A look at the trend in diabetes-related complications in the U.S. over the past two decades: looking ahead

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It has been more than two decades since the publication of the Diabetes Control and Complications Trial (DCCT) and the Stockholm Diabetes Intervention Study. These two landmark studies demonstrated unequivocally that lowering blood glucose delayed the onset and slowed the progression of microvascular complications in type-1 diabetes (1,2). Five years later, the United Kingdom Prospective Diabetes Study (UKPDS) confirmed that microvascular and macrovascular complications in type-2 diabetes can be reduced by lowering blood glucose levels, lipid levels and blood pressure through intensive therapy (3-6). These studies are widely considered milestones because they fundamentally shifted the focus of diabetes care to tighter control of blood glucose, lipid levels and blood pressure to reducing the risk of diabetes-related complications. Gregg and colleagues wanted to find out whether public health effort implemented based on findings from these important studies had any impact on the burden of diabetes-related complications in the United States. Using data from the National Health Interview Survey, the National Hospital Discharge Survey, the U.S. Renal Data System, and the U.S. National Vital Statistics System, they examined time trends [1990-2010] in rates of lower-extremity amputation, end-stage renal disease, acute myocardial infarction, stroke and death from hyperglycemic crisis (7). Between 1990 and 2010, the rates of all five "complications" decreased significantly among the population with diabetes, and the decline was even more dramatic than in the population without diabetes. If we compare diabetics and non-diabetics, declines of acute myocardial infarction were –67.8% *vs.* –31.2%, declines of death from hyperglycemic crisis were –64.4% *vs.* –5.5% and declines in amputation were –52.7% *vs.* –12.9%. End-stage renal disease declined by –28.3% in diabetics but actually increased by 65% in the non-diabetics.

In most cases, the greatest declines in diabetes-related complications were observed in the older than 75 years age group, with –67.1% lower rates of acute myocardial infarction, –62.6% lower rates of stroke, –74.0% lower rates of amputation, and –89.6% lower rates of hyperglycemic death. Such extraordinary reductions in diabetes-related complications clearly show that aggressive screening and management of diabetes and diabetes-related complications by the medical community is paying off. Efforts include, but are not limited to, advancements in revascularization procedures and intensive care management; public health efforts in smoking cessation and weight management; and more emphasis in screening for diabetes, tight control of blood glucose, lipid levels and blood pressure; as well as management of diabetes-related complications such as hemodialysis and wound care.

While it is important to celebrate the progress made in reducing diabetes-related complications, we should also recognize that the diabetes epidemic is still expanding. Between 1990 and 2010, based on self-report, the number of U.S. adults with diabetes more than tripled, from 6.5 to 20.7 million. Over 40% of those with diabetes, or 7.9 million, are older than 65 years of age (7). Rising number diabetics partially explained by demographic changes, particularly the doubling of the U.S. population 65 years and older predicted over the next 25 years, will further increase the burden of diabetes to our society (8). To monitor this transformation, and hopefully to track the effectiveness of future medical and public health intervention we need robust diagnostic criteria and epidemiological metrics. Unfortunately, and eye to the literature clearly shows that the prevalence of diabetes varies depends on the diagnostic criteria used. This is especially true in the elderly population where postprandial hyperglycemia is a prominent characteristic (9). Using both

fasting glucose and hemoglobin A1c (HbA1c) as diagnostic criteria for diabetes, the Centers for Disease Control and Prevention (CDC) in 2010 estimated that 25.6 million of U.S. adults have diabetes and almost one-third of them are undiagnosed. However, of those individuals with undiagnosed diabetes, HbA1c can only detect 30% of them. Using HbA1c and fasting glucose together only increase the detection rate to 52%. The other 48% of undiagnosed diabetes can only be diagnosed by 2-hour glucose levels during an oral glucose tolerance test (OGTT) (10). For adults aged 65 or older, HbA1c can only detect 14.5% of the undiagnosed diabetes, while HbA1c and fasting glucose can only increase the detection rate to 42%. The other 58% of undiagnosed diabetes in this older age group can only be diagnosed by 2-hour glucose during an OGTT (10). Therefore, using HbA1c and or fasting glucose to diagnose diabetes, a majority of diabetes in the older age group may be missed. This is an enormous problem, as prevention of diabetes-complications may be delayed or missed completely when proper diagnosis is not made early.

As our understanding of pathophysiology of diabetes in old age improves, we need to apply this new knowledge to the development of better criteria, tailored to be more sensitive and specific for older persons. Broadly speaking, diabetes in this age group can be grouped into those with incidence diabetes diagnosed after age 65 or those with long-standing diabetes diagnosed in middle-age or earlier, which have different demographics and clinical characteristics (11). Older adults are at increased risk of developing diabetes because of age-associated increase in insulin resistance and decline in islet-cell function. Age-associated increase in insulin resistance can be attributed to increase in adiposity and sarcopenia, and decrease in physical activity (12). The age-related decline in islet-cell function would explain why a majority of the diagnosis of diabetes in the older age group is made by 2-hour OGTT only (13,14). Those older individuals with primary islet-cell dysfunction would not have their diabetes diagnosed until the disease is much more advance.

Over the years, tremendous efforts have been put into screening and management of diabetes. Efforts to identify at-risk individuals are made in order to prevent or delay diabetes (15). However, the risks of developing diabetes or diabetes-related complications may already be present prior to the current cut-point for at-risk individuals (16). There are data showing that at 13 years prior to the development of diabetes, fasting glucose, 2-hour OGTT glucose, insulin resistance and beta-cell function in individuals who eventually developed diabetes, were already significantly different than those who did not developed diabetes (17). Exactly when the glucose values or markers of insulin resistance and beta-cell function between these two groups diverge is not known.

Gregg and colleagues have shown that over the past twenty years, the healthcare community in the U.S. has gained an upper hand in handling diabetes-related complications. However, it is clear that the diabetes epidemic has not been stopped. We need to find better biomarkers to identify individuals who are at risk for diabetes so that we can actually "prevent" this terrible disease.

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