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Commentary

The future is now: SGLT2 inhibitors and type 1 diabetes – What about exercise?



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In vibrant times of innovation, adjuvant therapy strategies are continuously released for individuals with type 1 diabetes (T1D), which open clinicians a variety of options for T1D management. Newer insulin analogues, continuous glucose monitoring systems and (hybrid) closed-loop systems have become more advanced in the management of T1D but appear to be only imperfectly mimicking the physiological metabolism due to the complexity and variability of this disease, the location of glucose measurement, insulin application and individual factors of the people involved. Notwithstanding, the subcutaneous insulin application is still the fundamental therapy which is accompanied by dietary management and increased physical activity according to the current guidelines of treatment (NICE) in this population. However, individuals with T1D rarely reach target glycated haemoglobin (HbA_{1c}) and thus, leave room for improvements to avoid micro- and macrovascular complications especially in young adults to avoid later complications [1]. To overcome the limitations of current therapy options, the European Medicines Agency (EMA) has approved a complementary medication in March 2019 to support insulin therapy in individuals with T1D, namely the sodium glucose cotransporter-2 (SGLT2) inhibitors. This novel drug class, which has received wide attention in its glucose-lowering and cardiovascular-protective properties in the management of type 2 diabetes, also bears potential for individuals with T1D who are struggling with achieving glycaemic targets. Insulin-independent

SGLT2 prevent the reuptake of the filtrated glucose in the early proximal convoluted tubule of the kidney, leading to blood glucose lowering also in people with T1D [2]. Besides the beneficial effects on glycaemic control, SGLT2 inhibitors seem to potentiate the risk for diabetic ketoacidosis (DKA), in particular in T1D [3,4]. A possible mechanism might be that as blood glucose is lowered due to increased urinary glucose excretion, exogenous insulin is reduced to avoid hypoglycaemia. This decline in exogenous insulin supply culminates into a critical insufficiency of circulating insulin leading to an increased production of free fatty acids, which via beta-oxidation are turned into ketone bodies in the liver [4].

However, evidence on the risk-benefit balance from randomized controlled trials for individuals with T1D is not yet fully convincing, which attributes to the fact, that not all of the SGLT2 inhibitors have or are seeking for market approval in T1D. To date, Dapagliflozin and Sotagliflozin have received approval by the EMA for individuals with T1D. According to the labels, they can only be used in those individuals having a body mass index (BMI) of ≥ 27 kg/m² and if insulin therapy does not adequately reduce blood glucose itself, based on the results of the DEPIC and in Tandem trials [5–7].

Apart from SGLT carrier proteins, the glucose transporter facilitators (GLUT) family, but mainly GLUT-4 are the principal transporter proteins for the management of blood glucose levels. However, in the absence of insulin, only 5% of GLUT-4 are located at the cellular membrane. Only an

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external stimulation such as exercise or an exogenous insulin injection induces the recruitment of GLUT-4 from an intracellular storage pool to the cellular membrane allowing blood glucose to enter the cell which results in a >10-fold increase in glucose uptake in T1D [8]. In addition, it has to be taken into account that several exercise modalities, e.g. type of exercise or intensity and volume as well as time under tension are having a direct or indirect impact on GLUT-4 expression [9]. Furthermore, appropriate pre-exercise arrangements must be made e.g. insulin reductions prior to exercise or scheduled meals. These pre-exercise arrangements are necessary to maintain euglycaemia and to reduce the risk of DKA and hypoglycaemia around exercise [10,11]. Nevertheless, physical exercise is an important supportive therapy for overweight and obese individuals to enhance weight loss, which applies for about 60% of individuals living with T1D. Interestingly, this population might also be eligible for a potential treatment with Dapagliflozin. Considering this, there is abundant need for precise exercise prescription and dietary management combined with SGLT2 inhibitor supported insulin treatment to identify possible dose-response interactions for effective diabetes management.

Following the approval of SGLT2 inhibitors in individuals with T1D, several questions for clinicians in daily practice remain unanswered. Until today, no clinical trial has investigated if the combined approach of insulin therapy and exercise is influenced by the addition of an SGLT2 inhibitor in T1D. Existing evidence is solely available in obese adults with a risk for developing insulin resistance [12]. Simple questions such as to which extent insulin should be further reduced during exercise without increasing the risk for DKA will be difficult to answer without solid studies. Even though individuals may be considered as physically inactive, short bouts of more or less intensive physical activity are an integral part in daily life situations, which bear an unknown challenge to the individual. Both exercise and SGLT2 inhibitors may increase the risk for hypoglycaemia, which can be reduced in almost all situations with the application of intermittently viewed continuous glucose monitoring (iCGM) systems [13]. Earlier research has shown that bolus insulin reductions of up to 75% prior to exercise do not demonstrate an increased risk of ketone body formation and reduce the risk of hypoglycaemia [11]. Furthermore, basal rate reductions by 50–80% (pump therapy) starting 90 min before exercise and basal insulin dose reductions by 20% (pen therapy) on days with prolonged physical activity are considered as safe and are advocated in the recent consensus statement on exercise management in type 1 diabetes from 2017 [14]. However, today these strategies would become void, since with additional SGLT2 inhibitor intake exogenous insulin doses would already be decreased, as shown in the DEPICT-2 trial following a 24-week intervention with Dapagliflozin leading to mean insulin total daily dose decrease of about 16–23% leaving insufficient space for further insulin dose reductions in the management around physical exercise [6].

This is underpinned by the recent international consensus statement on SGLT management in type 1 diabetes by Danne et al. [15]. They highlighted that for vigorous/prolonged exercise, bolus insulin reduction by 10–20% and insulin pump use have a low to moderate risk for DKA. Whereas reducing the

basal insulin dose by 10–20% increases the risk for DKA to moderate/high. These unclear recommendations around exercise in individuals with type 1 diabetes leave clinicians with unsatisfying guidance and highlight the urgent need for thoroughly designed clinical trials in people with type 1 diabetes taking SGLT2 inhibitors. Hence, individuals with T1D might need to monitor their blood ketone values around exercise when taking SGLT2 inhibitors and act accordingly via insulin administration if necessary, or adapt exercise intensity as recommended by Riddell et al. [14].

This uncharted area in research demands rapid exploration to deliver guidelines and safety for physically active individuals for this combined therapy approach. Until then, clinicians must be prudent and vigilant when considering the prescription of SGLT2 inhibitors in overweight individuals with T1D. It is now upon researchers to set up clinical trials to enlighten this unexplored area. Results from these trials will support health care professionals to provide evidence based treatment recommendations and to allow individuals with T1D to look forward to a modern and more personalized diabetes management.

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