Original Article

Opportunistic screening of at risk asymptomatic adolescent children for prediabetes

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) once considered an adult disease is now being reported in children and adolescents all over the world due to a parallel increase in obesity. Prediabetes is an intermediate stage between no diabetes and diagnosis of DM. **Objective:** To screen at risk asymptomatic adolescent children for prediabetes state. **Methods:** A prospective descriptive study was conducted in the outpatient department of a tertiary care hospital in South India. All adolescent children between the age group of 10 and 18 years with evidence of overweight as per the World Health Organization age and sex specific centile charts for body mass index (BMI) were enrolled. The study period was 18-month. Anthropometric and demographic data were collected among these subjects and investigated for oral glucose tolerance test (OGTT), fasting blood glucose (FBG), and glycosylated hemoglobin (HbA1c) as per the designed protocol. **Results:** Prediabetes was diagnosed in 13% of the study population with a combination of OGTT, FBG, and HbA1c tests. Prediction of prediabetes by OGTT was 10%, HbA1c 5% and by FBS was 3%. Combination of impaired glucose tolerance test with HbA1c had high sensitivity (92%) and specificity (100%). **Conclusions:** Our study had 13% population with increasing risk of developing T2DM. Further longitudinal studies are required to screen at risk asymptomatic adolescent children for prediabetes.

Key words: *Glycosylated hemoglobin, India, Obesity, Prediabetes*

Type 2 diabetes mellitus (T2DM) once considered an adult disease is now being reported in children and adolescents all over the world with the highest prevalence being in American Indian, Hispanics, African Americans, and Asian children. It is comparatively less in European country parts [1]. The incidence of T2DM in adolescent children is due to a parallel increase in overweight and obesity. This is due to change in dietary habits, decreased physical activity and sedentary behavior. India currently has 62 million people with T2DM and this is expected to exceed 100 million by 2030 [1]. Early detection of prediabetes in the adolescent age group and initiation of lifestyle changing interventions can result in reduction of full blown T2DM [1].

The term impaired glucose tolerance (IGT) represents a biochemical intermediate between normal glucose metabolism and that of diabetes; experience has shown that few children with IGT go on to acquire diabetes; estimates range from 0% to 10% [2]. Subjects with IGT do have a high risk of developing diabetes; although, not all do so. Some revert to normal glucose tolerance (NGT), and others continue to have IGT for many years. Subjects with IGT have a greater risk of developing arterial disease than the persons of similar age with NGT [3].

The International Expert Committee did not recommend the level of glycosylated hemoglobin (HbA1c) that could be used to diagnose states of intermediate hyperglycemia but recognized that levels of HbA1c just <6.5% may indicate increased risk of future diabetes. The committee recommended that people with an HbA1c between 6.0% and 6.5% were at a particularly high risk and could therefore be considered for a diabetes prevention intervention. Subsequently, the American Diabetes Association (ADA) has recommended that individuals with an HbA1c of 5.7-6.4% be considered at increased risk for diabetes and cardiovascular disease (CVD) and receive counseling to lower their risk [4].

The purpose of diagnosing prediabetes is to identify a segment of the population at increased risk for the development of both diabetes and CVD so that interventions (lifestyle modifications and pharmacological interventions) can be initiated. Diagnosis has traditionally been made by measuring blood glucose levels during either fasting blood glucose (FBG) or by oral glucose tolerance test (OGTT). Careful analysis of longitudinal data shows that impaired fasting glucose (IFG) and IGT are similar to each other in their ability to predict diabetes and CVD. However, because populations with IFG and IGT have limited overlap with each other, performing the OGTT to identify those with IGT provides the opportunity to identify a greater proportion of the at-risk population. Although various methods are available

to identify individuals at risk, their practical approach and the number of individuals identified by these methods also varies with the method used [5]. HbA1c estimation has also been recently recommended for diagnosis of prediabetes, and although it seems to predict the development of future diabetes, its use is not yet widely accepted [6]. This study intends to use HbA1c as diagnostic markers of prediabetes along with OGTT and FBG. We planned this study to screen at risk asymptomatic adolescent children for prediabetes with special reference to HbA1c.

METHODS

This prospective descriptive study was conducted at the outpatient department of a tertiary care teaching hospital of South India over a period of 18-month. Ethical clearance was obtained from Institutional Ethical Committee. Adolescent children of age group 10-18 years were selected from the children coming to OPD for other reasons using purposive sampling keeping in view the operational feasibility. Children who were overweight (body mass index [BMI] >85th percentile for age and sex, weight for height >85th percentile) satisfying the ADA criteria were included in this study [7]. Known diabetics, children on steroid/drug therapy that enhance glycemic status and children with syndromic features were excluded from the study.

All adolescent children meeting the ADA criteria were eligible for inclusion in the study. The participants were explained about the need for the study, procedures involved (blood investigations, anthropometry, and demographic data) and benefits from the study to the subjects and to the population in general. Informed consent/assent was taken from the children who were willing to participate in the study and recruited in the study.

Children were investigated on OPD basis with demographic data, and anthropometric measurements like Height and Weight were measured and BMI was calculated. BMI values were plotted in the World Health Organization growth charts to differentiate from overweight, and obese from normal [8]. All subjects underwent general and physical examination. Blood pressure (BP) was recorded thrice in each subject using manual sphygmomanometer at an interval of 10 min and mean BP was recorded. Clinical features such as acanthosis Nigricans, skin tag, buffalo hump, striae, and PCOD in females were also recorded.

After this, the participants were asked to come with 8 h fasting and normal 24 h diet previously. On arrival to OPD, blood samples were collected under aseptic precautions in 2 tubes for fasting blood sugar, HbA1c and OGTT. Followed by, the participants were given an anhydrous glucose solution of 1.75 g/kg up to maximum of 75 g diluted in 200 ml of water and were asked to consume over 5-10 min. 2 h later another sample of blood was collected for OGTT. The blood samples were produced to laboratory within 10 min of blood drawing. FBS measurement was taken by venous blood sampling, glucose levels were determined by glucose oxidase method. Fasting Insulin levels were assessed by chemiluminescent immunoassay. HbA1c was analyzed using

a Labona check™ HbA1c analysis, using a boronate affinity assay. Prediabetes was diagnosed in those individuals in whom HbA1c levels were between 5.7% and 6.4%, FBG between 100 and 125 mg/dl and OGTT values between 140 and 199 mg/dl. All the above data collection and blood sampling were carried out by two pediatric residents [9].

Descriptive statistics were reported using mean and SD for the continuous variables, number and percentages for categorical variables. The prevalence of prediabetes status was reported using proportions. Independent t-test was used to compare the anthropometric measures between prediabetes and normal groups. Chi-square test was used to find the association between the demographic variables with pre-diabetic status. $p < 5\%$ was considered as statistically significant. All the analysis was performed using SPSS version 21.0 software.

RESULTS

Out of 115 subjects enrolled in the study, 100 subjects completed the study (Fig. 1). Mean age of the study population was 13.7±1.7 years. The maximum number (59%) of subjects belonged to 13-15 years age group; and 55% of total subjects were females. Among these subjects, 82.2% had family history of T2DM. The mean BMI of the study population was 25.5±1.9. Out of these, 44 were overweight (mean BMI - 24.1±1.9) and 56 were obese (mean BMI - 28.3±2.1) according to age and sex specific BMI centile charts (Table 1).

Subjects diagnosed with prediabetes by all 3 parameters of HbA1c, OGTT and FBS were 13%. 2 of this prediabetes group had all 3 indicators to be positive and 2 had HbA1c and OGT to be positive. Prediabetes was diagnosed by HbA1c in 5% of the study population, among them 3 (6.7%) were males and 2 (3.6%) were females. The mean HbA1c level in the study population was
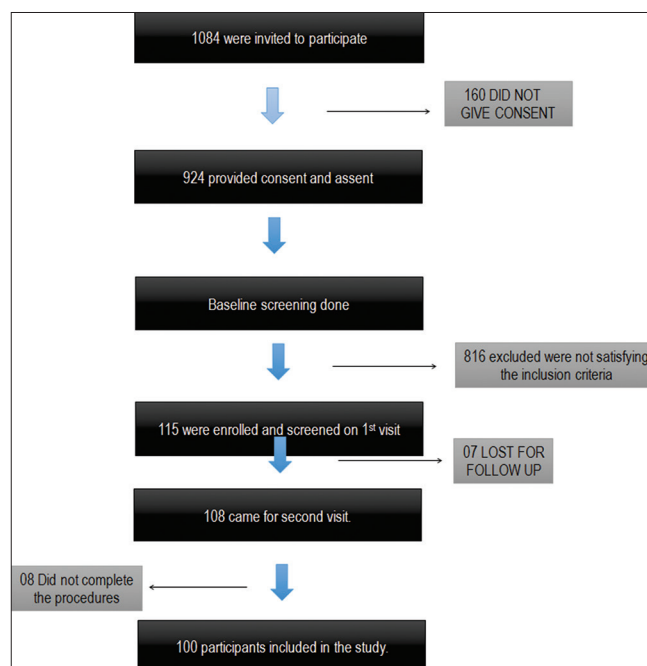
Figure 1: Cohort flow diagram recruitment and assessment of study population

4.95±0.54 as compared to 5.50±0.50 in the prediabetic group. In the FBS group, 3% were diagnosed to have prediabetes, and all 3 were male. The mean FBS level in the study population was 82.9±10.5 compared to 91.20±15.5 in the prediabetic group. Prediabetes by OGTT was diagnosed in 10% of the study population, among them 6 (13.3%) were diagnosed in males and 4 (7.3%) in females. The mean OGT level in the study population was 107.3±22.1 compared to 146.80±19.50 in prediabetic group. In the overweight category, prediabetes was diagnosed in 3 (6.8%) cases and in obese category and it was diagnosed in 10 (17.9%) cases.

The measure of comparison of diagnostic test with continuous variables was analyzed using partial correlation. Partial correlation of FBS with BMI was 0.35, OGT with BMI was 0.42 and HbA1c with BMI was 0.29. BMI had better correlation with OGT than the other two diagnostic tests.

Table 2 shows the sensitivity and specificity of the combination of tests in prediabetes children. In relation to sensitivity and specificity of combination of tests in predicting prediabetes, OGT with HbA1c combination had a highest sensitivity and specificity of 92% and 100%, respectively, with least sensitivity and specificity in FBS and Hba1c combination with 46% and 100%, respectively, and IGT with HbA1c was 85% and 100%. "p" value was significant in all three categories.

Table 1: Study characteristics in relation to prediabetes

Variables	Prediabetes	Normal glucose tolerance	p value
Age	14.00±1.50	13.7±1.70	Not significant
Sex (male/female)	7 (53.8)/6 (46.15)	37 (42.5)/50 (57.4)	Not significant
BMI	27.30±2.80	25.1±1.60	<0.001
Systolic blood pressure	120.0±14.2	113.9±12.1	Not significant
Diastolic blood pressure	80.6±6.0	76.3±7.5	0.05
Sexual maturity scoring	2.4±0.96	2.3±0.96	Not significant
Fasting blood sugars	91.20±15.50	81.5±9.20	<0.002
OGTT	146.80±19.50	101.60±15.60	<0.001
HbA1c	5.50±0.50	4.9±0.50	Not applicable

BMI: Body mass index, OGTT: Oral glucose tolerance test, HbA1c: Glycosylated hemoglobin

DISCUSSION

The mean BMI of the study population was 25.5±1.9, 24.1±1.9 in overweight group and 28.3±2.1 in obese children. Study conducted by Sinha et al. [10] to determine IGT among children and adolescent had a mean BMI of 30±1. In this study, the subjects were having morbid obesity. In another study, mean BMI of 31.29±5.89 [11]. Most of the studies in children and adolescent age group, obese children were considered. In our study, subjects consisted of both overweight and obese.

In our study, prediabetes increased from 6.8% in overweight to 17.9% in obese children. This indicates that increase in BMI is directly proportional to risk of prediabetes and diabetes. In our study, blood pressure was categorized according to age and sex specific centile charts. Systolic blood pressure among the prediabetes and NGT subjects was not significant. Diastole blood pressure had significant "p" value in comparison of prediabetes to NGT [12]. In our study, BMI >85th centile was cut off for inclusion. Most of the studies conducted on prediabetes are with BMI. Limited data are available for the study of prediabetes with other anthropometric measures.

Although adult studies have found that BMI, waist/height ratio and sagittal abdominal diameter are all powerful predictor of incident diabetes, much data is not available in pediatric population to correlate this anthropometry with prediabetes and diabetes. Diagnosis of prediabetes by HbA1c was 5%. In our study, the cutoff value of HbA1c was 5.7-6.4% based on ADA 2009 recommendations. Nowicka et al. [13] study, the prevalence of prediabetes using HbA1c alone was 21% with similar cutoff. These results were much higher than our study. The reason could be due to ethnicity, proper cutoff values for South East Asian population is not available. These cutoff were derived from European population.

Prediction of prediabetes by FBS diagnostic method was 3%. The mean may be low due to ethnicity as proper cutoff values for South East Asian population is not available. These cutoffs were derived from European population. In Narayanappa et al. [13], cross-sectional study conducted in Mysore, using FBS alone as the diagnostic of prediabetes between 5 and 10 years, the prevalence was 3.75% though our study population was between 10 and 18 years the prevalence was similar [13].

Prediction of prediabetes by OGT diagnostic measure yielded 10% in our study population with the prediction of prediabetes by OGT was highest compared to other two measures by FBS and HbA1c. In this study, the overall incidence of prediabetes

Table 2: Sensitivity and specificity of combination of tests in prediabetes

Combination	IFG+HbA1c+IGT	Present	Normal	p value	Specificity	Sensitivity
IFG+HbA1c	Abnormal	6 (46.15)	0 (0.00)	<0.001	100	46
	Normal	7 (53.85)	80 (100.00)			
IFG+IGT	Abnormal	11 (84.62)	0 (0.00)	<0.001	100	85
	Normal	2 (15.38)	80 (100.00)			
IGT+HbA1c	Abnormal	12 (92.31)	0 (0.00)	<0.001	100	92
	Normal	1 (7.69)	80 (100.00)			

IFG: Impaired fasting glucose, HbA1c: Glycosylated hemoglobin, IGT: Impaired glucose tolerance

by all three diagnostic measures was 13% among the adolescent overweight/obese children. In the study conducted by Sinha et al. [10] between the age group of 11 and 18 years, 21% of the population was prediabetes.

About 2 of these prediabetes children had all 3 indicators to be positive and 2 had HbA1c and OGT to be positive. Hence, we did a chi square test with confidence interval of 95% to determine the sensitivity and specificity of various combinations of tests. IFG with HbA1c combination had lower sensitivity in on the study. Further large population studies are required in South East Asian population to determine the cutoff values of HbA1c in the diagnosis of prediabetes and to be followed up in long duration, to know how many get converted to DM and duration required.

Patients who cannot fast overnight, walk in patients can be subjected to HbA1c and if found to be positive, can be subjected to lifestyle changes. If feasible all 3 tests should be offered for better prediction of prediabetes. However, this study had certain limitations. The sample size was smaller and requires further larger population-based studies for generalizability. This study was a cross-sectional study, and we did not follow these children to know whether they eventually developed diabetes or not.

CONCLUSION

Our study found that 13% of the study population consisting of both overweight and obese adolescents was prediabetes. Further longitudinal studies are required to screen at risk asymptomatic adolescent children for prediabetes; thereby, to delay the development of overt Type 2 diabetes and its complications. These at risk population should be targeted for lifestyle intervention and dietary modifications to prevent these converting into full blown diabetic sequel.

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