a composite exposure in a randomized clinical trial. Despite that a genetic risk score has been used in Mendelian randomization analyses, utilization of GRS has been challenged since (1) the individual variants of the GRS may not be of similar importance to T2D, and (2) the more important variants in the GRS may be affected negatively. Furthermore, since diabetic-associated CKD may continue to progress even after blood glucose normalization, suggesting a metabolic memory of the

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prior glycemic state, epigenetic studies are necessary to clarify the mechanisms for metabolic memory (Villeneuve et al., 2011).

These limitations notwithstanding, the findings of Xu et al.'s study may have important implications for the prevention of diabetic kidney disease since a potential causal relationship between T2D and CKD has been strongly suggested by this investigation.

Conflicts of Interest

The author declared no conflicts of interest.

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