Original Article

A Cross-Sectional Multicentre Study to Validate Insulin Sensitivity Index Cut-Offs for Detection of Metabolic Syndrome in Indian Adolescents with Type-1 Diabetes

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Abstract

Background: A previous study compared insulin sensitivity indices for the detection of double diabetes (DD) in Indian adolescents with type-1 diabetes (T1D) and derived a cut-off to predict future risk for the development of metabolic syndrome (MS) in adolescents with T1D. We conducted the current study with the aim to validate these cut-offs for detecting DD among Indian subjects with T1D from various geographical locations. **Methods:** This multicentric cross-sectional study included 161 Indian adolescents with T1D. Demographic, anthropometric, clinical, and biochemical data were collected using standard protocols. Insulin sensitivity (IS) was calculated using various equations developed to determine insulin sensitivity in subjects with T1D. Metabolic syndrome was diagnosed using International Diabetes Federation (IDF) Consensus Definition 2017. **Results:** We report 4.3% prevalence of MS in Indian adolescents with T1D with an additional 29.8% of study participants at risk of development of MS. Low High density lipoprotein (HDL) (23.6%) was the commonest abnormal component of the MS definition. Insulin sensitivity calculated by an equation derived by the SEARCH group was the most appropriate index to identify MS and metabolic risk in Indian adolescents with T1D. The proposed cut-off of 5.48 had high specificity, positive predictive value, and negative predictive value in identifying the risk of the development of DD. **Conclusions:** Insulin sensitivity calculated by the equation proposed by the SEARCH group together with cut-offs derived in earlier study may be used effectively to identify risk of development of MS/DD in Indian adolescents with T1D from various geographical locations.

Keywords: India, insulin sensitivity index, multicentre, SEARCH, type-1 diabetes

Introduction

Type-1 diabetes (T1D) is one of the most common metabolic/endocrine disorders diagnosed in children.[1] The health burden of T1D, a disorder affecting approximately 229 thousand children and adolescents in India, is progressively increasing due to the prevalence of the associated macro and microvascular complications.[2-5] More recently, despite modern advances in technology and better glycaemic control, significant insulin resistance (IR) has been documented in adolescents and adults with T1D; IR may be attributed to increasing rates of obesity.[6] Some studies have demonstrated that higher estimated insulin sensitivity (IS) in adolescents with T1D is inversely associated with the risk of cardiovascular disease.[7]

The term "double diabetes" (DD) refers to those cases with T1D where the patient demonstrates characteristics that are an admixture of T1D and type-2 diabetes (T2D). Double diabetes can be a major cause of concern in individuals with

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young onset (11–19 years old) diabetes, which can be a result of weight gain and IR.[8] The gold standard for measurement of IS in T1D is glucose disposal rate (GDR) assessed by a euglycemic–hyperinsulinemic clamp (EHC).[9] However, as this is difficult and cumbersome for use in routine clinical practice, newer IS estimation equations derived by various study groups have been published.[10,11] These equations demonstrate a fairly good agreement with measured IS and thus offer promise in the clinical setting[7,12]

As individuals with T1D are administered insulin exogenously, the homeostatic model for assessment of insulin resistance cannot be used in them. Few equations have been developed and validated against data from gold standard EHC tests to estimate IS. These equations are illustrated in Table 1. They include (1) The Epidemiology of Diabetes Complications (EDC) equation that was initially developed in the Pittsburgh EDC Study, (2) Estimated insulin sensitivity (eIS) score that was developed using data of youth with diabetes participating in the SEARCH study in Colorado, USA, and (3) eIS-coronary artery calcification in T1D (CACTI) equation was developed on participants recruited from the CACTI cohort.[7,12,13]

A previous study compared IS indices for the detection of DD in Indian adolescents with T1D and derived a cut-off to predict future risk for the development of metabolic syndrome (MS) in these subjects.[14] These cut-offs were derived from subjects with T1D from a single center, thus, we conducted the current study with the aim to validate these cut-offs among Indian subjects with T1D from various geographical locations in detecting DD.

Methods

Study design and subjects

This study was an observational, cross-sectional study conducted at multiple centers between December 2021 and June 2022. The centers were four tertiary care paediatric endocrine and diabetes clinics located in urban centers in four geographic regions of India: north (Jalandhar), west (Pune), east (Kolkata), and south (Chennai) as shown in Figure 1. Each center collected data from outpatients with an initial diagnosis of T1D who attended the clinic during the study period. Subjects in the age range of 10–18 years with a duration of illness of at least six months (as fluctuation of weight and metabolic instability are usually seen at the onset and during the initial therapy) with haemoglobin levels greater than 11% and no known comorbidities like hypothyroidism and celiac disease were included in the study.[15] Written informed consent for the study was obtained from the parents or guardians of patients and assent was obtained from the study participants.

Table 1: Equations to determine insulin sensitivity in patients with T1D

Study Group	Equation
EDC	24.31−12.22 × (WHR) − 3.29 × (hypertension) − 0.57 × (HbA1c)
SEARCH	exp (4.64725 - 0.02032 (waist) – 0.09779 (HbA1c) - 0.00235 (Tg)
CACTI-exA	exp (4.1075−0.01299 × (waist) − 1.05819 × (insulin dose) − 0.00354 × (Tg) − 0.00802 × (DBP))

(exA- best-fit model excluding adiponectin), DBP-diastolic blood pressure in mmHg, Tg-triglyceride in mg/dl, WHR-waist–hip ratio, hypertension=0 if no and 1 if yes, HbA1c=glycated Hemoglobin in %, waist in cm, insulin dose in IU/kg/day

Descriptive data

The clinical history and examination, anthropometry, blood pressure (BP), and biochemical measurements were conducted at each center uniformly in accordance with the study conducted to derive the cut-offs and using standard protocols.[14]

Anthropometry

Height (Seca Portable stadiometer, Hamburg, Germany up to 0.1 cm accuracy) and body weight (Seca 876 Flat scale, Hamburg, Germany, up to 100 g accuracy) were measured using standard protocols. Body mass index (BMI) was computed using the following formula: BMI = weight (kg)/height (m^2). Waist circumference (WC) and hip circumference were measured using the World Health Organization guide to physical measurements.[16] Subsequently, the height, weight, WC, and BMI were converted to *Z* scores using Indian reference data.[17,18] Waist to hip ratio was calculated as WC divided by the hip circumference.

Blood pressure

Blood pressure was measured on the right arm with the child lying down quietly. The cuff was leak tested prior to the

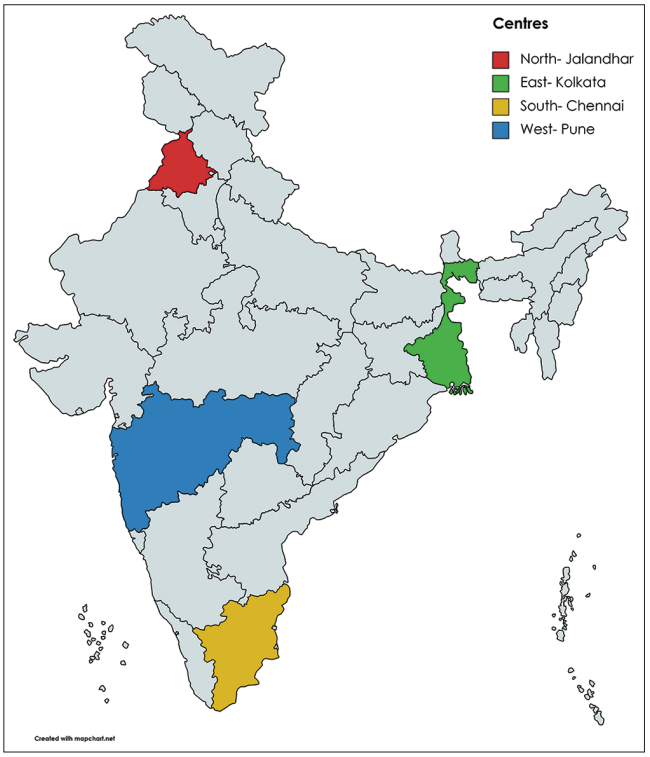

Figure 1: Centers with participants of T1D selected in study based on geographic regions

commencement of the study. All air was removed from the cuff, the cuff was wrapped snuggly and neatly around the limb to allow one finger under the cuff. The cuff was placed 2–5 cm above the elbow crease. All BP measurements were recorded manually using similar oscillometric noninvasive BP (NIBP) devices (Goldway™ Multipara Monitor—Model Number GS20).

Biochemical measurements

Six to eight ml of blood was drawn by an experienced phlebotomist after a minimum of eight-hour fast. Fasting blood samples were then assessed for lipid profile (total cholesterol, triglycerides, and High density lipoprotein cholesterol (HDL-c) using the enzymatic method and low-density lipoprotein-cholesterol (LDL-c) concentrations were calculated by the Friedewald formula.[19] Glycaemic control was evaluated by measuring glycosylated haemoglobin (HbA1c) using high-performance liquid chromatography (BIO-RAD, Germany). Microalbumin in spot urine was detected by immunoturbidimetry, creatinine by Jaffe w/o deproteinization, and albumin creatinine ratio by Jaffe method.

Definition of metabolic syndrome

The IDF definition (Consensus 2017) was used to classify study participants aged 10 years or older as follows—MS may be diagnosed with abdominal obesity (waist circumference >90th centile for age and gender or adult cut-off of >80 cm in females or >90 cm in males as per ethnicity-specific values) and the presence of two or more other clinical features of elevated triglycerides (≥150 mg/dl), low high-density lipoprotein cholesterol (HDL-c: <40 mg/dl in males and <50 mg/dl in females), high BP (≥130 mmHg systolic and/or ≥85 mmHg diastolic), and increased fasting plasma glucose (≥100 mg/dl). Since all patients with T1D had elevated fasting blood sugar, those having central obesity with one more of the above criteria were defined as having MS. Patients who had one or more criteria as per the definition of MS (except elevated FBS) but did not fulfil the criteria of having MS (i.e., abdominal obesity + two or more risk factors) were termed to have "Metabolic Risk" (MR).[20]

Insulin sensitivity indices

Insulin sensitivity was calculated using the formulae mentioned in Table 1.

Glycaemic control

Glycaemic control was assessed by HbA1c concentrations), which were measured locally at each center. The American Diabetes Association (ADA) has suggested the following target values for HbA1c in relation to age: <8.0% at age 6–12 years, <7.5% at age 13–18 years, and <7.0% at age 19+ years. Individuals who met the ADA target were classified as "good" control; those with HbA1c ≥9.5% regardless of age were classified as "poor" control, and those with HbA1c values between the definition of "good" and "poor" control were classified as "intermediate" control.[21]

Statistical analysis

SPSS for Windows software program, version 26 (SPSS, Chicago, IL, USA) was used for statistical analyzes. Differences in means were tested using Student's *t*-test for parametric data and Mann–Whitney U test for non-parametric data. Correlation analysis was performed using Spearman's correlation coefficient. We evaluated the area under the receiver operating characteristic (ROC) curve (area under curve (AUC), with 95% confidence intervals) of each IS index to identify subjects at risk of development of DD. Chi-square test and Cramer's V test were used for the correlation analysis of categorical variables. Sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV) for identifying subjects at risk for the development of DD by using IS cut-off criteria were calculated. *P* values <0.05 were considered statistically significant.

Ethical Clearance Statement

The study was approved by the Jehangir Clinical Development Centre ethics committee on March 4, 2022. All study procedures follows the guidelines laid down in Declaration of Helsinki (1964).

Results

A total of 161 adolescents with T1D were studied as shown in Figure 1 (30 from North, 13 from East, 61 from South, and 56 from Western India). Of these, 87 (54%) were boys and 74 (46%) were girls. The participants in the study were in the age range of 10–18 years with mean age of 13.9 ± 2.4 years. The mean age at the onset of diabetes and duration of illness were 9.0 ± 3.7 years and 5.0 ± 3.4 years, respectively. The mean insulin requirement and HbA1c concentrations were 1.0 ± 0.3U/kg/day and 9.8 ± 2.4%, respectively. The prevalence of hypertension and combined overweight/obesity in our study group were 5% (n = 8) and 25.5% (n = 41), respectively. Low HDL (23.6%) was the commonest abnormal metabolic parameter. Central obesity and hypertriglyceridemia were noted in 7.5% participants, respectively. Clinical characteristics of study participants stratified by glycaemic control are illustrated in Table 2. Only 11.2% of subjects achieved the glycemic control goal (HbA1c <7%) as recommended by the Internal Society for Paediatric and Adolescent Diabetes 2022. The subjects with poor glycaemic control were older and had higher insulin requirements. They were also lighter with lower WC. They had lower HDL-c and higher LDL-c and lower IS as computed by all the eIS formulae (particularly, CACTI equation that does not take HbA1c into account). A post hoc power of more than 0.8 was achieved given ά error problem of 0.05 using the difference in mean IS by SEARCH between two independent groups using G-power 3.1.9.4.

Spearman coefficients for correlations of IS using various formulae with clinical, anthropometric, and laboratory parameters are presented in Table 3. In comparison to the previous study,[14] the correlations were mostly similar with an additional significant negative correlation of all equations

Table 2: Comparison of clinical, anthropometric, and biochemical parameters of study group classified by presence or absence of metabolic risk

Parameter	Fair to good glycaemic control (*n*=79)	Poor glycaemic control (*n*=82)	*P*
	Mean±SD	Mean±SD	
Clinical			
Age (years)*	13.4±2.4	14.5±2.2	0.02
Disease duration (years)	4.7±3.3	5.2±3.6	0.386
Systolic blood pressure (mmHg)	107±12	107±12	0.906
Diastolic blood pressure (mmHg)	68±9	68±9	0.745
Insulin requirement (U/kg/day)*	0.9±0.3	1.1±0.3	0.001
Anthropometry			
Height Z-score	-0.1±1.1	-0.3±1.0	0.155
Weight Z-score*	0.01±1.0	-0.4±0.8	0.004
BMI Z-score*	0.04±1.1	-0.3±0.8	0.018
Waist circumference Z-score*	-0.8±1.3	-1.2±1.0	0.047
Waist hip ratio	0.8±0.1	0.8±0.1	0.09
Biochemistry			
Cholesterol (mg/dl)	161±34	171±46	0.13
HDL-c (mg/dl)*	53±12	48±11	0.016
LDL-c (mg/dl)*	91±27	103±38	0.022
Triglycerides in mg/dl	86±50	96±59	0.23
HbA1c %*	7.8±1.0	11.7±1.7	0.001
Insulin Sensitivity Indices			
eGDR*	9.0±1.4	7.2±1.3	0.001
SEARCH*	9.7±2.5	6.6±1.8	0.001
CACTI*	4.2±1.8	3.2±1.2	0.001

*Statistically significant difference between two groups. HDL-c High-density lipoprotein cholesterol. LDL-c Low-density lipoprotein cholesterol. HbA1c Glycated haemoglobin

with age, LDL-c, and total cholesterol. Additionally, estimated glucose disposal rate (eGDR) had a significant negative correlation with insulin requirement. In contrast, SEARCH did not have any correlation with the female gender and had a significant positive correlation with HDL (0.166 vs. -0.161).

The strongest positive correlation among IS indices was noted between IS by SEARCH and eGDR (0.69 vs. 0.76, $P < 0.001$) and the highest AUC for MS was noted for the SEARCH equation (0.74 vs. 0.82). Figure 2 illustrates the comparison of ROC curves of IS derived by each of the three equations in determining MS. A cut-off of 5.48 has been proposed to detect MS in Indian adolescents with T1D.[14] The Cramer's V showed a significant correlation between low IS by SEARCH equation and MS categories (Cramer V = 0.16, $P < 0.05$). The odd's ratio (OR) for the development of MS in T1D in subjects with IS by SEARCH equation less than the cut-off of 5.48 was 4.5 (95% CI - 0.94–21.49) and the relative risk to develop MS was 4.08 (95% CI - 0.97–17.13).

Table 3: Correlation coefficients of the three estimated insulin sensitivity equations with clinical and biochemical parameters

Parameter	eGDR	SEARCH	CACTI
Age	-0.173*	-0.495*	-0.187*
Disease duration	0.014	-0.134	-0.213*
Gender	-0.044	-0.054	-0.06
Insulin requirement	-0.240*	-0.12	used in equation
BMI Z-score	0.027	-0.243*	-0.111
Waist circumference Z-score	-0.143	Used in equation	Used in equation
Systolic blood pressure	used in equation	-0.188*	-0.220*
Diastolic blood pressure	used in equation	-0.190*	used in equation
Cholesterol	-0.227*	-0.338*	-0.258*
HDL-c	0.047	0.166*	0.15
LDL-c	-0.221*	-0.332*	-0.260*
Triglycerides	-0.174*	used in equation	used in equation
HbA1c	used in equation	used in equation	-0.288*

*Statistically significant difference between two groups. HDL-c High-density lipoprotein cholesterol. LDL-c Low-density lipoprotein cholesterol. HbA1c Glycated haemoglobin

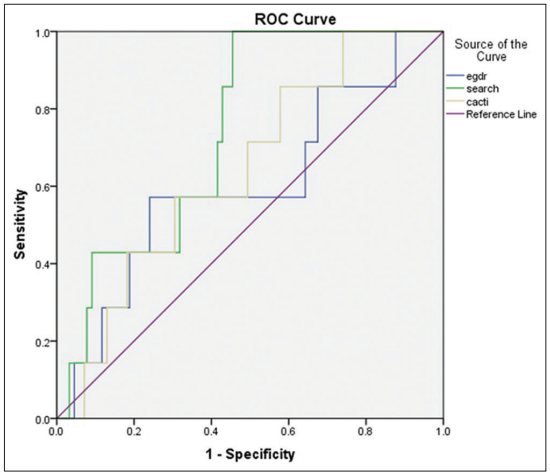

Figure 2: ROC for identification of metabolic syndrome by IS formulas

The AUC of the eIS by SEARCH equation to detect metabolic risk in subjects with T1D was 0.74 (95% CI - 0.65–0.82) as shown in Figure 3. In the present study, we found that 76% of subjects with eIS calculated by the SEARCH equation lower than the cut-off had metabolic risk as opposed to only 26.5% with eIS by SEARCH greater than 5.48 ($P < 0.05$). Cramer's V showed a significant correlation between low eIS by SEARCH equation and MR categories (0.38, $P < 0.05$). The OR for the development of MR in T1D in subjects with eIS by SEARCH equation less than the cut-off of 5.48 was 8.79 (95% CI - 3.25–23.76) and the relative risk to develop MR was 2.87 (95% CI - 2.01–4.1). The comparison of sensitivity, specificity, PPV, NPV, positive likelihood ratio, and negative likelihood ratio of the proposed

eIS by SEARCH equation cut-offs for the development of MS and MR in Indian adolescents with T1D are illustrated in Table 4.

Discussion

In this multicenter study, we report 4.3% prevalence of MS in Indian adolescents aged 10–18 years with T1D with an additional 29.8% of study participants being at risk of development of MS. Low HDL (23.6%) was the commonest abnormal parameter of the MS definition. We also observed that the IS calculated by the equation derived by the SEARCH group was the most appropriate index to identify MS and MR in Indian adolescents with T1D. The proposed cut-off of 5.485 had very high specificity, PPV, and NPV in identifying the risk of the development of DD.

The reported prevalence of MS is similar to that of 4.2% reported by Singh *et al*.[22] from a study on nondiabetic north Indian school-going adolescents.[22] They also noted low HDL as the most common abnormal component of MS in their study participants (25.8%). This is much lower than the approximate average of 23.7% reported by a meta-analysis that also reported the prevalence of 17% from subgroup analysis from Asia.[23] This variation may be due to differences in diagnostic criteria, study design, sample size, socioeconomic status, and characteristics of the population participating in the studies.

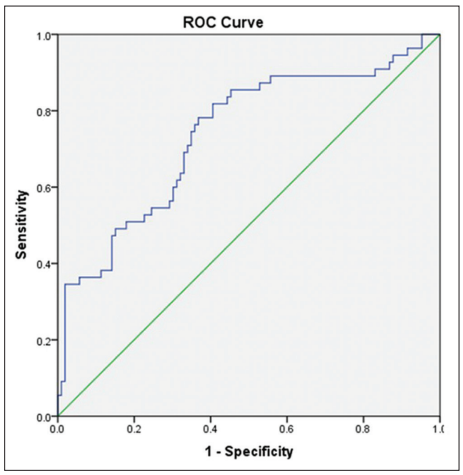

Figure 3: ROC curve of SEARCH equation of IS for predicting metabolic risk in subjects with T1D

Table 4: Performance of insulin sensitivity cut-off in identifying metabolic risk and metabolic syndrome in Indian adolescents with type-1 diabetes

	Metabolic Syndrome (%)	Metabolic risk (%)
Sensitivity%	42.85	34.50
Specificity%	85.71	94.33
Positive Predictive Value %	12.00	76.00
Negative Predictive Value%	97.05	73.50
Positive Likelihood Ratio	3.00	6.08
Negative Likelihood Ratio	0.67	0.69

As the metabolic profile of Indian adolescents with T1D is similar to non-diabetic peers, ethnicity may be an important factor for prediction of MS in individuals.

The SEARCH for Diabetes in youth study undertook a comprehensive evaluation of childhood diabetes wherein they developed and validated a surrogate marker of IS using the EHC in a subset of SEARCH participants aged 12–19 years from Colorado, USA.[12] The participants with diabetes in the clamp study were non-Hispanic White (70%), Hispanic (25%), and African-American (5%). As variation in IS is noted across ethnicities, a nationally representative cut-off is needed for Indian adolescents with T1D owing to high prevalence of T1D, rapid increase in new cases of T1D per annum, and increase in childhood obesity which may contribute to the development of MS in adolescents with T1D.

A previous study from a single center from India proposed a cut-off of 5.48 for IS calculated by the SEARCH equation. There was a strong correlation between the MR categories and subjects with low eIS by SEARCH equation. The OR and relative risk for the development of MR in subjects with T1D with eIS lower than the cut-off was 8.8 and 2.9, respectively. The number of subjects with low eIS by SEARCH equation with no features suggestive of MS, i.e., false positive was high. This may be due to higher prevalence of overweight/obesity (25.5% vs. 15.5%) and negative correlation of HDL-c with IS in the current study (0.166 vs. -0.161). The cut-off of IS validated by the current study is close to the cut-off of 6.2 for adiposity and acanthosis nigricans as markers of IR proposed by Teixeira *et al*.[24] on Brazilian individuals with T1D. The cut-off derived by them was based on the quartile method. Besides, the SEARCH equation was derived by performing a clamp study on participants of age 12–19 years, HbA1c <12%, creatinine <114µmol/L, and normal HbA1c and haematocrit.[12] In the present study, however, there were 34 subjects with HbA1c values of more than 12%, which may have yielded high numbers of false negatives causing a decrease in sensitivity.

Ours is the first study to assess IS indices in adolescents with T1D from various geographical regions of India. As there is an increase in the prevalence of obesity globally, and obesity is a risk factor for the development of IR, the SEARCH IS equation cut-off of 5.48 to identify IR in Indian adolescents with T1D and thereby, the risk of DD may be useful. The main limitation of our study is the lack of comparison of IS indices cut-offs with the gold standard EHC technique to detect IR in T1D. Further, we have also not collected data on the pubertal status of study participants.

To conclude, IS calculated by the equation proposed by the SEARCH group together with cut-offs derived in an earlier study may be used effectively to identify the risk of development of MS in Indian adolescents with T1D. However, more studies with larger cohorts and longitudinal follow-up are required to further assess its utility.

Data availability

The authors agree to deposit data that support the findings of their research in a public repository.

Author contributions

All the listed authors played a role in the clinical management, planning, execution, analysis, writing of the manuscript, and they all agree and accept responsibility for the contents of the manuscript submitted.

Ethical approval

The local Institutional Review Board has approved the proposal.

Consent to participate

Informed consent was obtained from all individual participants included in the study and informed consent was obtained from the parents.

Consent for publication

The participants have consented to the submission of the article to the journal.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Saxena S. Type 1 Diabetes in Children - Causes, Symptoms, Diagnosis, Complications & Treatment. Medindia 2021. Available from: https://www.medindia.net/patientinfo/type-1-diabetes-in-children.htm. [Last accessed on 2022 Aug 25].
2. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium; 2021. Available from: https://www.diabetesatlas.org.
3. Amutha A, Unnikrishnan R, Anjana RM, Shanthi Rani CS, Rajalakshmi R, Venkatesan U, *et al*. Clinical profile and incidence of microvascular complications of childhood and adolescent onset type 1 and type 2 diabetes seen at a tertiary diabetes centre in India. Pediatric Diabetes 2021;22:67-74.
4. Amutha A, Anjana RM, Venkatesan U, Ranjani H, Unnikrishnan R, Narayan KMV, *et al*. Incidence of complications in young-onset diabetes: Comparing type 2 with type 1 (the young diab study). Diabetes Res Clin Pract 2017;123:1-8. doi: 10.1016/j.diabres.2016.11.006.
5. Chetan MR, Miksza JK, Lawrence I, Anjana RM, Unnikrishnan R, Amutha A, *et al*. The increased risk of microvascular complications in South Asians with type 1 diabetes is influenced by migration: Results from the UK-India multi-ethnic migration study. Diabet Med 2020;37:2136-42.
6. Ye J. Mechanisms of insulin resistance in obesity. Front Med 2013;7:14-24.
7. Duca LM, Maahs DM, Schauer IE, Bergman BC, Nadeau KJ, Bjornstad P, *et al*. Development and validation of a method to estimate insulin sensitivity in patients with and without type 1 diabetes. J Clin Endocrinol Metab 2016;101:686-95.
8. Khawandanah J. Double or hybrid diabetes: A systematic review on disease prevalence, characteristics and risk factors. Nutr Diabetes 2019;9:1-9. doi: 10.1038/s41387-019-0101-1.
9. Tam CS, Xie W, Johnson WD, Cefalu WT, Redman LM, Ravussin E. Defining insulin resistance from hyperinsulinemic-euglycemic clamps. Diabetes Care 2012;35:1605-10.
10. Staimez LR, Weber MB, Ranjani H, Ali MK, Echouffo-Tcheugui JB, Phillips LS, *et al*. Evidence of reduced beta cell function in Asian Indians with mild dysglycemia. Diabetes Care 2013;15:315-22.
11. Mohan V, Amutha A, Ranjani H, Unnikrishnan R, Datta M, Anjana RM, *et al*. Associations of b-cell function and insulin resistance with youth-onset type 2 diabetes and prediabetes among Asian Indians. Diabetes Technol Ther 2013;15:315-22.
12. Dabelea D, D'agostino RB, Mason CC, West N, Hamman RF, Mayer Davis EJ, *et al*. Development, validation and use of an insulin sensitivity score in youths with diabetes: The SEARCH for diabetes in youth study. Diabetologia 2011;54:78-86.
13. Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: "Double diabetes" in the diabetes control and complications trial. Diabetes Care 2007;30:707-12.
14. Oza C, Khadilkar A, Karguppikar M, Gondhalekar K, Khadilkar V. Comparison of insulin sensitivity indices for detection of double diabetes in Indian adolescents with type 1 diabetes. J Paediatr Endocrinol Metab 2022;35:1010-9.
15. Couper JJ, Haller MJ, Ziegler AG, Knip M, Ludvigsson J, Craig ME. Phases of type 1 diabetes in children and adolescents. Pediatr Diabetes 2014;15:18-25.
16. Oza C, Khadilkar V, Karguppikar M, Ladkat D, Gondhalekar K, Shah N, *et al*. Prevalence of metabolic syndrome and predictors of metabolic risk in Indian children, adolescents and youth with type 1 diabetes mellitus. Endocrine 2022;75:794-803.
17. Khadilkar VV, Khadilkar AV. Revised Indian Academy of Paediatrics 2015 growth charts for height, weight and body mass index for 5-18-year-old Indian children. Indian J Endocrinol Metab 2015;19:470-476.
18. Khadilkar A, Ekbote V, Chiplonkar S, Khadilkar V, Kajale N, Kulkarni S, *et al*. Waist circumference percentiles in 2-18 year old Indian children. J Pediatr 2014;164:1358-62.
19. Warnick GR, Knopp RH, Fitzpatrick V, Branson L. Estimating low density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. Clin Chem 1990;36:15-9.
20. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, *et al*, IDF Consensus Group. The metabolic syndrome in children and adolescents–an IDF consensus report. Pediatric diabetes. 2007;8:299-306.
21. Petitti DB, Klingensmith GJ, Bell RA, Andrews JS, Dabelea D, Imperatore G, *et al*. Glycemic control in youth with diabetes: The SEARCH for diabetes in youth study. J Pediatr 2009;155:668-72.
22. Singh R, Bhansali A, Sialy R, Aggarwal A. Prevalence of metabolic syndrome in adolescents from a north Indian population. Diabet Med 2007;24:195-9.
23. Belete R, Ataro Z, Abdu A, Sheleme M. Global prevalence of metabolic syndrome among subjects with type I diabetes mellitus: A systematic review and meta-analysis. Diabetol Metab Syndr 2021;13:1-3.
24. Teixeira MM, Diniz MD, Reis JS, Ferrari TC, de Castro MG, Teixeira BP, *et al*. Insulin resistance and associated factors in patients with type 1 diabetes. Diabetol Metab Syndr 2014;6:1-0. doi: 10.1186/1758-5996-6-131.