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Hemoglobin A1c in combination with fasting plasma glucose trumps fasting plasma glucose alone as predictive indicators for diabetes mellitus: an ambidirectional cohort study of Thai people with impaired fasting glucose

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ABSTRACT

Introduction This ambidirectional cohort study aimed to assess the performance of combining hemoglobin A1c (HbA1c) to fasting plasma glucose (FPG) for estimation of progression rate to diabetes mellitus (DM) and to explore the risk factors of DM in patients with impaired fasting glucose (IFG).

Research design and methods Patients with IFG were eligible for this study. IFG was defined as FPG of 100–125 mg/dL. Progression rates to DM were estimated using Kaplan-Meier analysis. Risk factors of DM were explored by Cox regression analysis.

Results 3011 patients were enrolled with median follow-up time of 8 years (range: 6 months–29 years). Progression rates to DM in patients with FPG 100–109 mg/dL and 110–125 mg/dL were 2.64 and 4.79 per 100 person-years. After adjusting covariables, compared with patients with FPG 100–109 mg/dL plus normal HbA1c (<5.7%), hazard ratios (95% CI) of patients with FPG 110–125 plus normal HbA1c, FBG 100–109 plus abnormal HbA1c (5.7%–6.49%), and FPG 110–125 plus abnormal HbA1c were 5.89 (2.37 to 14.63), 16.30 (8.59 to 30.92), and 33.84 (16.41 to 69.78), respectively. Body mass index ≥27.5 kg/m^2, serum triglyceride level ≥150 mg/dL, family history of DM, and low level of high-density lipoprotein-cholesterol were independently associated with risk of DM in patients with IFG.

Conclusions Patients with both IFG and abnormal HbA1c had higher risk of DM than patients with IFG alone. Therefore, performing HbA1c in combination with FPG helps to identify subgroups of people with IFG at highest risk of DM. These patients should have the highest priority in diabetes prevention programs, especially in countries with low and limited resources.

Significance of this study

What is already known about this subject?

- Patients with pre-diabetes have significantly higher risk of diabetes mellitus (DM) than people with normoglycemia. However, different criteria are applied to define pre-diabetes status and may confer the different risks of developing DM.

What are the new findings?

- Progress rate to DM was highest (5.46 per 100 person-years) in patients having fasting plasma glucose of 110–125 mg/dL with abnormal hemoglobin A1c (HbA1c) (5.7%–6.49%). This was significantly higher than progression rate in patients having fasting plasma glucose 100–109 mg/dL with normal HbA1c level (0.24 per 100 person-years).
- Body mass index ≥27.5 kg/m^2, serum triglyceride level ≥150 mg/dL, and having family history of DM significantly increased risk of diabetes in patients with impaired fating glucose.
- Contrastingly, high level of high-density lipoprotein-cholesterol significantly decreased risk of DM in patients with impaired fasting glucose.

How might these results change the focus of research or clinical practice?

- Using HbA1c in combination with fasting plasma glucose for screening DM is beneficial for classifying people who are at high risk of DM. Patients having fasting plasma glucose of 110–125 mg/dL with abnormal HbA1c should have the highest priority in diabetes prevention programs, especially in countries with low and limited resources.

INTRODUCTION

Pre-diabetes is recognized as an intermediate stage between normoglycemia and overt diabetes mellitus (DM).[1] The population with pre-diabetes is at a high risk not only of overt type 2 DM[1 2] but also cardiovascular diseases (CVDs) and all-cause mortality,[3 4] as microvascular and macrovascular changes are present

since the onset of glycemic dysregulation.[5] Therefore, pre-diabetes should be treated to decrease the probability of progression to DM and prevent the potential effects of pre-diabetes itself.[6]

Diagnostic criteria used for defining pre-diabetes have been changed over time and also varied depending on the institutions of origin. For instance, the American Diabetes Association (ADA)[7] defines pre-diabetes as (1) impaired glucose tolerance (IGT), that is, 2-hour glucose level of 140–199 mg/dL after a 75-gram oral glucose load; (2) impaired fasting glucose (IFG), that is, fasting plasma glucose (FPG) level of 100–125 mg/dL; or (3) abnormal hemoglobin A1c (HbA1c) of 5.7%–6.49%[7]; whereas the WHO defines IFG as FPG level of 110–125 mg/dL,[8] and the International Expert Committee (IEC) defines abnormal HbA1c as HbA1c of 6.0%–6.49%.

Despite being the same 'pre-diabetes' category, there is evidence that differences in glycemic indices confer different risks of DM progression.[9 10] For instance, the results from a meta-analysis found that the risk of DM progression in people with HbA1c of 5.7%–6.49% was higher than risk in people with FPG 100–125 mg/dL,[11] and people with both IFG and HbA1c might have a higher risk than people with either IFG or abnormal HbA1c. This difference may result from different underlying pathogeneses between IFG and abnormal HbA1c.[12 13] In addition, different thresholds of FPG level used for defining pre-diabetes would affect the magnitude of prevalence and burden of pre-diabetes globally. For instance, lowering the threshold of FPG level will increase the prevalence of pre-diabetes, which may pose as an issue to low/middle-income countries with limited healthcare and economic resources. Therefore, this ambidirectional cohort study primarily aiming to assess whether performing HbA1c in combination with FPG could improve the ability to predict diabetes risk more than performing FPG alone and to estimate the progression rate to DM according to different criteria of IFG. Additional factors (eg, body mass index (BMI), family history of DM, and history of hypertension), known to be associated with DM risk,[10 14] will also be considered. The results from this study will be useful in identifying people with IFG who are at a high risk of progression to DM, enabling group-specific diabetes prevention strategies and allowing efficient utilization of resources in limited settings.

METHODS

This study was an ambidirectional cohort of patients with IFG that combined retrospective with prospective data collection. Patients with IFG who visited the outpatient clinic of the Department of Family Medicine, Ramathibodi Hospital, Bangkok, Thailand during October 2014 through October 2017 were enrolled for this study, and they were followed until January 2019 for this analysis. IFG was defined according to the ADA criteria (ie, FPG ranging from 100 to 125 mg/dL). Patients were excluded, if they took anti-diabetic medications or were not willing to participate in the study.

Data collection

Three methods were applied for data collection as follows: (1) demographic data (eg, age, sex, marital status, education), family history of DM, health risk behavior (eg, smoking and alcohol drinking), and risk of obstructive sleep apnea (OSA) were obtained from interviewing by well-trained research assistants. Risk of OSA was assessed by adapting the questions from category I of Berlin questionnaire[15] asking about presence and severity of snoring, and frequency of cessation of breathing during sleep. Participants were classified as being high risk of OSA, if the total score of this category was equal or greater than 2. Height and waist circumference were obtained at the time of enrollment by trained research assistants. Height was measured without shoes to the nearest 0.1 cm. Waist circumference (cm), to the nearest 0.1 cm, was measured at the middle point between the lowest rib and iliac crest in the standing position using a plastic tape. (2) Date of IFG diagnosis and history of underlying diseases (ie, chronic kidney disease (CKD), CVD, hypertension, dyslipidemia, gestational DM, and cancer) were collected through medical record reviews by trained physicians. (3) Body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and laboratory data including FPG, HbA1c, serum uric acid, triglyceride, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) were retrieved from the Medical Statistics Unit, Ramathibodi Hospital since the date of IFG diagnosis to the date of last follow-up or the end date of the study (31 January 2019). These laboratory assays were performed in the clinical laboratory of Ramathibodi Hospital. FPG was measured using hexokinase glucose-6 phosphate dehydrogenase. HbA1c levels were measured using turbid metric inhibition immunoassay that has been certified by the National Glycohemoglobin Standardization Program. Serum triglyceride and serum uric acid levels were measured by lipase/glycerol kinase glycerol-3-phosphate oxidase and uricase methods, respectively. HDL-C and LDL-C levels were measured by accelerator selective detergent method.

BMI was calculated by dividing weight in kilogram with height in square meter and then classified into normal weight (BMI<23 kg/m^2), overweight (BMI 23–27.49 kg/m^2), and obesity (BMI ≥27.5 kg/m^2) in accordance with WHO recommendations for Asian population.[16] Age of participants was calculated based on the date of IFG diagnosis and categorized into three groups as (1) <65 years, (2) 65–74 years, and (3) ≥75 years. SBP and DBP levels incorporated with history of hypertension were categorized into three groups as (1) normal blood pressure (ie, SBP <140 and DBP <90 mm Hg) without history of hypertension, (2) well-controlled blood pressure (ie, SBP <140 and DBP <90 mm Hg) with history of hypertension and/or antihypertensive drugs, and (3) high blood

pressure (ie, SBP ≥140 and/or DBP ≥90 mm Hg) with or without history of hypertension. Serum uric acid was classified into normal uric acid level and hyperuricemia (ie, serum uric acid ≥6.2 mg/dL in female and ≥7.2 mg/dL in male). Triglyceride, LDL-C, and HDL-C levels were categorized into normal and high triglyceride (≥150 mg/dL), high LDL-C (≥130 mg/dL), and low HDL-C (≤40 mg/dL in male and ≤50 mg/dL in female) levels.

Baseline FPG measured at the date of IFG diagnosis was used for prediction of the DM progression. FPG was classified into two groups as (1) FPG 100–109 mg/dL and (2) FPG 110–125 mg/dL. Abnormal HbA1c was defined as HbA1c of 5.7%–6.49%. When considering both FPG and HbA1c together, participants were classified into four groups as (1) FPG 100–109 mg/dL with normal HbA1c ($FPG_{100–109}$ and $HbA1c_{<5.7}$), (2) FPG 110–125 mg/dL with normal HbA1c ($FPG_{110–125}$ and $HbA1c_{<5.7}$), (3) FPG 100–109 mg/dL with abnormal HbA1c ($FPG_{100–109}$ and $HbA1c_{5.7–6.49}$), and (4) FPG 110–125 mg/dL with abnormal HbA1c ($FPG_{110–125}$ and $HbA1c_{5.7–6.49}$). HbA1c measured within 2 years after diagnosis of IFG was used for prediction of DM in patients who had not measured HbA1c at the time of IFG diagnosis.

Outcome of interest was time since IFG diagnosis to DM progression, which was defined by FPG of 126 mg/dL or higher, and/or HbA1c of 6.5% or higher on one occasion during follow-up time.[17] This definition was used only for the purposes of the epidemiological study, which had also been applied by previous studies.[18–20] All FPG and HbA1c values measured during the time of follow-up were used for outcome verification.

Multiple imputations

Baseline or fixed variables were missing which ranged from 0.03% (family history of DM) to 68.95% (HbA1c value at time of IFG diagnosis) (see online supplemental table 1), while time-varying variables were missing which ranged from 0.01% to 45.9% (see online supplemental table 2). The multiple imputation with chain equation was performed with 70 and 30 for fixed and time-varying variables, respectively. Type of predictors and model used were described in online supplemental table 3, including logit and linear regression models for categorical/ordinal and continuous variables. A maximum fraction of missing information (FMI) was used to assess if a number of imputations were sufficient, that is, the maximum FMI of 0.30 would require at least 30 imputations.

Statistical analysis

Demographic data were presented as mean and standard deviation (SD) for continuous data and as frequency and percentage for categorical data. Time to DM progression was calculated as the subtraction of progression date with date of IFG diagnosis (starting date). Patients who were free from DM progression were censored on the end date of study (31 January 2019) or the date of last visit if they were lost to follow-up. Progression rates to DM according to different cut-off points of FPG and HbA1c levels were estimated. In addition, probability of DM progression at different times was estimated using Kaplan-Meier analysis.

Potential factors associated with DM progression were collected including age, sex, educational level, family history of DM, smoking, alcohol drinking, OSA risk, underlying diseases, BMI, SBP, DBP, and laboratory values (ie, serum uric acid, triglyceride, LDL-C, and HDL-C). Some of them (ie, BMI, SBP, DBP, triglyceride, serum uric acid, LDL-C, and HDL-C levels) were changed over time during the follow-up, thus they were considered as time-varying covariates. Data were prepared as long format, in which each participant had multiple records according to number of visits at the outpatient clinic and/or occurrence of DM progression. A survival analysis was performed based on multiple-record data with a single event to estimate DM progression rate. Prognostic factors of DM progression were assessed using Cox proportional hazard model with time-varying covariates. Variables that had a p value less than 0.1 were then considered in a multivariate Cox proportional hazard model. A likelihood ratio test was applied to select only significant prognostic factors in the final model that contained FBG or HbA1c groups. A proportional hazard assumption between FBG/HbA1c groups was checked using a global χ^2 test and log–log (survival) plot. If the assumption was violated, that is, effects of FBG/HbA1c were not proportional over time, an interaction between FBG/HbA1c and time variable was added in a Cox regression model. All statistical analyses were performed using STATA program V.16. A two-sided p value less than 0.05 was considered as statistically significant.

Role of the funding source

This study was supported by the Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The funding of this study was not involved in study design, data collection, data analysis, data interpretation and report writing.

RESULTS

A total of 3019 patients with IFG were enrolled during the study period; 8 patients were later excluded due a lack of follow-up visits, leaving 3011 patients included in the study. The baseline characteristics of patients in overall and according to combined FPG and HbA1c categories are presented in table 1. The mean age was 64.1 (±9.3) years and the majority of the participants were female (65.9%). The majority of participants were married (69.7%) and received a healthcare reimbursement under civil servant system (59.6%). About one-fourth and nearly half of patients were ex-smokers or current smokers (24.4%) and ex-alcohol drinkers or current alcohol drinkers (46%). Nearly half of the participants reported a familial history of DM (40%). Most participants had comorbidities of hypertension (68.1%) and dyslipidemia (88.7%). The mean BMI was 26.3 (±4.0) kg/m^2. The mean levels of SBP and DBP were 137.1 (±14.1) and 77.0 (±6.3) mm Hg, respectively. The male

Table 1 Characteristics of study's participants

Characteristics	Total N=3011	FPG 100–109 mg/dL and HbA1c <5.7% (N=223)	FPG 100–109 mg/dL and HbA1c 5.7%–6.49% (N=456)	FPG 110–125 mg/dL and HbA1c <5.7% (N=68)	FPG 110–125 mg/dL and HbA1c 5.7%–6.49% (N=209)
Age at enrollment (year): mean (SD)	64.1 (9.25)	59.4 (9.51)	62.0 (8.45)	60.5 (8.62)	61.4 (9.17)
Female: frequency (%)	1985 (65.92)	140 (62.78)	310 (67.98)	36 (52.94)	137 (65.55)
Duration of pre-diabetes at date of enrollment (year); median (range)	4.91 (0.25–23.47)	2.55 (0.50–3.91)	2.78 (0.52–4.18)	2.58 (0.65–3.67)	2.47 (0.38–3.98)
Educational level: frequency (%)					
Lower than primary school	82 (2.73)	4 (1.79)	11 (2.42)	0 (0)	7 (3.35)
Primary school	971 (32.35)	69 (30.94)	129 (28.35)	24 (35.29)	66 (31.58)
Secondary school	864 (28.78)	70 (31.39)	130 (28.57)	18 (26.47)	57 (27.27)
College or higher	1085 (36.14)	80 (35.87)	185 (40.66)	26 (38.24)	79 (37.80)
Marital status: frequency (%)					
Single	368 (12.24)	29 (13.0)	59 (12.94)	8 (11.76)	21 (10.10)
Married	2094 (69.66)	160 (71.75)	310 (67.98)	53 (77.94)	153 (73.56)
Divorce	228 (7.58)	15 (6.73)	40 (8.77)	1 (1.47)	20 (9.62)
Widow	316 (10.51)	19 (8.52)	47 (10.31)	6 (8.82)	14 (6.73)
Reimbursement: frequency (%)					
Universal healthcare coverage	55 (1.84)	8 (3.64)	7 (1.55)	0 (0)	9 (4.33)
Social security scheme	284 (9.52)	27 (12.27)	41 (9.07)	5 (7.69)	20 (9.62)
Civil servant	1777 (59.55)	126 (57.27)	274 (60.62)	40 (61.54)	127 (61.06)
Others	868 (29.09)	59 (26.82)	130 (28.76)	20 (30.77)	52 (25.0)
Smoking status: frequency (%)					
Never	2278 (75.66)	166 (74.44)	351 (76.97)	46 (67.65)	9 (4.31)
Past smoker	613 (20.36)	46 (20.63)	87 (19.08)	16 (23.53)	47 (22.49)
Current smoker	120 (3.99)	11 (4.93)	18 (3.95)	6 (8.82)	153 (73.21)
Alcohol drinking: frequency (%)					
Never	1625 (54.02)	110 (49.55)	255 (55.92)	31 (45.59)	99 (47.37)
Past drinking	796 (26.46)	56 (25.23)	111 (24.34)	22 (32.35)	64 (30.62)
Current drinking	587 (19.51)	56 (25.23)	90 (19.74)	15 (22.06)	46 (20.01)
Having family history of diabetes mellitus	1205 (40.03)	83 (37.22)	202 (44.30)	20 (29.41)	96 (46.15)
Underlying diseases: frequency (%)					
Hypertension	2044 (68.09)	123 (55.16)	297 (65.71)	43 (63.24)	132 (63.46)
Dyslipidemia	2665 (88.74)	182 (81.61)	398 (87.86)	55 (80.88)	182 (87.50)
Chronic kidney disease	123 (4.10)	6 (2.69)	21 (4.65)	5 (7.35)	9 (4.33)
Coronary artery disease	16 (0.53)	1 (0.45)	2 (0.44)	0 (0)	2 (0.96)
Cerebrovascular disease	38 (1.27)	4 (1.79)	6 (1.33)	0 (0)	3 (1.44)
Fatty liver	118 (3.93)	12 (5.38)	22 (4.87)	2 (2.94)	11 (5.29)
Gestational diabetes mellitus	16 (0.81)	0 (0)	4 (1.29)	0 (0)	5 (3.65)
Cancer	54 (2.73)	6 (4.29)	7 (2.29)	1 (2.78)	5 (3.68)
Berlin category I ≥2: frequency (%)	1203 (39.95)	43 (30.71)	111 (35.81)	10 (27.78)	52 (37.96)
Body mass index (kg/m^2): mean (SD)	26.28 (4.01)	26.33 (4.22)	26.48 (4.09)	25.72 (3.76)	26.75 (4.36)
Waist circumference (cm): mean (SD)					
Male	93.27 (9.42)	91.79 (9.62)	94.45 (9.36)	91.64 (10.91)	93.99 (11.48)
Female	88.68 (9.81)	86.49 (11.41)	88.01 (9.83)	88.60 (9.10)	90.57 (10.15)

Continued

Table 1 Continued

Characteristics	Total N=3011	FPG 100–109 mg/dL and HbA1c <5.7% (N=223)	FPG 100–109 mg/dL and HbA1c 5.7%–6.49% (N=456)	FPG 110–125 mg/dL and HbA1c <5.7% (N=68)	FPG 110–125 mg/dL and HbA1c 5.7%–6.49% (N=209)
Systolic blood pressure (mm Hg): mean (SD)	137.09 (14.07)	134.45 (12.94)	136.48 (13.89)	136.80 (12.30)	136.92 (13.72)
Diastolic blood pressure (mm Hg): mean (SD)	76.99 (6.31)	77.87 (6.38)	77.54 (5.95)	78.59 (6.53)	77.71 (6.55)
Serum triglyceride level (mg/dL): mean (SD)	136.95 (61.36)	136.68 (58.41)	137.03 (62.29)	149.7 (76.89)	135.15 (51.74)
Serum uric acid (mg/dL): mean (SD)					
Male	6.43 (1.17)	6.51 (1.37)	6.43 (1.10)	5.81 (1.63)	6.59 (1.20)
Female	5.36 (1.19)	5.10 (1.12)	5.31 (1.04)	5.23 (1.07)	5.29 (1.25)
LDL-cholesterol (mg/dL): mean (SD)	122.77 (23.19)	124.60 (26.46)	124.51 (23.20)	121.83 (24.51)	126.12 (23.14)
HDL-cholesterol (mg/dL): mean (SD)					
Male	49.11 (10.78)	49.48 (11.46)	47.96 (10.12)	50.25 (9.42)	46.95 (9.45)
Female	56.15 (12.39)	56.22 (12.21)	56.23 (11.54)	56.43 (13.36)	54.86 (12.77)
FPG (mg/dL): mean (SD)	107.18 (5.61)	104.14 (2.67)	104.09 (2.60)	113.61 (3.35)	114.65 (4.11)
HbA1c (%): mean (SD)	5.89 (0.39)	5.41 (0.34)	6.02 (0.22)	5.38 (0.26)	6.06 (0.23)

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

and female participants had 6.4 (±1.2) mg/dL and 5.4 (±1.2) mg/dL of serum uric acid. Mean FPG and HbA1c levels were 107.2 (±5.6) mg/dL and 5.9% (±0.4). Characteristics of patients after performing multiple imputations are presented in online supplemental table 4.

Progression rate to DM

A total of 3011 patients contributed to 21 285 person-years with a median follow-up time of 8 years (range: 6 months–29 years). The earliest date of pre-diabetes diagnosis in the study's participants was August 1986. Of them, 695 patients developed DM by either abnormal FPG or HbA1c with an estimated DM progression rate of 3.27/100 person-years. A median time to DM progression was 15.23 years (95% CI: 14.11 to 16.70) indicating 50% of patients converted to DM at about 15 years or longer after diagnosis of IFG. The IQR of DM progression was 8.83–28.51 years. Furthermore, probabilities of DM progression at 5, 10, and 15 years were 11.52% (95% CI: 10.38% to 12.78%), 28.55% (95% CI: 26.46% to 30.77%), and 48.90% (95% CI: 44.64% to 53.33%), respectively.

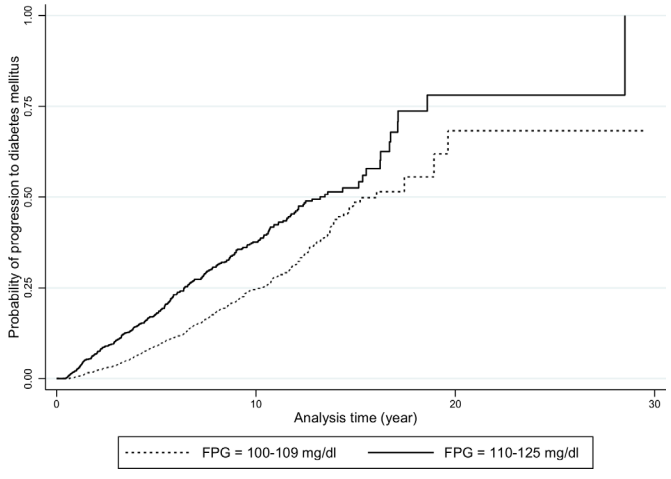

Figure 1 Progression rate to diabetes mellitus according to different cut-offs of fasting plasma glucose (FPG).

Progression rate to DM according to different FPG cut-offs

Regarding the different levels of FPG, DM progression rates were 2.64 and 4.79/100 person-years for FPGs of 100–109 and 110–125 mg/dL, respectively. In addition, time to DM conversion was shorter in patients with high FPG at baseline, that is, the median conversion times for these corresponding FPG groups were 16.05 and 13.22 years (see figure 1). Patients with FPG 110–125 mg/dL had significantly higher risk of DM progression with HR of 1.74 (95% CI: 1.50 to 2.02) relative to FPG 100–109 mg/dL, respectively (table 2).

Progression rate to DM when considering FPG and HbA1c together

Incidence rate of DM was highest in patients having $FPG_{110–125}$ and $HbA1c_{5.7–6.49}$ (5.46/100 person-years), followed by $FPG_{100–109}$ and $HbA1c_{5.7–6.49}$ (3.55/100 person-years), $FPG_{110–125}$ and $HbA1c_{<5.7}$ (1.05/100 person-years), and $FPG_{100–109}$ and $HbA1c_{<5.7}$ (0.24/100 person-years) (see figure 2). When compared with patients with $FPG_{100–109}$ and $HbA1c_{<5.7}$, those with $FPG_{110–125}$ and $HbA1c_{<5.7}$, $FPG_{100–109}$ and $HbA1c_{5.7–6.49}$, and $FPG_{110–125}$ and $HbA1c_{5.7–6.49}$ had significantly higher risk of DM with HRs (95% CI) of 4.20 (1.75 to 10.09), 14.53 (7.76 to 27.22), and 21.50 (11.44 to 40.39), respectively (table 2). In addition, patients with $FPG_{110–125}$ and $HbA1c_{5.7–6.49}$ had a significantly higher risk of DM than patients having $FPG_{110–125}$ and $HbA1c_{<5.7}$ (HR=5.74; 95% CI: 3.02 to 10.90).

Proportional hazards assumption of FPG–HbA1c effect was checked by constructing a log–log plot of FPG–HbA1c

Table 2 Factors associated with conversion of diabetes mellitus: a univariate Cox regression analysis

Factor	Time at risk	Number of event	Incidence rate/ 100 patient-years	HR	95% CI
FPG (mg/dL)					
100–109	15080	398	2.64	1	
110–125	6205	297	4.79	1.74	1.50 to 2.02
HbA1c (%)					
<5.7	5110	20	0.39	1	
5.7–6.49	16175	675	4.17	10.43	6.68 to 16.26
Combined FPG (mg/dL) and HbA1c (%)					
100–109 and <5.7	4160	10	0.24	1	
110–125 and <5.7	951	10	1.05	4.20	1.75 to 10.09
100–109 and 5.7–6.49	10920	388	3.55	14.53	7.76 to 27.22
110–125 and 5.7–6.49	5254	287	5.46	21.50	11.44 to 40.39
Age at diagnosis pre-diabetes (years)					
<65	16669	541	3.25	1	
65–75	3963	123	3.10	0.997	0.82 to 1.21
≥75	653	31	4.75	1.628	1.13 to 2.34
Sex					
Male	7213	225	3.12	1	
Female	14072	470	3.34	1.07	0.91 to 1.25
Educational level					
Non-educated	571	30	5.26	1	
Primary school	7090	232	3.27	0.59	0.40 to 0.86
Secondary school	6093	209	3.43	0.63	0.43 to 0.92
College or higher	7532	224	2.97	0.56	0.38 to 0.81
Reimbursement					
UHC	375	13	3.47	1	
SSS	1963	82	4.18	1.16	0.65 to 2.09
Civil servant	12785	402	3.14	0.87	0.50 to 1.51
Other	6162	198	3.21	0.88	0.50 to 1.55
Body mass index (kg/m^2)					
<23	4691	108	2.30	1	
23–27.5	9519	289	3.00	1.33	1.04 to 1.71
≥27.5	7074	299	4.20	1.90	1.48 to 2.43
Family history of DM					
No	12993	384	2.96	1	
Yes	8292	311	3.75	1.30	1.12 to 1.51
Smoking status					
Never	16270	536	3.29	1	
Past	4282	131	3.06	0.95	0.78 to 1.14
Current	733	28	3.82	1.27	0.87 to 1.85
Alcohol drinking					
Never	11720	391	3.34	1	
Past	5711	175	3.06	0.91	0.76 to 1.09
Current	3854	129	3.35	1.04	0.85 to 1.27
Berlin category I ≥2					
No	12857	379	2.95	1	
Yes	8427	316	3.75	1.27	1.10 to 1.48

Continued

Table 2 Continued

Factor	Time at risk	Number of event	Incidence rate/ 100 patient-years	HR	95% CI
Blood pressure					
Normal BP* and no HT*	4232	112	2.70	1	
Well-controlled BP* with HT and/ or antihypertensive drugs	7947	240	3.00	1.09	0.85 to 1.38
High BP† with or without HT	9106	342	3.80	1.33	1.05 to 1.68
Hyperuricemia					
No‡	15286	448	2.90	1	
Yes§	5999	247	4.10	1.40	1.19 to 1.64
Triglyceride					
<150 mg/dL	14029	398	2.83	1	
≥150 mg/dL	7255	297	4.10	1.45	1.24 to 1.70
LDL-cholesterol					
<130 mg/dL	13108	429	3.30	1	
≥130 mg/dL	8177	266	3.30	1.03	0.89 to 1.21
HDL-cholesterol					
<40 in male, <50 in female	6119	251	4.10	1	
≥40 in male, ≥50 in female	15165	444	2.90	0.70	0.60 to 0.82

*Systolic BP <140 mm Hg and diastolic BP <90 mm Hg.
†Systolic BP ≥140 mm Hg and/or diastolic 90 mm Hg.
‡Serum uric acid <6 mg/dL in female and<7.2 in male
§Serum uric acid ≥6 mg/dL in female and ≥7.2 mg/dL in male.
BP, blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio; HT, hypertension; LDL, low-density lipoprotein; SSS, social security scheme; UHC, universal healthcare coverage.

groups (see online supplemental figure 1) indicating the four curves looked parallel, except for $FPG_{100–109}$ and $HbA1c_{5.7–6.49}$, and $FPG_{110–125}$ and $HbA1c_{<5.7}$ groups that were cross-over, that is, effects of the two groups were varied over time. This was corresponded with the global X^2 test (X^2=27.25, df=3, p<0.001).

Factors associated with the risk of DM

Univariate Cox regression analysis indicated that age at IFG diagnosis, education, family history of DM, BMI, OSA risk, history of hypertension and blood pressure level, serum uric acid, triglyceride, and HDL-C level had a p value of less than 0.10 (table 2).

A multivariate Cox regression with FPG and HbA1c adjusting for time-varying effects indicated that $FPG_{110–125}$ and $HbA1c_{<5.7,}$ $FPG_{100–109}$ and $HbA1c_{5.7–6.49}$, and $FPG_{110–125}$ and $HbA1c_{5.7–6.49}$ significantly increased risk of DM conversion when compared with $FPG_{100–109}$ and $HbA1c_{<5.7}$ with HRs (95% CI) of 5.89 (2.37 to 14.63), 16.30 (8.59 to 30.92), and 33.84 (16.41 to 69.78), respectively (see table 3). In addition, family history of DM, BMI ≥27.5 kg/m^2, and high triglyceride level were also significantly associated with DM conversion after adjusting with baseline FPG–HbA1c with HRs (95% CI) of 1.27 (1.09 to 1.47), 1.67 (1.30 to 2.15), and 1.40 (1.19 to 1.64), respectively (see table 3). Contrastingly, high HDL-C level significantly decreased risk of DM with HR (95% CI) of 0.82 (0.70 to 0.96).

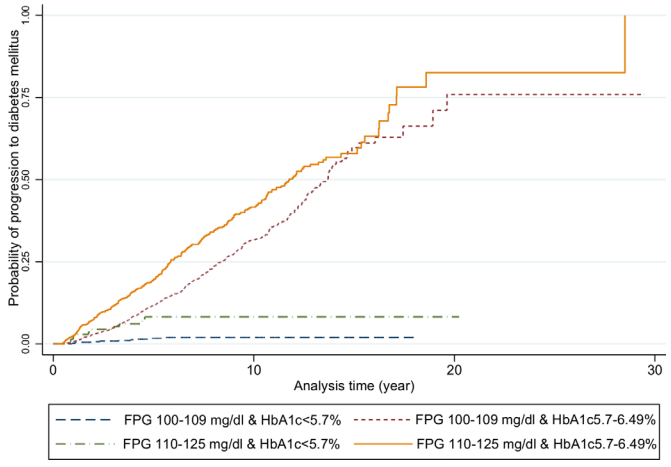

Figure 2 Progression rate to diabetes mellitus when considering fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) together.

DISCUSSION

We had conducted a cohort study of 3011 patients with IFG, with median follow-up time of 8 years. Our findings suggest that overall progression rate to DM was 3.27 per 100 person-years with a median DM conversion of 15 years. Risk of DM increased when levels of FPG increased such that patients having FPG 110–125 mg/dL progressed to DM significantly greater than patients having FPG 100–109 mg/dL. When considering FPG

Table 3 Factors associated with diabetes conversion: a multivariate Cox regression with time-varying model

Factor	HR	95% CI	P value
Combined FPG (mg/dL) and HbA1c (%)			
100–109 and <5.7	1		
110–125 and <5.7	5.89	2.37 to 14.63	<0.001
100–109 and 5.7–6.49	16.30	8.59 to 30.92	<0.001
110–125 and 5.7–6.49	33.84	16.41 to 69.78	<0.001
Body mass index (kg/m^2)			
<23	1		
23–27.5	1.26	0.98 to 1.62	0.067
≥27.5	1.67	1.30 to 2.15	<0.001
Family history of DM			
No	1		
Yes	1.27	1.09 to 1.47	0.002
Triglyceride (mg/dL)			
<150	1		
≥150	1.40	1.19 to 1.64	<0.001
HDL-cholesterol (mg/dL)			
<40 in male, <50 in female	1		
≥40 in male, ≥50 in female	0.82	0.70 to 0.96	0.015

DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio.

and HbA1c levels together, at the same FPG levels, incidence rate of DM was higher for those with abnormal HbA1c. Regarding the risk factor of DM, BMI ≥27.5 kg/m^2, having family history of DM, high triglyceride level greater than 150 mg/dL, and low HDL-C level are found to be independently associated with DM risk in patients with IFG.

Pre-diabetes referred to people with high glucose level but not within diabetes range. Several criteria based on FPG, HbA1c and oral glucose tolerance test (OGTT) have been used to define pre-diabetes stage. Although the ADA and IEC have adopted HbA1c as one of the diagnosis criteria, the HbA1c criterion has not been supported by WHO and other organizations. Results of previous studies suggested that HbA1c is an accurate method for DM and pre-diabetes diagnosis and had better predictive capacity than FPG.[21] Findings from our study also confirm the benefit of using HbA1c in combination with FPG to estimate the progression rate of DM and classify patients with IFG to be high or low risk of DM. Our results corresponded to the findings from previous meta-analyses[11 22] and cohort studies[19 20 23 24] that patients with combined IFG and abnormal HbA1c had significantly higher risk of DM than patients with IFG alone. In addition to the prediction of DM risk, results from large prospective cohort studies[23 25] found that pre-diabetes defined by HbA1c criteria conferred a significantly higher risk of CVDs, CKD and all-cause mortality. Therefore, using HbA1c in addition to FPG is useful for identifying people who are at high risk of DM and also CVD.

According to FPG-based criteria, the FPG thresholds used to define IFG are different between ADA (100–125 mg/dL) and WHO (110–125 mg/dL). Our study found that when compared with FPG 100–109 mg/dL, incidence rate of DM was significantly higher in those with FPG 110–125 mg/dL. In addition, incidence rate of DM in participants with $FPG_{100–109}$ and $HbA1c_{<5.7}$ was only 1.16 per 100 person-years, while incidence rate of DM in those with $FPG_{100–109}$ and $HbA1c_{5.7–6.49}$ was 4.62 per 100 person-years. Therefore, among all definitions of pre-diabetes, patients with $FPG_{100–109}$ and $HbA1c_{<5.7}$ had the lowest risk of DM progression.

The ADA applies FPG of 100–125 mg/dL to define IFG because this threshold is more comparable with IGT and can expand the sensitivity for predicting incidence of DM in many populations.[26] However, using the FPG 100–125 mg/dL for defining IFG will increase the prevalence of pre-diabetes and consequently might increase health and economic burdens, especially in low and limited-resource settings. Moreover, there has been no evidence of additional benefit of lowering FPG threshold to 100 mg/dL in terms of predicting the DM risk or complications of DM.[27] Therefore, our findings support the more advantage of using FPG combined with HbA1c values to predict risk of DM in the future.

Regarding the risk factors of DM, our study found that only BMI ≥27 kg/m^2, having family history of DM, serum triglyceride level ≥150 mg/dL, and low level of HDL-C were significantly associated with DM in patients with pre-diabetes. Risk factors of DM found in our study are similar to the established risk factors of DM that are applied as the criteria for DM screening in asymptomatic adults.[17] Previous systematic reviews and meta-analyses suggest significant relationship between OSA[28] and serum uric acid.[29 30] However, neither sleep factors nor serum uric acid was significantly associated with DM in our study.

Strength and limitation

Our study is an ambidirectional cohort study that combined retrospective and prospective data collection. The time since IFG diagnosis was used to estimate progression rate to DM instead of the time since enrollment. Thus, the follow-up time of our study is long enough to represent the natural history of IFG in the real-world setting. Moreover, since some variables (ie, BMI, SBP, DBP, serum uric acid, triglyceride, LDL-C, HDL-C) were measured more than once, our study considered all values of these variables and treated them as time-varying covariates in the analysis. This method is more accurate than considering only baseline value to estimate the risk of DM. However, our study has limitations. First, this study is a hospital-based cohort where study participants might have higher cardiometabolic risk than the general population. In addition, the proportion of female participants and per cent of current and past alcohol drinkers were high in our study, Therefore, the representativeness

of our study for Thai population might be questionable. Second, our study used some data, such as blood pressures and laboratory data from routine clinical practice. Thus, numbers of measurements and duration between each visit varied among participants. Third, about 68.9% of patients had missing HbA1c value at baseline, therefore, HbA1c measurements within 2 years after diagnosis of IFG were used along with applying multiple imputations to predict these missing HbA1c values and other missing covariables. Although imputation models were robust, effect size of HbA1c and the other prognostic factors might be still questionable. Finally, OGTT was not performed. Therefore, the progression rate of DM in patients with IGT could not be estimated. However, OGTT is generally not performed in a routine clinical practice due to its low reproducibility, high cost, and prolonged time required for the test.

Clinical implications

The data from the previous evidence showed that pre-diabetes is not only related to an increased risk of DM but also related to microvascular and macrovascular complications. However, not all people with pre-diabetes will progress to DM.[6] Therefore, the diabetes prevention strategies should focus on individuals with high risk of progression to DM in order to maximize the benefit from targeted prevention. The result of our study suggested that using HbA1c in combination with FPG in clinical practice could identify subgroups of people with IFG who were at highest risk of progressing to DM. However, HbA1c test may not be routinely performed, especially in low-resource settings, due to its high cost and requirement of test standardization. Thus, further research is needed to determine whether the use of combination of FPG and HbA1c for pre-diabetes diagnosis is cost-effective in terms of prevention of DM and its complications.

CONCLUSION

Patients with combined IFG and abnormal HbA1c had the highest risk of DM. Using HbA1c in combination with FPG could identify subgroups of people with IFG at highest risk of progression to DM. Therefore, in settings with limited resources, people with combined IFG and abnormal HbA1c should have the highest priority in diabetes prevention programs.

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Contributors ST, TA, SRe, and AT designed the study and developed the methodology. ST, TA, and KS recruited participants and collected the data. NU and SRa performed data management. SRa and AT analyzed the data. ST, TA, and KS wrote the manuscript and interpreted the results. TA, SRe, and AT reviewed the analysis, interpretations and manuscript and did the final review. ST, TA, KS, NU, SRa, SRe, and AT critically reviewed the manuscript. TA is the guarantor of this work and, as such, had access to all data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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