The hypoglycemia associated autonomic failure triggered by exercise in the patients with “brittle” diabetes and the strategy for prevention

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Abstract. Exercise is a fundamental component of diabetes management. However, choosing inappropriate type or timing of exercise is associated with mild or severe hypoglycemia either during exercise or several hours after exercise. Several studies have shown that impaired counterregulatory responses triggers hypoglycemia. Therefore, in this investigation, we explored the appropriate intensity and time of exercise in patients with diabetes. The mechanisms of counterregulatory responses and hypoglycemia associated autonomic failure (HAAF), as well as the strategies for preventing episodes of hypoglycemia after exercise were also investigated. In this study, we obtained the following results: 1) High intensity interval exercise is more suitable for diabetic patients. 2) Morning exercise reduces nocturnal hypoglycemia risks compared with midday, afternoon and evening exercise. 3) Hypoglycemia can be prevented by dietary approach, reduction or suspension of insulin dose, use of mini dose glucagon, caffeine, mitigation methods, prediction algorithm, autonomic feedback controlled close-loop insulin delivery, real time continuous glucose monitoring. Based on these results we concluded that exercise may cause severe hypoglycemia or induce blunted response in patients with diabetes. For Diabetes Mellitus (DM) patients, the intensity and time of exercise influence the occurrence of hypoglycemia. This review summarizes the clinical characteristics of different types of exercises and time of exercise that can be potentially used to educate and guide patients regarding the role of exercise in standard of care.

Key words: Exercise, Hypoglycemia, Counterregulatory response, Hypoglycemia associated autonomic failure, Diabetes

Introduction

According to 7 surveys on diabetes mellitus performed between 1981 and 2010 in China, the prevalence of Diabetes Mellitus has increased by 17-fold, from 0.67% to 11.6% of the population [1]. The international Diabetes Federation has estimated that there are 382 million people with diabetes worldwide [2]. These statistics indicate that DM poses a huge economic burden to the patients and society.

Among the 382 million people with DM, 5–10% have Type 1 diabetes mellitus (T1DM) or insulin-dependent diabetes, an auto-immune disorder involving pancreatic β-cell destruction and a high level of ketosis, with an onset generally but not exclusively below age of 40 (formerly called juvenile-onset diabetes). About 90% of DM patients suffer from type 2 diabetes mellitus (T2DM) or non-insulin-dependent diabetes, a condition characterized by insufficient insulin secretion and insulin resistance caused by a combination of environmental and genetic factors [3]. Some T1DM patients have very poor glycemic control. The regulation of blood glucose in these patients is so fragile that they easily suffer from hyper- or hypoglycemia. The term “brittle” diabetes is used to describe these patients [4]. For this reason, these patients lack a regular healthy lifestyle such as the inability to exercise.

If not controlled, diabetes, may lead to a many microvascular and macrovascular complications. For instance, diabetic retinopathy, a visual impairment may occur in diabetes patients as a consequence of retinal microangiopathy. Diabetic nephropathy is a major cause of morbidity and mortality in patients with diabetes. Diabetes may also increase the risk of coronary artery disease and peripheral vascular disease (The diabetic foot). It has been estimated that the 20-year survival rate after the diagnosis of diabetes is 50 to 80% of the expected survival rate of the healthy general population. About 12%
of individuals with T1DM die within 20 years after the onset of the disease [3].

Several large, multicenter randomized controlled trials for patients with T1DM or T2DM have shown that effective blood glucose management can prevent or delay the occurrence of diabetic complications such as retinopathy, microalbuminuria, and neuropathy [5]. Although the advantages of intensive glycemic control are well documented, it is associated with major drawbacks. The severity of hypoglycemia is influenced by the duration of T1DM and T2DM [6].

Generally, a decrease in the concentration of blood glucose leads to the activation of a series of physiologic counterregulatory mechanisms. Initially, the body responds by decreasing the endogenous secretion of insulin. As the blood glucose continues to decrease, the metabolic counterregulatory responses trigger the release of hormones such as glucagon, epinephrine, growth hormone, cortisol, norepinephrine, aldosterone, and adrenocorticotropic hormone. These hormones stimulate hepatic glucose production and adipose tissue lipolysis and inhibit skeletal muscle glucose uptake, thereby increasing blood glucose. In patient with T1DM and longer duration of T2DM, their counterregulatory mechanisms are not sufficient to restore blood glucose level after hypoglycemia.

It has been shown that severe hypoglycemia can lead to seizure, coma and even death. The fear of hypoglycemia is prevalent among patients with diabetes. This fear may prevent such patients from achieving ideal glycemic level.

Exercise is crucial for improving glucose metabolism in diabetic patients. It promotes weight loss, maintains hepatic and peripheral insulin sensitivity, increases glucose uptake and utilization thereby maintaining cardiovascular health. However, among individuals taking insulin or insulin secretagogue medications, even moderate exercise can lead to hypoglycemia. Moreover, hypoglycemia can occur during exercise and up to 24 hours after exercise.

The fear of hypoglycemia is a major deterrent factor for patients with DM to be physically active [7]. In light of the potential benefits of physical exercise, it is crucial for patients and physicians to fully understand the risks of hypoglycemia and develop effective strategies to prevent occurrence of severe hypoglycemia without compromising normal glycemic control.

In this review, we will provide a brief overview of different types of exercise recommended for patients with DM and how counterregulatory responses affect exercise-induced hypoglycemia in conjunction with implementation of strategies and techniques that prevent hypoglycemia episodes during and after exercise.

Exercise Time and Types

Physical activity refers to all movement that increase energy utilization and encompasses all activities, of any intensity, performed during a 24-hours day. On the other hand, exercise is a more specific form of physical activity that enhances or maintains physical fitness and overall health and wellness [8].

Exercise improves blood glucose control which reduces cardiovascular risk factors and contributes to weight loss. Although it has many benefits, it often leads to hypoglycemia.

Moreover, hypoglycemia after exercise is common in individuals taking insulin and/or insulin secretagogues. (especially patients with type 1 diabetes or long duration type 2 diabetes, “Brittle Diabetes”) [8]. For healthy individuals, any change in energy levels, even extremely low glucose levels, is generally normalized by physiological homeostatic processes [9]. For DM patients, the intensity and time of exercise as well as the amount of endogenous insulin infusion and insulin sensitivity influence the occurrence of hypoglycemia. In this section, we mainly discuss about the types and time of exercising that is suitable for patients.

Types of exercise

Exercise is classified into many types based on the intensity, i.e., low, moderate and intermittent high intensity/high intensity interval. (A combination of moderate and high-intensity exercise is typically performed in most sports and field activities).

In a study of 27 patients with T1DM, Darleen et al. [10] randomized participants into three teams to undergo low (30% VO2max), moderate (50% VO2max) intensity exercise or to sit in a chair (control subjects) for 90 minutes. This was followed by a 180-minutes resting period and a second exercise for 90 minutes at the same intensity described above. Glucose, insulin and counter-regulatory hormones were measured during and after exercise. Data analysis revealed that exercise at all intensities blunted autonomic neuroendocrine regulation (epinephrine and pancreatic polypeptide), metabolic function (fat oxidation), and symptomatic responses to subsequent hypoglycemia compared with control subjects.

In the past two decades, the popularity of high intensity interval exercise (HIIE) has been increasing. HIIE has been reported to promote hyperglycemia during early recovery phase. In a study in which 17 participants (Type 1 diabetes) completed 71 HIIE sessions, (90%) patients suffered from hyperglycemia. Although these patients were given different doses of insulin to correct hyperglycemia, 6 of them had nighttime hypoglycemia [11].

A study by Guelfi et al. [8] found that, in 90–150
such patients should take SE + HIIE in a reversed order compared with moderate intensity exercise. But in the longer period between midnight and 6:00 a.m., glucose levels were significantly lower after intermittent high-intensity exercise than moderate intensity exercise. In addition, the frequency of hypoglycemia episodes after intermittent high-intensity exercise was higher (seven vs. two) than for moderate intensity exercise.

Another study by Jayawardene et al. compared high intensity interval exercise (HIIE) with moderate intensity exercise (MIE). All participants in this study had type 1 diabetes and were put on insulin pump. Plasma glucose was monitored starting from exercise commencement to 120 minutes post-exercise. The glucose level of one participant fell to 3.4 mmol/L at the end of MIE, but the glucose levels after HIIE were ≥4.0 mmol/L. The mean plasma glucose was higher during HIIE exercise than in MIE. Which is consistent with the findings reported by Guelfi et al. [12].

Rooijackers et al. investigated the reduced awareness of subsequent hypoglycemia after high intensity interval exercise (HIIE) in Type 1 diabetes patients. It was found that HIIE only reduced symptoms of hypoglycemia in patients with normal awareness of hypoglycemia, but not in patients with impaired awareness or healthy participants [13].

Patients who tend to develop exercise-associated hypoglycemia should perform strength exercise (SE, 30 minutes) before high intensity interval exercise (HIIE, 30 minutes), because SE + HIIE could prevent glucose from decreasing at 60 minutes. For patients with high pre-exercise glucose levels and/or those with exercise-associated hyperglycemia, Farinha et al. suggested that such patients should take SE + HIIE in a reversed order according to their recent findings on T1DM patients [14].

A study found that a 10-second sprint before or after moderate intensity exercise performed under hyperinsulinemic conditions could prevent hypoglycemia after the moderate intensity exercise, without carbohydrate intake after exercise. But a 10-seconds sprint performed after moderate-intensity exercise does not affect the amount of carbohydrate required to maintain euglycemia post-exercise in diabetic patients [15].

Consequently, it can be inferred that HIIE is suitable because it results in a higher blood glucose level during and after exercise than moderate intensity exercise, although it causes a slight increase frequency of nocturnal hypoglycemia. Strength exercises performed before or after HIIE or MIE are beneficial for patients to maintain their blood glucose level.

**Time of exercise**

Once the type of exercise is selected, the next important question would be when should it be performed? Morning, midday, afternoon and evening are deemed suitable for exercising. But given the risk of nocturnal hypoglycemia in patients with diabetes, the appropriate time at which diabetes patients can participate in exercise becomes an important issue.

The effects of performing morning vs. afternoon exercise on hypoglycemia frequency in Type 1 diabetes patients have been reported by Ana et al. This study recruited a total of 35 patients with T1DM. Participants who performed morning exercise at 7 a.m. were provided with a standardized breakfast. Participants who performed afternoon exercise at 4 p.m. had their lunch at 12 p.m. The exercise was performed at a consecutive and moderate intensity. Based on continuous glucose monitoring (CGM) data, they found that the rate of hypoglycemia was significantly lower following morning exercise relative to afternoon exercise sessions (5.6 vs. 10.7 events per participant). Morning exercise had a lower risk of late-onset hypoglycemia than that of afternoon exercise [16].

In many studies, moderate intensity exercise was performed in late afternoon. These studies tested different durations of moderate intensity exercise (MOD). In a study conducted by Diabetes Research in Children Network (DirectNet) Study Group, 50 youths with T1DM who performed MOD for 60 minutes in the late afternoon showed doubled frequency (48%) of nocturnal hypoglycemia compared with sedentary days (Tomborlane 2007.12). Prolonged MOD (75 minutes) has also been found to increase the risk of nocturnal hypoglycemia compared with no exercise (sedentarynight) by the Direct Net Study Group [17]. McMahon et al. found that even when the time of MOD was reduced, the risk of nocturnal hypoglycemia was still higher compared with no exercise group. Franc et al. reported that with bolus or basal rate reduction, both moderate (60 minutes) or high intensity exercise (60 minutes) carried out 3 hours after lunch (late afternoon) causes no hypoglycemia event at all [18].

Since MOD alone is associated with the risk of nocturnal hypoglycemia. Some scholars have proposed combination of high intensity interval exercise (HIIE) with MOD. In fact, afternoon HIIE + MOD (45 minutes) can protect against nocturnal hypoglycemia compared with afternoon MOD only (45 minutes) in patients with T1DM [19].

Elsewhere, Raymond et al. investigated the influence of midday moderate intensity exercise on post-exercise hypoglycemia risk in individuals with T1DM. They recruited 10 adolescents with clinically diagnosed
T1DM. They performed either 45 minutes of moderate intensity exercise or rest. Results revealed that the risk of exercise-mediated hypoglycemia was sustained for 11 hours after exercise in adolescents with T1DM, suggesting that midday moderate intensity exercise could increase the risk of nocturnal hypoglycemia [20].

Evening exercise is characterized by late falls in glycemia typically at about 8 hours post-exercise, and 90% of patients experienced nocturnal hypoglycemia [21].

By analyzing the time and intensity of exercise, we suggest that patients should exercise early in the day and combine MOD with HIIE to minimize nocturnal hypoglycemic events. If combined with insulin reduction, exercise during late afternoon may also be safe.

**Duration of exercise**

As recommended by American Diabetes Association (ADA), most adults with type 1 and type 2 diabetes should engage in 150 minutes moderate to vigorous intensity aerobic activity per week, and at least 3 days/week with no more than 2 consecutive days without activity. In addition, sedentary lifestyle should be interrupted for every 30 minutes with light activity for efficient blood glucose control [22].

**The Mechanisms of HAAF**

To avoid the fatal hypoglycemia events both during and after exercise, it is important to understand the definition of hypoglycemia and the mechanism of hypoglycemia associated autonomic failure (HAAF) (Fig. 1).

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes stipulates that recent antecedent hypoglycemia causes both defective hormonal counterregulation (by attenuating the epinephrine response in the setting of absent insulin and glucagon responses) and impaired awareness of hypoglycemia (by attenuating sympathetic nervous response to hypoglycemia), resulting in a vicious cycle of recurrent hypoglycemia [22].

The counterregulatory response is a physiological mechanism by which the body prevents or corrects hypoglycemia. Many factors are involved in the counterregulatory response to hypoglycemia, in which glucagon plays an important role in preventing rapid decrease in blood glucose. Epinephrine is not particularly significant, but it is an important supplement to the action of glucagon deficiency. Therefore, the absence of epinephrine only partially affects the counterregulatory responses. However, when both epinephrine and glucagon are absent, the glucose counterregulatory response becomes insufficient, and then the progressive hypoglycemia occurs. Although other hormones, neurological or substrate effects, such as glucose autoregulation are also involved in glucose counterregulatory response, they are not strong enough to prevent or correct hypoglycemia without the glucagon and epinephrine. These findings are supported by experimental data from CM.A et al. [23]. In their study, baboons were intravenously injected with 2-deoxy-D-glucose to induce neuroglucopenia. Thereafter, β-adrenergic blockade (propranolol) was used to block the autonomic nervous system and the function of epinephrine. Somatostatin was administered to the baboons, alone or as a combination, to inhibit glucagon secretion. At the end of the experiment, the mean rise in plasma glucose was 6.2 ± 0.8 mmol/L (propranolol), 6.8 ± 0.8 mmol/L (somatostatin), 1.0 ± 0.1 mmol/L (combined), and 6.6 ± 0.9 mmol/L (no propranolol and somatostatin). This finding confirmed the different roles of glucagon and epinephrine in the counterregulatory response.

Impaired awareness of hypoglycemia is defined as the failure to recognize the alarming symptoms of impending hypoglycemia, such as anxiety, shakiness, palpitation, sweating, hunger, and paresthesias, especially in a group of people with type 1 diabetes (“Brittle Diabetes”).
The physiological mechanism of HAAF

The concept of HAAF is associated with two major physiological mechanisms. One is the inability to decrease insulin and the increase in glucagon. Impaired β-cells’ function significantly decreases the secretion of endogenous insulin, implying that the level of circulating insulin is dependent on the absorption rate and clearance rate of the injected insulin. In cases of low glucose, the corresponding decrease in insulin levels is not proportional. And this may be ascribed to β-cell failure [24].

Another component is attenuated sympathoadrenal-adrenalmedullary and sympathetic neural response, which is known can be caused by recent hypoglycemia, sleep and prior exercise. Unlike the insulin and glucagon, this response is related to the central nervous system (CNS) or its afferent or efferent connections [24].

The exercise related HAAF

HAAF is caused by three factors: recent antecedent hypoglycemia, prior exercise [25], and sleep. The post-exercise hypoglycemia normally has two phases, one during and immediately after exercise, another several hours after exercise which mainly occurs during sleep. Many of patients suffering from attenuated counterregulatory responses and hypoglycemia unawareness after exercise are considered to have exercise-related HAAF.

The mechanisms of HAAF in diabetic patients

Normally, insulin inhibits glucagon secretion in pancreatic islets. Thus, lack of insulin secretion results in a fall in plasma glucose due to decreased glucagon release [26]. Another important hormone involved in the counterregulatory response, epinephrine, is also reduced during HAAF [27]. Among the factors accounting for the decrease in epinephrine release, the lactate levels within central nervous system (CNS) play a key role. Infusion of lactate resulted in about two to four-fold elevation in plasma lactate which reduced the epinephrine response to hypoglycemia and symptoms of hypoglycemia in non-diabetic and diabetic individuals. Lactate also lowers the plasma glucose thresholds for these responses and increases brain lactate uptake [26] (Fig. 2).
Chan et al. [28] reported that direct application of lactate to ventromedial hypothalamus (VMH) in rats increased VMH γ-aminobutyric acid (GABA) levels by about 10 fold and suppressed epinephrine (and glucagon) responses to hypoglycemia [26]. Both in the HAAF model of diabetic and nondiabetic animals, GABAergic tone within the VMH contribute to glucose counterregulatory failure. The data shows that lactate might influence counterregulatory responses through VMH GABAergic neurons [26].

Lactate within the brain regions is derived from glycogen metabolism, which is stored in astrocytes. Lactate level increases while glycogen level decreases in the hippocampus, cerebellum, cortex, and brain stem. In contrast, Takashi et al. suggested that serotonin (5-HT) turnover increased in the hippocampus and brainstem and was associated with a decrease in glycogen. As a result, they concluded that serotonergic neurons in the hippocampus and brainstem are likely to regulate the intense exercise-induced brain glycogenolysis [29].

Other scholars found that β-endorphin released during antecedent exercise is associated with deterioration of counterregulatory response to subsequent hypoglycemia in the following day, which is similar to the effect of antecedent hypoglycemia. Furthermore, they found that the role of β-endorphin is independent of hormone levels, exercise intensity, body mass index (BMI), gender, or HbA1c measures. But in a trained subject, even exercise at the same percentage of VO2max, the release of β-endorphin is higher than the former ones unlike in an untrained subject. β-endorphin is an endogenous opioid peptide which is synthesized inside proopiomelanocortin (POMC) neurons of the hypothalamus and can respond to a range of stressors, including hypoglycemia and exercise. Naloxone is a nonselective opioid antagonist. When administered to repeated hypoglycemia condition, it can improve the attenuated hormonal responses indicating opioid inhibition can be considered as a potential therapy for hypoglycemia-associated autonomic failure (HAAF) in DM patients [30].

Management of Exercise-Induced HAAF

Having discussed the mechanism of HAAF and the inappropriate intensity and time of exercise associated with hypoglycemia occurrence (during and several hours later), it is important to explore the strategies for preventing exercise-related HAAF.

Reduction or suspension of insulin dose

A combination of reduced bolus insulin dose and low glycemic index carbohydrate (LGI) feeding strategy has been proved to protect patients treated with multiple daily injections from hypoglycemia during and 24 hours following evening exercise [21]. In addition, this strategy does not produce hyperglycemia. These patients were mainly treated with a 75% reduced bolus insulin dose at 17:00 (60 minutes before exercise), in addition to consuming a low glycemic index (LGI) meal. A 50% reduced bolus insulin dose was given to the patients 60 minutes after the exercise. Then, at about 23:00, participants were given an LGI bedtime snack. The outcome of this strategy reveals that exercise-induced hypoglycemia could be completely avoided without other metabolic disturbances.

What is the effect of suspending basal insulin in DM patients? A study conducted in 2006 using a randomized crossover design reported the effects of this practice [31]. Forty-nine children aged 8–17 with T1DM were studied; basal insulin was stopped during exercise and continued 45 minutes after exercise. The researchers found that discontinuing basal insulin during exercise was effective in reducing hypoglycemia, but this increased the risk of hyperglycemia 45 minutes after the completion of the exercise. In addition, although this strategy prevented hypoglycemia during exercise, the risk of late-onset or nocturnal hypoglycemia cannot be ruled out.

Another study investigated the effect of pre- and post-exercise bolus insulin reduction on early and late onset of hypoglycemia in patients with T1DM [32]. Eleven young male patients were recruited after a preliminary test and were tested on 3 separate days. Briefly, 25% rapid-acting insulin dose was administered 60 minutes prior to 45 minutes treadmill running exercise. At 60 minutes post-exercise, the patients ate and were administered with a full, 75%, or 50% rapid-acting insulin dose. Finally, they concluded that a 25% pre-exercise and 50% post-exercise rapid acting dose maintained glucose levels and protected patients against early (<8 h) but not late-onset hypoglycemia.

The food strategy

Apart from different insulin treatment methods, food strategies like LGI meal, LGI snack and other nutritional strategies have been separately studied.

The glycemic index (GI) is a number associated with a particular type of food that indicates the food’s effect on a person’s blood glucose level. Carbohydrate-containing foods can be classified as high-(≥70), moderate- (56–69), or low GI (<55) relative to pure glucose (GI = 100).

Meals that contain identical macronutrient compositions are digested and absorbed at varying rates, and therefore produce a range of glycemic responses [33]. Carbohydrate-rich food with a low glycemic index (LGI) elicits a more gradual rise and fall in blood glucose levels compared with other high glycemic index (HGI)
equivalents [33]. Therefore, investigating LGI foods can provide solutions to prevent post-exercise hypoglycemia. Matthew et al. studied the effect of a low-glycemic index meal and bedtime snack on postexercise hypoglycemia. Their research was done in two evenings for 10 male patients. They administered a 25% rapid-acting insulin dose with a carbohydrate bolus 60 minutes before 45 minutes of treadmill running. Sixty minutes after exercise, patients were given a 50% rapid-acting insulin dose. The patients were then separated into two groups given isoenergetic meals matched for macronutrient content but differentiated by LGI or HGI group take on LGI/HGI snack before going home. The results revealed that both meal types protected all patients from early hypoglycemia, but the risk of late-onset hypoglycemia (nocturnal hypoglycemia) was present [33].

Apart from LGI foods, Marie et al. studied whether protein supplements can prevent exercise-induced hypoglycemia in patients with T1DM. In their study, subjects exercise for 120 minutes after three different kinds of breakfast: (1) standardized breakfast + pre-exercise placebo beverage (PL), (2) standardized breakfast + pre-exercise carbohydrate (CHO) beverage, and (3) protein supplemented breakfast + pre-exercise placebo beverage (PROT). Their results show that taking CHO supplement before unplanned exercise was effective in preventing exercise-induced hypoglycemia. Moreover, they found that a protein supplement strategy may have benefits of limiting the rate of hypoglycemia during and immediately after exercise.

**Mini dose glucagon**

Although food strategies are effective in preventing hypoglycemia, excessive carbohydrates intake would be a counterproductive strategy from a weight management perspective. Therefore, mini dose glucagon has been proposed as a novel approach to prevent exercise-induced hypoglycemia in T1DM patients. This approach has been demonstrated by Michael et al. [34]. In their study, 15 adults with T1DM were treated with continuous subcutaneous insulin infusion and exercised while fasting in the morning at about 25% VO2max for 45 minutes under the condition of no intervention (control), 50% basal insulin reduction, 40-g oral glucose tablets, or 150 μg subcutaneous glucagon (MDG). During early recovery stage from exercise, patients who used MDG showed a slight increase in plasma glucose in contrast to the decrease in the control and insulin reduction group, and a higher increase with glucose tablets. In addition, patients who have MDG experienced least hypoglycemia episode. This study suggested that MDG is more effective in preventing hypoglycemia than insulin reduction or ingestion of carbohydrates.

**Caffeine**

It has been hypothesized that excess insulin in the blood and increased insulin sensitivity in the tissue may lead to exercise-induced hypoglycemia. A study found that caffeine can improve insulin-induced hypoglycemia in normal and malnourished rats. Insulin sensitivity in these rats was enhanced under food restriction conditions whereas several counterregulatory responses are impaired during severe hypoglycemia. This is similar to diabetic patients who undergo hypoglycemia episodes [35]. Caffeine was found to be ergogenic and interferes with the actions of insulin related to glucose homeostasis. Moreover, caffeine was found to antagonize muscle adenosine receptors in the tissues, which seems to be the most important mechanism of caffeine as far as glucose homeostasis is concerned. Moreover, caffeine stimulates the release of free fatty acids and adrenaline, which adds to the systemic insulin resistance. Inconsistent with this role, Thong et al. [36] observed that glucose uptake in the muscles is increased post-exercise, but decreased after administration of caffeine. All these findings add up to the conclusion by Lucas et al. that caffeine decreases the severity of hypoglycemia [35].

**The mitigation methods, prediction algorithm and autonomic feedback controlled close-loop insulin delivery**

Mitigation method is effective for patients using artificial pancreas (AP) systems to automatically control blood glucose levels. Since exercise-induced hypoglycemia is a major challenge, Arthur et al. combined a close-loop controlled algorithm with feedforward action (FF action) to address it [37]. The FF action was evaluated in two scenarios: (1) exercise sessions during the postprandial period and (2) exercise sessions during the fasting period. It was found that implementation of these mitigation methods minimized the occurrences of hypoglycemia in both scenarios. It, therefore, appears that mitigation methods are effective in patients using AP.

Another prediction algorithm was found to be effective in preventing exercise-induced hypoglycemia in T1DM [38]. This predictive algorithm serves as a supplement to the sensor-augmented pump therapy (SAPT), in which basal insulin is suspended when hypoglycemia is predicted. In a randomized, controlled cross-over study, 25 participants were studied for two days. Each day, 2 consecutive sessions of 30 minutes of moderate intensity exercise were performed while basal continuous insulin infusion was administered. The first day was the control day in which participants performed the exercise with SAPT alone. On the second day, participants combined SAPT with the predictive algorithm. As a result, only 6 participants (32%) required treatment for hypo-
glycemia compared with 17 participants (89%) in the control. In conclusion, SAPT plus predictive algorithm can reduce the need for hypoglycemia treatment after moderate intensity exercise.

So far, we have discussed the effect of feed forward action (mitigation method) and predictive algorithm on the prevention of exercise-induced hypoglycemia in DM patient. Another study investigated the effectiveness of autonomic feedback controlled closed-loop (CL) insulin delivery in preventing nocturnal hypoglycemia and maintaining blood glucose level within the target range of night with and without antecedent afternoon exercise [39]. A total of 12 subjects with type 1 diabetes, aged 12 to 26 years old, were recruited. Each subject completed two sessions of 48 hours of inpatient study periods with OL control or autonomic feedback-controlled CL insulin delivery. The 48 hours study period was composed of a sedentary day and an exercise day, and the exercise was 60 minutes of brisk treadmill walking. Among the 12 subjects, 6 to 8 events of nocturnal hypoglycemia occurred during open-loop control with antecedent exercise compared with only one nocturnal hypoglycemia event each on the night with and without antecedent exercise during closed-loop control with feedback algorithm. As expected, the overnight glucose values in the target range was also increased with closed-loop control with a feedback algorithm.

Real time continuous glucose monitoring

Feedforward, feedback and predictive algorithms have been used by patients to avoid hypoglycemia with exercise presented. On the other hand, real-time (RT) continuous glucose monitoring (CGM) accompanied by a new carbohydrate intake algorithm has also been tested to maintain euglycemia during exercise [40]. It turned out that with the use of RT-CGM and algorithm, euglycemia was largely maintained and simultaneously prevented hypoglycemia.

Even the single use of RT-CGM has been found be beneficial for diabetic patients. In a study carried out by Tumminia et al. 20 Type 1 diabetic patients with poor glycemic control were recruited. They tested RT-CGM or blood glucose self-monitoring (SMBG) for two months. After 2 months of wash out, participants were crossed over. The use of RT-CGM produced a better glycemic control using HbA1c as primary outcome [41].

Continuous glucose monitoring (CGM) is very convenient for doctors and patients to monitor blood glucose and therefore to eliminate hypoglycemia both during and after exercise. A traditional CGM works through a tiny sensor inserted subcutaneously, usually on belly or arm, monitoring interstitial glucose level. This device always needs external power and sophisticated readout instruments. These drawbacks may prevent patients from using it. But a newly invented paper-based, self-powered sensor patch might solve this problem [42]. This tool monitors glucose level in human sweat. It has a wearable, paper-based glucose/oxygen enzymatic fuel cell designed into a standard Band-Aid adhesive patch. This device does not need external power or any sophisticated readout instruments. This new device is expected to provide protection to many patients.

Aside from RT-CGM, there is another kind of system, flash glucose monitoring system (FGM). Unlike RT-CGM which provides blood glucose information passively to the patient, FGM provides blood glucose readings each time the patient actively scans the sensor. One advantage of FGM is that it does not require calibration by the patient, and hence it has a superior sensor accuracy compared with RT-CGM [43].

Comparing these two glucose monitoring systems, FGM has better accuracy but are not indicated in subjects with hypoglycemia unawareness. On the other hand, RT-CGM can provide timely BG and its trend, but lack of accuracy (needs timely calibration by patient) is its main drawback.

Conclusions

As discussed in this review, the intensity and time of exercise are important for DM patients. Different strategies of preventing hypoglycemia in patients with DM during and after exercise are also discussed in detail. However, further research is needed to better understand and provide additional strategies of preventing exercise-induced hypoglycemia.

Authors’ Contributions

All authors contribute equally to this article.

Competing Interests

The authors declare that they have no competing interests.

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