Diabetic complications and their implications on health care in Asia

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Diabetes mellitus is a growing health problem in the Asia-Pacific region. The acute and chronic complications of diabetes mellitus are major causes of hospital admissions, blindness, renal failure, amputations, stroke, and coronary heart disease in this region. Compared with the general population, the annual per capita health care expenditure is estimated to be four-fold for people with diabetes. Recent prospective studies have provided unequivocal evidence for the crucial role of prolonged hyperglycaemia in the development of chronic diabetic complications. Although the aetiology of hyperglycaemia-induced damage of the kidneys, eyes, nerves, and arteries still remains to be elucidated, observational and interventional studies show that the occurrence and progression of these complications can be prevented by the optimal control of blood glucose, hypertension, and dyslipidaemia. Lifestyle changes such as weight control, increased physical exercise, and smoking cessation are also potentially beneficial in preventing diabetes mellitus and coronary artery disease. Furthermore, the morbidity and mortality caused by diabetes mellitus can be reduced by secondary prevention through regular screening, early detection, and appropriate treatment of chronic complications. Improved diabetes education is needed among health professionals as well as the general and diabetic populations. Government and public health officials should be mindful of the economic impact of this major health problem so that adequate health care resources can be allocated for the primary and secondary prevention of diabetic complications.

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Introduction

There is a growing epidemic of diabetes mellitus, type 2 in particular, in the Asia-Pacific region.[1] According to current estimates, this region has the largest diabetic population in the world—namely, 47.3 million, which is 46% of the global burden of diabetes.[2] Population-based surveys from Asia show a wide range of prevalence rates of diabetes mellitus: from 1.3 % in Vietnam to 24.2% in certain Indian urban communities.[3-5] No doubt some of the reasons for the variability are differences in the age range surveyed, study methodology, sampling techniques, and criteria used to classify diabetes mellitus. Nevertheless, there is a rapidly increasing trend in the prevalence of the disease in Asian countries. For example, the prevalence has increased approximately three-fold, from 0.8% to 2.3%, between 1986 and 1994 in China.[6] More recent data from certain Chinese cities suggest this increase may be even more pronounced, with a prevalence of as high as 9.2% in Hong Kong.[7] The epidemiological transition from life-threatening infectious disease towards more chronic conditions, 'westernisation' in diet and lifestyle practices, and effects of 'thrifty genes' together probably account for this dynamic epidemic of diabetes mellitus in Asia.[2]

Diabetes is a major source of morbidity, mortality, and economic cost to society. Patients with diabetes are at risk of the development of acute metabolic complications such as diabetic ketoacidosis, hyperglycaemic hyperosmolar nonketotic coma, and hypoglycaemia. They are also at risk of experiencing chronic complications such as atherosclerotic diseases, retinopathy, nephropathy, neuropathy, and foot ulceration, as well as other general medical conditions unrelated to the acute or chronic complications specific to diabetes. It has been estimated that the annual per capita health care expenditure in the United States in 1997

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was four-fold for people with diabetes when compared with the general population.[8]

This article reviews the chronic complications of diabetes mellitus and considers the scientific basis, clinical care, economic impact, and public health implications of these co-morbidities on patients, doctors, and health care organisations in Asia.

The glucose hypothesis

Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia and alterations in fat and protein metabolism, and the occurrence of a specific set of chronic complications. The plasma glucose cut-off levels for diagnosing diabetes mellitus rest firmly in their association with diabetic complications such as retinopathy.[9] The tacit recognition of the close relationship between hyperglycaemia and chronic complications has led to the 'glucose hypothesis',[10,11] which proposes that hyperglycaemia is directly, or indirectly, related to the development or progression, or both, of diabetic complications, including the microvascular conditions of retinopathy, nephropathy, and neuropathy.[12] For macrovascular or atherosclerotic complications of diabetes mellitus, a subanalysis of the Framingham Heart Study cohort has demonstrated a clear dose-response association between glycated haemoglobin levels and the prevalence of cardiovascular disease.[13] In addition, recent interventional studies in patients with type 1[14] and type 2[15] diabetes mellitus have provided strong support for the glucose hypothesis. In the Diabetes Control and Complications Trial (DCCT), intensive therapy reduced the development and progression of all complications by approximately 50%.[14] This uniform salutary effect on retinopathy, nephropathy, and neuropathy further suggests that hyperglycaemia may play a similar role in the pathogenesis of these complications.[11]

Exactly what the pathogenetic mechanism is and how it works are still unanswered questions. Traditionally, there have been two major putative pathways: the aldose reductase–sorbitol and the glycation models. Results of animal studies support the former model, but results from human studies have been less convincing.[16-18] The efficacy of a potent protein glycation inhibitor was reported in a diabetic animal model in 1986,[19] but its effectiveness remains to be proven in an ongoing human clinical trial. A third pathway by which hyperglycaemia may cause long-term vascular complications, has recently been described.[20] This model suggests that the activation of the β_2-isoform of protein kinase C in vascular tissue is a key step in the cascade of events through which glucose triggers diabetic complications.[10,20]

The available evidence indicates that chronic hyperglycaemia is a causal link between diabetes mellitus and diabetic complications. However, the precise mechanism by which hyperglycaemia may cause complications in diabetic individuals remains to be clearly defined. Data from familial[21] and ethnic[22] clusterings of diabetic complications suggest that the susceptibility to hyperglycaemia-induced tissue damage may be determined by genetic factors. Candidate genes such as the aldose reductase gene[23-25] and fibrinogen gene,[26] which confer susceptibility to microangiopathic and macroangiopathic complications respectively, have been identified in various sib-pair linkage analyses[26] or case-control studies.[23-26]

Microvascular manifestations

Diabetes mellitus is the leading cause of blindness, end-stage renal disease, and non-traumatic amputation in industrialised countries.[27,28] These conditions are the direct end-points of microvascular complications that are specific to diabetes and which include retinopathy, nephropathy, and neuropathy. The risks of these conditions developing can be significantly reduced by optimising glycaemic control and if they are detected and treated early through patient education and regular screening.[14,15,28]

Retinopathy

Retinopathy is an important complication of diabetes mellitus in the Asian population. The prevalence between 1990 and 1996 for patients with newly diagnosed type 2 diabetes mellitus has been estimated to be 22% in Hong Kong,[29] and a population-based study performed in China in 1986 showed a prevalence of 31%.[30] Randomised controlled trials such as the DCCT and the United Kingdom Prospective Diabetes Study (UKPDS) have shown conclusively that improving glycaemic control can decrease the incidence of diabetic retinopathy.[14,15] This concept is also supported by prospective follow-up studies among Japanese and Chinese patients with type 2 diabetes mellitus.[31,32] Furthermore, the DCCT also demonstrated that strict glucose control retards the progression of background, non-proliferative retinopathy.[14] Thus, primary and secondary prevention of retinopathy can be effectively accomplished by intensive glycaemic management and regular ophthalmological screening.[14,15]

Proliferative retinopathy and macular oedema are late complications in the continuum of diabetic retinal

disease. Research on tertiary prevention has shown that these conditions can be treated using laser therapy, which reduces significantly the incidence of severe visual loss and blindness.[33] Despite these findings, only 35% to 60% of American diabetic people currently undergo annual ophthalmological screening.[34] There is no corresponding estimate for Asian countries, where the rate is conceivably even lower due to the long latent phase of retinopathy, a lack of health promotion activities, and scarce availability of resources and services. In Hong Kong, a recent cross-sectional study of 629 asymptomatic type 2 patients revealed that 19% and 3% of subjects had non-proliferative retinopathy and proliferative changes that required laser treatment, respectively.[35] Thus, it is recommended that all diabetic patients undergo an annual dilated fundal examination to screen for diabetic retinopathy.[28,36]

Nephropathy

Diabetic nephropathy (ie comprising microalbuminuria to end-stage renal disease) develops in approximately 35% of patients with type 1 diabetes mellitus and between 15% and 60% of patients with the type 2 disease.[37] It is the leading cause of chronic renal failure worldwide and is responsible for about one third of patients who undergo dialysis.[38] One of the initial markers of this condition is microalbuminuria, which indicates an increased risk of progression to nephropathy as well as an elevated risk of cardiovascular events.[39] The natural course of diabetic nephropathy is such that once overt nephropathy develops, renal function progressively declines and culminates in end-stage renal disease.[40,41] Hence, as with retinopathy, optimal glucose control is of paramount importance as a primary preventive measure against the development of diabetic nephropathy.[14,15]

In addition, all diabetic people should be screened for proteinuria and microalbuminuria annually.[28,36] There are various ways of performing urine tests; Table 1 shows the diagnostic criteria for albuminuria.[42] Measuring the random, spot albumin to creatinine ratio is a simple technique that can be used as a screening test.[28] Because of significant variations in urine albumin excretion, however, it is recommended that if the results of the first test are positive for albumin, the test be repeated for confirmation. If the second test gives negative results, a third test should be performed. Two of the three tests should give positive results and other potential aetiologies should be excluded before the presence of microalbuminuria can be concluded.[28,42] If albuminuria is diagnosed, treatment with an angiotensin-converting enzyme (ACE) inhibitor should be considered. This treatment can reduce albuminuria and delay or possibly halt the progression to nephropathy, independent of its blood pressure–lowering effect.[43] Aggressive blood pressure control is also of vital importance in preventing progression of declining renal function. Maintaining the blood pressure is the only modality that has consistently been shown to be effective in halting progression to overt nephropathy and renal failure.[44] Although absolute target blood pressure levels for patients with diabetic nephropathy have not been well delineated, there is a clear association between blood pressure and the rate of progression of diabetic renal disease, in both Caucasian and Chinese populations.[44,45]

There has recently been a renewed interest in the pathogenetic role of hyperlipidaemia in diabetic nephropathy.[46] Results from a prospective trial performed in Hong Kong have shown that effective normalisation of hypercholesterolaemia might retard the progression of nephropathy in patients with type 2 diabetes mellitus.[47] The full potential of lipid-lowering therapy remains to be established by longer-term studies with a larger sample of individuals.

Neuropathy

Diabetic patients have an increased risk of the development of neuropathy. Foot ulcers may develop, mainly because of the abnormal distribution of pressure owing to peripheral neuropathy. A study in the United States showed that one half of a group of patients who had had type 2 diabetes mellitus for more than 15 years also had diabetic neuropathy.[27] Even among newly diagnosed cases of type 2 diabetes mellitus, retrospective data from Hong Kong suggest a prevalence of neuropathy of approximately 13%.[29] As with retinopathy and nephropathy, a policy of

Table 1. Cut-off values for microalbuminuria using different types of urine test[42]

Test	Units	Normal	Microalbuminuria	Macroalbuminuria
24-hour	mg/d	<30	30-300	>300
Overnight	μg/min	<20	20-200	>200
1st morning or random test:				
albumin	mg/L	<20	20-200	>200
albumin : creatinine	mg/mmol	<2.5 for men	-	-
		<3.5 for women	-	-

strict glycaemic control reduces the incidence of neuropathy in patients with either types 1 or 2 diabetes mellitus.[14,15] The early detection of diabetic neuropathy results in fewer hospitalisations of patients with foot ulcers and fewer lower-extremity amputations.[48] Accordingly, all diabetic patients should regularly undergo sensory testing and be screened for foot ulceration at regular intervals. In the absence of clear evidence, consensus expert opinion suggests annual sensory examination and opportunistic screening for foot ulceration at each clinical encounter.[28,36] Educating patients and increasing physician surveillance regarding foot care and risk factors for amputation have been tested in a randomised controlled trial and a prospective study. Both studies reported significant reductions of serious foot ulceration in the intervention groups.[49,50]

Macrovascular manifestations

Diabetes mellitus is an independent risk factor for the development of atherosclerosis.[51] On the other hand, atherosclerotic or macrovascular disease is responsible for more than 50% of all deaths in patients with type 2 diabetes mellitus.[27] Cardiovascular disease accounts for most cases of diabetic macrovascular complications; the remainder are caused by cerebrovascular events and peripheral vascular disease.[52] The results from a population-based study suggest that there is a 10-fold increase in coronary artery disease among Chinese diabetic patient when compared with the characteristically low rate among non-diabetic controls.[30]

While hyperglycaemia has been conclusively shown to be the causal link between diabetes mellitus and microvascular complications, its association with macrovascular manifestations is much more tenuous, as reflected by the results of the UKPDS and the DCCT.[14,15] In the UKPDS, the number of macrovascular events greatly outnumbered that of microvascular complications, but the difference was found to be non-significant. This result was not wholly unexpected given the multifactorial nature of cardiovascular disease. Factors such as hypertension, hyperlipidaemia, and tobacco use contribute to the development of atherosclerosis in diabetic people. Hence, hypertensive control, lowering lipid levels, and smoking cessation are important preventive measures that can help prevent the development of macrovascular diabetic complications.[28,36]

Hypertension develops in people with type 2 diabetes mellitus at twice the rate of those who are non-diabetic.[53] Hypertension is a major contributor to atherosclerotic diseases and can lead to a more rapid progression of nephropathy and renal failure.[54,55] The UKPDS has demonstrated that a policy of rigorous blood pressure control reduces the risk of macrovascular and microvascular complications in patients with type 2 diabetes mellitus, even more so than the effect of strict glycaemic management.[44] Thus, screening and treating hypertensive diabetic patients are essential. There is no clear evidence to support a specified goal in blood pressure control, although the UKPDS used an upper limit of 150/85 mm Hg as its definition of stringent hypertensive control.[44]

Elevated serum lipid levels are also a significant risk factor in the development of macrovascular diseases in patients with type 2 diabetes mellitus. There are no large randomised controlled trials reported that evaluate the effectiveness of giving lipid-lowering treatment to diabetic patients who have an abnormal lipid profile and are at risk of heart disease. However, small subgroup analyses of two studies of high-risk diabetic individuals have shown that lowering low-density lipoprotein–cholesterol levels leads to a"significant reduction in cardiovascular mortality.[56,57] Given the high prevalence of cardiovascular disease in diabetic patients and its associated morbidity and mortality,[27] a conservative approach would be to screen for hyperlipidaemia annually and to treat the condition as soon as it is detected.

It is well known that tobacco use and diabetes mellitus are synergistic risk factors in the development of cardiovascular disease.[58] Smoking is also responsible for a whole spectrum of other diseases, which include numerous cancers and chronic lung disease. It follows that all possible measures should be used to prevent people from starting the habit, and to encourage smokers to stop, especially in the diabetic population.[28,36]

The traditionally ‘soft’ cardiovascular risk factors of obesity and a sedentary lifestyle may be particularly important in South Asian (Indian, Pakistani, and Bangladeshi) diabetic patients. Observational studies have demonstrated higher mortality and morbidity rates of cardiovascular disease in overseas migrants of South Asian descent who have diabetes, compared with other ethnic groups.[59] It has been hypothesised that the high mortality rate is due to metabolic disturbances related to insulin resistance.[59] Results from the United Kingdom have confirmed the existence of insulin resistance syndrome (glucose intolerance,

hyperinsulinaemia, hypertension, low levels of plasma high-density lipoprotein–cholesterol, and high levels of triglycerides), which is especially prevalent in South Asians and which is associated with a pronounced tendency to central obesity.[59] Thus, the management of obesity and increased physical exercise represent the most ideal preventive measures against diabetes mellitus and coronary artery disease in this vulnerable population.

The economic burden of diabetes mellitus and its complications

Diabetes mellitus is a major and increasing cause of chronic ill health and premature mortality in almost all Asian countries,[1-7] and results in rising costs because of absence from work and health care expenses.[8,60] To facilitate service planning and to allocate public health resources appropriately, there should be reliable estimates and projections of the economic costs associated with diabetes mellitus, its complications, and its co-morbidities. This is especially true in Asian countries where there is a dynamic, growing epidemic of diabetes.[1-3]

There are two main approaches to investigating the economic impact of diabetes mellitus and its complications. The first approach uses disability-adjusted life-years (DALYs) to measure the intangible costs associated with the disease, and combines the healthy life-years lost as a result of premature mortality with those lost due to disability or ill health. This method is valuable, because a substantial portion of health care expenditure is directed towards improving the quality of life and life expectancy in diabetic individuals. The largest relevant study that has been published so far was performed by the World Bank in 1993.[61] Their global study investigated the DALYs lost due to various diseases, including diabetes, and estimated that 1362 million DALYs were lost worldwide as a result of all illnesses in 1990. Of these, diabetes mellitus and its complications accounted for 7.97 million DALYs, as shown in Table 2.[61] The majority of losses were incurred in developing nations (eg China and India). When comparing the DALYs lost with per capita health expenditures in different countries, the data suggested that the countries in which 80% of the DALYs lost were attributable to diabetes mellitus shared only 13% of the world's health care expenditures.[60] For example, with an annual per capita expenditure on health care of US$21, the population of India lost 1.9 million DALYs because of diabetes mellitus. In contrast, established market economies such as the Organisation for Economic Cooperation and Development nations, which account for 15% of the world's population and 87% of its health care resources, together lost only 1.3 million DALYs because of diabetes mellitus.[60] In short, the heavy economic burden of this life-long condition due to loss of quality of life and premature mortality is concentrated in those countries with the lowest health care budgets, many of which are in Asia.[60,61] Despite some criticisms and caveats about methodological issues, the World Bank study provides strong support for the need to improve the provision of diabetic health services in Asian countries, particularly in those undergoing rapid demographic and economic development.[61]

The second and most frequently employed technique used to evaluate the economic implication of diabetes is the cost-of-illness approach, which examines the direct and indirect costs associated with the condition. In Asia, there has been little systematic effort to conduct comprehensive examinations of the economic consequences of diabetes mellitus. In the United States, direct medical expenditures attributable to diabetes mellitus in 1997 totalled US$44.1 billion. The breakdown was as follows: US$7.7 billion because of diabetes and acute glycaemic care, US$11.8 billion because of the excess prevalence of related microvascular and macrovascular complications, and US$24.6 billion because of the excess prevalence of general medical conditions.[8] Of these direct costs, 62%, 25%, and 13% were related to in-patient care, ambulatory services, and long-term care, respectively. Two thirds of all medical costs were borne by the elderly (aged >65 years) population. Attributable indirect costs totalled US$54.1 billion and comprised US$17.0 billion due to premature mortality and US$37.1 billion due to disability. Furthermore, total medical expenditure incurred by diabetic patients was US$10 071 per capita, compared with US$2669 for the non-diabetic population.[8] Likewise, the economic

Table 2. The number of diability-adjusted life-years lost as a result of diabetes mellitus in 1990[61]

Country/region	Disability-adjusted life-years (x10^6)	Health expenditure per capita (US$)
China	0.77	11
India	1.87	21
Other Asian countries	1.15	61
Established market economies	1.33	1860
Worldwide	7.97	329

burden of diabetes mellitus in Asia is enormous, anticipated by the prevalence and incidence of the disease and is predicted to increase more in Asia than in the industrialised western nations in the next few decades.[1-3,60] It has been estimated that the overall health care costs due to diabetes mellitus in the year 2010 will be doubled when compared with 1990.[60]

Implications of public health and health care

Given the very serious clinical and economic ramifications of diabetes mellitus, it is imperative that doctors, public health practitioners, and policy makers vigorously pursue health care strategies and medical innovations that can delay the onset and slow the progression of the disease and its complications. One strategy is to reduce the incidence of diabetes mellitus in Asia. While genetic factors have a definite role in the development of the disease, there are also environmental and lifestyle risk factors, such as a high saturated fat diet, obesity, and lack of physical activity.[1,3] These three risk factors are currently recognised as the most potentially modifiable. Although implementing lifestyle changes, as with any behavioural change, poses a difficult challenge, doing so is essential to improving public health and lessening the impact of the Asian diabetes epidemic.

A second, complementary strategy is to focus on the primary and secondary prevention of diabetic complications in individuals who have already developed diabetes mellitus. The DCCT and UKPDS have shown that optimal glycaemic control is the most ideal primary preventive measure against the development of complications.[14,15] It is also well known that treating complications such as eye and limb diseases, heart disease, neuropathy, and nephropathy contribute the most to the costs of diabetes care.[62] Once complications develop, the indirect costs of disability and premature mortality increase exponentially; hence, the secondary prevention of diabetic complications may be highly effective in reducing the health care burden of diabetes mellitus in general.[63] Such secondary preventive measures include a policy of strict blood pressure control,[44] institution of ACE inhibition in microalbuminuric patients,[43] normalisation of hyperlipidaemia,[47,56,57] smoking cessation,[28,36] and regular screening for all diabetic complications.[28,36]

A third major component in combating the diabetes epidemic in Asia involves health promotion and patient education. The reasons are two-fold. Firstly, there are many undiagnosed cases of diabetes mellitus in Asia. For example, the ratio of undiagnosed to diagnosed cases in Vietnam and Bangladesh is as high as 4:1.[1,4] There is thus a serious potential for severe diabetic complications to occur because of prolonged undiagnosed hyperglycaemia. Secondly, the clinical presentation of type 2 diabetes mellitus and its complications are usually insidious and have a long latent period. As a consequence, patient compliance with regular follow-up and screening may be poor because the conditions are asymptomatic. Patients therefore need to be adequately informed of the necessity and benefits of these clinical interventions. Financial constraints in some developing Asian economies, however, may render optimal diabetes care impossible. Even when the services are provided, they may be inadequate or inaccessible to patients.[34]

Finally, increases in both the cost of providing quality diabetes care and the number of people developing the disease have led to a search for more cost-effective models of care. One such model is the 'shared care' approach, the efficacy of which has been well documented.[64,65] In this approach, both specialists and primary care doctors participate in the planned delivery of care; they also exchange information over and above routine discharge and referral notes. Hallmarks of effective and efficient shared-care schemes include computerised central recall with prompts for patients and their family doctors, shared records, improved communication between doctors and patients, flexible and agreed management plans, the possibility of patients moving up and down the levels of care, and a fail-safe system of coordinated care.[64,65]

Conclusion

The growing Asian epidemic of diabetes mellitus, and its implications in terms of morbidity, mortality, and economic costs of its complications, calls for urgent attention from clinicians, public health officials, and governments. Doctors should be encouraged to implement primary and secondary preventive measures that have been proven to be effective, while community health workers should actively promote diabetes education to diagnosed patients as well as to the general public. Furthermore, government agencies should increase and redirect appropriate human and financial resources towards services for the diabetic population. When the demand exceeds the realistic possibility of supplying the needed services, which is the case in many developing countries in Asia, the limited health care resources must be rationally allocated to programmes of proven efficacy.[66] This is a tough challenge indeed, and the decisions made will influence the quality of diabetes care in Asia.

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