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Source / Izvornik: **World Journal of Diabetes, 2021, 12, 569 - 577**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.4239/wjd.v12.i5.569>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:088988>

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Download date / Datum preuzimanja: **2024-07-25**



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Fear of hypoglycemia, a game changer during physical activity in type 1 diabetes mellitus patients

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Author contributions: Cigrovski Berkovic M contributed to the conception and design of the study, drafted, and revised the manuscript critically; Bilic-Curcic I, Cigrovski V, La Grasta Sabolic L and Mrzljak A collected the data, drafted, and wrote the manuscript; All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no competing interests.

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Abstract

Hypoglycemia limits optimal glycemic management of patients with type 1 diabetes mellitus (T1DM). Fear of hypoglycemia (FoH) is a significant psychosocial consequence that negatively impacts the willingness of T1DM patients to engage in and profit from the health benefits of regular physical activity (e.g., cardiometabolic health, improved body composition, cardiovascular fitness, quality of life). Technological advances, improved insulin regimens, and a better understanding of the physiology of various types of exercise could help ameliorate FoH. This narrative review summarizes the available literature on FoH in children and adults and tools to avoid it.

Key Words: Hypoglycemia; Fear of hypoglycemia; Type 1 diabetes mellitus; Physical activity; Modern technology; Exercise management

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Core Tip: Fear of hypoglycemia (FoH) is a major barrier to achieving recommended

Manuscript source: Invited manuscript

Specialty type: Endocrinology and metabolism

Country/Territory of origin: Croatia

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

Received: December 2, 2020

Peer-review started: December 2, 2020

First decision: March 16, 2021

Revised: March 16, 2021

Accepted: March 29, 2021

Article in press: March 29, 2021

Published online: May 15, 2021

P-Reviewer: Lee CH

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Li X



childhood and adult levels of physical activity (PA) in type 1 diabetes mellitus patients. The main factor associated with FoH is the frequency of hypoglycemia. The occurrence of hypoglycemia can be mitigated by well-defined recommendations on performing PA and maintaining euglycemia, implementing modern technologies and improved insulin regimens, educational programs, and social media information.

Citation: Cigrovski Berkovic M, Bilic-Curcic I, La Grasta Sabolic L, Mrzljak A, Cigrovski V. Fear of hypoglycemia, a game changer during physical activity in type 1 diabetes mellitus patients. *World J Diabetes* 2021; 12(5): 569-577

URL: <https://www.wjgnet.com/1948-9358/full/v12/i5/569.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v12.i5.569>

INTRODUCTION

Hypoglycemia, a barrier to glycemic management in type 1 diabetes mellitus

Intensified insulin regimens aim to achieve a near-normal glucose level, which is the primary goal of type 1 diabetes mellitus (T1DM) management because it is associated with a decreased risk of long-term chronic micro- and macrovascular complications. On the other hand, intensive treatment increases the risk of acute side effects, such as hypoglycemia, which in itself correlates with increased morbidity and even mortality[1,2]. Hypoglycemia is often the limiting factor in the glycemic management of T1DM patients[3], and it can compromise patients' willingness to maintain a healthy lifestyle, primarily adversely affecting involvement in regular physical activity (PA)[4]. Reducing the risk of hypoglycemia and, at the same time, maintaining or improving glycemic control is imperative. Patient education, empowerment, modern technology, improved insulin regimens, and healthcare workers' support are deemed necessary.

BENEFITS OF PA FOR PATIENTS WITH T1DM

Regular PA beginning in early childhood is important for both physical and psychological development. For individuals with T1DM, PA offers many health benefits, including improved glycemic control and blood lipid profiles, better cardiovascular function, and psychological wellbeing[5,6]. Unfortunately, most people with T1DM do not regularly engage in adequate PA. As a direct or indirect consequence, as many as 60% of patients have hyperlipidemia, 40% have hypertension, and 60% are obese or overweight, thus having an increased cardiovascular risk[7]. On the other hand, the results of an extensive cross-sectional study suggest that regular PA that includes exercising ≥ 2 times weekly can improve cardiometabolic parameters and reduce microvascular complications (*e.g.*, nephropathy-microalbuminuria or retinopathy) of diabetes[8]. Exercise intervention studies have generally failed to show clinically meaningful improvements in hemoglobin A1c (HbA1c) with PA in T1DM[9]. That might be attributable to differences in study design and exercise dosage as well as adjustments of insulin dosing and/or carbohydrate intake while exercising intended to minimize exercise-induced hypoglycemia and ensure safe blood glucose levels[10]. The study by Dube *et al*[11] found that people with T1DM who were engaged in moderate or intense PA reported increased HbA1c, carbohydrate consumption, and weight gain, which was explained by their tendency to avoid hypoglycemia. Therefore, hypoglycemia and fear of hypoglycemia (FoH), in addition to lack of knowledge of exercise management in T1DM, are significant obstacles in reaching recommended PA targets.

IS FOH STILL THE MAIN OBSTACLE TO ACHIEVING PA TARGETS?

FoH encompasses an anxiety disorder in patients and their families that is caused by hypoglycemia and the associated behavioral changes affecting glycemic management, such as avoiding exercise, maintaining high blood glucose levels, and administering

low insulin doses[12]. FoH can have a severe impact not only on regular exercise but also on all aspects of life quality. Anxiety is the most common consequence of hypoglycemia-induced distress leading to two potential scenarios. One could be adaptive, instigating productive behavior regarding glucose management[13,14]. However, that could also be disruptive, triggering behavioral changes leading to poor glycemic control and impaired quality of life[15]. So far, it has been shown that, FoH frequently occurs in parents who report severe hypoglycemia in their children[16,17]. Several studies have confirmed a positive correlation between FoH and HbA1c in young children and adolescents and that high parent and adolescent scores in an FoH survey were associated with increased HbA1c levels[18-20]. Other factors affecting parental FoH were nonmodifiable sociodemographics (*e.g.*, age, education, nationality) and modifiable psychological factors (*e.g.*, mindful parenting)[21]. A study assessing FoH in adult patients identified the frequency of severe hypoglycemia as the most relevant factor associated with FoH[22]. In addition, several predictive factors such as female gender, hypoglycemia unawareness, and glucose variability seem to be associated with hypoglycemia[23]. Moreover, FoH was recently shown not to be time-dependent in most cases, but to be conditioned by change in hypoglycemia frequency, which emphasizes the significance of mitigating hypoglycemic events[24]. Results of the Diabetes MILES study in the Netherlands have shown that FoH in adults with T1DM was associated with a history of hypoglycemia and depressive symptoms[25]. Interestingly, although FoH is a major obstacle to performing regular PA, there are few data on FoH and exercise. However, existing studies identified FoH as a major culprit for inadequate exercise[26-28]. Surprisingly, in the SEARCH for Diabetes in Youth Case-Control Study, 82% of participants with T1DM achieved the recommended PA goals compared to healthy peers[29], in contrast to the 33% of young adults with T2DM who achieved the recommended PA targets[7]. Recently published data showed that increased levels of vigorous PA (VPA) were associated with increased FoH scores in SEARCH patients with T1DM. In addition, there was a decrease in VPA with age and an increase in moderate PA[30]. Therefore, we can assume that FoH does not affect PA or that VPA is considered a better option, given recent recommendations that include the benefits of high intensity interval training (HIIT) to avoid hypoglycemia[31]. In the same study, HbA1c positively correlated with pediatric FoH, resulting in poor glycemic control. On the other hand, lower HbA1c correlated with higher VPA, emphasizing a well-known positive effect of PA on glucose management[32].

PA: RECOMMENDATIONS FOR PATIENTS WITH T1DM

Although the recommendations on PA for people with T1DM and those with type 2 diabetes mellitus do not differ, some specifics need to be considered. In general, 150 min of accumulated aerobic PA is recommended weekly, with no more than 2 consecutive days without PA plus resistance training two to three times weekly, but not on consecutive days[33]. For children and adolescents, the recommendation is to be involved in PA at least 60 min daily[34,35].

What makes the difference in managing PA in the case of T1DM are the specific patient goals for exercise (*e.g.*, metabolic control, prevention of complications, fitness, weight loss, or competition and performance), which should be considered before decisions on diabetes management are made. For example, strategies behind exercising for weight loss should focus on reducing insulin doses during and after exercise instead of consuming carbohydrates. On the other hand, if sports results and exercise performance are the primary goals, nutritional guidance specific to the sporting activity is most important, while modifications in insulin dosing are secondary to match the new/additional nutritional requirements. Regardless of the set goals, blood glucose monitoring before, during, and after exercise is essential to avoid hypo and hyperglycemia[36-38]. Despite the perceived benefits, many young people with T1DM do not meet the proposed PA recommendations[39], and it is still unclear what would be the most effective type of exercise for improvement of metabolic control and cardiovascular health in people with T1DM[40,41].

From a practical standpoint, to minimize the risk of hypoglycemia, glycemic levels during, but also before and after exercise should be individually tailored. For the majority of patients with T1DM, the starting glucose range should be somewhere between 7-10 mmol/L when initiating aerobic exercise lasting up to an hour. When engaging in HIIT and anaerobic exercise, training can be initiated at the lower starting glucose concentration range, somewhere between 5-7 mmol/L, as during this kind of

exercise, glucose levels either remain stable or even tend to rise[31]. Although it is still unclear whether there is an optimal glycemic range during exercise, available data suggest that concentrations between 6-8 mmol/L should be preferred[42]. Strategies to prevent hypoglycemia rely on previous hypoglycemic episodes, which should be taken into account when planning subsequent PA[43]. An episode of severe hypoglycemia within the previous 24 h presents a contraindication to exercise[44]. As insulin sensitivity increases after exercise (and can remain increased for up to 48 h[45]), strategies to minimize exercise-related hypoglycemia, especially nocturnal occurrence, should be employed, including the avoidance of the exercise during the late afternoon[46-48].

PREVENTION OF HYPOGLYCEMIA-A ROLE FOR IMPROVED INSULIN REGIMENS AND MODERN TECHNOLOGY

Regular PA is usually recommended as an integral part of diabetes management in children and adults with T1DM[33,35]. However, it is frequently accompanied by unwanted blood glucose changes and requiring a range of potential preventive measures. Even if implemented, precautions are not always sufficient to avoid excessive glucose excursions. Moreover, handling different forms of PA can be particularly challenging for both individuals with T1DM and healthcare providers, whereby the decision-making process is often trial and error based[49]. In younger children, the tricky part about PA is that it is often unplanned and unpredictable.

Among the well-known barriers to regular PA, FoH and loss of glycemic control are shared by adults and youth with T1DM[26,27,31]. Consequently, the need for education on safe PA practices is widely recognized and acknowledged[30,31,50,51]. Recent advances in insulin formulations, delivery methods, continuous glucose monitoring (CGM) systems, applications (apps), and algorithms that integrate novel technologies are expected to improve glycemic control with less hypoglycemia and a better quality of life for people with T1DM.

Insulin therapy has been the cornerstone of diabetes management for almost a century, and despite the current availability of a wide array of insulin preparations, significant unmet needs remain[52]. With rapid-acting insulin analogs (*e.g.*, insulin aspart, lispro, glulisine), a reduction in bolus dose accompanying the meal before exercise is still required. On the other hand, with new long-acting basal insulin analogs (*e.g.*, degludec, glargine U300), dose adjustments for PA are impractical and cannot be performed without overall glycemic control disturbance[31]. A glucose-responsive insulin patch, an innovative and promising treatment option already successfully tested in diabetic animals, is awaiting clinical trials in humans.

In recent years there has been a great expansion of diabetes-specific technology, including CGM systems, insulin pumps, and automated insulin delivery systems. Glycemic management during exercise has been made easier with CGM technology. Most common CGM systems measure glucose in the interstitial fluid, providing real-time sensor glucose data (rtCGM) and triggering alerts for hypo and hyperglycemia. Intermittently scanned CGM systems (isCGM) measure interstitial glucose levels at the time of scanning and lack alarms. A lag time between blood and interstitial fluid glucose value exists and is particularly pronounced when blood glucose levels change rapidly, that occur during exercise. Furthermore, physiological changes during PA, such as alterations in blood flow rate, body temperature, and acidity, can theoretically disturb interstitial glucose-sensing accuracy[53]. General recommendations can be used as an initial guidance tool when using rtCGM/isCGM before exercise, during exercise, after exercise, and the nocturnal post-exercise phase[54]. However, for different groups of people with T1DM, different glycemic ranges around exercise may be required. Finally, all recommendations should be tailored individually, relying on the use of sensor glucose values accompanied by trend arrows while employing safe sensor glucose thresholds[54].

Insulin pumps offer better flexibility in insulin dose adjustments and management of exercise-associated glucose excursions than other insulin delivery methods[55-57]. Basal rate reduction mitigates the risk of hyperglycemia after moderate exercise more effectively than basal insulin suspension and appears to be associated with reduced risk of hypoglycemia both during and after PA[58]. However, the optimal timing and percentage of basal rate reduction have to be individually determined. Besides, for a more effective reduction of circulating insulin levels during PA, the remaining insulin from the bolus applied within the previous 2 h can be considered[59]. For intense exercise, the best option is to temporarily stop the pump, which coincides quite nicely

with the preference of patients who wish to remove their pump during activity. To prevent early exercise-related hypoglycemia after the meal, the premeal bolus dose reduction might be more effective than reducing the basal rate[58].

Sensor-augmented pump therapy combines insulin pumps, CGM systems, and therapy management software to automatically suspend insulin delivery for up to two hours when CGM detects a glucose level that has reached a prespecified threshold or to suspend insulin in anticipation of hypoglycemic events. In recent years, those devices have been connected to create a more automated glucose monitoring and insulin dosing combo marketed as a closed-loop system that automatically adjusts basal insulin delivery based on CGM readings[60]. Several studies have shown a reduction in hypoglycemia incidence and severity in patients using closed-loop systems in pediatric and adult patients[61,62]. However, although effective and highly promising, these systems warrant further research for an optimized use around exercise[63].

Digital health technology is developing rapidly, and numerous health-related apps installed on smartphones or other wireless devices are already available to support people with diabetes in lifestyle interventions or insulin adjustments in response to glucose monitoring data[64]. Several apps are primarily intended to support PA in people with T1DM, as they allow users to track activity, count calories, and set goals for exercise and weight management. However, the available evidence on the safety and efficacy of such stand-alone diabetes apps is still limited. Several issues, including inadequate or insufficient information on app accuracy, clinical validity, data security, and lack of user training, need to be resolved to ensure the full potential of such diabetes apps[65].

CONCLUSION

FoH-are we ready to discard it?

General guidelines for minimizing exercise-related glucose excursions exist, but their implementation is often burdensome for people with T1DM. As numerous factors influence glycemia during exercise, such as glucose level at the start of PA, the type, intensity, and duration of exercise as well as its' timing concerning meals, all the preventive actions require major individualization and are not always successful in avoiding hypoglycemia. Optimizing glycemic control around exercise is still demanding. Despite many advances in insulin formulations, delivery methods, and CGM systems, a thorough education is still essential. As technology continues to progress, people with T1DM are expected to achieve better glycemic control around exercise with less hypoglycemia and a lighter mental burden. However, many questions regarding availability, affordability, and adherence to expanding diabetes technology remain. Although FoH remains one of the main obstacles in achieving recommended PA levels, according to the latest research in young populations, it could even encourage more vigorous exercise patterns. Possibly, the development of new technologies, educational programs and social media information on the importance of PA, updated recommendations regarding the type and time of exercise, and necessary adjustments allowing euglycemia during and after the exercise have had a significant impact on alleviating FoH. Hopefully, future research embracing all of these FoH related aspects will enable us to minimize or disregard the problem of FoH. Finally, our understanding of exercise physiology and the different effects aerobic, anaerobic, resistance training and HIIT have on glycemic levels can minimize the risk of hypoglycemia and improve T1DM management, especially in the setting of new technology and improved insulin on board (Figure 1).

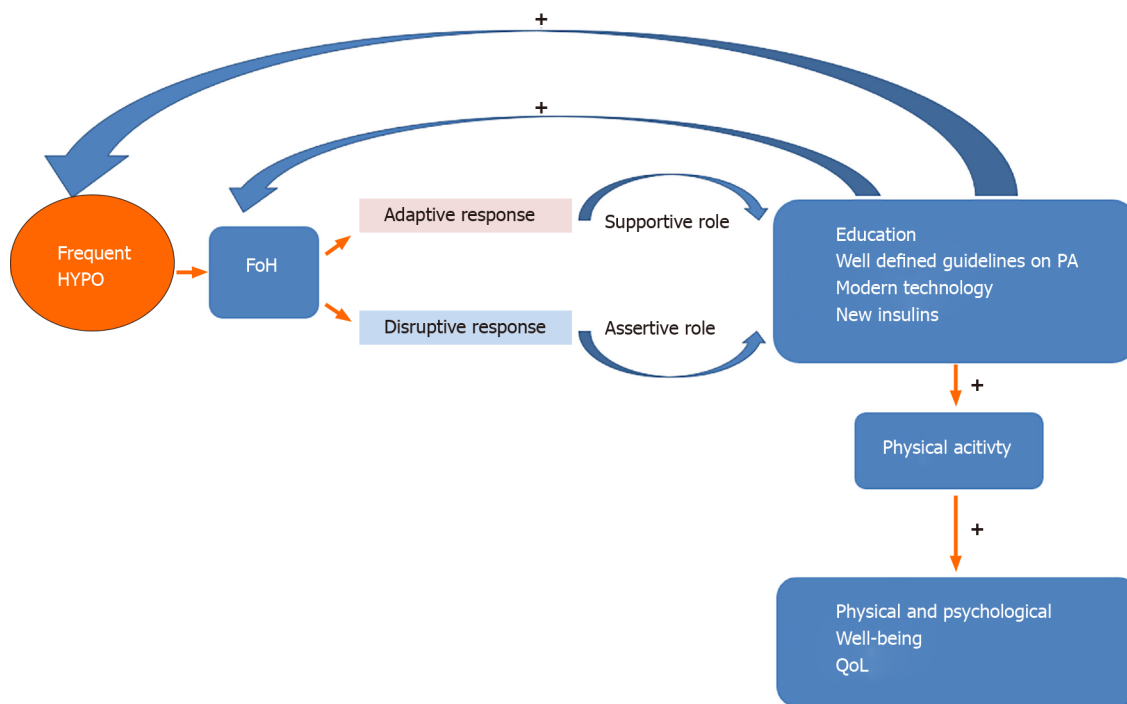


Figure 1 Potential mechanisms that can be used to minimize the frequency and fear of hypoglycemia to help type 1 diabetes mellitus patients reach the proposed physical activity levels and improve physical and psychological health. FoH: Fear of hypoglycemia; HYPO: Hypoglycemia; PA: Physical activity; QoL: Quality of life.

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