

## Diabetes Mellitus, Still Major Threat to Mortality from Various Causes

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Diabetes mellitus is one of the major metabolic disorders predisposing adverse health outcomes in the modern society. It is closely associated with the development of atherosclerotic vascular diseases as well as several microvascular complications, especially under uncontrolled hyperglycemia [1]. In addition, ongoing research has revealed that diabetes is also substantially related to the risk of non-vascular diseases, although whether diabetes is a direct cause or not is yet to be determined [2]. Even several types of cancer, infection of different organs, and Alzheimer's disease have been reported to be associated with diabetes. It is still not clearly understood whether the elevated risk of those non-vascular diseases is caused by diabetes-related factors including hyperglycemia and hyperinsulinemia, or shared conditions such as obesity and dysregulated immunity [3,4].

In this issue of the *Diabetes & Metabolism Journal*, Li et al. [5] provided important evidence about this issue with their analysis of population-based data from the National Health and Nutrition Examination Survey (1999 to 2010) in the United States. They reported that subjects with diabetes had higher risks of all-cause mortality and many types of cause-specific mortality than those without. However, after adjusting for confounders, some causes of death including cardiovascular diseases, chronic lower respiratory diseases, influenza, pneumonia, and kidney diseases remained significantly associated with diabetes, but cancer or Alzheimer's disease did not. In a subsequent analysis including prediabetes, they found that glycemic status was significantly associated with all-cause mortality and mor-

tality from cardiovascular diseases, chronic lower respiratory diseases, influenza, pneumonia, and kidney disease.

Among these findings, it should be noted that there was a negative association between diabetes and cancer mortality. In a review of previous literature, inconsistent results were observed about this association. The Verona Diabetes Study also reported that patients with type 2 diabetes mellitus did not have elevated risk of cancer mortality [6]. However, the Emerging Risk Factors Collaboration multi-national study found that mortality risk for some types of cancer including liver, pancreas, ovary, and colorectum were significantly elevated in patients with diabetes [7]. In a Korean Cancer Prevention Study, Korean men with diabetes had higher risk of mortality for any cancers, including cancers of esophagus and stomach, which were rarely reported in other studies [8]. In addition, a linear relationship between fasting serum glucose level and increment of hazard ratio of these types of cancer mortality suggested that hyperglycemia is a possible causal factor. Therefore, whether diabetes is associated with cancer mortality cannot be easily determined.

Prediabetes is an intermediate hyperglycemic state that precedes overt diabetes [9]. A clearer relationship between dysglycemia and morbidity or mortality can be achieved through analyses considering prediabetic state. Although trend analyses indicated that some cause-specific mortalities were significantly associated with glycemic status, prediabetes alone was not associated with higher risk of mortality by any cause compared with normal glucose tolerance group, especially after ad-

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justing for confounding factors. These results indicated that prediabetes did not solely contribute to increased risk of mortality. However, prediabetes comprises a wide range of dysglycemic and insulin-resistant subjects [10]. Therefore, some previous studies about this issue that provides insights regarding how to divide prediabetic state into subgroups (impaired fasting glucose, impaired glucose tolerance, or stage 1/2 impaired fasting glucose) showed inconsistent results [11,12]. For example, impaired fasting glucose stage 2 (110 to 125 mg/dL of fasting glucose), but not impaired fasting glucose stage 1 (100 to 109 mg/dL of fasting glucose), was significantly associated with higher all-cause mortality and cardiovascular mortality compared with normal glucose tolerance in a Korean study [13]. Therefore, even though it was not the main focus of the study by Li et al. [5], more extensive evidence on this topic will be needed later.

Beyond the diabetes-related mortality, a clinically important aspect of this issue is the changes in mortality rate in patients with diabetes. In a Korean National Health Insurance Service cohort study, all-cause and cardiovascular mortality rates decreased substantially during recent 10 years, and even the gap of mortality rates between subjects with and without diabetes has narrowed [14]. It was postulated that improvement in diabetes care including enhancement of medication adherence and management of cardiovascular risk factors might have contributed to lowering mortality in subjects with diabetes. Nonetheless, the mortality rate of people with diabetes is still about two-fold higher than those without diabetes. More advances in diabetes care and diabetes research are required to reduce mortality risk in patients with diabetes.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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