

BMJ Open Prediction of type 2 diabetes mellitus using fasting plasma glucose and HbA1c levels among individuals with impaired fasting plasma glucose: a cross-sectional study in Thailand

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ABSTRACT

Objectives About 11%–30% of individuals with impaired fasting plasma glucose (IFG) have type 2 diabetes mellitus (T2DM), diagnosed by the 75 g oral glucose tolerance test (75 g OGTT). This study investigated (1) the prevalence and cut-off levels for fasting plasma glucose (FPG) and glycated haemoglobin A1c (HbA1c) in IFG individuals that most effectively predict the presence of T2DM diagnosed by a 75 g OGTT; (2) the predictors associated with T2DM; and (3) the pathophysiological characteristics of patients with IFG.

Materials and methods A single-centre, cross-sectional study was conducted in a primary care setting. A standard 75 g OGTT was performed on 123 subjects with IFG. Their beta-cell function and insulin resistance were calculated through plasma glucose and insulin levels monitored during the 75 g OGTT.

Results In the IFG subjects, the prevalence of T2DM using the 2-hour postload plasma glucose (2hPG) criterion was 28.5%. Pre-diabetes and normal glucose metabolism were found in 48.7% and 22.8%, respectively, by 75 g OGTT. An HbA1c level $\geq 6.0\%$ or FPG ≥ 5.9 mmol/L were the optimal cut-off thresholds for the prediction of the presence of T2DM. HbA1c had a sensitivity of 76.7% and specificity of 55.7% (95% CI 57.7% to 90.1% and 95% CI 43.3% to 67.6%, respectively), while FPG had a sensitivity of 85.7% and specificity of 23.9% (95% CI 69.7% to 95.2% and 95% CI 15.4% to 34.1%, respectively). The presence of metabolic syndrome, a higher HbA1c and higher FPG levels were associated with the risk of T2DM in the Thai IFG population.

Conclusions Almost one-third of the people with IFG had T2DM diagnosed by the 2hPG criterion. HbA1c was more effective than FPG in predicting the presence of T2DM in the IFG subjects. IFG individuals with HbA1c $\geq 6.0\%$ or FPG ≥ 5.9 mmol/L should be advised to undergo a 75 g OGTT to detect T2DM earlier than otherwise.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a consequence of a combination of resistance to the action of insulin and an inadequate compensatory insulin secretory response. Provided beta-cells augment insulin secretion

Strengths and limitations of this study

- This was the first study on Thai impaired fasting plasma glucose (IFG) individuals to define the optimal cut-off threshold of HbA1c and fasting plasma glucose (FPG) for the prediction of the presence of type 2 diabetes mellitus.
- Each IFG participant had at least two consecutive IFG diagnoses by the FPG criterion, in order to ensure consistent disease classification.
- This study assessed insulin secretion and insulin resistance in each pre-diabetes subtype classified by 75 g oral glucose tolerance test.
- The generalisability of the study findings is limited to IFG individuals, not all pre-diabetes subtypes.

sufficiently to offset the insulin resistance, glucose metabolism and glucose tolerance remain normal. The progressive deterioration in insulin secretion as a compensation for the insulin resistance results initially in a prediabetic state (in the form of impaired fasting plasma glucose (IFG) and/or impaired glucose tolerance (IGT)) and eventually in diabetes mellitus (DM). Hyperglycaemia is an independent risk factor for macrovascular complications, the development of which begins in the prediabetic state.^{1 2} Furthermore, hyperglycaemia directly leads to microvascular complications related to DM. Large clinical trials have shown that prevention programmes for prediabetic individuals effectively delay the development of T2DM.^{3 4} In addition, achieving tight glycaemic control soon after the diagnosis of DM is effective in preventing or delaying the microvascular and macrovascular complications related to T2DM.^{5 6}

There are three standard tests for the diagnosis of abnormal glucose metabolism or DM in asymptomatic individuals. They are

the haemoglobin A1c (HbA1c) test, the fasting plasma glucose (FPG) test, and the 2-hour, 75 g oral glucose tolerance test (75 g OGTT). However, these tests have different sensitivities and specificities. The 75 g OGTT is regarded as the gold standard for the diagnosis of T2DM and pre-diabetes. Because it recognises altered postprandial metabolism, the 75 g OGTT detects T2DM more efficiently than FPG. Nevertheless, the 75 g OGTT is not commonly used in clinical practice in some hospitals because it is complex and time consuming to administer.⁷

A previous study showed that T2DM was not diagnosed in about half of patients with IFG when only FPG was used for the diagnosis of T2DM.⁸ The prevalence of T2DM diagnosed by a 75 g OGTT in individuals with IFG is 11%–30%.^{9–13} A recent meta-analysis has shown that the optimum threshold for the early detection of T2DM using the 2-hour, 75 g OGTT should be 6.2–6.4 mmol/L for FPG and 6.0%–6.2% for HbA1c.¹⁴ These two levels highlight that subjects with T2DM who have increasing postprandial glucose can be overlooked due to the low concordance rate of the standard tests for diagnosing T2DM with the FPG and the 2-hour postload plasma glucose (2hPG) criterion after the 75 g OGTT. Furthermore, there are no data related to Thai individuals to indicate whether their response to the tests might differ from other ethnicities.

We conducted this study to determine the optimum cut-off levels of FPG and HbA1c that can most effectively predict the presence of T2DM, as diagnosed by the 75 g OGTT, in Thai individuals with IFG. We also investigated the risk factors associated with the presence of T2DM in IFG individuals, as well as the pathophysiological characteristics of patients with pre-diabetes.

MATERIALS AND METHODS

Study design and participants

A single-centre, cross-sectional study was conducted at Siriraj Hospital. Participants with IFG levels (FPG 5.6–6.9 mmol/L) on at least two consecutive occasions during the preceding year were included. Individuals were excluded if they had a history of T2DM or were currently undergoing medical therapy affecting their glucose or insulin metabolism. All participants underwent a 75 g OGTT according to the standard protocol from the WHO. Informed consent was obtained from all participants.

Procedures and measurements

The study subjects were advised to follow an unrestricted diet for at least 3 days before undertaking the 75 g OGTT. The test was performed in the morning after an overnight fast of 8–12 hours. During the 75 g OGTT, each subject was asked to drink a 75 g glucose solution in 250 mL of water within 5 min before resting for 2 hours. The test timing started from the point when the patients began to consume the solution. The glycaemic status outcomes

were categorised into five groups in accordance with the American Diabetes Association criteria¹⁵:

- ▶ Normal group, an FPG level <5.6 mmol/L, with a 2hPG level of <7.8 mmol/L after the 75 g OGTT.
- ▶ Isolated IFG (iIFG) group, an FPG=5.6–6.9 mmol/L, with a 2hPG of <7.8 mmol/L after the 75 g OGTT.
- ▶ Isolated IGT (iIGT) group, an FPG <5.6 mmol/L, with a 2hPG of 7.8–11.1 mmol/L after the 75 g OGTT.
- ▶ Combined IFG with IGT group, an FPG=5.6–6.9 mmol/L, with a 2hPG of 7.8–11.1 mmol/L after the 75 g OGTT.
- ▶ T2DM group, either an FPG≥7.0 mmol/L or a 2hPG≥11.1 mmol/L after the 75 g OGTT, or both.

Pre-diabetes was defined as iIFG, iIGT and combined IFG with IGT. Sodium-fluoride-preserved and clotted blood samples were collected to measure the plasma glucose and insulin levels immediately before drinking the glucose solution, and at 30, 60, 90 and 120 min after the test start. Plasma glucose was measured with the hexokinase enzymatic method using an automated analyser (Roche cobas 8000 analyser; Roche Diagnostics, Mannheim, Germany). The plasma insulin levels were measured using an electrochemiluminescence immunoassay by cobas 8000, Roche Diagnostics analyser. The HbA1c samples were taken immediately before the 75 g OGTT; they were measured by an Integra 800 CTS, Roche Diagnostics analyser, using the turbidimetric inhibition immunoassay method.

The participants' abdominal circumferences were measured in the standing position at the mid-way point between the lowest costal margin and the anterior superior iliac crest. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg for two consecutive measurements, or the current use of an antihypertensive medication.¹⁶ The presence of metabolic syndrome was diagnosed according to the International Diabetes Federation/American Heart Association (AHA) 2009 criteria.¹⁷ Dyslipidaemia was defined as a serum-calculated low-density lipoprotein cholesterol ≥160 mg/dL or a serum triglyceride ≥200 mg/dL, or the current use of a lipid-lowering agent. Hypercholesterolaemia was defined as an elevated low-density lipoprotein cholesterol (≥160 mg/dL) or the current use of statins.¹⁸ Overweight was defined as a body mass index (BMI) 23–24.9 kg/m² while a BMI≥25 kg/m² was defined as obesity.¹⁹

Calculations

Insulin secretion was assessed by the homeostatic model assessment of pancreatic beta-cell function (HOMA-beta), while insulin resistance was evaluated using the homeostatic model assessment of insulin resistance (HOMA-IR).²⁰ These were calculated with the FPG and fasting insulin levels obtained during the 75 g OGTT using the following formulae:

$$\text{HOMA} - \text{IR} = (\text{Ins}_0 \times \text{Glc}_0) / 22.5$$

$$\text{HOMA} - \text{beta} = (\text{Ins}_0 \times 20) / (\text{Glc}_0 - 3.5)$$

Table 1 Baseline characteristic of 123 subjects categorised by the gold standard criterion, a 75 g OGTT

Characteristics	All (n=123)	Normal glucose metabolism 22.8% (n=28)	Pre-diabetes 48.7% (n=60)			Diabetes 28.5% (n=35)	p-value (DM group vs other groups*)
			iIFG (n=6)	iIGT (n=24)	IFG and IGT (n=30)		
Age (years)	60.7±10.4	59.6±10.9	63.7±11.2	60.7±9.8	59.3±10.1	62.3±10.7	0.271
Male, n (%)	46 (37.4)	10 (35.7)	2 (33.3)	8 (33.3)	15 (50)	11 (31.4)	0.72
BMI (kg/m ²)	26.0±4.3	25.9±4.5	23.4±4.5	25.9±4.1	26.8±4.7	26.1±4.2	0.938
Waist circumference (cm)	89.0±10.0	87.9±9.3	85.0±9.6	89.0±11.2	90.2±10.6	89.7±9.5	0.653
Waist/hip ratio	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.246
First-degree relatives with DM, n (%)	58 (47.2)	11 (60.7)	2 (33.3)	12 (50)	17 (56.7)	16 (45.7)	0.84
History of smoking, n (%)	31 (25.2)	4 (16.7)	1 (16.7)	7 (29.2)	10 (33.3)	9 (25.7)	1
Hypertension, n (%)	73 (59.3)	12 (42.9)	3 (50)	15 (62.5)	20 (66.7)	23 (65.7)	0.365
Dyslipidaemia, n (%)	93 (75.6)	20 (71.4)	5 (83.3)	20 (83.3)	17 (56.7)	31 (88.6)	0.035†
Metabolic syndrome, n (%)	66 (53.7)	10 (35.7)	2 (33.3)	13 (54.2)	16 (53.3)	25 (71.4)	0.013†
Highest FPG during preceding 6 months (mmol/L)	6.2±0.4	6.0±0.3	6.2±0.4	6.1±0.3	6.3±0.4	6.3±0.3	0.083
Highest HbA1c during preceding 6 months (%)	6.0±0.4	5.9±0.3	6.2±0.4	5.9±0.4	5.9±0.4	6.3±0.3	<0.001†
FPG‡ (mmol/L)	5.6±0.5	5.2±0.2	5.8±0.4	5.2±0.2	5.9±0.3	5.8±0.5	0.004†
HbA1c‡ (%)	5.9±0.4	5.8±0.2	5.8±0.4	5.8±0.3	5.8±0.4	6.1±0.3	<0.001†
2-hour PG at end of 75 g OGTT (mmol/L)	9.7±2.6	6.6±0.9	6.8±0.8	9.7±1.1	9.5±1.0	13.0±1.5	<0.001†
Fasting insulin (µU/mL)	11.8±6.4	9.6±4.8	10.6±3.7	10.9±5.8	13.8±8.5	12.6±5.9	0.378

*‘Other groups’ are the normal glucose metabolism group and the prediabetic group.

†Indicates a statistically significant result.

‡Results from the day the 75 g OGTT was performed.

BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; IFG, impaired fasting plasma glucose; IGT, impaired glucose tolerance; iIFG, isolated IFG; iIGT, isolated IGT; OGTT, oral glucose tolerance test; PG, plasma glucose.

where Ins_0 is the fasting plasma insulin (µIU/mL) and Glc_0 is the FPG (mmol/L).

Statistical analysis

PASW Statistics for Windows (V.18.0; SPSS) was used for the statistical analyses. The quantitative variables are presented as mean±SD while the qualitative variables are shown as n (%). The differences between the two groups were compared using the Student’s t-test and X^2 test for quantitative and qualitative variables, respectively. The correlation between parameters was evaluated by using backward multiple logistic regression. A p-value of <0.05 was considered statistically significant. The cut-off levels of FPG and HbA1c were evaluated by sensitivity and specificity tests as well as receiver operating characteristic (ROC) curves.

RESULTS

In all, 123 participants were enrolled. The baseline characteristics and metabolic parameters of the participants are listed in table 1. The mean (±SD) age of the study participants was 60.7 (±10.4) years (range: 36–90 years). Seventy-seven participants were females. No females reported a history of gestational DM. About half of the participants had a family history of DM among first-degree relatives. Most participants had a high BMI; one-quarter

were classed as overweight while half were diagnosed with obesity. Of the 123 participants, 66 (53.7%) had metabolic syndrome, 73 (59.3%) had hypertension and 93 (75.6%) had dyslipidaemia (most of whom had hypercholesterolaemia). Among the participants with dyslipidaemia who received statin therapy, 44.0% used low-intensity statins, 53.6% used moderate-intensity statins and 2.4% used high-intensity statins, according to the AHA 2013 guidelines.²¹ Only six participants (4.9%) had an atherosclerotic cardiovascular disease (ischaemic stroke).

Among the 123 IFG subjects, the prevalence of T2DM (diagnosed by the 2hPG criterion) was 28.5%, of pre-diabetes was 48.7% and of normal glucose metabolism was 22.8%. The prevalences of iIFG, iIGT and IFG with IGT were 7.1%, 40.5% and 52.4% for the prediabetic cases, respectively. On the day of the 75 g OGTT, and based on the American Diabetes Association guidelines,¹⁵ six subjects were diagnosed with T2DM using the HbA1c criterion, and five out of those six received a T2DM diagnosis using the 2hPG criterion. However, no subjects with T2DM were identified when the FPG criterion was used. The characteristics of the participants in each group are presented in table 1. The participants in the IFG with IGT group and in the T2DM group had higher mean BMIs than those in the normal glucose metabolism group. The prevalence of dyslipidaemia and metabolic syndrome was

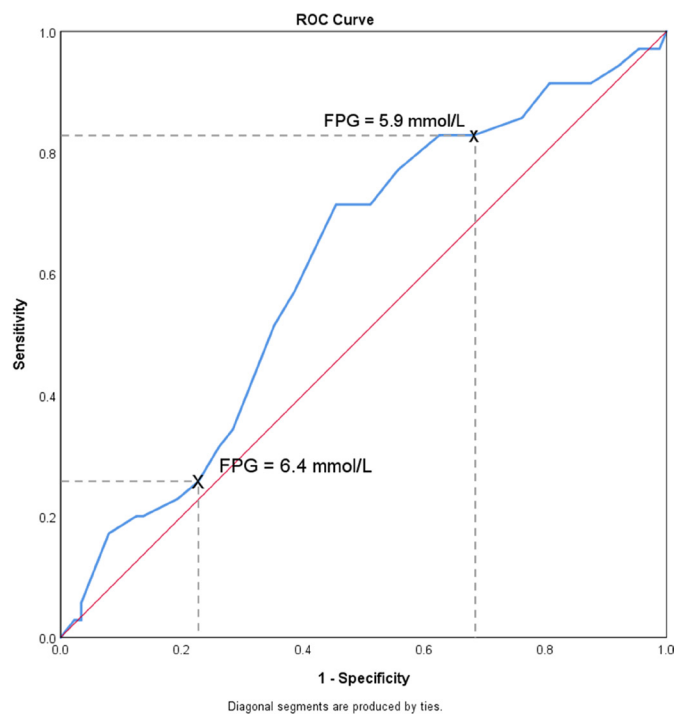


Figure 1 Receiver operating characteristic (ROC) curve of the highest fasting plasma glucose (FPG) level during the 6 months preceding the 75 g oral glucose tolerance test (OGTT), and the correlation with the diagnosis of diabetes mellitus via the 2-hour plasma glucose obtained during the 75 g OGTT (area under the curve=0.61).

significantly higher for the T2DM group than for the four other groups. Participants with the presence of T2DM diagnosed by the 2hPG criterion had a significantly higher previous maximum FPG and maximum HbA1c during the 6 months preceding the 75 g OGTT than those with a normal glucose metabolism (FPG, 6.3 ± 0.3 mmol/L vs 6.0 ± 0.3 mmol/L; HbA1c, $6.3\% \pm 0.3\%$ and $5.9\% \pm 0.3\%$, respectively; $p < 0.05$). Furthermore, a significantly higher HbA1c level was recorded on the day of administration of the 75 g OGTT for participants in the presence of diabetes group than for those in the normal glucose metabolism group (6.1 ± 0.3 vs 5.8 ± 0.2 ; $p < 0.05$).

Optimal cut-off levels of FPG and HbA1c

An ROC was conducted to determine the optimal FPG-level and HbA1c-level cut-off points for the prediction of the presence of T2DM (confirmed with the 2hPG criterion). An assessment was also made of the various values of the highest FPG and HbA1c levels obtained during the 6 months preceding the administration of the 75 g OGTT. The FPG level of 5.9 mmol/L had a sensitivity of 85.7% and specificity of 23.9% (95% CI 69.7% to 95.2% and 95% CI 15.4% to 34.1%, respectively; positive predictive value (PPV) 30.9%; negative predictive value (NPV) 80.8%). However, the FPG level of 6.4 mmol/L demonstrated a sensitivity and specificity of 31.4% and 73.9% (95% CI 16.9% to 49.3% and 95% CI 63.4% to 82.7%, respectively; PPV 32.4%; NPV 73.0%; [figure 1](#)). As to HbA1c, a level $\geq 6.0\%$ gave a sensitivity of 76.7% and specificity

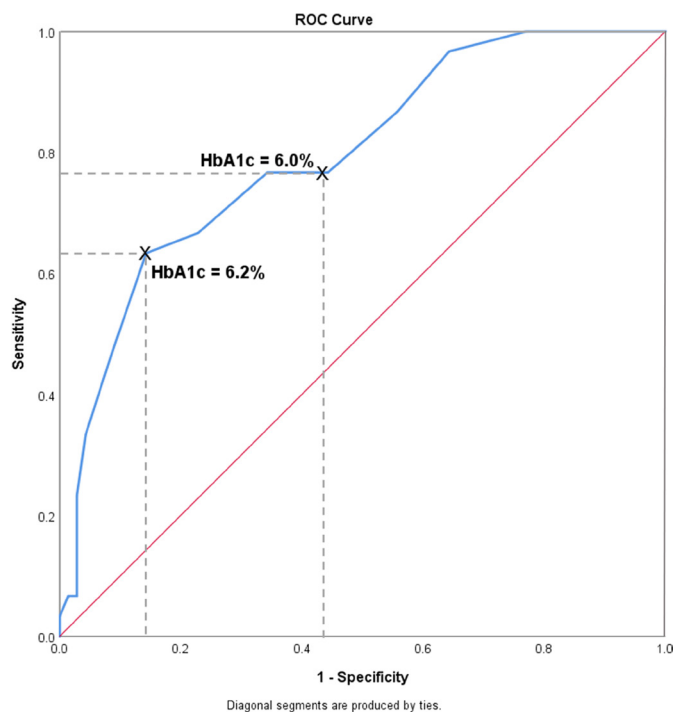


Figure 2 Receiver operating characteristic (ROC) curve of the highest HbA1c level during the 6 months preceding the 75 g oral glucose tolerance test (OGTT), and the correlation with the diagnosis of diabetes mellitus via the 2-hour plasma glucose obtained during the 75 g OGTT (area under the curve=0.79).

of 55.7% (95% CI 57.7% to 90.1% and 95% CI 43.3% to 67.6%; PPV 42.6%; NPV 84.8%). By contrast, an HbA1c level $\geq 6.2\%$ provided a sensitivity of 66.7% and specificity of 77.1% (95% CI 42.2% to 82.7% and 95% CI 65.6% to 86.3%; PPV 55.6%; NPV 84.4%; [figure 2](#)).

Risk factors

A logistic regression analysis was conducted to identify the predictors for the patients with IFG that were associated with the presence of T2DM using the 2hPG criterion. The factors revealed were dyslipidaemia; metabolic syndrome; the highest FPG and HbA1c levels in the preceding 6 months; and the FPG, HbA1c and fasting insulin levels on the day the 75 g OGTT was administered.

A subsequent multivariate logistic regression analysis found that the presence of metabolic syndrome, the highest HbA1c level during the preceding 6 months and the FPG level on the day of the 75 g OGTT were statistically significantly associated with the presence of T2DM by 2hPG criterion in the IFG individuals ([table 2](#)). Moreover, a 0.1% incremental increase in the highest HbA1c level during the preceding 6 months raised the risk of T2DM by 1.384 times (OR 1.384; 95% CI 1.175 to 1.631).

HOMA-beta and HOMA-IR were used to assess insulin secretion and insulin resistance. Relative to the normal group, there was a significant increase in insulin resistance in both the combined IFG with IGT and the T2DM groups. However, the impairment of insulin secretion

Table 2 Logistic regression of the risk factors associated with the presence of T2DM in patients with IFG

Variables	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Presence of dyslipidaemia	3.25 (1.04 to 10.14)	0.042		
Presence of metabolic syndrome	0.35 (0.15 to 0.81)	0.015	0.31 (0.10 to 0.93)	0.036*
Highest FPG during preceding 6 months	1.06 (0.99 to 1.12)	0.085		
Highest HbA1c during preceding 6 months	1.39 (1.19 to 1.62)	<0.001	1.38 (1.18 to 1.63)	<0.001*
FPG immediately before the 75 g OGTT	1.07 (1.02 to 1.13)	0.006	1.07 (1.001 to 1.136)	0.045*
HbA1c immediately before the 75 g OGTT	1.32 (1.15 to 1.52)	<0.001		
Fasting insulin level	1.14 (0.92 to 1.42)	0.235		

*Indicates a statistically significant result.

FPG, fasting plasma glucose; IFG, impaired fasting plasma glucose; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

demonstrated no significant differences between the groups (table 3).

DISCUSSION

Our results emphasised the use of the 75 g OGTT in addition to FPG and HbA1c for the diagnosis of T2DM, especially in individuals with persistent IFG. Using the 75 g OGTT, an unforeseen 28.5% of the Thai IFG individuals were found to have T2DM. In comparison, the prevalence rates reported by previous studies have ranged from 11.2% to 41.1%.^{9 12 13} Previous studies have also reported that Asians with IFG had a higher prevalence of T2DM diagnosed by a 75 g OGTT than Caucasians with IFG.^{9 13} Furthermore, the current research supported the results of other work that revealed that an increase in 2hPG levels after the administration of a 75 g OGTT occurs before any increases in FPG levels become apparent in older or Asian patients with pre-diabetes.^{12 13}

Among the 35 subjects in our study who were diagnosed with T2DM based on their 2hPG level after the 75 g OGTT, none had an FPG level ≥ 7.0 mmol/L. In addition, only 5 (14.28%) of those 35 subjects were also diagnosed with T2DM using the HbA1c criteria specified by the American Diabetes Association guidelines. These results suggest that using the HbA1c level to detect T2DM in IFG individuals was less effective than using the 2hPG level

after a 75 g OGTT. The lower efficacy of the HbA1c levels than the 2hPG levels and the high discordance between the HbA1c and 2hPG levels after the administration of a 75 g OGTT were similar to previous findings for Asian populations.^{12 13 22-24} It might be that the IFG subjects in the current study had been advised on their diagnosis of pre-diabetes to modify their lifestyles to control their abnormal glucose statuses. This may have prevented the development of significant chronic hyperglycaemia and the consequential increase in their HbA1c levels, but the issue of an abnormal glucose metabolism would have remained. Furthermore, Thailand has a high prevalence of individuals with thalassemia trait, which physiologically lowers HbA1c levels.²⁵ Therefore, a diagnosis of T2DM in IFG individuals based on either their HbA1c or FPG levels will miss many subjects who actually have T2DM. Despite the use of a 75 g OGTT in general practice being unappealing due to the time commitment involved and its relatively high cost, it may be indicated in IFG cases in which the FPG and/or HbA1c level is close to the diabetic range.

In differentiating DM from non-DM individuals, a standard HbA1c level of $\geq 6.5\%$ is highly specific in identifying people with T2DM. However, in a previous study, this level was found to have a low sensitivity of 33.2% in a Chinese study population.¹³ Our findings suggested

Table 3 Beta-cell function and insulin resistance during 75 g OGTT

Characteristics	Normal glucose metabolism 22.8% (n=28)	Pre-diabetes 48.7% (n=60)			Diabetes 28.5% (n=35)	p-value (DM vs normal glucose metabolism)
		IFG (n=6)	IGT (n=24)	IFG and IGT (n=30)		
Insulin secretion ▶ HOMA-beta	6.1±2.94	5.22±2.29	7.25±3.70	6.26±3.59	6.30±3.08	0.699
Insulin resistance ▶ HOMA-IR	0.13±0.06	0.15±0.05	0.14±0.08	0.20±0.13	0.18±0.09	0.007*

*Indicates a statistically significant result.

DM, diabetes mellitus; HOMA-beta, homeostatic model assessment of pancreatic beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; IFG, impaired fasting plasma glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

that the optimal cut-off level of HbA1c for IFG individuals for the prediction of T2DM was $\geq 6.0\%$, with a sensitivity of 76.7% and a specificity of 55.7%. Furthermore, the optimal cut-off level of the FPG value for predicting T2DM in our Thai IFG population was ≥ 5.9 mmol/L, with a sensitivity of 85.7% and a specificity of 23.9%.

The FPG level of ≥ 5.9 mmol/L and the HbA1c level of $\geq 6.0\%$ were chosen as the optimal cut-off levels because they demonstrated a high sensitivity for the detection of the presence of T2DM, as diagnosed by the 2hPG level after a 75 g OGTT. Only one-fifth to one-quarter of the subjects with T2DM were missed. Moreover, both the FPG and HbA1c tests had high NPVs. This meant that if the FPG or HbA1c levels were lower than the optimal cut-off levels, the probability of being diagnosed with T2DM would be low. However, if possible, we recommend the use of the HbA1c rather than the FPG cut-off value due to the former's higher performance and lower variation.

Our study suggests that the Thai IFG population should undergo a 75 g OGTT if an FPG or HbA1c level is ≥ 5.9 mmol/L or 6.0%, respectively, to screen for the presence of T2DM. IFG individuals with an FPG level of < 5.9 mmol/L and an HbA1c level of $< 6.0\%$ during follow-up visits have a low likelihood of having undisclosed DM. Lifestyle modifications or the use of metformin without the need for 75 g OGTT screening is recommended for this group.

Our cut-off levels agree with those of previous studies that reported an optimal HbA1c cut-off level of around 6.0%–6.3%.^{12–14 23 24 26–28} The minimal difference between our proposed HbA1c cut-off value and those of the previous studies might be due to differences in the timing of the HbA1c measurements. The other studies used the HbA1c level measured on the day of administration of the 75 g OGTT. However, that level might have been lower than the HbA1c levels measured some time before the 75 g OGTT due to the patients having undertaken lifestyle modifications, as shown in our study.

The multivariate logistic regression analysis revealed that the presence of T2DM in patients with IFG was strongly associated with three factors. They were the presence of metabolic syndrome, the highest HbA1c level during the 6 months preceding the 75 g OGTT and the FPG level on the day of the 75 g OGTT. The current work also found a significant increase in insulin resistance but lack of defect in insulin secretion in members of the combined IFG with IGT group and the T2DM group, compared with the individuals with normal glucose metabolism. The explanation for this might be that IFG individuals have a pre-existing impairment of first-phase insulin secretion.²⁹

There were some limitations to this study. First, its low number of participants resulted in small numbers of participants in each subgroup. In addition, fasting glucose levels typically demonstrate relatively sizeable day-to-day variations in their values. We took steps to minimise this variation by only enrolling IFG individuals who had a history of persistent IFG during the preceding

year. The aim of that approach was to improve the consistency of the disease classifications by avoiding the misdiagnoses of pre-diabetes that could possibly result from the use of single testing episodes.³⁰ On the day of the 75 g OGTT, the FPG levels tended to be significantly lower than the previously recorded FPG values, which resulted in a larger number of subjects having a normal FPG than expected. Moreover, we performed the 75 g OGTT only once. As the American Diabetes Association guidelines for T2DM diagnosis require a repeat test in asymptomatic individuals, the true prevalence of T2DM might have been lower than that based on a single testing episode. Finally, the generalisability of the findings in this study is limited to IFG individuals, not all pre-diabetes subtypes.

As glucose metabolism varies among ethnicities, there remains an unanswered question: can the recommended HbA1c and FPG cut-off levels be applied to other populations with IFG? To date, most of the data on HbA1c and FPG cut-off levels for T2DM screening have been derived from a healthy population. However, in the case of the FPG level, the cut-off level for a healthy population is higher than that for IFG individuals.¹⁴ This issue should be taken into consideration given that IFG individuals are likely to be following a strict diet to achieve acceptable FPG values at follow-up sessions. Practitioners should be aware of this while monitoring individuals with IFG: even if they have excellent FPG levels, they might still have unrevealed T2DM.

SUMMARY

In conclusion, almost one-third of individuals with IFG had T2DM diagnosed by the 2hPG criterion. HbA1c is a more effective parameter than FPG for the prediction of the presence of T2DM. IFG individuals with an HbA1c level of $\geq 6.0\%$ or an FPG level of ≥ 5.9 mmol/L during follow-up visits should be advised to have a 75 g OGTT to detect T2DM earlier than otherwise. IFG individuals with an FPG level of < 5.9 mmol/L and an HbA1c level of $< 6.0\%$ during follow-up visits have a low likelihood of having undisclosed DM; lifestyle modification without the need for a 75 g OGTT is therefore recommended for this group.

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