Original Article

The Indian Type 2 Diabetes Risk Score also Helps Identify those at Risk of Macrovasvular Disease and Neuropathy (CURES-77)

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Abstract

Aims : To see whether the diabetic individuals identified by the Indian Diabetes Risk Score (IDRS) also have a higher prevalence of diabetes related complications.

Methods: Type 2 diabetic subjects were selected from the Chennai Urban Rural Epidemiology Study in south India. Four field stereo retinal colour photography was done and diabetic retinopathy [DR] was classified according to Early Treatment Diabetic Retinopathy Study grading system. Coronary artery disease was diagnosed using Minnesota coding of 12-lead electrocardiograms. Diabetic peripheral neuropathy (DPN) was diagnosed if vibratory perception threshold [VPT] of the right great toe measured by biothesiometry was ≥20. The criterion for diagnosis of peripheral vascular disease (PVD) was an ankle-brachial index <0.9. Macroalbuminuria was diagnosed if urinary albumin excretion was ≥300 µg/mg creatinine. A total of 1476 individuals who had information on all test parameters were included for analysis.

Results: Subjects with IDRS score ≥60 had significantly higher prevalence of coronary artery disease (CAD) [9.2% vs 5.4%, p=0.043], DPN [29.2% vs 8.8%, p<0.001] and PVD [4.8% vs 1.9%, p=0.038] compared to subjects with IDRS score <60. However, the prevalence of DR and macroalbuminuria did not differ between the two IDRS subgroups. Age explained much of the observed differences in prevalence of CAD, PVD and DPN between the two IDRS subgroups.

Conclusions: This study further extends the clinical usefulness of IDRS to predicting diabetic complications like CAD, PVD and DPN as well.

Introduction

India has the largest number of type 2 diabetes mellitus (T2DM) cases in the world (40 million in 2007) and this is predicted to increase to 70 million by the year 2025.[1] Vascular complications of T2DM, such as visual impairment, limb amputations, end-stage renal disease (ESRD) and coronary artery disease are costly and devastating. Asian Indian diabetic subjects may be at greater lifetime risk for these complications due to the earlier onset of their disease.[2] Unfortunately nearly half of the individuals with diabetes in the community remain undiagnosed.

We have previously reported that a simple Indian Diabetes Risk Score (IDRS) developed by us can be a very cost-effective way to screen for type 2 diabetes mellitus (T2DM) in our population.[3] The IDRS is comprised of four simple clinical components namely age, family history of DM, waist circumference, and physical activity. We showed that an IDRS score ≥60 had a sensitivity of 72.5% and specificity of 60.1% for detecting undiagnosed T2DM in a population. Based on this, we proposed that individuals with an IDRS ≥60 could be screened in a population to make the screening program more cost effective.[3,4] However this means that 27.5% of the cases of T2DM in the community would be missed. We therefore wanted to compare the clinical profile of the diabetic individuals with an IDRS ≥60 to those with IDRS <60, with reference to the prevalence of diabetes related complications.

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Materials and Methods

The Chennai Urban Rural Epidemiology Study (CURES) is a large epidemiological study carried out in Chennai. The methodological details have been described in detail elsewhere[5] and the sampling frame is available at http://www.drmohansdiabetes.com/mdrf/CURES.pdf. In brief, CURES is a cross-sectional survey using a systematic random sampling of Chennai (formerly Madras) city in Southern India. Phase 1 of the study recruited 26,001 aged ≥20 years based on a representative sample of Chennai and various sub studies were performed in Phases 2 to 5. For this study, 1,169 known diabetic subjects (KD) and 307 newly diagnosed diabetic subjects (NDD) identified by oral glucose tolerance test from CURES were included. The institutional ethics committee approval was obtained for the study and informed consent was obtained from all study subjects.

Anthropometric measurements including weight, height, waist and hip measurements were obtained using standardized techniques according to the Anthropometric Standardization Reference Manual.[6] Blood pressure (BP) was recorded twice (5 minutes apart) in the sitting position in the right arm to the nearest 2 mm Hg with a mercury sphygmomanometer (Diamond Deluxe Industrial Electronic and Products, Electronic Co-op Estate, Pune, India) and the mean was taken as the final reading.

The IDRS was calculated in all subjects as detailed earlier[3,7] using the following scoring system. The IDRS was developed based on multiple logistic regression model using four simple parameters namely age, abdominal obesity, family history of diabetes and physical activity. The information for these risk factors was obtained based on four simple questions and one anthropometric measurement namely waist circumference. Subjects with an IDRS value of ≥60 was categorized as high risk

Table 1 : Baseline Characteristics of the Diabetic Participants by IDRS Category

Characteristic	IDRS category		
	IDRS <60 (n=261)	IDRS ≥60 (n=1215)	p value p* value
Age (years)	41.4 (0.7)	52.7 (0.3)	<0.001
Duration of DM (years)	3.4 (0.3)	4.9 (0.1)	<0.001 0.051
Body mass index (kg/m^2)	23.6 (0.2)	25.6 (0.1)	<0.001 <0.001
Waist circumference (cm)	84.5 (0.6)	91.3 (0.3)	<0.001 <0.001
Systolic blood pressure (mm Hg)	121.7 (1.3)	130.6 (0.6)	<0.001 0.044
Diastolic blood pressure (mm Hg)	76.0 (0.7)	77.8 (0.3)	0.022 0.022
Fasting blood glucose (mg/dL)	156.1 (4.1)	161.1 (2.0)	0.282 0.339
Total cholesterol (mg/dL)	192.0 (2.3)	202.1 (1.2)	<0.001 0.009
Triglycerides (mg/dL)	181.8 (8.3)	176.0 (3.5)	0.492 0.967
HDL-cholesterol (mg/dL)	39.5 (0.5)	42.3 (0.3)	<0.001 0.001
LDL-cholesterol (mg/dL)	119.7 (2.1)	126.5 (1.0)	0.005 0.078
Hemoglobin A1c (HbA1c) (%)	8.6 (0.15)	8.7 (0.06)	0.737 0.762

Data are presented as mean (SEM). p value is reported for student's t-test, while p* value is the significance of the beta coefficient for IDRS group in a multiple linear regression model of each continuous variable by age (continuous variable) and IDRS group (dichotomous variable). Abbreviations: T2DM (type 2 diabetes mellitus)

for diabetes.

Estimation of plasma glucose and serum lipids was done with a Hitachi 912 Autoanalyser (Hitachi, Germany) utilizing kits supplied by Boehringer Mannheim (Mannheim, Germany). HbA1c was estimated by high pressure liquid chromatography using the Variant machine (BIORAD, Hercules, California). Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.[8]

Urine samples were also collected after an overnight fast. Urinary albumin concentration was measured using an immunoturbidometric assay (Hitachi 902 autoanalyser, Roche Diagnostics, Mannheim, Germany).[9] Macroalbuminuria was diagnosed if the albumin excretion was ≥300 µg/mg of creatinine in the presence of retinopathy.

Four-field color retinal photography was performed by a trained photographer using a Zeiss FF 450 plus camera (Bangalore, India) with 35-mm color transparencies. Photographs were graded using the modified version of the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system.[10] The minimum criterion for diagnosis of DR was the presence of at least one definite microaneurysm in any field photographed. Briefly, level 10 represents no retinopathy, level ≥20 non-proliferative DR (NPDR) and level ≥ 60, proliferative DR (PDR).[10]

Neuropathy was assessed using Biothesiometer (Biomedical Instrument Co., Newbury,Ohio, USA). Vibratory perception threshold (VPT) of the great toes was measured in a standardized fashion by a single observer as reported earlier.[5,11] The mean value of three measurements of both legs was used for analysis. The mean +2 SD was used to derive the upper limit of normal for the non-diabetic study population aged 20-45 years, which was 19.7 V. Diabetic peripheral neuropathy [DPN] was diagnosed if the mean VPT was ≥ 20 V.

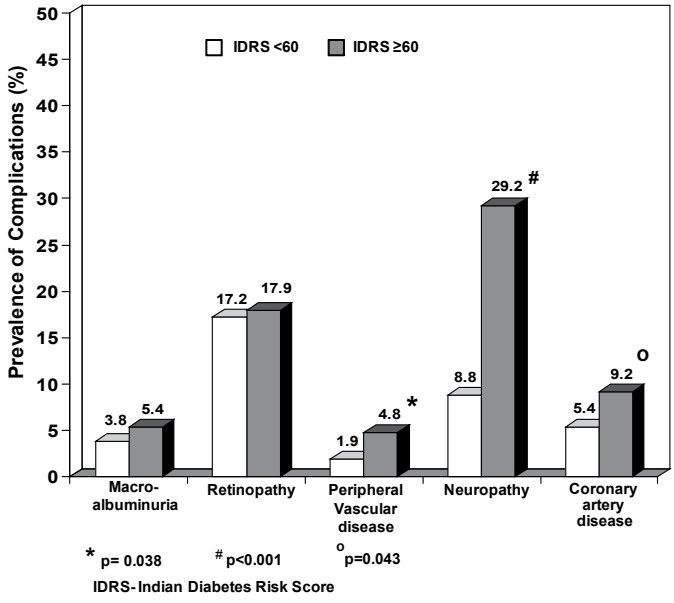

Fig. 1 : Prevalence of diabetic complications in type 2 diabetic subjects by IDRS subgroups

Coronary artery disease (CAD) was diagnosed based on positive medical history (documented myocardial infarction(MI), angina pectoris and coronary artery bypass graft) and/or ischemic changes on a conventional 12-lead ECG which included ST-segment depression (Minnesota codes 1-1-1 to 1-1-7) or Q-wave changes (Minnesota codes 4-1 to 4-2).[12,13]

Peripheral arterial doppler studies were performed by a single observer, which included recording of pressure tracings using the KODY Vaslab Machine (Kody Labs, Chennai, India). The ankle/brachial pressure index (ABI) ratio was calculated in every subject. PVD was defined as ABI <0.9.[14]

Statistical Analysis

Statistical analyses were performed with SPSS PC Windows version 10.0 (Chicago, Illinois, USA). We dichotomized diabetic subjects into two groups based on IDRS score ≥60 and <60. Means of continuous variables for each of the two IDRS groups were compared using the student's t-test. Multiple linear regression analysis was used to adjust these comparisons for age, and the p value reported for this comparison is the significance of the beta coefficient for the IDRS term in that analysis. Between-group complication prevalence rates were compared with Pearson χ^2 analysis. Univariate regression analysis was also done using diabetic complications as independant variables and IDRS subgroups as dependant variable. P values <0.05 were considered significant.

Results

A total of 1476 type 2 diabetic subjects, 1169 with known diabetes and 307 with newly detected diabetes participated in this study. Table 1 shows the characteristics of the study participants by their IDRS. Consistent with the inclusion of age and waist circumference in the calculation of the IDRS, the IDRS ≥60 group was significantly older, obese and had greater abdominal girth. They also had higher systolic and diastolic blood pressures (SBP and DBP), higher total cholesterol and LDL cholesterol levels. Adjustment for age eliminated the significance of the difference in some parameters between the two IDRS groups and BMI, waist circumference, systolic and diastolic blood pressures and total cholesterol still differed between groups.

Table 2: Prevalence of neuropathy, peripheral vascular disease and coronary artery disease by IDRS components among diabetic subjects

Components		Prevalence of complications		
		Neuropathy (%)	Peripheral vascular disease (%)	Coronary artery disease (%)
Family history of diabetes	**0** (n=910)	30.3	5.5	8.8
	1 (n=459)	19.0	1.7	7.6
	2 (n=107)	14.0	4.7	10.3
p value for trend		**<0.001**	**0.028**	0.947
waist circumference	**0** (n=429)	26.6	5.6	10.5
	1 (n=545)	26.2	2.8	8.4
	2 (n=502)	24.1	4.8	7.0
p value for trend		0.379	0.613	0.057
physical activity	**0** (n=70)	7.1	0	4.3
	1 (n=201)	20.9	3.5	6.5
	2 (n=1205)	27.5	4.6	9.1
p value for trend		**<0.001**	0.051	0.080
age	**0** (n=111)	0.9	0.9	0.0
	1 (n=539)	7.4	2.4	5.0
	2 (n=826)	40.8	5.9	12.0
p value for trend		< 0.001	<0.001	<0.001

Family history score corresponds to the number of parents with diabetes
Waist circumference, in men coded as 0 for <90 cm, 1 for 90-99 cm, and 2 for ≥100 cm. For females, waist circumference is coded as 0 for <80 cm, 1 for 80-89 cm, and 2 for ≥90 cm Physical activity is coded as 0 if the participant engaged in both leisure time physical activity and had a physically demanding occupation, 1 if he/she did just one of these, and 2 if he/she did neither
Age is coded as 0 for age<35 years, 1 for 35-49, and 2 for ≥50

Figure 1 shows the prevalence of five diabetic complications among the two IDRS subgroups. CAD [9.2% vs 5.4%, p=0.043], DPN [29.2% vs 8.8%, p<0.001] and PVD [4.8% vs 1.9%, p=0.038] were significantly higher among subjects in the high risk category [IDRS ≥60] compared to those with IDRS score <60. However there was no difference in prevalence of diabetic retinopathy or macroalbuminuria.

We further analyzed the association of CAD, PVD and DPN with respect to each component of the IDRS (Table 2). Age was the most significant factor associated with the increased prevalence of all these three complications. CAD was not present among diabetic subjects <35 years of age but its prevalence significantly increased in the other two age groups. Diabetic subjects aged ≥50 years, had a 2.5-fold increase in the prevalence of CAD and PVD and 5.5 fold increase in DPN compared to those aged 35-49 years. Family history of diabetes also showed a statistically significant association with DPN and PVD. A sedentary lifestyle was associated with a significantly greater prevalence of DPN and the most sedentary group had a 3.9-fold increase in prevalence of DPN compared to the most active group.

Logistic regression analysis was done using the IDRS subgroups as the dependent variable and diabetic complications as independent variables as shown in Table 3. The odds ratio [OR] for neuropathy was 4.27 (95% CI: 2.74–6.67, p<0.001), for PVD, 2.57 (95% CI: 1.02–6.46, p=0.045) and for CAD, 1.79 (95% CI: 1.01–3.18, p=0.046) in subjects with IDRS ≥60 category compared to those subjects with IDRS score <60. Neuropathy [OR: 4.03, 95% CI: 2.55–6.37, p<0.001) and PVD [OR: 2.54, 95% CI: 1.01–6.41, p=0.049] were associated with IDRS ≥60 category compared to those subjects with IDRS score <60, even after adjusting for duration of diabetes.

Table 3 : Regression analysis using IDRS ≥ 60 as dependent variable

Variables	Odds ratio	95% confidence interval	p value
Retinopathy			
Unadjusted	1.05	0.74 – 1.49	0.788
Adjusted for duration of DM	0.84	0.58 – 1.21	0.336
Neuropathy			
Unadjusted	4.27	2.74 – 6.67	**<0.001**
Adjusted for duration of DM	4.03	2.55 – 6.37	**<0.001**
Macroalbuminuria			
Unadjusted	1.44	0.73 – 2.84	0.291
Adjusted for duration of DM	1.26	0.64 – 2.50	0.508
Peripheral Vascular disease			
Unadjusted	2.57	1.02 – 6.46	**0.045**
Adjusted for duration of DM	2.54	1.01 – 6.41	**0.049**
Coronary artery disease			
Unadjusted	1.79	1.01 – 3.18	**0.046**
Adjusted for duration of DM	1.60	0.90 – 2.84	0.113

DM-Diabetes mellitus

Discussion

The important finding in this study is that among Asian Indian type 2 diabetic individuals, an IDRS ≥60 is associated with a higher risk of CAD, PVD and DPN but not of DR or macroalbuminuria. Much of the significant association with CAD, PVD and DPN is due to the inclusion of age in the IDRS.

It is not surprising that diabetic subjects with an IDRS ≥60 have a higher prevalence of CAD.[7] While age was the only component of the IDRS that was significantly associated with CAD, it is clear from Table 1 that even after age adjustment, the IDRS ≥60 was associated with several other CAD risk factors not included in the IDRS e.g. blood pressure and serum cholesterol. It therefore seems that a simple diabetes scoring system, composed of 3 questions and waist circumference measurement, acts as a good proxy for determining CAD risk among diabetic individuals even in the absence of biochemical analyses. This confirms our earlier study that IDRS helps to identify those with metabolic syndrome and CAD.[7] These data also suggest that the cases of T2DM that the IDRS misses, are at a lower risk of CAD.

IDRS ≥60 was also significantly associated with an increased prevalence of DPN. In the analysis of this association by individual IDRS components, age was significantly associated with a greater risk of DPN. This is consistent with two of the known risk factors for DPN: age and duration of T2DM.[11,15-17]

Glycemic control is another known risk factor for DPN.[15] The two IDRS groups however did not significantly differ in the HbA1c levels. Admittedly having only a single baseline HbA1c value for each participant, does not represent their glycemic control over the entire duration of their disease. The association between sedentary lifestyle and increased prevalence of DPN could be confounded by decreased physical activity among older participants. It may also represent reverse causation; those with neuropathic pain, foot ulcers, and lower extremity infections may have limited mobility as a result of their neuropathy.

It is difficult to explain the apparent protective effect of family history of DM on the prevalence of DPN and PVD among diabetic individuals and this may well be a statistical artifact. Earlier diagnosis of T2DM through targeted screening with tools such as the IDRS could hasten the identification of DPN, since this complication is present at the time of diagnosis in many individuals.[18–20] We[21] and others[22] have earlier reported that PVD is less common among T2DM patients in India compared to more developed countries, probably due to the younger age at onset of T2DM[23] and lower smoking rates in our population.[24]

IDRS ≥60 does not identify T2DM individuals with a significantly greater prevalence of DR or macroalbuminuria. Poor glycemic control and duration of diabetes are the important risk factor for the development of the microvascular complications such as DR and macroalbuminuria.[25] As these do not feature in the IDRS component, IDRS is not useful to identify those at high risk of these complications.

We have reported that the IDRS can be a cost-effective method to screen the Asian Indians for T2DM. However using a cut-off of IDRS ≥60 would miss 27.5% of the prevalent cases of the T2DM. This study shows that the cases of T2DM missed by IDRS would have a lower prevalence of CAD, PVD and DPN. Thus, use of IDRS for targeted screening would not only detect 70% of all cases of undiagnosed T2DM but also pick up those who are likely to have or develop CAD, PVD and DPN.

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