Management of prediabetes in Malaysian population: An experts' opinion

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ABSTRACT

Introduction: Prediabetes, typically defined as blood glucose levels above normal but below diabetes thresholds, denotes a risk state that confers a high chance of developing diabetes. Asians, particularly the Southeast Asian population, may have a higher genetic predisposition to diabetes and increased exposure to environmental and social risk factors. Malaysia alone was home to 3.4 million people with diabetes in 2017; the figure is estimated to reach 6.1 million by 2045. Developing strategies for early interventions to treat prediabetes and preventing the development of overt diabetes and subsequent cardiovascular and microvascular complications are therefore important.

Methods: An expert panel comprising regional experts was convened in Kuala Lumpur, for a one-day meeting, to develop a document on prediabetes management in Malaysia. The expert panel comprised renowned subject-matter experts and specialists in diabetes and endocrinology, primary-care physicians, as well as academicians with relevant expertise.

Results: Fifteen key clinical statements were proposed. The expert panel reached agreements on several important issues related to the management of prediabetes providing recommendations on the screening, diagnosis, lifestyle and pharmacological management of prediabetes. The expert panel also proposed changes in forthcoming clinical practice guidelines and suggested that the government should advocate early screening, detection, and intensive management of prediabetes.

Conclusion: This document provides a comprehensive approach to the management of prediabetes in Malaysia in their daily activities and offer help in improving government policies and the decision-making process.

KEY WORDS:
Impaired fasting glucose, impaired glucose tolerance, oral glucose tolerance test, prediabetes, Asia-Pacific

INTRODUCTION

Diabetes is one of the largest global pandemics of the 21st century and is one of the top 10 causes of mortality worldwide.[1] Diabetes, along with cardiovascular disease (CVD), cancer, and respiratory diseases, accounts for more than 80% of all premature deaths due to noncommunicable diseases.[2] Around 425 million people worldwide, or 8.8% of adults aged 20–79 years, are estimated to have diabetes. This figure is likely to increase to 48% and reach 629 million by 2045.[3,4] The Western Pacific (WP) and Southeast Asian (SEA) regions had 159 and 82 million people with diabetes in 2017, respectively and the figures are projected to increase by 15% and 84%, respectively, by 2045.[4] In Malaysia alone 3.4 million people with diabetes in 2017; the figure is estimated to reach 6.1 million by 2045.[4] A continuation of this alarming trend would mean that an estimated 60% of the diabetics in the world population would be in Asia. This trend is further accentuated by a high genetic predisposition to diabetes among Asians, in particular the SEA population, and increased exposure to environmental and social risk factors.[5]

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Despite increased awareness about diabetes and the rising prevalence of diabetes over the years, it often remains undetected.[6] Globally, 50% of the world's population with diabetes (212.4 million people) aged 20–79 years are unaware of their disease status.[7] The percentages of undiagnosed diabetes in SEA and the WP are 54% and 57%, respectively; these regions have the highest proportion of people with undiagnosed diabetes. China and India are the top two countries with the highest number of people with undiagnosed diabetes.[4,8]

Prediabetes/early diabetes, typically defined as blood glucose levels above normal but below diabetes thresholds, denotes a risk state that confers a high chance of developing diabetes.[6] According to the World Health Organization (WHO), people with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have a high risk of developing diabetes.[9] The American Diabetes Association (ADA) has introduced elevated haemoglobin HbA1c levels as a new category for high diabetes risk, in addition to IFG and IGT.[10] Different guidelines such as the ADA, the WHO, the National Institute for Health and Care Excellence (NICE), and the Malaysian Clinical Practice Guidelines (CPG) have different criteria for making the diagnosis of non-diabetic hyperglycaemia, the lower cut-off level of IGT being the common criterion used by all the guidelines (Table I).[11] Approximately 5%-10% of individuals with IGT develop diabetes annually.[12] About 70% of individuals with untreated IFG and/or IGT will eventually develop clinical type 2 diabetes (T2DM).[13] Prediabetes has also been shown to be associated with an increased risk of adverse cardiovascular outcomes and microvascular complications, including diabetic retinopathy and neuropathy.[14-16]

Currently, the global prevalence of IGT is estimated to be 7.3%, accounting for around 352.1 million people, and it is expected to increase to 531.6 million by 2045. The WP region currently has the highest number of people with IGT, with an estimated 127 million affected adults.[17,4]

Recognising the chronic, debilitating, and cost-implicating nature of diabetes, the General Secretariat of the United Nations (UN) called on all UN member states to develop national policies for the prevention, treatment, and cure of diabetes.[18] This has raised awareness of the need to detect individuals at risk of diabetes and to consider screening and intervention policies. Strategies and early interventions to treat prediabetes to prevent the development of overt diabetes and its complications are, therefore, very important – especially in the Asia-Pacific region.

METHODOLOGY

A prediabetes advisory board meeting was held in Kuala Lumpur, Malaysia, on 22 September 2018 to identify challenges and benefits of treating the Malaysian population with prediabetes in the primary-care sector and review available data on the treatment of prediabetes. The committee consisted of regional experts, including academics, researchers, clinicians, and policy makers, from Malaysian and international organisations. A qualitative question-and-answer–based format was used to facilitate discussion. A literature review was carried out in the PubMed Database to identify relevant articles published between January 1, 2000, and December 2017 using keywords such as prediabetes, impaired fasting glucose, impaired glucose tolerance paired with terms such as screening, guidelines, lifestyle modification and management. The articles were circulated among the expert panel members prior to the board meeting in order to guide the formulation of recommendations. After the group discussion, recommendations were formulated based on the opinions and agreement of the majority.

Four preidentified areas of prediabetes management were discussed based on key clinical evidence available: (i) screening and diagnosis of prediabetes; (ii) treatment of prediabetes through lifestyle interventions; (iii) pharmacological management of prediabetes; and (iv) dose and duration of metformin (MET) treatment. In addition, specific questions with respect to changes in upcoming guidelines and policy decisions were deliberated upon.

Experts' statements for each of these topics were recorded and is summarised in this manuscript. Table II summarises the experts' key opinions for prediabetes.

RESULTS AND DISCUSSION

Screening and Diagnosis of Prediabetes

Evolution from normal glycaemia to overt diabetes is progressive and encompasses different dysglycaemic stages. Prediabetes encompassing people with IFG and/or IGT is a transitional state and those with either or both states are at a heightened risk of progressing to diabetes.[19] A meta-analysis estimating the progression rates to diabetes in different prediabetes categories found that the rate of progression from prediabetes to T2DM was about 35.6 per 1000 for HbA1c (6.0%–6.4%) and 45.5 per 1000 for IGT, and 70.4 per 1000 when IGT was combined with IFG.[20] A study by Galderisi et al., suggested that 8% of obese, glucose-intolerant youths progressed to diabetes within a period of two years.[21] Patients with coronary artery disease (CAD) with no previous diagnosis of diabetes have been found to be associated with abnormal glucose metabolism suggesting a prediabetic state.[22–24] A meta-analysis of 53 prospective cohort studies with 1,611,339 patients and a median follow-up period of 9.5 years showed that, compared with normoglycaemia, prediabetes was associated with an increased risk of composite cardiovascular events, coronary heart disease, stroke, and all-cause mortality.[14]

The ADA guidelines suggest that screening for diabetes should be considered in asymptomatic adults who are overweight (body mass index (BMI) ≥25 kg/m^2) and have one or more known risk factors for diabetes, which include Asian ethnicity, family history of diabetes, high blood pressure, dyslipidaemia, cardiovascular disease, and/or women with a history of gestational diabetes or women at risk of giving birth to large-for-gestational-age infants. In the absence of these risks, initiating testing is recommended when 45 years old.[25] Multi-ethnic cohort studies investigating the link between adiposity and diabetes have reported the development of diabetes at a considerably lower BMI among

Asians compared with Caucasians. Also, Asians are prone to developing diabetes at a much younger age compared to other ethnicities.[8] The Joint Asia Diabetes Evaluation programme, which included 41,029 patients from nine countries/regions in Asia, found that 18% of the subjects had young-onset diabetes (onset of T2DM at the age of <40 years). In view of this evidence, the Malaysian CPG has recommended lower BMI cut-offs to define obesity (BMI 23 kg/m^2) and screening at a much earlier age of 30 years in the absence of risk factors.[26]

The ADA recommendation for screening tests for prediabetes are similar to those described in the Malaysian guidelines, and includes fasting plasma glucose (FPG), HbA1c, and/or 75-g OGTT. If the initial screening for prediabetes is negative, patients will be screened every 1–3 years, depending on risk factors.[25,26] Although OGTT is the "gold standard" for diagnosing diabetes, it may be cumbersome to perform and is not easily reproducible. Therefore, the recent Malaysian guidelines have included HbA1c levels as a screening test due to convenience of use and the fact that therapeutic decisions are often based on the HbA1c results, regardless of OGTT findings.[26] Risk assessment in asymptomatic adults may be carried out through an informal assessment of risk factors or through the use of validated tools, such as the ADA Risk test and Finnish Diabetes Risk Score (FINDRISC).[25,27]

Experts' Discussion

Prediabetes screening: The experts were of the opinion that tests suitable for screening of the prediabetes people depend on the nature of clinical practice in question. Fasting plasma glucose testing alone may not be enough for screening prediabetes in clinical practice. In primary healthcare centres, OGTT is used for screening of prediabetes. The feasibility of different tests as screening tests for prediabetes was discussed. The experts opined that random blood glucose (RBG) alone as a screening test may not be feasible, since the majority of patients do not return for a fasting plasma glucose test or an OGTT after a capillary random blood glucose test. The experts thought that HbA1c along with RBG performed at the same visit may be beneficial. However, HbA1c testing is significantly more expensive than plasma blood sugar tests. Since cost is one of the important factors to be considered while recommending screening tests for prediabetes, screening with HbA1c and RBG may be limited to high-risk patients.

Frequency and interval of screening for prediabetes: The experts opined that it may not be feasible to screen an entire population for diabetes in primary-care setups; hence, the presence of risk factors should be considered as a prerequisite for the initiation of screening in adults aged ≤30 years. Risk factors for screening include overweight or obesity, high blood pressure, dyslipidaemia, history of large-for-gestational-age infants, or gestational diabetes and family history of diabetes. Presence of metabolic syndrome (if three or more of the five criteria are met) can be one of the criteria for screening in younger patients. Previous studies have shown that around 15%–54% of patients with diabetes in Malaysia are likely to have a family history of diabetes.[28] The high prevalence of diabetes in the Malaysian population warrants annual and universal screening for adults aged >30 years and for those aged ≤30 years with risk factors.

Criteria for diagnosis of prediabetes: The experts opined that a random blood glucose level of 5.6 mmol/L as the cut-off level for screening asymptomatic individuals recommended by the Malaysian CPG is too low. However, such a low cut-off point is important for screening more patients, thereby reducing the cost of treating overt diabetes several years later.

Experts' key opinions: Screening and Diagnosis of Prediabetes

- A fasting blood glucose level of ≥6.1mmol/L should be considered for the diagnosis of IFG.
- Simultaneous assessment of HbA1c along with RBG may be beneficial during initial screening. The high prevalence of diabetes in the Malaysian population warrants annual and universal screening for adults aged >30 years and for those aged ≤30 years with risk factors.
- In adults aged ≤30 years and in cases of cost implication, the presence of risk factors (overweight/obesity, high blood pressure, dyslipidaemia, history of large-for-gestational-age infants, or gestational diabetes and family history of diabetes) should be considered as a prerequisite for initiation of screening.
- A simple, easy-to–use method for screening prediabetes, such as the ADA risk assessment form, may be used.

Treatment of Prediabetes Through Lifestyle Interventions

The primary aim of lifestyle interventions is to delay or prevent the onset of T2DM and its complications, by targeting the two most modifiable risk factors for diabetes development, obesity and physical inactivity.[6] Several clinical trials have shown the safety and efficacy of lifestyle modification in preventing T2DM in varied ethnic populations. The six-year Finnish Diabetes Prevention Study was the first randomised study to be published that assessed the effect of lifestyle intervention on progression to T2DM. The targets for lifestyle changes were a reduction in weight of ≥5%, reduction in total fat intake to <30% of energy consumed, reduction in intake of saturated fat to less than 10% of energy consumed, increase in fibre intake to ≥15g/100 kcal, and moderate exercise for ≥30 minutes per day. Lifestyle intervention was found to reduce the overall incidence of T2DM by 58%.[29] The Diabetes Prevention Programme (DPP) showed that the risk of developing T2DM was reduced by 58% in the group that had undergone intensive lifestyle modification.[30] The extended study by Da Qing conducted among the Chinese population showed a 43% reduction in the incidence of diabetes that was sustained for over 20 years,[31] and in a study among Japanese IGT males by Kosaka et al., the four-year reduction in diabetes incidence was 67.4%.[32] Diet modification and moderate-intensity physical activity (resulting in a modest weight loss of 5–7% of body weight) are recommended by the guidelines.[25,26] Patients not responding to lifestyle interventions may be considered for pharmacological interventions or surgery.[12] Given the known risk of progression of prediabetes to diabetes, a person with an HbA1c of 5.6–6.2%, IGT or IFG should be counselled on lifestyle changes, as indicated by the current Malaysian CPG. The ADA and the Malaysian CPG recommend 5–7% weight loss and moderate physical activity of at least 150 minutes/week.

Table I: Principal criteria for diagnosing prediabetes/early diabetes[11]

Impaired glucose tolerance	Post-load glucose: 7.8–11.1mmol/L (140–200 mg/dL) two hours after a 75-g oral glucose tolerance test
Elevated (non-diabetic) HbA1c	ADA: 5.7–6.4% (39–47mmol/mol) WHO: 6.1–6.9 mmol/L (110–125mg/dL) NICE: 6.0–6.4% (42–47mmol/mol)

ADA: American Diabetic Association; WHO: World Health Organization; NICE: National Institute for Health and Care Excellence; HbA1c: Glycated haemoglobin.

Adapted from: Hostalek U, *et al. Int J Diabetes Complicat.* 2018;2:1–6.

Table II: Summary of key consensus statements

No.	Consensus Statements
1	A fasting blood glucose blood glucose level of ≥6.1mmol/L should be considered for the diagnosis of IFG.
2	Simultaneous assessment of HbA1c along with RBG may be beneficial during initial screening.
3	The high prevalence of diabetes in the Malaysian population warrants annual and universal screening for adults aged >30 years and for those aged ≤30 years with risk factors.
4	In adults aged ≤30 years and in cases of cost implication, the presence of risk factors (overweight/obesity, high blood pressure, dyslipidaemia, history of large-for-gestational-age infants, or gestational diabetes and family history of diabetes) should be considered as a prerequisite for initiation of screening.
5	A simple, easy-to–use method for screening prediabetes, such as the ADA risk assessment form, may be used.
6	Lifestyle modification should be the first-line treatment for prediabetes and continued for at least 3–6 months, after which screening can be performed to assess results and decide the future course of treatment.
7	The decision to initiate pharmacotherapy must be based on identifiable risk factors and the estimated risk of potential progression to diabetes.
8	Metformin is recommended in individuals with an elevated fasting blood glucose level (>6.1 mmol/L) despite 3–6 months of lifestyle intervention and among those with high-risk factors for diabetes.
9	History of CVD, history of GDM in women, BMI, and high baseline HbA1c are some of the criteria that should be considered before initiating metformin therapy.
10	Treatment with metformin should be individualised, based on the clinician's discretion, risk factors, and blood glucose parameters.
11	Metformin can be initiated at a low dose of 500mg once daily and can be increased gradually, as tolerated, to up to 2000mg daily.
12	Life-long therapy with metformin may be recommended in patients whose blood glucose levels continue to remain in the prediabetes range. It is important to monitor patients for side effects associated with metformin therapy. Routine monitoring of vitamin B12 levels should be considered in such patients.
13	The metformin dose may be adjusted as per the patient's blood glucose levels, which may be monitored using standardised tests (HbA1c, FPG, or OGTT).
14	Clinical practice guidelines must consider adding risk stratification for deciding the treatment strategy, based on which individuals at high risk of developing overt T2DM may be considered for pharmacological intervention.
15	Clinical practice guidelines should consider updating the therapeutic labelling of metformin for the management of prediabetes. National policies should also advocate complementary approaches of diabetes prevention, such as health education in schools, food policy, active screening, and early detection.

Abbreviations: HbA1c: Glycated hemoglobin; RBG: Random blood glucose; ADA: American Diabetes Association; CVD: Cardiovascular disease; GDM: Gestational diabetes mellitus; FPG: Fasting Plasma Glucose; OGTT: Oral glucose tolerance test; T2DM: Type 2 diabetes mellitus;

Table III: Landmark clinical trials demonstrating the efficacy of metformin in prediabetes/early diabetes

Trials	Main inclusion	N, duration criteria	Control group	Active treatment	Decrease in overt diabetes % (CI)
DPP (2002)[30]	IGT and IFG (95–125 mg/dL)	3234 for 2.8 years	Placebo plus SLI	• Metformin (2X850 mg/day plus SLI • ILI	−31 (−17, −43) −58 (−48, −66)
DPPOS (Knowler *et al.*, 2009)[41]	IGT and IFG (95–125 mg/dL)	2766 for median 5.7 years	Placebo plus SLI	• Metformin (2X850 mg/day) plus SLI • ILI	−18 (−7, −28) 34 (−24, −42)
DPPOS (2012)[42]	IGT and IFG (95–125 mg/dL)	2155; 2 years for double-blind randomised phase; 7-8 years for open label phase	Placebo plus SLI for double-blind randomised phase; SLI only for open label phase	• Metformin (2X850 mg/day) plus SLI	-
DPP plus DPPOS (DPP and DPPOS, 2016)[43]	IGT and IFG	17 years	Placebo plus SLI	• Metformin (2X850 mg/day) plus SLI • ILI	−18 (−7, −28) −27 (−17, −35)

DPP: Diabetes Prevention Programme; DPPOS: Diabetes Prevention Programme Outcomes Study; IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; SLI: Standard lifestyle intervention; ILI: Intensive lifestyle intervention

Apart from obesity, smoking, blood pressure and lipids are considered as preventable risk factors for T2DM.[33] Active smoking increases the risk of T2DM[34], and smoking has been found to be strongly associated with prediabetes in young adults.[35] Thus, promoting smoking cessation is one of the important strategies for diabetes prevention.[36] Medications for controlling blood pressure and lipids should be considered in appropriate cases.[37,38] However, it is important to note the effects of some antihypertensive agents (β-blockers, diuretics) and statins on the risk of development of new-onset T2DM. Since these therapies have shown to reduce cardiovascular events, it may be important to carefully evaluate the benefits of these medications against the risk.[37,38] Furthermore, antihypertensive agents that block the renin–angiotensin system have been found to be associated with reduced risk of new-onset diabetes compared with other classes of antihypertensive drugs.[37]

Experts' Discussion

The goals set in the weight-loss intervention programmes may be difficult to achieve and maintain. The Finnish Study and the DPP had modest lifestyle goals, thus enrolling motivated participants. Despite substantial efforts undertaken to help participants randomised to the lifestyle intervention group to achieve recommended lifestyle goals, the desired objectives were met only partially. Furthermore, the beneficial effect on slowing the progression to T2DM seemed to reduce as time progressed in clinical studies. This may be attributed to the progressive weight gain at follow-up, after the active intervention.

Experts' key opinions: Treatment of Diabetes Through Lifestyle Interventions

- Lifestyle modification should be the first-line treatment for prediabetes and continued for at least 3–6 months, after which screening can be performed to assess results and decide the future course of treatment.

Pharmacological Management of Prediabetes

Metformin, used for decades to treat diabetes, has been proven to be safe and efficacious, with beneficial effects on BMI and lipid levels.[32] Among individuals with IGT, metformin has been found to lower the risk of T2DM by 45%.[6] The beneficial effect of metformin was found to be similar to lifestyle interventions in the Indian DPP (IDPP-1) study. Both lifestyle management (LSM) and metformin intake significantly reduced the incidence of diabetes (p=0.018 and 0.029, respectively).[39] A pooled analysis of two diabetes prevention studies in India showed that the three-year incidence of T2DM in subjects with both IGT and IFG was 56%, compared with 34% for subjects with isolated IGT. Only 18% of subjects with combined hyperglycaemia reverted to normal glucose tolerance under lifestyle change, compared with 32% with isolated IGT.[40]

The DPP, one of the largest randomised controlled clinical trials, was conducted among 3234 US adults with glucose intolerance and, unlike most previous studies, the cohort was diverse and included a large numbers of women (68%) and ethnic minorities (45%). The study participants were randomised to receive placebo, metformin (850mg twice daily), or lifestyle modification for a period of 2.8 years. The results of the above study found the incidence of diabetes to be 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively, showing that both lifestyle intervention and metformin had positive effects on the prevention of T2DM, restoring normal glucose tolerance in high-risk individuals.[30] In the 10-year follow-up of the Diabetes Prevention Programme Outcomes Study (DPPOS), the reduction in the risk of developing diabetes persisted with metformin and the modest weight loss due to metformin intake was maintained. The incidence rates of diabetes in this follow-up study were 5.9 per 100 person-years (5.1–6.8) for lifestyle, 4.9 (4.2–5.7) for metformin, and 5.6 (4.8–6.5) for placebo.[41] Table III shows landmark clinical trials demonstrating the efficacy of metformin in prediabetes.[30,41-43] The better results for metformin may be attributed to a gradual progressive weight gain in the lifestyle group, suggesting practical difficulties in sustaining weight loss with intensive lifestyle change alone. The long-term safety and efficacy of metformin have been established in the 15-year follow-up of DPPOS among 2776 participants, wherein the cumulative incidence of diabetes at 15 years was 62% in the placebo group, 56% in the metformin group, and 55% in the intensive lifestyle group–indicating the comparative long-term efficacy of the two treatments. The incidence of diabetes was delayed by about four years in the intensive lifestyle group and by two years in the metformin group, compared with placebo.[43]

Regarding the efficacy in relation to cardiometabolic risk factors, although fewer subjects on intensive lifestyle interventions required pharmacologic treatment for cardiovascular risk factors vs. placebo or metformin at three years during DPP, this difference disappeared over time in DPPOS. Hence, in relation to the long-term disease progression shown in DPPOS, metformin is as effective as change in intensive lifestyle in improving hypertension and dyslipidaemia.[44] In a long-term follow-up study evaluating the effect of metformin on body weight changes, safety, and tolerability, metformin used in overweight or obese individuals with elevated fasting glucose and IGT was associated with modest but sustained weight loss and was safe and well-tolerated for a period of at least 10 years.[42] The beneficial effects of metformin has also been evidenced in high-risk geographical areas, including India and China. In these studies, metformin therapy was associated with a relative risk reduction of 26.4% and 77%, respectively.[40,45]

Some individuals at high-risk may experience enhanced benefits with metformin therapy. It has been reported that metformin was as effective as lifestyle modification in participants with a BMI ≥35kg/m^2, but not significantly better than placebo in those aged >60 years.[41] In women with a history of gestational diabetes mellitus (GDM), metformin therapy and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk, as per the DPP study.[46] A double-blind, placebo-controlled study demonstrated improved insulin sensitivity in women with polycystic ovarian syndrome (PCOS) treated with metformin for six months.[47] In a study by Goldberg et al., metformin lowered the presence and severity of coronary atherosclerotic calcifications

in men, with no effect seen in women. No reduction in the prevalence of clinically significant plaque was observed (Agatston score >100), suggesting that metformin affects smaller, more recently calcified plaques, rather than well-established plaques.[48] In the most recent analysis of the benefits of metformin therapy in the DPP and DPPOS population, the metformin group had a 17% lower incidence of diabetes vs. the placebo group. The effect of metformin on the development of glucose-defined diabetes was greater among women with a history of prior GDM (hazard ratio [HR] 0.59, rate difference [RD] -4.57 cases/100 person-years) vs. those without GDM (HR 0.94, RD −0.38 cases/100 person-years [interaction p=0.03 for HR, p=0.01 for RD]). In the same study, metformin therapy demonstrated a greater effect in patients with higher baseline fasting glucose levels, in patients with a baseline HbA1c of <6% (RD−1.03 cases/100 person-years) and in patients with baseline HbA1c of 6.0–6.4% (RD −3.88 cases/100 person-years) (p=0.0001). Also, the highest BMI group benefited more from metformin therapy compared to the lower BMI group.[49] There is limited data on the benefits of metformin therapy in non-obese patients. Whilst there is limited data on the benefits of metformin therapy in non-obese patients, metformin may be considered in high risk individuals (e.g., history of gestational diabetes, overweight, high blood pressure, CVD and/or those with more severe or progressive hyperglycaemia). The Malaysian CPG and ADA guidelines suggest that metformin can be considered in individuals who are at very high risk (combined IFG and IGT, IGT + obesity [BMI >35 kg/m^2]), with IGT + <60 years of age, previous history of GDM, or among those who failed lifestyle therapy after six months.[25,26]

Besides metformin, several other drug classes such as thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) analogues and anti-obesity drugs have been evaluated in the management of prediabetes. In the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial, rosiglitazone was found to reduce the risk of occurrence of diabetes by 60% over a period of 3 years but was associated with increase in weight and risk of cardiovascular events.[50,51] Similar effects were observed with pioglitazone where the risk of occurrence of diabetes reduced by 70% but with side effect such as weight gain and edema.[52] The STOP-Noninsulin-Dependent Diabetes Mellitus (NIDDM) trial demonstrated a reduction in diabetes risk with acarbose during 3.3 years of follow-up although acarbose caused significant gastrointestinal side effects which resulted in its discontinuation by 31% of the participants.[53] Both exenatide and liraglutide have shown weight loss and improvement in other cardiovascular risk factors in obese patients resulting in reduced prediabetes prevalence.[54,55] Besides, anti-diabetes drugs, orlistat, a lipase inhibitor used for the treatment of obesity was evaluated in the XENical in the prevention of diabetes in obese subjects (XENDOS) study to prevent the incidence of T2DM. Orlistat along with lifestyle intervention was associated with reduction in the incidence of T2DM over a period of 4 years.[56] While these studies provide convincing evidence on the benefits of different pharmacological therapies in the management of prediabetes, it is important to adopt an individual case-based approach for the management of prediabetes in line with the guidelines recommendations.

Experts' Discussion: Pharmacological Management of Prediabetes

Some guidelines advise 3–6 months of lifestyle intervention before initiating pharmacotherapy, at the end of which screening tests are performed again to aid in decision-making. A fasting blood sugar level suggesting prediabetes (≥6.1mmol/L) should be considered a factor for pharmacotherapy. Hence, owing to a high conversion rate from IFG/IGT to overt diabetes, the panellists suggested that pharmacotherapy is of importance in prediabetes management. However, identifying factors predicting the conversion of prediabetes to diabetes and selecting patients in whom pharmacotherapy needs to be initiated may be difficult.

Experts' key opinions: Pharmacological Management of Prediabetes

- The decision to initiate pharmacotherapy must be based on identifiable risk factors and the estimated risk of potential progression to diabetes.
- Metformin is recommended in individuals with an elevated fasting blood glucose level (>6.1mmol/L) despite 3–6 months of lifestyle intervention and among those with high-risk factors for diabetes.
- History of CVD, history of GDM in women, BMI, and high baseline HbA1c are some of the criteria that should be considered before initiating metformin therapy.

Dose and Duration of Metformin

In the DPP study, treatment with metformin was initiated at a dose of 850 mg taken orally once a day. At one month, if well-tolerated, the dose of metformin was increased to 850 mg twice daily.[30] Metformin at a lower dose of 500mg twice daily was effective in reducing the progression rate of IGT to diabetes in the Asian Indian population.[40] A meta-analysis of three randomised controlled trials found that metformin decreased the rate of conversion from prediabetes to diabetes at higher (850mg twice daily) and lower dosages (250mg twice or three times daily).[57] In DPP and DPPOS, metformin immediate-release (IR) was used. The results of the study can reasonably be extrapolated to metformin extended-release (XR), given the bioequivalence demonstrated between this formulation and metformin IR in a comparative pharmacokinetic trial.[58] Metformin XR was well-tolerated at single doses of up to 2000mg once daily.[58] A study reported that, compared with metformin IR, metformin XR is associated with a lesser treatment burden due to once-daily dosing, improved tolerability without the gastrointestinal side effects associated with IR, and improved adherence to treatment.[59]

The National Institute of Care and Excellence (NICE) and the Malaysian guidelines suggest a low dose of 500 mg once daily that can be increased gradually, as tolerated, to up to 2000 mg daily.[19,46] Metformin is continued for 6–12 months initially. The NICE guidelines suggest monitoring of FPG or HbA1c levels at three-month intervals and to discontinue the drug if no effect is observed.[26,60]

Experts' Discussion: Dose and Duration of Metformin

Any gastrointestinal tract side effects that may occur due to metformin therapy may be minimised by starting metformin

at a low dose and gradually increasing the dose. However, the use of extended-release metformin can circumvent these gastrointestinal side effects, compared to IR formulations. The experts also agreed that a start-low, go-slow approach would yield maximum benefits with respect to metformin therapy. If patients are on the higher side of the prediabetic range in terms of blood glucose levels, a higher dose of metformin may be used. In patients who are unable to tolerate high doses of metformin XR/IR, down-titration of metformin should be considered. However, long-term use of metformin has been found to be associated with minor gastrointestinal symptoms, anaemia, and vitamin B12 deficiency. In DPPOS, long term use of metformin was associated with increased risk of vitamin B12 deficiency, anaemia and neuropathy. Routine monitoring of vitamin B12 levels should be considered in patients on long-term metformin therapy.[61] The risk of lactic acidosis was low (none in over 18,000 patient-years exposure to metformin) in the DPPOS long-term follow-up study.

Life-long metformin therapy may be recommended for patients with prediabetes in whom plasma blood sugar levels continue to be in the prediabetes range despite the use of other interventions. It is important for healthcare practitioners to educate patients on the role of metformin, both for diabetes and other indications. A strong family history, GDM, high BMI, and CVD are a few of the risk factors for continuing metformin. It was opined that there is no need for a washout period for metformin therapy. However, a washout period for metformin does not affect the benefits of the therapy. Regarding follow-up with metformin therapy, an interval of three months may be considered ideal for monitoring patients with prediabetes on metformin therapy. This interval can be increased to six months, later. Tests, such as HbA1c, FPG, or OGTT can be performed to monitor patients.

Experts' key opinions: Dose and Duration of Metformin

- Treatment with metformin should be individualised, based on the clinician's discretion, risk factors, and blood glucose parameters.
- Metformin can be initiated at a low dose of 500mg once daily and can be increased gradually, as tolerated, to up to 2000mg daily.
- Life-long therapy with metformin may be recommended in patients whose blood glucose levels continue to remain in the prediabetes range. It is important to monitor patients for side effects associated with metformin therapy. Routine monitoring of vitamin B12 levels should be considered in such patients.
- The metformin dose may be adjusted as per the patient's blood glucose levels, which may be monitored using standardised tests (HbA1c, FPG, or OGTT).

Positions on Specific Questions Addressed to Guide Recommendations

Influencing Policy Decisions and Proposed Changes in Forthcoming Guidelines

The feasibility and efficacy of translating lifestyle intervention strategies for the prevention of diabetes into clinical and community practice have been successfully demonstrated in several small studies. However, despite landmark trials, such as DPP and DPPOS, favouring the safety and efficacy of metformin therapy in diabetes, metformin has not been widely used for diabetes prevention.[62] A retrospective cohort analysis of 17,352 working-age adults with prediabetes found that fewer than 4% of patients with prediabetes received prescriptions for metformin within three years of diagnosis.[63] An economic analysis using 10 years of combined DPP/DPP outcomes study data demonstrated that, compared to lifestyle interventions, metformin treatment for diabetes prevention was cost-effective for more than 10 years.[64] Hence, trials such as DPP and DPPOS are considered as evidence to influence policy decisions in favour of metformin therapy for the management of prediabetes.

The proposed update in therapeutic labelling of metformin in Malaysia includes the following populations:

- At high risk for developing overt T2DM
- Still progressing to T2DM despite the implementation of intensive lifestyle changes for 3–6 months

Government Advocacy for Active Screening and Treatment

The incidence of CAD is on the rise among young individuals in Malaysia; this may be due to unhealthy diet and lifestyle. Diabetes mellitus is one of the biggest risk factors for CAD.[65] National approaches should, therefore, also focus on complementary approaches for the prevention of diabetes, including promoting healthy eating, aiming to positively influence the eating habits of the younger generation. The government must be encouraged to advocate interventions that promote early screening, detection, and intensive management of prediabetes. Patient-education leaflets would be helpful in creating awareness among patients.

Experts' key opinions: on Specific Questions Addressed to Guide Recommendations

- Clinical practice guidelines must consider adding risk stratification for deciding the treatment strategy, based on which individuals at high risk of developing overt T2DM may be considered for pharmacological intervention.
- Clinical practice guidelines should consider updating the therapeutic labelling of metformin for the management of prediabetes.
- National policies should also advocate complementary approaches of diabetes prevention, such as health education in schools, food policy, active screening, and early detection.

CONCLUSION

Prediabetes has severe implications, as well as carrying a high risk of progression to overt diabetes mellitus. Around 10% of individuals with IGT develop diabetes annually, and around 70% of individuals with IFG/IGT develop diabetes eventually. Prediabetes is associated with an increased risk of adverse cardiovascular outcomes and microvascular complications, such as diabetic retinopathy and neuropathy. The adoption of preventative measures, consisting of lifestyle modifications and metformin pharmacotherapy, has demonstrated a significant reduction

in progression to overt diabetes and, hence, must be considered for the optimal management of prediabetes. The recommendations aim to provide some important aspects to be considered in the management of individuals with IGT, based on the available evidence and current best clinical practice, particularly in the Malaysian population. Despite widespread evidence supporting the favourable safety, efficacy, and economic benefits of metformin in prediabetes management, its use in clinical practice has been sub-optimal. We see the need for updating the forthcoming Malaysian CPG, with respect to metformin, for the management of prediabetes and government action and policies on complementary approaches of diabetes prevention, such as health education in schools, food policies, active screening, and early detection at the regional and national levels.

FUNDING SUPPORT

We would like to thank Merck Malaysia, an affiliate of Merck KGaA, Darmstadt, Germany, for financial support for the manuscript development.

CONFLICT OF INTEREST

Author MM has received honoraria for lectures from Merck KGaA, Astra Zeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Servier. Authors EMK and HZ have received honoraria for lectures and advisory board meetings from Merck KGaA, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Servier, and Sanofi Aventis. Authors KM, and HL are employees of Merck Malaysia, an affiliate of Merck KGaA, Darmstadt, Germany.

ACKNOWLEDGEMENTS

We would like to thank BioQuest Solutions for providing their writing services.

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