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A Review of Insulin Resistance in Type 1 Diabetes: Is There a Place for Adjunctive Metformin?

Gagan Priya · Sanjay Kalra

ABSTRACT

There is a rising trend of overweight and obesity among individuals with type 1 diabetes. This is often associated with insulin resistance, increased insulin dose requirements and poor glycemic control. Insulin resistance is also seen during puberty and is strongly related to increased risk of cardiovascular disease. The role of metformin as an adjunct to ongoing intensive insulin therapy in type 1 diabetics has been evaluated in several randomized trials, including the recently concluded T1D Exchange Network trial in adolescents and the REMOVAL trial in adults. Metformin reduces the insulin dose requirement, insulin-induced weight gain, and total and LDL cholesterol, but results in an increased risk of gastrointestinal adverse effects and a minor increase in the risk of hypoglycemia. In addition, metformin has been shown to reduce maximal carotid intima media thickness and therefore may extend cardioprotective benefits in type 1 diabetes. The role of metformin as adjunctive therapy in type 1 diabetes needs to be explored further in outcome trials.

Keywords: Type 1 diabetes; Overweight and obesity; Insulin resistance; Adjunctive therapy; Metformin

INTRODUCTION

Type 1 diabetes (T1D) results from an autoimmune destruction of pancreatic β-cells, and the predominant pathophysiology is an almost absolute insulinopenia. Therefore, injectable insulin is the cornerstone of treatment, and advances in insulin therapy have led to an increase in life expectancy of T1D individuals. While there have been significant advances in the development of newer insulin analogs with more physiological pharmacokinetic profiles, continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring, attainment and maintenance of glycemic goals remain formidable challenges in T1D.

Insulin resistance has also been described in T1D and may be a potential target for intervention in addition to insulin therapy. The disease is also characterized by increased glucagon secretion in the postprandial period, and targeting such aberrant glucagon secretion may be another useful adjunctive strategy [1]. In Table 1, we list the limitations of insulin

G. Priya (✉)
Fortis Hospital, Mohali, India
e-mail: gagan.priya@fortishealthcare.com

S. Kalra
Bharti Hospital, Karnal, India

Table 1 Limitations of injectable insulin and role of adjunctive non-insulin antidiabetic therapies in type 1 diabetes

Limitations of injectable insulin therapy	Potential role of adjunctive non-insulin antidiabetics
Pharmacodynamic profiles of available insulins do not completely mimic physiological needs	Improve glycemic control
	Target glucagon dysregulation
Risk of iatrogenic hypoglycemia	Reduce glycemic variability
Insulin-induced weight gain	Reduce postprandial glycemic excursions
Poor patient adherence	Target insulin resistance
Unable to address glucagon dysfunction	Reduce insulin dose requirement
Psychological stress	Reduce insulin-induced weight gain
	Lipid management
	Reduce risk of microvascular and macrovascular complications

therapy and the potential role of adjunctive non-insulin antidiabetic agents in type 1 diabetes. Pramlintide is approved for use in T1D, and several other anti-diabetic drugs have been investigated for their add-on role, including metformin, thiazolidinediones, DPP4 inhibitors, GLP-1 analogs, α-glucosidase inhibitors, SGLT2 inhibitors and dual SGLT1-SGLT2 inhibitors [2, 3].

In this review, we discuss the role of insulin resistance in the pathophysiology of type 1 diabetes and the efficacy and safety of metformin as adjunctive therapy to insulin in type 1 diabetic individuals. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed.

RISING PREVALENCE OF OVERWEIGHT AND OBESITY IN TYPE 1 DIABETES

While the traditional view remains that type 1 diabetics are lean with normal body weight, the prevalence of overweight and obesity in type 1 diabetic individuals is increasing in parallel with the global population trends in weight gain [4]. Libman et al. reported that the prevalence of overweight and obesity at onset of insulin-dependent diabetes among children almost tripled from 12.6% to 36.8% between the time periods of 1979–1989 and 1990-1998, following the general population trend [5]. In several cohorts, the prevalence of overweight and obesity in T1D children was reported to be higher than in the normal population, with an estimated 22.1% of T1D children being overweight or obese in the US SEARCH for Diabetes in Youth study cohort [6]. The median BMI was greater than the national reference values in the T1D Exchange (US, $n = 11,435$) and Diabetes Prospective Follow-up (Europe, $n = 21,501$) registries (age 1-18 years), particularly in the US population [7].

Excess weight gain in children was suggested to be an "accelerating factor" [8] for development of T1D in the Pittsburgh cohort [5] and in another study from Finland [9]. A 10% increment in weight was associated with a 50–60% increase in risk of T1D before the age of 3 years and a 20–40% increase from the age of 3–10 years. Obesity after 3 years of age was associated with a two-fold risk of developing T1D [9]. There was also an inverse relation between age at diagnosis and BMI. It has been suggested that insulin resistance associated with childhood obesity increases the demand on β-cells,

increases antigen presentation and accelerates autoimmune damage.

Overweight and obesity may further increase during the individual's lifetime, related to intensive insulin therapy and over-insulization, recurrent hypoglycemia and defensive snacking [10]. In the DCCT trial, individuals in the intensive arm had a 33% increased risk of being overweight, and the mean weight gain was 4.6 kg more than in the conventional arm [11]. In the Pittsburgh Epidemiology of Diabetes Complications Study cohort of 589 type 1 diabetics, temporal patterns of weight were assessed for 18 years. At baseline, 28.6% individuals were overweight and 3.4% obese. The prevalence of overweight increased by 47% and prevalence of obesity increased sevenfold over 18 years [12].

INSULIN RESISTANCE IN TYPE 1 DIABETES

There are obvious technical difficulties in estimating insulin sensitivity in individuals with T1D using traditional methods, and the hyperinsulinemic euglycemic clamp remains the gold standard [13]. Insulin resistance is often observed in type 1 diabetics during pubertal development and inter-current illness. Puberty is associated with a physiological impairment of insulin sensitivity, related to the surge in growth hormone and sex steroids, especially during the later stages of pubertal development. Puberty-related insulin resistance mainly affects peripheral glucose utilization, with less effect on fat metabolism [14]. However, insulin resistance may be more common in T1D and was demonstrated as early as 1982 by DeFronzo et al. [15]. Poor glycemic control in type 1 diabetics is associated with hepatic insulin resistance, while whole-body glucose utilization was reported to be lower even in those who were well controlled [13, 14].

Insulin resistance may be related to obesity, sedentary lifestyle, family history of type 2 diabetes and weight gain associated with intensive insulin therapy. Table 2 enumerates the factors causing increased risk of insulin resistance in T1D. The term 'double diabetes,' coined in 2001, describes individuals who have T1D autoantibody positivity but develop significant insulin resistance [13, 16]. They have lower frequency of high-risk MHC alleles and greater association with genes contributing to risk of type 2 diabetes. These individuals may be at high risk of metabolic dysfunction including hypertension, dyslipidemia and polycystic ovary syndrome.

Some groups have reported that type 1 diabetic youth with insulin resistance do not have the typical phenotype of central adiposity, hepatic steatosis, low HDL or low adiponectin and have predominant peripheral insulin resistance with less hepatic involvement [17]. However, several other groups have shown an increased prevalence of cardiovascular risk factors including hypertension, dyslipidemia and metabolic syndrome in type 1 diabetics. In the Dutch cohort of 283 children with T1D (median age 12.8 years), 38.5% were overweight or obese. Compared to normal-weight children, they had a higher prevalence of hypertension (23.9% vs. 5.7%), metabolic syndrome (25.7% vs. 6.3%) and hypertransaminasemia (15.6% vs. 4.5%) [18]. Patients in the highest quartile of weight gain (mean BMI 31 kg/m^2) in the DCCT/EDIC trial had increased prevalence of central obesity, insulin resistance, dyslipidemia, blood pressure and more extensive atherosclerosis [11].

Insulin resistance has been proposed as one of the reasons for suboptimal glycemic control in T1D, associated with increased insulin dose requirements and further weight gain. Weight gain may create concerns about body image, especially in teenagers and females, and affect adherence to treatment. Hence, prevention of weight gain and long-term weight management should be considered in the treatment plan, and strategies to counter insulin resistance and prevent macrovascular disease are often needed. However, there is a need to better understand the role played by insulin resistance in the pathophysiology of T1D and to evaluate whether addressing insulin resistance would result in improved outcomes.

Table 2 Factors causing insulin resistance in type 1 diabetes

Factors causing insulin resistance in type 1 diabetes	
Genetic/familial	Overweight or obesity
	Family history of type 2 diabetes
	High risk ethnic group
	Double diabetes
Physiological	Puberty and adolescence
	Increasing age
Treatment related	Uncontrolled glycemia – chronic hyperglycemia/glucotoxicity
	Intensive insulin therapy and weight gain
	Hypoglycemia and defensive snacking
	Overinsulinization with resultant iatrogenic peripheral hyperinsulinemia
	Mismatch between physiological insulin profile needs and pharmadynamic profiles of available insulins
Lifestyle and psychological	Sedentary lifestyle
	Eating disorders/bulimia
Others	Drugs
	Intercurrent illness

INCREASED CARDIOVASCULAR RISK: RELATION WITH INSULIN RESISTANCE

There is a significantly high risk of cardiovascular disease in T1D, which is often attributed to hyperglycemia. Cardiovascular disease is the leading cause of death, with the life expectancy of adults aged 20 years with T1D reduced by 13 years [19]. Vascular dysfunction and increased carotid intima media thickness are evident as early as childhood and adolescence, within a few years since onset of diabetes [10]. The process is accelerated by insulin resistance, weight gain and obesity.

Indeed, insulin resistance may have a greater role in the development of cardiovascular disease in type 1 diabetics than the level of glycemic control. Reduced insulin sensitivity in adolescents was associated with increased risk of cardiovascular (CV) risk factors such as elevated waist circumference, blood pressure, cholesterol and C-reactive protein in the Determinants of Macrovascular Disease in Adolescents with T1DM study [20]. Insulin resistance in T1D adolescents has been associated with reduced cardiopulmonary fitness, as measured by peak oxygen consumption and oxygen uptake kinetics, diastolic dysfunction and left ventricular hypertrophy [17]. In a prospective cohort of 603 type 1 diabetics in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, insulin resistance but not HbA1c predicted coronary artery disease end points [21]. Similarly, insulin resistance was a more significant determinant of coronary artery calcifications than hyperglycemia in the Coronary Artery Calcification in Type 1 Diabetes study [22]. This suggests that insulin resistance may be an important therapeutic target for reducing CV risk in T1D.

THE RATIONALE FOR USE OF METFORMIN IN TYPE 1 DIABETES

Metformin inhibits complex 1 of the mitochondrial respiratory chain and alters the cellular energy state by triggering activation of AMP-activated protein kinase (AMPK) in liver and skeletal muscle, a nutrient sensor that is activated in states of low energy balance [23]. The predominant effect is reduced hepatic gluconeogenesis and hepatic glucose output, but there is also an increase in insulin-stimulated peripheral glucose uptake, especially in skeletal muscle. Metformin decreases intestinal glucose absorption and increases intestinal secretion of GLP-1, further contributing to its glucose-lowering effect [23]. An alteration in the composition of intestinal microbiota has also been suggested. In addition, metformin has pleiotropic effects mediated via AMP-activated kinase, leading to decreased fatty acid oxidation and lipid lowering, inhibition of the proinflammatory pathway in perivascular adipose tissue, inhibition of STAT3 and monocyte-to-macrophage differentiation in vascular tissue and improved endothelial function. Metformin also inhibits AGE formation by binding and inactivating methylglyoxal via an AMPK-independent pathway, which may further contribute to its cardioprotective effects [19].

In type 2 diabetes, metformin use is associated with a reduction in fasting plasma glucose, HbA1c, LDL cholesterol, serum triglycerides, VLDL cholesterol and C-reactive protein. There is a mild reduction in weight or a weight neutral effect. When used as an add-on to insulin therapy in type 2 diabetes, metformin can improve glycemic control, reduce insulin dose requirements, limit insulin-induced weight gain and improve complication risk. It has demonstrated a definite cardioprotective effect in type 2 diabetes. Metformin has a good safety profile and is generally well tolerated.

Hence, there has been a growing interest in exploring the role of metformin as an adjunct to injectable insulin therapy in T1D, with the aim of improving insulin sensitivity and glycemic control, limiting the insulin dose and weight gain and the long-term possibility of CV risk reduction. In 1985, Gin et al. demonstrated that metformin resulted in 18% improvement in insulin sensitivity measured by euglycemic hyperinsulinemic clamp in ten type 1 diabetic patients with normal weight [24]. Similar results were shown by Moon et al. more recently in 2007 [25]. Early pilot studies in adolescents and adults suggested that metformin could be used as an adjunct to insulin with reductions in HbA1c, insulin dose, BMI and lipids [25–28].

CLINICAL TRIAL EVIDENCE OF METFORMIN IN ADULTS WITH TYPE 1 DIABETES

Initial small uncontrolled studies of metformin in type 1 diabetics reported a reduction in insulin dose by almost 25% and a modest reduction in weight, with a variable effect on glycemia and lipids [25, 28–30]. Metformin was compared to placebo as an adjunct to CSII in 62 T1D patients and resulted in a significant reduction in the total daily insulin dose, basal insulin dose, total and LDL cholesterol after 6 months. There was no change in HbA1c or risk of hypoglycemia, but there was an increased incidence of gastrointestinal side effects [31]. Lund et al. [32] evaluated the effect of metformin versus placebo in 100 patients and found no improvement in HbA1c over 1 year. There was, however, a sustained reduction in weight and insulin dose. Forty percent of participants reported gastrointestinal side effects, but very few discontinued treatment. Hypoglycemia incidence, including severe hypoglycemia, was greater with metformin than placebo [32]. In their meta-analysis of five trials, Pang and Narendran (2008) reported a small but significant reduction in HbA1c (−0.27%), moderate reduction in insulin dose and improvement in total cholesterol, but no benefit in weight with metformin in type 1 diabetics who had BMI ≥ 25 kg/m² or had insulin resistance (insulin dose > 0.9 U/kg) [33].

The systematic review of nine trials by Vella et al. [34] found a decrease in insulin dose (5.7–10.1 U/day in 6 of 7 studies), HbA1c

(0.6–0.9% in 4 of 7 studies), weight (1.7–6 kg in 3 of 6 studies) and total cholesterol (0.3–0.41 mmol/l in 3 of 7 studies). In the five randomized, double-blind trials that had adequate data for combined effect estimates, metformin use in adolescents and adults resulted in a significant reduction in insulin dose requirements (6.6 U/day, $p < 0.001$) and weight reduction in some trials, but no consistent evidence for HbA1c reduction (absolute reduction 0.11%, p 0.42). Metformin was well tolerated, gastrointestinal side effects were minimal, and there was a slight increased trend towards hypoglycemia [34].

A recent meta-analysis (2015) by Liu et al. included eight trials of metformin versus placebo including 300 patients. Use of metformin was associated with a reduction in weight (mean difference −2.41, 95% CI −4.17 to −0.65, p 0.007), total daily insulin dose (mean difference −1.36, 95% CI −2.28 to −0.45, p 0.004) and lipids (reduced total and LDL cholesterol). There was an increased risk of gastrointestinal adverse effects but no increased risk of hypoglycemia or ketoacidosis. There was no effect on HbA1c, fasting plasma glucose or triglycerides [35].

Staels et al. (2017) identified 181 metformin users among 1986 type 1 diabetic patients in a retrospective real-world data from a hospital in Belgium. Those prescribed metformin had higher BMI and higher HbA1c at baseline. There was a downward trend in BMI in initial years after metformin initiation, but the difference in BMI from the control group was lost over 10 years. Metformin was not associated with any long-term beneficial effect on BMI, HbA1c or insulin dose [36].

REMOVAL (2017) was the largest multicenter, double-blind, placebo-controlled trial funded by JDRF assessing the effect of metformin over 3 years in 428 adults (age $\geq$ 40 years) with T1D and three or more cardiovascular risk factors [37]. Metformin resulted in a small transient improvement in HbA1c in the first 6 months. HbA1c was reduced by metformin over 3 years (−0.13%, 95% CI −0.22 to −0.04, p 0.006), but this was primarily accounted for by a reduction at 3 months (−0.24%, 95% CI −0.34 to −0.13, $p < 0.0001$). The difference in

HbA1c between metformin and placebo was not significant at 3 years. There was little difference in insulin dose between the treatment groups at 6 months, but thereafter, the metformin group showed a small albeit sustained reduction in insulin dose in post hoc analysis (−0.023 U/kg, 95% CI −0.045 to −0.0005, p 0.045, approximately 2 U/day from 6 months onwards). Reduction in body weight was significant with metformin compared to placebo (mean within-person change between the two groups was −1.17 kg, 95% CI −1.66 to −0.69, $p < 0.0001$). Reduction in LDL cholesterol was also significant (−0.13 mmol/l, 95% CI −0.24 to −0.03, p 0.0117) despite a high prevalence of background statin use. An unexpected acute rise in eGFR (by 4 ml/min/1.73 m^2) occurred on initiation of metformin. The risk of hypoglycemia or ketoacidosis was not increased, but gastrointestinal adverse effects were more common. The discontinuation rate due to gastrointestinal intolerance was twice that of placebo (27% vs. 12%), and a greater percentage of patients had vitamin B12 deficiency (12% vs. 5% over 3 years). Vitamin B12 deficiency may be particularly important in T1D, where there may be associated risk factors such as celiac disease, pernicious anemia or gastroparesis. Thus, REMOVAL demonstrated a favorable effect of metformin on body weight, insulin dose requirement and lipids, similar to previous meta-analyses of smaller studies [34, 35].

There is increased prevalence of polycystic ovary syndrome and hyperandrogenism in women with T1D [38, 39], though the phenotype is milder than seen in relation with type 2 diabetes [40]. In a 9-month randomized controlled trial, Codner et al. examined the effect of metformin in 24 type 1 diabetic females. There was a significant decrease in testosterone, free androgen index, androstenedione, 17-α hydroxyprogesterone and estradiol levels. Moderate to severe acne was reduced from 23.1 to 7.7%, but there was no improvement seen in the hirsutism score or ovulation rates. There was no difference in the HbA1c or insulin dose [41].

CLINICAL TRIAL EVIDENCE OF METFORMIN IN ADOLESCENTS WITH TYPE 1 DIABETES

Peri-pubertal insulin resistance is associated with increased insulin dose requirement, weight gain and poor glycemic control. Non-adherence and behavioral issues may further worsen the control. In DCCT, the average HbA1c achieved by adolescents was 1% higher than in adults in both intensive and conventional arms, despite a greater insulin requirement (U/kg) and weight gain [42]. Therefore, insulin sensitizers have long been considered adjunctive therapy to insulin during the peri-pubertal period.

The earliest report of the use of metformin in children was in 1961 by Ferguson et al. in ten children with brittle diabetes [43]. Schatz et al., in 1973, demonstrated that metformin use led to a reduction of the insulin dose in 43 children and adolescents with juvenile diabetes [44]. Early small studies of 3-month duration reported variable effects of metformin. Some studies reported improvements in insulin sensitivity, a reduction in HbA1c, lower total daily insulin dose, BMI and serum lipids, but there was a slightly increased risk of hypoglycemia [26, 45–47]. In an open-label study including 29 type 1 diabetic patients > 10 years age, addition of metformin led to a significant reduction in insulin dose and HbA1c at 12 months. Serum lipids were decreased but the weight and BMI increased [46]. A 2009 Cochrane review of two randomized studies found a reduction in HbA1c over 3 months and some reduction in insulin dose, but both trials were short term and had a small number of patients [48].

HbA1c was reduced by -0.39% in 28 overweight type 1 diabetic youth over a follow-up of 9 months, along with non-significant reductions in fasting plasma glucose and insulin dose in a randomized, double-blind, placebo-controlled trial [49]. Nadeau et al. reported significant reductions in BMI Z-score, waist circumference and insulin dose with low-dose metformin (500–1000 mg per day) in another RCT including 74 pubertal T1D adolescents. Metformin was well tolerated with no increased risk of hypoglycemia, ketoacidosis or severe gastrointestinal symptoms [50]. A recent randomized, placebo-controlled trial from India, including 19 adolescents with poor glycemic control (HbA1c > 9%) and high insulin dose requirement (> 1.2 U/kg), reported robust benefits. At 6 months, HbA1c was lower by 1.2% ($p < 0.001$), and this HbA1c reduction was achieved at a lower daily insulin dose (metformin -0.21 ± 0.2 U from baseline, placebo 0.05 ± 0.1 U/kg/day from baseline, $p < 0.001$). Use of metformin was, however, associated with more frequent hypoglycemia [51].

In the meta-analysis of 6 randomized trials, including 325 patients in the 6–19-year age group, Al Khalifah et al. found no effect of metformin on HbA1c, but there was a significant improvement in BMI compared to placebo (mean difference -1.46, 95% CI -2.54 to -0.38, $p < 0.01$) and a modest reduction in insulin dose (mean difference -0.15 U/kg, 95% CI -0.24 to -0.06, $p < 0.01$) [52]. A recent prospective analysis of a large diabetes registry of children with T1D from Germany and Austria reported similar findings. Konrad et al. identified 525 patients using metformin with insulin and 57,487 patients using insulin alone. Patients prescribed metformin were older (mean age 16.1 years versus 15.2 years), mostly females, had higher BMI-SDS (+2.03 vs. +0.51) and higher HbA1c (9.0% vs. 8.6%). Hypertension and dyslipidemia were more prevalent, and patients had a higher insulin dose (0.98 U/kg vs. 0.93 U/kg). Two hundred eighty-five patients on metformin were followed longitudinally (average 1.4 years), and there was a slight reduction in BMI-SDS [-0.01 (-2.01 to $+1.40$)] and insulin dose, but there was no improvement in HbA1c [53].

Type 1 Diabetes (T1D) Exchange study was the largest multicenter, double-blind, placebo-controlled randomized controlled trial conducted by JDRF to compare the effect of metformin and placebo as add-on to insulin in 140 overweight and obese adolescents with poor glycemic control (HbA1c 8.8%) and high insulin dose requirements (1.1 U/kg) [54]. Initial reduction in HbA1c (-0.3% at 3 months) was not sustained at 6 months. There was a 25% reduction in insulin dose in 23% participants

(compared with 1% in the placebo group) and > 10% reduction in BMI in 24% of those taking metformin (compared with 7% in nthe placebo group). There was no change in lipid levels. Mild gastrointestinal adverse effects were reported with metformin. Hence, the study did not support the use of metformin in overweight adolescents to improve glycemic control.

DOES METFORMIN HAVE A CARDIOPROTECTIVE EFFECT IN TYPE 1 DIABETES?

Metformin has an established cardioprotective effect in type 2 diabetes and a similar role in T1D has been the subject of recent research. Use of metformin in T1D is associated with a reduction in several cardiovascular risk factors, including BMI, waist circumference, HbA1c, LDL cholesterol and total cholesterol. In a pilot study including 33 obese type 1 diabetic individuals, Burchardt et al. demonstrated that the addition of metformin resulted in a significant reduction in HbA1c, triglycerides, glycated LDL and BMI [55]. In 100 type 1 diabetics randomized to metformin and placebo, Lund et al. demonstrated a significant reduction in total and LDL cholesterol (−0.3 mmol/l) with metformin, which remained significant even after adjustment for background statin use [56]. In addition, metformin improved endothelial function in type 1 diabetic individuals [57]. Use of metformin was associated with increased circulating endothelial progenitor cells, pro-angiogenic cells and decreased circulating endothelial cells [58].

Small studies have reported improvement in carotid intima media thickness (cIMT), a surrogate marker for atherosclerosis, with the use of metformin in type 1 diabetics [59]. In an open-label randomized trial involving 84 obese type 1 diabetic individuals by Burchardt et al., addition of metformin resulted in improved glycemic control, weight reduction, reduced LDL cholesterol, reduced glycated LDL and a reduction in carotid IMT (0.6 ± 0.1 cm vs. 0.53 ± 0.1 cm; $P = 0.002$) over 6 months [60]. The primary end point of the REMOVAL trial was the effect of metformin on cIMT over 3 years in adults with T1D who had three or more CV risk factors. More than 80% of patients were already on statins. There was a sustained reduction in LDL cholesterol even on a background of statin therapy. Both groups showed a progression of mean far wall cIMT, but the difference in mean within-person cIMT slopes between metformin and placebo groups was −0.005 mm per year, 95% CI −0.012 to −0.002, p 0.167. There was reduced progression of maximal cIMT with metformin, the difference in slope being −0.013 mm per year, 95% CI −0.024 to −0.003, p 0.0093 [37]. Thus, the primary outcome of mean far wall cIMT was not reduced, but there was a significant reduction in maximal cIMT, which was a tertiary outcome. Maximal cIMT is regarded as a measure of more advanced stages of atherosclerotic disease including focal thickening and plaque. There was no effect on endothelial function, measured by the reactive hyperemia index or retinopathy. Laboratory data were insufficient to reliably ascertain the microalbuminuria status.

REMOVAL suggests that metformin may have a direct effect on atherosclerosis progression in T1D, even in middle-aged patients with long disease duration, on a background of antihypertensive and statin therapy. This effect is unlikely to be mediated by improved glycemic control. It remains to be seen if these benefits translate into improved clinical outcomes and whether a similar reduction of cIMT occurs in adolescents and young adults who do not have CV risk factors yet.

CURRENT PLACE OF METFORMIN IN TYPE 1 DIABETES

Metformin is not approved for use in T1D by the US FDA. However, in the data from the T1D Exchange registry from the US, 6% of patients were identified as metformin users [61]. In another Scottish registry of 1850 type 1 diabetics, 7.9% with BMI > 27 kg/m^2 and 13% with BMI > 30 kg/m^2 were receiving metformin [62]. In its Standards of Care, the ADA notes that 'adding metformin to insulin therapy may reduce insulin requirements and improve

Table 3 Benefits and risks of adjunctive metformin in type 1 diabetes

Benefits of adjunctive metformin in type 1 diabetes	Risks associated with metformin in type 1 diabetes
Improved insulin sensitivity	Gastrointestinal adverse effects
Reduced insulin dose	Vitamin B12 deficiency
Reduction in BMI	Increased risk of hypoglycemia
Trend towards a reduction in HbA1c	? Lactic acidosis or ketoacidosis (not established in trials)
Reduced total and LDL cholesterol	
Reduced carotid intima media thickness and possible CV risk reduction	

Table 4 Possible indications for use of metformin as an adjunct to insulin therapy in type 1 diabetes

Patient subgroup	Relative indications for use of metformin
Pre-pubertal children	Not evaluated for use
Peri-pubertal adolescents and adults	Double diabetes
	Features of insulin resistance:
	Obesity/overweight (BMI $\geq$ 25 kg/m^2 or $\geq$ 23 kg/m^2 for South Asians or $\geq$ 85th percentile in adolescents)
	Acanthosis nigricans
	High insulin dose
	High insulin dose requirement (total daily dose $\geq$ 1 U/kg/day)
	Rapid weight gain with insulin
	Polycystic ovary syndrome
	Concomitant CV risk factors (central obesity, dyslipidemia, hypertension, family history of CVD) or established CV disease

metabolic control in overweight/obese patients with poorly controlled type 1 diabetes' [63]. In 2015, the UK NICE guidelines recommended use of metformin in adults with type 1 diabetes with BMI $\geq$ 25 or BMI $\geq$ 23 kg/m^2 for people of South Asian and related ethnic groups, who want to improve glucose control while minimizing their effective insulin dose [64].

However, there is little evidence to support that it can improve glycemic control in T1D, and the initial transient reduction in HbA1c is not maintained over time. This could be due to down titration of the insulin dose to avoid hypoglycemia. Thus, there is a need to revise the guidelines and acknowledge that there is no sustained glycemic benefit of adjunctive metformin in T1D and that there is no particular glycemic efficacy in overweight/obese individuals. On the other hand, adjunctive use of metformin in T1D results in significant reductions in the insulin dose requirement and insulin-induced weight gain and may therefore, be particularly useful in overweight/obese type

1 diabetics. Therefore, overall, metformin has an insulin-sensitizing effect in type 1 diabetics.

Recent evidence suggests that metformin reduces LDL cholesterol and maximal cIMT and may extend cardioprotective benefits in T1D. Metformin use may thus be warranted to improve CV risk management in T1D and to reduce insulin dose requirements. Further outcome studies are needed to assess whether there is an actual reduction in CV outcomes. Such studies may not be easily forthcoming as they would require many type 1 diabetics to be followed for a long time, and there may be difficulty in funding such trials, unlike in type 2 diabetes. In Tables 3 and 4, we summarize the risks and benefits of adjunctive metformin and enumerate the possible indications for use of metformin as an adjunct to insulin therapy in T1D.

CONCLUSION

The use of metformin as adjunctive therapy to insulin in type 1 diabetes results in a transient reduction in HbA1c that is not sustained with long-term use. However, there is a significant reduction in body weight and BMI, insulin dose and lipids. It also reduces the maximal carotid intima media thickness in individuals at high risk of cardiovascular disease. Therefore, the use of metformin as an add-on to intensive insulin therapy can be considered, and the potential for cardiovascular risk reduction should be explored further.

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