ORIGINAL ARTICLE

Advances in Exercise, Physical Activity, and Diabetes Mellitus

Trevor Teich¹, Dessi P. Zaharieva¹, and Michael C. Riddell^{1,2}

Introduction

WE HAVE LONG UNDERSTOOD THAT physical activity is an effective strategy for type 2 diabetes prevention and for the overall health and well-being of people already diagnosed with all forms of diabetes mellitus (1,2). Current clinical practice guidelines on physical activity and diabetes mellitus in North America suggest that patients living with a diagnosis of type 1 or type 2 diabetes should aim to accumulate at least 150 min each week of physical activity, with some form of resistance training done on 2 or 3 days each week (3). Regular exercise not only helps patients to achieve their target HbA1c, lipid, and body composition goals, but also allows patients to derive all of the other benefits of being physically active (brain, body, and spirit). Studies over the last several decades continue to refine this prescription as we discover new ways in which various forms of physical activity (e.g., structured resistance training, high-intensity interval training, simple walking) are helping muscle, adipose tissue, liver, and other key metabolic tissues adapt in such a way as to improve insulin action and glucose control (4–7). We are also learning how the brain, heart, kidneys, and other tissues and organs benefit from regular activity (8). Research in this field regularly establishes new and innovative ways to make exercise safer for individuals living with diabetes who may have difficulty maintaining safe and healthy glucose levels while performing or recovering from the sport or activity (9).

This year, we screened 1885 titles found on PubMed and other common search engines for manuscripts on exercise and diabetes published between July 1, 2017, and June 30, 2018. We found a number of original research papers and reviews on exercise mechanisms of action as well as a number of articles on how to best maintain glucose control while being physically active. This year, considerable progress was also made in artificial pancreas (automated insulin delivery) systems during and after exercise. The 10 key articles listed below represent the breadth of research related to reducing glucose disturbances caused by exercise in diabetes and why exercise is so beneficial for all forms of diabetes mellitus.

Key Articles Reviewed for the Article

Mini-dose glucagon as a novel approach to prevent exercise-induced hypoglycemia in type 1 diabetes

Rickels MR, DuBose SN, Toschi E, Beck RW, Verdejo AS, Wolpert H, Cummins MJ, Newswanger B, Riddell MC; for the T1D Exchange Mini-Dose Glucagon Exercise Study Group

Diabetes Care 2018; **41**: 1909–1916

¹School of Kinesiology and Health Science, Faculty of Health, Muscle Health Research Centre, York University, Toronto, Ontario, Canada

²LMC Diabetes & Endocrinology, Toronto, Ontario, Canada

Randomized outpatient trial of single- and dual-hormone closed-loop systems that adapt to exercise using wearable sensors

Castle JR, El Youssef J, Wilson LM, Reddy R, Resalat N, Branigan D, Ramsey K, Leitschuh J, Rajhbeharrysingh U, Senf B, Sugerman SM, Gabo V, Jacobs PG

Diabetes Care 2018; **41**: 1471–1477

Exercise training decreases pancreatic fat content and improves beta cell function regardless of baseline glucose tolerance: a randomised controlled trial

Heiskanen MA, Motiani KK, Mari A, Saunavaara V, Eskelinen JJ, Virtanen KA, Koivumäki M, Löyttyniemi E, Nuutila P, Kalliokoski KK, Hannukainen JC

Diabetologia 2018; **61**: 1817–1828

Assessment of mitigation methods to reduce the risk of hypoglycemia for announced exercise in a uni-hormonal artificial pancreas

Bertachi A, Beneyto A, Ramkissoon CM, Vehí J

Diabetes Technol Ther 2018; **20**: 285–295

Physical activity reduces risk of premature mortality in patients with type 1 diabetes with and without kidney disease

Tikkanen-Dolenc H, Wadén J, Forsblom C, Harjutsalo V, Thorn LM, Saraheimo M, Elonen N, Tikkanen HO, Groop PH; on behalf of the FinnDiane Study Group

Diabetes Care 2017; **40**: 1727–1732

Carbohydrate restriction with post meal walking effectively mitigates postprandial hyperglycaemia and improves endothelial function in type 2 diabetes

Francois ME, Myette-Cote E, Bammert TD, Durrer C, Neudorf H, DeSouza CA, Little JP

Am J Physiol Heart Circ Physiol 2018; **314**: h105–h113

Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study

Breton MD, Cherňavsky DR, Forlenza GP, DeBoer MD, Robic J, Wadwa RP, Messer LH, Kovatchev BP, Maahs DM

Diabetes Care 2017; **40**: 1644–1650

Functional high-intensity training improves pancreatic β -cell function in adults with type 2 diabetes

Nieuwoudt S, Fealy CE, Foucher JA, Scelsi AR, Malin SK, Pagadala M, Rocco M, Burguera B, Kirwan JP

Am J Physiol Endocrinol Metab 2017; **313**: E314–E320

A comparison of adipose tissue interstitial glucose and venous blood glucose during postprandial resistance exercise in patients with type 2 diabetes

Heden TD, Liu Y, Kanaley JA

J Appl Physiol 2018; **124**: 1054–1061

Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial

Dovc K, Macedoni M, Bratina N, Lepej D, Nimri R, Atlas E, Muller I, Kordonouri O, Biester T, Danne T, Phillip M, Battelino T

Diabetologia 2017; **60**: 2157–2167

Mini-dose glucagon as a novel approach to prevent exercise-induced hypoglycemia in type 1 diabetes

Rickels MR¹, DuBose SN², Toschi E³, Beck RW², Verdejo AS², Wolpert H³, Cummins MJ⁴, Newswanger

B⁴, Riddell MC⁵; for the T1D Exchange Mini-Dose Glucagon Exercise Study Group

¹Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania, Perelman School of Medicine, Philadelphia,

PA; ²Jaeb Center for Health Research, Tampa, FL; ³Joslin Diabetes Center, Harvard Medical School, Boston, MA; ⁴Xeris Pharmaceuticals, Inc., Austin, TX; ⁵Muscle Health Research Centre, York University School of Kinesiology and Health Science, Toronto, Ontario, Canada

Diabetes Care 2018; **41**: 1909–1916

Background

People living with type 1 diabetes engaging in aerobic forms of physical activity (e.g., walking, jogging, cycling) often develop hypoglycemia. Current approaches to prevent blood glucose levels from dropping while engaged in activity include basal/bolus insulin dose reductions and/or carbohydrate feeding (7), but these strategies are based on limited data and may result in either hypoglycemia or hyperglycemia. Glucagon is a counterregulatory hormone that is used to treat hypoglycemia, but its use to prevent hypoglycemia during exercise has not yet been fully tested. These researchers determined whether a small dose of glucagon (termed a mini-dose of glucagon or MDG) given subcutaneously just before exercise could prevent blood glucose from dropping during brisk walking exercise.

Methods

Fifteen participants living with type 1 diabetes (6 female, 9 male), all on insulin pump therapy, performed four in-clinic fasted exercise sessions (at ~55% of maximal aerobic capacity) lasting 45 min under conditions of (a) no intervention (control); (b) a 50% basal insulin reduction at exercise onset; (c) 40 g oral carbohydrate (20 g plus 20 g dextrose at exercise start and halfway through exercise); or (d) a 150 μ g subcutaneous dose of glucagon (i.e., MDG).

Results

During exercise and in early recovery, glucose levels increased slightly with MDG compared with a large decrease observed with the control strategy (i.e., no preventative strategy in place) or with a basal insulin dose reduction, while oral carbohydrate intake caused a significant rise in glycemia. Insulin levels were not different among sessions, whereas plasma glucagon levels increased rapidly and markedly with MDG. Six participants experienced hypoglycemia (plasma glucose <70 mg/dL) during the control visit, along with five subjects during the insulin reduction visit; none experienced hypoglycemia with either glucose tablets or MDG. Five subjects experienced hyperglycemia (plasma glucose $\geq$ 250 mg/dL) with glucose tablets, while one developed hyperglycemia with MDG.

Conclusions

MDG is more effective than insulin dose reductions for preventing exercise-associated hypoglycemia, if strategies are implemented just before exercise start time, and may result in less postexercise hyperglycemia when compared with carbohydrate feeding. Future studies should test the safety and efficacy of MDG in a variety of exercise settings.

Randomized outpatient trial of single- and dual-hormone closed-loop systems that adapt to exercise using wearable sensors

Castle JR¹, El Youssef J^{1,2}, Wilson LM¹, Reddy R², Resalat N², Branigan D¹, Ramsey K³, Leitschuh J², Rajhbeharrysingh U¹, Senf B¹, Sugerman SM¹, Gabo V¹, Jacobs PG²

¹Harold Schnitzer Diabetes Health Center, Division of Endocrinology, Oregon Health & Science University, Portland, OR; ²Department of Biomedical Engineering, Oregon Health & Science University, Portland, OR; ³Oregon Clinical and Translational Research Institute Biostatistics and Design Program, Oregon Health & Science University, Portland, OR

Diabetes Care 2018; **41**: 1471–1477

This manuscript is also discussed in the article on Decision Support Systems and Closed Loop, page S-42.

Background

Automated insulin delivery (sometimes called artificial pancreas or closed-loop) systems for type 1 diabetes are emerging as the standard of care, but hypoglycemia during most forms of aerobic exercise remains a challenge. This research team determined whether the addition of glucagon to the automated insulin delivery, along with a wearable sensor that detected exercise, would outperform other forms of closed-loop and open-loop therapies with insulin only and no exercise detector.

Methods

Participants (n=20) with type 1 diabetes underwent four treatment arms, dual-hormone, single-hormone, predictive low-glucose suspend, and continuation of current care, in randomized order over four outpatient days. Three moderate-intensity aerobic exercise sessions were included in each arm. The primary outcomes included the percentage of time spent in hypoglycemia (<70 mg/dL) and the time in a targeted range (70–180 mg/dL), as assessed from the start of the in-clinic exercise until the next meal.

Results

The lowest mean percent time (standard deviation) in hypoglycemia was during exercise with dual-hormone treatment: 3.4% (4.5) vs 8.3% (12.6) for single-hormone vs 7.6% (8.0) for predictive low-glucose suspend vs 4.3% (6.8) for current standard of care (i.e., preexercise insulin adjustments were allowed). Additionally, during the entire 4-day study, hypoglycemia duration was the lowest with dual-hormone: 1.3% (1.0) vs 2.8% (1.7) for single-hormone vs 2.0% (1.5) for predictive low-glucose suspend vs 3.1% (3.2) for standard of care. Time in range during the entire study was the highest with the single-hormone treatment arm, 74.3% (8.0) compared with 72.0% (10.8) for dual-hormone.

Conclusions

In adults with type 1 diabetes who are physically active, the addition of glucagon delivery to a closed-loop system

with automated exercise detection results in a reduction of time spent in hypoglycemia.

Comments

Aerobic exercise frequently promotes a large drop in blood glucose concentration in people with diabetes who are taking exogenous insulin. Although carbohydrate feeding can help attenuate the drop in glucose effectively, some patients dislike having to consume additional carbohydrates when they exercise, for a variety of reasons (e.g., weight maintenance/weight loss, feeding may interrupt the activity and promote gastric upset). The reduction of basal insulin before exercise onset, while recommended for individuals on continuous subcutaneous insulin infusion (10,11), is only partially effective at attenuating the drop in blood glucose unless it is done well in advance of the activity (12). All of these issues make exercise difficult to manage even with artificial pancreas prototypes and commercially available products. A seemingly straightforward approach would be to add a little glucagon to the circulation just prior to exercise in hopes that this might alleviate the problem of hypoglycemia. These two research studies tried two slightly different approaches to see if exogenous glucagon could help prevent hypoglycemia during exercise. In the first paper highlighted above, Rickles et al. showed that MDG (150 μ g of a soluble and stable form of glucagon) given just before exercise prevented hypoglycemia altogether in patients performing brisk walking for 45 min. The paper by Castle and colleagues demonstrated feasibility of using glucagon in a separate pump, along with insulin in another pump, to help stabilize glucose levels once they started to drop with exercise. The study was slightly less effective than the MDG approach, largely because the delivery of glucagon was reactive rather than proactive before the exercise had even started. Future studies may wish to have a head-to-head comparison of MDG and standard care vs dual-hormone artificial pancreas in preventing exercise-induced hypoglycemia. Our bet is that MDG would be a more effective approach in preventing hypoglycemia, but that it may also promote hyperglycemia in some situations where the exercise is much more intensive, when glucose levels tend to rise with the rise in catecholamines and/or lactate production, or when the activity is very mild and the amount of glucose needed by the working muscles is small.

Exercise training decreases pancreatic fat content and improves beta cell function regardless of baseline glucose tolerance: a randomised controlled trial

Heiskanen MA¹, Motiani KK¹, Mari A², Saunavaara V^{3,4}, Eskelinen JJ¹, Virtanen KA³, Koivumäki M¹, Löyttyniemi E⁵, Nuutila P^{1,3,6}, Kalliokoski KK¹, Hannukainen JC¹

¹Turku PET Centre, University of Turku, Turku, Finland;

²Institute of Neuroscience, National Research Council, Padova, Italy; ³Turku PET Centre, Turku University Hospital,

Turku, Finland; ⁴Department of Medical Physics, Turku University Hospital, Turku, Finland; ⁵Department of Biostatistics, University of Turku, Turku, Finland; ⁶Turku PET Centre, Åbo Akademi University, Turku, Finland

Diabetologia 2018; **61**: 1817–1828

Background

A fatty pancreas is correlated with impaired glucose tolerance, and this ectopic lipid accumulation may facilitate β -cell dysfunction. Although exercise induces a robust increase in whole-body insulin sensitivity, its role in regulating pancreatic fat content and β -cell dysfunction remains unclear. This randomized controlled trial evaluated the effect of exercise training programs of varying intensity on pancreatic fat and β -cell dysfunction in healthy individuals and individuals with type 2 diabetes and prediabetes.

Methods

In this study, 97 sedentary individuals (40–55 years old) were recruited and screened for their eligibility based on the American Diabetes Association criteria of prediabetes and type 2 diabetes. A total of 28 healthy men and 26 men and women with prediabetes or type 2 diabetes were randomized in a 1:1 ratio into either a high-intensity interval program (4–6 episodes of all-out effort during 30-second cycling sprints) or a moderate intensity continuous aerobic exercise program (40–60 min at 60% peak workload) for a period of 2 weeks. The primary outcome was pancreatic fat content, as measured by magnetic resonance spectroscopy, while secondary outcomes included β -cell function and whole-body insulin sensitivity, as determined from an oral glucose tolerance test, as well as pancreatic fatty acid and glucose uptake as measured by positron emission tomography.

Results

At baseline, the group of individuals with prediabetes and type 2 diabetes had significantly higher pancreatic fat content and impaired β -cell function vs healthy individuals. In contrast, the extent of pancreatic glucose and fatty acid uptake was similar between groups. Exercise training lowered pancreatic fat in both the healthy group (from 4.4% [3.0%, 6.1%] to 3.6% [2.4%, 5.2%] [mean, 95% CI]) and the prediabetes/type 2 diabetes group (from 8.7% [6.0%, 11.9%] to 6.7% [4.4%, 9.6%]; $P=0.036$ for a time effect), without any significant changes observed for pancreatic fatty acid and insulin-stimulated glucose uptake. The different exercise regimens similarly improved a number of variables relating to β -cell function.

Conclusion

Two weeks of high-intensity interval or moderate intensity continuous training improved β -cell function in individuals with prediabetes or type 2 diabetes and decreased pancreatic fat content regardless of pretraining glucose tolerance. Given that ectopic fat accumulation is a risk factor for type 2 diabetes, this study demonstrated that exercise training is therefore an effective strategy to lower the risk of developing type 2 diabetes.

Comments

The association between metabolic dysfunction, abdominal obesity, and ectopic fat accumulation has been observed in numerous studies (13,14). The pathogenesis underlying this association remains unclear but includes, among other explanations, the “portal theory,” which posits that direct exposure to the liver of certain metabolites and nutrients contributes to hepatic insulin resistance, steatosis, and thereby metabolic dysfunction. Other related theories include the adipose tissue inflammation hypothesis, which suggests that chronic, low-grade proinflammatory cytokines, derived particularly from within visceral adipose depots, contribute to metabolic dysfunction, cardiovascular disease, and type 2 diabetes (15,16). This study specifically investigated the relationship between pancreatic fat accumulation, β -cell dysfunction, and the role of exercise in improving these parameters in individuals with and without type 2 diabetes. Notably, this study demonstrated for the first time that just two weeks of exercise training reduced pancreatic fat content and markedly improved β -cell function regardless of pretraining glucose tolerance status. These are important findings given the critical role of β -cells in glucose metabolism and that pancreatic fat content has now gained recognition as a risk factor for type 2 diabetes (17). We agree with the authors that it would be valuable for future research to analyze the effect of an extended period of regular exercise on pancreatic fat content and its relationship to insulin sensitivity and glucose tolerance. In addition, this work contributes valuable information to our understanding of the vast benefits of exercise toward disease prevention and treatment.

Assessment of mitigation methods to reduce the risk of hypoglycemia for announced exercise in a uni-hormonal artificial pancreas

Bertachi A^{1,2}, Beneyto A¹, Ramkissoon CM¹, Vehí J^{1,3}

¹Institute of Informatics and Applications, University of Girona, Girona, Spain; ²Federal University of Technology - Paraná (UTFPR), Guarapuava, Brazil; ³Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain

Diabetes Technol Ther 2018; **20**: 285–295

Background

For patients with type 1 diabetes, moderate intensity physical activity improves overall health condition. However, the effects of exercise on glycemic control make insulin management difficult during and after exercise. Artificial pancreas systems aim to automatically regulate glucose levels, but exercise-induced hypoglycemia can still occur, as insulin levels may not drop fast enough to offset the increase in glucose disposal caused by muscular contractions (18). The aim of this work was to evaluate the ability of several feed-forward actions to prevent exercise-induced hypoglycemia in a closed-loop setting.

Methods

The University of Virginia/Padova type 1 diabetes simulator was used for *in silico* evaluation of a hybrid closed-loop control algorithm combined with feed-forward actions aimed at eliminating exercise-induced hypoglycemia. The simulator was modified with an exercise model along with the typical clinical data. The feed-forward actions were evaluated during postprandial exercise and during fasting exercise.

Results

The feed-forward mechanisms used in this study minimized the occurrence of hypoglycemia associated with exercise in both the fed and fasted states. Percent time in hypoglycemia during the 2 hours immediately following exercise dropped from 33% to 0% ($P < 0.01$) and from 41% to 0% ($P < 0.01$) in the fed and fasted state, respectively. The number of postexercise hypoglycemic events also dropped to 1 with feed-forward closed-loop vs 52 with closed-loop alone.

Conclusions

According to this *in silico* study, the combination of the feed-forward exercise detection actions within a hybrid artificial pancreas system appears to be a very effective strategy for eliminating hypoglycemia during and after aerobic exercise in people living with type 1 diabetes.

Comments

Single-hormone artificial pancreas systems continue to struggle with aerobic exercise. Unless the exercise is announced well in advance to the controller or pump, insulin levels do not drop in the circulation and may in fact rise during this form of activity (12,19). Announcing exercise to the artificial pancreas controller can help change the algorithm settings or raise the set-point of glucose, which effectively stops insulin delivery, hopefully in enough time to prevent glucose from dropping as soon as the exercise begins. Aerobic exercise dramatically increases insulin sensitivity and increases blood flow to adipose tissue and to muscle, which appears to increase insulin bioavailability (19). This study demonstrated, using an *in silico* model of ~4000 min of physical activity and 450 meals, that a feed-forward detector for exercise largely eliminates hypoglycemia during and after the activity. One of the potential limitations of announcing exercise well in advance, as in this study, is that preexercise glucose levels tended to be elevated (~175 mg/dL) compared to when the feed-forward technology was not used (~147 mg/dL). Moreover, this single-hormone hybrid artificial pancreas system utilizes snack announcements (i.e., 10 g of carbohydrate if the preexercise glucose level is between 90 and 124 mg/dL or 20 g if the preexercise glucose is <90 mg/dL) to help eliminate hypoglycemia. Nonetheless, this is a small price to pay for preventing hypoglycemia almost entirely in an aerobic exercising setting.

Physical activity reduces risk of premature mortality in patients with type 1 diabetes with and without kidney disease

Tikkanen-Dolenc ^{H1,2,3}, Wadén ^{J1,2,3}, Forsblom ^{C1,2,3}, Harjutsalo ^{V1-4}, Thorn ^{LM1,2,3}, Saraheimo ^{M1,2,3}, Elonen ^{N1,2,3}, Tikkanen ^{HO5,6,7}, Groop ^{PH1,2,3,8}; on behalf of the FinnDiane Study Group

¹Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Helsinki, Finland; ²Abdominal Center Nephrology, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland; ³Research Programs Unit, Diabetes and Obesity, University of Helsinki, Helsinki, Finland; ⁴Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland; ⁵Department of Sports and Exercise Medicine, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland; ⁶Foundation for Sports and Exercise Medicine, Clinic for Sports and Exercise Medicine, Helsinki, Finland; ⁷School of Medicine, Institute of Biomedicine, University of Eastern Finland, Kuopio, Finland; ⁸Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia

Diabetes Care 2017; **40**: 1727–1732

Background

Leisure time physical activity (LTPA) is associated with reduced premature mortality in healthy individuals as well as individuals with type 2 diabetes (20). However, the role of LTPA in all-cause and cardiovascular mortality in male and female patients with type 1 diabetes with and without chronic kidney disease has yet to be explored.

Methods

This prospective observational study included 2639 patients with type 1 diabetes from the ongoing Finnish Diabetic Nephropathy (FinnDiane) Study. Chronic kidney disease was present in 310 patients (11.7%) and was calculated using the Chronic Kidney Disease Epidemiological Collaboration Equation that uses a glomerular filtration rate cutoff of <60 mL/min/1.73 m². LTPA was evaluated using a validated self-reported questionnaire and included parameters such as exercise type, intensity, duration, and frequency. The mean follow-up time of patients was 11.4 ± 3.5 years.

Results

During the follow-up, 270 deaths occurred. This included 127 of the 310 patients with chronic kidney disease. LTPA and all of its components were associated with a reduction in all-cause mortality. These associations remained even after controlling for sex, diabetic nephropathy, duration, age at onset of diabetes, systolic blood pressure, triglycerides, body mass index, and HbA1c. However, only the intensity of exercise was specifically associated with reduced cardiovascular mortality after controlling for these founders.

Conclusion

LTPA is associated with a lower risk of premature all-cause and cardiovascular mortality in patients with type 1

diabetes with and without chronic kidney disease. Thus, exercise is a valuable tool that ought to be recommended to individuals with type 1 diabetes both with and without chronic kidney disease.

Comments

Diabetic nephropathy is a significant cause of morbidity and mortality in individuals with type 1 diabetes and is characterized by proteinuria, reduced glomerular filtration rate, and hypertension (21). Persistence and extent of proteinuria is used as a predictor of chronic kidney disease and risk of progression to renal failure (22). Exercise, particularly of a higher intensity, can induce proteinuria, and this raises concerns regarding exercise recommendations for individuals with chronic kidney disease, especially those with type 1 diabetes. Despite this challenge, it is important to note that no study has reported a worsening of kidney disease in response to exercise (23), and the extent of exercise-induced proteinuria is neither predictive of nor correlated with clinical nephropathy. This is the first study to examine the relationship between physical activity levels and mortality rates in patients with type 1 diabetes who do and do not have chronic kidney disease. This same research group previously showed that intensive exercise is associated with a lower risk of chronic kidney disease progression (24). These are encouraging findings because it demonstrates that exercise in this patient population appears safe, beneficial, and ought to be recommended. Indeed, the long-term health risks of maintaining a sedentary lifestyle are certainly higher in this population.

Carbohydrate restriction with post meal walking effectively mitigates postprandial hyperglycaemia and improves endothelial function in type 2 diabetes

Francois ^{ME1}, Myette-Cote ^{E1}, Bammert ^{TD2}, Durrer ^{C1}, Neudorf ^{H1}, DeSouza ^{CA2}, Little ^{JP1}

¹University of British Columbia Okanagan, Kelowna, British Columbia, Canada; ²University of Colorado, Boulder, CO

Am J Physiol Heart Circ Physiol 2018; **314**: h105–h113

Background

Postprandial hyperglycemia has detrimental effects on endothelial function. Postmeal walking and carbohydrate-restrictive diets have independently been shown to reduce postprandial hyperglycemia, but their combined effect on endothelial function has yet to be investigated. In this study, the authors evaluated markers of vascular health in patients with type 2 diabetes and the response to blunted postprandial hyperglycemia induced by a low-carbohydrate diet with or without postmeal walking.

Methods

Using a randomized crossover design, subjects with type 2 diabetes (n=11) underwent three 4-day interventions including (a) low-carbohydrate diet only (LC), (b) low-

carbohydrate diet plus 15 minutes of postmeal walking (LC + Ex), and (c) low-fat control diet (CON). Pre- and post-intervention fasted blood samples and brachial artery flow-mediated dilation (%FMD) measurements were made. The vascular health biomarkers that were evaluated included total circulating microparticles, endothelial microparticles, monocyte-platelet aggregates, and adhesion molecules.

Results

These authors observed a significant condition by time interaction for %FMD ($P=0.01$). Post hoc analysis revealed improved %FMD after LC + Ex ($+0.8 \pm 1.0\%$, $P=0.02$) but no change after LC or CON. There was a significant reduction in endothelial microparticles in the LC intervention (99 ± 60 to 44 ± 31 microparticles per μL , $P=0.02$) but no change after the LC + Ex or CON interventions (interaction: $P=0.04$). There was a significant reduction in total microparticles (main effect of time: $P=0.02$) and a significant increase in monocyte-platelet aggregates (main effect of time: $P<0.01$) following all interventions. No change was observed in plasma adhesion molecules or C-reactive proteins.

Conclusions

The combination of a low-carbohydrate diet and postmeal walking significantly improved endothelial function, and a low-carbohydrate diet alone lowered circulating endothelial microparticles in individuals with type 2 diabetes. Limiting carbohydrate intake plus postmeal walking attenuates postprandial hyperglycemia, and this combined approach appears to be an effective strategy to improve endothelial function in individuals with type 2 diabetes.

Comments

Considerable evidence demonstrate that type 2 diabetes and insulin resistance induce endothelial cell dysfunction and that endothelial damage precedes the development of overt hyperglycemia in type 2 diabetes (25). Specifically, postprandial hyperglycemia damages endothelial function by inducing a proinflammatory response, increasing oxidative stress, reducing nitric oxide release, and impairing flow mediated dilation (26,27). Both dietary restriction of carbohydrates and exercise improve glycemic control, but this is the first study to evaluate their combined effect on endothelial function in individuals with type 2 diabetes. This is a critical patient population to study vascular health because greater than 70% of individuals with type 2 diabetes will die due to cardiovascular disease (28). Importantly, this study found that the nonpharmacological intervention of postmeal walking plus carbohydrate restriction improved markers of vascular health in individuals with type 2 diabetes. These are noteworthy findings that should be considered as recommendations for individuals to improve their glycemic control as well as their cardiovascular disease risk. It would be valuable for future research to also evaluate the long-term impact on cardiovascular health using an intervention of carbohydrate restriction plus postmeal walking in type 2 diabetes.

Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study

Breton MD¹, Cherniavsky DR¹, Forlenza GP², DeBoer MD¹, Robic J², Wadwa RP², Messer LH², Kovatchev BP¹, Maahs DM^{2,3}

¹Center for Diabetes Technology, University of Virginia, Charlottesville, VA; ²Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, CO; ³Department of Pediatrics, Stanford University, Stanford, CA

Diabetes Care 2017; **40**: 1644–1650

This manuscript is also discussed in the article on Decision Support Systems and Closed Loop, page S-42, and the article on Diabetes Technology and Therapy in the Pediatric Age Group, page S-123.

Background

Glucose management with intensive physical activity is a major challenge for patients living with type 1 diabetes. Closed-loop control (CLC) systems (also known as artificial pancreas) have been used to improve glucose control during short-term physical activity at select intensities (29). This study aimed to examine CLC during extended vigorous outdoor exercise in an outdoor ski-camp setting in adolescents with type 1 diabetes.

Methods

Thirty-two adolescents with type 1 diabetes (10–16 years of age) participated in a 5-day ski camp (~ 5 h skiing/day), at two sites (Wintergreen, VA, and Breckenridge, CO), in a randomized controlled trial that included either the University of Virginia CLC system or a remotely monitored sensor-augmented pump (RM-SAP) as an open-loop control arm. The CLC and RM-SAP groups were similar in age and HbA1c, and the study team remotely monitored all participants 24 hours per day.

Results

Compared with RM-SAP, the percent time in target range (70–180 mg/dL) improved while using CLC (71.3% vs 64.7%; $P=0.005$), with the maximum effect observed late at night. Overall improvements in hypoglycemia exposure and carbohydrate treatments were observed with CLC ($P=0.001$ and $P=0.007$), but with ski level effects, with the largest benefit observed with CLC in the beginner skiers on these variables ($P=0.0001$ and $P=0.006$). CLC was not associated with any adverse events.

Conclusions

In adolescents with type 1 diabetes, CLC improved glycemic control and reduced exposure to hypoglycemia during prolonged intensive skiing, despite the added challenges of cold and altitude.

Comment

The CLC, the Diabetes Assistant developed at the University of Virginia, has been put to the test in a number of

studies using exercise (29). This was the first randomized controlled trial to test the system in a ski camp, where a range of conditions (temperature and other environmental challenges, activity levels of the subjects, food intake, and skiing levels of the participants) could test the system “in the wild.” Interestingly, the continuous glucose monitoring system used (Dexcom G4 with 505 software) had considerable deterioration in accuracy in this type of setting (mean absolute relative difference = 18.9%), perhaps because of the behavioral and environmental conditions. Nonetheless, percent time below target (70 mg/dL) almost dropped by half with CLC compared with RM-SAP ($1.8 \pm 1.5\%$ vs $3.2 \pm 3.1\%$, $P < 0.001$). Why the more experienced group did not have the same magnitude of a protective effect against hypoglycemia with CLC is unclear (2.9 to 2.3%) but may be related to the higher intensity of sustained physical effort in those more advanced at skiing or snowboarding. In fact, in the more advanced group of skiers/snowboarders, CLC was a little too tight overnight, with a rise in percent time below target from 1.9% to 3.2%. Future studies will need to address whether more-skilled athletes may need a more conservative approach to CLC to help reduce hypoglycemia risk.

Functional high-intensity training improves pancreatic β -cell function in adults with type 2 diabetes

Nieuwoudt S^{1,2}, Fealy CE^{1,3}, Foucher JA¹, Scelsi AR¹, Malin SK¹, Pagadala M^{1,4}, Rocco M⁵, Burguera B⁶, Kirwan JP^{1,2,3}

¹Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH; ²Department of Physiology and Biophysics, Case Western Reserve University, Cleveland, OH; ³Department of Biomedical Sciences, Kent State University, Kent, OH; ⁴Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH; ⁵Department of Cardiology, Cleveland Clinic, Cleveland, OH; ⁶Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, OH

Am J Physiol Endocrinol Metab 2017; **313**: E314–E320

Background

Type 2 diabetes is characterized by a reduction in β -cell function in the global environment of elevated insulin resistance. Aerobic exercise has been shown to improve β -cell function, despite a subset of type 2 diabetes patients who do not respond that well to regular physical activity (sometimes called “exercise-resistant”). This study examined the effects of a novel, 6-week CrossFit type of functional high-intensity interval training (HIIT) on β -cell function in a group of sedentary adults living with type 2 diabetes.

Methods

Twelve sedentary individuals with type 2 diabetes (54 ± 2 years of age, mean $\pm$ SEM, fasting glucose of 166 ± 16 mg/dL) underwent supervised HIIT sessions 3 days per week for

6 weeks. The active phase of each training session lasted 10–20 min per session. All subjects completed an oral glucose tolerance test and anthropometric measures at baseline and following the intervention.

Results

β -cell function, as measured by the disposition index, was increased with training (pre, 8.4 ± 3.1 ; post, 11.5 ± 3.5 , $P = 0.02$), while insulin processing inefficiency in the β -cell, expressed as the fasting proinsulin-to-insulin ratio, was also reduced (pre, 2.40 ± 0.37 ; post, 1.78 ± 0.30 ; $P = 0.04$). Increased β -cell function during the early-phase response to oral glucose correlated with the reduction in abdominal body fat ($R^2 = 0.56$; $P = 0.005$). With the high-intensity interval training, mean total body-fat percentage decreased (Δ , $-1.17 \pm 0.30\%$; $P = 0.003$), while lean body mass was preserved (Δ , $+0.05 \pm 0.68$ kg; $P = 0.94$).

Conclusions

High-intensity interval training (HIIT) is a highly effective strategy for improving β -cell function in adults living with type 2 diabetes.

Comments

HIIT is an effective way to improve cardiometabolic fitness, even in diseased cohorts (30), in a very short period of time (days to weeks rather than months with continuous aerobic training). Whether HIIT can improve β -cell function in adults living with type 2 diabetes is unclear. This study demonstrated subtle, but significant improvements in early-phase disposition index with HIIT and reductions in the proinsulin/insulin ratio, a measure of insulin-processing inefficiency. Interestingly, fasting plasma glucose, insulin, C-peptide, proinsulin, and free fatty acids, which are of general clinical importance to patients with type 2 diabetes, did not change significantly with HIIT, nor did the first-phase (0–30 min) and late-phase (30–180 min) plasma glucose, insulin, C-peptide, and proinsulin levels. Some participants—in particular, female participants—were deemed higher responders to HIIT with observed improvements in both insulin secretion and insulin sensitivity. Taken together, this study demonstrated that some improvements in insulin processing and secretion could occur in late-stage diabetes if HIIT is performed over a span of 6 weeks. Future studies should examine whether more prolonged training of this nature can further improve β -cell function, and if so, by what mechanism, and why some individuals tend not to respond favorably to this type of training.

A comparison of adipose tissue interstitial glucose and venous blood glucose during postprandial resistance exercise in patients with type 2 diabetes

Heden TD¹, Liu Y², Kanaley JA²

¹Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, MN;

²*Department of Nutrition and Exercise Physiology, University of Missouri, Columbia, MO*

J Appl Physiol 2018; **124**: 1054–1061

Background

The difference between subcutaneous adipose tissue interstitial glucose and venous glucose concentrations, especially around resistance exercise, remains inconclusive. The purpose of this study was to compare interstitial glucose and venous blood glucose concentrations during rest and postprandial resistance exercise in individuals living with type 2 diabetes.

Methods

A total of 11 individuals (3 male and 8 female) with type 2 diabetes participated in this study. The average age was 49 ± 13 years; body fat, $41.5 \pm 7.2\%$; fasting glucose, 7.9 ± 2.7 mmol/L; and HbA1c, $7.2 \pm 0.7\%$. Two trials were completed in random order and consisted of a no exercise condition and a resistance exercise condition. The exercise trial was ~ 45 min in duration, and subjects completed three sets of eight whole-body exercises. Meals were standardized on all testing days, and venous blood glucose and interstitial glucose (iPro, Medtronic, Minimed) were measured throughout each visit.

Results

Venous glucose levels were 11% lower during exercise compared with no exercise (8.0 ± 0.5 mmol/L vs 9.0 ± 0.5 mmol/L, respectively). However, during exercise, interstitial glucose levels were not different compared with no exercise (10.4 ± 0.7 mmol/L vs 10.1 ± 0.7 mmol/L, respectively). The bias between the interstitial and venous glucose levels was 2-fold greater during exercise vs no exercise (2.36 ± 2.07 mmol/L vs 1.11 ± 1.69 mmol/L, respectively).

Conclusions

This study found that specifically for individuals with type 2 diabetes, resistance training causes reductions in venous glucose concentrations, but not interstitial glucose concentrations. Overall, postprandial resistance exercise affects glucose concentrations differently depending on the specific compartment in the body where it is being measured.

Comments

Continuous glucose monitoring devices measure interstitial glucose concentrations and often better detect glucose excursions compared to capillary glucose in individuals living with diabetes (31). In the context of exercise and type 1 diabetes, they can also be valuable in detecting activity-related dysglycemia (32). However, studies have reported a lag in equilibrium between interstitial and blood glucose, which may be anywhere between 5 and 45 minutes (33). A recent study found that continuous glucose monitoring transiently gives lower accuracy during aerobic exercise, but then returns to regular operation a few hours after exercise ends, without the need for a recalibration (34). In this study, during

the first 15 minutes postmeal, venous glucose levels increased more rapidly than interstitial glucose both in the no exercise and exercise trials. Interestingly, during the entire 45-minute exercise period, interstitial glucose levels were greater compared to venous glucose levels; however, these differences disappeared at the cessation of exercise. One potential explanation is that exercise decreased subcutaneous adipose tissue glucose uptake, resulting in a lesser drop in interstitial glucose levels (35). These are clinically important findings as they highlight the importance of understanding the differences in interstitial and venous glucose measurements, particularly for closed-loop algorithms that rely on accuracy for decision-making.

Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial

Dovc K¹, Macedoni M², Bratina N¹, Lepej D³, Nimri R⁴, Atlas E⁵, Muller I⁵, Kordonouri O⁶, Biester T⁶, Danne T⁶, Phillip M^{4,7}, Battelino T^{8,9}

¹Department of Paediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; ²Department of Paediatrics – Diabetes Service Studies, University of Milan, Ospedale dei Bambini Vittore Buzzi, Milan, Italy; ³Department of Pulmonology, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; ⁴The Jesse and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Centre for Childhood Diabetes, Schneider Children's Medical Centre of Israel, Petah Tikva, Israel; ⁵DreaMed Diabetes Ltd, Petah Tikva, Israel; ⁶Diabetes Centre for Children and Adolescents, Kinder- und Jugendkrankenhaus Auf der Bult, Hannover, Germany; ⁷Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ⁸Department of Paediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; ⁹Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Diabetologia 2017; **60**: 2157–2167

This manuscript is also discussed in the article on Decision Support Systems and Closed Loop, page S-42, and in the article on Diabetes Technology and Therapy in the Pediatric Age Group, page S-123.

Background

For individuals living with type 1 diabetes, physical activity is often associated with an increased risk of glycemic disturbances. The goal of this study was to evaluate the safety and efficacy of closed-loop insulin delivery with unannounced afternoon exercise as well as the following night in children and adolescents living with type 1 diabetes.

Methods

This was an open-label, randomized, two-arm, crossover study that took place at the University Children's Hospital in

Slovenia. This study consisted of 20 participants (9 females, mean age 14.2 ± 2.0 years, $HbA1c\ 7.7 \pm 0.6\%$ [$60.0 \pm 6.6\text{ mmol/mol}$]) who completed four in-hospital visits. Of these four visits, two were unannounced exercise sessions: one at moderate intensity (55% of $VO_2\text{ max}$) and one integrated with high-intensity sprints (at 80% of $VO_2\text{ max}$) using either a closed-loop or open-loop delivery device. All exercise sessions were 40 minutes in length and performed in the afternoon on a cycle ergometer. The observation period was from 3:00 p.m. on the day of exercise to 1:00 p.m. on the following day.

Results

For both treatment modalities, the median proportion of time spent in hypoglycemia ($<3.3\text{ mmol/L}$) during exercise and the evening following was 0.00%. Closed-loop insulin delivery increased the time spent in target glucose range (i.e., $3.0\text{--}10.0\text{ mmol/L}$) vs open-loop (84.1% vs 68.7%, respectively). In the closed-loop group, there were 6 reported hypoglycemic events and 12 in the open-loop group during the study. Overall, the closed-loop device led to significantly lower total basal insulin delivery vs open-loop.

Conclusions

This study highlights the safety and efficacy of closed-loop insulin delivery during and after unannounced exercise and demonstrates an increased time in target range without an increased risk of hypoglycemia.

Comments

For individuals living with type 1 diabetes, although regular physical activity is associated with a number of health benefits (7), it can also lead to increased glucose excursions (36). Reduction of basal insulin (12) and/or additional carbohydrate consumption (7) have been recommended as strategies to reduce the risk of hypoglycemia during exercise. However, these strategies often require advanced planning and only focus on the periods involving exercise rather than how to effectively reduce hypoglycemia during exercise as well as in recovery. This is one of the first studies to demonstrate that closed-loop insulin delivery is safe and effective during and following exercise in adolescents living with type 1 diabetes. Further research is also needed on larger populations and incorporating the closed-loop insulin delivery during exercise in free-living conditions.

Author Disclosure Statement

No competing financial interests exist.

References

- Ostman C, Jewiss D, King N, Smart NA. Clinical outcomes to exercise training in type 1 diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract* 2018; **139**: 380–391.
- Grace A, Chan E, Giallauria F, Graham PL, Smart NA. Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2017; **16**: 37.
- Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. *Diabetes Care* 2016; **39**: 2065–2079.
- Colberg SR, Castorino K, Jovanović L. Prescribing physical activity to prevent and manage gestational diabetes. *World J Diabetes* 2013; **4**: 256–262.
- Ried-Larsen M, MacDonald CS, Johansen MY, Hansen KB, Christensen R, Almdal TP, et al. Why prescribe exercise as therapy in type 2 diabetes? We have a pill for that! *Diabetes Metab Res Rev* 2018; **34**: e2999.
- Borror A, Zieff G, Battaglini C, Stoner L. The effects of postprandial exercise on glucose control in individuals with type 2 diabetes: a systematic review. *Sports Med* 2018; **48**: 1479–1491.
- Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. Exercise management in type 1 diabetes: A consensus statement. *Lancet Diabetes Endocrinol* 2017; **5**: 377–390.
- Pedersen BK, Saltin B. Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports* 2015; **25** (Suppl 3): 1–72.
- Colberg SR. Exercise as medicine for diabetes: prescribing appropriate activities and avoiding potential pitfalls: preface. *Diabetes Spectr* 2015; **28**: 10–13.
- Franc S, Daoudi A, Pochat A, Petit MH, Randazzo C, Petit C, et al. Insulin-based strategies to prevent hypoglycaemia during and after exercise in adult patients with type 1 diabetes on pump therapy: The DIABRASPORT randomized study. *Diabetes Obes Metab* 2015; **17**: 1150–1157.
- Zaharieva D, Yavelberg L, Jamnik V, Cinar A, Turksoy K, Riddell M. The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous versus circuit-based exercise in individuals with type 1 diabetes on continuous subcutaneous insulin infusion. *Diabetes Technol Ther* 2017; **19**: 370–378.
- McAuley SA, Horsburgh JC, Ward GM, La Gerche A, Gooley JL, Jenkins AJ, et al. Insulin pump basal adjustment for exercise in type 1 diabetes: A randomised crossover study. *Diabetologia* 2016; **59**: 1636–1644.
- Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med*. 2014; **371**: 1131–1141.
- Smith U. Abdominal obesity: A marker of ectopic fat accumulation. *J Clin Invest* 2015; **125**: 1790–1792.
- Caprio S, Pierpont B, Kursawe R. The “adipose tissue expandability” hypothesis: a potential mechanism for insulin resistance in obese youth. *Horm Mol Biol Clin Invest* 2018; **33**: pii: /j/hmbci.2018.33.issue-2/hmbci-2018-0005/hmbci-2018-0005.xml. DOI 10.1515/hmbci-2018-0005
- Samuel VT, Shulman GI. Nonalcoholic fatty liver disease as a nexus of metabolic and hepatic diseases. *Cell Metab* 2018; **27**: 22–41.
- Tushuizen ME, Bunck MC, Pouwels PJ, Bontemps S, van Waesberghe JHT, Schindhelm RK, et al. Pancreatic fat content and beta-cell function in men with and without type 2 diabetes. *Diabetes Care* 2007; **30**: 2916–2921.
- Riddell MC, Zaharieva DP, Yavelberg L, Cinar A, Jamnik VK. Exercise and the development of the artificial pancreas: one of the more difficult series of hurdles. *J Diabetes Sci Technol* 2015; **9**: 1217–1226.

19. Mallad A, Hinshaw L, Schiavon M, Dalla Man C, Dadlani V, Basu R, et al. Exercise effects on postprandial glucose metabolism in type 1 diabetes: a triple tracer approach. *Am J Physiol Endocrinol Metab* 2015; **308**: E1106–E1115.
20. Wahid A, Manek N, Nichols M, Kelly P, Foster C, Webster P, et al. Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and meta-analysis. *J Am Heart Assoc* 2016; **5**: e002495.
21. Van Buren PN, Toto R. Hypertension in diabetic nephropathy: Epidemiology, mechanisms, and management. *Adv Chronic Kidney Dis* 2011; **18**: 28–41.
22. Tadida Meli IH, Tankeu AT, Dehayem MY, Chelo D, Noubiap JJN, Sobngwi E. Exercise-induced albuminuria vs circadian variations in blood pressure in type 1 diabetes. *World J Diabetes* 2017; **8**: 74–79.
23. Johansen KL, Painter P. Exercise in individuals with CKD. *Am J Kidney Dis* 2012; **59**: 126–134.
24. Wadén J, Tikkanen HK, Forsblom C, Harjutsalo V, Thorn LM, Saraheimo M, et al. Leisure-time physical activity and development and progression of diabetic nephropathy in type 1 diabetes: the FinnDiane study. *Diabetologia* 2015; **58**: 929–936.
25. Hadi HAR, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. *Vasc Health Risk Manag* 2007; **3**: 853–876.
26. Mah E, Noh SK, Ballard KD, Matos ME, Volek JS, Bruno RS. Postprandial hyperglycemia impairs vascular endothelial function in healthy men by inducing lipid peroxidation and increasing asymmetric dimethylarginine:arginine. *J Nutr* 2011; **141**: 1961–1968.
27. Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *J Am Coll Cardiol* 1999; **34**: 146–154.
28. Laakso M. Cardiovascular disease in type 2 diabetes: challenge for treatment and prevention. *J Intern Med* 2001; **249**: 225–235.
29. Breton MD. Handling exercise during closed loop control. *Diabetes Technol Ther* 2017; **19**: 328–330.
30. Blackwell JEM, Doleman B, Herrod PJJ, Ricketts S, Phillips BE, Lund JN, et al. Short-term (<8 weeks) high-intensity interval training in diseased cohorts. *Med Sci Sports Exerc* 2018; **50**: 1740–1749.
31. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017; **40**: 1631–1640.
32. Adolfsson P, Nilsson S, Lindblad B. Continuous glucose monitoring system during physical exercise in adolescents with type 1 diabetes. *Acta Paediatrica* 2011; **100**: 1603–1609.
33. Stout PJ, Peled N, Erickson BJ, Hilgers ME, Racchini JR, Hoegh TB. Comparison of glucose levels in dermal interstitial fluid and finger capillary blood. *Diabetes Technol Ther* 2001; **3**: 81–90.
34. Biagi L, Bertachi A, Quirós C, Giménez M, Conget I, Bondia J, et al. Accuracy of continuous glucose monitoring before, during, and after aerobic and anaerobic exercise in patients with type 1 diabetes mellitus. *Biosensors* 2018; **8**: 22.
35. Simonsen L, Henriksen O, Enevoldsen LH, Bülow J. The effect of exercise on regional adipose tissue and splanchnic lipid metabolism in overweight type 2 diabetic subjects. *Diabetologia* 2004; **47**: 652–659.
36. Colberg SR, Laan R, Dassau E, Kerr D. Physical activity and type 1 diabetes: time for a rewiring? *J Diabetes Sci Technol* 2015; **9**: 609–618.