Editorial on the original article entitled "Changes in diabetes-related complications in the United States, 1990-2010" published in the *New England Journal of Medicine* on April 17, 2014

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Abstract: The paper entitled "Changes in diabetes-related complications in the United States, 1990-2010" published recently in the *New England Journal of Medicine* examined the spectrum of diabetes complications over the past 20 years based on a unique, nationally representative database in the Unites States. It was noted that although adults with diagnosis of diabetes have more than tripled between the years 1990 and 2010, the rates of all five major complications of diabetes have declined significantly with the greatest absolute declines being noted for acute myocardial infarction followed by stroke, lower-extremity amputation, end-stage renal disease and finally the death from hyperglycemic crisis. The greatest declines in most of the diabetes-related complications were observed among elderly persons who are above the age of 75 years with the exception of end stage renal disease which declined only in younger people but not among elderly. These findings could be due to the fact that over the past years there have been great advancements with regards to creating diabetes education programs especially after the publication of many trials that looked at the importance of intensive versus conventional glucose control, along with the enhanced management of other associated risk factors such as blood pressure, lipid levels, and smoking cessation.

Keywords: Diabetes related complications; neuropathy; retinopathy; nephropathy; end stage renal disease; amputations; stroke; myocardial infarction

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It is known that diabetes is a metabolic disorder characterized by elevated blood glucose levels with its associated microvascular and macrovascular complications that would substantially increase the morbidity and mortality and hence reduce the quality of life. Moreover diabetes is considered to be one of the most common growing public health challenges globally, where it was estimated that around 285 million people, corresponding to 6.4% of the whole world's adult population were found to have diabetes. It is further expected that by year 2030, 552 million of the population would have diabetes corresponding to around 7.8% of the adult population. Type-2 diabetes accounts for 90-95% of all diabetic patients and diabetes is considered to be the seventh leading cause of death in the United States (1,2).

On April 17, 2014, a paper entitled "Changes in diabetes-related complications in the United States, 1990-2010" was published in the *New England Journal of Medicine* (3). This paper looked at how diabetes has changed over the past 20 years and examined the spectrum of diabetes complications, based on a unique, nationally representative database obtained from the nationally representative hospitalization and registry data of the United States which included the National Health Interview Survey (NHIS), the National Hospital Discharge Survey (NHDS), the U.S. Renal Data System (USRDS) and the National Vital Statistics System (NVSS). The data was collected and processed at the National Center for Health Statistics and the USRDS Coordinating Center.

This study noted that although adults with diagnosis

of diabetes have more than tripled between the years 1990 and 2010, with the overall increase in the U.S. adult population by approximately 27%, the rates of all five major complications of diabetes have declined significantly between the years 1990 and 2010, with the greatest absolute declines being noted for acute myocardial infarction (95.6 fewer cases per 10,000 persons per year) followed by stroke (58.9 fewer cases per 10,000 per year), lower-extremity amputation (30.0 fewer cases per 10,000 per year), end-stage renal disease (7.9 fewer cases per 10,000 per year) and finally the death from hyperglycemic crisis (2.7 fewer cases per 10,000 per year) which was noted to have declined least. When they looked at absolute number of cases (i.e., irrespective of changes in population size), it was noted that the annual numbers of stroke cases were actually found to be increased by 59,703 cases, amputation by 22,703 cases, and end-stage renal disease by 32,434 cases, whereas the number of acute myocardial infarctions declined by 4,379 cases and the number of deaths from hyperglycemic crisis declined by 529 deaths. The greatest declines in most of the diabetes-related complications were observed among elderly persons who are above the age of 75 years. The only exception to this was found for end-stage renal disease, which on the contrary was found to decline only among younger persons (20 to 44 years of age and 45 to 64 years of age) but not among elderly patients. This article also noted that although the trends were favorable for patients with diabetes, those without diabetes had a much smaller decrease in the rate of acute myocardial infarction with no significant change in rates of stroke and lower extremity amputation, and there was an increase in the rate of end-stage renal disease over time.

The findings of these study could be due to the fact that over the past years there have been great advancements done with regards to creating diabetes education programs, whose main aim is to reduce the burden of diabetes and pre-diabetes by facilitating the adoption of proven approaches to prevent or delay the onset of type-2 diabetes and its complications (4,5).

This has been mainly intensified after the publications of studies which showed the importance of strict management of diabetes.

The diabetes control and complications trial (DCCT) showed that the intensive blood glucose control in patients with type-1 diabetes was associated with 76% reduced risk of retinopathy, 50% reduced risk of progression of diabetic kidney disease and a 60% reduced risk of neuropathy. Its follow-up study, the epidemiology of diabetes interventions and complications (EDIC) showed a 42% reduced risk of any cardiovascular disease event with a 57% reduced risk of nonfatal heart attack, stroke, or death from cardiovascular causes (6,7). Moreover in a systematic literature search including 12 randomized controlled trials (RCTs) assessing the effects of intensive *vs*. conventional glycemic targets in patients with type-1 diabetes in terms of long-term complications, it was found that retinopathy occurred in significantly less patients in the intensive group (23/371) (6.2%) as compared to the conventional group (92/397) (23.2%); nephropathy occurred significantly less in the intensively treated group (119/732) (16.3%) *vs*. in the conventional group (211/743) (28.4%) with a RR of 0.56 and neuropathy as well was noted to occur significantly less in the intensive group (29/586) (4.9%) *vs*. (86/617) (13.9%) in the conventional group with a RR of 0.35. Major macrovascular outcomes (stroke and myocardial infarction) occurred very rarely, and this is why no firm evidence could be established and the quality of evidence was considered to be low. This study concluded that tight blood sugar control reduced the risk of developing microvascular diabetes complications with the benefit mainly observed in younger patients at early stages of the disease (8). Therefore most of the studies which included type-1 diabetes patents have mainly shown that intensive glucose lowering was very effective in reducing the microvascular and macrovascular complications. This can be mainly due to the fact that type-1 diabetes is diagnosed right from the beginning of the disease and hence early intensive management should rationally be very effective (9).

The United Kingdom Prospective Diabetes Study (UKPDS), which involved patients with type-2 diabetes, it was shown that intensive glucose-lowering regimen as compared to conventional therapy significantly reduced the composite outcome of seven diabetes-related events although its effects on cardiovascular events and mortality were not significant (10). Conversely, in the veterans affairs diabetes feasibility trial, intensive glucose lowering was associated with a non-significant increase in cardiovascular events but with no difference in mortality (11). The action to control cardiovascular risk in diabetes (ACCORD) trial, which was conducted at 77 sites nationwide, randomly assigned 10,251 participants between the ages 40 and 79 (average age 62) to standard or intensive blood sugar treatment goals and showed that the intensively treated group had an increased the rate of death from any cause after a mean of 3.5 years as compared to standard therapy with a relative increase in mortality of 22%. However most of those patients had several history of type-2 diabetes of

long duration and therefore it was thought that the increased mortality in such patients was mainly due to the established cardiovascular disease prior to getting assigned to the intensive therapy group (12).

Given the results of these studies, physicians and patients are now more aware of the importance of intensive glucose control especially when diagnosed early on, even before cardiovascular disease is even established, with the aim of reducing the microvascular and macrovascular complication of diabetes.

Patients are currently more involved in the care of their diabetes with regards to nutrition and dietary compliance and adjustment of their medications or insulin although there are still several adherence problems faced in the management of those patients. But now patients are also more aware of the importance of reaching their target glycosylated hemoglobin asked from their physicians as per latest diabetes guidelines. Therefore it was noted that there was an increased emphasis on the need for the integrated management of care for patients with diabetes including the importance of patient education in disease management, and their being involved in their own clinical decision-making support, with an emphasis on adopting a collaborative model of care in order to achieve a skillful use of behavioral change strategies (13,14).

This is in parallel to the enhanced management of other associated risk factors such as blood pressure, lipid levels, and smoking cessation, which as well are likely to have a major effect on decreasing the rates of myocardial infarction, stroke, end-stage renal disease, and amputation (15). It was noted that a reduction in cardiovasular events was noted with the intensive use of statin therapy in patients with diabetes and this correlated very closely with LDL cholesterol lowering (16). Randomized clinical trials have also demonstrated the reduction of coronary heart disease events, stroke, and nephropathy by lowering blood pressure to less than 140 mmHg systolic and 80 mmHg diastolic in patients with diabetes (17-19). Tight blood pressure control, as achieved in the UKPDS, also was shown to significantly reduce the risks of all cardiovascular and microvascular outcomes, with risk reductions ranging from 24% to 56% but a 21% reduction was seen in myocardial infarction which was not found to be significant (17,20). It is also important to note that the use of renin-angiotensin system blockade has provided additional benefits beyond the simple blood pressure-lowering effect in patients with diabetic nephropathy where several studies have actually demonstrated the renoprotective effects of treatment with ACE inhibitors and angiotensin receptor blockers (ARBs), which was independent of their blood pressure-lowering effects, possibly because of their effect on decreasing the intraglomerular pressure. Both ACE inhibitors and ARBs were found to decrease the risk of progression to macroalbuminuria in patients with microalbuminuria by as much as 60-70% and this is why these drugs are currently recommended as the first-line treatment of microalbuminuria, even in patients without hypertension (20).

For diabetic retinopathy it was shown that control of blood pressure, along with good glycemic control did reduce the risk of progression of retinopathy. Furthermore the inhibition of the renin-angiotensin pathway by an ACE inhibitor or angiotensin II receptor blocker seem to have effects on diabetic retinopathy beyond the impact of blood pressure control (21,22). Moreover control of dyslipidemia, possibly with fenofibrate, reduces the risk of progression of retinopathy (23,24).

In addition to these advances many other advances have been made in the revascularization approaches and wound treatment which probably have also had an important role to play as well (25,26).

Moreover it was noted that over the years there have been great improvements in the in-hospital management of patients with diabetes with protocols currently available on how to manage diabetic ketoacidosis and hyperosmolar hyperglycemic states appropriately which have further contributed to decreased mortality (27,28).

The increased usage of screening methods for diabetes have probably led to the early diagnosis of diabetes at a younger age where persons are being detected and managed for diabetes early on and this by itself could explain the reduction observed in the diabetes related complications. However it is important to note that in a large UK sample, screening for patients with type-2 diabetes in those who were at increased risk had no association with a reduction in all-cause, cardiovascular, or diabetes-related mortality within a 10 years' period (29).

As for the cause why rates of end-stage renal disease have decreased only in young people and not in elderly this is still not very clear. The authors proposed that this could have been due to the increase in the proportion of the U.S. population of patients with diabetes who are non-Hispanic blacks, where these individuals are known to have twice more end-stage renal disease as compared to whites. However it could also be possible that that the aging population is actually increasing and given the fact that now diabetes patients are better diagnosed and managed, these patients tend to live for a longer period of time. This

may have led to the increased incidence of end stage renal disease which is usually increased among the elderly where in one study it was found that the rates of treated ESRD among the elderly (>80 years) have risen by more than 50% in the last decade (30).

The authors concluded that these findings are positive but they were not able to provide us with a complete picture of trends in other risk factors. Similarly, they did not report any data on hypoglycemia, cognitive decline, Alzheimer's disease, depression, and physical disability. They also mentioned that the trends in diabetes-related complications provided was not able to be stratified based on persons with type-1 diabetes *vs*. those with type-2 diabetes.

In conclusion, it seems that diabetes related complications were noted to decrease over the years. But it is important to remember that the population with diabetes is actually increasing and is expected to increase more. This could be related to the more generous screening of diabetes over the years, however the lifestyle and environmental changes are for sure to play an important role as well. Efforts should be made to diagnose and treat diabetes as early as possible but also more importantly lifestyle changes should be adopted with the aim of decreasing the risk of diabetes development.

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