Diabetes in the Chinese Population and Its Implications for Health Care

JULIANA C.N. CHAN, MD, FRCP
CLIVE S. COCKRAM, MD, FRCP

Diabetes is a major public health problem. There is now a wealth of data confirming the marked increase in diabetes prevalence in nonwhite populations when they move rapidly from a rural or subsistent lifestyle to one of affluence. In the last decade, there is also accumulating data confirming the rising prevalence of diabetes in the Chinese population, which accounts for >20% of the world's population. Hong Kong is a cosmopolitan city with a population of 6 million, over 90% of whom are of southern Chinese origin. In many ways, Hong Kong is an epitome of future China. In this article, we review the prevalence and pattern of diabetes among Hong Kong Chinese, together with health care implications. The information provides insights into the potential problems faced by China's 1.2 billion people as they continue with economic and social reforms.

PREVALENCE OF DIABETES — In the Chinese population, the prevalence of diabetes rises from <1% in some rural areas in Mainland China to 6–12% among Chinese living in Hong Kong, Singapore, and Taiwan (1–3). In a small group of Chinese living in Mauritius, the prevalence of diabetes is as high as 16% (4). In Singapore, the age-adjusted prevalence appears to have approximately doubled during each of the last 2 decades, reaching 8% in the early 1990s (5). Most epidemiologists regard diabetes as a problem of epidemic proportions. It has been predicted that by the year 2010, the number of people with diabetes will exceed 200 million, the majority of whom will be in Asia (6).

To date, four large-scale epidemiological studies have been performed in Hong Kong. In 1987, based on a household sampling method, the prevalence of diabetes was reported to be 10% in 427 Chinese subjects aged ≥65 years. This percentage increased to 17% in those >75 years of age (7). Similar prevalence rates have also been reported in another study involving 1,467 ambulatory elderly subjects aged 60–90 years (8). In 1990, using the World Health Organization (WHO) criteria, the crude prevalence of diabetes was 4.5% in a workforce of 1,513 subjects aged 30–65 years. The prevalence increased from <1% in subjects younger than age 30 years to >15% in people older than age 50 years. Over 60% of these subjects were previously undiagnosed. The age-adjusted prevalence of diabetes was 9% in men and 6.3% in women, and the respective rates for impaired glucose tolerance (IGT) were 11.2 and 6.3% (9). In 1995, a population-based survey involving 3,000 subjects showed a prevalence of diabetes of 1.5% in men at age 25–34 years, increasing progressively to 21.1% in those age 65–74 years. The corresponding prevalence rates in women were 1.4 and 29.3% (10).

Studies in the 1980s from Mainland China show a low prevalence of diabetes ranging from 0.15% in Guizhou and 0.33% in Guangdong to ~1% in cities such as Beijing, Shanghai, and Nangxia (11,12). In the early 1990s, the Da Qing study used WHO criteria and involved 110,660 subjects aged 25–74 years. In this study, the prevalence of newly diagnosed diabetes was 6/1,000 and that of IGT was 5.5/1,000 (13). The latest epidemiological data from China showed age-adjusted prevalence rates of 3.6% for diabetes and 4.2% for IGT in 213,515 subjects aged 25–64 years. These figures confirm the rapid rise that has occurred in the last 10 years. The increase in diabetes prevalence was observed mainly in postmenopausal women (14).

PREDICTIVE FACTORS FOR DIABETES — In agreement with most studies (15), including those performed among Chinese from Mainland China (13), Taiwan (2), and Mauritius (4), the predictive factors for diabetes among Hong Kong Chinese include aging, obesity (both general and central), and a positive family history. In the 1990 study, >30% of diabetic subjects gave a positive family history of diabetes affecting at least one first-degree relative (parents, siblings, or children). Both BMI and waist-to-hip ratio (WHR) correlate with diabetes prevalence, with a high WHR conferring risk independently of BMI. The mean BMI in Hong Kong Chinese of working age (30–65 years) is 23 kg/m^2 in both men and women. In diabetic subjects, the mean BMI increases to 24 kg/m^2 in men and 26 kg/m^2 in women. The mean WHR in normal men and women is 0.87 and 0.79, respectively, compared with 0.92 in diabetic men and 0.86 in diabetic women (9). Using the conventional definition of obesity (BMI ≥25 kg/m^2 in women and ≥27 kg/m^2 in men) (16), 28% of women and 10% of men are obese. Despite the relatively slender build of the Chinese people, there are close associations between BMI, WHR, and waist circumference, and most cardiovascular risk factors including blood pressure, plasma glucose, insulin, and lipid concentrations as well as microalbuminuria (17). These findings emphasize the importance of establishing epidemiological data in different ethnic groups to allow valid assessment of cardiovascular risk. The degree of change of obesity from the baseline of a particular group may be at least as important as the absolute values reached.

DIAGNOSIS OF DIABETES — Although the 75-g oral glucose tolerance test (OGTT) remains the gold standard for the

From the Departments of Clinical Pharmacology (J.C.N.C.) and Medicine (C.S.C.), The Chinese University of Hong Kong, The Prince of Wales Hospital, Hong Kong, China.

Address correspondence and reprint requests to Juliana C.N. Chan, MD, FRCP, Department of Clinical Pharmacology, The Chinese University of Hong Kong, The Prince of Wales Hospital, Shatin, N.T., Hong Kong, China. E-mail: jchan@cuhk.edu.hk.

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Abbreviations: FFA, free fatty acid; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization; WHR, waist-to-hip ratio.

diagnosis of diabetes at the moment, its poor reproducibility has been demonstrated in many racial groups (18) including the Chinese (19). While the diagnostic 2-h plasma glucose value of ≥11.1 mmol/l was selected as a threshold value for the subsequent development of retinopathy (20), the definition of the fasting plasma glucose value of ≥7.8 mmol/l was more arbitrary. The latter has been shown to have low sensitivity and specificity in diagnosing diabetes in many racial groups (21–24). In Hong Kong, over 80% of diabetic subjects were diagnosed on an elevated 2-h plasma glucose concentration and had a fasting plasma glucose concentration <7.8 mmol/l. The fasting plasma glucose concentration corresponding most closely to a 2-h post–glucose loading plasma glucose concentration lies between 5.7 and 5.8 mmol/l (25). We have further shown that nondiabetic Chinese subjects with a fasting plasma glucose between 5.7 and 7.8 mmol/l were more obese and had higher blood pressure, plasma lipid, and insulin concentrations compared with those subjects with a value <5.7 mmol/l despite adjustment for age (26). Taken together with the known increased cardiovascular risk in subjects with IGT, our findings in Chinese subjects lend strong support to suggestions that plasma glucose concentration (dysglycemia) should be viewed as a continuum of risk in a similar manner to other cardiovascular risk factors such as obesity, hypertension, and dyslipidemia (27).

HETEROGENEITY OF NIDDM AND IDDM — As in other nonwhite populations (28), classical IDDM is relatively uncommon in Chinese populations, including that of Hong Kong. The incidence of childhood IDDM in Hong Kong has been estimated at 1.8/100,000 per year (29). In an adult diabetes clinic-based population, only 3% of patients were considered to have classical IDDM as defined by an acute ketotic presentation or continuous requirement of insulin treatment within 1 year of diagnosis (30). The proportion of patients with clear-cut clinical IDDM is only 10% even among patients with young onset of disease (<35 years). However, over 25% of NIDDM patients require insulin therapy, and this increases to over 50% among patients with young onset of disease (31).

Clinical overlap between IDDM and NIDDM is increasingly recognized. Despite being insulin-deficient, white patients with latent autoimmune diabetes in adults (LADA) may present as primary oral drug failure without a history of ketosis (32). Conversely, some African-Americans present with ketoacidosis but subsequently revert to a clinical course that resembles NIDDM. These patients are often obese, non–insulin-deficient, markedly insulin-resistant, and do not have antibodies to GAD, a marker for autoimmune IDDM (33).

Hong Kong Chinese patients with clinical IDDM exhibit marked heterogeneity of pancreatic β-cell function. Only 74% of such patients are insulin-deficient based on post–glucagon-stimulated plasma C-peptide concentration. Antibodies to GAD were present in 23%, increasing to 31% in insulin-deficient patients. Two obese patients in the series mentioned were subsequently treated with oral hypoglycemic agents, despite presentation with diabetic ketoacidosis (34). In a further cohort of 150 patients with young onset of disease, only 10% had clinical IDDM. Although 50% of these patients were insulin-deficient, only 12% had antibodies to GAD. The prevalence of antibodies to GAD was 29% in patients who had both insulin deficiency, based on C-peptide status, and an IDDM-type presentation clinically. This was compared with 6% in those who were non–insulin-deficient and presented as NIDDM. Obesity and a positive family history were particularly prevalent in those young patients who did not have antibodies to GAD (35). This low prevalence of antibodies to GAD has also been reported in other Asian ethnic groups such as Japanese and Korean diabetic patients (36).

Subtypes of diabetes caused by various genetic mutations are being reported (37,38). These include mitochondrial DNA (39) and glucokinase gene mutations (40). These mutations have also been reported in some Chinese diabetic patients (41–43). These findings emphasize the heterogeneity of genotypes and phenotypes in Chinese patients with young or acute onset of disease. Despite the high prevalence of insulin deficiency, autoimmune IDDM remains uncommon and other causes should be sought. The clustering of obesity and other cardiovascular risk factors (44) in many of these young patients suggests that the metabolic syndrome may have the potential for earlier onset in the Chinese population.

THE METABOLIC SYNDROME — The majority of NIDDM patients, frequently though not invariably, have clustering of risk factors including obesity (especially visceral fat), hypertension, dyslipidemia (increased plasma triglyceride and reduced HDL cholesterol), hyperinsulinemia, and microalbuminuria. This is often referred to as the metabolic syndrome and increases the risk of early mortality, cardiovascular morbidity, and renal failure (44). In Hong Kong Chinese subjects, the prevalence of hypertension increases from <5% in normal subjects to 15–25% among subjects with glucose intolerance (45). Similar findings have been reported from Taiwan (46,47). In agreement with data on white subjects, several studies in Chinese populations have also confirmed the intimate associations between glucose intolerance and multiple cardiovascular risk factors, including hyperinsulinemia, insulin resistance, microalbuminuria, hyperlipidemia including apolipoprotein B (45,48) and apolipoprotein(a) (49), increased levels of fibrinogen (50), and coagulation factors (51) as well as vasoactive hormones (52–54).

VISCERAL FAT SYNDROME — Hyperinsulinemia has been proposed as a linking factor for the metabolic syndrome (44). However, this is increasingly being challenged due to inconsistent relationships between insulin and blood pressure in clinical and epidemiological studies (55). On the other hand, central adiposity, reflecting visceral fat accumulation, has been shown to be a robust correlate with cardiovascular risk factors (56). In Hong Kong Chinese NIDDM patients, visceral fat, as measured by magnetic resonance imaging, is also associated with multiple risk factors including insulin resistance, dyslipidemia, microalbuminuria, and higher 24-h ambulatory blood pressure readings (57). Age-related declines in growth hormone and sex steroids as well as activation of stress hormones such as cortisol may encourage the deposition of visceral fat. Visceral adipocytes are particularly sensitive to the lipolytic effects of catecholamines which result in increased free fatty acid (FFA) flux. The latter can induce insulin resistance and hyperinsulinemia. The interactions between these hormonal systems may then lead to diverse clinical manifestations (58). To test this hypothesis in our local population, we have used structural equation modeling to examine the interrelationships between the clinical and biochemical characteristics in 1,513 Chinese subjects. Although insulin was

shown to have minor effects on blood pressure and albuminuria, most of the variance in the components of the metabolic syndrome including blood pressure, plasma triglyceride, and glucose as well as albuminuria were explained by age, family history, BMI, and WHR. Our findings therefore also argue against a central role for hyperinsulinemia and lend support for other central neurohormonal mechanisms (45). The sharp rise in diabetes prevalence in postmenopausal women is particularly interesting in this context (59,60).

MORBIDITY AND MORTALITY OF DIABETES — As in most developed countries, there is a high use of health care resources by diabetic patients in Hong Kong. Over 30% of prescriptions issued from both the government primary health care and hospital medical clinics contain antidiabetic drugs (61). Over 30% of patients admitted with stroke (62–64), heart failure (65), acute myocardial infarction (66), or requiring renal dialysis have diabetes as a major contributing factor. Often, diabetes is diagnosed for the first time when it presents with these complications. Drug-induced hypoglycemia accounts for nearly 50% of all hospital admissions resulting from adverse drug reactions. Most episodes result from sulphonylurea usage rather than insulin with advanced age and renal impairment as major precipitating factors (67).

More than 30% of diabetic patients referred to a hospital clinic have evidence of previously undiagnosed retinopathy (68). About 200 new cases of blindness a year in Hong Kong are caused by diabetes (69). A major concern is the high prevalence and severity of microvascular complications in many young diabetic patients (70). Apart from the known risk factors such as long duration of (undiagnosed) disease, glycemic, and blood pressure control, genetic predispositions (mutations of the aldose reductase gene) may contribute to these complications (71). In the Da Qing IGT and Diabetes Study involving more than 110,000 Chinese subjects, 15% of newly diagnosed diabetic subjects were found to have diabetic retinopathy (72).

In contrast to Western countries where coronary arterial disease is the main cause of mortality in diabetic patients, renal failure and cerebrovascular accident are the leading causes of death among diabetic patients in Hong Kong Chinese (73,74). This may be in part due to the high prevalence of hypertension and albuminuria (50%) (31,45). Similar findings have also been reported in other nonwhite NIDDM populations (75). Furthermore, the risk factors for proteinuria in NIDDM patients appear to differ from those for retinopathy or neuropathy. While retinopathy and neuropathy rates increase with increasing duration of disease from diagnosis in Chinese NIDDM, microalbuminuria bears little relationship to disease duration. Microalbuminuria occurs in 40% of patients with <5 years of disease duration from diagnosis compared with 49% in those with >5 years of disease. Although patients with albuminuria had poorer glycemic control and higher blood pressure, 40% of normoalbuminuric patients had coexisting hypertension (31). A random spot urine albumin:creatinine ratio >5.4 mg/mmol predicts early mortality (mainly due to cardiovascular disease and renal failure), progression of albuminuria, and deterioration of renal function (74). Genetic factors, such as polymorphisms of the renin angiotensin system, have been implicated in the pathogenesis of diabetic nephropathy. One such example is the ACE deletion-insertion *DD* polymorphism associated with increased serum ACE activity. Some studies have shown associations between this genotype and diabetic nephropathy although reports are not always consistent (76). In Hong Kong Chinese, there is a high prevalence of homozygosity for the T235 allele of the angiotensinogen gene. We have further shown associations between the angiotensinogen *TT* genotype and ACE D allele with albuminuria in our local NIDDM patients suggesting that these genotypes may be relevant to proteinuria in the Chinese population (77).

THRIFTY GENOTYPES AND PHENOTYPES: HOW RELEVANT ARE THEY TO THE CHINESE POPULATION? — Several hypotheses have been put forward to explain the rapid increase in prevalence of NIDDM in modern societies. The thrifty gene hypothesis states that individuals who possess genetic traits allowing efficient storage of energy during a subsistent lifestyle may have a survival advantage. However, these traits may become disadvantageous during times of affluence by predisposing to obesity and NIDDM (78). A chronically stressful lifestyle may lead to neurohormonal changes such as chronic activation of the sympathetic nervous system and pituitary-adrenal axis. These in turn may be associated with abnormal fat and glucose metabolism (79), structural changes in muscle and vasculature as well as altered pancreatic β-cell function leading to insulin resistance, NIDDM, and hypertension (80). Psychosocial stress has been implicated in the development of ischemic heart disease (81), hypertension (82), and diabetes (83,84). On the basis of an association between low birth weight and development of NIDDM in later life in whites (85) and Pima Indians (86), environmental factors such as in utero nutritional deprivation and reduced pancreatic β-cell function may also contribute to the pathogenesis of the disease in later life. Given the recent rapid increases in food intake and psychosocial stress together with low physical activity, these factors may be particularly relevant to Asian, including Chinese, populations and may have additive or synergistic effects. Advances in affluence and urbanization are proceeding in China and other Asian countries at a rate that is historically unique.

DELIVERY OF QUALITY DIABETES CARE: AN ACHIEVABLE TARGET IN CHINA? — There are now clear data showing that diabetes and its complications are preventable and treatable in both IDDM (87) and NIDDM (88). However, given the magnitude of the problem and the finite resources for health care, the challenge lies in the effective delivery of quality care. Primary prevention as well as integration between primary health care teams and hospital specialists appear to be the optimal way to deliver care (89). However, for many reasons, these strategies and theoretical models are difficult to implement in Asian countries, such as China.

Lifestyle modification is the single most effective measure to contain NIDDM. These include correction and prevention of obesity, avoidance of a high-fat diet, high intake of fiber and unrefined carbohydrates as well as increased physical activity (90). These measures have been shown to prevent NIDDM in Chinese subjects with IGT (91). However, attempts to influence whole populations to alter their diet, increase exercise, and lose weight are almost impossible to achieve (92). This is particularly true in Asian countries where there was previously much hardship. Moreover, food is an important component of the Asian culture and is often used to express hospi-

tality and affection. Obesity has already emerged as a major health problem among children in Singapore (93) and Hong Kong (94,95). The overcrowded, high-rise living conditions in Hong Kong as well as the emphasis on scholastic achievement compared to play and sports or outdoor activities also contribute to the relatively stressful and inactive lifestyle for children. Given the current one-child policy in Mainland China, the problem of childhood obesity is likely to escalate rapidly.

Even in developed countries such as the U.K. and the U.S., the majority of health spending is still directed at the treatment of established complications rather than on preventive measures (96). In Hong Kong with its system of low taxation, <5% of the Gross Domestic Product is spent on health care provision compared with 14% in the U.S. and 10% in Britain. The situation is further aggravated by the fact that over 80% of frontline community-type care is offered by the private sector, which charges a fee for service (97). While visits are often haphazard and doctor shopping is common, there is also little or no incentive for private doctors to practice preventive care. Traditional medical teaching in Asian countries often emphasizes high technology and intervention. As a result, preventive medicine often has low appeal to the medical profession. Many patients also take recourse to herbal remedies or Chinese traditional medicine and present late to Western-style practitioners when complications occur. Other patients may take medical advice initially but then self-medicate with drugs procured directly from pharmacies with no medical supervision. Finally, the insidious nature of the disease, together with the difficulty in quantifying benefits resulting from preventive measures also conspire to make diabetes a low-priority issue at all levels including patients. The lack of either government-run or third-party insurance programs means that more people with chronic or serious diseases are using the low-cost public health sector, which is becoming rapidly overwhelmed. Traditional medical practice in Hong Kong is often highly compartmentalized. This compounds the difficulties in implementing shared-care programs. The lack of an intermediate, affordable, managed care infrastructure means that many patients are denied quality care despite increasing personal affluence and phenomenal socioeconomic success in Hong Kong.

The health care system in Hong Kong is one of many similar examples in Asia. With its enormous population and rapid economic growth, Asia is at a crisis point in relation to diabetes and related diseases. In 1996, it has been estimated that there were at least 15 million people in Mainland China aged 25 years and over with diabetes, of whom only 30% (5 million) had been diagnosed. An approximate estimate of direct costs incurred in the care of diagnosed diabetic subjects is $3.5 billion (U.S. dollars) (X.R. Pan, personal communication, 1996). This cost would be very much higher if indirect costs were included, if estimates of the costs incurred by the undiagnosed subjects were also included, and if the estimated total size of the diabetic population were increased. With the exception of countries, such as Singapore and Taiwan, where the government has a long-term health policy, the situation appears bleak. Radical changes are required in the philosophy and attitudes of not only the medical profession, but also administrators, politicians, and the lay public. In the short term, with the help of international bodies such as the World Health Organization and International Diabetes Federation, specialists and academics must actively disseminate all relevant information to the frontline health care teams as well as patients. In the long term, both the public and all parties concerned must work together to develop long-term health care policies aiming at health education, population surveillance programs, effective screening, and treatment programs at affordable costs. This will be extremely difficult to achieve, but the consequences of failure will be devastating.

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