Diabetes, Metabolic Syndrome and Obesity

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EDITORIAL

Diabetes: A Subspecialty of Medicine and a Matter of Public Health

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Shortly after starting my first tenure track faculty position in epidemiology at West Virginia University, I was visiting my previous postdoctoral mentor in diabetes epidemiology at Vanderbilt University Medical Center, the late Dr. Michael E. May, MD, PhD, an endocrinologist and investigator in the landmark Diabetes Control and Complications Trial/Epidemiology of Diabetes and its Interventions Study (DCCT/EDIC), who died earlier this year. We were talking about both the salaries of endocrinologists compared to that of physicians in other branches of medicine (one neurologist had recently told me "there is not a lot of money for just managing people's blood sugar") as well as the then current research funding environment. I told him that I had been encouraged to consider cancer research rather than diabetes because the federal government had so much more money in its coffers for cancer research than for diabetes. He was reflective and then said solemnly, "there is not a lot of money for public health". I thought, that is interesting. I am not a physician but an epidemiologist in a school of public health. He is a practicing endocrinologist and a physician scientist in a school of medicine yet he considers diabetes and diabetes care to be a matter of public health as much as a medical subspecialty per se. Upon reflection, it made sense. Diabetes consistently ranks among the top ten leading causes of death in the United States and as one of the top ten globally,[1,2] despite the fact that people at least in the United States and other high income Western nations rarely die from acute hyperglycemic or hypoglycemic crises. Yet diabetes is a major cause or contributor to so many other chronic diseases in medicine, including cardiovascular disease, the leading cause of death in the US and globally,[2] and contributes to many others such as Alzheimer's, liver disease and cancer.

Overview

In the following, I will argue why diabetes needs to be considered an issue of public health as much as of medical science. Reasons include its high prevalence and economic burden, and the morbidity and disability associated with complications of the disease. Reasons also include the excess mortality due to diabetes, both in relative terms and in absolute number of lives.

Globally, approximately 1 in 9 adults are living with diabetes.[3] In addition to the acute complications of the disease, namely hypoglycemic and hyperglycemic crisis, diabetes results in chronic complications affecting most major organs systems, causing considerable morbidity and an increased risk of early mortality for those with the disease. It ranks number 7 globally for years lived with disability[4] and in 2023, it was a cause of approximately 2 million deaths, or 3.3% of all deaths among all ages, globally.[5] In 2024, health care costs for treating diabetes exceeded over $1 trillion USD.

Diabetes, a metabolic disorder of glucose metabolism (or homeostasis) resulting in hyperglycemia, is broadly classified into three major types, type 1 and type 2 diabetes and gestational diabetes, although there are many distinct subtypes within those broad categories. Its causes are many, but in the end shares the features of pancreatic beta cell deficiency, dysfunction and/or failure. Its primary pathophysiological features are hyperglycemia that result in microvascular and macrovascular dysfunction and damage caused by this hyperglycemia, leading to widespread end organ damage. While the two major subtypes of chronic diabetes primarily differ in the initial mechanisms leading to

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dysregulation of glucose metabolism, the late-stage end organ complications are similar though they may differ in distribution and in the time course in the natural history of diabetes. Some of those complications are described below.

Diabetic Retinopathy

Diabetic retinopathy is a microvascular complication of the eye characterized by retinal ischemia and microaneurysms, neovascularization in the retina and posterior surface of the vitreous, hemorrhaging of these new blood vessels, hard exudate formation, and tractional retinal detachment. Globally, diabetic retinopathy affects from 17–27% of the population with diabetes,[6,7] though this number is much higher among those with type 1 diabetes where the majority of those individuals with type 1 diabetes are expected to develop diabetic retinopathy in their lifetimes.[8–10] The leading risk factors for vision threatening diabetic retinopathy are poorly controlled hyperglycemia, hypertension, and diabetes duration, or, simply stated, the number of years lived with diabetes. Diabetic retinopathy is a leading cause of preventable blindness among working age adults and is the fifth leading cause of blindness in adults globally.[11] World-wide, approximately 1.3 million individuals are estimated to be blind from diabetes.[12] Given that hyperglycemia and years lived with diabetes are the strongest risk factors for diabetic retinopathy and its progression, adequate medical management of diabetes could have a major impact on the global burden of blindness.

Diabetic Neuropathy

Diabetic neuropathy, an often debilitating microvascular complication of diabetes, is a cluster of neuropathic syndromes resulting from diffuse and/or focal damage to the nerves supplying the peripheral and autonomic nervous systems. It is arguably the most common of the complications of diabetes and can result in significant morbidity and reduced quality of life, play a role in other end organ complications among persons with diabetes and in their substantially increased mortality rate, particularly for cardiac autonomic neuropathy.

Distal symmetrical polyneuropathy, a length dependent neuropathy, results in both the hyperesthesia of painful neuropathies and the hypoesthesia, ie loss of sensation, resulting from damage to or loss or proprioceptors and nociceptors. While painful diabetic neuropathies, inclusive of both distal symmetrical polyneuropathy and focal neuropathies, affect approximately 47% of the diabetic population,[13] distal symmetrical polyneuropathy is also a leading contributor to non-traumatic lower extremity amputations among persons with diabetes.[14]

Neurologic damage to the autonomic nervous system in particular results in orthostatic hypertension, delated gastric emptying, bladder dysfunction, constipation, diarrhea, erectile dysfunction, vaginal dryness and painful sexual intercourse for women, anhidrosis, facial and gustatory sweating, hypoglycemia unawareness, sinus tachycardia, orthostatic hypotension, reduced sensation to ischemic pain and thus silent cardiac ischemia, increased risk of myocardial infarction and sudden cardiac death. Diabetic autonomic neuropathy is associated with a greatly reduced quality of life among persons with diabetes. Cardiac autonomic neuropathy in particular, affecting 29–54% of those with type 1 diabetes[15] and 12–73% of those with type 2 diabetes,[15–17] is associated with a nearly 3-fold increased risk of death compared to persons with diabetes but without cardiac autonomic neuropathy.[18,19] The leading etiologic factor in cardiac autonomic neuropathy is hyperglycemia; thus, while managing patients' blood sugar may not be lucrative, it may greatly decrease their risk of early mortality.

Neuropathy in diabetes has a particularly strong public health association insofar as it has been shown that it is actually manifest in prediabetes and thus is susceptible to early intervention by life style modification.[20]

Nephropathy

Globally, nearly 10% of the global population is living with some stage of chronic kidney disease,[21,22] with over 20% of those cases being diabetic nephropathy.[22] It is the leading cause of progression to end stage kidney disease (ESKD), and persons with diabetes account for approximately half of the new ESKD cases. Twenty to 50% of those with type 2 diabetes[23] and by contemporary estimates approximately one-third of those with type 1 diabetes will eventually develop chronic kidney disease (CKD).

Diabetic nephropathy, currently affecting 2% of the global population, is defined as impaired renal function (an eGFR <60 mL/min/1.73 m^2) or elevated urinary albumin excretion (albumin/creatine ≥30 or albumin excretion rate ≥30 mg/dL) or both. Classically, the progression of diabetic nephropathy was characterized by increasing albuminuria, followed by a decline in kidney function, increased renal impairment and finally ESKD. However, this is not seen universally, as most with microalbuminuria

never progress to macroalbuminuria, many can revert to normoalbuminuria (due in part to effective interventions); and many with CKD do not have any albuminuria. Further, much of the CKD among persons with type 2 diabetes is related to factors that co-occur in type 2 diabetes, such as hypertension and obesity, rather than purely as a consequence of it, suggesting that for many with type 2 diabetes and even for some with type 1 diabetes, CKD is a comorbidity rather than a complication that is part of the natural history of the diabetes.

Due to improvements in treatment and management of diabetes and its comorbidities, the incidence of diabetic nephropathy has declined. It is for this same reason, however, that the prevalence of CKD in diabetes continues to rise as the increased survival rate of persons with diabetes translates into a larger number of individuals living with diabetes - there are over 100 million people living with diabetic nephropathy worldwide.[24] While most people with diabetes do not die from end stage kidney disease, underlying kidney disease accounts for much of the excess mortality among persons with diabetes, particularly for those with type 1 diabetes.[25,26]

Cardiovascular Disease

Cardiovascular disease, inclusive of atherosclerotic heart disease, myocardial infarction, heart failure, stroke, and peripheral vascular disease, is common in diabetes, with prevalence estimates of 13–47% after 30 years of diabetes duration in type 1 diabetes[27,28] and estimates of approximately 30 to 35% in type 2 diabetes.[29,30]

While often considered a comorbidity rather than a complication of diabetes, particularly among persons with type 2 diabetes, hyperglycemia, hyperinsulinemia and albuminuria have direct effects of diabetes on the cardiovascular system. Hyperglycemia, for example, induces endothelial dysfunction, and the initiation and progression of the atherosclerotic process in the vasculature. Hyperinsulinemia, also omnipresent in diabetes due to either exogenous insulin in type 1 and type 2 diabetes or hyperproduction on endogenous insulin in type 2 diabetes, activates inflammatory pathways and also contributes to the induction and progression of atherosclerosis. More atherosclerotic vessels and a greater plaque burden within these vessels are observed among those with diabetes. Hyperglycemia in diabetes also contributes to atherosclerotic plaque destabilization by increasing the necrotic core, macrophage infiltration, and collagen deposition in atherosclerotic plaques and reducing the ratio of cap to plaque size in atherosclerotic lesions. The increase in vulnerable atherosclerotic plaques and plaque destabilization translates into an increased risk of myocardial infarctions and strokes among persons with diabetes. Cardiovascular disease risk is increased 2-fold in type 2 diabetes[31] and 5-to-10-fold in type 1 diabetes.[32,33] Stroke is increased 50 to 80% in diabetes.[31]

Heart failure, another common comorbidity of diabetes, may also be a consequence of the diabetic milieu. Specifically, the hyperglycemia and oxidative stress induced physiological and structural alterations in the myocardium lead to diabetes induced cardiomyopathy, including left ventricle fibrosis and increased left ventricle stiffness, and subsequent progression to clinical heart failure. Diabetes accounts for 12% of all heart failure in the United States.[1]

All other things being equal, diabetes increases the risk of cardiovascular death approximately 2-fold among persons with diabetes,[31,34] though this varies by diabetes type. There is a roughly 1.5 to 2.5 excess risk among persons with type 2 diabetes[35,36] and four to eight-fold excess risk among persons with type 1 diabetes,[37–39] though the excess risk varies by age with a higher excess risk at younger ages,[37,40] and at least for those with type 2 diabetes, almost no excess risk in the elderly. Cardiovascular disease is the leading cause of death in the general population[41] and is the leading cause of death among persons with diabetes, whether type 1 or type 2 diabetes. Of the 20.5 million cardiovascular deaths in 2021,[42] over 40% of them were among persons with prediabetes or diabetes and diabetes itself was directly responsible for 1.6 million of these deaths.[43,44]

Peripheral Vascular Disease/Lower Extremity Arterial Disease

The global prevalence of lower extremity arterial disease (LEAD) ranges from 1.52%-9.7% overall,[45,46] with persons with diabetes accounting for a substantial number of these cases and for 82%[47] of LEAD amputations. Peripheral artery disease (PAD), the atherosclerotic vascular manifestation of the lower extremities, and peripheral nerve damage are two complications of diabetes that work together to reduce vascular blood flow and limit sensation in the feet. Due to this limited sensation, individuals with diabetes are particularly susceptible to foot ulcers, which are prevalent in 6.3% of the population with diabetes.[48] Due to the metabolic milieu of hyperglycemia and poor peripheral vascular circulation in diabetes, these ulcers heal more slowly and can develop into subsequent infections, which can progress to osteomyelitis and necessitate lower-limb amputation if not properly

managed. Diabetes is the leading cause of non-traumatic lower extremity amputations,[49] with major amputations occurring in 94.82 per 100,000 persons with diabetes annually.[50]

Early Mortality

Finally, individuals with diabetes on average have a decreased lifespan compared to those without diabetes. Diabetes is associated with an approximate two-fold higher mortality rate, though this varies by age and years lived with diabetes, with higher excess mortality rates at younger ages as well as for more years lived with diabetes.[51–53] It also varies by geographic region and national economic status, with greater excess mortality in middle and low income countries. Persons with insulin treated diabetes diagnosed in childhood or young adulthood, regardless of diabetes type, have been reported to have a 3-to-5-fold excess mortality rate compared to those without diabetes.[37,38,54] In 2023, it was a cause of approximately 2 million deaths, or 3.3% of all deaths globally.

By the Numbers

So why would that sage mentor, that endocrinologist and diabetologist, housed in a school of medicine where his primary patient and research population were persons with diabetes, say to me the epidemiologist that diabetes is public health rather than what it is, a field of medicine? Perhaps reasons included its high prevalence and economic burden, as well as the fact that in many cases it is preventable. Moreover, the measures that can be taken to promote prevention of the disease and its morbidities include public education and public policy (eg access to affordable health care, promotion of an environment that encourages healthy behaviors, and others).

Simply by the numbers, persons with diabetes represent the one of the largest proportion of preventable blindness cases, approximately half of all cases of neuropathy, and approximately half of all cases of chronic kidney disease and kidney failure. It is the leading cause of non-traumatic lower extremity amputations and is a significant contributor of cardiovascular disease – the leading cause of death globally. Public health is the organized, concerted effort to prevent, eliminate, or mitigate the effects of a disease at the population level. While simply managing patients' blood sugars may not be very lucrative, it may help to reduce the approximately 2 million deaths due to diabetes, 1.5 million deaths due to kidney disease, and the nearly 20 million deaths due to cardiovascular disease annually,[55] not to mention the morbidity associated with these medical conditions. Treating diabetes, a disease which in many cases is preventable, now exceeds $1 trillion USD.[3] The late Dr. Michael E. May was right: Diabetes is a matter of public health as much as it is a subspecialty of medicine.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Author Contributions

Rebecca Baqiyyah Conway: Conceptualization, Methodology, Resources, Investigation and Writing – review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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