Diabetes as “Coronary Artery Disease Risk Equivalent”:
A Historical Perspective

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INTRODUCTION

Diabetes mellitus (DM) is a cardiovascular disease. It may be inappropriate to make such statement because traditionally, diabetes is a disease in the realm of internal medicine. However, coronary heart disease (CHD), stroke, peripheral arterial disease, nephropathy, retinopathy, and possibly even neuropathy and cardiomyopathy are the complications of diabetes. Therefore, we can safely claim that the cardiac complications of diabetes make this disease a major risk factor in the causation of CHD.

The Framingham study demonstrated that the presence of diabetes increased the risk of clinical atherosclerotic disease from twofold to threefold, with coronary artery disease (CAD) as its chief sequela. Morbidity and mortality were higher for diabetic women. After adjustment for other associated risk factors, cardiovascular mortality was increased for both diabetic women and men.

The prevalence of diabetes is increasing worldwide, especially in developed countries (USA and Europe) because of aging of the population and an increasing prevalence of obesity and sedentary life habits.

The WHO Global report on diabetes issued the following statistics: (1) the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014; (2) the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014; (3) diabetes is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation; (4) almost half of all deaths attributable to high blood glucose occur before the age of 70 years; (5) in 2012, an estimated 1.5 million deaths were directly caused by diabetes and another 2.2 million deaths were attributable to high blood glucose; (6) diabetes prevalence has been rising more rapidly in middle- and low-income countries; (7) the WHO projects that diabetes will be the 7th leading cause of death in 2030; (8) diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening, and treatment for complications.

In Qatar, the prevalence of diabetes in adults in 2015 was 13.5%. The annual mortality rate per 100,000 population from diabetes is 7.8%. From our HMC CCU Registry in the Heart Hospital, Hamad Medical Corporation, Doha Qatar, the prevalence of diabetes among those with CAD over a 10-year-period (2004–2013) is 7.2%. Mortality from CAD with diabetes is 3.3%. The presence of heart failure increases mortality to 5.6%.

Clearly, these statistics are sobering. The good news is that with proper education and health awareness, the disease can be treated and its complications avoided or delayed.

CHD or ischemic heart disease or CAD and stroke are the world’s biggest killers and have remained the leading causes of death globally for the last 15 years. Diabetes was ranked 6th, with 1.6 million people dying from it in 2015, up from less than a million in 2000.

Diabetes and CHD have been with us since antiquity but until now, the underlying pathology or mechanisms by which they cause disease are still poorly understood. We know that diabetes is a major risk factor for CHD and we have just begun to unravel why they cause disease. We understand that genetics and environment are central, but their interplay is extremely complex.

Here, we shall consider a brief history of diabetes and why diabetes is considered CAD equivalent. Only

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by understanding the evolution of the pathophysiology of a disease can we hope to develop ways of curing or treating or at least avoiding its complications.

**EARLY UNDERSTANDING OF DIABETES**

DM is a disease which was recognized in ancient times, but medical understanding of it has been characterized by cycles of discovery, neglect, and rediscovery.

Diabetes is mentioned in the Edwin Smith Papyrus (Ebers Papyrus), the oldest and most important medical papyri of ancient Egypt and which dates to 1550 BC. Medical information in it dates from as early as 3000 BC.[6] It is full of magic, i.e. incantations and foul applications meant to turn away disease-causing demons. However, it also contains descriptions of various other ailments and their remedies. It describes a condition characterized by “too great emptying of the urine”, perhaps in reference to diabetes, and advocated the use of wheat grains, fruit, and sweet beer.[7]

Ancient physicians in India in the 5–6th centuries AD noted that the urine from people with diabetes attracted ants and flies. This observation can be considered as the first clinical test for diabetes. They named the condition “madhumeha” or “honey urine,” noting that patients with “madhumeha” suffered from extreme thirst and foul breath (probably because of ketosis).[7]

It seems that Indian physicians distinguished two forms of diabetes: one affecting older, fatter people and the other thin people who did not survive long. Chinese and Japanese physicians also described diabetes and the sweetness of diabetic urine. They also observed that people with diabetes were prone to develop boils and various other ailments and their remedies. It describes a condition characterized by “too great emptying of the urine”, perhaps in reference to diabetes, and advocated the use of wheat grains, fruit, and sweet beer.[7]

The earliest reasonably accurate account of diabetes comes from Aretaeus, the Cappadocian (81–138 AD). Aretaeus is one of the most celebrated of the ancient Greek physicians. He coined the term diabetes using the Greek word that means “siphon,” “to pass through”, after noting the frequent urination displayed by patients.[8]

Apparently, diabetes was quite rare in ancient times and the middle ages. It is mentioned that Avicenna (960–1037 A.D.) gave an account of DM in his Canon of Medicine. He described a number of clinical features relating to diabetes, most notably the sweetness of the urine produced by diabetic patients. In addition, he mentions two specific complications of the disease, namely, gangrene and “collapse” of sexual function.[8]

During the Renaissance period in Europe, uroscopy or inspection of the urine was a highly developed art. In the 16th century, the Swiss physician, Paracelsus, reported that diabetic urine contained an abnormal substance which remained a white powder after evaporation and concluded that this substance was salt and that diabetes was due to deposition of salt in the kidneys, causing “thirst” and polyuria.[10]

Crucial to our understanding of diabetes was the work of Mathew Dobson (1735–1784), a British physician and physiologist. He confirmed through a series of experiments that the sweet-tasting substance in the urine of diabetic individuals is sugar. He also made the observation that the blood serum was sweet to taste and deduced that diabetic urine always contains sugar which is not formed in the kidney but “previously existed in the serum of the blood”. He concluded that diabetes is associated with a persistently raised blood sugar concentration. This led diabetes research toward a study of the mechanisms, by which the body deals with carbohydrate foods.[10]

**INSULIN**

Before a treatment intervention can be designed for a disease, it is necessary to understand what causes it. So, it was with diabetes. For many years, scientists believed that some kind of internal secretion of the pancreas was the key to preventing diabetes and controlling normal metabolism. A milestone for diabetes was the discovery of the hormone “insulin” by Banting, Best, and Macleod in the pancreatic extract of dogs. This hormone was then injected into a diabetic dog. They found that it effectively lowered the dog’s blood glucose levels to normal. By the end of 1922, insulin was used to successfully treat a boy suffering from severe diabetes. Banting and Macleod shared the 1923 Nobel Prize for Physiology and Medicine for their work.[11,12]

Before the discovery of insulin, a diagnosis of diabetes meant certain death. The discovery of insulin changed the life of millions of people with diabetes. The 1970s and 1980s are a turning point in the treatment of diabetes. In our technology driven era, technical innovations such as blood glucose readers and strips measuring blood glucose levels gave people with diabetes and their physicians’ indispensable tools. With these tools, it is now easier for diabetics to monitor their blood sugar and keep it within normal level. In addition, the discovery that sugar attaches to red blood cells (hemoglobin) led to the creation of glycated hemoglobin (A1C) test which averages blood sugar in the previous two to 4 months and helps determine blood sugar level control. It is now understood that good glucose control prevents complications.[13]

**DIABETES AS MAJOR RISK FACTOR FOR CORONARY ARTERY DISEASE**

**Coronary artery disease risk equivalent**

Diabetes is a major risk factor in cardiovascular disease. In 1998, Haffner et al.[14] reported in the *New England
Journal of Medicine that adults with diabetes had the same risk for future myocardial infarction (MI) as adults with previous MI and without diabetes.

The traditional risk factors for CAD are high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, high blood pressure, family history, diabetes, smoking, being postmenopausal for women, and being older than 45 for men. The conventional view is that having high LDL cholesterol level increases risk of dying of cardiovascular disease which became known as the cholesterol hypothesis. This view has its origins in the Framingham Heart Study which identified a number of risk factors for CAD, among them high-blood cholesterol. This finding was published in 1961.[16] Some experts, however, did not believe in the cholesterol hypothesis as a cause or risk of cardiovascular disease. Publication of the result of the Coronary Primary Prevention Trial, a multicenter, randomized, double-blind study, showed that lowering blood cholesterol leads to a reduction in heart attacks.[16]

This should have convinced the cholesterol skeptics, but the debate is still ongoing up to the present time.

The plasma cholesterol level is a strong predictor of the risk of cardiovascular events both in patients with diabetes[17,18] and in patients with CHD.[19,20]

However, a systematic review and meta-analysis published in JAMA in 2009 challenged the claim that “diabetes is a CAD risk equivalent.”[21] Since then, such assertion has been controversial and this matter has remained unresolved.

THE AMERICAN CHOLESTEROL PANEL AND DIABETES MELLITUS

In 2001, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines listed “diabetes as a CAD risk equivalent.”[22] This American program has been running since 1985 and its goal is to reduce increased cardiovascular disease rates due to hypercholesterolemia.

What does CAD risk equivalent mean? According to the above panel, ATP III, “CAD risk equivalent” is the risk of developing a major coronary event (MI + coronary death) over 10 years >20%.

The 10-year risk estimate is not the only rationale for recommending that diabetes is a CAD risk equivalent. The panel (ATP III) cites other studies that show that mortality at the time of acute MI is essentially doubled in patients with diabetes compared with those without diabetes.[23,24] Furthermore, in survivors of MI, follow-up mortality in patients with diabetes is essentially doubled compared to patients without diabetes.[25-27]

The panel (ATP III) says that the high risk of developing CHD in diabetics following onset of CAD justifies more intensive primary therapy even if their 10-year risk is in the range somewhat below 20%.

Furthermore, there are several strong clinical trials that have documented the benefit of statin therapy in patients with diabetes.[28-31] These trials reassured many clinicians that more intensive cholesterol-lowering therapy is warranted when diabetes is present.

The panel recently updated its guidelines in 2004 and introduced the term “CAD risk equivalent category”, claiming that the term is more broad or general and less touchy. Although the term “CAD risk equivalent” is controversial, there is increasing acceptance of the concept that most patients with diabetes are at high risk for developing atherosclerotic heart disease and that cholesterol-lowering therapy is an important component of risk reduction in patients with diabetes.

CONCLUSION

For those who object calling diabetes a CAD risk equivalent, it is sufficient to say that the disease is high risk for cardiovascular disease development. When we are confronted with a patient with diabetes, we should be mindful as well as vigilant to lower such risk through cholesterol-lowering therapy and control hyperglycemia.

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