Type 2 Diabetes and Vascular Complications: A pathophysiologic view

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Abstract

Diabetes mellitus (DM) represents a range of metabolic disorders characterized by hyperglycemia resulting from insulin deficiency or insulin resistance or both. Hyperglycemia, the primary clinical manifestation of diabetes, is strongly associated with development of the diabetic complications. Complications caused by hyperglycaemia involve damage to the small vessels such as in neuropathy, nephropathy, and retinopathy, and large blood vessels as in cardiovascular diseases. It is well known established that in diabetes, long-term complications ensue from abnormal regulation of glucose metabolism. In fact, all manifestations of cardiovascular disease, coronary heart disease, stroke and peripheral vascular disease are substantially more common in patients with type 2 diabetes than in non-diabetic individuals. For example, patients with type 2 diabetes (T2DM) have a two- to fourfold increased risk of fatal and non-fatal coronary events. Diabetes can lead to microvascular and macrovascular damage through a number of mechanisms, each of which may worsen or accelerate the others. The present review summarizes the information on the mechanisms of how vascular complications will develop in type 2 diabetes and this might be useful as a direction for further research to provide new strategies for prevention and treatment of these complications in their early stages.

Introduction

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion and/or insulin action. Diabetes can be classified into two major classes: type 1 diabetes (T1DM) and type 2 diabetes (T2DM). T1DM is the classical form of diabetes and these subjects cannot survive without insulin treatment. T2DM is a group of genetically determined diseases which may be controlled by diet, hypoglycemic agents and/or exogenous insulin [1]. T2DM is mainly characterized by insulin resistance, but impairment in insulin secretion also occurs in type 2 diabetes [2,3].

Subjects with T2DM cannot compensate for insulin resistance at hyperglycemic levels by increasing insulin secretion [1]. Several human monogenic forms of diabetes have been identified including: maturity-onset diabetes of the young (MODY) [4], which can be caused by mutations in the glucokinase gene. MODY is characterized by

β-cells dysfunction and young age at diagnosis, usually less than 25 years, leading to early-onset T2DM. In addition, other minor classes include gestational diabetes, extreme insulin resistance caused by a defective insulin receptor gene, the diabetes-deafness and optic atrophy syndrome which is due to defects in mitochondrial genes [5], and latent autoimmune diabetes in adults (LADA) [6,7] which was introduced to define adult diabetic patients who initially present as type 2 diabetics but with immune markers of type 1 diabetes which, in a number of cases, progress to insulin dependency. However, LADA more closely resembles and shares common characteristics of T1DM including genetics, metabolic dysfunction, and autoimmune features, but LADA does not affect children and is classified distinctly as being separate from juvenile diabetes. T1DM and the minor classes of diabetes will not be discussed any further in this review.

Type 2 diabetes mellitus

Epidemiology

It is well established that the most common form of diabetes is type 2 diabetes. The global rise in diabetes [8, 9]

occurs because of population growth and ageing, and because of increasing trends towards an unhealthy diet, obesity, and sedentary lifestyles [10]. Type 2 diabetes represents about 85% to 95% of the people with diabetes in developed countries and an even higher percentage in   developing countries [11]. Amos et al. estimated that there were 124 million persons with diabetes in the world in 1997 and predicted this number would grow to 221 million in 2010 [12]. Another study group estimated that the number of persons with diabetes was 150 million in 2000 and this number is expected to double by 2025 [13]. In 2003, it was estimated that approximately 194 million people worldwide, or 5.1% in the age group 20-79, have diabetes.

The largest increase in the prevalence numbers is thought likely to appear in India, China and other developing countries. This estimate is expected to increase to 6.3% in the adult population, by 2025. In the United States, the National Health and Nutrition Examination Surveys (NHANES) I and II showed that the prevalence of DM between 1976 and 1994 among American adults increased from 6.6% to 7.8% [14]. Although the absolute increase is relatively small, when the U.S. population growth during this period is considered, the number of patients with DM almost doubled from an estimated 8 million to 15.6 million people. Similar pictures have been observed in Europe, in which DM affects about 8.5% of the adult population [15]. The European Region with 48 million and Western Pacific Region with 43 million currently have the highest number of people with diabetes. However, the prevalence rate of 3.1% for the Western Pacific Region is significantly lower than 7.9% in the North American Region and 7.8% in the European Region. By 2025, the region with the greatest number of persons with diabetes is expected to change to the South-East Asian Region with about 82 million. The region's prevalence of 7.5% will however continue to be lower than that of North America, estimated at 9.7%, and Europe at 9.1%. [16].

Table 2: List of countries with the highest numbers of estimated cases of diabetes for 2000 and 2030

Ranking	2000		2030	
	Country	People with diabetes (millions)	Country	People with diabetes (millions)
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	U.S.	17.7	U.S.	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9
6	Pakistan	5.2	Brazil	11.3
7	Russia	4.6	Bangladesh	11.1
8	Brazil	4.6	Japan	8.9
9	Italy	4.3	Philippines	7.8
10	Bangladesh	3.2	Egypt	6.7

Gu et al. conducted a national study to investigate the prevalence of diabetes in 15,540 adults from 31 provinces in China. The authors reported that in China three out of four individuals with diabetes were undiagnosed and the prevalence of diabetes was 5.5% among the population aged 35 to 74 years in 2000. In   addition, the age-standardized prevalence of diabetes of the population aged 35 to 74 living in urban area (7.8%) was higher than that of those living in rural area (5.1%) [17]. In Sweden, about 50,000 people are diagnosed with type 2 diabetes every year, with a prevalence of 4% or more [18]. Table 1 showed the 10 countries estimated to have the highest numbers of people with diabetes in 2000 and 2030 [19]. The 40-59 age group currently has the greatest number of persons with diabetes. By 2025, because of the aging of the world's population, there will be 146 million aged 40-59 and 147 million aged 60 or older with diabetes.

Pathogenesis and major risk factors

Impaired insulin action and impaired pancreatic insulin secretion represent the principal pathophysiological abnormalities leading to increase blood glucose levels [20,21]. These are present to varying degrees in almost all patients with the common form of T2DM. Insulin resistance is a common pathologic state in which target cells fail to respond to the physiological effects of insulin occurring in peripheral organs and leading to abnormalities in glucose, lipid and protein metabolism [22]. When the

target tissue does not respond to even high levels of insulin, glucose builds up in the blood resulting in high blood glucose or type 2 diabetes. In fact, insulin resistance is present in the majority of patients with impaired glucose tolerance or T2DM, and it is also found in up to 25 % of the general, apparently healthy population [23].

In response to elevated blood glucose concentration due to insulin resistance, pancreatic β-cells need to increase the insulin secretion to maintain homeostasis in glucose levels. Finally, β-cells become unresponsive to glucose due to pancreatic β-cells dysfunction and eventually type 2 diabetes develops. Although the etiology of the β-cell dysfunction of diabetes is incompletely understood, it is thought to result from both genetic and environmental factors [24,25]. Current study provided evidence to emphasis that both insulin resistance and β-cell dysfunction are associated processes and that β-cell dysfunction must be present for even minimal increases in blood glucose [26]. Family history, diet, and lack of physical activity are all major risk factors for developing T2DM. Dyslipidemia and high blood pressure are other risk factors that often appear before the clinical disease is evident [27]. Elevated levels of free fatty acids are also strong predictor of diabetes and correlate with hepatic glucose output, a major cause of diabetic hyperglycemia [28], high glucose levels, and obesity.

Type 2 diabetes and metabolic syndrome

A majority of patients with T2DM have features of the so-called metabolic syndrome, which has also been called "Syndrome X" [23]. The major components of the metabolic syndrome include abdominal obesity, glucose intolerance/T2DM, dyslipidemia and hypertension [29]. The prevalence of the metabolic syndrome has varied markedly between different studies, most likely because of the lack of accepted criteria for the definition of the syndrome [30, 31]. WHO proposed a unifying definition for the syndrome and chose to call it the metabolic syndrome, rather than the insulin resistance syndrome [32]. The main reason was that it was not established that insulin resistance is the cause of all the components of the syndrome.

Cardiovascular disease

Cardiovascular disease (CVD) has for a long time been among the worldwide public health problem. Since 1919, cardiovascular disease has remained the leading cause of death in the United States. The direct and indirect costs of CVD in this country are estimated to reach $403 billion in 2006 alone. Although CVD includes several types of vascular and heart diseases, atherosclerosis is the cause of approximately 75% of all CVD-related deaths [33]. The

problems associated with CVD are severe in all parts of the world; however, the manifestations vary between different countries. In China, Japan and many Africans countries for example, stroke is more common than coronary heart disease whereas, among Caucasian populations, coronary heart disease is more common. In some developed nations, such as the USA, Australia and Europe, where coronary heart disease rates were previously very high, mortality has fallen in recent decades [34]. However, in other areas such as Eastern Europe and the Middle East, the opposite is true. The "top ten" countries for both coronary and cerebrovascular disease mortality rates are now mainly from Eastern Europe and the former Soviet Union.

The clinical manifestations of CVD include coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease. The underlying disease mechanism is accelerated atherosclerosis. The atherosclerotic process starts from fatty streaks, consisting of intimal deposits of lipids and macrophages with lipid droplets (foam cells), gradually developing into more advanced plaques. The process ends up in complicated atherosclerotic lesions, which through a plaque rupture and thrombosis can cause an acute myocardial infarction [35].

Type 2 diabetes and macrovascular complications

Macrovascular complications of DM are due to accelerated atherosclerosis and have an important role in the increased morbidity and mortality suffered by these individuals [36]. The mechanism behind the relation between diabetes and atherosclerosis is not fully understood. Oxidative stress caused by production of reactive oxygen species (ROS) has been proposed as the main cause underlying insulin resistance, type 2 diabetes and vascular complications [37]. Additionally, both impaired glucose metabolism [38] and diabetic dyslipidemia [39] might contribute to the atherosclerotic process. Patients with T2DM are more at risk to develop macrovascular disease, both at an earlier age and in a higher frequency as compared to the general non-diabetic population.

The severity of cardiovascular complications in diabetes is demonstrated by the statistic that diabetics are 2 to 4 times more likely to have a stroke or die of heart disease than non-diabetics. Cardiovascular disease accounts for about 70% of all deaths in patients with diabetes [40]. It has been established in a more recent report that heart disease is the leading cause of diabetes-related deaths in the United States alone [41]. The presence of diabetes, in addition to any or all the other risk factors (such as smoking, hypertension, dyslipidemia, and genetic factors),

approximately doubles the probability of developing macrovascular diseases and the available evidence suggests that strict diabetic control does not prevent or delay these complications [42]. Cardiovascular complications are often present already at the time of diagnosis of T2DM and subjects with impaired glucose tolerance (IGT) have an approximately two-fold increase in the risk of macrovascular diseases [43]. Epidemiological studies have shown that the risk of cardiovascular mortality is two to three times higher in men and three to five times higher in women with diabetes than in non-diabetic subjects [44]. Ryden et al. showed that there is a steep rise in diabetes prevalence after the age of 50 in men and after the age of 60 in women [45].

Pathogenesis and major risk factors of diabetic complications

Hyperglycemia

A strong consistent relationship has been postulated between hyperglycemia and the incidence and progression of micro- and macrovascular complications in people with diabetes [46]. Studies on nondiabetic subjects have observed that even slightly elevated serum glucose concentrations increase risk for cardiovascular disease [47]. Epidemiological data have revealed hyperglycemia to be a major player in the development of the macrovascular complications such as CAD and stroke [41]. Prospective clinical studies in T2DM patients have shown an association between level of hyperglycemia and increased risk for mortality due to macrovascular disease [48,49]. The

San Antonio Heart Study demonstrated that hyperglycemia is a risk factor not only in Caucasians, but also in other ethnic groups [50]. The data of the UK prospective diabetes study (UKPDS) suggest that any improvement in glycemic control among patients with T2DM is likely to reduce the risk of diabetic complications [51].

Protein kinase C

Protein kinase C (PKC) is a family of serine-threonine kinases that plays an important role in signal transduction mechanisms [52]. The PKC pathway is activated in diabetes as a result of hyperglycemia (Fig. 1). In this pathway, PKC is activated by the increased amounts of diacylglycerol (DAG), which are synthesized directly from glycolytic intermediates such as dihydroxyacetone phosphate and glyceraldehyde-3-phosphate [53]. It is possible that also advanced glycation end products and oxidants increase formation of DAG and activate PKC [54]. PKC appears to be activated in a range of diabetic tissues including the retina, kidney, heart, and aorta [55]. An activation of PKC has been implicated in many processes relevant to diabetic complications, including regulation of vascular permeability and flow, increased production of cytokines, and increased synthesis of basement membranes [56]. In diabetes microvascular complications, for example, PKC affects the activation of a number of growth factors and changes the function of vasoactive factors. These vasoactive factors include vasodilators such as nitric oxide (NO) as well as vasoconstrictors such as angiotensin II and endothelin-1 [57, 58].
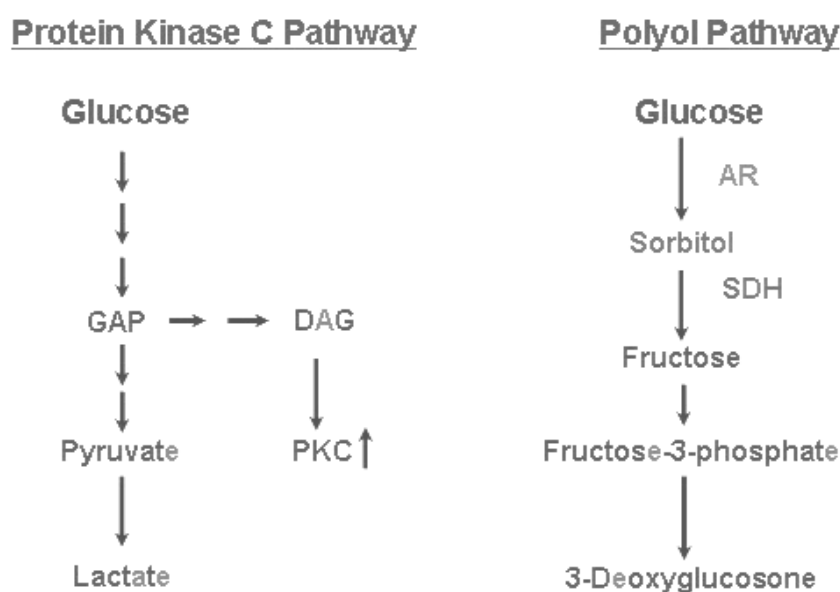

Figure 1. Scheme represents protein kinase C and polyol pathways in the pathogenesis of diabetic complications. GAP, glyceraldehydes-3-phosphate; DAG, diacylglycerol; PKC, protein kinase C; AR, aldose reductase; SDH, sorbitol dehydrogenase.

Polyol pathway

Only a small proportion of glucose is metabolized to sorbitol during normoglycemia, while in hyperglycemia the enzyme aldose reductase is activated, leading to an accumulation of intracellular sorbitol and fructose that increases the flux through the polyol pathway [59]. Sorbitols and other polyols accumulate intracellularly, leading to osmotic damage and swelling. Aldose reductase (AR) is the first and rate-limiting enzyme of the polyol pathway, which converts monosaccharides (e.g. glucose) to their polyols or sugar alcohols (e.g. sorbitol) as seen in Fig. 1. This enzyme is widely distributed throughout the body, including those tissues that are susceptible to chronic diabetic complications (e.g. retina, lens, cornea, glomerulus, nervous system and the blood vessels) [60, 61]. In fact, alterations in sorbitol and fructose metabolism are implicated as factors contributing to vascular complications in diabetes mellitus [60].

Advanced glycation end products

Non-enzymatic glycation has recently attracted increasing interest as a crucial pathophysiologic event behind hyperglycemia-related alterations and in the pathophysiology of the development of diabetic complications. Proteins and lipids exposed to aldose sugars go through reactions, which ultimately lead to the formation of advanced glycation end products (AGEs), a heterogeneous mixture of complex structures [62]. Although the series of reactions producing AGEs occurs at a very slow rate under normal circumstances, in diabetes their formation is accelerated to an extent related to the level and duration of hyperglycemia [63,64].

The potential pathophysiological significance of AGEs is associated with their accumulation in plasma, cells and tissues and their contribution to the formation of cross-links, generation of reactive oxygen intermediates, and interactions with particular receptors on cellular surfaces [65]. It has been reported by Cipollone and co-workers that advanced glycation end products might contribute to the atherosclerotic process seen in T2DM [66]. More details about AGEs and the well-characterized form of AGEs; N^{ε}-(carboxymethyl)lysine were discussed by Ahmed et al. [67].

Genetic factors

Despite the crucial role of hyperglycemia on diabetic complications, other factors such as hypertension, obesity, and hyperlipidemia undoubtedly contribute. There are patients with longstanding hyperglycemia without complications and patients with short duration of disease who seem to be very prone to complications. Genetic factors are obviously important as prevalence is affected by the background population. Studies using several techniques including twin studies and diabetic animals have revealed definitive genetic predispositions to the development of diabetes [68,69] and these predispositions might be dependent on environmental stimulants.

An important variability in the incidence of diabetes-derived chronic complications exists, which may indicate the existence of a predetermined genetic susceptibility in its onset. The association between obesity and T2DM is well known and studies have started to focus on the biological basis for this link. In fact, about 60-90% of T2DM patients are overweight or obese thereby providing ample support for the term "diabesity" used to describe obesity-related T2DM [70,71]. A strong support for the presence of an underlying genetic predisposition in those obese individuals who progress to T2DM has been provided by fact that while most T2DM patients are obese, most obese patients not necessary to have overt T2DM.

Type 2 diabetes and microvascular complications

Diabetic retinopathy

Diabetes results in characteristic lesions in the retinal blood vessels. Diabetic retinopathy is still the most common cause of acquired blindness in the Western world [72]. Its prevalence increases most steeply between 5 to 15 years of diabetes duration, being about 60% after 20 years in the European population. This can result in formation of microaneurysms (minimal retinopathy), haemorrhages and increased leakage, causing retinal edema and lipid exudates (background retinopathy). When pathological development of new vessels in the retina or abnormal blood vessels and fibrous tissue (i.e. neovascularisation) occurs, the retinopathy is classified as proliferative retinopathy [73]. The formation of fibrous tissue may eventually cause retinal detachment and severe visual impairment [74]. Also, an excess of glucose activates the polyol pathway, which causes accumulation of sorbitol in the lens and is accompanied by cataracts [75]. The etiology of retinopathy includes hyperglycemia-associated biochemical, anatomical, and functional changes.

Diabetic nephropathy

Diabetic nephropathy is estimated to develop in one third of both main types of diabetes [76]. Nephropathy is characterized by glomerular basement membrane thickening and arteriosclerosis of small arterioles. The hallmark of renal damage in diabetes is increased excretion

of albumin in the urine. The natural history of diabetic nephropathy has been viewed as a descending path from normoalbuminuria to microalbuminuria, clinically overt diabetic nephropathy; i.e macroalbuminuria, and eventually to end-stage renal disease. The term microalbumiuria; i.e. incipient diabetic nephropathy, has been defined as urine albumin excretion rate 20-200 μg/min in a timed overnight or 30-300mg/24h urine collection [77] as determined by sensitive laboratory measurements. Urine albumin excretion rate exceeding these values is called macroalbuminuria and considered a sign of manifest diabetic nephropathy. It has been estimated that approximately half the patients with microalbuminuria will progress to overt nephropathy [78]. In fact, most of the hemodialysis patients and the patients receiving renal transplants have diabetes [79].

Diabetic neuropathy

The term diabetic neuropathy includes either a clinical or subclinical disorder without any additional causes of peripheral neuropathy other than diabetes. In fact, damage to the microvasculature in peripheral nerves is now becoming recognized as a major pathogenic factor in diabetic neuropathy [80]. It may affect both sensory and autonomic nerves, but distal symmetric polyneuropathy is probably the most common consequence which, together with peripheral vascular disease, is an important etiologic factor for foot ulcerations and lower limb amputations. Autonomic dysfunction is common in people with diabetes, but is only clinically apparent in a small percentage.

Diabetic neuropathy is encountered in about half of all people with diabetes either as a polyneuropathy or mononeuropathy [81] especially in patients over 60 years age with T2DM [82]. Although exact prevalence depends on the diagnostic criteria used to identify neuropathy, most studies suggest that 50% of patients with a 20-years history of either type 1 or type 2 diabetes have neuropathy [83,84]. Around 10% of these cases of neuropathy are associated with abnormal sensations and pain [85]. The incidence of neuropathy increases with duration of diabetes and is accelerated by poor control [86]. Additionally, the death rate is as high as 50% at three years after diagnosis of overt autonomic neuropathy [82].

How big is the problem?

Normally properly treated diabetes is symptomless, but continuing hyperglycemia seen in type 2 diabetes can give rise to chronic complications [87] including retinopathy, neuropathy and nephropathy [88], and macrovascular complications [89]. A common denominator for all microvascular and macrovascular complications is extensive vascular damage. Both of these conditions are life threatening and may result in an altered mental state, loss of consciousness, and possibly death; therefore prompt medical attention is necessary to avoid adverse outcomes. Microvascular complications comprise changes in the small blood vessels of the eye that result in diabetic retinopathy, in the peripheral nerves, causing neuropathy, and finally in the kidney, causing diabetic nephropathy. As a result, diabetes is the most common cause of blindness, end-stage renal disease [90], and limb amputation [91].

In macrovascular complications, accelerated atherosclerosis results in cardiovascular disease (CVD) such as coronary heart disease (CHD) and acute myocardial infarction (AMI). Through its effects on cardiovascular disease (70-80% of people with diabetes die of cardiovascular disease), diabetes is also now one of the leading causes of death. While the pathogenesis of these complications has been extensively studied for the past 50 years, no single etiology exists to explain all types of complications. Instead, multiple etiologies exist that are specific to each. The cost to care for patients with DM in the U.S. was approximately $132 billion. Of those costs, $40 billion was indirect medical expenses (disability, work loss, and premature deaths), and $92 billion dollars was direct medical expenses (those attributable to the disease itself, i.e. microvascular and macrovascular complications) [92]. In fact, approximately 25% of the total Medicare budget is used for the treatment of DM and its complications [93, 94].

In Africa, the burden of diabetes cost is huge and depending upon the individual and the family. It has been established that 50% of diabetes care is paid by the patients, 44% by the family, 2% by the employer, 2% charities and others, and only 2% by the government [95]. Therefore, recommendations founded on the results of Guerci et al. study showing benefits of intensive glycemic control [96]. Thus, development of tools and models for diabetes health care could potentially result in a substantial decrease in diabetes-associated vascular complications.

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