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PREDICTORS OF INCIDENT TYPE 2 DIABETES MELLITUS IN RURAL SINDH POPULATION WITH NORMAL FASTING GLUCOSE LEVEL

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Abstract:

Background: *Little is known about the natural course of normal fasting glucose (NFG) in Asians and the risk factors for future diabetes.*

Methods: *A total of 370 people from OPD of LUMHS Hyderbad/Jamshoro (163 men, 207 women) with NFG levels and no history of diabetes, aged 34 to 71 year, were enrolled. Oral glucose tolerance tests were performed at baseline, 1 year, 1.5 year and 2 years after enrollment.*

Results: *During 2 years of follow-up, 16.1% of participants met criteria for diabetes diagnosis, and 39.6% of subjects still had NFG levels at the time of diabetes diagnosis. During 2 year of follow-up, age (odds ratio [OR], 1.05; 95% confidence interval [CI],*

1.01 to 1.10; P=0.026) and family history of diabetes (OR, 3.24; 95% CI, 1.42 to 7.40; P=0.005) were independently associated with future diabetes diagnosis; however, fasting glucose level was not an independent predictor. During 2 years of follow-up, family history of diabetes (OR, 2.76; 95% CI, 1.37 to 5.54; P =0.004), fasting insulin level (OR, 1.01; 95% CI, 1.00 to 1.02; P=0.037), and fasting glucose level (OR, 3.69; 95% CI, 1.13 to 12.01; P=0.030) were associated with diabetes diagnosis independent of conventional risk factors for diabetes.

Conclusion: *A substantial number of subjects with NFG at baseline still remained in the NFG range at the time of diabetes diagnosis. A family history of diabetes and fasting insulin and glucose levels were associated with diabetes diagnosis during 2 years of follow-up; however, fasting glucose level was not associated with diabetes risk within the relatively short-term follow-up period of 1.1 year in subjects with NFG.*

Keywords: *Blood glucose; Diabetes mellitus, type 2; Epidemiology; Fasting; Glucose tolerance test.*

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INTRODUCTION:

The upper limit value for normal fasting glucose (NFG) has been redefined twice over the past 20 years by the American Diabetes Association. In 1997, it was set at 6.1 mmol/L, with values above but below the diabetes threshold defined as impaired fasting glucose (IFG). In 2003, the upper limit value for NFG was lowered from 6.1 to 5.6 mmol/L [1]. Following this revision, people with fasting plasma glucose (FPG) levels of 5.6 to 6.0 mmol/L have been additionally included as having IFG; thereby, identifying more individuals who may be at increased risk of diabetes [2].

It has been suggested; however, that higher FPG levels with in the normoglycemic range are independently associated with an increased risk for type 2 diabetes mellitus (T2DM), and the annual incidence of diabetes has been reported to be approximately 0.3% to 0.6% [3-5]. For example, in a study performed with 13,163 young Israeli men with NFG, the risk for T2DM increased progressively within the normoglycemic range during a mean follow-up period of 5.7 years. In addition, although the absolute risk of diabetes is very low, measurement of either the body mass index (BMI) or triglyceride levels along with FPG levels helped to identify apparently healthy men with NFG who were at increased risk for T2DM [3].

However, it has been suggested that fasting and postchallenge hyperglycemia may be phenotypes with distinct natural histories in the development of T2DM [6]. In addition, impaired glucose tolerance (IGT) is a more common form of prediabetes than isolated IFG in Asians compared to Europeans [7,8]; thus, not measuring the 2-hour post load glucose (2PG) during an oral glucose tolerance test (OGTT) will therefore underestimate the prevalence of diabetes in Asians [9,10].

Therefore, the aims of this study were to determine (1) how many individuals with NFG already have abnormal glucose tolerance by OGTT, (2) how frequently individuals who have NFG develop T2DM, and (3) which demographic, lifestyle, clinical, and metabolic variables predict future diabetes diagnosis in rural population of Sindh with NFG at baseline.

METHODS:

Study subjects:

The study received approval from the Liaquat University of Medical and health Sciences , Jamhsoro and written informed consent was obtained from all subjects. The study population consisted of general population coming to OPD Among the total of 658 subjects in the original cohort, 126 subjects were excluded for having a history of diabetes at baseline, and then 162 subjects with FPG ≥5.6 mmol/L were further excluded. Finally, a total of 370 subjects (163 men, 207 women) with NFG levels, aged 34 to 71 year, were enrolled in this study. Among these 370 subjects, seven had 2Plasma Glucose levels ≥11.1 mmol/L during the baseline OGTT; however, since we were interested in the subsequent OGTT category of all individuals who would have been diagnosed as normal based solely upon a FPG measurement, they were included in the analysis of the occurrence of a future diabetes diagnosis. Subjects were followed up at 1, 1.5 and 2 years respectively, after the baseline examination.

Clinical and laboratory examination:

BMI was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level of the umbilicus. Blood pressure was measured with a mercury sphygmomanometer to the nearest 2 mm Hg with the subject in a recumbent position. Systolic blood pressure was determined by the first perception of sound, and diastolic blood pressure was determined at the disappearance of sounds (fifth-phase Korotkoff). Average blood pressure was calculated from the second and third of three consecutive measurements.

Biochemical measurements were performed on fresh samples at the time of sample collection as reported previously [14]. All blood samples were obtained following an overnight fast of 10 hours. Plasma glucose was measured by the automated analyser hitachi (Diagnostic and research laboratory, LUMHS) Plasma insulin was measured by a serum insulin elsia kit biotech assay. The insulinogenic index, a marker of early-phase insulin secretion, was calculated as the ratio of the increment in insulin to the increment in glucose above fasting during the first 30 minutes of the OGTT [15]. Lipid and lipoprotein measurements were performed by hitachi roche automated analyser.

In this study, T2DM was defined by the presence of one of the following: (1) fasting glucose level ≥7.0 mmol/L; (2) treatment involving oral hypoglycemic agents or insulin therapy; or (3) 2PG ≥11.1 mmol/L [16]. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or taking antihypertensive medications. The presence of cardiovascular disease was diagnosed by a clinical history of one of the following: (1) coronary artery disease (acute myocardial infarction, angina, coronary artery bypass graft, or coronary angioplasty); (2) cerebrovascular disease (transient ischemic attack, carotid endarterectomy, atherosclerotic stroke, or nonatherosclerotic stroke); (3) peripheral artery occlusive disease (claudication or bypass surgery in

lower extremities); or (4) abdominal, thoracic, or other type of aortic aneurysm.

Statistical analyses:
Data are expressed as mean±standard deviation for continuous measures or as proportions for categorical variables, except for skewed continuous variables, which are presented as the median (interquartile range). A variance inflation factor >3.0 was used as an indicator of multicollinearity. Multiple logistic regression analysis was used to identify independent associations of clinical and biochemical variables with future diabetes risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the independent variables included in the logistic models, with a 1-SD increment used for OR calculations for continuous measurements. The presence of interaction was assessed in multivariate models through evaluation of the significance of first-order interaction terms. The presence of nonlinearity was assessed via insertion of the quadratic transformation of FPG into models that contained the linear term. All statistical analyses were performed with SPSS version 22.0, Chicago, IL, USA). A $P<0.05$ was considered significant.

RESULTS:
Tables 1 and 2 depict the baseline characteristics of the study subjects. The mean age was 50.0 years and 55.9% of the subjects were women. Approximately one-third of the study subjects had a family history of diabetes. In terms of personal history, 15.7% and 12.4% of the subjects were moderate alcohol drinkers and current smokers, respectively, and 24.1% of the subjects performed regular physical activity at a more than

Table 1. Baseline characteristics

Variable	Value
Age, yr	50.0±12.0
Female sex	55.9 (207)
Family history of diabetes	34.3 (127)
Current smoking	12.4 (46)
Alcohol consumption	
Moderate consumption	15.7 (58)
Non-moderate consumption	84.3 (312)
Regular physical activity	24.1 (89)
Cardiovascular disease	3.5 (13)
Hypertension	26.5 (98)
Body mass index, kg/m^2	23.6±3.2
Waist circumference, cm	80.1±10.2
Systolic blood pressure, mm Hg	125.6±16.7
Diastolic blood pressure, mm Hg	75.2±9.5
Fasting plasma glucose, mmol/L	4.94 (4.66–5.22)
2-Hour postload glucose, mmol/L	7.01±1.75
Fasting insulin, pmol/L	76.4 (62.5–104.2)
Insulinogenic index	0.94 (0.60–1.56)
Total cholesterol, mmol/L	5.72±1.01
Triglycerides, mmol/L	1.13 (0.80–1.65)
HDL-C, mmol/L	1.57±0.44
LDL-C, mmol/L	3.53±0.90
Non-HDL-C, mmol/L	4.15±1.07

Values are presented as mean±standard deviation, percentage (number), or median (interquartile range). Moderate alcohol consumption was defined as consuming 6 to 48 g of alcohol daily. HDLC, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 2. Baseline characteristics according to the development of diabetes

Characteristic	1 Years of follow-up			2 Years of follow-up		
	iabetes (–) (*n*=301)	iabetes (+) (*n*=33)	*P* value	iabetes (–) (*n*=260)	iabetes (+) (*n*=50)	*P* value
Age, yr	49.1±11.6	57.2±10.9	<0.001	49.0±11.5	54.9±12.0	0.001
Female sex	53.8 (162)	63.6 (21)	0.282	55.0 (143)	60.0 (30)	0.514
Family history of diabetes	30.2 (91)	63.6 (21)	<0.001	29.2 (76)	58.0 (29)	<0.001
Current smoking	13.3 (40)	15.2 (5)	0.766	11.9 (31)	16.0 (8)	0.426
Moderate alcohol consumption	17.3 (33)	3.0 (1)	0.041	16.2 (42)	4.0 (2)	0.025
Regular physical activity	24.9 (75)	9.1 (3)	0.050	23.8 (62)	8.0 (9)	0.370
Cardiovascular disease	2.3 (7)	15.2 (5)	<0.001	2.7 (7)	10.0 (5)	0.014
Hypertension	24.6 (74)	48.5 (16)	0.003	23.8 (62)	44.0 (22)	0.003
Body mass index, kg/m^2	23.6±3.1	24.5±3.6	0.104	23.5±3.1	24.5±3.4	0.057
Waist circumference, cm	80.0±10.3	82.8±10.7	0.150	79.6±10.3	82.9±10.2	0.042
Systolic blood pressure, mm Hg	124.5±15.5	136.9±20.3	<0.001	124.5±15.4	134.6±19.2	<0.001
Diastolic blood pressure, mm Hg	75.0±9.3	79.0±9.3	0.019	74.9±9.3	79.3±9.0	0.002
Fasting plasma glucose, mmol/L	4.94 (4.66–5.22)	5.11 (4.83–5.33)	0.032	4.94 (4.66–5.22)	5.16 (4.86–5.33)	0.001
2-Hour postload glucose, mmol/L	6.73±1.57	9.65±1.45	<0.001	7.00±1.58	9.02±1.57	<0.001
Fasting insulin, pmol/L	76.4 (62.5–104.2)	97.2 (62.5–145.8)	0.056	76.4 (60.8–97.2)	97.2 (62.5–145.8)	0.008
Insulinogenic index	0.96 (0.61–1.58)	0.62 (0.44–1.26)	0.013	0.96 (0.61–1.54)	0.65 (0.47–1.59)	0.078
Total cholesterol, mmol/L	5.66±1.00	6.10±1.11	0.019	5.67±0.97	6.08±1.04	0.008
Triglycerides, mmol/L	1.13 (0.80–1.65)	1.46 (1.01–2.23)	0.007	1.10 (0.79–1.63)	1.45 (1.05–1.99)	0.001
HDL-C, mmol/L	1.57±0.44	1.46±0.39	0.208	1.58±0.45	1.45±0.36	0.053
LDL-C, mmol/L	3.50±0.91	3.68±0.94	0.296	3.49±0.88	3.78±0.92	0.041
Non-HDL-C, mmol/L	4.10±1.05	4.63±1.18	0.006	4.09±1.03	4.63±1.12	0.001

Values are presented as mean±standard deviation, percentage (number), or median (interquartile range). Moderate alcohol consumption was defined as consuming 6 to 48 g of alcohol daily. HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol At baseline, the mean FPG and 2PG levels were 4.9 and 7.0 mmol/L, respectively.

Over 1 year of follow-up, the status of T2DM could be assessed in 334 subjects, among whom a total of 33 met criteria for diabetes, leading to a cumulative rate of 9.9%. Over 2 years of follow-up, the cumulative rate of diabetes was 16.1% (50/ 310). Of the subjects diagnosed with diabetes over 1 year, two subjects were excluded from the classification of diabetes subtypes because they were already taking glucose-lowering medication at the time of the OGTT. Of the remaining 31 subjects with diabetes diagnosed during 1 year of follow-up, 17 subjects (54.8%) still had NFG levels with an elevated 2PG (≥11.1mmol/L) at the time of diabetes diagnosis, while 10 subjects (32.3%) had IFG levels, and only four subjects (12.9%) were diagnosed with diabetes based on having FPG levels ≥7.0 mmol/L. Similarly, of the 48 subjects with diabetes diagnosed during 2 years of follow-up, 19 subjects (39.6%) had NFG at the time of diabetes diagnosis, 23 subjects (47.9%) had IFG levels, and only six subjects (12.5%) had FPG levels ≥7.0 mmol/L during 2 years of follow-up (Table 3).

Table 3. Number of diagnosed cases of diabetes by fasting plasma glucose and 2-hour postload glucose concentrations at 5 and 2 years follow-up assessments

Fasting plasma glucose, mmol/L	2-Hour postload glucose, mmol/L	During 1 years (*n*=31)	During 2 years (*n*=48)
<5.6	≥11.1	17 (54.8)	19 (39.6)
5.6–6.9	≥11.1	10 (32.3)	23 (47.9)
5.6–6.0		6 (19.4)	11 (22.9)
6.1–6.9		4 (12.9)	12 (25.0)
≥7.0	≥11.1	3 (9.7)	5 (10.4)
≥7.0	7.8–11.0	1 (3.2)	1 (2.1)
≥7.0	<7.8	0	0

Values are presented as number (%).

Table 4. Risk of diabetes diagnosis during 1 year of follow-up among participants with normal fasting glucose at baseline (<5.6 mmol/L)

Variable	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.06 (1.03–1.10)	<0.001	1.05 (1.01–1.10)	0.026
Female sex	1.50 (0.71–3.16)	0.285	1.95 (0.72–5.29)	0.191
Family history of diabetes	4.04 (1.91–8.56)	<0.001	3.24 (1.42–7.40)	0.005
Fasting plasma glucose	3.62 (1.20–10.86)	0.022	2.21 (0.56–8.82)	0.260
2-Hour postload glucose	3.27 (2.32–4.60)	<0.001		
Current smoking	1.17 (0.43–3.19)	0.766		
Moderate alcohol consumption	0.15 (0.02–1.12)	0.064		
Regular physical activity	0.30 (0.09–1.02)	0.053		
Hypertension	2.89 (1.39–6.00)	0.004	0.69 (0.22–2.22)	0.537
Cardiovascular disease	7.50 (2.23–25.19)	0.001	3.99 (0.92–17.29)	0.064
Body mass index	1.09 (0.98–1.22)	0.105		
Waist circumference	1.03 (0.99–1.06)	0.152		
Systolic blood pressure	1.04 (1.02–1.06)	<0.001	1.03 (0.99–1.07)	0.185
Diastolic blood pressure	1.05 (1.01–1.09)	0.021	0.99 (0.93–1.06)	0.770
Fasting insulin	1.01 (1.003–1.02)	0.003	1.01 (1.00–1.02)	0.064
Insulinogenic index	0.64 (0.38–1.08)	0.093		
Total cholesterol	1.48 (1.06–2.06)	0.021		
Triglycerides	1.41 (1.10–1.80)	0.007	1.29 (0.98–1.69)	0.070
HDL-C	0.56 (0.23–1.38)	0.208		
LDL-C	1.22 (0.84–1.79)	0.296		
Non-HDL-C	1.53 (1.12–2.08)	0.008	1.12 (0.75–1.68)	0.584

Moderate alcohol consumption was defined as consuming 6 to 48 g of alcohol daily. Blanks indicate variables not included in the multivariate model. OR, odds ratio; CI, confidence interval;; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 5. Risk of diabetes diagnosis during 2 years of follow-up among participants with normal fasting glucose at baseline (<5.6 mmol/L)

Variable	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.04 (1.02–1.07)	0.002	1.03 (0.99–1.07)	0.167
Female	1.23 (0.66–2.27)	0.515	1.44 (0.54–3.83)	0.467
Family history of diabetes	3.34 (1.80–6.23)	<0.001	2.76 (1.37–5.54)	0.004
Fasting plasma glucose	5.42 (2.09–14.08)	0.001	3.69 (1.13–12.01)	0.030
2-Hour postload glucose	2.41 (1.88–3.09)	<0.001		
Current smoking	1.41 (0.61–3.27)	0.428		
Moderate alcohol consumption	0.22 (0.05–0.92)	0.039	0.22 (0.04–1.35)	0.102
Regular physical activity	0.70 (0.32–1.52)	0.370		
Hypertension	2.51 (1.34–4.70)	0.004	0.71 (0.26–1.93)	0.500
Cardiovascular disease	4.02 (1.22–13.21)	0.022	1.92 (0.46–8.06)	0.373
Body mass index	1.09 (0.997–1.20)	0.059		
Waist circumference	1.03 (1.001–1.06)	0.044	0.99 (0.94–1.03)	0.552
Systolic blood pressure	1.03 (1.02–1.05)	<0.001	1.02 (0.99–1.06)	0.253
Diastolic blood pressure	1.05 (1.02–1.09)	0.003	1.01 (0.95–1.06)	0.850
Fasting insulin	1.01 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.037
Insulinogenic index	0.80 (0.57–1.13)	0.209		
Total cholesterol	1.50 (1.11–2.03)	0.009		
Triglycerides	1.35 (1.07–1.70)	0.012	1.23 (0.95–1.60)	0.114
HDL-C	0.47 (0.22–1.02)	0.055		
LDL-C	1.41 (1.01–1.97)	0.042		
Non-HDL-C	1.58 (1.20–2.09)	0.001	1.19 (0.82–1.71)	0.360

Moderate alcohol consumption was defined as consuming 6 to 48 g of alcohol daily. Blanks indicate variables not included in the multivariate model. OR, odds ratio; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

DISCUSSION:

In the current prospective study performed on Rural population of Sindh, men and women with NFG at baseline, 16.1% of subjects were diagnosed with T2DM during 2 years of follow-up. However, a substantial number of these subjects still showed NFG levels at the time of diagnosis of diabetes (54.8% during 1 year of follow-up and 39.6% during 2 years of follow-up). On the other hand, only 12.5% of the diabetes cases were diagnosed based on FPG levels ≥7.0 mmol/L. Age, family history of diabetes, and fasting insulin level were independently associated with future diagnosis of T2DM during 2 years of follow-up, but an independent association between FPG levels and diabetes diagnosis risk was not evident during the first 1 year of follow-up.

Previous studies performed in subjects with NFG have consistently demonstrated that higher FPG levels are associated with future diabetes risk even within the normoglycemic range, although the absolute risk of diabetes was relatively low, with an annual incidence of approximately 0.3% to 0.6% [3-5]. However, our results contradicted those of previous studies by demonstrating that FPG levels within the NFG range did not independently predict future diabetes diagnosis during a relative short-term follow-up period of up to 1 year, but were a significant predictor for diabetes upon long-term follow-up (2 years). We do not know the reason for this discrepancy, but may offer the following explanations. First, T2DM in Asians has been suggested to differ from that in Caucasians [17]. T2DM is characterized by both deterioration of insulin sensitivity and □-cell dysfunction [18]. In many non-

Asian individuals who have IGT, there is hyperinsulinemia to compensate for insulin resistance, but eventually insulin secretion becomes lower during the development of overt diabetes. Studies have shown that an inadequate insulin secretory capacity to compensate for insulin resistance is a key factor in the development of glucose intolerance in the Asians [19]. In addition, it was suggested that postchallenge hyperglycemia is more common in Asians than in Caucasians [22,23], and isolated IGT or an isolated high 2PG level of ≥11.1 mmol/L is closely related to defective early-phase insulin secretion, which is commonly seen in Asians, and is related to a lesser extent to insulin resistance [24]. Second, in previous studies [3-5] on this subject, non-Asian populations were evaluated, OGTTs were not performed, and only FPG levels and/or medical records were used to diagnose incident diabetes. Therefore, incident diabetes cases with high 2PG levels of ≥11.1 mmol/L could not be identified, so the incidence of diabetes was undoubtedly underestimated [3-5]. In support of our finding, the annual rate of diabetes was 1.6% during the 2 years of followup, while previous studies reported an annual incidence of approximately 0.3% to 0.6%.

Our study also has some limitations. First, the sample size was smaller than those of previous studies. Second, glycated hemoglobin levels were not available for the diagnosis of diabetes. Glycated hemoglobin level may be an early indicator of diabetes, especially for patients in whom an NFG level is available while OGTT is not, and thus the frequency of diabetes diagnosis might have been underestimated. Lastly, although it was an acceptably low level, 16.2% of subjects were lost to follow-up over the 2 years of the study period. This study also has several clinical implications. In clinical practice, physicians should not view NFG as a benign condition with low risk for future diabetes diagnosis and thus be complacent regarding patients who have NFG levels. This may be especially true for Asian patients. Moreover, FPG levels may have limited clinical relevance in the assessment of the risk of future diabetes diagnosis among subjects with NFG, at least within a short-term follow-up period. Instead, physicians should pay attention to age, degree of insulin resistance, and family history of diabetes when predicting future diabetes diagnosis in subjects with NFG levels. In addition, the value of the OGTT should not be underestimated as a way to detect diabetes earlier and thus provide an opportunity to institute measures to prevent diabetic complications in subjects with NFG.

CONCLUSION:

In summary, our results suggest that a substantial proportion of individuals in our population of Sindh with NFG progress to T2DM diagnosis over 2 years of follow-up. However, the actual level of FPG does not predict future diabetes diagnosis within a short-term follow-up period of 1 year. On the other hand, age, family history of diabetes, and fasting insulin level may be predictors of future diagnosis in subjects with NFG.

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