



Evolution of Diabetes Care in Hong Kong: From the Hong Kong Diabetes Register to JADE-PEARL Program to RAMP and PEP Program

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The rapid increase in diabetes prevalence globally has contributed to large increases in health care expenditure on diabetic complications, posing a major health burden to countries worldwide. Asians are commonly observed to have poorer β -cell function and greater insulin resistance compared to the Caucasian population, which is attributed by their lower lean body mass and central obesity. This “double phenotype” as well as the rising prevalence of young onset diabetes in Asia has placed Asians with diabetes at high risk of cardiovascular and renal complications, with cancer emerging as an important cause of morbidity and mortality. The experience from Hong Kong had demonstrated that a multifaceted approach, involving team-based integrated care, information technological advances, and patient empowerment programs were able to reduce the incidence of diabetic complications, hospitalizations, and mortality. System change and public policies to enhance implementation of such programs may provide solutions to combat the burgeoning health problem of diabetes at a societal level.

Keywords: Diabetes mellitus, type 2; Diabetes complications; Integrated care

INTRODUCTION

In Hong Kong, the prevalence of diabetes in adults was estimated to be 10% [1]. The Hospital Authority of Hong Kong, a government-subsidized non-profit organization, provides over 65% of primary health care services and more than 90% of secondary and tertiary health care services in the city. Approximately 40% of patients with diabetes have one or more complications [2], which are mostly managed in the public health care sector. In a recent local health economics analysis, the annual public direct medical cost for a typical 65-year-old Chinese with diabetes

free of complications was estimated to be US dollar (USD) 1,521 [3]. New events of cardiovascular and renal complications increased the incremental annual costs by 4 to 9 times, with lower limb ulcer being the most expensive complication. The annual medical costs in subsequent years remained more than 1.5 times for various macro- and microvascular outcomes, making diabetic complications an enormous economic burden to the health care system. The early identification and optimization of risk factors could reduce events and save health care costs. This review will discuss the evolution in the provision of diabetes care in Hong Kong focusing on type 2 diabetes melli-

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tus (T2DM). This started from the establishment of a research-driven diabetes register and a series of disease management programmes at a teaching hospital, which was eventually adopted by the Hospital Authority for development into territory-wide quality care programs resulting in improvement in control of risk factors and reduction of diabetic complications. This large body of published data has also contributed to a better understanding of the epidemiology and treatment of diabetes which are relevant to Asian populations.

DIABETES COMPLICATIONS IN HONG KONG CHINESE

In 1995, The Chinese University of Hong Kong (CUHK) and Prince of Wales Hospital (PWH) jointly pioneered a research-driven quality improvement programme to understand the

causes and consequences of diabetes and improve the quality of ambulatory diabetes care (Fig. 1). This involved a diabetes nurse-coordinated comprehensive risk assessment programme, in which patient data on risk factors and complications was collected prospectively to establish the Hong Kong Diabetes Register (HKDR). After accrual of data for a decade, the CUHK diabetes team developed and validated risk equations and structured care protocols for the local population which were subsequently confirmed to reduce incidence of hospitalizations, morbidities, and premature mortality. The HKDR also served as a foundation for many published pharmaco-epidemiological analyses that provided insights into the effects of various disease-modifying drugs on clinical outcomes including cardiovascular-renal complications and cancer events in real-world practice [4,5].

In 2007, this integrated care model was digitalized to form the

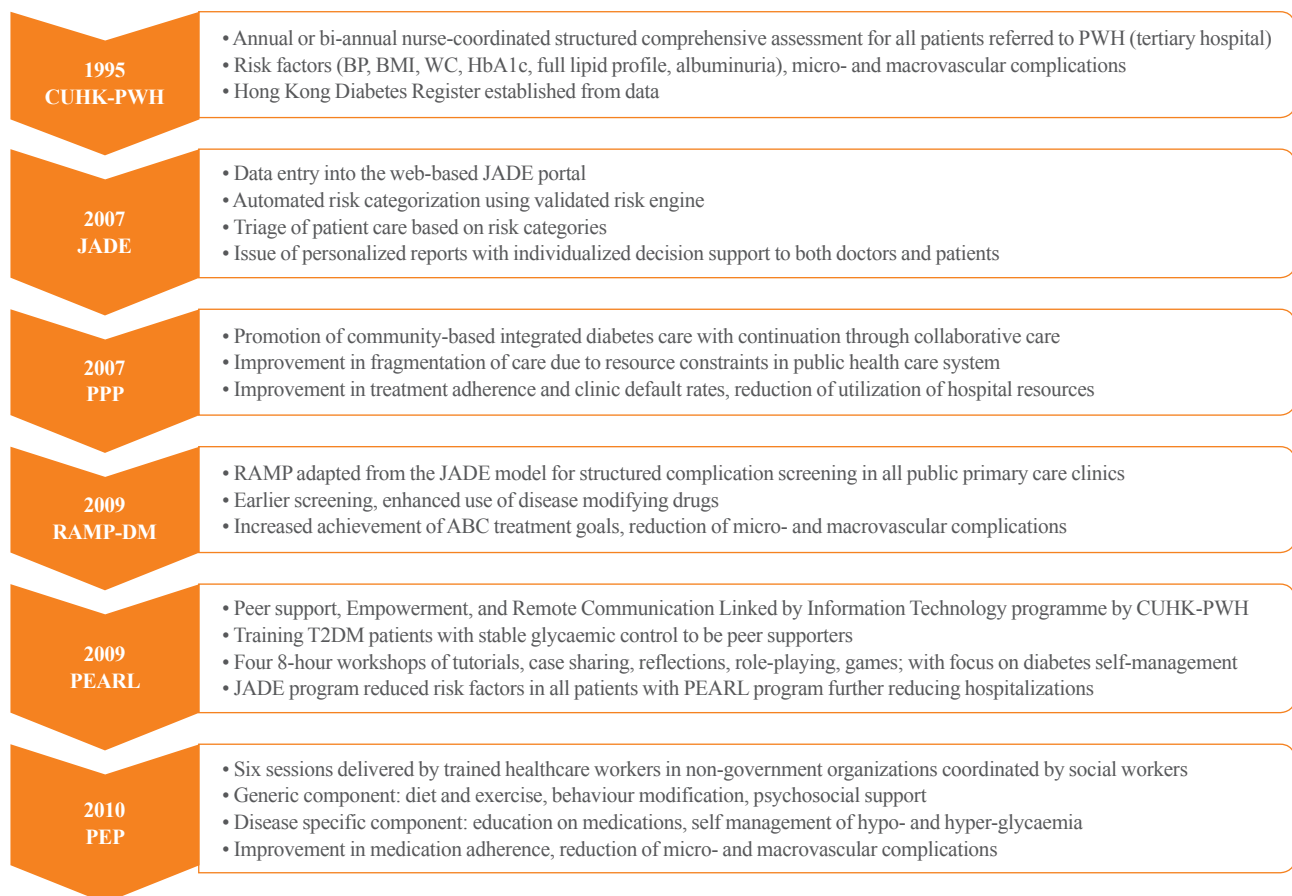


Fig. 1. Evolution and Implementation of Territory-wide Diabetes Quality Care Programs in Hong Kong. CUHK-PWH, Chinese University of Hong Kong-Prince of Wales Hospital; BP, blood pressure; BMI, body mass index; WC, waist circumference; HbA1c, glycated hemoglobin; JADE, Joint Asia Diabetes Evaluation; ABC, HbA1c, BP, low density lipoprotein cholesterol (LDL-C); PPP, Public Private Partnership; RAMP-DM, Risk Assessment and Management Program-Diabetes Mellitus; PEARL, Peer Support, Empowerment and Remote Communication Linked by Information Technology; T2DM, type 2 diabetes mellitus; PEP, Patient Empowerment Program.

Joint Asia Diabetes Evaluation (JADE) programme, a web-based portal that incorporated data entry, validated risk engine, personalized reporting with built-in clinical decision support tools to streamline patient care. Once enrolled into the JADE Program, all patients were classified into four risk categories via the JADE risk engine comprising various combinations of risk stratifiers and risk scores derived from the HKDR risk equations, each with its associated 5-year major event probabilities and management protocols. Those patients identified to be of low risk may be managed by general practitioners while higher risk patients are recommended to be managed by diabetes specialists with more frequent review as appropriate. The annual comprehensive assessment provided quality assurance to identify treatment gaps, reinforce self-management, and promote collaborative care. Both health-care providers and patients were provided with regular JADE reports upon clinic visits, outlining the patient's risk category, trends in 'ABC' (i.e., glycated hemoglobin [HbA1c], blood pressure [BP], low density lipoprotein cholesterol [LDL-C]) and body weight targets, as well as clinical decision support based on attained levels of risk factor control. The ABC targets were set at HbA1c less than 7%, BP less than 130/80 mm Hg, LDL-C less than 2.6 mmol/L in accordance to the recommendations by the International Diabetes Federation [6]. These personalized graphic reports served as a powerful tool in facilitating communication and shared decision-making between physicians and patients, as well as empowering patients to optimize their treatment targets through lifestyle and medication adherence. The JADE database also facilitated international collaborative research efforts to implement holistic and evidence-based care in the region. In 2009, the Hospital Authority adopted the JADE model to become the multidisciplinary Risk Assessment and Management Program for patients with diabetes mellitus (RAMP-DM). Since then, structured complication screening was extended to all public primary care clinics in Hong Kong.

In the 1990s, stroke and end stage renal disease (ESRD) were the predominant causes of death in Asians with diabetes while Caucasians were more likely to develop coronary heart disease (CHD) [7]. As mortality from these conditions improved with enhanced access to dialysis and better control of BP, deaths due to CHD started to increase in the early 2000s. Subsequent increase in the use of statins and coronary interventions then reduced mortality from CHD with cancer emerging as the next rising cause of death in Asian patients with diabetes (Table 1) [8]. With reference to the Hong Kong Cancer Register, patients with T2DM in Hong Kong had 30% higher risk of all-site can-

cers in all age groups and in both genders compared to the general population [9].

Cancer

The HKDR was the first to report a linear relationship between HbA1c and cancer risk, with every 1% increase in HbA1c associated with 18% increased risk of all-site cancer [10]. Patients treated with insulin and various glucose-lowering drugs including metformin, sulphonylurea and thiazolidinediones had 40% to 60% lower cancer risk compared to non-users [11]. Apart from hyperglycaemia, the CUHK-PWH team also identified non-linear risk associations of cancer with body mass index (BMI), LDL-C, high density lipoprotein cholesterol (HDL-C), triglycerides (TG), and white blood cell (WBC) count in V-shaped or A-shaped manners [4]. Supported by experimental studies in animals, we first reported that the use of statins and renin-angiotensin system (RAS) blockers was associated with reduced risk for cancer in patients with T2DM in the HKDR. Subsequent detailed analysis revealed various drug-subphenotype interactions associated with cancer risk [12].

- (1) Statin non-users who had both LDL-C less than 2.8 mmol/L and albuminuria had 5-fold increased risk of all-site cancer compared with statin users with or without both risk factors [13].
- (2) Non-users of metformin with HDL-C less than 1 mmol/L had 5-fold increased risk of all-site cancer compared to metformin users with HDL-C greater than 1 mmol/L [14].
- (3) Users of RAS blockers had 64% lower cancer risk than non-users in those with WBC count greater than 8.2×10^9 count/L [4].
- (4) Patients with all three risk factors of HbA1c higher than 7%, non-use of RAS inhibitors and non-use of statins had 4-fold higher adjusted risk of all-site cancer than users of both drugs with HbA1c less than 7% [11].

These subphenotypes suggested complex pathways linking lipid and glucose metabolism with cancer biology (Fig. 2). Due to the close links between diabetes, obesity and insulin resistance and given the co-sharing of insulin and insulin-like growth factor 1 (IGF-1) receptors, hyperinsulinaemia was often proposed as a major mechanism for promoting tumorigenesis through activation of insulin receptors and IGF-1 receptors expressed by tumor cells. However, insulin played a key role in *de novo* lipogenesis through activation of multiple sterol regulatory element-binding proteins (SREBPs). Thus, insulin deficiency might lead to reduced SREBP-1 and low TG. This might upregulate the IGF-1 pathway to increase other SREBPs which regu-

Table 1. Incidence of Cardiovascular-Renal Complications in Hong Kong Chinese with Type 2 Diabetes and the Benefits of Team-Based Structured Care in High and Low Risk Patients Managed in Both Public and Private-Public Partnership Settings since 1995

CUHK-PWH Hong Kong Diabetes Register [8]		
1995–2007, 1 public hospital, 8,558 patients, median duration of diabetes 5 years		
Patients with complications after median follow-up 6.7 years, %		
CKD	32.5	
CVD	15.1	
Death	11.8 (cancer 23.7, circulatory disease 23.3, renal disease 13.4)	
Territory-wide Hong Kong Diabetes Database [50]		
2000–2012, primary and secondary care settings, subgroup with duration of diabetes >15 years		
Cohort year	2000–2003	2010–2012
No. of patients	33,143	147,819
Incidence (per 1,000 person-years [95% CI])		
ESRD	25.75 (22.35–29.67)	22.46 (20.86–24.17)
Stroke	13.53 (11.06–16.56)	10.13 (9.04–11.34)
AMI	8.68 (6.75–11.18)	5.76 (4.94–6.71)
Death	29.03 (25.46–33.11)	26.55 (24.84–28.38)
Risk Assessment Management Program in public primary care setting [53]		
2009–2011, territory-wide public primary care clinics in low risk patients		
	Public-RAMP	Propensity-score matched control
No. of patients	8,570	8,570
Mean duration of diabetes, yr	8.67	8.54
Patients with events after 5 years follow-up period, %		
CVD	12.33	23.97
Stroke	5.19	8.48
Death	7.96	21.35
Public vs. PPP-JADE Program [57]		
2007–2015, PPP: university-affiliated diabetes centre, private doctors and JADE technology		
	Public	PPP-JADE
No. of patients	3,570	3,424
Median duration of diabetes, yr	9	7.4
Median follow-up, yr	3.2	5.1
Incidence (per 1,000 person-years [95% CI]) ^a		
CKD	86.6 (80.32–93.39)	39.96 (36.38–43.54)
ESRD	15.6 (13.44–18.11)	7.06 (5.92–8.43)
CHD	7.19 (5.71–9.06)	5.56 (4.5–6.87)
Stroke	6.39 (5.03–8.13)	4.09 (3.22–5.19)
Death	15.19 (13.09–17.62)	8.54 (7.28–10.03)

CUHK-PWH, The Chinese University of Hong Kong–Prince of Wales Hospital; CKD, chronic kidney disease; CVD, cardiovascular disease; CI, confidence interval; ESRD, end stage renal disease; AMI, acute myocardial infarction; RAMP, Risk Assessment and Management Program; PPP-JADE, Private Public Partnership–Joint Asia Diabetes Evaluation; CHD, coronary heart disease.

^aConsistent benefits in favor of PPP in patients with different risk profiles.

lated the cholesterol pathway through activation of the hydroxymethylglutaryl-CoA reductase (HMGCR). The latter could lead to increased synthesis of mevalonate and farnesylated proteins,

the latter being upstream signaling pathways of cell mitogenesis. Besides, hyperglycaemia resulting from insulin deficiency could activate the RAS to promote cellular growth [15,16]. In a

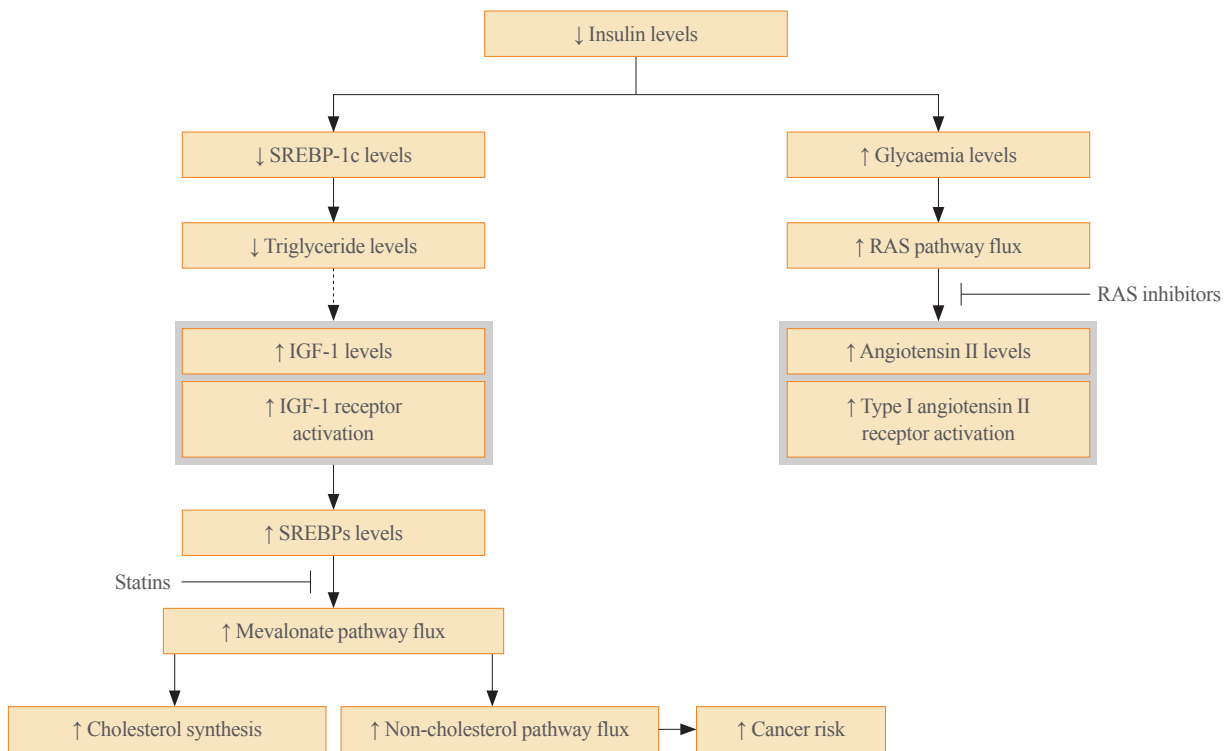


Fig. 2. Hypothetical consequences of insulin deficiency and activation of the renin-angiotensin system (RAS) and insulin-like growth factor 1 (IGF-1) cholesterol pathways. Figure illustrates how insulin deficiency and activation of the RAS and IGF-1-cholesterol pathways might explain the link between type 2 diabetes mellitus and an increased risk of cancer. The possible benefits of insulin, statins and RAS inhibitors in reducing the risk of cancer in individuals with different subphenotypes: low density lipoprotein cholesterol (LDL-C) levels <2.8 mmol/L+triglyceride levels <1.7 mmol/L for those with upregulated IGF-1-cholesterol pathway; and LDL-C levels <2.8 mmol/L+albuminuria for those with hyperglycaemia-activated RAS pathway are shown. Double-headed arrow indicates crosstalk between pathways. Dashed arrow indicates pathway without supporting mechanistic evidence. Reprinted from Yang et al., with permission from Springer Nature [16]. SREBP, sterol regulatory element-binding protein.

series of experimental studies, we reported development of renal cell carcinoma in uninephrectomized rat which exhibited a combined phenotype of hyperglycaemia, albuminuria and high LDL-C levels with upregulated expression of HMGCR and components of the RAS and IGF-1 pathways. Angiotensin converting enzyme inhibitors (ACEIs) treatment normalized expression of these proteins and reduced renal cell carcinoma formation. These findings suggested crosstalk between the RAS, HMGCR, and IGF-1 pathways in carcinogenesis which might explain the clinical observations of reduced cancer risk in patients treated with RAS blockers and statins [12].

Hepatocellular carcinoma (HCC) was a leading cause of cancer deaths in Hong Kong due to the high local prevalence of chronic hepatitis B viral (HBV) infection. The CUHK-PWH diabetes team was among the first to report the unfavorable modifying effect of chronic HBV infection on cardiovascular-renal outcomes in patients with diabetes [4,7]. Using the data from

the HKDR, we first reported that HbA1c greater than 7% and the lipid phenotype (LDL-C less than 2.8 mmol/L plus TG less than 1.7 mmol/L) markedly increased the hazard ratios for incident HCC amongst HBV carriers, which were attenuated by the use of insulin and statins [17]. These results also corroborated the findings from an experimental study where insulin treatment reversed the increased liver tumors in insulin-deficient cancer-prone mice [18].

Both metformin and apolipoprotein A-I (APOA-I), the latter being the main fraction of HDL-C, were activators of the adenosine 5'-monophosphate-activated protein kinase (AMPK) pathway, a master regulator of energy metabolism [15]. In animal studies, inhibition of this pathway led to tumor formation whereas use of metformin activated the pathway and inhibited cancer cell growth. Insulin played a key role in regulating lipid metabolism and patients with insulin resistance were prone to have low HDL-C and APOA-I levels which might explain the

Table 2. Key Drug-Subphenotype Interactions with Attenuated Cancer Risk—Analysis of the Hong Kong Diabetes Register

Key phenotypes	Drugs associated with reduced cancer risk	Hypothesized pathways
LDL-C <2.8 mmol/L+albuminuria [13]±HbA1c >7% [11] LDL-C <2.8 mmol/L+low TG <1.7 mmol/L [15]	Statins and RAS blockers	RAS+IGF-1+HMGCR crosstalk
HDL-C <1 mmol/L [14]	Metformin	AMPK
BMI >27.4 kg/m ² [4]	Not applicable	Not applicable
WBC >8.2×10 ⁹ count/L [15]	RAS blockers	RAS

LDL-C, low density lipoprotein cholesterol; HbA1c, glycated hemoglobin; TG, triglycerides; RAS, renin-angiotensin system; IGF-1, insulin-like growth factor; HMGCR, hydroxymethylglutaryl-CoA reductase; HDL-C, high density lipoprotein cholesterol; AMPK, adenosine 5'-monophosphate-activated protein kinase; BMI, body mass index; WBC, white blood cell.

interaction between metformin and low HDL-C phenotype in reducing all-cancer risk as reported in the HKDR [15].

In summary, detailed analysis of the HKDR have provided new insights into the potential cross-talks amongst these four biological pathways (HMGCR, RAS, IGF-1, and AMPK), explaining the diabetes-cancer link (Table 2). Dysregulation of these pathways have been reported in experimental studies of cancer which supported these clinical observations. Thus, hyperglycaemia, either due to insulin resistance and/or insulin deficiency could trigger these pathways to increase oxidative stress, inflammation and RAS activity to promote atherogenesis and oncogenesis. Similar to the multi-pronged approach needed to reduce cardiovascular-renal complications, the CUHK-PWH diabetes team hypothesized that an integrated approach was needed to optimize the metabolic milieu for reducing cancer risk in T2DM, although randomized clinical trials would be needed to confirm this hypothesis [11].

Chronic kidney disease and albuminuria

Asians had higher prevalence of diabetic kidney disease than Caucasians, accounting for 40% to 55% of those on dialysis, compared with less than 30% of those in Western countries [19]. They also had a greater propensity for earlier development of micro- or macroalbuminuria, affecting 60% of diabetic patients compared with 30% to 40% in Caucasians, given similar duration of diabetes or risk factor control [20]. The JADE risk equation for ESRD comprised of only three independent predictors: urinary albumin-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR), and haematocrit. Of these predictors, urinary ACR was the most modifiable risk factor for controlling multiple cardiometabolic risk factors [21]. In a cohort study from the HKDR, for every 10 mm Hg increase in systolic BP above 130 mm Hg, CHD risk was increased by 1.13-fold amongst Hong Kong women with T2DM [22]. However the

significance was lost after adjustment of urinary ACR and/or eGFR, suggesting that the effects of elevated BP on increased CHD risk was mediated by urinary ACR, which might be a surrogate marker of endothelial dysfunction [23,24]. In another analysis, we found a linear association between albuminuria and ischemic stroke most notably amongst those with HbA1c greater than 6.2% [25]. Based on these findings, it may be inferred that in patients whose HbA1c could not be reduced safely to less than 6.2%, stroke risk may still be reduced by aggressive control of albuminuria using RAS blockers [26]. Both the CHD and stroke risk equations (which included urinary ACR as a predictor) derived from the HKDR performed better than the respective United Kingdom Prospective Diabetes Study (UKPDS) risk engines (which did not include urinary ACR) in our local population [27,28]. This series of analyses highlighted the critical importance of screening for and reducing albuminuria in Asian patients with diabetes. Apart from albuminuria, intrarenal arterial resistance (resistance index greater than 0.8) as measured by Doppler was associated with deterioration in renal function as well as other microvascular complications [29]. These findings suggested that abnormal microvascular flow in the kidney might reflect generalized vasculopathy in diabetes. Taken together, all these findings supported the utility of using albuminuria as a prognosticator for cardiovascular-renal complications.

In Chinese patients with T2DM, components of metabolic syndrome (central obesity, hypertriglyceridaemia, and hypertension) predicted new onset of chronic kidney disease (CKD) (eGFR less than 60 mL/min/1.73 m²) independent of disease duration, glycaemic control, and albuminuria [30]. As a surrogate marker of visceral adiposity, waist circumference but not BMI was associated with increased intrarenal atherosclerosis and glomerulosclerosis, suggesting adverse effects of adipokines on renal haemodynamics and glomerular inflammation. In

T2DM, the frequent coexistence of cardiometabolic risk factors and insulin resistance caused earlier onset of nephropathy than type 1 diabetes, making multifactorial management of T2DM of paramount importance in preventing ESRD [31].

In the HKDR, use of statins was associated with over 60% risk reduction in the development of CKD and 40% risk reduction in new onset CHD. These benefits were independent of LDL-C levels, use of RAS inhibitors, glucose lowering drugs or insulin, and other baseline risk factors [5,32]. These findings echoed recent recommendations from international guidelines, which advocated the use of statins based on a patient's absolute cardiovascular risk rather than a specific LDL-C level. In a regional expert statement for lipid management in Asians, due to its safer pharmacokinetics and more potent effects on reducing proteinuria, atorvastatin was preferred over rosuvastatin [33]. Should rosuvastatin be chosen, it should be prescribed at a lower starting dose (5 mg daily) in Asians, as the plasma concentra-

tions in Japanese and Chinese were approximately double that in Caucasians.

In the landmark trials Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT), angiotensin receptor blockers (ARBs) delayed progression to ESRD in T2DM patients independent of BP reduction [34,35]. In a subgroup analysis from the RENAAL study, the renoprotective effect of ARB was more pronounced in Asians compared to Caucasians [36]. Although Chinese patients were more prone to develop cough from ACEI use (up to 50% chance) [37], the use of ARB as an alternative RAS blocker was far from optimal, ranking second to calcium channel blockers in Hong Kong (Table 3). That said, apart from usage of RAS blockers, optimal control of BP was of paramount importance for organ protection. In a *post hoc* analysis of the Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT-BP), re-

Table 3. Impact of Diabetes RAMP Adapted from the Joint Asia Diabetes Evaluation Programme on Treatment Goals and Clinical Outcomes in Primary Care Setting in Hong Kong

Study	Outcomes	HR (95% CI; <i>P</i> value) vs. usual care
Jiao et al. (2016) [52] 3 Years propensity matched cohort (RAMP-DM vs. usual care) 14,835 Patients/group	Microvascular complications	0.73 (0.66–0.81; <0.001)
	STDR/blindness	0.55 (0.39–0.78; 0.001)
	ESRD	0.4 (0.24–0.69; 0.001)
	LL ulcers/amputation	0.49 (0.30–0.80; 0.005)
Wan et al. (2018) [51] 5 Years propensity matched cohort (RAMP-DM vs. usual care) 26,718 Patients/group	Microvascular complications	0.881 (0.834–0.93; 0.001)
	CVD	0.434 (0.4144–0.0455; 0.001)
	All cause mortality	0.339 (0.321–0.357; 0.001)
	Hospitalizations	0.415 (0.403–0.4428; 0.001)
	Emergency attendance	0.588 (0.575–0.602; 0.001)
Fung et al. (2015) [49] Longitudinal study (2009 vs. 2013) 127,977 Patients in primary care	Specialist clinic attendance	0.65 (0.636–0.664; 0.001)
	Proportions of patients reaching treatment goals (2009 vs. 2013)	
	LDL-C <2.6 mmol/L	25.9%→65.6%
	HbA1c <7%	47.5%→56.5%
	SBP <130 mm Hg	47.5%→56.5%
	DBP <80 mm Hg	65.7%→77.5%
	Waist hip ratio ≤0.9 male; ≤0.85 female	22.9%→18.7%
	Urine ACR ≤2.5 mg/mmol male; ≤3.5 mg/mmol female	77%→73.7%
	Drug use pattern (2009 vs. 2013)	
	Statin	9%→55%
OAD+insulin	0.5%→3%	
ACEI/ARB	59.4%→58.3%	
CCB	73.9%→71%	

RAMP, Risk Assessment and Management Program; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; STDR, sight threatening diabetic retinopathy; ESRD, end stage renal disease; LL, lower limb; CVD, cardiovascular disease; LDL-C, low density lipoprotein cholesterol; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACR, albumin-creatinine ratio; OAD, oral anti-diabetic drug; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers.

ducing systolic BP to less than 130 mm Hg improved renal outcomes in Asians with T2DM, especially in those with heavy proteinuria (greater than 1 g/g Cr). However, similar to blood glucose control, BP targets should be individualized since patients with atherosclerotic diseases might not benefit from tight control of BP [38].

Young onset diabetes

Compared with Caucasians in whom the rising prevalence of diabetes was driven by aging, we are now seeing a rapid increase in the incidence of young onset diabetes (YOD; defined as diagnosis of diabetes before 40 years old) in Asian countries. In a recent national survey in China, the prevalence of YOD and pre-diabetes was approximately 45%, with the majority being undiagnosed [39]. In the HKDR, one in five adult patients had YOD [40]. In a 7-year prospective analysis of 9,509 patients with T2DM, those with YOD had 30% to 50% higher age-adjusted incidence of cardiovascular and renal events compared with patients with late onset diabetes (LOD) for the same attained age. The increased risk was mainly driven by the prolonged disease duration of the YOD group. Despite being younger by 20 years on average, those with YOD had poorer metabolic profiles than those with LOD. Another prospective analysis of patients with YOD from the HKDR showed that overweight patients with T2DM had 15- and 5-fold greater hazard of progression to cardiovascular disease (CVD) and ESRD respectively compared with patients with type 1 diabetes, even when adjusted for age, sex, time from diagnosis, and HbA1c [41]. Adjustment of other metabolic risk factors (BMI, BP, lipids) rendered the difference non-significant. Moreover, there was no difference in hazards for either CVD or ESRD between patients with type 1 diabetes and those with normal weight T2DM. These results suggested that apart from glycaemic control, early implementation of a multifaceted approach to control blood glucose and optimize other aspects of the metabolic syndrome was of particular importance in YOD. This was in line with suggestions from the landmark UKPDS [42] and Steno-2 studies [43], both demonstrating reduction in long-term risk of complications with early control of cardiometabolic risk factors.

In Hong Kong Chinese, a family history of YOD was associated with 6- to 7-fold odds of developing incident diabetes during a follow-up period of 12 years [44]. Although these participants had poorer metabolic profiles than the control subjects, the risk association of T2DM with family history of YOD remained robust after controlling for baseline glycaemic indices and metabolic risk factors. From genome-wide association stud-

ies, the majority of identified genetic loci for T2DM were implicated in β -cell biology compatible with the importance of reduced insulin secretory capacity as a main culprit in T2DM [45]. In support of this, those with family history of YOD had lower β -cell function (disposition index) and insulin sensitivity than those with family history of LOD or those without a family history. This suggested that in the younger population, heritability or shared environment reflected by positive family history, took on greater significance in the prediction of progression to diabetes, over and above the presence of metabolic syndrome. These findings called for earlier detection of diabetes in young individuals who had first degree relatives with YOD [44].

Recent epidemiological analyses from the HKDR revealed high rates of complications and low rates of achievement of treatment goals especially in patients with YOD. In the HKDR, 5% of YOD already had CVD or CKD at enrollment [40]. As many as 37% had micro- or macroalbuminuria, and yet only 15% of them were treated with RAS blockers. More than half had hypertension and three-quarters had dyslipidaemia, yet they were often less intensively treated with BP or lipid lowering therapies than their older counterparts, especially during the early stages of their disease. An analysis of the JADE Register which enrolled more than 40,000 patients from nine Asian countries revealed similar treatment gaps amongst the YOD group, despite diversity in health-care policies, clinical practices, and insurance coverages [46]. On the one hand, there is the lack of management guidelines for YOD and clinical inertia by the treating physician, and on the other hand, there is the poor treatment adherence. In these young patients, competing priorities in other aspects of life and difficult behavioral characteristics contributed to their poor control of cardiometabolic risk factors. Although the American Diabetes Association (ADA) guideline suggested statins for patients with diabetes aged less than 40 years with any cardiovascular risk factors [47], in real world practice, statins were seldom prescribed to these young patients. Further research and interventional studies are required to target patients with YOD for aggressive metabolic control and empowerment in order to reduce the burden of chronic diabetic complications.

EFFECTIVENESS OF SYSTEMATIC DIABETES CARE & PATIENT EMPOWERMENT PROGRAMS

In the Steno-2 randomized trial, intensive multi-target intervention (with focus on hyperglycaemia, hypertension, and hyper-

lipidaemia) in patients with T2DM and microalbuminuria reduced the risk of cardiovascular and microvascular events by 50% compared to conventional treatment after a mean follow-up period of 8 years [43]. The absolute 20% reduction in cardiovascular outcomes was higher than that achieved through single-risk factor intervention strategies reported by other studies. Similarly, in the SURE (Effects of Structured versus Usual Care for Renal Endpoints in type 2 diabetes) study, Chinese patients with T2DM and renal impairment managed by a diabetes specialist team using structured protocol with predefined treatment targets for 2 years were three times more likely to reach multiple treatment targets than those managed in the usual care setting. Patients who attained three or more treatment targets (HbA1c <7%, BP <130/80 mm Hg, TG <1.7 mmol/L, LDL-C <2.6 mmol/L, persistent use of RAS blockers) had 60% to 70% lower risk of developing ESRD or deaths compared to those who met less than three treatment targets [31]. In the Steno-2 study, after 21 years of observation, patients who were intensively managed during the 8-year trial period had gained 8 years of lifespan compared to those who were switched from conventional to intensified treatment after the trial completed [48]. These findings suggested that the maximum benefit of multifactorial intervention could only be derived if started early before the development of vascular complications and when patients were still at low risk for intensive treatment.

Since the implementation of the RAMP-DM program in the public primary care clinics in Hong Kong, there had been a significant increase in the use of disease-modifying drugs, especially statins (from 9% to 55%) between 2009 and 2013 (Table 3) [49]. In an analysis comparing the 2000 to 2002 and 2010 to 2012 cohorts of T2DM patients followed up at primary care clinics, more patients achieved any one of the three treatment targets (32.9% vs. 50% for HbA1c less than 7%; 24.7% vs. 30.7% for BP less than 130/80 mm Hg; 25.8% vs. 38.1% for LDL-C less than 2.6 mmol/L), with reduction in all DM-related complications and death [50]. This improvement remained significant after adjustment for disease duration, likely reflecting the more prevalent use of organ protective drugs, as well as enhanced accessibility to complication screening (from 3.1% to 81.9%) [49]. However, the little improvement in albuminuria (23% vs. 26.3%) and central obesity (77.1% vs. 81.3%) called for further efforts to control these risk factors (Table 3).

In three propensity-matched cohort analyses, patients under the RAMP-DM had greater reductions in CVD by 12% to 57%, microvascular complications by 12% to 27%, and mortality by 13% to 66%, when compared to patients under usual care (Table

3) [51-53]. Those with low baseline CVD risks (less than 65 years old, disease duration less than 2 years) benefited most from the RAMP-DM programme. After entering the programme for 5 years, hospitalizations, emergency attendances, and specialist clinic attendances were reduced by 58.5%, 41.2%, and 35%, respectively [51]. Although these were not randomized controlled trials, the large sample size and relatively long observation period suggested that a structured programme of risk assessment followed by triage into appropriate interventions could be highly effective in reducing the incidence of diabetic complications. By improving the standard of care in the primary care setting, a reduced burden on the secondary/tertiary care would be anticipated.

In another retrospective cohort analysis of 144,271 T2DM patients under primary care, the treatment effect size was the greatest for LDL-C control (42% CVD reduction), compared to BP (18% CVD reduction), and glycaemic control (13% CVD reduction) [54]. Given the challenges of controlling hyperglycaemia and polypharmacy which requires education and empowerment, efforts should be prioritized to first reduce the LDL-C level followed by BP and HbA1c to reduce CVD risk.

Apart from pharmacological treatment, lifestyle modification through patient empowerment is an integral component of diabetes care. In 2010, the Hospital Authority launched the territory-wide Patient Empowerment Program (PEP) to further enhance the quality of care. The curriculum comprised of six patient education and support sessions delivered by trained health-care workers, supplemented by doctor's visit to improve treatment adherence and self-care (Fig. 1). After adjusting for confounding variables, several propensity-matched prospective cohort analyses of more than 12,000 participants each indicated that PEP participants had 50% lower incidences of all-cause mortality and 15% to 30% lower incidence of macro- and microvascular events compared to non-PEP participants [55]. These participants also had reduced utilization of health services, 10% reduction in emergency department attendances, and 15% reduction in hospitalizations. Other programs focusing on peer support and telephone support have also shown great promise in improving medication adherence, patient self-management skills, hospitalizations, and overall quality of care [56].

IMPROVING COMMUNITY CARE THROUGH PUBLIC PRIVATE PARTNERSHIP

Due to the high service demands on the public health care sys-

tem in Hong Kong, patients were often seen by different doctors with short consultation times at each clinic visit. Although comprehensive complication assessments were provided in both hospital and primary care settings under the Hospital Authority, most patients did not have access to their personalized assessment reports, making communication of treatment goals and informed decision-making difficult. Furthermore, an interdisciplinary team approach involving diabetes nurse, nutritionist, podiatrist, psychologist and peer support groups was often needed to help patients understand their disease and to motivate them in the management of their own health. Given the limitations in the public health infrastructure with short consultation time and frequent changes of care team, the CUHK developed a public private partnership (PPP) program in 2007, with the vision of promoting community-based integrated diabetes care using the JADE program and a university-affiliated self-funded nurse-led diabetes centre to support private doctors. Based on more than 15,000 patients followed since 2007 in three care settings, participants of the PPP had the lowest event and hospitalization rates compared with patients attending usual care under the Hospital Authority (Table 1) [57]. On a self-funded basis, PPP participants could seek treatment from private doctors at more flexible hours. Some patients attended both private and public clinics in which they sought medical consultations from their private doctors while obtaining drugs and investigations at lower cost from the Hospital Authority. By undergoing regular comprehensive assessment at the CUHK affiliated nurse-coordinated diabetes centre, these patients received yearly personalized JADE reports with written recommendations by endocrinologist and face-to-face explanation of reports by nurses. This was followed by prompt clinical decisions by their attending doctors in the community. These joint efforts between specialists, nurses, and primary care doctors not only improved continuation of care, but also enhanced treatment adherence and reduced clinic default rates.

Hong Kong has a population of 7 million with the Hospital Authority managing nearly 400,000 patients with diabetes. On average, each patient with diabetes spent three nights of hospitalization (USD 600 per night) per year, i.e., USD 1,800 per patient per year. Researchers estimated that if the JADE model was implemented in the community setting through PPP, the Hospital Authority might save up to USD 1,000 per patient per year due to hospitalizations alone which amounted to nearly 6% of the annual public health care expenditure [57]. However, given the large differences between private and public care, subsidies from government, insurers, and employers would be need-

ed to motivate care providers and patients to participate in these PPP in order to improve the sustainability of diabetes and chronic care.

PERSONALIZED DIABETES MANAGEMENT

Epidemiological studies thus far had characterized the “Asian phenotype” as a double hit of early-onset β -cell insufficiency marked by poor insulin secretory capacity and insulin resistance due to concomitant obesity and metabolic syndrome. These metabolic insults have put these patients with long disease duration at high risk of developing renal disease and cancer. Patients with early β -cell failure were more likely to have low BMI and might benefit more from early insulin therapy. On the other hand, those who were obese or had predominant visceral adiposity often required high dose insulin treatment and might benefit from use of insulin sensitizers, incretin therapy, and bariatric surgery to reduce excessive use of insulin. It is against this multicausality of insulin deficiency and resistance, phenotypic heterogeneity and pluralistic needs that makes periodic comprehensive risk assessment critically important to define subphenotypes, stratify risk, identify unmet needs and provide the most optimal treatment in order to maximize benefits and minimize harm [58].

Bariatric surgery

Asians are more likely to have a higher percentage of body fat at a lower BMI and waist circumference compared with Europeans. Thus, for similar BMI cut-off points, they were more likely to harbor cardiovascular risk factors and obesity-related comorbidities [59]. In the United Kingdom Biobank Study, the prevalence of diabetes at a BMI of 22 kg/m² among South Asian participants was comparable to that at a BMI of 30 kg/m² amongst participants of white European descent [60]. In a cross-sectional study on Asian Americans, lowering the cut-off value of BMI from 25 to 23 kg/m² increased the sensitivity of detecting pre-diabetes and diabetes from 50.2% to 74.1% [59]. Accordingly, the latest consensus suggested that the BMI thresholds for bariatric surgery should be 2.5 kg/m² lower for Asians across all risk groups [61]. Surgical outcomes in Asians showed favorable results similar to that seen in the Western population, and these favorable outcomes are likely due to the rapid reduction of insulin resistance and recovery of early insulin secretion postoperatively. In a prospective cohort of patients who underwent laparoscopic sleeve gastrectomy at the CUHK, half of

them achieved remission of T2DM starting from the second year after surgery, and this figure was maintained at 5 years. Amongst insulin-treated patients, two-thirds were able to discontinue insulin therapy upon follow-up [62]. In addition, 64% of patients had resolution of metabolic syndrome with sustained weight loss (defined as 50% or more reduction of excessive weight) at long term follow-up. In long-term observational studies, bariatric surgery reduced risk of microvascular complications compared with usual care, regardless of baseline glycaemic status [63]. Using the ABCD Diabetes Surgery Score system, young age, high BMI, high C-peptide level, and short duration of diabetes predicted remission of T2DM after metabolic surgery [61]. Taken together, patients with YOD who often had higher metabolic burden might benefit more from metabolic surgery than patients with LOD. However, bariatric surgery remained an invasive treatment modality which might not be well accepted by patients. In Asia, there remained uncertainty over long-term adverse health consequences, especially if supporting service for follow-up were suboptimal. Therefore, medical options for management of diabetes remained the cornerstone option for most patients.

Insulin

The ADA recommended combination therapy with insulin and/or multiple oral glucose lowering drugs if the target HbA1c of less than 7% was not achieved after 3 months of lifestyle modifications plus metformin alone [47]. In Asians with predominant insulin insufficiency, as suggested by lean body mass and especially in those with YOD, early insulinization might preserve β -cell dysfunction by alleviating glucotoxicity [64]. Thus, in contrast to guidelines from the West, the Standards of Care in China 2016 recommended short term intensive insulin therapy in patients with HbA1c higher than 9% or symptomatic hyperglycaemia at presentation (fasting plasma glucose ≥ 11 mmol/L) [65]. In the International Diabetes Management Practice Study (IDMPS), short disease duration, use of few oral glucose lowering drugs, and absence of microvascular complications were predictors for achieving glycaemic control [66]. These findings supported avoidance of delayed use of insulin in patients treated with multiple oral glucose lowering drugs with inadequate glycaemic control. However, in real world practice, these algorithms were seldom adhered to and insulin was often delayed despite failure on dual or triple oral glucose lowering drugs. Even for those who were initiated on insulin, without adequate patient education and empowerment, titration to goal was often delayed [67,68]. In the IDMPS, self-adjustment of insulin dosages was

identified as a predictor of glycaemic control in Asians [66].

A pooled analysis of 16 randomized controlled trials had shown that Asians required higher basal insulin doses to achieve adequate glycaemic control compared with Caucasians (0.18 units/kg vs. 0.16 units/kg, $P < 0.001$), despite the fact that they were often younger with lower BMI, and had similar disease duration. In this cohort, the C-peptide level was 20% lower in Asian than in non-Asian patients. Even when similar fasting plasma glucose targets were achieved, Asian patients were less likely to achieve HbA1c target less than 7% compared with Caucasians, suggesting a need to control postprandial hyperglycaemia [69]. In another observational survey of Chinese patients with T2DM, insulin-treated patients with low fasting C-peptide levels had better cardiovascular outcomes than those with high fasting C-peptide levels and treated with insulin, supporting the potential role of using C-peptide levels to guide therapy [70].

Incretin therapy

Large scale epidemiological studies indicated that postprandial blood glucose was a better independent predictor of cardiovascular risk than fasting blood glucose or HbA1c [71]. In a cross-sectional study in Asian Americans, screening for diabetes with HbA1c and fasting plasma glucose identified only half of those with diabetes compared to the use of 75 g oral glucose tolerance test which only missed 15% of people with diabetes [59]. Asians had higher propensity for postprandial glucose excursions due to their preference for high-carbohydrate diets, reduced early-phase insulin secretion and blunted incretin effect. Compared with the use of short-acting insulin, short-acting glucagon-like peptide-1 receptor agonists (GLP-1RAs) offered additional advantages of weight reduction and reduced risk of hypoglycaemia. In Japan, patients had lower endogenous GLP-1 levels and meal-induced GLP-1 secretion than Caucasians, rendering them more responsive to lixisenatide, a GLP-1RA in postprandial glucose reduction [72]. Asians with lower BMI often required a lower dose of GLP-1RAs compared to their Caucasian counterparts due to higher rates of gastrointestinal side effects and greater drug exposure. The combination of insulin and GLP-1RA theoretically worked best for those with poor β -cell reserve, impaired incretin effect and obesity.

For those with needle phobia or difficulties in handling needle injections, oral dipeptidyl peptidase-4 (DPP-4) inhibitors is an alternative to GLP-1RAs as an incretin-mimetic drug in augmenting postprandial insulin secretion and suppressing glucagon secretion, especially when used in the early stage of the disease. In a meta-analysis, Asians exhibited better response to

DPP-4 inhibitors in HbA1c reduction than Caucasian patients, along with improvement in β -cell function [73]. In patients with newly diagnosed T2DM and HbA1c greater than 9%, the ADA guideline suggested initial combination therapy to achieve a target HbA1c of less than 7% earlier [47]. Here, metformin reduced fasting plasma glucose by inhibiting hepatic gluconeogenesis while DPP-4 inhibitor reduced postprandial glucose. In a *post hoc* subgroup analysis of pooled data from randomized clinical trials, more than half of the Asian patients with initial HbA1c 8.5% to 12% started on metformin and linagliptin achieved glycaemic control within 24 weeks, without weight gain or hypoglycaemia [74].

Sodium-glucose cotransporter-2 inhibitors

A number of randomized controlled studies have demonstrated similar blood glucose lowering efficacy of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in Asians compared with Caucasians [75]. By decreasing glucotoxicity through insulin-independent mechanisms, this class of drugs improved both β -cell function and peripheral insulin sensitivity. Moreover, the favorable effects on BP, body weight, visceral fat, and waist circumference made SGLT-2 inhibitors an attractive treatment choice for patients with T2DM and metabolic syndrome. In the EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose) trial, empagliflozin reduced the rate of decline of renal function as well as cardiovascular-renal events in high risk patients with T2DM, when added to usual care [76]. Since Asians were more prone to developing renal complications, further real-world data and longer-term clinical trials in this population would be useful to support the preferred use of this class of drugs in Asian patients with T2DM. Here, a combination of SGLT-2 inhibitors and GLP-1RAs with different mechanisms of action and fewer drug interactions showed potential promise given their efficacy in reducing body weight and cardiometabolic risk factors.

DIABETIC COMPLICATIONS ARE HIGHLY PREVENTABLE

The alarming rise in the prevalence of obesity, metabolic syndrome and diabetes in Asia during the past few decades carries onerous implications on the affected persons, their families and society where they live in. Rapid urbanization with the associated changes in diet and lifestyle has created an obesogenic environment leading to the current “diabesity” epidemic. Early screening and aggressive control of risk factors is of utmost im-

portance especially in those with YOD. Given the silent nature of diabetes during its early stage, the golden window for intervention may be lost unless a more proactive approach is adopted instead of intensive treatment during advanced stages of the disease when patients become symptomatic. Abundant evidence from both randomized controlled trials and observational longitudinal studies have demonstrated the powerful effects of using structured care protocols and multifactorial intervention to achieve treatment targets, reduce hospitalizations, morbidity, and premature mortality. In particular, the combined use of RAS blockers, statins, and glucose lowering drugs including the appropriate use of insulin have the strongest evidence in reducing cardiovascular-renal outcomes and possibly cancer events. Obese patients with metabolic syndrome and adequate pancreatic islet reserve are ideal candidates for bariatric surgery. For those who opt for medical treatment, early use of metformin, incretin mimetics and SGLT-2 inhibitors will result in lower risk of hypoglycaemia and neutral or favorable weight benefits. This treatment option together with good clinical care and self-management may provide more durable glycaemic control and favorable cardiovascular outcomes. Lean subjects with rapid decline of β -cell function are more likely to benefit from incretin and early basal-bolus insulin therapy, as needed.

USING DATA TO INFORM PRACTICE AND POLICY

Through systematic collection of data to document the pattern of risk factors, complications and medication use, the HKDR had provided a rich knowledge resource with validated risk equations applicable to the local population. The JADE Program is a prototype of how information technology could be used to translate knowledge accrued to facilitate doctor-patient dialogues and deliver evidence-based care. Its adoption across all primary care clinics in the public health sector of Hong Kong has substantially increased the early detection and control of risk factors especially the use of statins with reduction in clinical outcomes and health care expenditures. Besides reducing clinical inertia and increasing the prescription of disease modifying drugs by health care providers, the launch of territory-wide PEP also contributed to improvement in lifestyle changes and medication adherence.

CONCLUSIONS

Hong Kong has one of the lowest tax system (17% salary tax

and 17% corporate tax) in the world and together with the heavily subsidized public health care system without a mandate on compulsory health insurance, the long term financial sustainability of these public-funded programmes is an area of concern. It is here where PPP might provide an additional option to relieve the growing burden on the public healthcare system which has the primary mandate of supporting the poor and the sick and in training healthcare personnel. Given the large body of evidence in support of the benefits of these multi-component programs in improving diabetes care, strengthening of the healthcare infrastructure supported by appropriate financing schemes with establishment of community-based integrated care centres would be a highly feasible and cost-effective solution for reducing care fragmentation, promoting health literacy, and improving patient-provider relationship. Such strategies should be applicable to many countries in our pursuit of prevention and control of diabetes and its comorbidities.

CONFLICTS OF INTEREST

Juliana C.N. Chan is the Chief Executive Officer, on a pro bono basis, of the Asia Diabetes Foundation which designs and operates the JADE Programme (www.adf.org.hk). Other authors reported no conflict of interest relevant to this article.

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