Young-Onset Diabetes in East Asians: from Epidemiology to Precision Medicine

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Precision diagnosis is the keystone of clinical medicine. In East Asians, classical type 1 diabetes is uncommon in patients with young-onset diabetes diagnosed before age of 40, in whom a family history, obesity, and beta-cell and kidney dysfunction are key features. Young-onset diabetes affects one in five Asian adults with diabetes in clinic settings; however, it is often misclassified, resulting in delayed or non-targeted treatment. Complex aetiologies, long disease duration, aggressive clinical course, and a lack of evidence-based guidelines have contributed to variable care standards and premature death in these young patients. The high burden of comorbidities, notably mental illness, highlights the numerous knowledge gaps related to this silent killer. The majority of adult patients with young-onset diabetes are managed as part of a heterogeneous population of patients with various ages of diagnosis. A multidisciplinary care team led by physicians with special interest in young-onset diabetes will help improve the precision of diagnosis and address their physical, mental, and behavioral health. To this end, payors, planners, and providers need to align and re-design the practice environment to gather data systematically during routine practice to elucidate the multicausality of young-onset diabetes, treat to multiple targets, and improve outcomes in these vulnerable individuals.

Keywords: Precision medicine; Epidemiology; Young-onset diabetes; East Asians

INTRODUCTION

According to the noncommunicable disease (NCD) Risk Factor Collaboration, between 1980 and 2014, the age-standardized prevalence of diabetes in adults aged 20 to 64 years increased from 3.2% to 7.8% in men, and from 3.9% to 6.8% in women [1]. In a nationwide study in Korea, from 2006 to 2015, the overall incidence of diagnosed diabetes decreased by 0.1% per year, but increased from 0.5 to 0.7 per 1,000 individuals in the 20 to 29 age group and from 2.0 to 2.6 per 1,000 individuals in the 30 to 39 age group. Importantly, the proportion of obese young adults with diabetes increased from 51.4% in 2006 to 72.4% in 2015 [2].

YOUNG-ONSET DIABETES – A SILENT KILLER

In a simulation model based on a territory-wide diabetes surveillance database curated from electronic medical records (EMRs) including 2,608,973 individuals followed from 2001 to 2019, researchers from Hong Kong estimated that a 20-year-old Chinese individual with prediabetes would live with diabetes for 32.5 years—or 51.6% of his or her remaining life years—with diabetes, versus the corresponding figures of 12.7 years and 18.4% in an individual with normoglycaemia at 20 years old [3]. In a Korean national database including 2,101,599 young
adults aged 20 to 39 years without prediabetes, diabetes, or cardiovascular disease (CVD) at baseline who were followed up for 10 years, incident diabetes, defined by fasting plasma glucose (PG), was associated with a hazard ratio (HR) of 1.60 for all-cause death and 1.13 for CVD [4]. In a pooled analysis of 22 prospective studies of the Asia Cohort Consortium, which included 1,002,551 Asian individuals aged 30 years or above, conducted between 1963 and 2006, 148,868 deaths were ascertained after a median follow-up period of 12.6 years. Individuals with diabetes had a 1.89-fold higher risk of all-cause death than those without diabetes; notably, the HR decreased from 2.43 in the <50 age group to 1.51 in the ≥70 age group [5].

Using data from the Hong Kong Diabetes Register [6], researchers from Asia first reported a high risk of premature death in patients with young-onset diabetes. In 9,509 Chinese patients with type 2 diabetes who were followed up for 7.5 years, 21% of whom were diagnosed before the age of 40 years, patients with young-onset diabetes had age- and sex-adjusted HRs of 1.48 for CVD and 1.35 for chronic kidney disease (CKD) compared to patients with later-onset diabetes, despite an age difference of 20 years. These hazards were attenuated after adjustment by disease duration, highlighting its importance in driving the development of complications [7].

On average, type 2 diabetes was found to shorten the lifespan by at least 4 years [8], and the loss of life expectancy was increased to 14 years or more if individuals were diagnosed at a young age [9,10]. Other meta-analyses have also reported a high risk of premature death associated with youth-onset diabetes (age of diagnosis <20 years) [11] and young age of diagnosis [12]. In the latter report, which included 26 observational studies comprising 1,325,493 individuals from 30 countries, the risk of all-cause death and macrovascular and microvascular disease was negatively associated with age at diagnosis of diabetes. For every 1-year increase in age at diagnosis, there were 4%, 3%, and 5% decreased risks of all-cause death, macrovascular disease, and microvascular disease, respectively, adjusted for current age [12].

**YOUNG-ONSET DIABETES: INSIGHTS FROM PIMA INDIANS**

In the early 1970s, the high prevalence of type 2 diabetes and obesity in Pima Indians provided a glimpse of the impact of rapid acculturation on the development of metabolic diseases in non-European populations. In a recent review of 40 years of research among Pima Indians [13], the authors summarized the epidemiological lessons learnt from this population, which shared many similarities with diabetes in Asians. These include the rarity of autoimmunity in young people with diabetes, in whom genetics, gestational diabetes mellitus (GDM), obesity, beta-cell dysfunction, and kidney disease are key features [14-17].

**IMPORTANT OF USING THE ORAL GLUCOSE TOLERANCE TEST TO DETECT HYPERGLYCAEMIA**

One of the key observations in Pima Indians was the bimodal distribution of 2-hour PG levels during a 75-g oral glucose tolerance test (OGTT) in adults aged 25 to 65 years. These findings suggested that during a glucose challenge, a group of individuals had a high blood glucose response, which formed the basis of im-
paired glucose tolerance (IGT) (Fig. 1) [18]. A prospective analysis in Pima Indians confirmed the associations of high 2-hour PG during the OGTT with progression to type 2 diabetes and its complications, including retinopathy and albuminuria [13].

Precise diagnosis is the keystone of clinical medicine. It has long been recognized that up to 50% of Asians with diabetes are diagnosed by 2-hour PG during OGTT [19]. In non-Europeans, there are pitfalls in using glycated haemoglobin (HbA1c) alone to diagnose diabetes or prediabetes. This is particularly true for Asians, who not uncommonly have hemoglobinopathy, which can confound HbA1c values [20,21]. In a recent analysis of more than 80 contemporary studies among adults aged 20 to 79 years, the global prevalence of IGT exceeded that of impaired fasting glucose (IFG) in 2021 (9.1% vs. 5.8%), suggesting that a substantial number of individuals could be missed if only fasting PG or HbA1c were used to diagnose prediabetes for prevention purposes [22].

In the late 1990s, two community-based prospective cohorts (the Hong Kong Family Diabetes Study [HKFDS] and Better Health for Better Hong Kong [BHBHK] Survey) were established in a workforce in Hong Kong to study gene-environment interactions in diabetes. In these young participants, with a mean age of 40 years, over 50% of individuals with prediabetes or diabetes were diagnosed by 2-hour PG during OGTT [23-25]. There is now confirmatory evidence showing that the progression from IGT to diabetes can be prevented by structured lifestyle intervention and drugs such as metformin and acarbose [9]. However, these benefits were not observed in individuals with isolated IFG [26]. Thus, OGTT shall remain the gold standard for the detection, prevention, and treatment of prediabetes and diabetes, especially in young individuals with risk factors [27,28].

**INSULIN RESISTANCE AND BETA-CELL DYSFUNCTION IN YOUNG-ONSET DIABETES**

The high prevalence of type 2 diabetes in Pima Indians was in part driven by the high prevalence of obesity, which was associated with hepatic insulin resistance—a condition accompanied by increased hepatic glucose production and reduced clearance.
of insulin. However, irrespective of the presence of obesity, individuals who developed diabetes or IGT exhibited a loss of acute-phase insulin secretion during OGTT, suggesting the importance of beta-cell dysfunction in these individuals [29]. In this light, the importance of beta-cell dysfunction in Asians with type 2 diabetes has long been highlighted as a feature in contrast to Europeans [30–32]. In a 10-year community-based study in Korea, although insulin resistance increased with age, often accompanied by increased insulin secretion, individuals with an insufficient insulin response went on to develop diabetes [33].

A cross-sectional analysis of 5,170 Chinese patients with type 2 diabetes found negative associations of beta-cell function indicated by homeostasis model assessment (HOMA2-beta%) with a family history of diabetes, the number of affected family members, and body mass index (BMI). The slope of the decline in HOMA2-beta% by diabetes duration was also greater in individuals with young-onset diabetes than in those with later-onset diabetes amongst individuals with a BMI <27.5 kg/m² (Fig. 2) [34].

Using prospective data from the Hong Kong Diabetes Register, which was established in 1995 as a research-driven quality improvement program with detailed documentation of baseline clinical profiles, laboratory tests, medications, hospitalization diagnosis, and causes of death [6,35], researchers reported a consistently higher HbA1c level and its steep upward trajectory, likely related to rapid beta-cell deterioration, in the first decade after diagnosis in individuals with young-onset diabetes, which translated to a very large glycaemic burden over time [36].

FAMILIAL HERITABILITY AND GENETICS OF YOUNG-ONSET DIABETES

In monozygotic twins, the concordance for the lifetime risk of type 2 diabetes approached 100%, compared to 50% for type 1 diabetes [37]. The attenuated risk of type 2 diabetes amongst Pima Indians with genetic admixture [13], as well as the strong heritability of insulin secretion and body fat in family-based studies [38,39], lent support to the importance of genetics in type 2 diabetes. In the HKFDs, which included 179 families with 913 individuals, 78% of families had at least one individual with diabetes diagnosed at the age of 40 years or younger. Amongst these families with young-onset diabetes, 25% of siblings had metabolic syndrome, and the study found high heritability for diabetes, hypertension, central obesity, insulin resistance, and beta-cell function of 0.4 to 0.6 [24]. In the Botnia Family Study, the heritability of type 2 diabetes was 0.69 in individuals diagnosed at 35 to 60 years, which dropped to 0.31 in those diagnosed at 35 to 75 years [40]. In Hong Kong Chinese, a family history of young-onset diabetes was associated with a 6- to 8-fold increased risk of incident diabetes versus less than a 1.6-fold increased risk for a family history of diabetes diagnosed after the age of 50 years compared to no family history of diabetes [25].

More than two decades of global efforts using genome-wide association studies (GWAS), whole-exome sequencing (WES), and whole-genome sequencing have implicated common and rare variants in coding and non-coding regions of hundreds of loci across the human genome as playing causal roles in the onset and progression of type 2 diabetes [41]. However, the majority of participants in these studies had European descent, raising the issue of the generalisability of these results to non-European populations. Indeed, similar studies in Asian populations have revealed inter-ethnic differences in genomic architecture, as well as in the location, frequency, and effect sizes of these risk alleles [42]. In the latest meta-analysis of GWASs, including data from 77,418 individuals with type 2 diabetes and 356,122 healthy control individuals from Asia, the authors identified 61 new loci associated with diabetes implicated in pancreatic, adipose, and muscle biology not found in European populations [43].

Considering potential aetiological differences between young-onset diabetes and later-onset diabetes, only a few studies have specifically addressed genetic associations stratified by age of diagnosis [44–46]. In a recent GWAS of the UK Biobank stratified by the age of diagnosis (<50, 50–60, 60–70, and >70 years), researchers discovered three independent single nucleotide polymorphisms (SNPs) mapped to transcription factor 7 like 2 (TCF7L2) in patients diagnosed less than 50 years, and another 17 SNPs identified in the overall GWAS displayed differences in effect size dependent on age of diagnosis. In another analysis of the UK Biobank stratified by BMI and age of diagnosis, researchers reported 18 SNPs that showed subgroup differences, including one in neurogenin-3 (NEUROG3), a gene linked to maturity-onset diabetes of the young (MODY) [45].

In this light, nearly 40 subtypes of monogenic diabetes, including MODY, have been reported [47]. In the largest WES study, including 20,791 individuals with type 2 diabetes and 24,440 control participants from five ancestries, rare variants located in pancreatic and duodenal homeobox 1 (PDX1), glucokinase (GCK), and HNF1 homeobox A (HNF1A) were associated with 1.5 to 3.5 increased odds of type 2 diabetes [48]. In family-based studies, common variants of monogenic diabetes have been shown to modulate the age of diagnosis of MODY. For example, the common HNF1A variant I27L was associated with a younger age of diagnosis of HNF1A-MODY with pro-
tein-truncating mutations [49]. On the other hand, polygenic risk scores of the common form of type 2 diabetes also jointly advanced the age of diagnosis of HNF1A-MODY [50]. We and others have reported that common variants of type 2 diabetes, including some located in genes for monogenic diabetes and MODY, independently predicted a younger age of diagnosis of type 2 diabetes and earlier insulin requirement in both Caucasians and Asians [51,52]. By using patients with familial young-onset diabetes as cases in the discovery cohort, researchers from Asia have reported genetic associations of dachshund family transcription factor 1 (DACH1) [53], paired box 4 (PAX4) [54], carboxypeptidase E (CPE), and insulin degrading enzyme (IDE) [55] with type 2 diabetes. These genes are strongly implicated in islet biology, in keeping with the importance of beta-cell dysfunction in Asian patients with young-onset diabetes [30].

**GESTATIONAL DIABETES, IN UTERO EXPOSURE TO HYPERGLYCAEMIA AND CHILDHOOD OBESITY**

In Pima Indians, *in utero* exposure to hyperglycaemia was associated with a high risk of youth-onset obesity and type 2 diabetes in offspring born to women with GDM. This was in contrast to the low risk of diabetes in offspring born to the same woman during her other uncomplicated pregnancies [56,57]. In a prospective cohort of Chinese women and their offspring recruited to the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study, offspring born to women with GDM had a higher incidence of abnormal glucose tolerance and overweight/obesity, as well as higher BMI, blood pressure and lower oral disposition index and a trend toward reduced beta-cell function than offspring born to women without GDM. For each standard deviation increase in maternal fasting, 1-hour, and 2-hour PG during OGTT at 24 and 32 weeks of the index pregnancy, there was a corresponding increase in the adjusted odds ratio of 1.85 to 2.00 for abnormal glucose tolerance in the offspring [58].

In a systematic review on GDM, Asian women had the highest risk of developing GDM amongst all populations. These women were at high risk of developing young-onset diabetes, and their children also had a high risk of adiposity in later life [59]. In a meta-analysis including 71,998 children and 353,513 adolescents from Asia, the pooled prevalence for obesity was 5.8% in children aged 5 to 11 years and 8.6% in adolescents aged 12 to 19 years [60]. In a school-based survey including 2,115 Chinese adolescents from Hong Kong, the prevalence of metabolic syndrome using the criteria for Asian adults was 2.4%, with 32.2% having hypertension; 10.9%, increased triglycerides; 9.0%, central adiposity; 2.4%, low high-density lipoprotein cholesterol; 0.3%, IFG and 17%, increased albuminuria. Overweight (adjusted odds ratio, 32.2), a positive family history of diabetes (4.3) and studying at schools of lower academic grading (5.5) were independent risk factors, suggesting the importance of nature and nurture in youth-onset metabolic syndrome [61].

**MULTICAUSALITY OF YOUNG-ONSET DIABETES**

Age, obesity, and family history are major risk factors for diabetes [62]. Thus, individuals who develop diabetes at young age, especially if lean, require comprehensive profiling to elucidate additional etiologies. In a recent review article [63], we summarized the multiple challenges in the diagnosis and management of young-onset diabetes, which affects one in five adult patients with type 2 diabetes in clinic settings in Asia [64]. Based on 30 years of data collection in real-world practice accompanied by a biobank with linkage to hospitalization data, we have reported that 8% of patients diagnosed with type 2 diabetes before the age of 40 years had positive anti-islet autoantibodies measured in stored serum, suggesting a diagnosis of latent autoimmune diabetes in adults (LADA). Compared to patients with classical type 1 diabetes, these young patients with LADA had a 2.8-fold increased risk of end-stage kidney disease (ESKD), in part due to missed diagnosis and delayed insulin treatment [65]. On the other hand, 3% to 5% of these young patients might have monogenic diabetes or MODY, and if diagnosed early, those individuals might benefit from sulphonylureas or dipeptidyl peptidase 4 inhibitors in the presence of residual beta-cell function [16,66]. However, these subtypes of diabetes cannot fully explain the low beta-cell function [34] and poor glycaemic control despite high usage of insulin [67-69], as well as the high prevalence of family history of diabetes in the majority of young patients [15,17].

Taking a life-course approach and considering other family, personal, and environmental factors, Fig. 3 summarizes the myriad of factors that may contribute to the development of young-onset diabetes, calling for further investigations to define the causes, trajectories, and consequences of young-onset diabetes [63]. To this end, diabetes is a typical example of multicausality, an important concept where a disease may occur due to different causal mechanisms made up of multiple components, with each component having different strengths, and the clinical manifestation will depend on interactions across these components (Fig. 3) [70,71].
Given the differences in genetic architecture, ethnicity, ecosystem, cultures, lifestyles, and healthcare systems across different populations, all of which can contribute to the predisposition, precipitation, and perpetuation of diabetes [72], there is a need to conduct more population-specific investigations based on families and prospective cohorts with multidimensional data, including not just multiomic data, but also data on demographic and biomedical-psycho-social-behavioral factors, and—most importantly—access to and quality of care to allow the use of big data to unravel missing aspects of the heritability of young-onset diabetes and, evaluate the effects of interventions on outcomes in order to bring precision medicine into clinical practice [63,73].

**YOUNG-ONSET DIABETES AND CHRONIC KIDNEY DISEASE**

In the 1970s, Pima Indians with diabetes diagnosed before the age of 25 years had a high incidence of ESKD after 15 to 20 years, which was the leading cause of death [74]. Similar patterns were reported in Aboriginal Australians with type 2 diabetes [75]. In Japanese [76,77] and Chinese populations, patients with young-onset diabetes had a higher incidence of nephropathy than their counterparts with type 1 diabetes [78]. In the follow-up study of the World Health Organization Multinational Study of Vascular Disease in Diabetes (WHO MSVDD) including 10 countries, the authors reported marked inter-country variations in the incidence of complications. While Chinese, Japanese, and Native American patients with type 2 diabetes had a very low incidence of coronary arterial disease but a high incidence of ESKD, the reverse was observed in European patients [79].

In Hong Kong, the rising incidence of both type 1 diabetes and type 2 diabetes in Chinese under the age of 40 years [80] concurred with the most rapid rate of increase in kidney replacement therapy in the 45 to 65 age group [81]. In Korea, amongst 84,384 patients with type 2 diabetes with 5.16 years of follow-up, patients with young-onset diabetes had 1.70 odds ratios of developing CKD compared to those with later-onset diabetes after adjusting for clinical variables [82]. Although disease duration is one of the key drivers of ESKD, in the Hong Kong Diabetes Register, the increased risk of CKD with longer diabetes duration decreased with an older age at diabetes diagnosis. For every 5-year increase in diabetes duration, the adjusted HR for CKD was 1.37 in patients diagnosed at 20 to 29 years versus 1.01 in those diagnosed at ≥70 years, highlighting the vulnerability of these young patients to ESKD [83].

The close link between CKD and CVD has been highlighted in many practice guidelines, which recommend the use of estimated glomerular filtration rate (eGFR) and urinary albumin creatinine ratio.
ratio (ACR) as time-tested biomarkers for vascular and kidney health [84]. In a set of risk equations developed from the prospective Hong Kong Diabetes Register, different combinations of clinical and cardiometabolic parameters predicted coronary arterial disease, stroke, ESKD, heart failure, and all-cause death in Chinese patients with type 2 diabetes. However, eGFR and ACR, which are closely associated with a long disease duration due to a young-onset of diabetes, were common parameters in all risk equations [6]. To this end, there is now a global consensus on the importance of cardiovascular-kidney-metabolic syndrome, for which a global risk assessment—including eGFR and ACR, along with other biomarkers, notably HbA1c and low-density lipoprotein cholesterol—should be measured at least annually. This is particularly important for patients with young-onset diabetes, who are at high risk of heart and kidney disease [85].

THE COMORBIDITIES OF YOUNG-ONSET DIABETES CALL FOR EARLY DIAGNOSIS, PREVENTION, AND TREATMENT

The epidemiological data gathered over four decades support the importance of familial factors including genetic and possibly epigenetic influences, secondary to early and prolonged exposure to hyperglycaemia and metabolic insults, which contribute to poor outcomes in patients with young-onset diabetes [9]. In the clinic-based Joint Asia Diabetes Evaluation (JADE) Register including 41,029 patients from nine countries in Asia, one in five adults with diabetes in Asia had young-onset diabetes diagnosed before the age of 40 years. Compared to their older-onset counterparts, these patients had worse cardiometabolic risk factors and were less likely to receive organ-protective drugs despite the presence of complications [64].

Given the universal health coverage with provision of medical care by the Hong Kong Hospital Authority, which operates all publicly-funded clinics and hospitals, researchers from Hong Kong have tracked diabetes-related trends and outcomes in the territory since 1995. The Hong Kong Diabetes Surveillance Database included EMRs from 4 million people receiving publicly-funded medical care, of whom 0.8 million had diabetes based on disease codes, laboratory results, or their use of medications. More than 50% of them had undergone structured assessments, based on the protocol of the Hong Kong Diabetes Register de-

Fig. 4. The Hong Kong Diabetes Surveillance Database showing declining death rates (A, B) and standard mortality ratios in all age groups in patients with type 2 diabetes in 2001 to 2016 in men and women, except for the 20 to 44 age group (C, D). (E) It shows the declining proportions of patients with diabetes with poor glycaemic control, as indicated by glycated haemoglobin (HbA1c) ≥9%, with the least improvement in the 20 to 44 age group. Adapted from Yang et al. [69]; and Wu et al. [89], with permission from Springer Nature. CI, confidence interval. *Average annual percent change is significantly different from zero at the alpha=0.05 level.
veloped by academics as a research-driven quality improvement program since 1995 [35,86]. Using data from this database and register, we reported a 2- to 6-fold increased risk for hospitalization in patients with young-onset diabetes, notably for kidney disease, mental illness, and infections [87,88]. Despite a 50% to 80% decline in all-cause and cause-specific death rates between 2001 and 2016 in the overall population, the standard mortality ratio in the 20 to 44 age group fluctuated between 4.92 and 7.86 [89]. During the same period, while the proportion of patients with poor glycaemic control (HbA1c ≥9%) fell in all age groups, patients with young-onset diabetes continued to have the worst glycaemic control despite having access to many glucose-lowering drugs (Fig. 4) [69].

Apart from an incomplete understanding of the aetiologies of young-onset diabetes, the missed diagnosis of diabetes subtypes (e.g., LADA and MODY) requiring specific treatment, the random nature of management in the absence of evidence [90], the aggressive clinical course with rapid beta-cell failure compounded by poor adherence, suboptimal self-management, and psychosocial stress can all contribute to the poor outcomes in these young individuals [63].

The ongoing International Diabetes Management Practices Study (IDMPS) aimed to detect trends and quality of care practices outside North America and Western Europe. In an analysis of data from 21 countries, 30% to 40% of patients reported depressive symptoms using the Patient Health Questionnaire (PHQ-9), with 8% to 16% indicating moderate depression indicated by a PHQ-9 score ≥10. Female gender, complications, poor glycaemic control, and low socioeconomic status were independently associated with depressive symptoms [91].

Using EMR data in patients with diabetes, researchers from Singapore reported that the highest users of tertiary healthcare services were clusters of young women with short-to-moderate disease duration and comorbid depression, as well as older patients with moderate-to-long disease duration and multiple morbidities [92]. Using register and EMR data from 0.42 million Chinese adults with incident type 2 diabetes observed between 2002 and 2014, we estimated that patients with young-onset diabetes spent an average of 100 hospital days from diagnosis to age of 75, with one-third of the hospitalizations due to mental illness before the age of 40. We further estimated that by delaying the onset of diabetes or optimizing control of all cardiometabolic risk factors, the hospitalization rates in patients with young-onset diabetes could be reduced by 30% to 60% (Fig. 5) [87].

**CLOSING THE IMPLEMENTATION GAP TO IMPROVE OUTCOMES IN YOUNG-ONSET DIABETES**

After nearly half a century of research, high-level evidence now shows that type 1 and type 2 diabetes, as well as their complications, are preventable and treatable. For autoimmune type 1 diabetes, teplizumab, a humanized monoclonal antibody to CD3 on T cells, has been approved in the United States to delay the onset of clinical type 1 diabetes in relatives of patients with type 1 diabetes and improve beta-cell function in patients with newly diagnosed type 1 diabetes.
diagnosed type 1 diabetes [93,94]. The availability of these preventive treatments strongly supports the inclusion of testing for auto-islet antibodies and beta-cell function in the risk assessment and management of young-onset diabetes.

For type 2 diabetes, multiple studies from different populations (including Asians) have confirmed that structured lifestyle interventions and medications such as metformin and acarbose could delay the onset of diabetes [9]. These early prevention programs for type 2 diabetes are particularly effective [95] and cost-effective [96] in young people with IGT. Importantly, the results of these early prevention efforts are expected to translate to a long-term reduction in microvascular and macrovascular complications and all-cause death [97].

A randomized controlled trial found that a weight reduction of 15 kg could cause remission of type 2 diabetes for up to 2 years in obese patients with type 2 diabetes [98]. However, in a recent analysis of the Hong Kong Diabetes Surveillance Database including 37,326 individuals with newly diagnosed type 2 diabetes followed in 2002 to 2017, only 6.1% achieved diabetes remission, with an overall incidence rate of 7.8 per 1,000 person-years. Despite this low rate of remission in real-world practice, a greater weight reduction in the first year of diagnosis was associated with an increased likelihood of remission, and any period of disease remission was associated with a reduced death rate [99].

On the other hand, early glycaemic control in patients with type 2 diabetes, often using combination drugs, improved glycaemic durability and reduced the likelihood of treatment escalation including insulin, especially in patients with a young age of diagnosis [100,101]. In the Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3) study, using commonly used glucose-lowering drugs to treat patients intensively to multiple targets, supplemented by self-management and education, was associated with extremely low events, with no cases of ESKD after 8 years [102]. Importantly, both interventional [103] and observational studies [104] have shown that early glycaemic control had legacy effects that translated to long-term reductions in complications.

**Fig. 6.** A conceptual framework explaining (A) how reduced endowment of beta-cell mass or function due to genetic factors may predispose individuals to earlier age of diagnosis of diabetes given the same trajectory of beta-cell function decline with same metabolic stress; (B) how increasing metabolic stress can cause accelerated decline in beta-cell function to bring forward the age of diagnosis; and (C) how by changing lifestyles and using medications to control multiple risk factors may delay the progressive decline in beta-cell function and delay the use of insulin and development of complications. Adapted from Chan et al. [63].

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tions and death.

Fig. 6 provides a conceptual framework explaining how individuals with different beta-cell capacities, likely to be endowed at birth, might present with diabetes at different ages given the same trajectory of beta-cell failure under the same metabolic stress. Given the same beta-cell capacity, different combinations of stress factors may cause different trajectories of beta-cell function, with different ages of diagnosis reflecting the significant loss of beta-cell function. By changing lifestyle and using medications to control multiple risk factors, it is possible to preserve beta-cell function and delay the onset of diabetes, treatment escalation (including insulin use), and eventually the development of complications (Fig. 6).

USING A MULTI-COMPONENT STRATEGY TO REDEFINE YOUNG-ONSET DIABETES FOR PRECISION CARE

Researchers from Sweden used plasma C-peptide, HOMA-beta, HOMA-insulin resistance, glutamic-acid-decarboxylase autoantibodies (GADA), age of diagnosis, and BMI to classify patients into five clusters with different genetic profiles, which predicted early insulin requirement and incident CKD [105]. This clustering approach to classify diabetes has been verified in other populations including Asians [106]. In an ongoing 3-year randomized controlled trial (Precision medicine to Redefine Insulin Secretion and Monogenic diabetes [PRISM]), our group extended this concept and recruited 884 patients with young-onset diabetes aged less than 50 years who underwent structured clinical assessments and comprehensive biogenetic profiling, including measurement of HOMA-indices, C-peptide, and GADA to diagnose LADA and assess beta-cell function. These patients also had genome-wide genotyping to compute polygenic risk scores for beta-cell function and complications, targeted gene-sequencing to detect mutations of 34 genes for monogenic diabetes including MODY, and assessments of patient-reported outcome measures including psychosocial-behavioral factors and quality of life. Half of the patients were randomized to receive 1-year specialist-led multidisciplinary care in a diabetes centre, guided by their biogenetic profiles with counselling and support, aimed at attaining multiple treatment targets. After this 1-year multi-component management [107,108], these patients will return to their usual clinics for follow-up with a yearly review at the diabetes centre, while the other half will receive usual care. All patients will undergo re-evaluation at 3 years to determine the primary outcome, defined by the incidence of all diabetes-related endpoints (https://clinicaltrials.gov/ct2/show/NCT04049149).

In this implementation study, the analysis will be conducted according to the Reach, Effectiveness, Adoption, Implementation, and Evaluation (REAIM) framework [109] to inform planners, practitioners, and policymakers about the resources, infrastructure, personnel, logistics, and technology needed to bring about precision medicine in young-onset diabetes in clinical practice and assess its cost-effectiveness. Importantly, the establishment of this PRISM cohort will allow us to verify, modify, and develop risk algorithms for prognostication and treatment individualization. Meanwhile, the first-degree relatives of the trial participants are invited to undergo screening for diabetes/prediabetes using OGTT to complete an integrated detection-prevention-treatment program [110]. The creation of these cohorts, databases, and biobanks will provide valuable opportunities for multiomic and big data analysis to discover Asian-relevant novel common and rare variants supported by familial cosegregation analysis to confirm their validity and utility.

CONCLUSIONS

Establishing causal relationships is the most important principle in our pursuit of precision medicine through observations, experiments, and real-world practice [63,111,112]. In the case of young-onset diabetes, while many genetic, family, and lifestyle factors may not be avoided or changed, there are indeed many opportunities where nurture at a personal, family, and societal level can alter the disease trajectory and improve the outcome of these high-risk individuals [66,113,114]. According to the Pareto principle (or the “80 to 20 rule”), 80% of the effects come from 20% of the causes [115]. Given our current understanding of the burden of young-onset diabetes, which affects one in five adult patients with diabetes in clinic settings in Asia, there is indeed strong justification to call for more investigations, investments, and interventions in these young patients and their family members which will bring long-term benefits not only to affected individuals and their families, but also to society at large.

CONFLICTS OF INTEREST

Juliana C.N. Chan holds patents for using genetic markers to predict diabetes and its complications for personalized care and is a co-founder of a start-up biotech company partially supported by the Technology Start-up Support Scheme for Universities (TSSSU) of the Hong Kong Government Innovation and Tech-
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