Received: 11 June 2024 | Accepted: 9 August 2024

DOI: 10.1002/jcp.31419

REVIEW ARTICLE

Journal of Cellular Physiology WILEY

Mechanisms of insulin resistance in type 1 diabetes mellitus: A case of glucolipotoxicity in skeletal muscle

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Funding information
Natural Sciences and Engineering Research Council of Canada (NSERC), Grant/Award Number: RGPGP-2020-06479

Abstract

Insulin resistance (IR), a hallmark of type 2 diabetes mellitus, develops in a significant number of patients with type 1 diabetes mellitus (T1DM) despite the use of insulin therapy to control glycemia. However, little is currently understood regarding the underlying mechanisms of IR in T1DM, especially within the context of chronic insulin treatment. Recent evidence suggests an important influence of glucolipotoxicity in skeletal muscle on insulin sensitivity in T1DM. Thus, this review summarizes our current knowledge regarding impairments in skeletal muscle lipid, glucose, and oxidative metabolism in the development of IR in insulin-treated T1DM.

KEYWORDS
glucolipotoxicity, insulin resistance, skeletal muscle, type 1 diabetes mellitus

1 | INTRODUCTION

From 1982 to 1993, the Diabetes Control and Complications Trial (DCCT) was conducted in patients with type 1 diabetes mellitus (T1DM) to compare the effects of tightly controlled glycemia through intensive insulin therapy (IIT) versus moderately controlled glycemia through conventional insulin therapy (CIT) on long-term secondary complications (Nathan, 2014). The rationale for this trial was based on the "glucose hypothesis" which posits that chronic hyperglycemia is the primary driver of T1DM-related vascular disease (Nathan, 2014). Poor glycemic control and chronic hyperglycemia can result in the buildup of advanced glycation end products, which damage vasculature and contribute to T1DM-related complications (Fowler, 2008; Goldin et al., 2006; Singh et al., 2014). Indeed, results from the DCCT found that rigid glycemic control through IIT reduces the development and progression of complications including retinopathy, nephropathy, and neuropathy, and improves mortality compared to CIT in patients with T1DM (Diabetes Control and Complications Trial Research Group et al., 1993; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group, 2016; Orchard et al., 2015). As such, IIT remains the current standard of care for patients with T1DM. However, despite the advent of this current therapeutic insulin strategy, insulin resistance (IR) develops in a significant proportion of both poorly and adequately controlled patients with T1DM, which furthers the risk of micro and macrovascular disease (Pozzilli & Buzzetti, 2007).

While the underlying causes of IR development in T1DM remain unclear, the aim of this review is to summarize the current literature pertaining to the molecular mechanisms in skeletal muscle with an emphasis on the interplay between impaired glucose, lipid, and oxidative metabolism, termed "glucolipotoxicity." To maintain relevance within the current era of insulin therapy, this review will focus on data in insulin-treated patients and animal models of T1DM.

2 | IR IN TYPE 1 DIABETES MELLITUS

The concept of IR was first described by Himsworth in 1936 after the observation that concurrent administration of glucose and insulin resulted in a reduction of blood glucose in "insulin-sensitive" patients,

[Correction added on 12 December 2024, after first online publication: *insulin-sensitizing* DAG corrected to *insulin-desensitizing* DAG]

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or an increase in blood glucose in "insulin-insensitive" patients with diabetes (Himsworth, 1936). Today, IR refers to the attenuation of insulin action on cells in the body. Specifically, impaired peripheral tissue (e.g., skeletal muscle and adipose) glucose uptake, impaired suppression of adipose lipolysis, and impaired suppression of endogenous hepatic glucose production in response to a physiologic concentration of insulin (Freeman & Pennings, 2022; Li et al., 2022).

The hyperinsulinemic-euglycemic clamp (HEC), developed by DeFronzo et al. (1979), is considered the "gold standard" for assessing IR (DeFronzo et al., 1979). This test involves fasting patients overnight, followed by an intravenous infusion of insulin at a constant rate to achieve hyperinsulinemia. Insulin infusion will stimulate tissue uptake of glucose and a subsequent reduction in blood glucose. Blood glucose is measured at set intervals (usually every 5–10 min) and dextrose is infused simultaneously at a variable rate to reach normoglycemia. A greater glucose infusion rate (GIR) suggests greater insulin action and sensitivity, while a lower GIR indicates reduced insulin action. Alternatively, administering a glucose challenge either orally with an oral glucose tolerance test (OGTT) or intravenously with an intravenous glucose tolerance test (IVGTT) is often used to indirectly assess IR by following the rise and fall in blood glucose in response to a bolus of glucose (Muniyappa et al., 2021). The area under the curve (AUC) of blood glucose during an OGTT and IVGTT is indicative of insulin sensitivity, whereby a lower and greater AUC reflects greater and lower glucose clearance (i.e., greater, and lower insulin sensitivity), respectively. Finally, a proxy measure of IR referred to as the Homeostatic Model Assessment for Insulin Resistance can be calculated from fasting glucose and insulin concentrations (Muniyappa et al., 2021).

While IR is typically a hallmark of type 2 diabetes mellitus (T2DM), significant whole-body IR has been established in a considerable number of patients with T1DM (Cleland et al., 2013; Donga et al., 2013; Koivisto & Yki-järvinen, 1990; Pang & Narendran, 2008; Šimonienė et al., 2020). The presence of IR in T1DM is often referred to as "double diabetes" as both the loss of endogenous insulin production and resistance to insulin are present (Bielka et al., 2024; Pozzilli & Buzzetti, 2007). Of clinical concern is the increased risk of micro and macro-vascular complications such as retinopathy and coronary artery disease (CAD) that IR poses in patients with T1DM (Chaturvedi et al., 2001; Kilpatrick et al., 2007; Orchard et al., 2003; Šimonienė et al., 2020). Indeed, IR is a better predictor of CAD compared to glycemia in patients with T1DM (Orchard et al., 2003). Considering that cardiovascular disease is one of the leading causes of mortality in T1DM, the importance of mitigating IR in this population cannot be understated (Laing et al., 2003; Soedamah-Muthu et al., 2006). Recently, it has become clear that IR development in T1DM is distinct from that observed in other metabolic disease states (Perseghin et al., 2003). Specifically, patients with T1DM who develop IR are often phenotypically different from individuals with T2DM and metabolic syndrome. It has been shown that IR is present in those with T1DM who are lean and of normal body mass index (BMI) compared to healthy controls (Donga et al., 2013). IR is also observed in otherwise healthy and normal-weight adolescents and young adults with T1DM (Cree-Green et al., 2018; Nadeau et al., 2010; Reinehr et al., 2005) which is associated with reduced cardiovascular function such as left ventricular hypertrophy, diastolic dysfunction, and poor cardiopulmonary fitness including reduced peak oxygen consumption and oxygen uptake (Cree-Green et al., 2018; Nadeau et al., 2010). Hyperglycemia cannot completely explain IR development in this population as IR persists in many patients with T1DM despite adequate glycemia maintained with IIT (Donga et al., 2013). In support of this, findings from Bergman et al. (2012) report that IR in T1DM is not attributable to common predictive factors such as BMI, plasma lipids, visceral adiposity, physical activity level, or acute glucotoxicity and glycemic control (Bergman et al., 2012). The distinct development of IR in patients with T1DM suggests similar yet alternative mechanisms regulating glucose intolerance in this population, compared to other insulin-insensitive states. Moreover, it was also shown that IR in T1DM is tissue-specific, developing primarily in the liver and skeletal muscle of patients (Bergman et al., 2012).

3 | SKELETAL MUSCLE INSULIN SIGNALING AND GLUCOSE METABOLISM

By mass, skeletal muscle tissue represents the largest depot in the body for glucose disposal and free fatty acid (FFA) metabolism in the postprandial state and is responsible for ~80% of glucose uptake under euglycemic-hyperinsulinemic conditions (DeFronzo & Tripathy, 2009). As such, skeletal muscle is an important metabolic tissue in the regulation of whole-body insulin sensitivity and substrate metabolism. In skeletal muscle cells, the initiation of the insulin signaling cascade involves the binding of circulating insulin to the extracellular domain of the tyrosine kinase insulin receptor (INSR) on the sarcolemma (Figure 1) (Lizcano & Alessi, 2002). The binding of insulin to the INSR results in auto-phosphorylation of tyrosine residues on the intracellular domain of the INSR, subsequently phosphorylating and activating signaling proteins, including insulin receptor substrate (IRS) (Fröjdö et al., 2009; Lizcano & Alessi, 2002). IRS proteins interact with phosphoinositide 3-kinase (PI3K), activating and targeting the molecule to the plasma membrane, where it generates phosphatidylinositol 3,4,5-triphosphate (PIP3) (Chang et al., 2004). Generation of PIP3 subsequently leads to the phosphorylation of Akt, promoting Glucose transporter type 4 (GLUT4)-containing intracellular vesicles to the sarcolemma (Chang et al., 2004; Fröjdö et al., 2009; Lizcano & Alessi, 2002). GLUT4 vesicles fuse with the sarcolemma, increasing the abundance of membrane-bound GLUT4 and glucose uptake from circulation into the muscle cell. Once inside the muscle cell, glucose is phosphorylated by hexokinase (HK) to glucose-6-phosphate (G6P), "trapping" glucose in the cell (Hulett et al., 2022). G6P may then proceed through glycolysis to produce pyruvate, which is subsequently oxidized in the mitochondria to produce ATP. Insulin also leads to the activation of glycogen synthase (GS), thus promoting the storage of glucose as glycogen (Adeva-Andany et al., 2016). G6P is converted

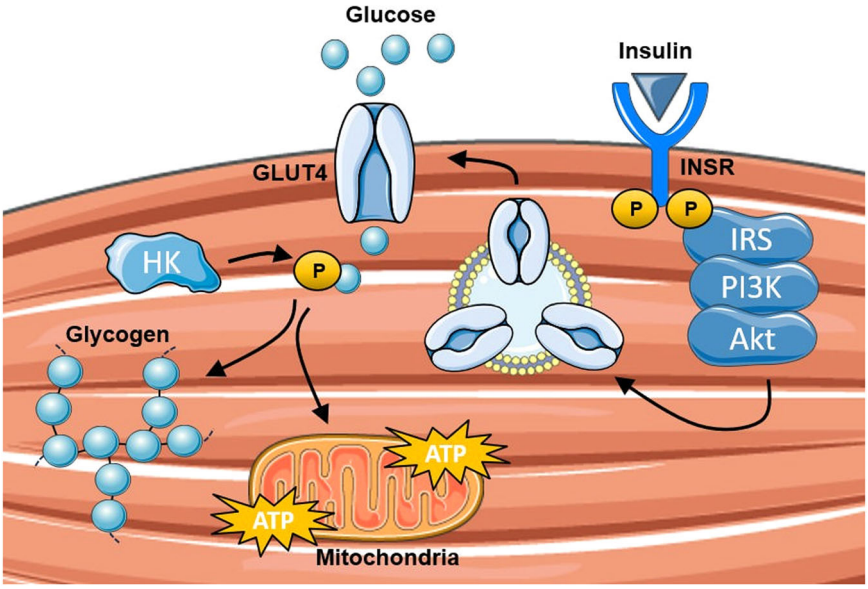


FIGURE 1 Skeletal muscle insulin signaling and glucose metabolism. The binding of insulin to the insulin receptor (INSR) results in autophosphorylation of the intracellular domain of the INSR which recruits insulin receptor substrate (IRS) and activates phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). Activation of Akt eventually leads to the translocation of intracellular vesicles containing glucose transporter type 4 (GLUT4) which fuse to the plasma membrane and increase glucose uptake via increased GLUT4 abundance. Glucose is phosphorylated by hexokinase (HK) once inside the cell and is primarily metabolized through glycolysis, and oxidized in the mitochondria to produce ATP, or stored as glycogen. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software.

to glucose-1-phosphate (G1P), then uridine diphosphate-glucose (UDP-glucose) by UDP-glucose-phosphorylase and assembled into glycogen via GS (Adeva-Andany et al., 2016). The relative flux through each intracellular pathway depends on the energy demand of the cell such that during high energy demands (e.g., during exercise), oxidation of G6P will increase, whereas, during low energy demands (e.g., at rest), glycogen storage will increase (Hulett et al., 2022).

4 | SKELETAL MUSCLE IR

As skeletal muscle is the largest insulin-sensitive tissue, it is implicated in the development of IR (DeFronzo & Tripathy, 2009; Merz & Thurmond, 2011). The exact mechanisms underlying the development of IR in skeletal muscle are multifaceted and still unclear. However, one of the primary prevailing theories in those with obesity and T2DM is the muscle lipotoxicity model of IR (Gilbert, 2021). This theory implicates ectopic lipid accumulation in the attenuation of the intracellular insulin signaling cascade in skeletal muscle. Lipids are readily stored in skeletal muscle in inert forms such as triacylglycerol (TAG) where they are used for energy production by the mitochondria. The pathology of IR may begin when the influx and storage of lipids in the muscle cell, also known as intramyocellular lipid (IMCL), exceeds the cells' ability to handle such a lipid burden, that is, lipid loads exceed the oxidative abilities of the cell resulting in "metabolic overload" (Unger & Orci, 2001). The lipid influx may be a result of increased levels of circulating FFAs in the blood due to adipose tissue IR (impaired suppression of lipolysis), liver lipid "spillover," and/or excess caloric or dietary lipid consumption, among other reasons (Gilbert, 2021; Meex et al., 2019). With such a lipid influx, lipid intermediates, including diacylglycerol (DAG) and ceramides, may begin to accumulate inside the cell (Meex et al., 2019; Unger & Orci, 2001). DAG and ceramides exhibit an insulin-desensitizing effect inside muscle cells by activating signaling proteins, such as protein kinase C θ (PKCθ) leading to the inhibitory phosphorylation and inactivation of insulin signaling proteins, such as IRS and Akt, thus attenuating the insulin signaling cascade (Hajduch et al., 2001; Meex et al., 2019; Montell et al., 2001; Szendroedi et al., 2014). Additionally, insulin-desensitizing lipid intermediates may result in inflammatory signaling, mitochondrial dysfunction, oxidative stress, and downregulation of genes involved in glucose metabolism that further interfere with intracellular insulin signaling in muscle (Gilbert, 2021).

While skeletal muscle IR has been established in patients with T1DM exhibiting whole-body insulin sensitivity impairments (Bergman et al., 2012; Millstein et al., 2018; Williams et al., 2020), the etiology of its development and underlying mechanisms in T1DM are unknown and have received relatively limited examination compared to other metabolic diseases such as T2DM and obesity.

5 | IMPORTANCE OF SKELETAL MUSCLE FOR INSULIN SENSITIVITY IN T1DM

Physiologic insulin release from the pancreas involves the passing of insulin through the portal vein of the liver, where ~80% of insulin is cleared from circulation (Najjar & Perdomo, 2019). This is known as the "first-pass effect," such that the resulting concentration of circulating insulin seen at peripheral tissues (i.e., skeletal muscle) is substantially less than what was released from the pancreas. In contrast, with subcutaneous injections of exogenous insulin in patients with T1DM, the first-pass effect through the liver is lost (Figure 2), and skeletal muscle is exposed to levels of circulating insulin ~2.5 times greater than that of non-T1DM individuals (Gregory et al., 2020). Such hyperinsulinemia at the periphery implicates skeletal muscle as the "first-pass" tissue for insulin and the primary tissue for managing dysglycemia in T1DM. As such, skeletal muscle health should be considered an important aspect of T1DM management.

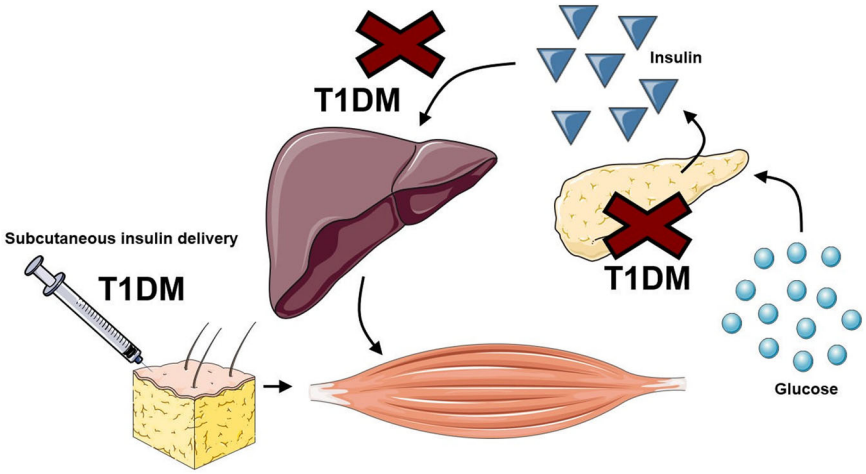


FIGURE 2 Differences in the flow of insulin between T1DM and non-T1DM physiology. With non-T1DM physiology, elevations in blood glucose will stimulate insulin secretion from the pancreas, which will then pass through the hepatic portal vein and liver before reaching peripheral tissues such as the skeletal muscle. In T1DM, exogenously administered subcutaneous insulin bypasses the first pass through the liver directly into the peripheral circulation. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. T1DM, type 1 diabetes mellitus.

6 | MOLECULAR MECHANISMS OF IR IN SKELETAL MUSCLE IN T1DM

6.1 | Lipid metabolism

Literature investigating IMCL content and IR in T1DM yields conflicting results. Multiple studies have reported elevated IMCL in insulin-treated patients with T1DM which is associated with IR (Ebeling et al., 1998; Perseghin et al., 2003). However, other studies have shown nonelevated IMCL in individuals with T1DM which was unrelated to insulin sensitivity (Cree-Green et al., 2015; Kacerovsky et al., 2011). This puts into question the mechanistic role of IMCL in the development of IR in T1DM, unlike T2DM and obesity. Based on clinical and experimental data, factors such as glycemic control, lipid species, and IMCL localization may influence the role of IMCL on insulin sensitivity in T1DM.

Generally, patients with T1DM exhibiting poor glycemic control (e.g., higher HbA1c% and hyperglycemia) have elevated IMCL (Perseghin et al., 2003) compared to patients with tightly controlled glycemia (Cree-Green et al., 2015; Kacerovsky et al., 2011). However, total IMCL content alone per se may not be as relevant to insulin sensitivity as the specific species of IMCL, that is, insulin-sensitizing DAG and ceramide versus neutral TAG. For example, an athlete's paradox has been reported where highly trained individuals exhibit elevated IMCL content despite being markedly insulin-sensitive (Bergman & Goodpaster, 2020). Accordingly, both IMCL content and species should be considered in the context of physical activity levels.

Data in rodent models help reveal lipid species unique to the skeletal muscle of insulin-resistant T1DM. The streptozotocin (STZ)-induced rodent model of T1DM exhibits increased skeletal muscle neutral lipid staining (specifically DAG), Ceramide Synthase 1 (involved in ceramide synthesis) protein content, long-chain fatty acid-acyl-coenzyme A esters (precursors to DAG and ceramide), and several lipid metabolites such as octadecenoic acid, linoleic acid, arachidonic acid, docosahexaenoic acid, and palmitic acid, despite well to moderately controlled glycemia with insulin treatment (Dotzert et al., 2016; Zabielski et al., 2014). Such fatty acids have been linked to IR through the formation of inflammatory cytokines, direct interaction with proteins in the insulin signaling cascade, and reduction of GLUT4 expression in vitro (Kain et al., 2015; Manco et al., 2000; Martins et al., 2012; Poletto et al., 2015; Yuan et al., 2001).

Adapted from Brownlee's theory of diabetic complications (Brownlee, 2005), Monaco et al. (2017) propose that regular injections of exogenous insulin in those with T1DM may result in periodic hyperglycemia within skeletal muscle. Thus, it is plausible that excess glucose influx and oxidation in muscle cells during these periods of intracellular hyperglycemia result in significant production of acetyl-CoA, which may overload the Krebs cycle, producing excess citrate (Figure 3) (Dulloo et al., 2004). Citrate is an allosteric activator of acetyl-CoA carboxylase (ACC), which catalyzes the production of malonyl-CoA, a precursor in fatty acid synthesis. Malonyl-CoA also inhibits carnitine palmitoyltransferase-1 (CPT-1) and limits the entry of lipids into the mitochondria for β-oxidation (Dulloo et al., 2004). Further, citrate will provide acetyl-CoA for ACC via citrate lyase (Dulloo et al., 2004). This results in de novo lipogenesis (DNL) within the muscle and increases the pool of IMCL, including DAG species. Indeed, increased skeletal muscle DAG and TAG accumulation are observed in IIT and CIT-treated STZ-induced T1DM rats, respectively, following acute glucose and insulin stimulation with an HEC (Dotzert et al., 2023). Insulin promotes the activity of glycerol-3 phosphate acyltransferase, resulting in phosphatidic acid synthesis and conversion into DAG and TAG (Farese et al., 1987; Lewis et al., 2002). The accumulation of intramyocellular TAG is also likely pathological in sedentary T1DM, stemming from reduced oxidative capacity (Dotzert et al., 2018) (discussed in-depth later in this review), and is accompanied by IR. This is supported by Liu et al. (2009), who reported that chronic exposure to insulin in nonobese diabetic (NOD) mice induces IR, which is accompanied by elevations in skeletal muscle TAG content. These data support the potential role of chronic insulin stimulation, hyperglycemia, and excess glucose uptake into skeletal muscle driving the accumulation of IMCL and insulin-desensitizing lipid metabolites. However, the contribution of DNL to

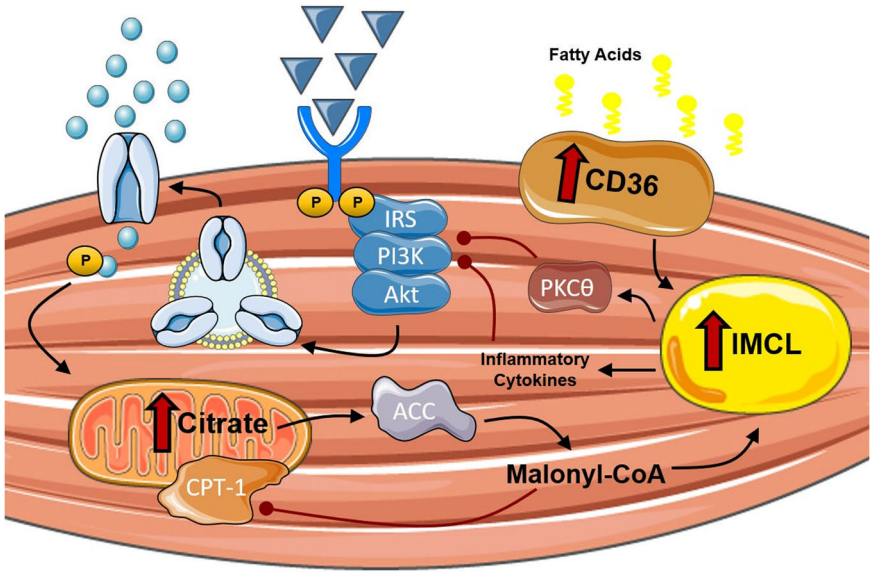


FIGURE 3 Potential impairments in skeletal muscle lipid metabolism in T1DM. Excess glucose uptake resulting from recurrent insulin injection overloads the Krebs cycle resulting in increased citrate concentrations. Citrate activates acetyl-CoA carboxylase (ACC), thus increasing the production of malonyl-CoA which is used for de novo synthesis of IMCL and inhibits carnitine palmitoyltransferase-1 (CPT-1). Excess uptake of fatty acids via FAT/CD36 also contributes to the IMCL pool. Increased IMCL and lipid intermediates activate proteins including protein kinase c θ (PKCθ) which inhibits insulin signaling. Lipid intermediates also contribute to inflammatory cytokines. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. T1DM, type 1 diabetes mellitus.

the intracellular lipid pool in skeletal muscle is still poorly understood and is likely less than that in the liver and adipose tissue (Watt & Hoy, 2012).

Excess uptake of FFAs into muscle cells may also mediate IMCL accumulation in T1DM. The fatty acid transporter (FAT/CD36) which is associated with IR in myocytes and upregulated following hyperglycemia, is upregulated in the skeletal muscle of moderately hyperglycemic STZ-induced T1DM rats exhibiting IR with insulin treatment (Bastie et al., 2004; Chen et al., 2006; Dotzert et al., 2018). Interestingly, Koves et al. (2008) have shown that increased FFA exposure leads to IR development via "mitochondrial overload" and involves excessive β-oxidation, incomplete fatty acid oxidation, and the buildup of insulin-desensitizing lipid intermediates which interfere with insulin signaling. Additionally, Zabielski et al. (2016) have reported downregulation of proteins involved in β-oxidation in the skeletal muscle of insulin-treated mice with T1DM, further suggesting a mismatch between FFA uptake and oxidation. Therefore, a combination of DNL and excess lipid uptake in skeletal muscle may contribute to the accumulation of insulin-desensitizing metabolites in T1DM.

While the accumulation of IMCL has been established in animal models and patients, the functional impact of lipid metabolites such as DAG on intracellular insulin signaling remains unclear in the context of T1DM. Jelenik et al. (2014) reported increases in myocellular DAG in noninsulin-treated NOD mice, which was associated with increased PKCθ-mediated inhibitory phosphorylation of IRS-1 (ser1101) upon insulin stimulation, and a subsequent decrease in the insulin-stimulated membrane-to-cytosol ratio of Akt and GLUT4 (Jelenik et al., 2014). While this supports the inhibitory role of myocellular DAG on the insulin signaling cascade, few studies have investigated these processes in the context of chronic insulin treatment. Despite an elevation in myocellular DAG (Dotzert et al., 2016, 2023), no increase in inhibitory IRS-1 phosphorylation of ser1101 in the basal (Dotzert et al., 2018) or insulin-stimulated (Dotzert et al., 2023) state has been observed in insulin-treated rodent models of STZ-induced T1DM, suggesting an alternative mechanism of insulin signaling attenuation compared to T2DM (Petersen & Shulman, 2018; Szendroedi et al., 2014). Conflicting data exists regarding Akt activation in the skeletal muscle of T1DM rodent models where both a reduction (Zabielski et al., 2014) and no change (Dotzert et al., 2023) in insulin-stimulated Akt phosphorylation have been observed in insulin-treated STZ-induced rodents. This uncoupling of insulin signaling, specifically Akt, and insulin function has been reported, including in the STZ-induced rodent model of T1DM (Dotzert et al., 2023; Jaiswal et al., 2019; Sammut et al., 2024). Rather, these data may suggest an Akt-independent mechanism of IR development in insulin-treated T1DM. However, the mechanistic role of skeletal muscle Akt in glucose homeostasis in T1DM remains unclear.

Localization of IMCL may further mediate the insulin-desensitizing effects of lipid metabolites in T1DM. Preclinical data suggests that exercise-trained insulin-sensitive T1DM rodents may preferentially store IMCL in type I myofibers which are well-equipped to oxidize and utilize lipid stores for energy metabolism (McBey et al., 2021). Conversely, sedentary T1DM rodents may store IMCL in less "ideal" fibers such as type II myofibers which are less oxidative

and less equipped to utilize lipids, therefore leading to the accumulation of insulin-desensitizing lipid metabolites that may interfere with insulin signaling. Ultimately, the role of IMCL species in the development of IR in T1DM remains unclear and requires further investigation, especially in the context of chronic insulin therapy.

6.2 | Glucose metabolism

Before current-day IIT, Koivisto and Yki-järvinen (1990) observed that patients with T1DM on chronic insulin therapy exhibited defects in both oxidative and nonoxidative glucose disposal in skeletal muscle. Patients exhibited a significant reduction in total glucose disposal which was associated with similar reductions in oxidative and nonoxidative glucose disposal compared to non-T1DM individuals (Koivisto & Yki-järvinen, 1990). Indeed, under HEC conditions, patients exhibit impaired insulin-stimulated pyruvate dehydrogenase (PDH) activity and glycogen synthesis within skeletal muscle (Koivisto & Yki-järvinen, 1990). However, oxidative and nonoxidative glucose disposal (and muscle glycogen synthesis) were normalized in these patients once blood glucose levels were raised during the HEC such that total glucose disposal was matched to non-T1DM individuals via glucose mass-action (insulin-independent stimulation of glucose uptake by glucose itself). This normalization occurred without changes in intracellular G6P concentrations, suggesting that glucose transport into muscle cells is the primary defect resulting in IR in these patients. In support of this, Cline et al. (1997) assessed glucose disposal in poorly controlled patients with T1DM to determine the impaired signaling component of insulin-stimulated muscle glycogen synthesis (Cline et al., 1997). Similarly, patients exhibited significantly reduced glucose uptake and net glycogen synthesis compared to control participants. Impaired glycogen synthesis in these patients was associated with reduced glycogen turnover rates and a reduced increment in G6P concentration in response to glucose infusion. Once nonoxidative glucose disposal was matched to that of control participants, G6P concentration did not differ. This suggests that the impairment in glycogen synthesis likely does not occur at the level of GS as this would be associated with a buildup of intracellular G6P. Elevations in oxidative glucose disposal and markers of elevated glycolysis (e.g., blood lactate) were also not observed in these patients. Therefore, it is likely that reduced glucose transport and/or phosphorylation are the rate-limiting steps involved in the insulin-stimulated glycogen synthesis impairment (Figure 4), at least with the use of traditional insulin therapies (e.g., CIT).

Impairments in HK activity have been reported in the skeletal muscle of insulin-treated patients with T1DM, however, these results are inconsistent (Costill et al., 1979; Harmer et al., 2008; Wallberg-Henriksson et al., 1984). Work by Yki-Järvinen et al. (1992) investigating insulin-action impairments in the skeletal muscle of insulin-treated patients with T1DM with poor glycemic control reported defects in the insulin-stimulated increase in GLUT4 mRNA and protein content. Additionally, it has been shown that STZ-induced hyperglycemic T1DM rodents exhibit reduced skeletal muscle GLUT4 protein content, despite insulin treatment, which is normalized upon euglycemia (Dimitrakoudis et al., 1992; Hall et al., 2013; RAMLAL et al., 1989). This suggests that hyperglycemia likely impairs glucose transport into muscle cells via glucotoxicity. Hyperglycemia contributes to IR via increased hexosamine pathway activity, producing UDP-N-acetylgalactosamine (UDPGalNAc) which O-GlNAcylates IRS-1 and GLUT-4 (Buse, 2006; Kaul et al., 2015). While hyperglycemia likely contributes to glucose intolerance development in patients with poorly controlled T1DM, it does not necessarily explain IR development in patients with well-controlled glycemia (~4–9 mmol/L) through IIT. As such, alternative intracellular mechanisms may be involved with IR in this state of tightly controlled glycemia.

Evidence suggests that peripheral hyperinsulinemia is a strong inducer of IR in T1DM rodent models (Liu et al., 2009). Okamoto et al. (2011) reported that high (6 and 9 units/day) compared to moderate (3 units/day) doses of insulin treatment in male alloxan-induced T1DM Wistar rats induced IR and decreased insulin-stimulated GLUT4 translocation in skeletal muscle, despite providing superior glycemic control. Interestingly, STZ-induced T1DM rats treated with IIT exhibit elevations in basal and post-IVGTT glycogen content within type IIa myofibers and white gastrocnemius muscle, respectively, compared to non-T1DM control rodents (McBey et al., 2021; Sammut et al., 2024). It is plausible that hyperinsulinemia at the level of the skeletal muscle resulting from intensive insulin exposure may lead to an elevation of basal glycogen content in glycolytic myofibers which exhibit a greater capacity to store glucose compared to oxidative fibers (De Bock et al., 2007). In support of this theory, Liu et al. (2009) found that chronic insulin exposure in NOD T1DM mice induced IR and increased the level of basal insulin signaling (PI3K and Akt activity) in the gastrocnemius muscle. Persistent stimulation of this pathway by chronically elevated levels of circulating insulin may continuously drive the synthesis of intramyocellular glycogen. Elevated basal glycogen content within fast-twitch but not slow-twitch muscle has been shown to reduce insulin sensitivity, possibly via reduced insulin-stimulated Akt activation and GLUT-4 translocation (Derave et al., 2000). These data suggest that elevated glycogen content in fast-twitch skeletal muscle may negatively influence insulin-stimulated glucose uptake in T1DM treated with IIT. In healthy humans without T1DM, experimental chronic hyperinsulinemia, similar to that observed in T1DM patients treated with IIT, increased basal intramyocellular glycogen content and impaired insulin-stimulated glucose uptake and GS activity, inducing IR (Shannon et al., 2018). Authors suggested that hyperinsulinemia may inhibit insulin-stimulated GS flux via a combination of allosteric inhibition by increased glycogen content and inhibitory phosphorylation by glycogen synthase kinase 3β. Therefore, hyperinsulinemia in IIT-treated T1DM may reduce nonoxidative glucose disposal via elevations in basal intramyocellular glycogen content.

In contrast, invasive and noninvasive measurements of skeletal muscle glycogen content in IIT-treated patients with T1DM show no differences compared to individuals without T1DM (Bally et al., 2015; Buehler et al., 2016; Dial et al., 2021). It is important to note that

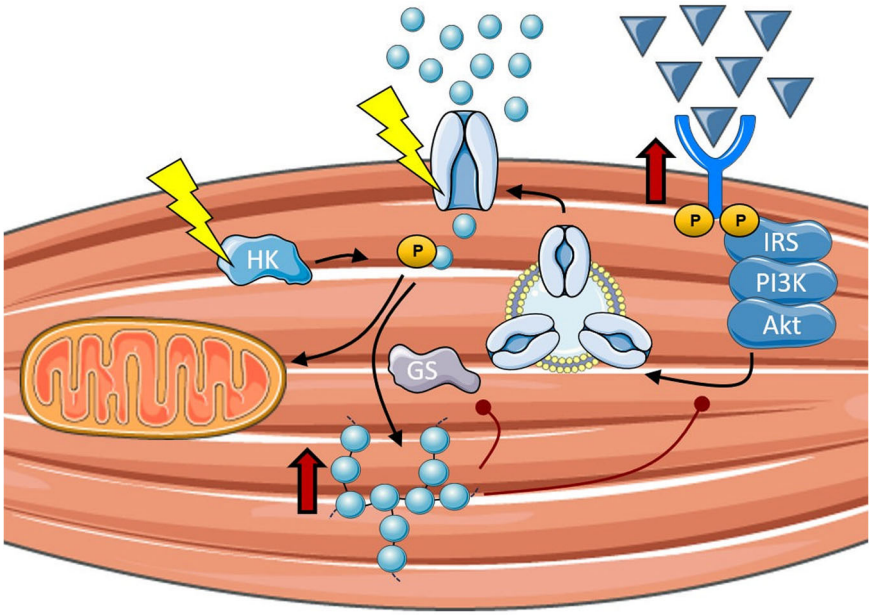


FIGURE 4 Potential impairments in skeletal muscle glucose metabolism in T1DM. Reduced glucose transporter type 4 (GLUT4) on the sarcolemma, and impairments in glucose transport and phosphorylation limit glucose entry into the cell. Elevated basal intramyocellular glycogen content inhibits flux through glycogen synthase (GS), and insulin signaling and/or GLUT4 translocation, further limiting glucose uptake. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. T1DM, type 1 diabetes mellitus.

these studies did not assess the glycogen content of different fiber types, which suggests that changes in glycogen metabolism with T1DM may be fiber-specific as is with T2DM (He & Kelley, 2004). Much of the previous literature pertaining to skeletal muscle glycogen content and metabolism in T1DM has been conducted in the context of insulin deprivation and untreated/newly treated T1DM. As such, more work is required to understand the relationship between intracellular glycogen and IR development following chronic IIT in patients with T1DM.

6.3 | Glucolipotoxicity and mitochondrial alterations

While the causative role of mitochondrial alterations in the development of IR remains highly debated (Holloszy, 2009), recent evidence suggests that skeletal muscle mitochondrial dysfunction contributes to impairments in insulin sensitivity (Lee et al., 2021). Individuals with T1DM have been shown to exhibit significant impairments in skeletal muscle mitochondrial oxidative capacity, bioenergetics, and ultrastructure (Minnock et al., 2022; Monaco et al., 2018, 2020, 2021). Using in-vivo methods such as ^{31}P-MRS, individuals with T1DM demonstrate impairments in skeletal muscle phosphocreatine recovery, an indirect measure of oxidative capacity (Crowther et al., 2003). Insulin-stimulated oxidative ATP production assessed with ^{1}H/^{31}P-MRS in skeletal muscle is also impaired and is positively associated with whole-body insulin sensitivity measures in individuals with T1DM who exhibit IR (Kacerovsky et al., 2011). Cree-Green et al. (2015) also reported delayed skeletal muscle ADP recovery which was associated with IR in youth with T1DM using ^{31}P-MRS. Recently, Gottlieb et al. (2024) reported impairments in in-vivo mitochondrial efficiency and oxidative capacity in adults with T1DM compared to matched controls. Moreover, in-vitro assessments using muscle biopsies from young adults with T1DM have found intrinsic impairments in mitochondrial respiration and elevated reactive oxygen species (ROS) production (Monaco et al., 2018, 2020). Insulin-treated STZ-induced T1DM rats exhibiting IR also show impairments in skeletal muscle oxidative capacity and downregulation of proteins involved in the electron transport chain and Krebs cycle (Dotzert et al., 2018; Zabielski et al., 2016). Therefore, impairments in oxidative metabolism may represent an important contributing mechanism governing IR in T1DM, given that skeletal muscle oxidative capacity is a superior predictor of insulin sensitivity compared to IMCL status (Bruce et al., 2003).

The mechanisms responsible for mitochondrial dysfunction in T1DM are unclear; however, hyperinsulinemia resulting from IIT may impair mitochondrial function and increase oxidative stress (Liu et al., 2009). ROS are neutralized by cellular antioxidant systems, such as glutathione coupled to nicotinamide adenine dinucleotide (NADH), which neutralizes H_2O_2 to $2H_2O$ (Aon et al., 2014). However, the accumulation of ROS may overwhelm the antioxidant system, resulting in oxidative stress such that ROS that is not neutralized can in turn negatively influence the insulin signal, particularly via c-Jun N-terminal kinase (JNK) phosphorylation of IRS-1 (Figure 5) (Martins et al., 2012). As previously mentioned in this article, Monaco et al. (2017) propose that recurrent peripheral hyperinsulinemia resulting from exogenous insulin injection results in the excess influx of glucose into myofibers. Intracellular glucose and lipid (IMCL) overload would increase substrate oxidation and ROS production, resulting in oxidative damage to mitochondrial proteins and reduced oxidative phosphorylation. Additionally, authors theorized that increased pyruvate flux into the mitochondria would result in inhibitory phosphorylation of PDH, thereby further reducing substrate flux and mitochondrial respiration. Accumulation of IMCL metabolites may also play a role in the inhibition of oxidative glucose metabolism via impaired switching to carbohydrate substrate, and/or inhibition of PDH (Dulloo et al., 2004; Koves et al., 2008). Nevertheless, the reduction in pyruvate transport

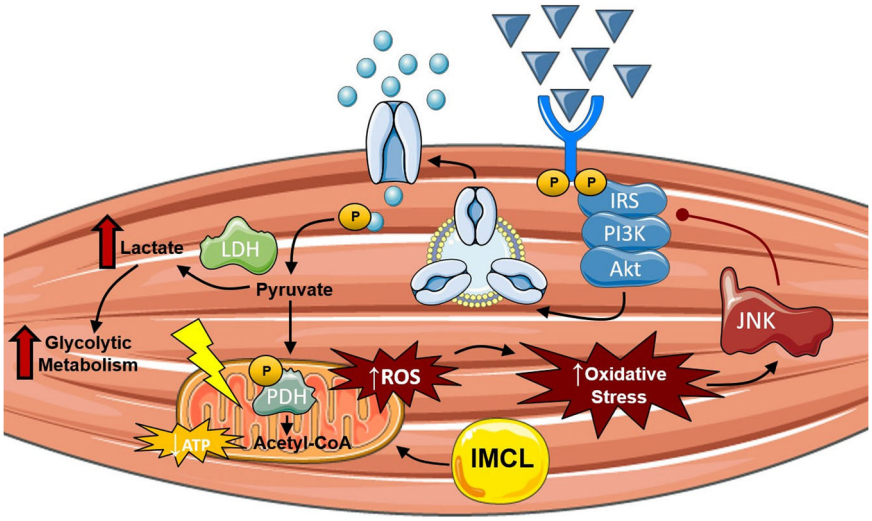


FIGURE 5 Potential mechanisms of mitochondrial dysfunction in skeletal muscle in T1DM. Excess glucose and IMCL result in excess oxidation and "overload" the mitochondria, leading to inhibitory phosphorylation of pyruvate dehydrogenase (PDH) which increases cytosolic pyruvate concentrations. Increased metabolism of pyruvate to lactate shifts the muscle cell to glycolytic metabolism. Impairments in oxidative phosphorylation result in excess production of reactive oxygen species (ROS), resulting in oxidative stress which interferes with insulin signaling. This figure was created using Servier Medical Art (https://smart.servier.com/) and PowerPoint software. T1DM, type 1 diabetes mellitus.

and oxidation within the mitochondria would result in the increased reduction of pyruvate to lactate via lactate dehydrogenase (LDH), thereby causing a shift toward glycolytic/anaerobic as opposed to oxidative metabolism in skeletal muscle. Indeed, it has been shown that the skeletal muscle of patients with T1DM exhibits a shift toward anaerobic glycolytic metabolism, increased LDH enzyme activity, and elevated postexercise lactate (Crowther et al., 2003; Gottlieb et al., 2024; Harmer et al., 2008; Wallberg-Henriksson et al., 1984). Furthermore, insulin-treated STZ-induced T1DM mice exhibit upregulation of several proteins involved in glycolysis and glycogenolysis in skeletal muscle (Zabielski et al., 2016). While few studies have investigated muscle fiber type composition with T1DM, a greater composition of fast-twitch fibers has been reported (Andreassen et al., 2014; Dial et al., 2021; Fritzsche et al., 2008). Importantly, it has been shown that the relative composition of slow-twitch type I and fast-twitch type II myofibers relates to greater and reduced insulin sensitivity, respectively (Lillioja et al., 1987; Stuart et al., 2013). Therefore, impairments in mitochondrial oxidative capacity and respiration may contribute to IR development in patients with T1DM via reductions in substrate oxidation, increased ROS production, and a shift toward glycolytic metabolism. However, the causative role of mitochondrial dysfunction in the development of IR remains unclear as the uncoupling of mitochondrial oxidative capacity and insulin sensitivity has been reported in human patients and preclinical models of T2DM and T1DM (Gottlieb et al., 2024; Holloszy, 2009; Sammut et al., 2024). As such, further investigation is warranted to determine the functional impacts of T1DM on skeletal muscle mitochondria and the relationship with insulin sensitivity.

7 | LIMITATIONS

It is important to note the potential differences between the physiology of human patients and preclinical rodent models of T1DM discussed within this review. First, T1DM in rodent models is induced genetically (e.g., NOD) or chemically (STZ and Alloxan) which causes pancreatic ß-cell destruction and subsequent hypoinsulinemia. As such, preclinical models fail to completely mimic the pathophysiology of human T1DM, which involves both genetic and environmental factors (Simmons, 2015). Additionally, chemical induction of T1DM (e.g., STZ) can have off-target actions on nonpancreatic tissues, including the skeletal muscle; however, this can be avoided with the multiple low-dose approach utilized in some preclinical T1DM rodent models. Different methods of T1DM induction may also exert different skeletal muscle phenotypes in preclinical T1DM models as highlighted by Krause et al. (2009), potentially resulting in diverging mechanisms involved in IR in T1DM. Another relevant difference between rodents and humans is the discrepancy in skeletal muscle fiber composition heterogeneity, where rodents exhibit a much more robust distinction between red and white muscle tissue. As such, this may limit the relevance of certain mechanisms related to IR in human T1DM skeletal muscle. Finally, the difference in insulin therapies between studies and preclinical models of T1DM must be considered. Subcutaneous insulin pellets are routinely used for chronic insulin treatment in rodent models of T1DM which sustain consistent insulin release into the systemic circulation, whereas modern-day human insulin therapy is much more dynamic and depends on various factors including physical activity and carbohydrate intake throughout the day. Diverging results regarding intracellular mechanisms of IR in skeletal muscle may also result from inter-study differences in insulin treatment, particularly between studies before and after the advent of modern insulin therapy (e.g., CIT vs. IIT).

8 | CONCLUSION

Despite the discovery of insulin and the advent of the current insulin therapy strategies, a significant proportion of patients with T1DM develop IR which increases their risk of vascular disease including CAD. The presence of IR in young and normal-weight individuals with T1DM suggests distinct molecular mechanisms underlying insulin insensitivity in this population. Given the importance of skeletal

muscle for insulin sensitivity, this article reviewed the evidence for the role of muscle glucolipotoxicity in the development of IR in T1DM. Future investigations are required to further our understanding of glucolipotoxicity-related mechanisms in skeletal muscle underlying IR in this population, especially with chronic insulin treatment.

ACKNOWLEDGMENTS

This study was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC)—Discovery Grant (RGPGP-2020-06479). M. Sammut was a recipient of an NSERC graduate scholarship.

DISCLOSURE

This manuscript is adapted from a thesis by the first and second authors Mitchell J. Sammut (Sammut, 2023) and Michelle S. Dotzert (Dotzert, 2017).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: Sammut, M. J., Dotzert, M. S., & Melling, C. W. J. (2024). Mechanisms of insulin resistance in type 1 diabetes mellitus: A case of glucolipotoxicity in skeletal muscle. *Journal of Cellular Physiology*, *239*, e31419. https://doi.org/10.1002/jcp.31419