# Exercise-associated glucose metabolism in individuals with type 1 diabetes mellitus

*Lia Bally, Markus Laimer, and Christoph Stettler*

**Purpose of review**
The primary focus of this review is threefold: first, to summarize available knowledge on exercise-associated glucose metabolism in individuals with type 1 diabetes mellitus (T1DM); second, to elucidate physiological mechanisms predisposing to glycemic variations in patients in T1DM; and third, to describe novel approaches derived from physiological perceptions applicable to stabilize exercise-related glycemia in individuals with T1DM.

**Recent findings**
Recent studies corroborate the concept that despite partial differences in counter-regulatory mechanisms individuals with T1DM do not fundamentally differ in their glucose response to exercise when compared with healthy individuals if studies are performed under standardized conditions with insulin and glucose levels held close to physiological ranges. Novel approaches derived from a better understanding of exercise-associated glucose metabolism (e.g., the concept of intermittent high-intensity exercise) may provide alternative ways to master the challenges imposed by exercise to individuals with T1DM.

**Summary**
Exercise still imposes high demands on patients with T1DM and increases risks for hypoglycemia and hyperglycemia. Deeper insight into the associated metabolic pathways has revealed novel options to stabilize exercise-associated glucose levels in these patients.

**Keywords**
counter-regulatory hormones, glucose, glycogen, insulin, type 1 diabetes

## INTRODUCTION

Although the beneficial effects of physical activity are well documented in individuals with type 2 diabetes [1], the role of exercise is ambiguous in patients with type 1 diabetes mellitus (T1DM) with studies even revealing worsening of glycemic control associated with frequent exercise [2,3]. In healthy individuals, exercise-associated glucose homeostasis is maintained by a complex endocrine interplay with insulin as the glucose-lowering hormone on one side and its counterparts [mainly, glucagon, catecholamines, cortisol, and growth hormones (GH)] on the other side. This balance is compromised in patients with T1DM in whom regulation of endogenous insulin (and at least partly also of glucagon) is impaired. Although modern insulin therapy reveals many options to adapt insulin doses and levels to the requirements by physical exercise, current approaches are still far from perfect. The purpose of this review is to summarize available knowledge regarding exercise-associated glucose metabolism in individuals with T1DM, elucidate physiological mechanisms predisposing to glycemic fluctuations in these patients, and describe novel approaches derived from physiological perceptions that may be applied to stabilize exercise-related glycemia in individuals with T1DM.

## GENERAL ASPECTS OF EXERCISE-ASSOCIATED GLUCOSE METABOLISM

During exercise, the skeletal muscle initially uses local glucose and, in a second step, converts muscle glycogen to glucose as an energy substrate. In addition to these intramyocellular stores, glycogen

Division of Endocrinology, Diabetes, and Clinical Nutrition, University Hospital and University of Bern, Bern, Switzerland

Correspondence to Christoph Stettler, MD, Division of Endocrinology, Diabetes, and Clinical Nutrition, University Hospital and University of Bern, Bern CH-3010, Switzerland. Tel: +41 31 632 40 70; e-mail: christoph.stettler@insel.ch

**Curr Opin Clin Nutr Metab Care** 2015, 18:428–433
DOI:10.1097/MCO.0000000000000185

## KEY POINTS

- Although exercise is established to be beneficial in individuals with type 2 diabetes, its role is more ambivalent in patients with T1DM.
- The loss of endogenous regulation of insulin secretion and the consequent need of exogenous insulin delivery (with the related risk of unphysiological insulin levels) predispose to an increased risk of exercise-associated glucose fluctuations in individuals with T1DM.
- Supraphysiological insulin levels may impair hepatic glucose output and limit the physiological shift from glucose to fatty acid oxidation in the course of exercise – the corresponding literature is, however, still controversial.
- When studied under standardized conditions approximating physiological levels of glucose and insulin, there is little evidence of a generic difference in exercise-associated fuel metabolism in individuals with T1DM compared with their healthy counterparts.
- A thorough understanding of exercise-associated fuel metabolism may lead to novel therapeutic approaches (e.g., IHE) to improve stability of exercise-associated glucose.

reserves are also stored in the liver, the latter differing from the muscle by its ability to convert glucose-6-phosphate (derived from glycogen) to glucose that can then be systemically distributed to the working muscle in a third step. Glucose transport across the myocellular cell membrane is the rate-limiting step in this process. Blood glucose enters skeletal muscle through specific glucose transporters [glucose transporter isoform 4 (GLUT4)]. *GLUT4* gene expression in working muscle directly increases after a single bout of exercise [4]. Expression of GLUT4 as well as recruitment of GLUT4-containing vesicles is, therefore, a rapid process that has been shown to be regulated through two different pathways. On the one hand, recruitment follows stimulation by insulin via insulin receptors, followed by the intracellular pathway of insulin receptor substrate 1 and PI-3-kinase. On the other, physical exercise itself increases transport of GLUT4 toward cell membrane. The precise mechanisms of this latter pathway are not yet entirely understood, but it is assumed that autocrine and paracrine effects following muscle contraction associated with a release of intracellular calcium from the sarcoplasmatic reticulum may be involved. As the two stimuli (insulin and exercise) use different pathways, the effect of both stimuli together is additive. As a consequence, physiologically, insulin is downregulated during exercise in healthy individuals, thereby reducing the risk of overstimulation of GLUT4 in skeletal muscle (e.g., balancing the increased insulin sensitivity) and increasing hepatic glycogenolysis (inhibited by higher insulin levels). These adjustments in the insulin secretion are essential to preserve normoglycemia in nondiabetic individuals during physical activity.

## EXERCISE-ASSOCIATED GLUCOSE METABOLISM IN INDIVIDUALS WITH TYPE 1 DIABETES MELLITUS

The above-mentioned hormonal adaptations are essentially lost in patients with T1DM. As outlined before, treatment in T1DM consists of exogenous insulin that is applied subcutaneously (as opposed to the physiological portal insulin secretion in healthy individuals), resulting in an imbalance of comparably high peripheral but relatively low portal insulin levels. In addition, exogenous insulin has to cover insulin requirements through periods with considerably differing requirements. Guidelines for patients with T1DM generally recommend reduction of insulin before, during, and also after physical exercise and/or to ingest additional carbohydrates, if necessary, to balance the increased insulin sensitivity induced by exercise [1]. However, these adaptations may be difficult to implement in reality. Insulin treatment in patients with T1DM today either consists of multiple daily injections of rapid-acting insulin (used to cover meals and correct increased glucose levels) and long-acting basal insulin (covering basal insulin requirements). Alternatively, treatment is performed by continuous subcutaneous insulin infusion (CSII). Although, in general, both treatments have shown to be effective in the reduction of long-term diabetic complications, they fundamentally differ in their flexibility with regard to rapid dose adjustments: almost instant reductions of insulin delivery are feasible for patients using CSII. However, a considerable percentage of individuals with T1DM decide against CSII but still regularly perform physical exercise. The most frequently used long-acting insulin analogs today induce glucose-lowering effects over 12–24 h, some even as long as 48 h. Although this is convenient to the patient who needs to inject basal insulin only once or twice daily, it precludes a flexible dose reduction for active patients. In addition to insulin therapy, many other factors may impact on exercise-related glucose metabolism such as site of insulin injection; duration, intensity, and timing of exercise; composition and timing of the last meal before as well as nutrition during and after exercise; and pre-exercise blood glucose levels [5].

The specific role of the levels of insulin and glucose on exercise-associated fuel metabolism, respectively, has been assessed in several recent studies. Chokkalingam *et al*. [6] showed in their study comparing differing insulin levels that hyperinsulinemia translated into an increased exogenous glucose utilization during exercise, however, without sparing of intramyocellular glycogen. In a further study, they investigated exercise-induced hepatic glycogen consumption in individuals with T1DM compared with healthy controls. Despite the significantly higher insulin and glucose levels in T1DM, there were no differences in substrate oxidation and hepatic glycogen consumption between the groups [7]. In a complementary setting, we investigated the impact of differing glucose levels at identical and comparably low insulinemia on fuel metabolism during aerobic exercise in patients with T1DM [5]. We found a higher rate of carbohydrate oxidation during exercise in hyperglycemia than in euglycemia with inverse findings for lipid oxidation. Interestingly, intramyocellular glycogen was not spared in hyperglycemia and glycogen breakdown was even increased in this condition compared with euglycemia. This latter finding may be because of the fact that in the presence of identical insulin concentrations, hyperglycemia rapidly increased pre-exercise intramuscular glycogen, and higher pre-exercise glycogen levels have *per se* been shown to induce higher exercise-associated glycogen consumption [5]. Still, these results corroborate the concept that under euglycemic conditions with near-physiological insulin doses, patients with T1DM behave similarly to nondiabetic individuals, revealing a shift from carbohydrate oxidation toward a predominance of lipid oxidation in the course of aerobic exercise in euglycemia. The corresponding metabolic mechanisms for the deviations found under hyperglycemic conditions (e.g., persistence of artificially high glucose oxidation) are currently not entirely clarified. In addition to difference in the secretion of counter-regulatory hormones (e.g., cortisol and GH) according to glycemic levels [8], interleukin-6 and acetylcarnitin have been suggested as potential candidates [9,10,11▪]. Taken together, current findings speak strongly against generic metabolic defects in exercise-associated fuel metabolism in individuals with T1DM if exercise is performed under near-physiological conditions (e.g., euglycemia and comparably low insulin levels). This goes along with very recent data showing that glycogen storage capacity in liver and skeletal muscle of well controlled patients with T1DM is fully comparable to healthy individuals if studied under standardized conditions [12].

## HORMONAL RESPONSE DURING EXERCISE AND IMPLICATIONS FOR INDIVIDUALS WITH TYPE 1 DIABETES MELLITUS

Depending on exercise intensity, the hormonal response to exercise includes a broad variety of hormonal players, due to their potential glucose-increasing effect generally labeled as antagonists to insulin or counter-regulatory hormones. Essentially, these encompass glucagon, catecholamines, cortisol, and GH. In moderate-intensity exercise of limited duration in healthy individuals, the portal glucagon-to-insulin ratio is thought to be the main determinant in the regulation of endogenous glucose production and, consequently, energy supply to the working muscle. In contrast, catecholamines (e.g., norepinephrine and epinephrine) become more important during exercise of longer duration or higher intensity [13]. In individuals with T1DM, however, the hormonal interplay may be affected by several disease-specific factors; on the contrary, in addition to insulin, glucagon secretion also has been shown to be affected in the course of T1DM although there appears to be a difference between reactions to hypoglycemia (impaired) and exercise (preserved) [14]. Of note, counter-regulatory measures encountered during intense exercise are also involved in the physiological reaction to hypoglycemia, which is a relevant incident in patients with T1DM. Previous studies have shown that pronounced and repetitive hypoglycemia prior to exercise may reduce subsequent secretion of counter-regulatory hormones, thereby increasing the risk of exercise-associated hypoglycemia and potentially giving way to a vicious circle [15]. Reciprocally, prior exercise can impair the counter-regulatory response to subsequent episodes of hypoglycemia [15]. Interestingly, a sex-specific difference in the hormonal-regulatory response to euglycemic exercise has recently been reported, revealing a reduced increase in catecholamines and GH in female patients with T1DM [16]. In contrast, after antecedent hypoglycemia, the same group suggested better preserved neuroendocrine (glucagon and catecholamines) and metabolic homeostatic responses during exercise in women compared with men [17]. Finally, it has been suggested that individuals with T1DM may reveal defects in the secretion of GH, further contributing to a limited counter-regulation during hypoglycemia and/or during exercise. However, more recent reports have shown that exercise-induced GH secretion in T1DM patients in good metabolic control and studied under highly standardized conditions is entirely comparable to nondiabetic individuals [8]. It is, therefore, not unlikely that many of the findings in earlier studies pointing toward impaired counter-regulation

in T1DM may be essentially due to settings including patients in suboptimal metabolic control rather than proving generic differences.

## IMPACT OF HIGH-INTENSITY EXERCISE TO GLUCOSE METABOLISM IN TYPE 1 DIABETES MELLITUS

In healthy individuals, high-intensity exercise and the corresponding increase in counter-regulatory hormones may transiently lead to moderate hyperglycemia that is rapidly counterbalanced by an increase in endogenous insulin [18]. Lack of endogenous insulin regulation precludes this automatic compensation in patients with T1DM, adding the risk of hyperglycemia to the fear of hypoglycemia, thereby underscoring the complexity of exercise-associated glucose variations [3]. The induction of hyperglycemia has previously been described as an undesired side-effect of high-intensity exercise in T1DM. Interestingly, more recent studies now suggest that counter-regulatory hormones may even be of potential use to stabilize exercise-related glucose by compensating for the increased insulin sensitivity generally associated with exercise. For example, it has been shown that a single all-out sprint of 10 s directly after exercise may counterbalance the postexercise decrease of glucose induced by activation of GLUT4 [19]. Interestingly, the identical single intervention performed before exercise did not prevent a drop in glucose during exercise but still induced a stabilization of postexercise glucose levels [20]. Similar glucose-stabilizing effects have been suggested by adding resistance exercise (which relies on similar fuel sources and involves comparable amounts of counter-regulatory hormones) to aerobic exercise [11▪,21,22].

## NOVEL CONCEPTS BASED ON PHYSIOLOGICAL PERCEPTIONS

Based on the glucose-stabilizing effects of single bouts of intense exercise, it has recently been suggested that the combination of repetitive bouts of high-intensity exercise with exercise of low or moderate intensity (commonly referred to as intermittent high-intensity exercise or IHE) may provide a novel way to overcome the problem of exercise-related hypoglycemia [19,20,23▪▪,24,25]. In a study of seven individuals with T1DM assessing the impact of short sprints (4 s) performed every 2 min over an exercise duration of 30 min at low-to-moderate intensity, Guelfi *et al.* [25] found a reduction in exercise-related glucose decline and a stabilization of postexercise glucose levels. Maran *et al.* [26] used sprints of comparable duration (5 s) every 2 min over 30 min of exercise and investigated eight participants with T1DM. Despite a slight albeit not significant increase of short-term postexercise glucose in IHE, they reported an increased risk of delayed hypoglycemia after the exercise, potentially related to an increased consumption of glycogen reserves. Conversely, a recent study in 11 athletes with T1DM assessed the impact of all-out sprints of 15 s performed every 5 min over 45 min of exercise (50% of max workload) and found similar declines of glucose during exercise but a lower risk of nocturnal postexercise hypoglycemia associated with IHE [24]. The discrepancy regarding postexercise hypoglycemia found in these two trials may on the one hand be due to the difference in training status of the study population; Maran *et al.* [26] included comparably untrained individuals with T1DM whereas Iscoe and Riddell [24] investigated well trained type 1 diabetic athletes. There may also be an impact of sex as Maran *et al.* included male individuals, exclusively, whereas Iscoe and Riddell allowed for the inclusion of both sexes. In addition, both studies did not quantify pretrial levels of glycogen stores in liver or skeletal muscle. Therefore, higher pre-exercise glycogen stores as a potential stabilizing factor in the study of Iscoe and Riddell may not be ruled out.

Taken together, a limited number of studies have so far investigated the impact of IHE on glucose levels during and after exercise in individuals with T1DM. Results differ considerably with regard of the amount of glucose stabilization and important discrepancies appear regarding delayed postexercise hypoglycemia. Such disparities may be related to differing inclusion criteria and varying standardization procedures but also to a variety of IHE strategies. In essence, IHE in previous studies reflected activity patterns of typical team sports. However, the problem of exercise-associated hypoglycemia is frequently encountered during aerobic exercise of longer duration (e.g., running or biking for 1 or 2 h), thereby limiting the direct applicability of previous study results to daily clinical practice. To the best of our knowledge, only one study has so far investigated the impact of IHE during exercise of longer duration [27], but in this study sprints of 10 s were performed every 2 min, again making this regimen demanding to the individual and, thus, making it difficult to draw conclusions for strategies in endurance exercise. It is, thus, currently unknown, whether a regimen using less-frequent sprints but over a longer exercise duration may induce stabilization of glucose levels throughout but also after exercise. In addition, previous studies did not focus on pretrial standardization of glycogen stores in liver and muscle, as well as quantification of glycogen before and after exercise. Thus, the issue of postexercise hypoglycemia potentially associated with IHE remains unsolved. In a current research project, our group investigates the impact of repetitive all-out sprints of 10 s performed

every 10 min during an aerobic exercise (e.g., 45–50% of maximum workload) over 90 min. Preliminary results show a significantly reduced amount of exogenous glucose requested to maintain euglycemia in IHE compared with continuous exercise without sprints. The difference is essentially traced back to increased amounts of hepatic and to a lesser amount of myocellular glycogen consumption in IHE [28]. These findings corroborate the potential of IHE to reduce exercise-associated glucose variations. However, there is the potential downsize of an increased consumption of glycogen stores and, consequently, an increased risk of postexercise hypoglycemia associated with IHE.

## CONCLUSION

Although in healthy individuals glucose homeostasis is permanently maintained by a complex metabolic interplay, this delicate balance is significantly compromised in patients with T1DM rendering glucose metabolism prone to variations toward both hyperglycemia and hypoglycemia. Although modern therapeutic approaches provide important tools to improve the necessary adaptations, current treatment is still far from perfect. A better understanding of exercise-associated fuel metabolism will further our attempts to improve therapeutic recommendations. Novel approaches derived from physiological perceptions may offer alternative ways to answer to these challenges. Importantly, recent studies speak against generic differences in exercise-associated glucose metabolism in individuals with T1DM compared with their healthy counterparts if studies are performed under standardized and near-physiological conditions.

### Acknowledgements

*None.*

### Financial support and sponsorship

*This work was supported by the Swiss National Science Foundation grant (no. 320030_149321/1) to C.S.*

### Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. American Diabetes Association. Standards of medical care in diabetes: 2014. Diabetes Care 2014; 37 (Suppl 1):S14–S80.
2. Kennedy A, Nirantharakumar K, Chimen M, *et al.* Does exercise improve glycaemic control in type 1 diabetes? A systematic review and meta-analysis. PloS One 2013; 8:15.
3. Tonoli C, Heyman E, Roelands B, *et al.* Effects of different types of acute and chronic (training) exercise on glycaemic control in type 1 diabetes mellitus: a meta-analysis. Sports Med 2012; 42:1059–1080.
4. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. Physiol Rev 2013; 93:993–1017.
5. Jenni S, Oetliker C, Allemann S, *et al.* Fuel metabolism during exercise in euglycaemia and hyperglycaemia in patients with type 1 diabetes mellitus: a prospective single-blinded randomised crossover trial. Diabetologia 2008; 51:1457–1465.
6. Chokkalingam K, Tsintzas K, Norton L, *et al.* Exercise under hyperinsulinaemic conditions increases whole-body glucose disposal without affecting muscle glycogen utilisation in type 1 diabetes. Diabetologia 2007; 50:414–421.
7. Chokkalingam K, Tsintzas K, Snaar JE, *et al.* Hyperinsulinaemia during exercise does not suppress hepatic glycogen concentrations in patients with type 1 diabetes: a magnetic resonance spectroscopy study. Diabetologia 2007; 50:1921–1929.
8. Jenni S, Christ ER, Stettler C. Exercise-induced growth hormone response in euglycaemia and hyperglycaemia in patients with type 1 diabetes mellitus. Diabetic Med 2010; 27:230–233.
9. Jenni S, Wueest S, Konrad D, *et al.* Response of interleukin-6 during euglycaemic and hyperglycaemic exercise in patients with type 1 diabetes mellitus. Diabetes Res Clin Pract 2010; 89:26.
10. Boss A, Kreis R, Jenni S, *et al.* Noninvasive assessment of exercise-related intramyocellular acetylcarnitine in euglycemia and hyperglycemia in patients with type 1 diabetes using (1)H magnetic resonance spectroscopy: a randomized single-blind crossover study. Diabetes Care 2011; 34:220–222.
11. ■ Turner D, Luzio S, Kilduff LP, *et al.* Reductions in resistance exercise-induced hyperglycaemic episodes are associated with circulating interleukin-6 in Type 1 diabetes. Diabetic Med 2014; 31:1009–1013.

This study compared the impact of an increasing number of sets of resistance exercise in T1DM on blood glucose. Blood glucose rose after one and two sets of resistance exercise, but inclusion of a third set attenuated hyperglycemia.

12. Bally L, Bühler T, Stettler C. Quantification of liver and muscle glycogen after two days of diet and activity standardization: a 13C MRS reproducibility study in individuals with type 1 diabetes and matched healthy controls. Abstract, Annual Meeting of the Swiss Society of Endocrinology and Diabetes Switzerland; 27th/28th November 2014; Bern, Switzerland.
13. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab 2013; 17:162–184.
14. Siafarikas A, Johnston RJ, Bulsara MK, *et al.* Early loss of the glucagon response to hypoglycemia in adolescents with type 1 diabetes. Diabetes Care 2012; 35:1757–1762.
15. Basu R, Johnson ML, Kudva YC, *et al.* Exercise, hypoglycemia, and type 1 diabetes. Diabetes Technol Therap 2014; 16:331–337.
16. Galassetti P, Tate D, Neill RA, *et al.* Effect of gender on counterregulatory responses to euglycemic exercise in type 1 diabetes. J Clin Endocrinol Metab 2002; 87:5144–5150.
17. Galassetti P, Tate D, Neill RA, *et al.* Effect of sex on counterregulatory responses to exercise after antecedent hypoglycemia in type 1 diabetes. Am J Physiol Endocrinol Metab 2004; 287:2.
18. Fahey AJ, Paramalingam N, Davey RJ, *et al.* The effect of a short sprint on postexercise whole-body glucose production and utilization rates in individuals with type 1 diabetes mellitus. J Clin Endocrinol Metab 2012; 97:4193–4200.
19. Bussau VA, Ferreira LD, Jones TW, *et al.* The 10-s maximal sprint: a novel approach to counter an exercise-mediated fall in glycemia in individuals with type 1 diabetes. Diabetes Care 2006; 29:601–606.
20. Bussau VA, Ferreira LD, Jones TW, *et al.* A 10-s sprint performed prior to moderate-intensity exercise prevents early postexercise fall in glycaemia in individuals with type 1 diabetes. Diabetologia 2007; 50:1815–1818.
21. Yardley JE, Kenny GP, Perkins BA, *et al.* Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. Diabetes Care 2012; 35:669–675.
22. Yardley JE, Kenny GP, Perkins BA, *et al.* Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. Diabetes Care 2013; 36:537–542.
23. ■■ Campbell MD, West DJ, Bain SC, *et al.* Simulated games activity vs continuous running exercise: a novel comparison of the glycemic and metabolic responses in T1DM patients. Scand J Med Sci Sports 2015; 25:216–222.

This study investigated the glycemic and metabolic responses in intermittent and continuous running exercise in T1DM. Intermittent running exercise was associated with greater counterregulatory hormone and lactate levels and a lower risk of early-onset postexercise hypoglycemia.

24. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. Diabetic Med 2011; 28:824–832.

**25.** Guelfi KJ, Jones TW, Fournier PA. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. Diabetes Care 2005; 28:1289–1294.
**26.** Maran A, Pavan P, Bonsembiante B, *et al.* Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. Diabetes Technol Therap 2010; 12:763–768.
**27.** Dube MC, Lavoie C, Weisnagel SJ. Glucose or intermittent high-intensity exercise in glargine/glulisine users with T1DM. Med Sci Sports Exercise 2013; 45:3–7.
**28.** Bally L, Züger T, Stettler C. Carbohydrate requirements during intermittent high intensity exercise compared to continuous moderate intensity exercise in individuals with type 1 diabetes mellitus. Abstract, Annual Meeting of the Swiss Society of Endocrinology and Diabetes Switzerland; 27th/28th November 2014; Bern, Switzerland.