

# Guidelines on the Management and Prevention of Prediabetes

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### **ABSTRAK**

*Pandemi obesitas dan diabetes mellitus (DM), khususnya DM tipe 2 (DMT2) kini menjadi ancaman yang serius bagi umat manusia di dunia. International Diabetes Federation (IDF) menyebutkan bahwa prevalensi DM dunia adalah 1,9% dan telah menjadikan DM sebagai penyebab kematian urutan ke-7 dunia. Proyeksi prevalensi diabetes tahun 1994 sampai 2010 diperkirakan 215,6 juta jiwa, namun dari evaluasi tahun 2007 jumlah penderita diabetes sudah mencapai 246 juta jiwa bahkan tahun 2025 dikhawatirkan jumlah tersebut akan meningkat sampai lebih dari 300 juta jiwa.*

*Pasien DM berpotensi menderita berbagai komplikasi, meliputi penyakit makrovaskular (penyakit jantung, stroke, dan penyakit pembuluh darah tepi) dan penyakit mikrovaskular (retinopati, neuropati, dan nefropati). Komplikasi DM sudah dimulai sejak dini sebelum diagnosis DM ditegakkan. Sekitar 50% pasien ketika didiagnosis telah menyandang satu komplikasi kronik. Karena itu, perlu adanya panduan yang dapat menatalaksana prediabetes terkait dengan pencegahan risiko komplikasi kronik diabetes dan risiko kardiovaskular. Panduan ini diharapkan dapat menambah keahlian tenaga medis untuk mengenali prediabetes, mengidentifikasi orang-orang dengan risiko tinggi diabetes, dan memberikan penatalaksanaan yang tepat agar kejadian DM dan komplikasinya dapat dikurangi.*

**Kata kunci:** *diagnosis, risiko, prediabetes, diabetes mellitus, penatalaksanaan.*

### **ABSTRACT**

*Pandemic obesity and diabetes mellitus (DM), particularly type-2 DM (T2DM) now has become a serious threat for people worldwide. The International Diabetes Federation (IDF) suggests that the prevalence of DM in the world is 1.9% and it has made DM as the 7th leading cause of death worldwide. It has been estimated that the prevalence of diabetes between 1994 and 2010 was projected as much as 215.6 million people; however an evaluation in 2007 revealed that the number of diabetic patients has reached 246 million people and it has been concerned that the number would increase in 2025 reaching more than 300 million people.*

*Patients with DM may have various complications, including macrovascular diseases (heart disease, stroke and peripheral vascular disease) and microvascular diseases (retinopathy, neuropathy and nephropathy). Complications of DM have started early before the diagnosis of DM has been made. About 50% of patients have already had one chronic complication at the time of diagnosis. Therefore, it is necessary to have a guideline on management of prediabetes condition associated with prevention of chronic complication and cardiovascular risk of diabetes. The guideline is expected to improve the skills of health care professionals in recognizing prediabetes condition, identifying people at high risk for diabetes and providing an appropriate management so that the incidence and complication of DM can be reduced.*

**Key words:** *diagnosis, risk, prediabetes, diabetes mellitus, management.*

## INTRODUCTION

Results of basic health care research/riset kesehatan dasar (RISKESDAS) reported by Department of Health Care in 2008 revealed that the prevalence of DM in Indonesia at that time was 5.7%. According to WHO, the number of diabetic patients in Indonesia will increase from 8.4 million people in 2000 and it will become 21.3 million people in 2030. The high morbidity rate has made Indonesia on the 4th rank worldwide after China, India and United States. Without prevention measures and an effective controlling program, the prevalence will be continuously increasing.<sup>1</sup>

Patients with DM may have various complications, including macrovascular diseases (heart disease, stroke and peripheral vascular disease) and microvascular diseases (retinopathy, neuropathy and nephropathy).<sup>2</sup> Complications of DM have started early before the diagnosis of DM has been made. About 50% of patients have already had one chronic complication at the time of diagnosis, 21% among them have retinopathy, 18% have an abnormal electrocardiogram (ECG) findings, and 14% have impaired blood flow to the limb causing undetected limb pulse or leg ischemia. Those various complications of diabetes has caused modified lifestyle and reduced life expectancy in individuals with DM. The life expectancy rate has become 15 years lower and 75% of them died due to macrovascular complications.<sup>3,4</sup> In keeping with the development of normal glucose tolerance into obvious DM, the morbidity and mortality associated with diabetes and its complication has also been increasing.<sup>5</sup>

Blood glucose level is a continuous spectrum. The limit of blood glucose levels considered as normal, prediabetes and diabetes is determined arbitrarily based on a consensus. Currently, the diagnosis of diabetes is established when the fasting blood glucose level is  $>126$  mg/dl or when the 2-hour postprandial blood glucose level  $>200$  mg/dl. In oral glucose tolerance test (OGTT), it is determined based on blood glucose level associated with the development of microangiopathy complications, which have specific characteristics for diabetes, particularly retinopathy. Prediabetes is diagnosed when the

blood glucose level is above normal but still below the blood glucose level for diabetes. The diagnosis of prediabetes is established when the fasting blood glucose level is 100-125 mg/dl (impaired fasting glucose = IFG) or when the 2-hour postprandial blood glucose level is 140-199 mg/dl (impaired glucose tolerance = IGT), or both (impaired glucose homeostasis = IGH).<sup>6,7</sup>

Based on observations, individuals with prediabetes may develop into 3 possibilities: approximately 1/3 of cases will develop into T2DM, the other 1/3 of cases will stay unchanged as prediabetes and the other remaining 1/3 cases may be back to normoglycemia condition. Prediabetes condition raises absolut risk by 2- to 10-fold; moreover, the risk of cardiovascular disease in prediabetes is comparable with DM. Those conditions provide more convincing facts that early prevention measures and programs of DM is very essential, inter alia through management of prediabetes condition, identification and early management of patients with prediabetes condition that may reduce the incidence and complications of DM, which will be very useful not only for patients, but also their families and the government.<sup>8</sup>

Different epidemiological data between IGT and IFG shows that there are different mechanisms of pathophysiology of both conditions. Although the determination of IGT and IFG is made based on insulin resistance, but both show differences on the site of insulin resistance occurs. Insulin resistance in IFG is mainly occurs in liver; while the insulin sensitivity in muscle tissues is still normal. In IGT, insulin sensitivity in the liver stays normal or slightly reduced; while in the muscle tissues, the insulin resistance has occurred. The patterns of insulin resistance in both conditions are also different. In IFG, phase-one reduced insulin secretion occurs (in the first 10 minutes) after intravenous glucose is given and initial-phase of reduced response of insulin secretion (in the first 30 minutes) after oral glucose administration; while the delay-phase of insulin secretion (60-120 minutes) during the OGTT stays normal. In IGT, there is also impaired initial-phase insulin secretion after oral glucose administration, which is accompanied by significant decrease on

end-phase of insulin secretion.<sup>9</sup> Type-2 diabetes emerges due to progressive impairment of insulin secretion with a background of insulin resistance. Both impairment of insulin secretion and insulin resistance have been affected by genetic and environment risk factors, which also includes the embryonic environment. Obesity, particularly central obesity, is one of the most important risk factors for type-2 diabetes.

Obesity may cause insulin resistance through two mechanisms, i.e.: secretion of various adipokines (Tumor Necrosis Factor)<sup>5,6,8</sup> Until now, there is no recommendation on management of prediabetes in Indonesia. This guideline discusses the aims and goals of prediabetes management associated with prevention of diabetes chronic complication risks and cardiovascular risks. By having this guideline, health care professionals are expected to have improved skills in recognizing prediabetes condition, identifying people at high risk for diabetes and providing an appropriate management so that the incidence and complication of DM can be reduced.

## DIAGNOSIS AND RISK FACTORS OF PREDIABETES

### Diagnosis

Prediabetes (IFG and/or IGT) is diagnosed according to WHO recommendation. Diagnosis of IFG is made when the blood glucose level after 8-to 10-hour fasting is 100–125 mg/dl. Diagnosis of IGT is established when the blood glucose level after 2-hour postprandial challenge with 75 gram glucose is between 140 and 199 mg/dl.<sup>6,7,10</sup>

Preparation and procedures of OGTT according to WHO (appendix):

- Preparation. In the days before the test, the patient is instructed to consume carbohydrate intake in adequate amount. On the test day, patient should not do excessive physical activities or having caffeine intake or other drugs that may affect blood glucose level.
- Procedures
  - Patient is instructed to fast for at least 8 hours.
  - Blood is withdrawn first for measurement of fasting blood glucose

- Subsequently, the subject is given 75 gram glucose solution in 300 cc water to drink
- 2 hours after the glucose loading, blood is drawn for measurement of 2-hour postprandial or post challenge glucose level.<sup>11</sup>

**Table 1.** Diagnosis criteria for prediabetes

Impaired Fasting Glucose (IFG), whenever:
- Fasting blood glucose level is 100-125 mg/dl (5.6-6.9 mmol/L)
- 2-hour postprandial blood glucose level is <140 mg/dL
Impaired Glucose Tolerance (IGT), whenever:
- Normal fasting blood glucose level is <100 mg/dL
- After 75 gram glucose challenge, the 2-hour postprandial blood glucose level is 140-199 mg/dL, (7,8-11 mmol/L)

Prediabetes, if there is IFG and/or IGT

Not all of various epidemiological studies have incorporated the use of 2-hour postprandial blood glucose level to establish the diagnosis of prediabetes and only use the fasting blood glucose level. It may result in false negative since the IGT would be undetected. Individuals with normal fasting blood glucose would be categorized as IGT when OGTT is performed. Detecting the presence of IGT should be performed considering that it may develop into T2DM and higher risk of cardiovascular complication in subjects with IGT than individuals with IFG.<sup>2,10</sup>

Several cardiovascular risk factors are found concomitantly along with risk factors of diabetes in an individual. Those risk factors are: obesity, hypertension, a low cholesterol level of high density lipoprotein (HDL), increased triglycerides level, and glucose metabolism disorder, which is known as the metabolic syndrome. Metabolic syndrome is considered to a prediabetes equivalent. Approximately 50% patients with IGT meet the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) criteria for the diagnosis of metabolic syndrome.<sup>5,11,12</sup>

### Risk Factors for Prediabetes

Risk factors for prediabetes are similar with the risk factors for the development of T2DM.

Those risk factors can be categorized into modifiable and non-modifiable risk factors. The most important factors are obesity (particularly abdominal obesity) and lack of physical activity.

Non-modifiable risk factors:

- a. Genetic factors. Until now, genes associated with the risk for DM have not been confirmed. However, there is an obvious difference of DM event among different ethnic groups although they live in the same environment, which indicates that genetic factor may have considerable contribution in the development of DM (Alberti et al, 2007).<sup>8</sup>
- b. Age. The prevalence of DM is increasing with age. In the last decades, the age of DM onset has decreased, particularly in countries with an imbalance between energy intake and output.
- c. Gestational diabetes. In gestational diabetes, glucose tolerance returns to normal after birth; however, the woman is at risk of developing DM in the future.<sup>8</sup>

Modifiable risk factors:

- a. Obesity. Obesity is the most important risk factor. Some longitudinal studies show that obesity is a strong predictor for the development of T2DM. Furthermore, an intervention aimed to reduce obesity may actually also reduce the incidence of T2DM. Various longitudinal studies have also demonstrated that waist circumference or waist-to-hip ratio which represents visceral (abdominal) fat condition, is actually a better indicator than body mass index as the risk factor for prediabetes. Those data confirm that fat distribution is more important than the total amount of fat.
- b. Physical activities. In last decades recently, reduced intensity of physical activities in various populations has been a great contributor to increased obesity worldwide. Various cross-sectional and longitudinal studies have shown that reduced physical activity is an independent predictor for the development of T2DM either in men or women.
- c. Nutrition. High total caloric intake, low fiber diet, high-glycemic load and low

ratio of polyunsaturated fatty acid (PUFA) to saturated fats are risk factors for the development of DM.

- d. Other risk factors. Although genetic factor and lifestyle have been the greatest risk factors for the development of DM, some risk factors are modifiable including low birth weight, exposure to intrauterine diabetic environment and some of inflammatory components.<sup>8</sup>

### **Blood Glucose Spectrum and Cardiovascular Risks**

Blood glucose spectrum. Actually, blood glucose level is a continuous spectrum between the glucose level considered normal (fasting glucose level of <100 mg/dl; postprandial glucose level of <140 mg/dl) and the level of blood glucose, which is considered as diagnostic for diabetes (fasting glucose level of >126 mg/dl; postprandial glucose level after 75 gram glucose challenge of >200 mg/dl). The limits of those blood glucose levels are associated with the onset of complications specific for diabetes (end-organ complication), particularly the retinopathy. Various population studies indicate that values of fasting blood glucose level and the 2-hour postprandial glucose levels associated with the development of complication are actually lower than the threshold limit of blood glucose level used currently for diagnosing diabetes. It is assumed that despite the blood glucose level still below the “normal” threshold limit, the individual may already have increased risk for microvascular and macrovascular diabetes complications.<sup>11</sup>

The natural history of illness shows that 6-10% patients with IGT will have progression to diabetes in 1 year period of time; while for patients with both IGT and IFG, the cumulative incidence of diabetes by 6 years is as much as 60%. In addition, for individuals with normal glucose tolerance level, the incidence of diabetes is only about 5%.

Prediabetes and risks for cardiovascular disease (CVD). Various studies demonstrated a linear correlation between glycemia status and the risks for CVD. Subjects in prediabetes group had an equal risk for the development

of complication as subjects in diabetes group. Regarding diabetes and CVD risks in the prediabetes group, IGT is more associated with both risks compared to those with IFG.<sup>4</sup>

The results of epidemiologic studies on CVD incidence rate, such as AusDiab (Australian diabetes, obesity, and lifestyle study), Framingham Study and intervention studies such as Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) and Diabetes reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study, suggest that cardiovascular risk in individuals with IFG and IGT doubles compared to those without IFG or IGT.<sup>3</sup> The results of The Nurse Health Study showed that women destined to convert to T2DM have 3 times the risk of CVD risks compared to those remained as non-T2DM individuals. A meta-analysis conducted by Levitan et al confirmed that prediabetes is associated with increased fatal and non-fatal risk of CVD. The increased risks were comparable between individuals in IFG and IGT groups. Cardiovascular risks increased with linear pattern when associated with blood glucose level after meal; while when it was associated with fasting blood glucose, the assumed threshold of increased risk was 99 mg/dl.<sup>13</sup>

A cohort study of The Diabetes Epidemiology Collaborative Analysis of Diagnosis Criteria in Europe (DECODE) and a similar study in Asia (DECODA) have also found that the 2-hour postprandial glucose level after glucose challenge is a better predictor for cardiovascular mortality than fasting glucose level. Moreover, other various studies have also demonstrated a association of postprandial hyperglycemia with increased risk of retinopathy, thickening of carotid intima-media layers, endothelial dysfunction, oxidative stress, inflammation, reduced blood flow volume to cardiac myocytes, cognitive impairment in elderly and increased risk for cancer.<sup>4</sup>

#### **A REVIEW OF STUDIES ON DM PREVENTION**

Some immediate measures of prevention are necessary to reduce the number of patients with prediabetes, T2DM and cardiovascular disease associated with diabetes. Those prevention

measures include:

#### **Lifestyle intervention**

Lifestyle modification should be the core of treatment and it should be provided to all patients even should be reinforced in every patient's visit. Lifestyle is a fundamental management approach that can effectively prevent or delay the progression from prediabetes to diabetes, as well to reduce both microvascular and macrovascular disease risks. More importantly, lifestyle interventions improve all risk factors for diabetes and components of the metabolic syndrome, obesity, hypertension, dyslipidemia and hyperglycemia. In accordance with the Diabetes Prevention Program (DPP) findings, patients with prediabetes should reduce weight by 5% to 10% and should maintain this level for a long-term. A moderate degree of weight loss results in reduced fat mass, decreased blood pressure, glucose, low density lipoprotein (LDL) cholesterol and triglycerides levels. These benefits can also appear in long-term outcome, especially if weight loss and lifestyle intervention are maintained. A long-term follow-up in a Finish Diabetes Prevention Program showed that lifestyle intervention in patients at high risk for T2DM has resulted in reduction in diabetes incidence, which persisted even after the individual lifestyle counseling was stopped.<sup>6,8</sup>

A program of regular moderate-intensity physical activity for 30 to 60 minutes daily, at least 4 days weekly or minimal 150 minutes/week, is recommended.<sup>8</sup>

The recommended diet includes calorie restriction, increased fiber intake and limitations in carbohydrate intake. Specifically for patients with hypertension, dietary recommendations include lower sodium intake and limitation in alcohol consumption.<sup>6,8</sup>

Although adjustment on individual basis may be necessary, lifestyle modification can be recommended for all ages but it may be difficult to maintain. Physicians should focus and emphasize on the importance of maintaining weight loss as the long-term goal. Some efforts expected to increase the likelihood success are: patient self-monitoring, realistic and stepwise goal setting, social support, reinforcement on the importance of healthy lifestyle.<sup>8</sup> The following

studies demonstrate the benefit of lifestyle intervention as an effective prevention measure:

**Malmö Study.** This study was a preliminary study about the role of lifestyle intervention on T2DM prevention in Sweden; the study was conducted in men aged 47-49 years old. Some patients with prediabetes and normal glucose tolerance (NGT) received usual care/treatment; while patients with prediabetes and the other T2DM underwent a lifestyle intervention. Those who received lifestyle intervention had demonstrated a lower incidence of T2DM compared to the group receiving usual treatment and had reversal of IGT to normal value. At the 12-year follow-up, patients in prediabetes group who received lifestyle intervention showed no difference in mortality rate when compared to those in the NGT group. Moreover, the mortality rate was less than half of men who did not receive lifestyle intervention.<sup>8</sup>

**Da Qing Study.** The Da Qing study examined the effect of 6-year diet and exercise intervention in Chinese subjects with a mean age of 45 years and prediabetes. The diet intervention alone reduced the risk of developing type-2 DM of 31%; while the intervention of physical activity alone reduced the risk about 46%. A combination of diet and physical activity reduced the risk as much as 42%.<sup>8</sup>

**The Finnish Diabetes Prevention Study.** It was the first randomized trial which specifically evaluate the effect of lifestyle intervention on T2DM prevention. This lifestyle intervention was followed for 3.2 years and it was joined by 522 overweight/obese subjects with IGT and a control group without lifestyle intervention.

Lifestyle intervention was provided by individualized counseling focused on achieving and maintaining ideal body weight, reducing fat intake and increasing fiber intake and increasing physical activity. After 2 years of follow-up, the incidence of DM reduced as much as 50% in the intervention group compared to those in control group. The study also reported that the effect of lifestyle modification in reducing DM incidence may last for at least 4 years after the intensive intervention study completed.<sup>8</sup>

**Diabetes Prevention Program (DPP).** DPP is one of the largest randomized clinical trials,

which included 3234 individuals with prediabetes in America involving women (68%) and minorities (45%). The study compared lifestyle intervention and drug intervention (metformin) with a control group over 2.8 years. The study reported that both lifestyle modification and metformin had positive effects on DM prevention and restoring the prediabetes into a normal condition. Furthermore, it is known that lifestyle intervention was more effective than metformin. There was a lower mortality rate in the group with lifestyle intervention compared to those receiving metformin. The cost-effectiveness of generic metformin is comparable with lifestyle intervention without using any medication.

Results of DPP study published afterward suggested that an increase of physical activity in individuals without weight loss helps them to maintain body weight and independently reduces diabetes risks. In addition, there was also positive effect on fasting glucose and post-prandial glucose tolerance. Lifestyle intervention has also improved lipid parameters of the metabolic syndrome and reduced the risks of hypertension.<sup>8</sup>

**Indian Diabetes Prevention Program (IDPP).** IDPP was a prospective community-based study that examined whether lifestyle interventions and medication could influence the progression to DM in Asian-Indians population with IGT who were leaner and more insulin resistant than other population (multiethnic American, Finnish and Chinese population). The results showed that progression of IGT to DM in the population was high.

Both lifestyle modification and metformin may significantly reduce the development of IGT to T2DM; however, there was no added benefit from combining them compared to separate treatment alone. With lifestyle modification, metformin and combination of both treatment, the risk of DM was reduced by 28.5%, 26.4%, and 28.2%, respectively.<sup>8</sup>

### Pharmacologic Intervention

In reality, lifestyle modification is very difficult to be applied without help and monitoring from a professional health care practitioner. The potential parameter to determine successful lifestyle intervention is reduced body weight of

2 kg in 1 month or 5% body weight reduction in 6 months. It is similar to reduced glucose plasma level as the expected response of lifestyle intervention. However, not all of individuals at high risk can accept lifestyle modification and to achieve this goal, another intervention is necessary, i.e. with medication.

Pharmacologic intervention for DM prevention is usually recommended as secondary intervention to follow or to be use in conjunction with lifestyle modification intervention. If with lifestyle intervention, the weight loss has not occurred, then the use of medication should be started.<sup>8,14</sup>

**Metformin.** The rationale for the use of metformin is largely based on its 40-year-long-term safety record. The data on safety was obtained through results of the DPP and IDPP studies. Results of DPP showed that metformin in the dose of 850 mg twice daily with meals reduced the development of DM by 31% and the development of metabolic syndrome by 17% in 2.8 years compared to placebo. The relative risk reduction was found more obviously in the group with body mass index (BMI) >30 kg/m<sup>2</sup>. The reduction of relative risk in this group reached 16-35%; while those with BMI of 22-30 kg/m<sup>2</sup>, the relative risk reduction was only as much as 3%.

Different results were found in IDPP, which showed a benefit with metformin in those with BMI <30 kg/m<sup>2</sup> considering that obesity in Asians presents at a lower BMI, i.e. >25 kg/m<sup>2</sup>.

However, metformin is not recommended for everyone with IGT. It may cause lactic acidosis (ischemic disorder in kidney and liver). DPP results also demonstrated that metformin was less effective in DM prevention in individuals aged >65 tahun. Metformin limitation may also be caused by gastrointestinal side effects, which can be overcome by increasing the dose gradually.<sup>8</sup>

**Acarbose.** Acarbose acts by inhibiting enzymes that digest carbohydrate. In the study of STOP-NIDDM with 3.3 years of follow-up, acarbose reduced the risk for DM as much as 25% and the risk for cardiovascular disease as much as 49%. The presence of gastrointestinal side-effects have caused a 31% drop-out rate (vs. 19% in the placebo group); therefore,

these facts limited its use for DM prevention. STOP-NIDDM study results recommend the use of acarbose in those who can tolerate the gastrointestinal side-effects for DM prevention and cardiovascular risk reduction.<sup>15</sup>

In China, Japan and other Asian countries, acarbose is often used as the first line drug for patients with newly diagnosed type 2 DM. It is also applied for countries with high consumption of complex carbohydrates.

In some patients, acarbose may reduce body weight. Results of long-term studies in patients with IGT and T2DM showed that acarbose significantly reduced body weight of 0.7 – 0.9 kg. In STOP-NIDDM study, the incidence of newly diagnosed hypertension has also reduced by 34%. Acarbose may also reduce the lipid levels, particularly the fasting lipid and triglycerides levels of 15%. Acarbose may also reduce atherogenicity of LDL in patients with IGT.<sup>8,15</sup>

**Glitazones.** In the DPP, troglitazone treatment was withdrawn after about one year due to hepatotoxicity. In the Troglitazone in prevention of diabetes (TRIPOD) study, troglitazone treatment for more than 3 years has caused cumulative reduction in incidence of diabetes to zero point. Results of a cohort study (DREAM study) using rosiglitazone and ramipril with a large number and multiethnic population showed that subjects in IFG and/or IGT group who had received rosiglitazone for 3 years showed a 60% decrease in progression to diabetes compared to 25% in placebo group and 70% among them returned to normal glucose tolerance. The group receiving rosiglitazone showed a higher likelihood of significant body weight increase and increased incidence of congestive heart failure.<sup>8,16</sup>

**Orlistat.** Orlistat is a drug acts by a mechanism of inhibiting enzyme that breaks down triglycerides in the intestine. Results of one study showed that orlistat may cause weight loss of 3-5 kg over 6 months, which could be maintained over 4 years. Treatment of obese subjects with IGT by orlistat as an adjuvant treatment to diet and lifestyle modification can reduce the risk of developing T2DM. In Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study, all of 3304 non-diabetic obese

subjects received intensive lifestyle modification and were randomized into either orlistat or placebo group. After 4 years, the orlistat group had 6.9 kg weight loss; while the placebo group had 4.1 kg weight loss. The weight loss was associated with reduced risk for developing DM as much as 37%. The high number of drop out (52%) in the orlistat group was associated with gastrointestinal side-effects and therefore, limiting its use.<sup>8</sup>

**Poly-e-pill.** Considering the high probability on classification of various risk factors for T2DM and CVD (obesity-metabolic syndrome) in one individual, the concept of “polypill” - one drug that can manage all of those various risk factors - has been attractive for the experts since a long while ago. However, until now, the expectation to find the abovementioned drug has not been satisfied. Actually, the concept of polypill is integrated in physical activity (exercise). Physical activity has been proven to be relatively safe (almost without any side effects). It can be applied for all ages with dose-dependent results and inexpensive. It also contributes a good effect on targets at molecular level of all components for obesity and metabolic syndrome.

A systematic review and meta-analysis comparing lifestyle intervention and drug treatment showed that both interventions may lower the progression of prediabetes to diabetes with equal effectiveness.<sup>17</sup>

## STRATEGY FOR DIABETES MELLITUS PREVENTION

Results of studies showed that early detection and intervention to improve glucose control and to prevent the progression of prediabetes to T2DM in individuals at high risk will result in reduced incidence, comorbidity and complication of diabetes. According to the IDF, T2DM prevention strategy is based on controlling modifiable risk factors (modifiable risks). The prevention strategy can be categorized into 2 target groups.<sup>8</sup>

### A High-Risk Population

The high-risk approach:

The IDF proposes a three-step plan for T2DM prevention for those in in high-risk group:

- Step 1: identification of those groups who may be at high risk
- Step 2: measurement of risk
- Step 3: Intervention

### Step 1. Identification of high-risk group

The first step is the identification of individuals who have higher risk than average population. The IDF recommend the use of opportunistic screening by health-care personnel (general physicians, nurses and pharmacists).

Strategies to predict future risk of diabetes usually use demographic and clinical data from prospective cohort studies, statistical models and risk scores. In the first step, the strategy usually has not relied on measurements of blood glucose but has utilized various personal measures or family history of high blood glucose level. In longitudinal approach, age and history of high blood glucose level appear to be the most important data.

In general, these strategies can not be applied for different population due to differences in population characteristics. For different ethnic group, different strategies are recommended.

Questionnaire is a simple, practical, non-invasive and inexpensive method to identify individuals at high risk for prediabetes and diabetes. It is also used to reduce the application of OGTT. The IDF recommend the use of brief questionnaires to help health-care professionals to quickly identify population at high risk that need further investigation. The questionnaire can also be used for self-assessment.<sup>8</sup>

Some criteria that should be included in the questionnaire:

- Central obesity is most easily calculated by measuring abdominal circumference with cut-off points that are gender and ethnic group specific (**Table 2**).
- The presence of family member diagnosed with diabetes
- Age >35 tahun
- Cardiovascular history
- History of hypertension and/or heart disease
- Gestational history
- Previous occurrence of gestational diabetes
- History of treatment. Use of drugs that predispose type-2 DM, including: nicotinic acid, glucocorticoids, thyroid hormones.



If there are some items present in an individual at high risk, further investigation should be undertaken to evaluate the level of risk.<sup>8</sup>

### Step 2. Measuring level of risk

If a person is at high risk for type-2 diabetes, we will proceed to step 2. At this stage, other risk factors are assessed and determined.

The measurement for level of risk is performed by health-care professionals. The key investigation in the step 2 is the measurement of blood glucose level.

- Plasma glucose. Measurement of blood glucose level with glucose challenge will not only able to detect IFG or IGT cases, but also cases of undiagnosed diabetes. Positive findings of IFG and/or IGT may increase the risk for progression to T2DM. Interventions aimed for individual target provide an opportunity to delay or prevent the onset of T2DM.
- Other risk factors include: increased abdominal circumference, hypertension, family history of diabetes, increased triglycerides/TG level or previous cardiovascular disease (**Table 2**). Further investigation on other cardiovascular risk factors should also be performed such as HDL cholesterol, LDL cholesterol, and smoking. The presence of the abovementioned factors can increase the risk of developing diabetes and those individuals should receive appropriate treatment.<sup>8</sup>

**Table 2.** Other risk factors for diabetes

Risk factors	
Triglycerides	>150 mg/dl (>1.7 mmol/L)
HDL cholesterol	Male <40 mg/dl (<1.03 mmol/L) Female <50 mg/dl (<1.29 mmol/L) or dyslipidemia on treatment
Waist circumference	Male >90 cm Female >80 cm
Blood pressure	>130/80 mmHg or hypertension on treatment
Family history of DM	Father / mother / siblings
Preexisting heart disease	CHD, cerebrovascular disease, peripheral arterial disease

### Step 3. Intervention

Various substantial evidences showed that lifestyle modification can prevent the progression of prediabetes to T2DM. Therefore, lifestyle modification must be the initial intervention for all patients. For patients who can not change their lifestyle sufficiently and those with a high level of risk (for developing diabetes), pharmacotherapy should be encouraged along with lifestyle modification. Lifestyle changes should be maintained since it will continue to deliver long-term health benefits.

- Lifestyle modification (lifestyle changes). In order to prevent or delay the development of diabetes, lifestyle modification should be the first choice measure for all patients. The lifestyle modification must be emphasized in each visit. In addition to its effectiveness in preventing the development of T2DM, lifestyle modification can also improve risk factors for diabetes and other components of metabolic syndrome such as obesity, hypertension, dyslipidemia, and hyperglycemia.
- Weight. Obesity, particularly abdominal obesity is “central” to the development of T2DM and other associated disorders. Therefore, abdominal obesity has become a focus of attention in reducing the risk of T2DM. In short term period, weight loss improves insulin resistance, hyperglycemia and dyslipidemia as well as reduces hypertension. Patients should be encouraged to achieve and maintain a healthy body composition. A structured approach of long-term weight loss program as has been taken in DPP study can reduce 5-7% of initial baseline body weight. The target is gradual weight loss (0.5-1.0 kg/week) through calorie restriction and increased physical activity. A self-monitoring of weight and waist circumference must be performed daily/weekly. Standard weight-loss diet recommend reducing daily intake calorie by 500 – 1000 calorie (depending on gender and age), which is aimed to maintain body weight. Although very-low calorie diet and meal-replacement plans can produce impressive results in short-

term period, but the long-term benefits are limited. A complete change of dietary habits and restricting calorie and fat consumption are the most important actions to achieve sustained weight loss. Moreover, control of carbohydrate intake also has important role. Simple carbohydrates with a high glycemic index will cause additional metabolic load to patients.

- Physical activity. Increased physical activity is also important in maintaining weight loss. Regular physical activity improves insulin resistance, reduces insulin level in patients with hyperinsulinemia, improves dyslipidemia and lowers blood pressure. Physical activity increases metabolic activity of muscle tissue and improves cardiovascular health in general. Increased physical activity also reduces the risk of T2DM. Moderate physical activity (brisk exercise) of at least 30-60 minutes (brisk walking, swimming, cycling, dancing) for at least 4 days of the week, may reduce the risk of diabetes by 35-40%. The determination of physical activity should consider the condition of patient comprehensively and identification of any contraindication is a very essential issue. For patients who have had usual sedentary lifestyle, exercise program should be initiated slowly and increased gradually.
- Pharmacological intervention. The IDF recommend that when lifestyle intervention alone has not achieved adequate desired weight loss, and/or improved glucose tolerance, then metformin at the dose of 2 x 250-850 mg/day (depending on tolerance) should be considered as a diabetes prevention strategy. Pharmacological therapy with metformin is aimed for patients aged <60 years with BMI >30 kg/m<sup>2</sup> (in Indonesia, BMI >25 kg/m<sup>2</sup>) and FPG >110 mg/dl (6.1 mmol/l) who do not have any contraindication. For those who consume large amount of carbohydrates in their diet, acarbose is worthy of consideration to be the first line drug. Acarbose can be administered at the dose of 3 x 50 mg/day taken during the meal and the dose can be increased up to 3 x 100 mg/day. Peroxisome proliferator

activated receptor-g agonist (PPARg) had shown promising results, but its side-effects on weight gain and congestive heart failure has become a great concern and its routine use is not recommended. A further option for the obese patients is orlistat. Newer agents such as rimonabant has also been very promising, but long-term safety and efficacy data on diabetes prevention are lacking and it is not recommended for prevention in individuals at high risk.<sup>8,17</sup>

#### **(All) Population Approach**

In planning the national prevention measures, both population groups should be targeted simultaneously. Moreover, all important activities should be adjusted to the characteristic local situation. The aim of population approach is to bring important changes in the health of a large percentage of population. It is based on promoting healthy lifestyle which is quite effective in preventing T2DM, including cardiovascular disease, hypertension, and many other non-communicable and chronic diseases. The most dominant effect of obesity is to induce glucose intolerance along with all of its consequences. The occurrence of epidemic diabetes can only be prevented by substantial lifestyle modification and it must be performed immediately. The prevention of T2DM is based on an increase in daily activity and healthier eating habits, thus resulting in a better balance between energy intake and energy utilization.<sup>8</sup>

Population approach to prevent diabetes according to the IDF recommendation based on results of lifestyle prevention studies:

- Everyone is encouraged to perform moderate physical activity (e.g. brisk walking) at least 4 times of the week.
- Everyone is encouraged to maintain a healthy weight.
- Adults with BMI >23/kg/m<sup>2</sup> should be encouraged to achieve and maintain a healthy weight and/or 5-10% weight reduction
- Children should be encouraged to achieve and maintain the normal range weight for height.
- The approach taken needs to be culturally sensitive. Cultural beliefs (e.g. about obesity) have to be understood and addressed.<sup>8</sup>

The National Diabetes Prevention Plans should include:

1. Advocacy for community groups by supporting national associations and non-government organizations.
2. Community support on :
  - Providing education at school about nutrition and physical activity
  - Promoting opportunities for physical activity through urban design (e.g. improving the facilities for walking, cycling and play grounds)
  - Supporting sports facilities for the general population
3. Fiscal and legislative / regulation policy, by:
  - 'Organizing' food pricing, labeling and advertising
  - Enforcing environmental and infrastructure regulation (e.g. urban planning and transportation policy to enhance physical activity)
4. Engagement of private sector
  - Promoting health in the workplace
  - Ensuring healthy food policies in food industry
5. Utilization of communication media (press, TV, radio) to improve the level of knowledge and motivation of the community.<sup>8</sup>

## RECOMMENDATION

### General Recommendation

1. Prediabetes may be associated or increase the risk of cardiovascular disease and microvascular complication and will progress to type-2 diabetes; therefore, it should be managed appropriately.
2. All patients with prediabetes must receive adequate treatment including intensive lifestyle changes, which is safe and effective in order to improve the glycemic condition and to reduce cardiovascular risk.

### Target

1. Target blood glucose level in subjects with prediabetes is similar to those with diabetes (A1c < 6.5%, FBG < 100 mg/dl, 2-hour postprandial blood glucose (PPBG) < 140 mg/dl)
2. Target lipid level in subjects with prediabetes

is similar to those with diabetes (triglycerides <130 mg/dl, HDL >45 mg/dl, LDL <100 mg/dl)

3. Target blood pressure in subjects with prediabetes is similar to those with diabetes (sistolik <130 mmHg, diastolic <80 mmHg)

### Diet

Recommended diet is low fat, low saturated fat and trans-fatty acid and low sodium intake. Avoid alcohol intake and get an adequate fiber intake.

### Physical activities

1. Individuals with prediabetes need to have 5-10% weight loss of their initial weight and maintain their weight for long-term period
2. Regular and moderate physical activities are recommended for 30-60 minutes daily and it should be performed at least 4 days in a week.

### Pharmacological treatment

1. In individual with prediabetes at high risk, pharmacological treatment is considered as adjuvant treatment of lifestyle modification/ changes.
2. No drug has been approved today by the Food Drug Administration (FDA) for prediabetes; therefore, the decision for treatment is based on risk-benefit analysis
3. Metformin and acarbose are safe and effective to help preventing diabetes
4. Although thiazolidinediones reduces the risk of prediabetes progression to diabetes, but there is a risk of developing congestive heart failure and fracture that should be concerned.
5. Statins are recommended to achieve treatment target of LDL cholesterol (<100 mg/dl), nonHDL (<130 mg/dl), and apolipoprotein B (<90 mg/dl)
6. In some patients, fibrate, bile acid sequestrants, ezetimibe and other drugs may be beneficial as adjuvant treatments.
7. Niacin improves lipid profile but it has a potency to cause glycemic effect
8. When there is a hypertension, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended as the first line treatment and calcium channel blockers are recommended as the second line.

9. Thiazides and/or b-blocker are utilized by taking the effect of glycemia into account
10. All individuals with prediabetes who have no risk of gastrointestinal, intracranial or other bleeding should receive low-dose aspirin.

### Monitoring

1. Monitoring of patients with prediabetes includes annual OGTT and microalbuminuria examination. Investigations on FBG, HbA1c and lipid levels are performed at least twice a year.
2. For patients at a very high risk, monitoring must be performed more often.

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