The Asian diabetes phenotypes: challenges and opportunities

Juliana CN Chan, Roseanne Yeung, and Andrea Luk
Asia is home to two-thirds of the world’s population, where the two most populous countries of India and China are undergoing rapid socioeconomic, technological, and cultural transitions. While these transitions have alleviated poverty, they have come with considerable health consequences. Amongst the 382 million people affected with diabetes in 2013, over 200 million come from Asia, including four of the top ten countries with the most cases of diabetes: China, India, Indonesia and Japan. The severity of this problem is best illustrated in China, where the most recent national study found that 12% of people were reported to have diabetes and 50% were reported to have prediabetes. Of particular concern is how diabetes is affecting younger people in Asia where the largest number of people with diabetes are aged 40-59 years old, compared to Europe where most people with diabetes are over 60 years old (Figure 1).

Biologically, there is evidence to show that Asians are more likely to develop diabetes for the same level of body mass index or waist circumference than their Caucasian counterparts. This is thought to be partly due to their propensity to store fat viscerally rather than subcutaneously, which is not captured in the traditional measures of adiposity such as body mass index and waist circumference. Besides, even in relatively lean subjects, Asians are more insulin resistant than non-Asians with increased concentrations of free fatty acids and inflammatory markers. Further, Asian subjects exhibit higher glucose excursion during oral glucose challenge, suggesting lower beta cell function to overcome insulin resistance than non-Asians. These biological differences put Asians at high risk of developing diabetes in the presence of external stressors, such as obesity. Examples of common clinical features in Asian populations with diabetes are given in the table – the so called ‘Asian phenotypes’.

**Diabetes and its co-morbidities**

Diabetes is a disorder of energy metabolism which determines survival. Irrespective of the amount of energy intake and expenditure, blood glucose levels should be maintained between 5 and 8 mmol/L at all times through intricate interplays between insulin, the only hormone which lowers blood glucose and many other stress hormones which tend to elevate blood glucose. Failure to maintain this fine balance results in chronic hyperglycaemia which over time will cause generalized vascular and nerve damage with multiple organ failure.

Thus, if undiagnosed, untreated, or uncontrolled, diabetes can reduce life expectancy by six years on average. In Asia, 1%-3% of people with diabetes die every year. However, the considerable
diversity in socioeconomical development and cultures as well as subtle differences in genetic makeup give rise to many subphenotypes and consequences in Asian populations. For example, in East and Southeast Asia, where traditional diets contain high carbohydrate, low fat and high sodium content, the low incidence of coronary heart disease and high prevalence of hypertension may give rise to high rates of kidney disease while coronary heart disease remains an important cause of death in South Asian populations.11

In Asia, the diabetes-cancer link is a major health threat where endemic low grade infections and environmental toxins may contribute to the high rates of cancer in the region, further amplified by the abnormal metabolic milieu associated with diabetes and obesity. Against this backdrop, especially in areas where access to medications, revascularisation and renal replacement are limited such as the Pacific Islands, end stage renal disease, stroke, sepsis and leg amputation are often the leading causes of death. In more developed areas with better healthcare, coronary heart disease, heart failure, chronic kidney disease and cancer have become major causes of premature mortality and morbidities in Asian people with type 2 diabetes.1,9 These life-threatening consequences of diabetes are particularly important to young subjects who face long disease duration. These young subjects pose major therapeutic challenges as they often have poor risk factor control, poor follow-up rates within the healthcare system, and poor treatment compliance. Apart from the silent and non-urgent nature of diabetes and its risk factors, competing priorities, difficulty accepting lifelong disease and delayed intervention by healthcare providers over uncertain long term side-effects of chronic medications are some possible reasons for suboptimal control in these young subjects.12

In a nine-year follow up study of over 2000 Chinese people diagnosed before the age of 40 years, 10% had type 1 diabetes, 60% were overweight type 2 diabetic patients, and 30% were normal-weight type 2 diabetic patients. Overweight type 2 diabetic patients had the worst metabolic profile with 15-fold higher risk of cardiovascular disease and 5-fold higher risk of kidney failure compared to people with type 1 diabetes who had the lowest event rates.12

**Heterogeneity of diabetes in youth and young adults**

**Type 1 Diabetes**

In Caucasians, the majority diagnosed with diabetes under the age of 40 have autoimmune type 1 disease presenting with acute symptoms such as thirst, weight loss, frequent urination, precoma, or coma. By contrast, less than 10% of young Asian people with diabetes have typical type 1 presentation. Compared to a diagnosis rate of 4–45 per 100,000 person-years in the European population, the corresponding diagnosis rate of childhood type 1 diabetes was 2 per 100,000 person-years in Japan.1

**Type 2 Diabetes**

While the incidence of type 1 diabetes among Asian children and adolescents has remained static over time, the incidence of type 2 diabetes has doubled or even tripled in some countries, closely mirroring the rising rates of childhood obesity. With the introduction of urine glucose screening programmes in countries like Japan and Taiwan, more cases of childhood type 2 diabetes are being detected with a rate of 3 per 100,000 person-years in Japan.13,14 China has reported type 2 diabetes in 4%–6% of people in the 18–40 age group. Moreover, features of the metabolic syndrome are present in a substantial proportion of these young subjects at the time of diabetes diagnosis.2

**Challenges in diabetes classification**

With the rise in obesity prevalence, atypical presentation of diabetes with features of both type 1 and type 2 diabetes, also called ‘double diabetes’, are

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**Table. Examples of clinical features in Asian populations with diabetes, so called ‘Asian phenotypes’ which may be applicable to populations which undergo rapid acculturation and socioeconomic transition.**

<table>
<thead>
<tr>
<th>Low body mass index</th>
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<tbody>
<tr>
<td>Increased body fat, especially visceral fat</td>
</tr>
<tr>
<td>High rate of central obesity and metabolic syndrome</td>
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<tr>
<td>Increased inflammatory markers</td>
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<tr>
<td>Insufficient beta cell response to counter insulin resistance</td>
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<tr>
<td>Low rate of autoimmune type 1 diabetes</td>
</tr>
<tr>
<td>High rate of young-onset type 2 diabetes</td>
</tr>
<tr>
<td>High rate of childhood obesity</td>
</tr>
<tr>
<td>High rate of gestational diabetes</td>
</tr>
<tr>
<td>Social disparity and psychosocial stress</td>
</tr>
<tr>
<td>High rate of renal disease</td>
</tr>
<tr>
<td>High rate of cancer especially those with viral causes, e.g. liver cancer</td>
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</tbody>
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increasingly common and reflect the challenges of a disease that is subject to the lifestyle changes of modernization, among many other secular changes. The changing face of diabetes poses diagnostic and therapeutic challenges, as our traditional classification systems must evolve to account for emerging disease types.\textsuperscript{15}

Furthermore, developments in antibody testing and laboratory measurement of hormones are enabling us to better characterise autoimmune diabetes, although large gaps exist. In a large Chinese study involving ketosis-free subjects with diabetes over 30 years old, 6\% were considered to have latent autoimmune diabetes in adults (LADA) based on positivity of glutamic acid decarboxylase antibodies (GADA).\textsuperscript{16} These subjects also tended to have lower body mass index and were less likely to have the metabolic syndrome, with predominant beta cell insufficiency. Still, a large proportion of Chinese patients with type 2 diabetes are lean with low C-peptide levels at diagnosis, have strong family history of diabetes, but do not exhibit autoimmunity based on absence of circulating islet cell antibodies. Other large scale and family-based genetic studies have discovered genetic variations implicated in beta cell biology and protein metabolism which support their causal roles especially in young subjects with familial diabetes.\textsuperscript{17,18}

Advances in genetics have also allowed for better characterisation and classification of diabetes. In the early 1990s, small case series indicated that 10\%-20\% of young adult Asian subjects diagnosed before the age of 40 had monogenic diabetes, a form of diabetes due to the mutation of a single gene. Unlike most patients with type 2 diabetes, these subjects are often lean and fail to control their blood glucose with oral drugs alone, requiring insulin for disease control earlier than one would expect for those with type 2 diabetes.\textsuperscript{19} Access to genetic testing for these subtypes is still a barrier for most living in Asia, but hopefully the cost and availability of these tests will improve as technology progresses. Ongoing and future genetic studies offer an opportunity for better identification of specific subsets of diabetes and targeted therapies to allow for more personalized treatment.

Nature meets nurture
Apart from genetic causes, we now recognize the field of epigenetics where environmental or ‘nurture’ exposures affect gene expression. For example, fetal exposure to maternal malnutrition during pregnancy may result in a fetal phenotype that promotes survival in a nutrient poor environment but substantially increases the risk of diabetes and cardiovascular-renal disease during a time of nutrient abundance. Asian women have a high prevalence of gestational diabetes, which is another important risk factor linked to future diabetes.
development by the offspring. Metabolic health in childhood has also been associated with future risk of obesity and diabetes, where childhood obesity increases the risk of future diabetes development. These factors result in increased trans-generational diabetes with increasingly early onset of disease, thus setting up a vicious cycle of ‘diabetes begetting diabetes’.20

In Asia, while diabetes has been a ‘rich man’s disease’, it is becoming more of a ‘poor man’s disease’ as seen in more affluent societies due to a combination of poverty, poor education, poor food quality, and high level of physical inactivity. The lack of awareness and health literacy often result in high rates of smoking, consumption of energy-dense food, poor sleep hygiene, and sedentary time on the computer and television. These adverse lifestyle choices can be further compounded by psychosocial stresses associated with rapid acculturation.21 Additionally, chronic exposure to endemic low-grade infections (e.g. hepatitis B infection) and environmental pollutants may result in abnormal neuro-hormonal responses manifesting as obesity, metabolic syndrome, and diabetes.11

Reducing social disparity and setting up systems to prevent the preventable
Considerable advancement has now been made in our understanding of the natural history and management of diabetes and its complications. From a public health perspective, reduction of poverty, social disparity and health illiteracy through a multisectorial strategy22 and using a life course approach such as maternal and child health, vaccination programmes, nu-
tritional policies, universal education and health coverage, tobacco control and city planning are needed to create a health-enabling environment. In order to protect the most vulnerable, outreach detection and support programmes targeting difficult-to-reach populations such as the manual workforce and the socially deprived and isolated may give high yield of positive cases for early intervention. Such programmes need to be fully integrated with a seamless healthcare system to ensure that intervention measures proven to be effective, e.g. structured lifestyle modification and early drug therapy can be introduced in a timely manner to prevent silent deterioration of disease with late presentation.\textsuperscript{1,2,3}

Despite the highly preventable and treatable nature of diabetes and its complications, a major task at hand is to translate the existing evidence into clinical practice.\textsuperscript{2,4} We need to develop innovative solutions to ensure that people with or at risk of diabetes have the necessary information to change behaviour, minimize risk, and manage their health. Care providers need the information to stratify risk, assess needs, and individualize intervention. Given the growing size of the problem and the need to sustain our healthcare systems, policymakers and payers need information to ensure that these individuals are detected early and treated to multiple targets (HbA\textsubscript{1c}, blood pressure, LDL-cholesterol) to reduce risk of expensive and difficult to treat complications. To achieve these interlinking goals, a multipronged strategy including changing workflow, task delegation, case management, registry, decision support and patient empowerment with ongoing evaluation are some measures which have been proven to be effective in improving risk factor control (Figure 2).\textsuperscript{2,5}
The way forward
A disease epidemic is typically caused by rapid changes in the ecology of the host population resulting in biological maladaptation.24 In Asia, the rapid modernisation from an energy-scarce to energy-rich environment has led to high rates of metabolic syndrome and diabetes. Depending on different combinations and permutations of external stressors, such as infection, pollution, nutrition, lifestyle, psychosocial stress, and access to care, genetically predisposed subjects can have different clinical outcomes ranging from health preservation to multiple organ failure. These clinical features have also been reported in Pima Indians and indigenous populations who underwent rapid acculturation, suggesting that these ‘Asian phenotypes’ may also be expected in other emerging economies, each with its own characteristics and nuances.9

During the last three decades, the multidimensional nature of this epidemic including societal, technological and behavioural factors continues to unfold in Asia. Importantly, Asia has risen to the challenge and provided notable examples of prevention, such as tobacco control for global risk reduction, national detection programmes for childhood diabetes, lifestyle modification programme for prevention of diabetes, information technology for care integration with decision support, diabetes registry for quality assurance and protocol-augmented collaborative care for prevention of diabetic complications. While different countries and areas in Asia are at different stages of this journey of health evolution, the diabetes epidemic in Asia has provided many insights in our common goal to reverse this trend of adversity to new hopes through societal, system and personal changes.1

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References