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REVIEW ARTICLE

Surrogate markers of metabolic syndrome and insulin resistance in children and young adults with type 1 diabetes: a systematic review & meta-analysis (MetS and IR in T1DM)

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Abstract

Objective Metabolic syndrome (MetS) and insulin resistance (IR) are associated with diabetes. Insulin therapy in type 1 diabetes (T1DM) may complicate the diagnosis of both these conditions. Therefore, investigation of the diagnostic efficacy of MetS and IR components is important in paediatric population with type 1 diabetes mellitus (T1DM).

Methods SCOPUS, Web of Science, and PubMed were searched for studies that have MetS and IR in paediatric populations with T1DM. We assessed the strength of association for MetS and IR components. A random effect model was used for the meta-analysis and the effect size was reported in terms of Hedge's g.

Results A total 30 studies were identified relevant to our systematic search. Insulin dosage and HbA1c, markers for glycemic condition showed very small effect on MetS with T1DM. In the lipid profile, triglyceride (TG) and low-density lipoprotein (LDL) showed better effect size than high-density lipoprotein (HDL). In case of IR, heterogeneous nature of studies made it difficult to carry out a meta-analysis. A descriptive review of existing and novel markers is thus provided.

Conclusion In children with T1DM, lack of association between markers of glycemic condition suggested that MetS may develop independent of glycemic level. Other than TG and HDL, LDL may be used in the diagnosis of MetS. A universally accepted diagnosis protocol would enhance accuracy and comparability across research and clinical settings, as observed in the descriptive review.

Keywords Biomarkers · Insulin resistance · Metabolic syndrome · Type 1 diabetes · Children

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune condition which results in the loss of pancreatic beta cells. This leads to dependency of the person on exogenous insulin therapy. The peak age for T1DM diagnosis is 5-9yrs and 10-14yrs with the prevalence increasing among young individuals [1, 1–5]. People with recently diagnosed T1DM generally have a lower body mass index; however, obesity rates has risen in this population [6]. Notably, metabolic syndrome (MetS) and insulin resistance (IR) can also be observed in lean individuals with T1DM [7–9]. MetS and IR are the risk factors for cardiovascular diseases (CVD). Therefore, diagnosis and management of MetS and IR are crucial for the prevention of cardio metabolic risks.

The prevalence of MetS in people with T1DM is suggested to be 23.7% and is increasing [10, 11]. The diagnosis of MetS is based on three different criteria that are laid down by the World health Organization (WHO), the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), and the International Diabetes Federation (IDF) [12]. These criteria are based on anthropometric measurements such as waist circumference (WC), hypertension (HTN) and biochemical parameters such as the lipid profile (Table 1).

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Table 1 Diagnostic criteria for metabolic syndrome according to different organization

Criteria laid by	Components of MetS	Cut-offs for adults
WHO (1998) [13]	Insulin resistance (by impaired fasting glucose (FG) or impaired glucose tolerance (IGT) or Hyperinsulinemic Euglycaemic Clamp (HEC)) with (any 2 of the following: obesity, dyslipidemia, high systolic, high diastolic blood pressure, increased urine microalbumiuria)	FG > 100 mg/dl, IGT > 140 mg/dl 120 min after ingestion of 75 g of glucose, WHR: ≥ 0.90(M), 0.85(F) or BMI ≥ 30 kg/m2, TG ≥ 150 mg/dl or HDL-C ≤ 35 mg/dl(M), 39 mg/dl(F), BP ≥ 160/90 mmHg, Urinary albumin excretion of 20 µg/min or albumin-to-creatinine ratio of 30 mg/g
NCEP ATP III (2005 revised) [12]	Any 3 of five: Obesity, Hyperglycemia, dyslipidemia, high systolic or high diastolic BP	Waist circumference: ≥ 40 inches (M), ≥ 35 inches (F), Fasting glucose ≥ 100 mg/dl or Rx, TG ≥ 150 mg/dl or Rx, HDL cholesterol ≤ 40 mg/dl (M), ≤ 50 mg/dl (F); or Rx, HTN ≥ 130 mmHg systolic or ≥ 85 diastolic or Rx
IDF(2007) [14]	Central obesity (by waist circumference) with (2 of the four criteria: FG, TG, HDL, BP) *If BMI > 30 kg/m^2 central obesity can be assumed	Waist circumference: ≥ 94 cm(M), ≥ 80 cm(F), FG ≥ 100 mg/dl, TG ≥ 150 mg/dl, HDL ≤ 40 mg/dl(M), ≤ 50 mg/dl(F), BP ≥ 130 mmHg or ≥ 85 mmHg diastolic or Rx

WHR waist to hip ratio, *HDL* High Density Lipoprotein, *BP* Blood Pressure, *BMI* Body Mass Index, *Rx* on drugs of management for the condition

Most of the cut-offs for the diagnosis of MetS are developed for the adult population [15–17]. These parameters are modified only by changing the threshold for use in paediatric population. Along with MetS, the prevalence of IR in children with T1DM termed as double diabetes is also risen in children [18–22].The term double diabetes has been used to refer to individuals with T1DM who are overweight, have family history of diabetes, and have clinical features of insulin resistance [18]. Factors such as food habits, reduced physical activity, gender, age, and genetic predisposition may contribute to the development of IR in children with T1DM [23, 24]. Presence of IR in children with T1DM increases the risk of development of various macro and microvascular complications [25]. Hence, the diagnosis of IR may help clinicians to implement preventive measures or add an adjuvant therapy.

The diagnosis of IR in Type 2 diabetes (T2DM) depends on measurement of fasting insulin levels which are negligible in T1DM. Therefore, the indices used for the diagnosis of IR in T2DM have little use in T1DM. The gold standard method for the diagnosis of IR in children with T1DM is the Hyperinsulinemia Euglycemic Clamp (HEC) in which the glucose concentration is maintained by variable infusion of exogenous glucose and insulin [26]. However, the HEC technique is expensive, and space and time consuming. Therefore, various alternate methods have been developed for the diagnosis of IR that rely on indirect markers such as estimated glucose disposal rate (eGDR) [27–30], Insulin Sensitivity Score (ISS) [31] and, insulin sensitivity equation (eIS) [32] provided by Epidemiology of Diabetes Complications (EDC), Search for diabetes in youth (SEARCH), and Coronary Artery Calcification in T1DM (CACTI) respectively (Table 2).

The indices for IR in T1DM have been validated by direct comparison with HEC [8, 31, 35, 36]. There are no threshold or cut-offs provided for these indices. However, many authors have provided cohort based thresholds. Most of these studies include adults with T1DM (Supplementary Table 1) [37–41]. The exogenous insulin administration and pubertal age may interfere with the existing parameters of MetS and IR. Therefore, a systematic review and meta-analysis is needed for both these conditions.

Table 2 Indices provided for calculation of insulin resistance in Type 1 diabetes

Groups	Equations	Target population
IDF (2007) [33]	eGDR = 24.31–12.22 × (WHR)-3.29 × (HTN)-0.57 × (A1C[%])	Adult participants with T1DM (compared with HEC)
SEARCH (2011) [8, 31, 34]	IS scores = Exp(4.64725–0.02032(waist[cm])-0.09779(HbA1c[%])-0.00235(TG[mg/dlL]))	Adolescence participants with T1DM, T2DM and with no diabetes (compared with HEC)
CACTI (2011) [35]	eIS = Exp(4.1075–0.01299 × (waist[cm])-1.05819 × (insulin dose)-0.00354 × (TG[mg/dL)-0.00802 × (DBP[mmHg]))	Adult participant with T1DM (compared with HEC)

EDC Epidemiology of Diabetes Complications, *SEARCH* SEARCH for Diabetes in Youth, *CACTI* Coronary Artery Calcification in T1DM, *eGDR* estimated glucose disposal rate, *IS* insulin sensitivity score, *eIS* estimated insulin sensitivity, *WHR* waist to hip ratio, *TG* Triglycerides, *DBP* Diastolic Blood Pressure

Methods

This is an exploratory meta-analysis and follows the PRISMA (Preferred Reporting of Systematic Review and Meta-analysis) guidelines.

Search strategy, and Inclusion and exclusion criteria

Two authors independently searched for the relevant keywords in three databases (PubMed, SCOPUS, Web of Science) for identification of research articles related to MetS and IR in children, adolescents, and young adults with T1DM. The search was performed till May 5, 2023. The articles were from 1982 to 2023. The search for the relevant keywords was as follows.

((("Type 1 Diabetes" OR "IDDM" OR "insulin dependent diabetes" OR "T1DM") AND ("insulin resistance" OR "IR" OR "Metabolic syndrome" OR "MetS" OR "insulin sensitivity" OR "IS")) AND ("Molecular markers" OR "markers" OR "Biological markers" OR "Clinical markers" OR "gene expression markers")) AND ("Paediatric" OR "child" OR "children" OR "adolescent" OR "adolescence" OR "young adult").

The search was limited to peer reviewed English articles. Only original research articles were included for this review. Studies that had type 1 diabetes population with the age group < 25yrs were retained. The studies were then imported to a Rayyan software for screening and removal of duplicates [42]. Studies using animal models, cell lines, and organ tissue samples were excluded. Studies including children with complications associated with diabetes and on medication other than insulin therapy were excluded.

Selection of studies and data extraction

We segregated the studies based on presence or absence of MetS and IR in the T1DM population. The studies that provide markers for such conditions, either standard (insulin dose, eGDR for IR, IDF criteria for MetS) or surrogate (body mass index: BMI, WC etc.), were included in this review. Meta-analysis was performed only if multiple studies with similar parameters were available. Other studies were utilized for descriptive review. Parameters such as duration of diabetes, insulin dosage, HbA1c, and lipid profile were assessed in each study. The sample size, mean, and standard deviation (sd) for each parameter were recorded accordingly. If median and interquartile range were provided they were converted to estimated mean and variance depending on sample size [43]. Author names, publication year, ethnicity, and gender details of the population were also recorded for the studies that were part of the systematic review (Table 3).

Statistical analysis and evaluation

Meta-analysis was performed when two or more studies reported mean, standard deviation, and sample size. Metaphor package was applied for the analysis [69]. Standard Mean Difference (SMD) was calculated using R (version 4.1.1). We calculated the effect size (ES) in terms of hedges g that corrects for the sample size providing unbiased adjusted ES. Random effects model (REM) was used for quantitative meta-analysis. A forest plot was used to visualize summary of results [70]. Chi-squared test was used to measure heterogeneity (p val < 0.1). The I^2 statistic was used to estimate if the heterogeneity was considerable ($I^2 > 40\%$) [71]. The strength of relationship between parameters and traits was estimated based on the effect size (0–0.2: no effect; 0.2–0.5: small; 0.5–0.8: moderate; 0.8–1: large; > 1: very large effect) [72].

Assessment of Sensitivity and publication bias

Funnel plots were used for visualization of publication bias [73]. The pooled results were analysed for their sensitivity by sequential removal of individual studies and their effect on heterogeneity.

Results

Identification of studies for diagnostic markers of MetS and IR

We identified 67 research articles on PubMed, 930 on SCOPUS, and 88 on Web of Science by searching keywords in titles and abstracts. After applying the filters for language and exclusion criteria, 66, 739, and 86 articles were retained. Manual search provided 3 additional studies. These articles were then imported in Rayyan [42]. In this software 78 duplicate articles were removed and 816 unique original research articles were retained. Based on the screening of abstracts and titles, 743 articles were omitted. Full text scrutiny identified 73 research articles, and 30 research articles were retained based on inclusion and exclusion criteria (Fig. 1).

The general nature of these research articles is mentioned in Table 3. All were observational studies with a cross-sectional or longitudinal design. The data in the studies was

Table 3 Characteristic of studies included in the systematic review

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
1	Nadeau et al. 2010 [44]	C,P	Black (8.3%), Hispanic (8.3%), White(75%), other(8.3%)	Case (6/6), Control (6/6)	Children without diabetes	HEC with VO2 peak ($r=0.61$, $p=0.007$)	12–19
2	D. Dabelea et al. 2011 [31]	C,P	Non-hispanic whites, Hispanics, African American)	Case (26/43) Control (8/17)	Children with T2DM	HEC with IS score (SEARCH) ($r=0.65$, $p=0.0001$)	12–19
3	D. Dabelea et al. 2011[45]*	C,P	67.9% Non-Hispanic whites (NHWs), 13.3% Hispanics, 13.4% African Americans (AAs), 4.1% Asian/Pacific Islanders (APIs), and 1.3% American Indians (AIs)	Case(218/228), Control(646/602)	Children with T2DM	IS score by SEARCH (IR < 8.15)	< 20
4	Davis et al. 2012 [46]	C,P	NA	Case (18/12), Control (8/6)	Children without diabetes	Higher insulin dose, high HbA1c	0–18
5	Rathsman et al. 2012 [47]	C,P	Caucasian	Case (12/8), Control(7/13)	Children without diabetes	MetS by NCEP ATP III, WHO, IDF HEC(Si) to cIMT: $r=0.22$	14–20
6	Narges Safai et al., 2015 [48]	L, R	18 immigrants, 12 unreported ethnicity, others Danish origin	Case (255/227), Control (266/231)	Children without diabetes	Adiponectin, leptin (increase in both increases insulin sensitivity)	0–15
7	Chan et al. 2017 [49]	C,P	NA	Case (46/54), Control (11/31)	T2D	HEC with AST & cholesterol ($r=-0.21$, $p<0.05$), BMI% ($r=-0.40$, $p<0.001$), TG($r=-0.34$, $p<0.001$), WC($r=-0.45$, $p<0.001$)	12–19
8	Cree-Green et al. 2018 [50]	C,P	T1DM are more Caucasian	Case (16/19), Control(6/16)	T2D	HEC with FFA ($r=-0.46$, $p=0.005$), Leptin ($r=-0.44$, $p=0.008$)	14–17
9	E Gourgari 2020 [51]*	L,P	Non-Hispanic White 72%, other 28%	Case(196/180), Control(55/102)	T2D	IS score by SEARCH (ISS > 8.15 included for T1DM)	18 ± 4.1
10	Hamed et al. 2021 [52]	L,P	NA	Case (3/4), Control(22/37)	T2D	Acanthosis nigricans, family history of DM, c-peptide, HbA1c	9–12

Table 3 (continued)

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
11	Calcaterra et al. 2021 [53]	C,P	NA	Case (0/14), Control (0/18), Control (0/20)	Children without diabetes	eGDR = 21.158 + (−0.09 * WC) + −3.407 x (HTN) + −0.551 x (HbA1c) eGDR < 8.77 mg kg^{-1} min^{-1} low adiponectin and high kisspeptin in IR	12.1 ± 4.1
12	Monika Grabia et al. 2021 [11]	C,P	Polish	Case (33/27), Control(44/16)	Children having T1DM with MetS vs children without MetS	MetS by IDF, NCEP ATP III, WHO, eGDR by 21.158 − (0.090 × WC) − (3.407 × HT) − (0.551 × HbA1c) ≤8 mg/kg/min (for MetS diagnosis)	10–17
13	Stone et al. 2006 [54]	L,R	NA	Cohort(161)	NA	Higher BMI, higher insulin dose, DHEAS	13.7 ± 2.2
14	Szadkowska et al. 2008 [8]	C,P	NA	Cohort (112/90)	Correlation to Lipid parameters and adiposity markers	HEC (M_{lbm}) with lipid [Cholesterol ($r = -0.18$, $p = 0.012$), HDL ($r = 0.15$, $p = 0.035$), LDL ($r = -0.22$, $p = 0.002$), TG ($r = -0.32$, $p < 0.001$)], SBP($r = -0.15$, $p = 0.029$), Adiposity [BMI($r = -0.29$, $p < 0.001$), WC($r = -0.35$, $p < 0.001$), Tricep ($r = -0.16$, $p = 0.027$), Subscapular ($r = -0.22$, $p = 0.002$), Body fat($r = -0.19$, $p = 0.006$)]	> 8–< 18
15	Mazumder et al. 2009 [55]	C,P	Asian	Cohort (30/28)	NA	Increased insulin dose, acanthosis nigricans, increased body fat	16.5 ± 2.3
16	Girgis, Scalley, and park 2012 [56]	C,P	NA	Cohort (29/32)	girls vs boys	eGDR = 24.31–12.2 x (WHR)-3.29 x (HTN)-0.57 × HbA1c obese vs non-obese T1DM (eGDR 6.5 ± 1.6 8.6 ± 1.8 mg/ kg min respectively, $p = 0.29$)	16–25

Table 3 (continued)

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
17	G. Valerio 2012 [57]	C,P	Caucasian of Italian origin	Cohort (219/193)	Children having T1DM with MetS vs children without MetS	IDF for MetS, logistic regression: [insulin dose (OR = 1.04, 95% CI 1–1.07, $p = 0.025$),WHR (OR = 11.03, 95% CI 5.23–23.24, $p = < 0.001$)	16–19
18	Maya jesic et al., 2013 [58]	C,P	NA	Cohort (51/49)	Normo vs micro albuminuric	High insulin dose, hypercholesterolemia, DHEAS	11–19.4
19	Lecaire and Palta 2015 [59]	L,P	White (97%)	Cohort (99/88)	Follow-up study	Insulin dose, Adiponectin	11.2(6.8)
20	Cedillo et al. 2015 [60]	C,P	NA	Cohort (155/108)	Children with central obesity vs children with non-central obese	BMI > 95th percentile for obesity, WHtR > 0.5 for central obesity (obesity driven IR)	< 19
21	Siraz et al. 2017 [61]	C,P	NA	Cohort (40/40)	Children with NAFLD vs children without NAFLD (represents peripheral IR)	Fetuin A (AUC = 0.672, 95% CI 0.558–0.773; $p = 0.022$), higher ALT	9–17
22	Bjornstad et al.2017 [62]	C,P	NA	Cohort (20/21)	leptin tertiles	HEC, leptin tertiles related to VO2 peak independent of IS	12–21
23	Sevaliev et al. 2019 [63]	C,R	84% Jewish, 16% Arab	Cohort (48/48)	girls vs boys	Children with high BMI showed component of MetS such as high SBP, low HDL compared to children having normal BMI	5–21
24	Soliman, Mosaad, and Ibrahim 2019 [15]	C,P	NA	Cohort (77/83)	Children having T1DM with MetS vs children without MetS	IDF for MetS, eGDR correlates with Age($r = -0.27$, $p = 0.001$), duration of diabetes($r = -0.18$, $p = 0.02$), weight($r = -0.35$, $p < 0.001$), BMI($r = -0.27$, $p = 0.001$), SBP($r = -0.48$, $p < 0.001$), DBP($r = -0.4$, $p < 0.001$), WC($r = -0.5$, $p < 0.001$), HbA1c($r = -0.69$, $p < 0.001$), LDL & TG ($r = -0.18$, $p = 0.02$), cholesterol ($r = -0.16$, $p = 0.04$)	13.38 ± 2.17

Table 3 (continued)

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
25	Marigliano et al. 2020 [64]	C,P	Caucasian	Cohort (8/7)	NA (but lean population)	eGDR with exogenous CHOs oxidized ($r=0.7$, $p<0.02$), differential enrichment of C12/C13 in the expired breath test ($r=0.59$, $p<0.05$) ISS with exogenous CHOs oxidized($r=0.61$, $p<0.05$), differential enrichment of C12/C13 in the expired breath test($r=0.62$, $p<0.05$)	8–14
26	Nishtala et al. 2020 [65]	C,R	Caucasian, African, Caribbean, South Asian, others	Cohort (108/67)	eGDR tertiles	$eGDR_{BMI}$ tertiles correlated with clinical parameter. Low eGDR had high cholesterol and TG	22 ± 1.6
27	Koken et al. 2020 [16]	L,P	NA	Cohort (104/96)	Children having T1DM with MetS vs children without MetS	IDF, WHO, NCEP ATP III WC, TG significantly high ($p<0.001$) and LDL also high ($p=0.05$) in MetS positive	8–18
28	Morandi et al. 2021 [66]	C,P	NA	Cohort (82/72)	girls vs boys	CACTI(eIS) for IR D6D activity with eIS ($r=-0.32$, $p=6.6\times10^{-5}$), TG($r=0.24$, $p=0.003$)	15.5–18.9
29	Gomes et al. 2022 [67]*	C,P	Caucasians 48%	Cohort (183/184)	overweight vs non-overweight	IDF for MetS for 10 to 16, and IDF adult for above 16yrs	10–19
30	Shah et al. 2023 [68]	C,P	Asian	Cohort(38/41)	ALR < 1 vs ALR > 1	Adiponectin to Leptin ratio as MetS marker	10–21

C cross-sectional, *L* longitudinal, *P* prospective, *R* retrospective, *ISS* insulin sensitivity score, *SI* insulin sensitivity, *eGDR* estimated glucose disposal rate, *GIR* glucose infusion rate, *ALT* alanine amino transferase, *eIS* estimated insulin sensitivity, *ALR* Adiponectin to Leptin ratios

*Multicentre study. All other are single centre studies

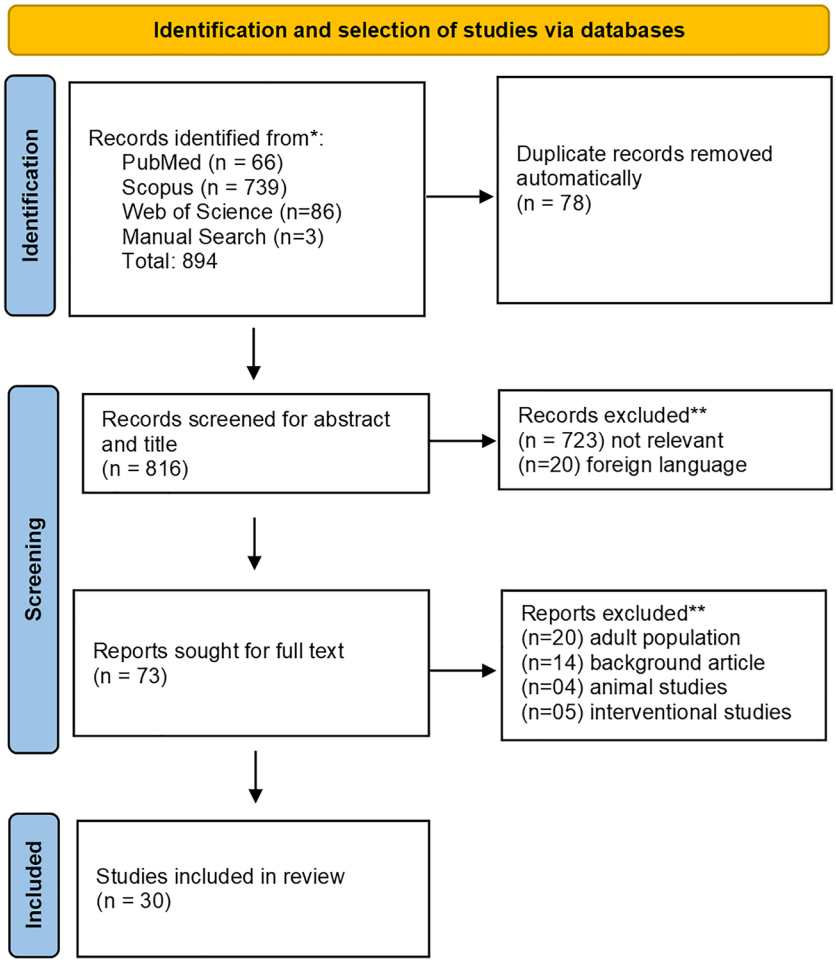

Fig. 1 PRISMA flow diagram for illustration of the identification and screening process. Search terms were used to compile the results in different databases and imported together in software Rayyan for duplicates removal and screening

either prospectively collected or used retrospectively from registries and hospitals.

Qualitative summary and characteristics of studies

As mentioned earlier, we limited our search to observational studies. There were a total of 30 studies with standard and surrogate markers of MetS and IR in T1DM. 12 studies were based on case–control and 18 studies were cohort based. Six studies provided novel markers for IR whereas, 24 studies used existing parameters for IR and MetS. Information about ethnicity was not available for 15 studies (Table 3). Five of the 30 studies compared children with T1DM with children whereas, another 5 studies compared children with T1DM to children with T2DM. Four studies assessed MetS in children with T1DM by grouping them according to IDF criteria. The grouping of studies for IR was difficult as only two studies have classified the children with T1DM on the basis of IR indices (eGDR) [45, 65] (Table 4).

Assessment of markers for MetS in T1DM Four studies out of thirty have grouped T1DM children as being MetS positive and MetS negative (Table 4). The parameters such as units of insulin, HbA1c, WC and lipid profile were selected for our meta-analysis. Summary statistics for fasting glucose and hypertension were not available.

Random Effect Model (REM) was used where, WC ($d = 1.34$, [95% CI: 0.79–1.90]) and TG ($d = 0.85$, [95% CI: 0.14–1.55]) showed significantly large effect size whereas, HbA1c ($d = 0.75$, [95% CI: −0.20–1.71]), and LDL ($d = 0.73$, [95% CI: 0.15–1.32]) showed a moderate effect on MetS. The effect size was significant for LDL but not for HbA1c. On the other hand, HDL ($d = 0.37$, [95% CI: −0.65–−0.10]) showed a significantly small negative effect. Units of insulin dosage ($d = 0.17$, [95% CI: −0.06–0.4]) also showed no significant effect on MetS (Fig. 2).

Assessment of publication bias

No heterogeneity was observed for insulin dose and HDL, however; a heterogeneity was observed for HbA1c, LDL, TG, and WC in the identified datasets (Fig. 2). Since, the latter showed a significant heterogeneity, we decided to

Table 4 Studies that have categorized children with T1DM based on presence or absence of metabolic syndrome and insulin resistance

no	Author	Sample number	Parameters in the study	Origin/other
A. Studies based on the presence or absence of metabolic syndrome				
1	Giuliana Valerio et al., 2012 [57]	411 (39/372)	Insulin dose(U/kg/day), WC (cm), BMI(kg/m^2), W/H ratio, HbA1c(%)	Caucasian of Italian origin, > 1 yr of duration of diabetes
2	M Soliman et al., 2021 [52]	160 (21/139)	Duration of diabetes(yr), insulin dose(U/kg/day), HbA1C, weight, height, BMI(%), SBP(mmHg), DBP(mmHg), WC(cm), TG(mmHg),	Afrocentric ethnicity, 1yrs or > 1 yr diabetes duration
3	OY Koken et al., 2020 [16]	200 (21/179)	Duration of diabetes(yr), family history, insulin dose, Acanthosis, WC(cm), HbA1c(%), TG(mg/dl), HDL(mg/dl), LDL(mg/dl)	Turkish, 4.6 + 3.3yrs of diabetes duration
4	Monika Grabia et al., 2022 [74]	60 (20/40)	WC(cm), W/H ratio, WHtR, BMI (kg/m^2), HbA1C(%), eGDR(mg/kg/min), TC(mg/dl), LDL(mg/dl), HDL(mg/dl), TG(mg/dl), SBP(mmhg), DBP(mmhg)	Polish, 2-7yrs of diabetes duration
B. Studies based on the presence or absence of insulin resistance				
1	Nishtala R et al., 2020 [65]	175 (eGDR < 7.34 = 58, eGDR 7.34–8.92 = 56, eGDR > 8.93 = 61))	Age, sex, ethnicity, duration of diabetes, BMI, HbA1c, eGDR, eGFR, SBP, DBP, TC, HDL, LDL, TG	Mixed(Caucasian 81.7%, African carribean2.3%, south Asian 6.3%, other 2.3%)
2	Dabelea et al., 2011 [45]	1694 (IS = 1248, IR = 446)	Onset age, duration of diabetes, family history, IS score, FCP, GADA titres, BMI as z score, WC	67.9% Non-Hispanic whites (NHWs), 13.3% Hispanics, 13.4% African Americans (AAs), 4.1% Asian/ Pacific Islanders (APIs), and 1.3% American Indians (AIs)

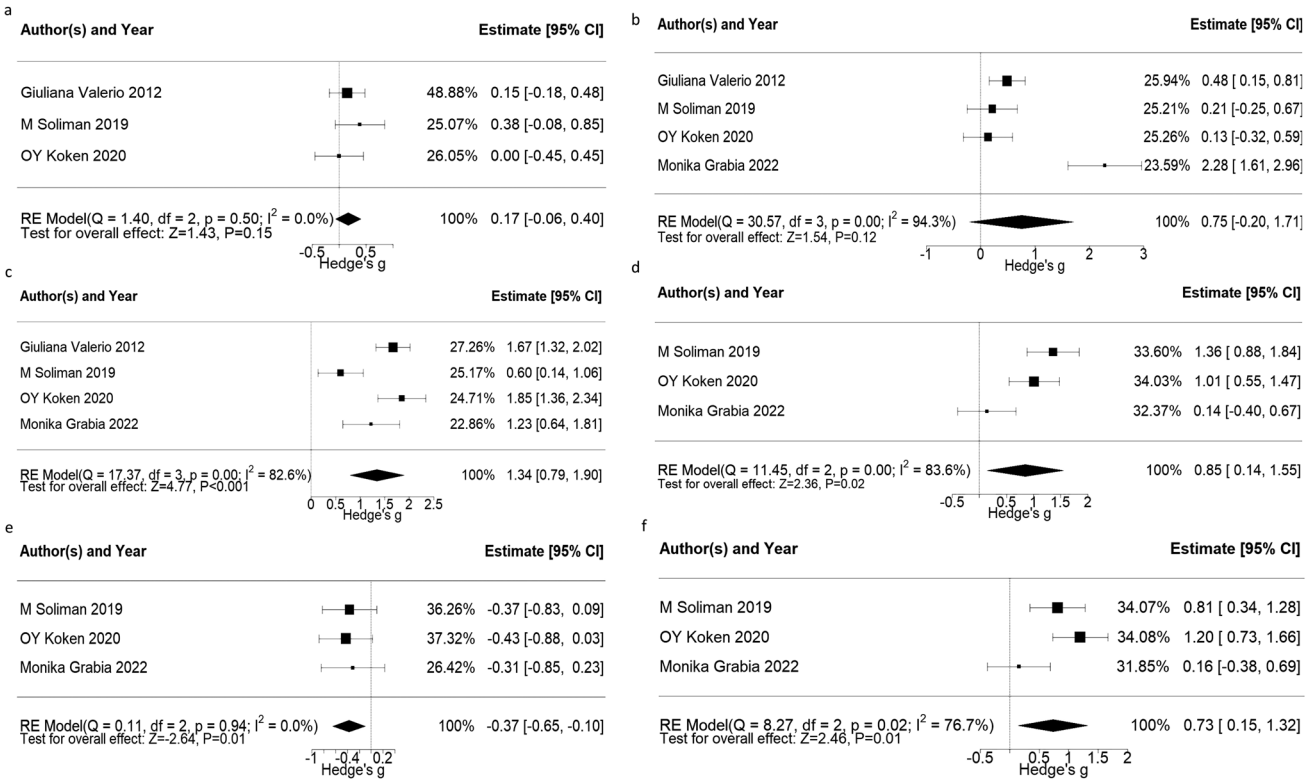

Fig. 2 Comparison between parameters of metabolic positive and metabolic negative groups of type 1 diabetes. (**a**) Insulin dosage, (**b**)HbA1c, (**c**)waist circumference, (**d**)Triglycerides, (**e**) High density lipoprotein, (**f**) Low density lipoprotein

assess the publication bias. A funnel plot analysis was performed for all the markers mentioned above (Supplementary Fig. 1). HDL and the units of insulin did not show any outliers. The publication bias was assessed for the remaining parameters such as HbA1c, WC, TG, and LDL by sequential removal of each study. The study by Monika Grabia et al. 2022 strongly contributed to the heterogeneity for HbA1c, TG, and LDL. Removal of this dataset removed the heterogeneity and improved the effect size of TG (from 0.85 to 1.18) and LDL (from 0.73 to 1). The effect size of HbA1c (from 0.75 to 0.32) on the other hand, reduced. In case of WC, strong heterogeneity was contributed by the study by Soliman et al. 2019. Removal of this dataset improved the effect size of WC (from 1.34 to 1.63). The possible sources of heterogeneity are discussed later. In summary, TG, LDL, and WC seem to have a significantly large effect on MetS (Supplementary Fig. 2).

Assessment of markers for IR in T1DM Out of the 30 studies, only two studies had grouped the participants based on presence or absence of IR [45, 65]. In both these studies the measurement of IR was performed by using eGDR. However, Nisthala et al., 2020, divided the children having T1DM by $eGDR_{BMI}$ and the association of $eGDR_{BMI}$ with different clinical parameters was observed. The study suggested that the population in lower quartiles of $eGDR_{BMI}$ had significantly higher levels of total cholesterol and triglycerides. Dabelea et al., 2011 attempted to segregate the population of children with T1DM and T2DM based on eGDR. The study found stronger association of IR in children with T2DM than in T1DM. The parameters to calculate eGDR and the study design were not consistent between these two studies (Table 4). As a result, we provide a descriptive review of other markers for IR. Some of the markers that include Volume of Oxygen uptake during peak exercise ($VO2_{peak}$), Free Fatty Acid (FFA), Leptin, cIMT (carotid intima media thickness), have been validated using HEC. A few others markers have been validated using indices such as eGDR, SEARCH, and CACTI (Table 3).

Quantitative markers frequently used by clinicians include measurement of insulin dosage in combination with HbA1c [46], central obesity [54], and body fat [8]. Along with HbA1c, family history for T2DM is an important parameter. Central obesity measured by waist to height ratio > 0.5 and BMI > 95 percentile are also suggested parameters for IR [60]. Body fat estimated by thickness of triceps and subscapular skin fold have been used to predict body fat [8]. A qualitative marker: acanthosis nigricans is also used as an indicator of IR; however, it is more related to obesity than IR [45, 52, 53, 55].

Some of the novel quantitative markers such as adiponectin, leptin, fetuin A, and kisspeptin are being investigated for the assessment of IR. A longitudinal study in T1DM children suggested that levels of adiponectin, (a hormone produced by adipocytes with a role in insulin sensitization) were strongly related to WC and insulin dose in 20 yr old adults with T1DM [59]. Adiponectin and leptin (another hormone produced by adipose tissue involved in maintenance of normal body weight), both have been studied in association with IR [48]. It has recently been suggested that leptin may act as a potential biomarker for the detection of IR in T2DM. In case of T1DM, the association of leptin with IR is not very well studied. However, a few reports suggest that fluctuations in leptin levels are observed in children and adolescents with T1DM [48, 62]. Increase in fetuin A, a hepatokine and an adipokine, is associated with IR and obesity. In T1DM, this association was limited to glycemic levels and as a risk predictor for complications of diabetes. Further studies to assess the role of fetuin A in IR are needed. Another hormone, Kisspeptin (produced in the hypothalamus) inversely associates with adiponectin levels and in turn, to insulin sensitivity [75]. However, the association was only studied in reproductive age female population. Further studies will be required to conclude kisspeptin as a marker for IR. Two studies have shown an association of IR markers (increased insulin dose, increased BMI and, increased Dehydroepiandrosterone sulphate (DHEAS) with increased micro-albuminuria [54, 58]. The DHEAS is a precursor for sex hormones and is known to act as an insulin sensitizer. $VO2_{peak}$ which is a measure of cardiovascular and skeletal muscle oxidative function shows a significant moderate positive correlation with HEC (reduced GDR by HEC indicate IR) [44].

Other less studied novel indicators include carbohydrate (CHO) oxidation and Delta 6 desaturase (D6D) activity. The CHO oxidation which estimates the capacity to oxidise a meal in the form of differential 13C/12C enrichment in the expired air using flow isotope mass spectrometry, has been associated with IR. The CHO oxidation showed a moderate correlation with eGDR in T1DM [64]. A high activity of D6D, a rate limiting enzyme in production of long chain Poly Unsaturated Fatty Acids (PUFA) has been associated with decreased insulin sensitivity therefore, increased activity of D6D has been suggested to be a strong marker for IR in T1DM adolescents [66] and non-diabetic adults [76]. All the novel quantitative markers are still under investigation and are not part of routine clinical applications.

Discussion

Metabolic syndrome (MetS) and Insulin resistance (IR) in combination and independently can be the risk factors for CVD. Usually surrogate markers are used for the diagnosis of MetS and IR in children with T1DM. We performed a systematic review and a meta-analysis to study the effect size of the parameters for the diagnosis of MetS in children with T1DM. Participants with T1DM aged < 25yrs were included due to the lack of experimental evidence for the cutoffs in this age group. To focus specifically on metabolic syndrome, we excluded participants with complications related to T1DM or those taking medication other than insulin therapy. Inconsistency in measurement methods made it challenging to perform a similar meta-analysis for IR (Table 4).

In our meta-analysis, insulin dosage and HbA1c showed low effect size suggesting that the MetS appears independent of glycemic condition in children with T1DM (Fig. 2a, b). WC was strongly associated (with large effect size) with MetS in T1DM (Fig. 2c). Since, all four studies made use of the IDF criteria which require central obesity as a mandatory component for the assessment of MetS, this association was expected. However, this association was observed with a considerable heterogeneity that was contributed by Soliman et al. (2019). The study cohort was from Egypt and the population has been shown to have a different cut-off for WC for obesity [77]. Removal of this study removed the heterogeneity and increased the effect size (Supplementary Fig. 2). Our results fall in line with previous studies where WC predicted MetS in adults with T1DM [78] and was significantly associated with MetS in children who did not have diabetes [79].

Increased TG and LDL were also associated (large and moderate effect size respectively) with MetS in children with T1DM (Fig. 2f). The source heterogeneity contributed to this association may have been from the attempt to convert median and interquartile range provided by Monika Grabia et al. (2021) to mean and standard deviation [43]. The omission of this study did not alter the effect size for TG whereas, effect size for LDL improved from moderate to large (Supplementary Fig. 2). TG are already a part of IDF criteria and together with WC provide a better diagnostic efficiency for MetS [80]. Considering that LDL is not a part of the IDF criteria for MetS, the strong association of LDL with MetS is noteworthy. Increased LDL is suggested to be a risk factor for CVD [81]. Significantly increased LDL was observed in children who do not have diabetes but, had predisposition to MetS [82]. Moreover, reduction in LDL levels are suggested as a treatment strategy by the IDF [83]. This reflects the significance of LDL in MetS. Therefore, increased LDL can be used as one of the parameters to screen for MetS in children with T1DM. However, LDL alone might be an insufficient indicator and may thus be used along with other parameters in the assessment of MetS [84]. HDL is one of the parameters proposed by the IDF, WHO, and NCEP III to screen MetS. HDL is known to have a negative association with MetS

which was reflected in our analysis. All datasets showed homogeneity for HDL; however, the cumulative effect size of HDL was moderate. Other than lipid profile, some inflammatory markers such as adiponectin and leptin are under investigation for their association with cardiometabolic risk in children with MetS [68].

For IR, we came across only two studies where young people having T1DM were classified based on presence or absence of IR. Diverse designs and varying parameters to test IR made the compilation of studies difficult. We came across a large number of non-invasive and invasive parameters used to assess IR in T1DM. Most of them are quantitative in nature (Supplementary Table 2). Routinely used quantitative measures include BMI and waist-to-height ratio. Increased BMI was one of the components for IR detection. However, with recent observations of IR in lean children with T1DM [46], it has become evident that people especially of Asian ethnicity may follow a 'thin fat' phenotype with low normal BMI, and high percent fat [55]. Therefore, waist-to-height ratio may be a better marker than BMI for IR detection. Increased dose of insulin is observed in children having T1DM with IR. Insulin dosage may vary depending on the meal type, physical activity etc. Thus, insulin dose may not represent the accurate status of IR in children with T1DM. A qualitative marker-Acanthosis Nigricans (AN) may be observed as a result of abnormal proliferation of keratinocytes due to excessive binding of insulin to insulin like growth factor receptor rather than insulin receptor [85]. Acanthosis is observed to be associated with obesity more than IR.

Among the novel markers, breath test and cIMT offer least invasive methods for detection of IR. The breath test assesses the capacity to oxidize exogenous carbohydrates which directly correlate with eGDR and ISS significantly. This is presented by enriched C12/13 in expired breath [64]. This method being non-invasive can be more applicable to large paediatric cohorts. The cIMT (carotid intima media thickness), an early sign of atherosclerosis correlates moderately with insulin sensitivity is not a direct measure for IR. Its use in assessing the cardiovascular risk is limited. Moreover, the test is expensive and difficult to add in to a routine check-up.

Investigations of hormones involved in the pathogenesis of IR could provide valuable insights. Most of these hormones are novel and under investigation. These hormones actively participate in metabolic regulation and include adiponectin, leptin, fetuin A, kisspeptin etc. Adiponectin an insulin sensitizer produced by adipose tissue, involved in regulation of gluconeogenesis is suggested to be reduced in participants with T1DM [48] (Table 3). Adiponectin showed a strong discriminatory power for detection of IR in adolescents who did not have diabetes [86, 87]. Leptin, an appetite suppressing hormone, plays a role in energy balance by reducing energy uptake and increasing energy expenditure. Similar to adiponectin, leptin it is produced by white adipose tissues and shows negative correlation with insulin sensitivity. The evaluation of the ratio of both these hormones has been limited in adolescents who do not have diabetes [88]. Fetuin A, an inhibitor of insulin receptor tyrosine kinase activity is a suggested marker for IR in adolescents with no signs of diabetes [89]. Kisspeptin was observed to be higher in people with IR [75]. All these hormones lack assessment of their role as marker in children with T1DM and validation against HEC. An understanding of the pattern of these hormones with respect to IR provides a window for development of novel indices for the diagnosis of IR.

Other markers that are least understood and are under investigation include reduced D6D activity. Erythrocyte D6D activity has been suggested to be a strong marker of IR in T1DM [66]. D6D is a desaturase enzyme that introduces a double bond in a specific position of long chain fatty acids. Reduced activity of D6D can interfere with the fatty acid composition. The detailed explanation of this reduced activity is beyond the scope of our review. However, to consider D6D as an IR marker, more detailed studies are required.

Strengths and limitations of the study

To the best of our knowledge, this is the first systematic review and meta-analysis for assessment of surrogate markers for MetS and a systematic review for IR in children with T1DM. However, for the IR, the studies are reported in different forms of indices which made it difficult for us to compile them for the assessment of IR markers. Also, this systematic review could not assess the effect of age and pubertal status on the accuracy of markers of MetS and IR. The number of studies available for meta-analysis are very small hence, with increasing reports there are chances that the results may improve in future.

Conclusion

From the results it can be concluded that in the children with T1DM, markers of glycemic levels are not associated with MetS. Other than TG and HDL, LDL may also be considered in the diagnostic criteria for MetS. A combination of WC and TG may increase the efficacy of MetS diagnosis in paediatric population living with T1DM. Many novel markers currently under investigation for the diagnosis of IR need evaluation against HEC. These markers may be used in combination to increase the accuracy of IR diagnosis.

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Data Availability No new data generated. Data sharing not applicable.

Code availability https://github.com/macdlab/2023_SK_T1DM_metanalysis

Declarations

Systematic review registration PROSPERO CRD42023418954.

Ethics declaration No ethical approval was needed as the data was collected from previous published studies in which the informed consent was obtained by primary investigators.

Conflict of interest The authors declare that they have no conflict of interest.

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