Challenges in achieving optimal glycemic control in type 2 diabetes patients with declining renal function: The Southeast Asia perspective

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ABSTRACT

It is well recognised that Asia is at the epicenter of the global type 2 diabetes epidemic. Driven by socioeconomic changes involving industrialization, urbanization and adoption of Western lifestyles, the unprecedented increases in the prevalence of diabetes are particularly evident in Southeast Asia. The impact of diabetes is immense, and despite evidence of the benefit of optimal glucose control in reducing the risk of disease progression and development of macrovascular and microvascular complications, many individuals in this region remain poorly controlled. Chronic kidney disease (CKD) is an increasingly common diabetes-associated complication in Asian patients. Furthermore, Southeast Asia has one of the highest rates of end-stage renal disease (ESRD) in the world. Consequently, CKD in diabetes is associated with considerable morbidity and cardiovascular-related mortality, highlighting the need to screen and assess patients early in the course of the disease. The management of type 2 diabetes patients with declining renal function represents a significant challenge. Many of the older antidiabetic agents, such as metformin and sulfonylureas, are limited in their utility in CKD as a result of contraindications or hypoglycemic episodes. In contrast, dipeptidyl-peptidase IV inhibitors have provided a welcome addition to the therapeutic armamentarium for achieving glycemic control in these special populations. With comparable efficacy to and more favorable pharmacokinetic and side-effect profiles than traditional therapies, agents in this drug class, such as linagliptin, offer a more tailored approach to disease control in type 2 diabetes patients with declining renal function.
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KEY WORDS: Chronic kidney disease, Dipeptidyl-peptidase IV inhibitors, Type 2 diabetes

CURRENT BURDEN OF TYPE 2 DIABETES IN SOUTHEAST ASIA

Type 2 diabetes continues to present a public health burden across the world, and Asia is considered to be at the epicenter of this diabetes epidemic, with 60% of the disease burden borne by this region[1–3]. The increase in diabetes prevalence across Asia has been rapid, fuelled by increasing obesity, aging populations and urbanization, which in turn have been driven by rapid economic development, a sedentary lifestyle and increased consumption of refined foods[3]. These socioeconomic changes have been particularly significant in countries across Southeast Asia[4], and reflected by dramatic rises in type 2 diabetes prevalence over the past decade (Figure 1). Indeed, Indonesia and the Philippines are projected to be among the top 10 countries in the world with the highest number of estimated cases by 2030[1]. Another issue curtailing the type 2 diabetes rise in Asia is the high number of undiagnosed individuals. For instance, in Hong Kong and Taiwan it was reported that almost 53% of diabetic patients remain undiagnosed[5]. Furthermore, the prevalence of pre-diabetes (impaired glucose tolerance) further adds to the already burgeoning burden of overt diabetes and its consequences in this region (Figure 1).

It is widely recognized that diabetes is a major source of morbidity, mortality and economic burden[6]. Prolonged and poor glucose control increases the risk of developing macrovascular (coronary artery disease, stroke) and microvascular (nephropathy, retinopathy and neuropathy) complications[7], which can greatly reduce life expectancy and quality of life[8]. In fact, the risk of all-cause mortality (cardiovascular and non-cardiovascular) is

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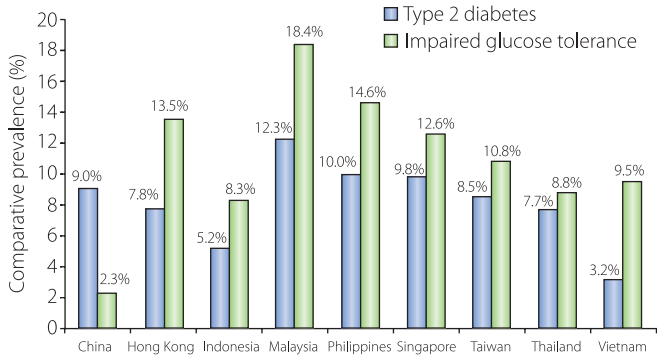

Figure 1 | Comparative prevalence of diabetes in countries across Southeast Asia in 2011 (calculated by assuming that every country and region has the same age profile). These data are based on figures compiled by the International Diabetes Federation in the International Diabetes Atlas, 2011 (available at: http://www.idf.org/atlasmap/atlasmap).

higher in diabetic than non-diabetic patients[9,10]. Consequently, the rapidly growing prevalence of diabetes in Asia is likely to result in large increases in diabetes-associated mortality[10].

From an economic perspective, the impact of diabetes on healthcare resources and personal expenditure, as well as the financial implications associated with loss in productivity and disability, is enormous[11]. In Taiwan, the direct healthcare cost associated with diabetes was 11.5% of the total national healthcare cost and was 4.3-fold higher than the care of non-diabetic individuals[12]. In Hong Kong, the annual total cost of type 2 diabetes equated to USD 1,725 ± 2,044 per patient. These costs increased considerably if complications were present[13]. Furthermore, complications increased treatment costs associated with inpatient hospital stay by between 6 and 300% compared with treatment of type 2 diabetes patients without complications[14]. Of note is the considerable heterogeneity in healthcare spending for diabetes between countries across Southeast Asia. The International Diabetes Federation estimated that, in 2010, treatment of diabetes accounted for 5 and 7% of the total healthcare expenditure in Vietnam and Indonesia, respectively, compared with 15 and 16% in Singapore and Malaysia, respectively[11]. Taken together, it is clear that early diagnosis and disease control are important healthcare initiatives to improve the lives, outcomes and economies of these at-risk countries.

In determining the optimal management approach, recognizing the differences in clinical characteristics and risk of diabetes between Asian and Caucasian populations is important to understand. For instance in Asians, diabetes develops over a shorter time, in younger people and in those with a lower body mass index (BMI)[15]. Furthermore, Asians have a higher proportion of body fat and abdominal obesity, putting them at a higher risk of developing insulin resistance[16,17]. Reports that Asians show early β-cell dysfunction might further explain their increased susceptibility to type 2 diabetes[16,17].

The thrifty gene and thrifty phenotype hypotheses have been proposed as plausible explanations for the increasing diabetes epidemic seen across Asia[18]. Although considered protective during periods of famine or food shortage, thrifty genes have rendered individuals highly predisposed to obesity in times of plenty. Alternatively, the thrifty phenotype relates to the impact of an unfavorable intrauterine environment (e.g. undernutrition) and low birth weight on the subsequent development of diabetes and metabolic syndrome in adults[18].

Several diabetes-associated genes have been implicated to account for the heightened predilection in Asians, especially Asian Indians, and include polymorphisms of the peroxisome proliferator-activated receptor co-activator-1 alpha (PGC-1 alpha) gene, plasma cell glycoprotein (PC-1) gene and insulin receptor substrate (IRS-2) gene (reviewed in Radha and Mohan)[19].

Given the increased prevalence of diabetes among younger populations in Asia and early exposure to hyperglycemia, it has been suggested that they are also at a high risk of end-organ damage and are likely to have to live with complications for longer[20]. Indeed, the Asia–Pacific Cohort Studies Collaboration (APCSC), which assessed the impact of diabetes on cardiovascular outcomes and mortality, found a greater risk of fatal coronary heart disease, hemorrhagic and ischemic stroke among younger compared with older individuals[21]. APCSC also showed an association between diabetes and increased risk of death as a result of renal disease, cancer, respiratory infections, and other infective and inflammatory causes[21]. Although optimal blood glucose control has been shown to reduce the risk of both macrovascular and microvascular complications[6], the marked prevalence of renal dysfunction in Asia reflects, in part, the continuing challenge in achieving this goal[22].

The aim of the present article was to review the barriers to achieving optimal blood glucose control in Asian patients with type 2 diabetes who have declining renal function and to discuss the treatment modalities that might be appropriate for the management of these special patient populations.

DIABETES AND CHRONIC KIDNEY DISEASE COMPLICATIONS IN ASIA

Of the diabetes-associated complications, the most debilitating is chronic kidney disease (CKD) and its pathogenic progression to end-stage renal disease (ESRD) that requires dialysis or transplantation[23]. Defining and diagnosing CKD in clinical practice has evolved since its first classification by the National Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002[24]. In these guidelines, CKD was categorized into five stages according to the severity of disease as defined by decreasing glomerular filtration rates (GFR) alone[24]. In the more recent update, the assessment criteria have been modified to encompass both GFR and albuminuria measures as correlates of a patient's prognosis. In addition, a subdivision of the previously described GFR stage 3 has been proposed to help further define the severity of kidney dysfunction in patients with CKD[25].

Risk factors for the development of reduced kidney function in Southeast Asian populations have been identified and

include the presence of diabetes, systolic hypertension (>159 mmHg), hyperuricemia (>6.29 mg/dL), elevated BMI (>24.9 kg/m^2) and hypercholesterolemia (>248.3 mg/dL)[26].

Microalbuminuria and Type 2 Diabetes

Microalbuminuria is the earliest clinical manifestation of CKD in type 2 diabetes and persistent microalbuminuria represents an early clinical marker for the development of diabetic nephropathy (DN)[27]. Although the number of studies exploring the epidemiology of microalbuminuria across Asia has been limited, the Microalbuminuria Prevalence Study (MAPS) of 6,800 hypertensive diabetic patients from 10 countries in the region reported an overall prevalence rate of 39.8% (95% confidence interval [CI] 39.2–40.5)[22]. The prevalence in individual countries across Southeast Asia is given in Table 1. These data show how a high proportion of hypertensive, type 2 diabetes Asian patients are showing early signs of declining renal function, and further support a need for early intervention so as to reduce accelerated progression of cardio-renal complications and the associated healthcare burden[28–31].

In recognition of the utility of measuring microalbuminuria, guidelines recommend annual screening of this clinical marker for identifying at-risk populations[32]. Patients identified with microalbuminuria early in the course of disease might require stricter glycemic and blood pressure control targets. Indeed, several prospective studies have shown the importance of tight glycemic control alone and combined with blood pressure lowering in the prevention of microvascular complications. For instance, the UK Prospective Diabetes Study compared the effects of intensive blood-glucose control with either sulfonylureas or insulin and conventional treatment (including diet) on the risk of microvascular and macrovascular complications in type 2 diabetes patients. Intensive glucose control with sulfonylureas or insulin resulted in a 33% relative risk reduction in the development of microalbuminuria. Furthermore, this reduction in risk was sustained in the 10-year follow-up study during which long-term benefits on cardiovascular disease (CVD) risk also emerged[33,34].

Table 1 | Prevalence of microalbuminuria in selected countries across Southeast Asia

Country	Prevalence of microalbuminuria (%)
Hong Kong	24.9
Indonesia	33.0
Malaysia	39.7
Singapore	48.5
Taiwan	26.9
Thailand	43.3

With the exception of Taiwan (Chiang SC *et al. JCMA* 2011; **74**: 3–10), these data are based on subanalyses of the Microalbuminuria Prevalence Study of 6,800 hypertensive diabetic patients from 10 countries across Asia (Wu AY *et al. Diabetologia*. 2005; **48**: 17–26.)

In the Kumamoto study, the frequency and severity of diabetic microvascular complications were assessed in Japanese type 2 diabetes patients after treatment with either intensive glucose control (multiple insulin injections of three or more) or conventional therapy (insulin injections administered once or twice daily). There was a significant reduction in the progression of nephropathy and other microvascular complications (retinopathy) after intensive insulin therapy ($P < 0.05$)[35].

The effect of an intensive, step-wise multifactorial intervention, targeting hyperglycemia, hypertension, dyslipidemia and microalbuminuria, on the initiation and progression of microvascular complications in type 2 diabetes patients with microalbuminuria was assessed in the Steno-2 study. Type 2 diabetes patients receiving early intensive diabetes management including tight glucose control and angiotensin converting enzyme inhibitors (ACEI) to reduce blood pressure were significantly less likely to develop nephropathy than patients receiving standard therapy (odds ratio 0.27; 95% CI 0.10–0.75). This reduction in risk was maintained in an observational follow up of 5.5 years[36,37].

In the most recent analysis of the Action in Diabetes and Vascular disease: preterAx and diamicroN-modified release Controlled Evaluation (ADVANCE) trial, which included a large number of Asian type 2 diabetes patients, further support for the benefits of combining blood-pressure lowering with intensive blood glucose control was provided[38]. Patients received either intensive glucose control (target glycated hemoglobin [HbA_{1c}] ≤ 6.5%) or standard glucose control (defined by local guidelines) with placebo or ACEI plus indapamide therapy. A combination of intensive glucose control plus ACEI plus indapamide therapy led to a significant percentage in risk reduction in new or worsening nephropathy (95% CI 12–50%; $P = 0.005$); a 54% reduction in the development of new-onset macroalbuminuria (95% CI 35–68%; $P < 0.001$), and a 25% reduction in the risk of new-onset microalbuminuria (95% CI 16–33%; $P < 0.001$). Furthermore, the effects of blood pressure lowering and intensive glucose control were independent of each other, so that on combining these agents, additive benefits were observed, particularly on renal outcomes[38].

Indeed, the benefits of early and tight target control strategies on the prevention of DN in Chinese type 2 diabetes patients have been observed. In this Asian cohort with normoalbuminuria, achievement of American Diabetes Association (ADA)-recommended targets of HbA_{1c} (<7%), systolic blood pressure (<130 mmHg), diastolic blood pressure (<80 mmHg) and lipid profiles (low-density lipoprotein [LDL] <100 mg/dL; triglycerides <150 mg/dL; high-density lipoprotein >40–50 mg/dL) reduced the risk of developing new-onset microalbuminuria compared with those who were unable to attain these targets[39]. Interestingly, in a separate study of Taiwanese type 2 diabetes patients with microalbuminuria, almost 36% of patients achieved remission to normoalbuminuria following a tight, multifactorial target control approach[40].

Impact of CKD in Type 2 Diabetes

Worldwide, rates of CKD have been increasing, and have accompanied the increasing prevalence of type 2 diabetes, hypertension and CVD. For instance, in the USA, it is estimated that 30% of patients with type 2 diabetes will develop some form of kidney disease as reflected by protein leakage, microalbuminuria, macroalbuminuria or a decline in the glomerular filtration rate (GFR)[41].

Nephropathy is a common complication of Asians with type 2 diabetes, as reflected by the accelerating prevalence and incidence rates of observed CKD[23,42]. Indeed, incidence rates of ESRD across Asia have shown increases over a 6-year period (2003–2008) of 15.8% in Hong Kong, 22% in Malaysia and Thailand, 24% in Singapore, and up to 31% in the Philippines[43,44]. Although incidence rates of ESRD appear to have declined in Taiwan since 2005, this country has the third highest rate of ESRD in the world, with an incidence rate of 384 per million population (pmp), highlighting the disparity between the rate of kidney disease and a country's economic status[42]. Furthermore, it has become apparent that a high proportion of ESRD cases are as a result of diabetes, ranging from 41% to 62% in individual countries across Southeast Asia (Figure 2)[43,44].

Morbidity and mortality associated with CKD itself is enormous. The presence of CKD is also associated with a high CVD risk, which is further exacerbated by the presence of diabetes and hypertension[45]. Indeed, CVD remains the main cause of death in patients with CKD rather than kidney failure, and it is estimated that CVD-associated mortality is 10–30-fold higher in patients with advanced CKD receiving dialysis than the general population[46]. Given that the prevalence of hypertension in Asia is increasing, and that diabetes and hypertension commonly coexist (type 2 diabetes patients are twice as likely to have elevated blood pressure than non-type 2 diabetes patients), screening these high-risk patients for CKD early might help slow the course of renal function decline and reduce the greater cardiovascular mortality risk observed in such individuals[47–49].

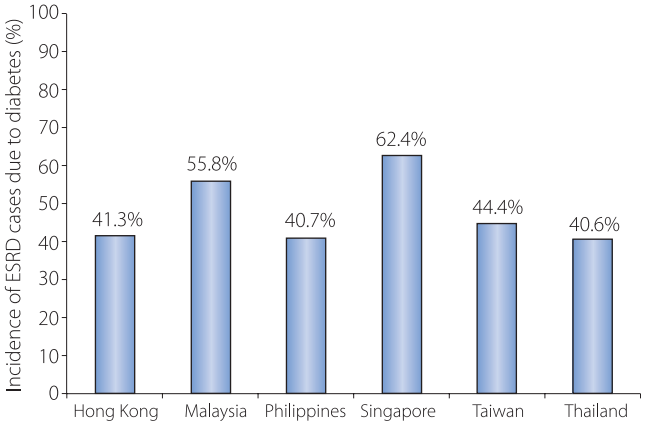

Figure 2 | Incidence of end-stage renal disease (ESRD) as a result of diabetes in selected countries across Southeast Asia in 2008. These data are based on figures compiled by the US Renal Disease System (Figure adapted from *2010 US Renal Disease System Annual Report* Chapter 12 International Comparisons; volume 2; pages 383–396). For Singapore, the 2008 data have been extracted from the National Registry of Diseases Office, Released 1 March 2011 (INP-11-1).

IMPACT OF DECLINING RENAL FUNCTION ON TYPE 2 DIABETES CONTROL

Despite the advent and availability of a range of antidiabetic and blood pressure lowering agents, many patients in Asia remain suboptimally controlled and therefore at risk of developing complications. In the MAPS study, just 10.6% of type 2 diabetes Asian patients with microalbuminuria achieved blood pressure targets below 130/80 mmHg and mean HbA_{1c} levels of 7.9%[22]. Similarly, in a cross-sectional survey in China, the majority of type 2 diabetes patients with nephropathy (66.9%) had a mean HbA_{1c} level of >7.5%, indicating poor glycemic control in patients with complications[50]. These data are supported by the recent International Diabetes Management Practice Study (IDMPS) that explored the barriers to achieving optimal glycemic control across Asia, Latin America and Eastern Europe[51]. In Asia, of the 5,372 type 2 diabetes patients assessed, 35.8% had microalbuminuria and just 37.3% achieved the HbA_{1c} target of <7.0%; 21.8% achieved the blood pressure target of <130/80 mmHg; and 37% achieved the LDL cholesterol target of <100 mg/dL. Another significant and worrying finding was that just 4.7% of patients in Asia attained all three treatment targets[51].

Factors that might be contributing to such low control rates have been reported to include: difficult medical access by patients in some developing countries, physician perception of target levels, prescribing habits, as well as knowledge of guidelines – these findings highlight a discord between evidence and practice[22,51]. An aging population provides additional challenges in managing type 2 diabetes, as aging itself is associated with changes in kidney structure and function, and these age-related renal changes can be accelerated by the presence of comorbid conditions[52,53]. Furthermore, a study of the Hong Kong Diabetes Registry revealed how long disease duration and complexity of treatment regimens might also play a role in suboptimal glycemic control[54]. Poor control might also result in type 2 diabetes patients who present and commence treatment when their renal function is normal, but subsequently go on to develop kidney disease. Without appropriate monitoring of GFR levels and diagnosis of kidney disease or its progression, the need for dose adjustments or re-evaluation of prescribed therapies might be missed and, consequently, adverse side-effects might arise[55].

Hypoglycemia is a particular challenge in the management of type 2 diabetes, especially in patients with a decline in renal function. For instance, diabetic patients with CKD are twice as likely to experience hypoglycemic events than those without kidney disease[56]. This might be a result of reduced insulin clearance, reduced gluconeogenesis by the kidney and increased

accumulation of drugs excreted by the kidney[57]. The reduction in drug clearance results in prolonged exposure to the drug itself or its metabolites, which can lead to adverse side-effects. This is a major issue in moderate to severe CKD (stages 3–5) when renal dysfunction is particularly pronounced[55].

CURRENT ORAL ANTI-DIABETICS IN DIABETIC PATIENTS WITH CKD

The American Diabetes Association guidelines recommend target HbA_{1c} levels of <8% for patients with more advanced microvascular complications and increased risk of hypoglycemia, such as those with more advanced CKD. However, in practice, the use of antidiabetic medications in achieving these glycemic targets is often challenging[58].

There are now an array of anti-hyperglycemic agents available that include both injectable, such as insulin and the incretin mimetics – GLP-1 analogs (exenatide, liraglutide), and oral antidiabetics (OADs). Among the OADs are biguanides (metformin), second generation sulfonylureas (glimepiride, glipizide, glicazide), meglitinides (nateglinide, repaglinide) α-glucosidase inhibitors (acarbose), thiazolidinediones (TZD; pioglitazone) and incretin-based therapies that include dipeptidyl-peptidase IV (DPP-4) inhibitors (linagliptin, sitagliptin, vildagliptin, saxagliptin). In addition, oral sodium-glucose transporter 2 (inhibitors are currently in development (empagliflozin, dapagliflozin). Despite the range of medications available for the treatment of type 2 diabetes and its complications, many of these require dose modification or avoidance and close monitoring[55]. This poses a particular challenge in more advanced disease (CKD stages 3–5), where contraindications or the increased risk of hypoglycemia serve to limit the number of treatment options (Table 2)[55].

As all these agents differ in their mechanism of action, efficacy, side-effects and costs, the choice of therapy should be guided by several factors. Patient demographics, presence of comorbid conditions, risk or severity of renal function decline, tolerability, and risk of developing adverse events, such as hypoglycemia, weight gain and edema, should help in the treatment decision process[57,59].

With most of the OADs currently available for the treatment of type 2 diabetes, their use in patients with kidney dysfunction is compromised[55]. Sulfonylrueas are one of most commonly prescribed oral antihyperglycemic agents in Southeast Asia[60]. However, sulfonylureas and their metabolites are affected by kidney function by increasing in potency as renal function declines. Furthermore, in type 2 diabetes patients with ESRD receiving dialysis, treatment with sulfonylureas might lead to severe and prolonged episodes of hypoglycemia[61]. Consequently, sulfonylureas are contraindicated in patients with advanced CKD[55]. However, second-generation sulfonylureas, such as gliclazide and glipizide, which have inactive metabolites, carry less risk of hypoglycemia than the first-generation sulfonylureas and might therefore be used in type 2 diabetes patients with declining renal function, but with caution.

Similarly, the meglitinide, nateglinide, undergoes hepatic metabolism that gives rise to weakly active metabolites that are excreted predominantly through the kidneys. Furthermore, 15% of the drug is excreted unchanged in urine. Given the reduced clearance in CKD and the likelihood of hypoglycemic episodes, cautious use in these special populations, particularly in more advanced stages of CKD, is warranted. In contrast, repaglinide appears to have a lower risk of hypoglycemia and might be of use in CKD stages 3 and 4, but requires low initial dosing and careful dose titration in these patients[62].

The use of metformin, the standard first-line therapy of type 2 diabetes, also poses a risk for diabetic patients with CKD as a result of lactic acidosis, and is therefore contraindicated in patients with advanced renal dysfunction[57]. Whether this medication provides an additional risk to the underlying comorbidity or acts directly to bring about lactic acidosis requires further investigation[63]. Treatment with α-glycosidase inhibitors in type 2 diabetes patients with CKD (stage 3–5) is

Table 2 | Oral antidiabetics and their use in patients with moderate to severe chronic kidney disease

Class	Agent	CKD stage 3–5	Complication
Second-generation sulfonylurea	Glimepiride Glipizide Glicazide	Low dose at stage 3, avoid beyond stage 3	Hypoglycemia
α-Glucosidase inhibitors	Acarbose	Avoid beyond stage 3	Possible hepatic toxicity
Biguanide	Metformin	Contraindicated beyond stage 3b	Lactic acidosis
TZDs	Pioglitazone	No dose adjustment	Volume retention
Incretin mimetic	Exenatide	No dose adjustment	
Dipeptidyl-peptidase IV inhibitors	Linagliptin	No dose adjustment	
	Sitagliptin Vildagliptin Saxagliptin	At least 50% dose reduction required	
Meglitinides	Nateglinide Repaglinide	Initiate low dose	Hypoglycemia

TZDs, thiazolidinediones.

also not recommended, because of the potential risk of hepatic damage as a result of cumulated dose effects[57].

In contrast, a few small, short-term studies have implicated a renoprotective role for TZD, as it resulted in greater reductions in albuminuria than metformin or sulfonylureas. Whether this translates into direct prevention of renal function decline, however, requires further study[64–66]. Nevertheless, TZD undergo hepatic metabolism and have a low risk of hypoglycemia, making them appropriate for use in CKD. Of note, fluid retention is a known side-effect of TZD, and in CKD patients this outcome could be exacerbated.

DPP-4 inhibitors are the most recent addition to the type 2 diabetes treatment paradigm and have been developed in recognition of the multifactorial nature of type 2 diabetes pathology. This drug class mediates its antihyperglycemic effects by preventing the degradation of the incretin hormones – glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP). These hormones are released in the intestine after a meal, and target the pancreas by increasing glucose-dependent insulin secretion and suppressing glucagon secretion, which subsequently improves both fasting plasma glucose (FPG) and post-prandial glucose (PPG) levels. DPP-4 inhibitors are therefore important in regulating glucose homeostasis[67]. Furthermore, beneficial effects on pancreatic β-cells have also been reported with this drug class and therefore it might play a role in preventing or slowing the progression of β-cell dysfunction[68–71].

There are currently five DPP-4 inhibitors approved for type 2 diabetes: sitagliptin, vildagliptin, saxagliptin, alogliptin (Japan) and linagliptin; and their efficacy and tolerability have been studied in several clinical trials[72]. Although there are limited direct head-to-head studies between DPP-4 inhibitors that have been carried out to date, observations across studies suggest that all five agents have comparable efficacy as reflected in their levels of HbA_{1c} reduction. This is in line with their similar inhibitory potentials[72]. When compared with other antihyperglycemic agents, head-to-head studies showed DPP-4 inhibitors to have similar efficacy to metformin, sulfonylureas, TZD and α-glycosidase inhibitors[73–78]. In terms of tolerability, all five DPP-4 inhibitors have been shown to be well tolerated with low rates of adverse effects and, in general, comparable with placebo or comparator[72]. Furthermore, the issues of hypoglycemia and weight gain frequently seen with the more traditional antihyperglycemic therapies are not readily observed with DPP-4 inhibitors.

Although there is little to differentiate between these agents in terms of observed efficacy, each differs in their chemistry and pharmacokinetic profile, which might translate into differences in their clinical applicability[79]. Indeed, DPP-4 inhibitors differ in their half-lives: sitagliptin, alogliptin and linagliptin have long-half lives, allowing for once-daily administration; vildagliptin has a short half-life and twice-daily dosing is recommended. Saxagliptin has a short half-life, but given its active metabolite, once-daily dosing is adequate[79]. Furthermore, on examining their metabolism and excretion profiles, differences between the DPP-4 inhibitors have emerged. Sitagliptin, vildagliptin, alogliptin and saxagliptin are predominantly excreted through the kidneys[72]. Despite the renal excretion profiles of these agents, their favorable tolerability in patients with various severity of renal dysfunction still permits their use in such patients, although dose modifications are recommended in line with increasing kidney dysfunction (Table 2). In contrast, linagliptin is excreted through the bile and with approximately 5% being renally excreted[80]. Furthermore, recent data suggest that dose modifications of linagliptin are not required irrespective of the severity of renal dysfunction (Table 2)[81]. Linagliptin might therefore represent an important addition to the currently limited therapeutic armamentarium for achieving glycemic control in type 2 diabetes patients with declining renal function.

In recognition of the favorable clinical profile of DPP-4 inhibitors, recent international guidelines recommend DPP-4 inhibitors as an option in both first-line (when FPG and PPG levels are elevated) and combination therapy[82]. Thus, type 2 diabetes patients, particularly special populations like those who are renally impaired, benefit from the emergence and evolution of newer antidiabetic agents, such as the DPP-4 inhibitors, that address the limitations of older therapies, and allow for a more tailored and effective approach to disease control. Long-term studies to assess the impact of DPP-4 inhibitors on reducing the risk of diabetes complications are awaited.

CONCLUSIONS

The burden of type 2 diabetes and its complications across Southeast Asia continues. DPP-4 inhibitors represent a good choice of OAD for patients with type 2 diabetes. Within this drug class, linagliptin, a novel DPP-4 inhibitor, possesses favorable and comparable profiles in terms of both efficacy and adverse events, and is indicated for use in all patients with type 2 diabetes.

Furthermore, linagliptin is the only DPP-4 inhibitor that is not predominantly dependent on renal metabolism. Many antidiabetic therapies are often of little use in renally-impaired type 2 diabetes patients because of contraindications or increased risk of hypoglycemia. The favorable pharmacokinetic profile of linagliptin has advantageous implications given the importance of addressing the decline in renal function in Asian patients with type 2 diabetes early. In addition, the lack of dose modification requirements and ease of dosing (one dose, once daily) further support the suitability of linagliptin in these difficult-to-treat populations.

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