Insulin Resistance in Adolescents and Youth With Type 1 Diabetes: A Review of Problems and Solutions

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ABSTRACT: Though insulin resistance (IR) was previously considered a feature of only type 2 Diabetes (T2DM), its development in type 1 Diabetes (T1DM) is not an uncommon occurrence, the causes of which are multifactorial (gender, pubertal status, diabetes duration, ethnicity, genetics, adiposity, glycemic control, chronic inflammation). Despite improvements in glucose, blood pressure and lipid profile, vascular complications (coronary artery disease and nephropathy) continue to remain common causes of morbidity and mortality in T1DM. Aggressive glycemic control reduces but does not eliminate the risk of IR. IR accelerates the development of micro and macrovascular complications, many of which can be potentially reversed if diagnosed and managed early. Lack of endogenous insulin production makes estimation of insulin sensitivity in T1DM difficult. As hyperinsulinemic-euglycemic clamp studies are cumbersome and invasive, the use of prediction equations for calculating estimated insulin sensitivity may prove to be useful. Along with intensive insulin therapy, dietary modifications and increasing physical activity, the role of Metformin in managing IR in T1DM is becoming increasingly popular. Metformin adjunct therapy in T1DM has been shown to improve insulin sensitivity, glycemic control, lipid profile, body composition, vascular smooth muscle function, thereby reducing the risk of vascular complications, as well as reversal of early vascular dysfunction. However, further studies to assess long-term efficacy and safety of Metformin use in adolescents and youth with T1DM are needed. This review aims at revisiting the pathophysiology of IR in T1DM and techniques of identifying those at risk so as to put into action various strategies for management of the same.

KEYWORDS: Insulin resistance, double diabetes, Metformin, hyperinsulinemic-euglycemic clamp, intima media thickness

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Introduction

Type 1 Diabetes mellitus (T1DM) is a chronic condition caused by progressive destruction of the pancreatic beta cells and is characterized by insulinopenia and the need for exogenous insulin administration. As per the International Diabetes Federation 2021 report, the incidence and prevalence of both type 1 and 2 diabetes is increasing globally.[1] Insulin resistance (IR) defined as defective insulin-stimulated glucose uptake in muscle and adipose tissue and impaired insulin suppression of hepatic glucose output was previously considered to be a distinct feature of only the type 2 Diabetes (T2DM) phenotype.[2] However, there is now increasing evidence of IR in T1DM. A study by our group has demonstrated an increased prevalence of obesity and metabolic syndrome in Indian children and adolescents, including in children with T1DM.[3,4]

IR implies an attenuated response of target tissues to the action of insulin. Initially thought to occur only as a result of poor glycemic control and obesity, it has now been demonstrated that even with aggressive insulin therapy, the risk of IR is not completely eliminated. Despite improvements in glucose, blood pressure and lipid profile, vascular complications such as coronary artery disease and nephropathy continue to remain common causes of morbidity and mortality in T1DM.[5] Moreover, although IR has been documented in adolescents with T1DM possibly as a result of increasing rates of obesity, non-obese adolescents with T1DM too have been shown to have higher insulin resistance as compared to BMI-matched healthy peers.[6,7] Thus, besides poor glycemic control and obesity, a complex interplay of various other governing factors have been postulated to cause IR in T1DM.

The development of IR in T1DM poses a threat as it is known to initiate and accelerate both micro and macrovascular complications. Studies have demonstrated an inverse association of cardiometabolic disease risk with estimated insulin sensitivity (IS) in adolescents with T1DM.[8] Various studies have observed correlations of reduced IS with microalbuminuria and predicted glomerular function decline over 6 years and have also predicted remission of albuminuria in adults with T1DM following improvement in insulin sensitivity.[9-11] Similarly, the odds of developing diabetic retinopathy and neuropathy are predicted by baseline estimated insulin sensitivity.[10,11]

Methodology

In this narrative review article, we focus our attention on pathophysiology of IR in T1DM and techniques for identifying those at risk to put into action various strategies for management of the same. The major databases that we searched included PubMed, MEDLINE, Embase, and Cochrane and the search terms we used were type 1 diabetes mellitus, children, adolescents, insulin resistance, metabolic syndrome and double diabetes. We reviewed randomized control trials, narrative reviews and meta-analysis, recommendations, and guidelines, pertaining to insulin resistance in children and adolescents with T1DM.

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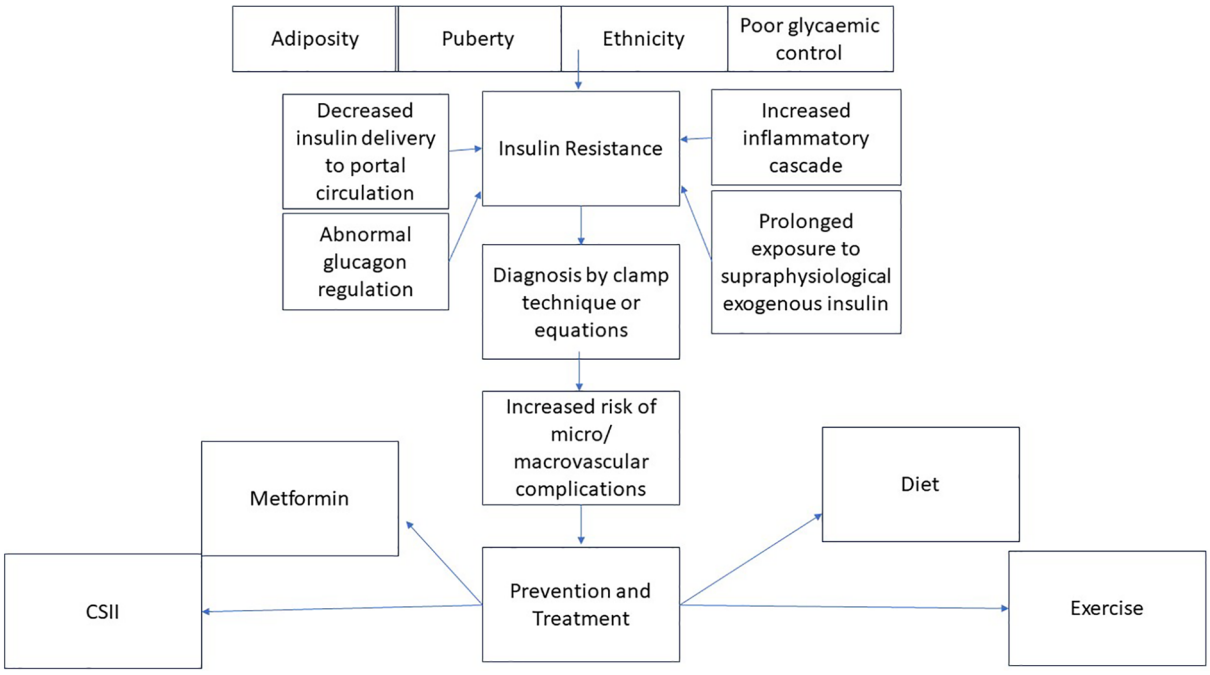

Figure 1. A diagrammatic representation of pathophysiology of insulin resistance in T1DM, triggering factors and as strategies for management.

Risk Factors and Pathophysiology

The pathogenesis of IR in T1DM involves a complex interplay between genetics, glycemic control and environmental factors. Various plausible hypotheses have been proposed based on animal models and hyper insulinemic-euglycemic clamp studies in humans.[12] A diagrammatic mechanism of pathophysiology of insulin resistance in T1DM, triggering factors those at risk as well as strategies for management are highlighted in Figure 1.

Role of chronic hyperinsulinemia

As IR is characterized by reduced responsiveness of tissues to the action of insulin, it is associated with increased insulin secretion following a meal or an increased requirement of exogenous insulin to maintain euglycemia. However, chronic hyperinsulinemia itself can aggravate IR, thus leading to a cause-effect vicious cycle.[13] Chronic exposure to elevated insulin levels leads to internalization and degradation of insulin receptors, thereby requiring higher insulin dosage to elicit the same response, thus perpetuating the cycle. Hyperinsulinemia also triggers weight gain by causing polyphagia due to hypoglycemia, as well as by lipogenesis. Thus, a self-perpetuating cycle of hyperinsulinemia, obesity, increased insulin requirement and insulin resistance is likely to set in.[13]

Role of obesity and adiposity

Similar to the role of obesity in the development of IR in metabolic syndrome or T2DM, its role in the development of IR in T1DM cannot be undermined. Increased adiposity results in a cascade of pro-inflammatory cytokine and adipokine (leptin) production and impaired insulin receptor signaling thereby resulting in IR.[12] Excessive adiposity leads to overproduction of antagonist hormones namely growth hormone (GH), glucagon, cortisol and catecholamines as well as increased free fatty acids (FFA). Chronically elevated FFA levels are used in preference to glucose as energy sources leading to elevated blood glucose levels, thus increasing the insulin requirement.[13] Elevated FFA's also interfere with insulin-mediated signal transduction, thereby attenuating the response to insulin.[5] Chronic hyperglycemia and hyperlipidemia induce a state of oxidative stress. This in turn interferes with insulin signaling by affecting glucose transporter 4 (GLUT4) transcription, mitochondrial activity or insulin receptor substrate phosphorylation.[13]

Role of inflammatory cascade

T1DM is characterized by a pro-inflammatory state, with the presence of auto-antibodies against insulin, islet cells and insulin receptors. These antibodies may also interfere with the action of exogenous insulin. Development of antibodies to exogenous insulin and erratic absorption from lipodystrophic sites causing wide fluctuations in blood glucose may also contribute to IR in T1DM. Moreover, chronic hyperglycemia leads to the production of advanced glycation products which have been demonstrated to trigger and propagate inflammation.[12] Oxidative stress, adipose tissue enlargement (producing pro-inflammatory adipokines like leptin) and endothelial damage as a consequence of gluco and lipotoxicity lead to a pro-inflammatory state and increase the production of tumor necrosis factor α (TNF- α) and interleukin-6 (IL-6), which in turn cause pancreatic beta cell damage, modulation of regeneration processes and thus IR.[13]

Exogenous administration of insulin

In healthy individuals, in response to a glucose load, insulin is secreted into the portal circulation whereby it reaches the liver to suppress hepatic glycogenolysis and gluconeogenesis and increases glucose utilization. Exogenously administered insulin lacks delivery into the portal circulation, thereby bypassing the hepatic effects of insulin, with subsequent lower IGF-1 production and lesser feedback suppression of antagonist hormones.[5,12]

Role of gender and pubertal status

Various studies have observed gender differences in insulin sensitivity in patients with T1DM.[14] Millstein et al observed greater differences in FFA concentration in women compared to men with T1DM during the first and second stages of hyperinsulinemic-euglycemic clamp studies.[15] Even in euglycemic clamp studies on healthy children, girls were found to be more insulin resistant at all Tanner stages, which could only partly be explained by differences in skinfold thickness (adiposity).[16] Irrespective of the presence of T1DM, insulin resistance in puberty has been demonstrated in various studies owing to elevated GH and sex steroids. The presence of diabetes aggravates pubertal IR. A study on non-obese pre-pubertal children with T1DM demonstrated a 42% lower insulin sensitivity compared to healthy pre-pubertal controls, with a further drop in sensitivity by 30% during mid-puberty.[17] IR during puberty has been attributed to alterations in the GH/IGF-1 (Insulin-like Growth Factor-1) axis. Patients with T1DM exhibit pronounced GH secretion but low IGF-1 levels. Impaired hepatic IGF-1 production owing to intervals of relative hepatic insulin deficiency (probably as a result of portal bypassing of exogenous insulin) provides negative feedback, leading to a rise in GH levels with a consequent insulin-antagonizing effect.[5,14]

Ethnicity and genetics

There exists a spectrum of severity of IR in T1DM. A complex interplay of genetic, ethnic and hereditary factors together with modifiable factors is postulated to be causative. Asian Indians are known to have a greater degree of insulin resistance compared to Caucasians.[18,19] Mohan et al demonstrated for the first time that Asian Indians have higher insulin levels following a glucose load compared to Europeans.[20] Euglycemic clamp studies have demonstrated that insulin resistance is greater among Asian Indians versus age, sex and body mass index matched Europeans.[21] IR assessed by the estimated glucose disposal rate (eGDR), was reported to be higher in non-Hispanic blacks and Hispanics than in non-Hispanic whites.[22,23]

Another study has also demonstrated that even after adjustments for factors like age, gender and adiposity, non-Hispanic Whites and African Americans had significantly higher insulin sensitivity than their South Asian and East Asian counterparts.[24] The race/ethnic disparities in IR are explained by evolutionary changes made in some factors like body composition and energy dynamics that affect insulin sensitivity. As these factors altered, novel genetic variations or mutations may have pushed some subpopulations to different points of stability.[25]

Apart from the above factors, family history of T2DM is found to have a strong association with IR in T1DM. A study conducted by the authors group demonstrated an increased risk of development of metabolic abnormalities in patients with T1DM whose parents had metabolic syndrome.[26] Many single nucleotide polymorphisms (SNPs) are associated with IR in the general population.[27] Miller et al demonstrated that the A allele of rs12970134 was associated with significantly worse IR ($P = .02$).[28] Todd et al postulated that the amino acid at 57th position of the DQB3-chain is strongly correlated with IR in T1DM.[29]

Diagnosis

Many methods and indices are available for the estimation of IR. For clinical use, homeostasis model assessment (HOMA-insulin resistance), quantitative insulin sensitivity check index (QUIKI), and Matsuda are suitable, while HES, McAuley, Belfiore, Cederholm, Avignon and Stumvoll index are suitable for epidemiological/research purposes.[30] Due to lack of endogenous insulin in T1DM, the use of these methods which are based on oral (OGTT) and intravenous glucose tolerance tests (IVGTT) to assess insulin sensitivity (IS) are not accurate. There are no guidelines that make specific recommendations on how to test for IR in subjects with T1DM.

Hyperinsulinemic–euglycemic clamp

The hyperinsulinemic-euglycemic clamp is the gold standard method of measuring IS in T1DM by estimating the glucose disposal rate (GDR).[5] The hyperinsulinemic-euglycemic clamp method, first described by DeFronzo et al involves intravenous insulin infusion at a steady rate in subjects after overnight fasting.[31] The blood glucose is maintained at a predetermined level by titrating the glucose infusion rate (GIR). Hyperinsulinemia enhances glucose uptake in skeletal muscle and adipose tissue and suppresses lipolysis and endogenous glucose production. The amount of glucose needed to maintain euglycemia is inversely related to degree of IR.[32] However, as performing the clamp study is too cumbersome in routine clinical practice, IS estimation equations demonstrating strong association with measured insulin sensitivity have shown promising results. IR is increasingly being identified as a risk factor for coronary artery disease and other complications of diabetes, but due to the difficulty of executing clamp studies, it is not practical to measure IS directly in large epidemiological studies.

Insulin sensitivity prediction equations

The application of an equation to estimate IS using easily measured clinical factors could therefore be used to further examine the relationship of IS with complications and the impact of interventions on IS in people with T1DM. These equations could be used to identify those at highest risk of complications and would allow clinicians to individualize preventive strategies. Insulin sensitivity prediction equations from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC), the SEARCH Study (SEARCH) and the Coronary Artery Calcification in Type 1 diabetes study (CACTI) are available, with others currently under development.[8,33,34]

Pittsburgh epidemiology of diabetes complications study (EDC). The EDC Study prospectively evaluated subjects with childhood-onset T1DM and developed an Insulin Resistance Score (IRS) based on waist hip ratio (WHR), hypertension, high density lipoprotein cholesterol (HDL-c), triglyceride concentration and family history of T2DM. An ascending order of scores (1 -3) for likelihood of IRS was assigned for each risk factor. Based on IRS score tertiles, 24 eligible subjects were recruited from the study cohort and were administered an overnight insulin infusion to normalize glucose levels. GDR was determined during the last 30 minutes of a 3-hour hyperinsulinemic-euglycemic (60 mU/m^2/min) clamp. Using linear regression, the combination of WHR, hypertension, and glycated hemoglobin yielded the highest adjusted R^2 value. The term glycated hemoglobin encompasses both haemoglobinA1(HbA1) and haemoglobinAlc (HbA1c). HbAl refers to the non-enzymatic binding of several species of carbohydrate to hemoglobin, whereas in HbAlc the carbohydrate is specifically glucose.[35] This model estimated GDR, in mg/kg/min as follows: 24.31 – 12.22 (WHR) – 3.29 (HTN) – 0.57 (HbA1).[33] This formula has been modified for the use of HbA1c instead of HbA_1.[36]

Search. The SEARCH for Diabetes in Youth study (Colorado, USA) evaluated 60 subjects aged 12 to 19 years with childhood T1DM, along with subjects of T2DM and normal healthy controls for the hyperinsulinemic-euglycemic clamp procedure.[37] Participants with HbA1c below 12%, normal hemoglobin and hematocrit and serum creatinine below 114 µmol/L were included in the study. Those with a history of recent use of medications likely to affect insulin sensitivity, those who were unable to stop metformin intake before the clamp procedure or those with history of severe illness/diabetic ketoacidosis in the past 60 days were excluded. The hyperinsulinemic-euglycemic clamp was started with an infusion of regular human insulin at a steady rate of 80 mU/m^2/min for a duration of 3 hours, during which the plasma glucose was sustained at 5.5 mmol/L by simultaneous intravenous infusion of 20% dextrose, based on plasma glucose determinations every 5 minutes. The mean glucose infusion (mg/kg/min) needed to preserve euglycemic status during the last 30 minutes of the clamp was used to calculate GDR (M value). Authors regressed the log eGDR value on demographic (age, gender, ethnicity) and clinico-metabolic parameters (BMI, waist circumference, Tanner stage, blood pressure, serum lipids, fasting C-peptide, HbA1c, urine albumin: creatinine ratio). The equation for estimated IS score calculation was derived as: log eIS = 4.64725 – 0.02032 (waist; cm) – 0.09779 (HbA1c; %) – 0.00235 (Triglyceride; mg/dL).[34] However, in the light of the apparent differences in the presentation of insulin resistance in T1DM and T2DM, combining participants with T1DM and T2DM into a single equation may also be less than ideal for studies focused on T1DM alone.

Coronary artery calcification in type 1 diabetes study (CACTI). An IS prediction equation (eIS) was developed from the CACTI study from youth and adults (36 with T1DM, 41 nondiabetic) subjected to the hyperinsulinemic-euglycemic clamp to develop a clinically useful eIS for T1DM and nondiabetic individuals. The best fit formula to calculate eIS was stated as: exp (4.06154-0.01317 × waist [cm] – 1.09615 × insulin dose [daily units per kg] – 0.02027 × adiponectin [µg/mL] – 0.27168 × triglycerides [mmol/L] – 0.00733 × DBP [mm Hg]). As fasting is not always feasible and adiponectin is not routinely measured, an additional non-fasting model (eIS-nf) and a model excluding adiponectin (eIS-exA) were developed as follows: non-fasting eIS = exp (4.61476 – 1.53803 [daily insulin dose per kg body weight] – 0.02506 [waist circumference in cm]); eIS excluding adiponectin = exp (4.1075 – 0.01299 [waist circumference in cm] – 1.05819 [daily insulin dose per kg body weight] – 0.00354 [triglycerides, mg/dL] – 0.00802 [diastolic blood pressure, mm Hg]).[8]

A consensus on the best accepted measure of eIS appropriate for clinical use is yet to be achieved. eGDR is the most commonly used equation for calculating eIS. Various studies have compared insulin sensitivity using these equations and have found variable results.[8,38-40] The author's group in a study on subjects from their center found that IS by SEARCH equation had highest accuracy in identifying IR and hence proposed its use in clinical practice in adolescents with T1DM at risk of developing metabolic as well as microvascular complications.[41]

Complications

The role of IS in the development of vascular disease in insulin-dependent diabetics was first reported by Martin and Stocks. They reported that in their group of insulin-dependent diabetics, clinical microangiopathy and atherosclerotic disease were associated with insulin insensitivity.[42] Another study in 1993 demonstrated that micro-albuminuric insulin-dependent diabetes patients had reduced peripheral IS as compared to similar diabetic patients without micro/macro albuminuria.[43] Results from the EDC study showed that eGDR (insulin sensitivity) is a predominant predictor of overt nephropathy.[11] The author's group also found estimated glucose disposal rate as an important predictor of diabetic nephropathy.[44] The exact

pathogenesis of reduced IS causing diabetic nephropathy is not known. It has been postulated that insulin resistance possibly leads to elevated glomerular hydrostatic pressure leading to increased renal vascular permeability and thereby glomerular hyperfiltration. Another proposed mechanism suggested is that insulin resistance-mediated increased exposure to non-esterified fatty acids culminates in the development and progression of angiopathy.[5]

The Diabetes Control and Complication Trial (DCCT) demonstrated inverse association of low baseline eGDR with increased risk of development and progression of retinopathy, nephropathy, macrovascular disease and cardiovascular events even after adjusting for insulin dose and the presence of MS.[45] The EDC Study also reported an association of low eGDR with increased risk of peripheral vascular disease, coronary artery disease and nephropathy.[11,46,47] The author's group also reported eGDR as a significant predictor of development of metabolic risk in Indian children with T1DM.[4] Insulin resistance predicts the extent of coronary artery calcification and may contribute to the increased risk of cardiovascular disease in patients with type 1 diabetes.[48]

Retinopathy is a common complication of T1DM affecting 70% to 100% patients. Approximately 12% of intensively managed patients develop it despite of adequate glycemic control.[49] The EURODIAB study found association between serum triglyceride levels and WHR with retinopathy independent of glycemic control. They concluded that insulin resistance is the most likely reason to cause this association which could not be simply explained by obesity because no association with weight was noted. Central obesity (elevated WHR) was observed as the second most important predictor after glycemic control.[49] Chillarón et al reported significantly lower eGDR level in patients with diabetic neuropathy as compared to those without and also observed that all patients with microvascular diseases in T1DM were in the lowest eGDR tertile.[50] Thus insulin resistance in subjects with T1DM is implicated in micro as well as macrovascular complications.

Prevention and Treatment

A multi-pronged approach is needed to tackle the various amendable influences implicated in the genesis of IR. Interventions known to improve metabolic parameters in T2DM are also beneficial in T1DM. Exercise and diet are crucial targeted interventions to prevent and treat IR in T1DM. Table 1 enlists study results related to improvement in insulin sensitivity in children and youth with T1DM

Dietary modifications

Certain studies have demonstrated higher levels of saturated fat consumption among individuals with T1DM as compared to their non-diabetic counterparts.[51,52] High fat intake in turn influences the development of dyslipidemia, IR and coronary artery disease. In a study conducted by Grabia et al among adolescents with T1DM, it was observed that patients with low HDL cholesterol or elevated triglyceride levels consumed high amounts of saturated fats, low monounsaturated fatty acids, Ecosapentanoic acid, Docosahexanoic acid, and Linoleic acid.[53] International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends the inclusion of vegetables, whole grains, fruits and low fat foods in the diet.[54] Dietary modifications have been shown to improve insulin sensitivity, despite no changes in body weight or glycemic control.[12] Studies have shown that HDL concentrations increase by 0.4 mg/dL for every kilogram of body-weight loss and by 6 mg/dL following moderate physical activity of approximately 300 minutes/week.[55] However, reducing trans-fats and carbohydrates in the diet and favoring unsaturated fatty acids yields the best results.[56] Lowering triglycerides requires preventing under-dosing of insulin and reduction in body weight and in consumption of simple carbohydrates together with replacing saturated fatty acids with polyunsaturated fatty acids and regular physical activity. This leads to improved tissue insulin sensitivity, and lowers triglyceride levels.[56-58] Omega-3 fatty acid consumption (approx. 2-4 g/day) not only reduces triglycerides by 25% to 30%, but is also shown to have a beneficial effect on inflammatory markers.[59] The author's group in an attempt to study the role of dietary macronutrient composition in development of double diabetes (DD) in Indian youth found diet to be an important modifiable risk factor in the development of IR in subjects with T1DM and reported that high protein, low fat and optimum carbohydrate diet may lead to an improvement in IR. They also concluded that increased intake of dietary fiber may prevent the development of IR in subjects with T1DM and thereby, reduce the burden of DD [unpublished work] Another study has demonstrated that low-fat diet improves peripheral insulin sensitivity in patients with T1DM.[60]

Physical fitness

Studies have demonstrated an association of higher physical fitness with lower HbA1c in youth with T1DM.[61,62] A few small studies have observed a decrease in daily insulin requirement following strength training and aerobic exercise compared to routine daily activities.[63] Higher energy expenditure is shown to be associated with an increase in cardiorespiratory fitness in adults with T1DM.[64] Long-term exercise routines have demonstrated a dramatic (20%-60%) improvement in whole body insulin sensitivity, with low or moderate hepatic insulin sensitivity changes.[65-67] Six to 12 weeks activity training (cycling or aerobic training) has shown improved insulin sensitivity, reduced daily insulin dosages, despite no changes in HbA1c.[66]

Metformin adjunct therapy

Metformin, a biguanide compound has been widely used for the treatment of T2DM. The activation of energy regulating

Table 1. Study results related to improvement in insulin sensitivity in children and youth with T1DM.

STUDY/TRIAL NAME	STUDY PARTICIPANTS	INTERVENTION	RESULT
Yki-Järvinen et al[65]	Seven T1DM patients treated CSII, and Six controls	6-wk training program consisting of cycle ergometer exercise 1 h/day 4 times a week.	Insulin sensitivity as determined by the euglycemic clamp technique was 25%-40% better in the training group
Wallberg-Henriksson et al[66]	Nine male, insulin-dependent diabetic patients	16-wk training program consisting of 1 h of jogging, running, ball games, and gymnastics, performed 2-3 times/wk.	Insulin sensitivity as determined by the insulin clamp technique increased 20%
Landt et al[67]	nine adolescents with T1DM; six age-matched adolescents with T1DM of equivalent duration served as controls	exercise training consisting of three weekly sessions, each 45 min long, for 12 wk	Insulin sensitivity, assessed via the euglycemic clamp technique showed an increase of insulin sensitivity of 23 ± 5%
Rosenfalck et al[60]	Ten T1DM patients and Ten non-diabetic, matched controls	Isocaloric low-fat diabetes diet during two, 3-mo	There was a significant improvement in insulin sensitivity in the isocaloric, low-fat diet compared with the standard diabetes diet [7.06 ± 2.16 mg/kg/min vs 5.52 ± 2.35 mg/kg/min]
Bjornstad et al[70]	Forty-eight adolescents with T1DM who were 12 to 21 y of age (40% body mass index [BMI] ⩾90th percentile; 56% female) and 24 nondiabetic control participants of similar age, BMI, and sex distribution	Adolescents with T1DM were randomized 1:1 to 3 mo of 2000 mg metformin or placebo daily	Adolescents with T1DM in the metformin versus placebo group had improved glucose infusion rate/insulin ratio
Särnblad et al[71]	26 adolescents with T1DM (18 females, 8 males) in a double-blind placebo-controlled trial.	The participants were randomized to receive oral metformin or placebo for 3 mo.	Peripheral glucose uptake divided by mean plasma insulin concentration was increased in the metformin group ($P < .05$) but not in the placebo group.
Oza et al[76]	59 Indian adolescents with T1DM were distributed uniformly by gender and puberty across two groups	The intervention group received metformin (weight <60 kg received 500 mg twice daily and more than 60 kg received 1 g twice daily) and non-metformin group received standard of care for diabetes.	The mean improvement in IS ranged from 1.4% to 4.6% in participants on metformin as opposed to deterioration of 2% to 14.1% in non metformin group.
Yki-Järvinen et al[65]	10 T1DM patients whose mean duration of diabetes was 8 y.	CSII therapy for 6 wk	Total glucose uptake increased by 27%

enzyme AMP-activated protein kinase (AMPK) in the muscles and liver is thought to be the predominant mechanism of its action, thereby suppressing hepatic glucose production and increasing glucose utilization. It also plays a minor role in decreasing glucose absorption.[68] Owing to its action on increasing lipoprotein lipase activity, it lowers total and LDL cholesterol and triglycerides.[13] Its use in T2DM decreases fasting plasma glucose, improves HbA1c and induces weight loss. Apart from modest reductions in LDL and triglyceride concentrations, Metformin has also been shown to have anti-inflammatory effects by decreasing C-reactive protein, platelet activation and pro-coagulant factors.[69] The favorable effect on dyslipidemia is postulated to be via mechanisms different than those for glycemic control. Thus, Metformin could be a potential drug for improving insulin sensitivity as well as improving cardiometabolic parameters in T1DM.

Few studies have been conducted to assess the effect of Metformin adjunct therapy in adolescents and youth with T1DM. A randomized controlled trial by Bjornstad et al demonstrated a significant reduction in weight, BMI, fat mass, daily insulin dose per kg body weight, improvement in insulin sensitivity (assessed by glucose infusion rate/insulin) regardless of weight, insulin dose, fat mass, improvement in markers of vascular health (far wall carotid intima media thickness [cIMT], MRI-derived maximal aortic wall shear stress) without any significant changes in HbA1c, blood pressure, lipid profile following 3 months of Metformin adjunct therapy.[70] Särnblad et al observed a significant reduction in HbA1c from 9.6% to 8.7% and an increase in peripheral glucose uptake: mean plasma insulin ratio among adolescents with T1DM following 3 months of Metformin treatment thus implying a beneficial effect on glycemic control.[71] A study by Lund et al in

adults with T1DM revealed a significant reduction in total and LDL cholesterol (even after adjusting for statin use and cardiovascular disease) without any significant reduction in HbA1c following 12 months of Metformin adjunct therapy compared to placebo.[72] A systematic review and meta-analysis by Liu et al in 2016 reports slightly lower HbA1c levels on Metformin compared with placebo (MD = −0.37, 95% CI: −0.64 to −0.09), reduction in total daily insulin per kg (MD = −0.11, 95% CI: −0.15 to −0.06), significantly reduced BMI, body weight and variable effects on lipid profile, metabolic effects and blood pressure.[68] A review by Khalifah et al yielded similar results.[73] A study by Anderson et al in children and adolescents with T1DM on Metformin for 12 months demonstrated a significant improvement in vascular smooth muscle function (glyceryl trinitrate mediated dilatation of brachial artery), HbA1c and insulin doses with the greatest effect observed at 3 months of Metformin therapy.[74] The Cardiovascular and Metabolic Effects of Metformin in Patients with Type 1 Diabetes (REMOVAL) study assessed cardiovascular and metabolic parameters in adults with T1DM on Metformin adjunct versus placebo and observed a significant reduction in maximal cIMT over 3 years among those on Metformin, and reduction in HbA1c at 3 months time-point which was not sustained thereafter.[75] Bjornstad et al observed significant improvement in vascular structure as observed from reduction in cIMT in the metformin group after adjusting for change in BMI (−0.04 ± 0.01 mm vs −0.00 ± 0.10 mm; $P = .04$) among adolescents with T1DM.[70] Thus, although the effects of Metformin on glycemic control are variable, Metformin holds a promising role in having a cardioprotective effect as evidenced from its beneficial effects on insulin sensitivity, lipid profile and markers of early vascular dysfunction. The author's group in a pilot study to assess the effect of Metformin therapy on prevention of DD in Indian adolescents with T1DM found that the odds ratio and relative risk for the development of DD in participants not subjected to Metformin therapy were 2.0 and 1.4, respectively, as compared to participants on Metformin therapy. The mean improvement in IS ranged from 1.4% to 4.6% in participants on metformin as opposed to deterioration of −2% to −14.1% in the non-metformin group. We thus concluded that Metformin may prevent deterioration in IS in Indian adolescents with T1D.[76]

In T1DM, the favorable effects of Metformin are not only restricted to the reduction of insulin resistance but also to the reversal of micro and macrovascular complications when diagnosed sufficiently early. In a study by Pena et al on adolescents with T1DM, a significant association between early signs of atherosclerosis (as evidenced from cIMT) and retinal microvascular changes was observed irrespective of age, gender, HbA1c and blood pressure. For every 0.1 mm increase in mean cIMT, retinal arteriolar caliber increased by 7.90 µm (95% CI 4.50, 11.30, $P < .0001$) and venular caliber by 9.61 µm (95% CI 4.16, 15.06, $P = .0008$).[77] Increased mean aortic IMT was associated with an increase in arteriolar tortuosity (2.61, 95% CI 0.50, 4.71, $P = .02$), emphasizing the importance of early diagnosis and management in an attempt to reverse these changes.[77] Thus, the beneficial effect of Metformin on cIMT could possibly prevent or retard the development of not only coronary vascular disease, but also retinopathy.

Diabetic nephropathy is also associated with increased systemic as well as local inflammation, and the development of insulin resistance accelerates it.[78] One of the early markers of diabetic nephropathy is the development of microalbuminuria, observed much before decline in glomerular filtration rate, creatinine elevation and clinical evidence. As early as 1993, the role of insulin resistance in diabetic kidney disease was demonstrated by Yip et al who observed a significantly lower total-body glucose disposal rate and higher daily insulin dose among T1DM patients with microalbuminuria compared to normoalbuminuric diabetics.[43] The REMOVAL study, reported that metformin could possibly have a nephro-protective effect in adults with T1DM and cardiovascular risk factors as evidenced from better maintained serum creatinine and estimated GFR (eGFR) following metformin therapy administered for a period of 3 years as compared to placebo group.[75] The "Effects of Metformin on cardiovascular function in adolescents with Type 1 Diabetes (EMERALD)" study, also reported an increase in eGFR by serum creatinine following Metformin use for 3 months in 48 youth with T1DM in comparison with the placebo group. No differences were observed in cystatin C, urinary albumin/creatinine ratio or systemic inflammatory markers despite improved eGFR.[78] The nephro-protective effect of Metformin can be postulated to be due to various mechanisms including improvements in insulin sensitivity, dyslipidemia, microvascular dysfunction, glycemic control and possibly by anti-inflammatory effects.

Metformin is a relatively safe drug with few minor side effects, predominantly gastrointestinal that is, nausea, vomiting and diarrhea. Studies evaluating lactate, vitamin B12, serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) as markers of safety have not reported values out of normal reference ranges, nor have they reported any significant increase in hypoglycemic episodes thus rendering Metformin a safe and effective drug in the management of IR in T1DM.[70,74] However, larger multicentric studies with longer duration of Metformin adjunct therapy are needed to further strengthen the evidence for use of Metformin in T1DM.

Continuous subcutaneous insulin infusion (CSII)

Intensive glycemic control using subcutaneous insulin infusion has been postulated to improve insulin sensitivity in patients with T1DM by reducing chronic glucotoxicity and hepatic glucose production.[12] The use of closed loop systems with continuous glucose monitoring on one hand and prediction-based

insulin delivery on the other may possibly improve glycemic control and reduce resistance. In a study on patients with T1DM duration >8 years, 6-weeks continuous subcutaneous insulin administration via infusion improved insulin sensitivity by 27%.[65] A randomized controlled trial (RCT) of closed-loop control in children with T1DM over a period of 16-weeks reported that glucose level was in the target range for a greater percentage of time with the use of a closed-loop system than with the use of a sensor-augmented insulin pump.[79] An improvement in glycemic control may yield improved insulin sensitivity. However, to the best of our knowledge its impact on IR is yet to be studied.

Limitations

Our study is limited by the fact that due to the lack of endogenous insulin in T1DM, we have not been able to report accurate methods for estimation of IR/ IS. Further, we have also not been able to make specific recommendations for assessment of IR in T1DM as no guidelines were identified. Studies describing long term impact of IR on micro and macrovascular complications were also not identified. Long term studies describing studies describing efficacy and safety of Metformin use in T1DM were also scarce. A more comprehensive investigation of hepatic insulin sensitivity, and its possible underlying mechanisms is also needed to shed light on factors contributing to IR in T1DM. Further studies are thus needed to evaluate the factors responsible for and the long-term impact of insulin resistance in TIDM.

Conclusion

To summarize, development of insulin resistance in T1DM is not an uncommon occurrence, the causes of which are multifactorial. IR accelerates the development of micro and macrovascular complications, many of which may be potentially reversed if diagnosed and managed early. Lack of endogenous insulin production makes estimation of insulin sensitivity in T1DM difficult; the use of prediction equations developed from hyperinsulinemic-euglycemic clamp studies may prove to be useful. Along with intensive insulin therapy, the role of Metformin in managing IR in T1DM is becoming increasingly popular. However, further studies to assess long-term efficacy and safety of Metformin use in adolescents and youth with T1DM are the need of the hour.

Declarations

Ethics approval and consent to participate

Not applicable as this is a review article and no participants were involved.

Consent for publication

Not applicable as this is a review article and no participants were involved.

Author contributions

Anuradha Khadilkar: Conceptualization; Supervision; Writing—original draft; Writing—review & editing. Chirantap Oza: Conceptualization; Writing—original draft; Writing—review & editing. Shruti A Mondkar: Conceptualization; Writing—original draft; Writing—review & editing.

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Availability of data and materials

Not applicable.

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