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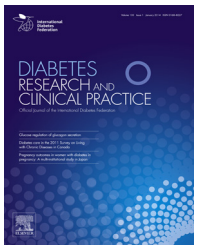

International Diabetes Federation

The Asian diabetes phenotypes: Challenges and opportunities☆

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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 [1]. Among 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 [1]. 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 [2]. 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 (Fig. 1) [3].

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 [4]. 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 [5]. Besides, even in relatively lean subjects, Asians are more insulin resistant than non-Asians with increased concentrations of free fatty acids and inflammatory markers. [6] 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 [7,8]. Examples of common clinical features in Asian populations with diabetes are given in Table 1 – the so-called 'Asian phenotypes'.

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 [9].

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 [10]. However, the considerable diversity in socioeconomical development and cultures as well as subtle differences in genetic makeup gives 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,

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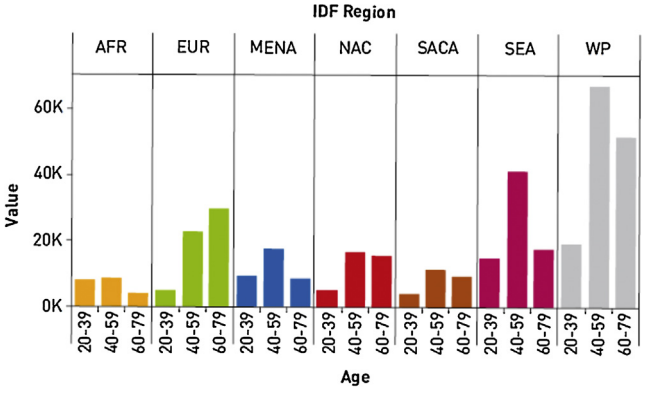

Fig. 1 – Distribution of diabetes by regions and age groups with South East Asia (SEA) and Western Pacific (WP) regions having the highest number of affected people especially in the 40–59 age group (International Diabetes Federation).
Source: **IDF Diabetes Atlas, 6th ed. International Diabetes Federation, Brussels, 2013. www.idf.org/diabetesatlas.**

Table 1 – 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.

Low body mass index
Increased body fat, especially visceral fat
High rate of central obesity and metabolic syndrome
Increased inflammatory markers
Insufficient beta cell response to counter insulin resistance
Low rate of autoimmune type 1 diabetes
High rate of young-onset type 2 diabetes
High rate of childhood obesity
High rate of gestational diabetes
Social disparity and psychosocial stress
High rate of renal disease
High rate of cancer especially those with viral causes, e.g. liver cancer

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].

1. Heterogeneity of diabetes in youth and young adults

1.1. *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, pre-coma, 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].

1.2. *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].

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 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 [15].

Furthermore, developments in antibody testing and laboratory measurement of hormones are enabling us to better characterize 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