Progression from optimal blood glucose and pre-diabetes to type 2 diabetes in a high risk population with or without hypertension in Isfahan, Iran

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ABSTRACT

Aim: To estimate the progression rates from normal glucose tolerance (NGT), isolated impaired glucose tolerance (IGT), isolated impaired fasting glucose (IFG) and combined IFG/IGT to type 2 diabetes (T2D) in a high risk population with and without hypertension (HTN) in Isfahan, Iran.

Methods: During a mean (SD) follow-up period of 6.8 (1.7) years, 1489 non-diabetic first-degree relatives of patients with T2D with or without HTN were followed for the occurrence of T2D. At baseline and through follow-ups, participants underwent a standard 75 g 2-h oral glucose tolerance test. Blood pressure was measured by standardised protocols and HTN was defined according to the criteria of the JNC7.

Results: The progression rate (95% confidence interval) from NGT, isolated IFG, isolated IGT, and combined IFG/IGT to T2D was 10.0 (4.3, 19.6), 21.7 (9.5, 42.3), 28.2 (12.3, 54.7) and 64.7 (41.0, 96.4) per 1000 person-years in participants with HTN and 3.1 (1.5, 4.7), 16.3 (10.3, 24.2), 25.9 (17.0, 37.7) and 57.9 (46.1, 71.7) per 1000 person-years in participants without HTN based on 10,134 person-years of follow-up. Compared with individuals with NGT and without HTN, individuals with NGT and HTN, isolated IFG, isolated IGT, and combined IFG/IGT with or without HTN at baseline were more likely to progress to T2D. Compared with participants without HTN, individuals with concomitant HTN were not significantly more likely to progress to T2D.

Conclusions: Compared with individuals without HTN, the presence of NGT, isolated IFG, isolated IGT, and combined IFG/IGT with concomitant HTN was not associated with higher likelihood of progression to T2D in high-risk individuals in Iran.

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1.   Introduction

Compared to individuals with normal glucose tolerance (NGT), individuals with pre-diabetes are at substantial risk of developing type 2 diabetes (T2D) [1]. The role of hypertension (HTN) as a risk factor for diabetes remains unsettled. HTN appears to be increased risk of T2D in most [2,3] but not all studies [4].

Although there are not many supporting evidences on the progression rate from NGT or pre-diabetes to T2D in individuals with or without HTN [5,6], the role of concomitant HTN and pre-diabetes as a risk factor for progression to T2D remains unsettled. Francis et al. [6] reported that pre-diabetic patients with concomitant HTN were significantly more likely to progress to T2D. A recent study performed in Chinese subjects revealed that individuals with impaired fasting glucose (IFG) were more likely to develop T2D if they were hypertensive [5]. However, while these two studies [5,6] referred to co-morbid HTN as a predictor of progression to T2D, it is likely that genetic factors also influence HTN and T2D. HTN and T2D have similar risk factors such as adiposity that are determined by genetic and early environmental influences. First degree-relatives (FDR) of patients with T2D which have a genetic basis are at higher risk of developing glucose intolerance and T2D [7,8] and might be more appropriate for testing this hypothesis.

Studies also suggest that HTN and T2D run in families [9]. This may be due to shared environment and lifestyle or genetic. Information on the risk of progression from NGT and pre-diabetes to T2D in individuals with or without HTN in these high risk individuals is highly relevant as progression to T2D is preventable or delayed with lifestyle changes or pharmacological interventions [10–15].

The objective of this study therefore was to estimate the progression rates from NGT, isolated impaired glucose tolerance (IGT), isolated impaired fasting glucose (IFG) and combined IFG/IGT to T2D in a high risk Iranian population with or without HTN.

2.   Subjects and methods

2.1.   Data collection

This study was conducted within the framework of the Isfahan Diabetes Prevention Study (IDPS), an ongoing cohort in central Iran to assess the various potential risk factors for diabetes in subjects with family history of T2D (one of the main risk factors for diabetes). The study was established in 2003–2005 when 3370 (875 men and 2495 women) FDRs of a consecutive sample of patients with type 2 diabetes attending clinics in Isfahan Endocrine and Metabolism Research Center which is affiliated to Isfahan University of Medical Sciences, Iran, completed clinical and laboratory tests including standard 75 g 2-h oral glucose tolerance test (OGTT) and a questionnaire on their health status and on various potential risk factors for diabetes. Participants receive follow-up tests according to Standard of Medical Care in Diabetes [16] to update information on demographic, anthropometric, and

lifestyle factors and on newly diagnosed diabetes, IGT and IFG. Accordingly, if OGTT was normal at baseline; repeat testing was carried out at least at 3-year interval. Otherwise, repeat testing was carried out annually. The IDPS baseline methods have been described in detail elsewhere [17]. The participants included siblings and children of patients with T2D.

2.2.   Ascertainment of impaired glucose metabolism

Cases of NGT, isolated IGT, isolated IFG, combined IFG/IGT and diabetes were identified from baseline and follow-up OGTTs according to American Diabetes Association criteria [18]. Individuals who were not diabetic at baseline and who had at least one subsequent examination were included. Pregnant women and patients with type 1 diabetes were excluded. Among 3370 persons who participated at baseline, 308 subjects were excluded because of diagnosis of T2D at baseline and 1526 have no follow-up, and 67 with missing data leaving 1489 participants (361 men and 1128 women) with a mean (standard deviation [SD]) age 43.1 (6.5) (range 30–70) years for this longitudinal analysis, all of whom had at least one subsequent review during a mean (SD) follow-up period of 6.8 (1.7) (range 1–11) years. Attendees at the follow-up visit did not differ significantly from non-attendees regarding most baseline characteristics: age, height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR) and levels of HbA1c, cholesterol, low-density lipoprotein cholesterol (LDLC), triglyceride, systolic and diastolic blood pressure (BP) and obesity. However, non-attendees had slightly lower fasting plasma glucose (FPG) (94.7 mg/dl versus 95.7 mg/dl, $P < 0.05$), and plasma glucose (PG) at 30 min. (138.7 mg/dl versus 145.6 mg/dl, ($P < 0.001$), 60 min. (141.1 versus 151.0, $P < 0.001$) and 120 min. (111.2 mg/dl versus 120.6 mg/dl, $P < 0.001$), but higher levels of high-density lipoprotein cholesterol (HDLC) (46.4 mg/dl versus 45.0 mg/dl, $P < 0.05$).

2.3.   Procedures

Information on age, gender, body size, HbA1c, cholesterol, LDLC, HDLC, triglyceride and BP, family and personal medical history was collected at the baseline and through follow-ups. The same methodology was used for both the prevalence and incidence studies. Participants reported to clinics in the morning after an overnight fast. Subjects were asked to abstain from vigorous exercise in the evening before and in the morning of the investigations. Smokers were encouraged to abstain from smoking in the morning of the investigations. First on arrival at the clinic, the information given by the participants in the questionnaire on family history was verified. Then, with the subjects in light clothes and without shoes height, weight, waist, and HC were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, waist, and HC were measured to the nearest 0.5 cm with a measuring tape. Waist was measured midway between the lower rib margin and the iliac-crest at the end of a gentle expiration. HC was measured over the greater trochanters directly over the underwear. Resting BP was measured after subjects had been seated for 10 min by using a mercury column sphygmomanometer and

appropriately sized cuffs, using standard techniques. FPG was measured using the glucose oxidase method. Subjects with FPG <126 mg/dl underwent a standard OGTT (75 g glucose 2-h) at baseline and the follow-ups. Venous blood was sampled at fasting, 30, 60, and 120 min. after oral glucose administration. Plasma samples obtained after centrifuge were analyzed on the same day.

HbA1c (measured by ion-exchange chromatography), total cholesterol, triglyceride, HDLC, and LDLC (calculated by the Friedewald equation [19] provided total triglycerides did not exceed 400 mg/dl) were also assessed. All the blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method. Tenets of the Declaration of Helsinki were followed, Institutional Ethical Committee approval was granted, and an informed consent form was signed by each participant.

2.4. Definitions

We calculated BMI as the ratio of weight (kg) to squared height (m^2), the latter being assessed at baseline only. Those participants with FPG $\geq$ 200 mg/dl or pharmacological treatment were considered as diabetic. If FPG was $\geq$126 and <200 mg/dl, a second FPG was measured on another day. If the second FPG was also $\geq$126 mg/dl, participants were considered as diabetic. FPG $\geq$ 126 mg/dl or 2-h PG of $\geq$200 mg/dl defined diabetes mellitus [18]. Isolated IGT was defined as FPG <100 mg/dl, but with 2-h PG concentration 140–199 mg/dl. If FPG was in the range of 100–125 mg/dl with 2-h PG < 140 mg/dl, it was considered as Isolated IFG. If FPG was in the range of 100–125 mg/dl but with 2-h PG 140–199 mg/dl, it was considered as combined IFG/IGT. If the FPG was below 100 mg/dl and 2-h PG smaller than 140 mg/dl, it was considered a sign of NGT [20]. Cases of HTN was identified according to the criteria of the Seventh Report of the Joint National Committee (JNC7) on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [21] as systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg and/or the current use of antihypertensive medications.

2.5. Analysis

Progression rates were estimated as the number of cases of progression to T2D per 1000 person-years of follow-up beginning on the date of completion of the baseline examination in 2003–2005 and continuing until the diagnosis of T2D, the date of the last completed follow-up, death, or end of follow-up on December 31, 2011, whichever came first. Statistical methods used included the Student's t-test, chi-squared test, and survival analysis with the Cox proportional hazards model and product-limit (Kaplan–Meier) estimates to assess time-dependent variables, in order to obtain hazard ratios (HR) with 95% confidence intervals (CI) and P values. The time to onset of T2D was analyzed for NGT, isolated IFG, isolated IGT, and combined IFG/IGT with or without HTN using Kaplan–Meier method of survival analysis. Survival curves were compared with the log-rank test. Cox proportional hazards model was used to identify risk factors affecting progression to T2D. We considered the following covariates in

the multivariate-adjusted analyses: age, gender, BMI, triglyceride, and total cholesterol. Variables age, BMI, triglyceride, and total cholesterol were entered in models as continuous variables, while gender was categorical. Variables that were significant at 10% in univariate analyses were entered in Cox proportional hazards model. Age-adjusted means were calculated and compared using general linear models. Analysis was performed using software SPSS version 21 for windows$^{\copyright}$ (SPSS IBM, New York, USA). All tests for statistical significance were two-tailed, and performed assuming a type I error probability of <0.05.

3. Results

3.1. Characteristics

Baseline characteristics of the 1212 (81.9%) participants without and 267 (18.1%) with HTN are shown in Table 1. As expected, those who had HTN were older and had higher age-adjusted mean BMI, WC, HC, WHR, FPG, and PG at 30, 60 and 120 min, higher HbA1c, triglyceride, cholesterol, LDLC, systolic and diastolic BP and lower HDLC at baseline and a higher proportion of obesity. The mean (SD) age was 45.1 (6.4) years for those with and 42.7 (6.5) years for those without HTN. The incidence of T2D in HTN group was higher than that of non-HTN group (25.6/1000 person-years [95% CI: 18.9, 34.0] vs. 16.9/1000 person-years [95% CI: 14.1, 19.7]).

Baseline characteristics of the 760 (49.7%) participants with NGT, 198 (12.9%) with isolated IGT, 304 (19.9%) with isolated IFG, and 268 (17.5%) with combined IFG/IGT are shown in Table 2. In comparisons of variables at baseline, all variables except HDLC were more likely to increase in isolated IGT, isolated IFG, or combined IFG/IGT than NGT. The mean (SD) age was 42.9 (6.9) years for those with isolated IGT, 44.4 (6.7) years for those with isolated IFG, 44.1 (6.6) years for those with combined IFG/IGT and 42.2 (6.2) years for those with NGT.

Baseline characteristics of the 187 (12.6%) participants who did and 1302 (78.4%) who did not progress to T2D are shown in Table 3. As expected, participants who progressed to T2D were older and had higher age-adjusted mean weight, BMI, WC, HC, follow-up duration, FPG, and PG at 30, 60 and 120 min, higher HbA1c, triglyceride, and cholesterol at baseline and a higher proportion of obesity, hypertension, combined IFG/IGT with or without HTN and lower NGT with or without HTN at baseline. Among participants who progressed to T2D, 24.6% had HTN, while 17.1% of participants who did not progress to T2D had HTN.

3.2. Progression to T2D

The progression rates from NGT, isolated IGT, isolated IFG, or combined IFG/IGT to T2D by HTN status are presented in Table 4. Among 1489 participants, 42.1% had NGT without HTN and 7.5% had HTN; 15.4% had isolated IFG without HTN and 4.1% had HTN; and 10.1% had isolated IGT without HTN and 3.0% had HTN; and 14.4% had combined IFG/IGT without HTN and 3.5% had HTN. During 10,134 (2437 men and 7697 women) person-years of follow-up, 187 (12.6%) (38 men and 149 women) incident cases of T2D occurred. The overall progression rate to

Table 1 – Age, age-adjusted mean (SE) and proportion characteristics[†] of first-degree relatives of patients with type 2 diabetes by hypertension status in the Isfahan Diabetes Prevention Study.

Baseline characteristic	With HTN (n = 267)	Without HTN (n = 1212)	Difference (95% CI)
Age (year)	45.1 (0.40)	42.7 (0.19)	2.4 (1.5, 3.3)[***]
Height (cm)	160.1 (0.50)	159.3 (0.23)	0.8 (−0.5, 1.7)
Waist circumference (cm)	92.8 (0.55)	87.9 (0.26)	4.9 (4.1, 6.5)[***]
Hip circumference (cm)	109.7 (0.54)	107.1 (0.25)	2.6 (1.5, 3.8)[***]
Waist-to-hip ratio	0.85 (0.004)	0.82 (0.002)	0.03 (0.02, 0.04)[***]
Body mass index (kg/m^2)	30.5 (0.25)	28.5 (0.12)	2.0 (1.5, 2.5)[***]
Follow-up duration (year)	6.8 (0.11)	6.8 (0.05)	0.0 (−0.02, 0.02)
Fasting glucose baseline (mg/dl)	97.0 (0.74)	95.5 (0.34)	1.5 (0.7, 3.9)[*]
Plasma glucose 30 min (mg/dl)	149.0 (1.96)	144.8 (0.92)	4.2 (1.6, 10.2)[*]
Plasma glucose 60 min (mg/dl)	157.9 (2.67)	149.7 (1.25)	8.2 (5.0, 16.6)[**]
Plasma glucose 120 min (mg/dl)	122.9 (2.11)	120.5 (0.98)	2.4 (0.7, 3.9)[*]
HbA1c (%)	5.3 (0.05)	5.0 (0.02)	0.3 (0.2, 0.4)[***]
HbA1c (mmol/mol)	34 (2.2)	31 (2.2)	3 (2.7, 3.3)[***]
Cholesterol (mg/dl)	204.4 (2.52)	194.9 (1.16)	9.5 97.0, 18.0)[**]
LDL-cholesterol (mg/dl)	125.5 (2.27)	118.3 (1.03)	7.2 (3.9, 13.7)[*]
HDL-cholesterol (mg/dl)	42.8 (0.75)	45.5 (0.34)	−2.7 (−4.2, −1.0)[**]
Triglyceride (mg/dl)	192.8 (6.17)	161.2 (2.86)	31.6 (20.9, 47.5)[***]
Systolic BP (mm Hg)	137.1 (0.74)	110.4 (0.34)	26.7 (26.3, 29.7)[***]
Diastolic BP (mm Hg)	91.2 (0.56)	71.5 (0.26)	19.7 (18.9, 21.3)[***]
Men, no. (%)	79 (29.5)	281 (23.0)	6.5 (0.5, 12.4)[*]
Obesity (BMI ≥ 30), no. (%)	137 (51.1)	388 (32.0)	19.1 (12.5, 25.6)[***]
Developed type 2 diabetes, no. (%)	46 (17.2)	141 (11.5)	5.7 (0.8, 10.5)[***]

CI = confidence interval, HTN = hypertension. Due to missing data, total number of subjects with and without HTN = 1479.
[†] Age-adjusted means were calculated using general linear models. Data are express as mean (SE) or number (%). The difference in the mean or percentage of the variables between participants with and without hypertension.
[*] P < 0.05.
[**] P < 0.01.
[***] P < 0.001.

Table 2 – Age, age-adjusted mean (SE) and proportion characteristics[†] of first-degree relatives of patients with type 2 diabetes by glucose tolerance status in the Isfahan Diabetes Prevention Study.

Baseline characteristic	NGT (n = 760)	Isolated IGT (n = 198)	Isolated IFG (n = 304)	Combined IGT/IFG (n = 268)
Age (year)	42.2 (0.24)	42.9 (0.46)	44.4 (0.38)	44.1 (0.40)[***]
Height (cm)	159.9 (0.29)	157.6 (0.57)	161.2 (0.47)	157.6 (0.49)[***]
Waist circumference (cm)	87.7 (0.33)	88.9 (0.65)	90.2 (0.53)	90.6 (0.56)[***]
Hip circumference (cm)	107.1 (0.32)	107.3 (0.63)	107.9 (0.52)	109.0 (0.54)[*]
Waist-to-hip ratio	0.82 (0.002)	0.83 (0.005)	0.84 (0.004)	0.83 (0.004)[***]
Body mass index (kg/m^2)	28.4 (0.15)	29.0 (0.29)	29.2 (0.24)	30.0 (0.25)[***]
Fasting glucose baseline (mg/dl)	87.6 (0.26)	90.9 (0.52)	106.7 (0.42)	109.7 (0.44)[***]
Plasma glucose 30 min (mg/dl)	132.4 (1.04)	148.7 (2.00)	155.7 (1.67)	170.1 (1.77)[***]
Plasma glucose 60 min (mg/dl)	129.7 (1.28)	173.6 (2.48)	150.7 (2.07)	194.2 (2.16)[***]
Plasma glucose 120 min (mg/dl)	100.8 (0.73)	157.5 (1.42)	106.2 (1.17)	164.7 (1.22)[***]
HbA1c (%)	5.0 (0.03)	5.1 (0.06)	5.1 (0.05)	5.3 (0.05)[***]
HbA1c (mmol/mol)	31 (2.2)	32 (2.2)	32 (2.2)	34 (2.2)[***]
Cholesterol (mg/dl)	191.5 (1.46)	194.8 (2.86)	201.2 (2.32)	205.3 (2.46)[***]
LDL-cholesterol (mg/dl)	116.3 (1.30)	115.7 (2.56)	124.8 (2.08)	123.5 (2.19)[**]
HDL-cholesterol (mg/dl)	44.7 (0.44)	45.3 (0.86)	45.4 (0.70)	45.2 (0.73)
Triglyceride (mg/dl)	157.9 (3.63)	175.8 (7.12)	165.8 (5.75)	184.8 (6.07)[**]
Systolic BP (mm Hg)	113.9 (0.58)	116.0 (1.12)	117.3 (0.92)	116.3 (0.97)[**]
Diastolic BP (mm Hg)	73.9 (0.43)	76.1 (0.84)	76.6 (0.69)	75.8 (0.72)[*]
Men, no. (%)	194 (25.4)	31 (15.6)	107 (35.2)	43 (16.0)[***]
Obesity (BMI≥30), no. (%)	234 (31.0)	72 (36.5)	117 (38.9)	124 (46.4)[***]
Hypertension, no. (%)	111 (15.0)	44 (22.7)	61 (21.0)	52 (19.5)[*]
Developed type 2 diabetes, no. (%)	23 (3.0)	36 (18.1)	35 (11.5)	101 (37.7)[***]

NGT = normal glucose tolerance, IGT = impaired glucose tolerance, IFG = impaired fasting glucose.
[†] Age-adjusted means were calculated using general linear models. Data are express as mean (SE) or number (%). The difference in the mean or percentage of the variables between normal, isolated impaired glucose tolerance, isolated impaired fasting glucose, and both IGT & IFG.
[*] P < 0.05.
[**] P < 0.01.
[***] P < 0.001.

Variables	Progressed to T2D	Did not progress to T2D	Difference (95% CI)
	Mean (SE)	Mean (SE)	
Age (yr)	44.5 (0.47)	42.9 (0.18)	1.6 (0.61, 2.59)[**]
Height (cm)	158.5 (0.59)	159.6 (0.22)	−1.1 (−2.43, 0.03)
Weight (kg)	76.5 (0.84)	73.0 (0.32)	3.5 (0.86, 5.74)[***]
Body mass index (kg/m^2)	30.5 (0.30)	28.7 (0.11)	1.8 (0.93, 2.67)[***]
Waist circumference (cm)	91.8 (0.66)	88.4 (0.25)	3.4 (2.31, 5.09)[***]
Waist-to-hip ratio	0.83 (0.005)	0.82 (0.002)	0.01 (0.00, 0.03)
Hip circumferences (cm)	110.3 (0.63)	107.2 (0.24)	3.1 (1.67, 4.33)[***]
Follow-up duration (yr)	7.2 (0.12)	6.8 (0.05)	0.4 (0.05, 0.56)[**]
Systolic BP (mmHg)	116.7 (1.16)	115.0 (0.44)	1.7 (−0.56, 6.6)
Diastolic BP (mmHg)	76.2 (0.86)	74.9 (0.33)	1.3 (−0.04, 3.64)
Baseline fasting glucose (mg/dl)	105.6 (0.82)	94.2 (0.31)	11.4 (10.20, 13.60)[***]
Plasma glucose 30 min (mg/dl)	169.2 (2.27)	142.3 (0.84)	26.9 (23.10, 32.70)[***]
Plasma glucose 60 min (mg/dl)	194.5 (2.88)	144.5 (1.10)	50.0 (45.40, 57.60)[***]
Plasma glucose 120 min (mg/dl)	150.7 (2.31)	116.2 (0.88)	34.5 (30.30, 39.90)[***]
HbA1c (%)	5.5 (0.06)	5.0 (0.02)	0.5 (0.38, 0.62)[***]
HbA1c (mmol/mol)	37 (2.2)	31 (2.2)	6 (5.7, 6.3)[***]
Triglyceride (mg/dl)	193.5 (7.22)	162.7 (2.73)	30.8 (17.40, 47.80)[***]
Cholesterol (mg/dl)	205.4 (2.94)	195.0 (1.10)	10.4 (6.12, 18.70)[**]
HDL cholesterol (mg/dl)	45.1 (0.88)	45.0 (0.33)	0.1 (−1.73, 1.93)
LDL cholesterol (mg/dl)	123.8 (2.66)	118.5 (0.98)	5.3 (1.44, 12.80)
	%	%	
Men	21.0	24.9	−3.9 (−10.10, 2.30)
Overweight (BMI ≥25)	50.3	33.9	16.4 (8.82, 23.80)[***]
Hypertension	24.6	17.1	7.5 (1.05, 14.1)[*]
NGT without HTN	7.5	47.1	−39.6 (−44.20, −34.90)[***]
NGT with HTN	4.3	7.9	−3.6 (−6.88, −0.38)[***]
Isolated IGT without HTN	13.9	9.5	4.4 (−0.83, 9.59)
Isolated IGT with HTN	4.3	2.8	1.5 (−1.52, 4.55)
Isolated IFG without HTN	12.3	15.9	−3.6 (−8.71, 1.51)
Isolated IFG with HTN	4.3	4.1	0.2 (−2.89, 3.30)
Combined IFG/IGT without HTN	41.7	10.4	31.3 (24.00, 38.50)[***]
Combined IFG/IGT with HTN	11.8	2.3	9.5 (4.77, 14.10)[***]

CI = confidence interval.

[†] Age-adjusted means were calculated using general linear models. Differences in the mean or percentage values of variables between T2D and no T2D.

[*] P < 0.05.

[**] P < 0.01.

[***] P < 0.001.

diabetes was 18.5 (95% CI: 15.8, 21.1) per 1000 person-year. Progression rates to diabetes were slightly higher in women (19.4%, 95% CI: 16.3, 22.4 per year) than men (15.6%, 95% CI: 11.0, 21.3). This difference was not statistically significant. Of the 111 participant with NGT and HTN at baseline 8 (7.2%) subsequently progressed to T2D at a rate of 10.0 (95% CI 4.3, 19.6) per 1000 person-year. This was higher than the progression rates seen for those without HTN, 3.1 (95% CI 1.5, 4.7). Of the 44 participant with isolated IGT and HTN at baseline 8 (18.2%) subsequently progressed to T2D at a rate of 28.2 (95% CI 12.3, 54.7) per 1000 person-year. This was higher than the progression rates seen for those without HTN, 25.9 (95% CI: 17.0, 37.7). Of the 113 participant with IFG and HTN at baseline 30 (26.5%) subsequently progressed to T2D at a rate of 42.3 (95% CI 28.7, 59.9) per 1000 person-year. This was higher than the progression rates seen for those without HTN, 36.6 (95% CI: 30.0, 44.4). Progression to diabetes was 25.6 (95% CI 18.9, 34.0) per 1000 person-year in those with HTN at baseline. This was higher than the progression rates seen for those without HTN, 16.9 per 1000

person-year (95% CI: 14.1, 19.7). These differences were not statistically significant. As shown in Table 4, the progression to diabetes increased across the eight subject groups, from 3.1 per 1000 person-year in the NGT and no HTN group, to 64.7 per 1000 person-year in the combined IFG/IGT and HTN group. Compared with participants with NGT and without HTN, the risk of T2D was 9.4 times higher in those with isolated IFG and HTN at baseline (HR 9.4; 95% CI: 4.0, 22.5), 8.2 times higher in those with isolated IFG but without HTN (HR 8.2; 95% CI: 4.2, 16.0) and 9.9 times higher in those with isolated IGT and HTN (HR 9.9; 95% CI: 4.2, 23.7) in crude models. Controlling for age and gender did not appreciably alter the HR compared to the crude model (Table 4). Controlling for other time-dependent covariates attenuated the relationship between NGT, isolated IFG, isolated IGT and combined IFG/IGT with or without HTN and T2D compared to the model not adjusted.

When we re-analyzed the data, compared with participants with NGT and without HTN vs. NGT with HTN, isolated IFG without HTN vs. isolated IFG with HTN, isolated IGT without

Table 4 – Incidence rates and relative risks (95% CI) of type 2 diabetes by glucose tolerance and hypertension status, the Isfahan Diabetes Prevention Study, 2003–2011.

Variables	At risk no. (%)	Cases no. (%)	Person-year	Incidence/ 1000 person-year (95% CI)	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Age-, gender-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI)[†]
NGT without HTN	627 (42.1)	14 (7.5)	4578	3.1 (1.5, 4.7)	1.00	1.00	1.00	1.00
NGT with HTN	111 (7.5)	8 (4.2)	802	10.0 (4.3, 19.6)	3.0 (1.3, 7.2)[*]	2.9 (1.2, 6.9)[*]	2.9 (1.2, 7.0)[*]	2.4 (0.96, 6.1)
Isolated IFG without HTN	230 (15.4)	23 (12.3)	1409	16.3 (10.3, 24.4)	8.2 (4.2, 16.0)[***]	7.8 (4.0, 15.3)[***]	7.9 (4.0, 15.4)[***]	7.4 (3.7, 14.8)[***]
Isolated IFG with HTN	61 (4.1)	8 (4.3)	369	21.7 (9.5, 42.3)	9.4 (4.0, 22.5)[***]	8.6 (3.6, 20.6)[***]	8.6 (3.6, 20.5)[***]	7.6 (3.1, 18.7)[***]
Isolated IGT without HTN	150 (10.1)	26 (13.9)	1005	25.9 (17.0, 37.7)	10.0 (5.2, 19.1)[***]	9.9 (5.2, 19.0)[***]	9.9 (5.2, 18.9)[***]	9.4 (4.8, 18.6)[***]
Isolated IGT with HTN	44 (3.0)	8 (4.3)	284	28.2 (12.3, 54.7)	9.9 (4.2, 23.7)[***]	9.7 (4.1, 23.2)[***]	9.6 (4.0, 23.0)[***]	9.0 (3.7, 22.1)[***]
Combined IFG/IGT without HTN	214 (14.4)	78 (41.7)	1347	57.9 (46.1, 71.7)	26.7 (15.1, 47.2)[***]	26.2 (14.8, 46.3)[***]	26.0 (14.7, 46.1)[***]	22.5 (12.4, 41.0)[***]
Combined IFG/IGT with HTN	52 (3.5)	22 (11.8)	340	64.7 (41.0, 96.4)	24.5 (12.6, 478.0)[***]	22.9 (11.7, 44.9)[***]	22.7 (11.6, 44.6)[***]	19.5 (9.6, 39.7)[***]

CI = confidence interval, NGT = normal glucose tolerance, IFG = impaired fasting glucose, IFG = impaired glucose tolerance, HTN = hypertension, HR = hazard ratio.

[†] Hazard ratio (with 95% CI) calculated by Cox's proportional hazards model. Adjusted for age, gender, BMI, triglyceride, and total cholesterol.

[*] P < 0.05.

[**] P < 0.01.

[***] P < 0.001.

HTN vs. isolated IGT with HTN, and combined IFG/IGT without HTN vs. combined IFG/IGT with HTN the risk of T2D was not statistically significant in crude model. Controlling for age, gender, cholesterol, triglycerides, and BMI, did not appreciably alter the HR compared to the unadjusted model (Table 5).

Fig. 1 shows the Kaplan–Meier estimates of the probability of remaining free of T2D in subjects with NGT, isolated IFG, isolated IGT, and combined IFG/IGT with or without HTN within a mean (SD) 6.8 (1.7) year (median, 7; range, 1 to 11). At 5 years, 96.7% of participants with NGT but without HTN, 91.9% of participants with NGT and HTN, 77.0% of participants with isolated IFG but without HTN, 75.4% of participants with isolated IFG and HTN, 82.0% of participants with isolated IGT but without HTN and 77.3% of participants with isolated IGT and HTN, 78.5% of participants with combined IFG/IGT but without HTN and 78.8% of participants with combined IFG/IGT and HTN did not have T2D. At 7 years, 68.7% of those with NGT but without HTN, 65.8% of those with NGT and HTN, 47.8% of

those with isolated IFG but without HTN, 37.7% of those with isolated IFG and HTN, 61.3% of those with isolated IGT but without HTN and 50.0% of those with isolated IGT and HTN, 51.4% of participants with combined IFG/IGT but without HTN and 55.8% of participants with combined IFG/IGT and HTN did not have T2D. It can be seen that participants with NGT, isolated IFG, isolated IGT and HTN had slightly increased yearly probability of T2D, which was not significantly different compared with participants with NGT, isolated IFG, isolated IGT but without HTN (P > 0.05).

4. Discussion

In this cohort study, the level of plasma glucose at baseline was strongly associated with the development of T2D, which could be explained by progressive β-cell failure, which is required for deterioration in glucose homeostasis and

Table 5 – Hazard ratios (HR) (95% CI) of normal glucose tolerance (NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT) and combined IFG/IGT by hypertension status, The Isfahan Diabetes Prevention Study, 2003–2011.

Variables	Without hypertension	With hypertension			
		Crude HR (95% CI)	Age-adjusted HR (95% CI)	Age-, gender-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI)[†]
NGT	1.00	0.95 (0.78, 1.17)	0.94 (0.77, 1.15)	0.94 (0.76, 1.15)	0.92 (0.74, 1.13)
Isolated IFG	1.00	0.97 (0.73, 1.28)	0.92 (0.68, 1.22)	0.93 (0.69, 1.25)	1.14 (0.82, 1.58)
Isolated IGT	1.00	0.99 (0.71, 1.40)	0.98 (0.70, 1.38)	0.98 (0.70, 1.38)	1.04 (0.71, 1.51)
Combined IFG/IGT	1.00	0.86 (0.63, 1.16)	0.83 (0.61, 1.13)	0.83 (0.61, 1.13)	0.85 (0.62, 1.17)

Adjusted for age, gender, BMI, triglyceride, and total cholesterol.

CI = confidence interval.

[†] Hazard ratio (with 95% CI) calculated by Cox's proportional hazards model.
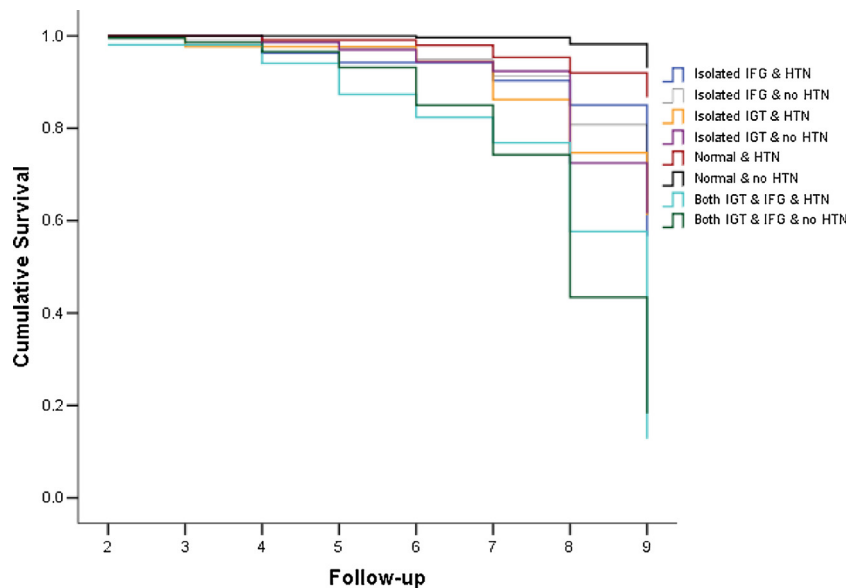
Fig. 1 – Kaplan–Meier survival curve showing progression rate to type 2 diabetes in individuals with normal glucose tolerance (NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), and both IFG & IGT with or without hypertension (HTN).

development of hyperglycemia [22]. In the present study, participants with NGT, isolated IFG, isolated IGT and combined IFG/IGT with concomitant HTN at baseline show higher likelihood of progression to T2D compared with participants with NGT, isolated IFG, isolated IGT and combined IFG/IGT but without HTN. This association was not statistically significant, possibly due to small number of participants' progressing to T2D. To the best of our knowledge, this is the first study to report on progression rates from NGT, isolated IFG, isolated IGT, or combined IFG/IGT with or without HTN in a high risk population without T2D in Iran. In contrast to the findings of two other studies, we showed concomitant HTN did not appear to be a more robust predictor of progression to T2D [5,6]. Estimates of progression to diabetes will depend upon the methodological factors, the definition of the isolated IFG, isolated IGT, and combined IFG/IGT and diabetes used, unknown time spent with isolated IFG, isolated IGT, and pre-diabetes, sample size, and the composition of the community examined by age and gender, making comparisons between studies of limited values. Fu et al. [5] reported that IFG predicted the development of T2D with an incidence rate of 0.047 in hypertensive individuals and 0.031 in non-hypertensive individuals in a Hong Kong Chinese primary care setting. In a large national managed care claims database, Francis et al. [6] examined the healthcare utilization and cost burden of patients with pre-diabetes, with and without co-morbid HTN, who progressed to T2D. The presence of concomitant HTN was strongly associated with progression from pre-diabetes to T2D. Another study found that IFG patients with concomitant HTN were more likely to progress to T2D [23].

All studies [24–29], as well as our study, agreed that the risk of developing diabetes was higher in individuals with either IFG or IGT as compared with individuals with NGT. Most of these studies agreed with us that IGT defined a larger number

of people who are at risk of developing diabetes than IFG [25–29]. Isolated IFG, Isolated IGT and combined IFG/IGT have a heterogeneous pathogenesis, and this may contribute to different rates of progression to diabetes.

The risk of diabetes was amplified in the presence of HTN in participants with NGT, isolated IFG, isolated IGT, and combined IFG/IGT. The participants who had HTN and NGT were at higher risk of diabetes than individuals without HTN. This suggests that blood pressure make a significant contribution to the subsequent development of diabetes.

The strengths of present study include the prospective cohort design, the sample consisting of both men and women of a wide age range, diagnosis of diabetes based on standard OGTT, information on potential determinants of diabetes, and long-term follow-up. Selection and information bias is considered unlikely by virtue of the prospective design. Our study was addressed to individuals at increased risk of developing T2D, because they had FDRs with the disease. The multiple examinations with OGTTs make the progression rates very accurate. Furthermore, those at greatest diabetes risk may have been tested more frequently, therefore increasing the likelihood of detection, causing an overestimation of progression rates. At follow-up, non-attendees of the entire population did not differ from attendees by major risk factors for progression, although a difference too small to explain the high progression rates in our study was seen in the mean levels of HDL and PG. However, our experience with other parts of the data set gives us some confidence that data quality is sufficient for this type of study. The relatively small sample size and the number of participants progressing to T2D in this study is a potential limitation. The present results clearly need to be replicated and extended across multiple centers and investigators. Despite the above limitations, the findings here add to our understanding of the progression rate from NGT, isolated IGT, isolated IFG and combined IFG/IGT to

T2D in FDRs of people with T2D with or without HTN in Iran. Furthermore, this study provides new data from Iran, a developing country that has been underrepresented in past studies.

In conclusion, the findings of this study illustrate for the first time the presence of concomitant HTN with NGT, isolated IFG, isolated IGT, and combined IFG/IGT at baseline was not associated with higher progression to T2D in a high risk population in Iran.

Conflict of interest statement

None.

Authors contributions

Janghorbani M conceived and designed the study, analyzed the data and wrote the manuscript, Amini M, recruited samples and contributed to the discussion and revision of the manuscript and obtained funding for the IDPS.

Acknowledgments

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