Thesis

The impact of physical exercise on sensor performance of continuous glucose monitoring (CGM) systems in people with type 1 diabetes

submitted by

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Graz, September 08, 2022

Affirmation under oath

I hereby declare under oath, that I have written the present thesis independently and without external help, that I have not used sources other than the listed, and that I have marked all passages that were quoted directly or contextual.

Graz, September 08, 2022 *Farah Abbas eh.*

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List of Abbreviations

Type 1 diabetes mellitus (T1D)
Type 2 diabetes mellitus (T2D)
Human leukocyte antigen (HLA)
Cytotoxic T-lymphocyte-associated protein 4 area (CTLA4)
Protein tyrosine phosphatase non-receptor type 22 gene (PTPN22)
Major histocompatibility complex MHC
Glutamic acid decarboxylase 65 (GAD65)
Zinc transporter-8 (ZnT8)
Glycated hemoglobin (A1C)
Carbohydrate unit CU
International unit IU
Intermittently scanned Continuous glucose monitoring (isCGM)
Continuous glucose monitoring (CGM)
Flash glucose monitoring (FGM)
Real-time CGM (rtCGM)
Physical activity (PA)
Cardiovascular diseases CVDs
Cardiorespiratory fitness (CRF)
The Epidemiology of Diabetes Interventions and Complications (EDIC)
The Diabetes Control and Complications Trial (DCCT)
International Society for Pediatric and Adolescent Diabetes (ISPAD)
the American Diabetes Association (ADA)
Self-monitoring of blood glucose (SMBG)
European Association for the Study of Diabetes (EASD)
Interstitial fluids (ISF)
High Intensity Interval Training (HIIT)
High-intensity interval exercise (HIIE)
Intermittent high-intensity exercise (IHE)
Interval exercise (IE)
Heart rate variability (HRV)
Maximal oxygen consumption (VO2max)
Continuous moderate exercise (CON)
Standard deviation (SD)
Body mass Index (BMI)
New York Heart Association (NYHA) scale
Electrocardiogram (ECG)
Lactate turn points (LTP1 & LTP2)
International Physical Activity Questionnaire (IPAQ)
Median absolute relative difference (MARD)
Absolute relative difference (ARD)
median absolute difference (MAD)

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Abstract in German:

Ziel

Ziel dieser Studie war es, die Messgenauigkeit eines kontinuierlichen Glukose Messgerätes (isCGM; Abbott Freestyle Libre I) während moderat-intensiver Ausdauerbelastungen mit dem kapillaren Blutzucker bei Menschen mit Typ-1-Diabetes zu vergleichen.

Methoden

Neunzehn Teilnehmer*innen [Acht Frauen und elf Männer, Mittelwert ± SD Alter 41.23 ± 13.02 Jahre, BMI 24.16 ± 2.58 kg/m^2, HbA1c 55.74 ± 6.85 mmol/mol] nahmen an 4 Sportvisiten am Ergometer mit jeweils 45 Minuten mit moderater Intensität teil. Während der Visite wurden alle 5 Minuten Kapillarblutproben aus dem Ohrläppchen und der Fingerbeere zur Blutzuckerkontrolle während der Sporteinheiten entnommen und gleichzeitig isCGM-Scans durchgeführt. Die Daten wurden gemäß Median Absolute Relative Difference (MARD), Clarke Error Grid und Bland-Altman analysiert.

Ergebnisse

Während der Sportvisiten wurden 846 isCGM-Scans durchgeführt und 846 Kapillarproben entnommen, einmal aus dem Ohrläppchen, ausgewertet mittels Labordiagnostik (Biosen-S-line, EKF, GER) und einmal aus der Fingerbeere, untersucht mit einem Blutzuckermessgerät (FreeStyle Libre, Abbott, USA). Die isCGM-Genauigkeit zeigte im Vergleich zur Labordiagnostik vom Ohrläppchen (Biosen-S-line, EKF, GER) eine mediane relative Differenz (MARD) ± SD von 10,3% ± 10,7% und im Vergleich zu Blutproben aus der Fingerbeere eine MARD von 11,3 % ± 9,8%.

Fazit

Obwohl das isCGM während des Sports grundsätzlich genau misst, kann eine zusätzliche Blutzuckermessung während des Sports erforderlich sein, um Behandlungsentscheidungen während des Trainings zu unterstützen. Insbesondere wenn Hypoglykämien drohen oder rasche Schwankungen des Blutzuckers vorliegen.

Abstract in English

Aim

This study aimed to comparing the accuracy of intermittently scanned glucose monitoring systems (isCGM) to capillary blood glucose throughout moderate-intensity exercise in people with Type 1 Diabetes.

Methods

Nineteen participants [eight women and eleven men, mean ± SD age was 41.23 ± 13.02 years, BMI 24.16 ± 2.58 kg/m^2, HbA1c 55.74 ± 6.85 mmol/mol] performed 4 trial visits, each with 45 minutes of moderate intensity exercise. Throughout the visit, capillary blood samples were collected from the ear lobe and the fingertip every 5 minutes throughout the goal workload, and at the same time isCGM-scans were performed. Data was analyzed according to Median absolute relative difference (MARD), Clarke Error Grid, and Bland-Altman method.

Results

Throughout the visits, 846 isCGM scans were performed, and 846 capillary samples were obtained, once from the ear lobe and evaluated with lab-diagnostic (Biosen-S-line, EKF, GER) and once from the fingertip and examined with a glucometer (Freestyle libre, Abbott, USA). The assessment of isCGM performance to lab-diagnostic (Biosen-S-line, EKF, GER) showed a median relative difference (MARD) ± SD of 10.3% ± 10.7% and the comparison of Self-monitoring of blood glucose (SMBG) performed by glucometers (Freestyle libre, Abbott, USA) to isCGM revealed 11.3% ± 9.8%.

Conclusion

While the MARD and Clark error showed reliable data, an additional SMBG during exercise may be required to support treatment decisions during exercise, especially when the people with type 1 diabetes are about to experience hypoglycemia or inject a significant dose of insulin.

1 Introduction

1.1 Definition of Diabetes Mellitus

Diabetes mellitus is a collection of metabolic diseases marked by an increase in blood glucose levels (hyperglycemia). [1] Type 1 diabetes (T1D) and type 2 diabetes (T2D) are the two most prominent members of the category; T2D, the most common type, has a high genetic component as well as a strong link to overeating and the metabolic syndrome. Hyperglycemia in this type of diabetes is caused by a disruption in the function of insulin on body cells (insulin resistance) and a firstly compensatory increased and subsequently reduced insulin secretory capacity by beta cells. [2] T1D is an organ specific endocrine autoimmune disease of the pancreas caused by an autoimmune mechanism that leads to a destruction of insulin-producing beta cells which consequently lose their ability to produce insulin. [3]

1.2 Epidemiology of T1D

T1D can strike at any age, but it is most common during childhood and adolescence. [1] Identifying the difference between T1D and T2D becomes more challenging as the age of onset of T1D in genetically susceptible people increases. Human leukocyte antigen (HLA) genes convey the majority of susceptibility. Differences in HLA haplotypes explain some of the geographic variance in incidence and familial aggregation. [4]. In several countries, males have a greater incidence than females, and most populations have a 1.3- to 2.0-fold male excess in incidence after roughly 15 years of age. Childhood-onset T1D has a wide range of prevalence across countries. East Asian and native American populations have modest incidence (0.1–8 per 100 000/year), but Finland (>60 per 100 000/year), Sardinia (40 per 100 000/year), and Sweden (47 per 100 000/year) have the greatest rates. Overall, the risk is greatest in those of European ancestry. [4]

The global prevalence of childhood-onset T1D has grown, according to studies examining temporal patterns. Each calendar year, the average relative rise is between 3% and 4%. In Finland, for example, the incidence is now 5 times higher than it was 60 years ago. At the same time, the age at which children develop T1D is getting younger. Nongenetic variables are thought to play a role in the development of T1D and its progression, but causative proof is lacking. The causes of this rising tendency and current epidemic are mostly

unknown at this time but besides genetic causes, nutritional, socioeconomic and environmental factors are discussed. [4,5]

1.3 Pathogenesis of T1D

The etiology of beta cell malfunction being present in T1D is only partly understood. Environmental variables are thought in addition to genetic influences, diet and infection to have an important influence in the formation of the autoreactive process. [3] The pathophysiology can be split into three stages: genetic predisposition, the initiation and progression of an autoimmune reaction to beta cells, and ultimately clinical manifestation with loss of remaining beta cells activity. [3]

The genetic disposition stage is given as following: the family history may explain some of the inherited risk. Children with T1D have a 5% chance of developing the disease themselves, compared to a 0.3% chance in the general population. [3] HLAs are responsible for the majority of familial risk. HLA genes play an important role in T-cell selection, antigen presentation, and immune response, therefore their impact on diabetes risk and the start of the autoimmune process is easy to grasp. People who have two or more affected first-degree relatives and the HLA high-risk types (HLA DRB1'03.'04; DQB1"0302) have the highest risk of being exposed tp the disease (up to 50%). [3] The HLA class II genes, which have already been mentioned, are most strongly linked to T1D. A second diabetes-associated genotype has been identified in the insulin gene promoter region. In addition, there are over 20 "new" T1D genes, including the cytotoxic T-lymphocyte-associated protein 4 area (CTLA4) and the protein tyrosine phosphatase non-receptor type 22 gene (PTPN22). [3] This is significant since nearly all genes linked to T1D are involved in immune response regulation. However, given that less than 10% of people with a higher genetic risk develop T1D, it appears that environmental factors, in addition to a hereditary component, play an important role in pathogenesis. It is hypothesized that the development and advancement of autoimmunity is triggered by certain environmental circumstances but also delayed by protective ones. These are primarily infections, dietary issues, and perinatal determinants. [3]

1.3.1 Virus infection

Enteroviruses (Coxsackie, echo, newer enterovirus kinds), rubella, mumps, cytomegalovirus, influenza, Ebstein Barr virus, and varicella zoster virus are all potential

triggers for diseases affecting autoimmunity. Of note, also previous COVID-19 infection has shown trends towards an increased risk for latter development of T1D. [6] There are various theories on the role of viruses in the etiopathogenesis of diabetes mellitus:

- Viruses directly attack and destroy ß- cells
- Induction of antigens that the immune system detects as foreign, causing the autoimmune destruction of ß- cells to begin.
- Molecular mimicry occurs when viruses and ß-cells express antigens that are similar, and the immune system begins to fight ß- cell structures rather than viruses.
- Major histocompatibility complex (MHC) gene activation and production of MHC class II proteins, which cause ß- cell death.

Even while other viruses are frequently cited as environmental factors that may be implicated in the autoimmune process, there is the most evidence for a link between infections with human enteroviruses and T1D; these are also the only viruses that have been demonstrated to kill beta cells. [3]

1.3.2 Perinatal influences

Children born via caesarean section have a higher chance of developing T1D than children born vaginally. It is hypothesized that this is due to a completely different bacterial colonization of the gut following caesarean surgery versus vaginal delivery, which leads to an enhanced release of cytokines. This causes the autoimmune process to progress more quickly. Diabetes is also more likely in families with older parents and greater socioeconomic level. A greater quality of hygiene is thought to be connected with a loss of tolerance and, as a result, a higher susceptibility to autoimmune disorders. [3]

1.4 Diagnosis of T1D

T1D is just one of the many kinds of diabetes mellitus. The first step is to determine whether or not you have diabetes. The second stage is to distinguish T1D from other types of diabetes depending on the patient's clinical appearance and laboratory tests. Independently from type of diabetes mellitus, diabetes is identified by one of the four indications of impaired glucose metabolism listed below:

- On multiple occasions, fasting plasma glucose was more than 126 mg/dL (7 mmol/L). Fasting is described as not eating or drinking anything for at least eight hours.
- In a patient with characteristic hyperglycemia symptoms, random venous plasma glucose was 200 mg/dL (11.1 mmol/L).
- In an oral glucose tolerance test, plasma glucose was measured at 200 mg/dL (11.1 mmol/L) two hours following a glucose load of 1.75 g/kg (maximum dose of 75 g). Because the vast majority of children and adolescents are symptomatic and have plasma glucose values much above 200 mg/dL (11.1 mmol/L), an oral glucose tolerance test is rarely required to identify T1D.
- ≥ 6.5% glycated hemoglobin (A1C). This criterion is more useful in adults for detecting T2D and should be verified by hyperglycemia. [7]

The A1C test determines the percentage of hemoglobin A bound to glucose by non-enzymatic glycation and reveals average blood sugar levels for the 10 to 12 weeks preceding the test. The A1C criteria of 6.5% is now widely used to diagnose diabetes in adults. The diagnostic value of A1C in youngsters, on the other hand, is not as well-established as in adults. [7] A1C levels of ≥ 6.5% are indicative of diabetes in adults, although results of < 6.5% do not rule out diabetes. [7] Glucosuria is suggestive but not definitive of diabetes. Patients with renal glucosuria or Fanconi syndrome, for example, will have glucosuria despite normal serum glucose levels. [7]

1.4.1 Type 1 diabetes vs. type 2 diabetes

It is essential to correctly classify a patient's diabetes in order to ensure that they receive the best care and management. Actual diabetic treatment strategies and guidelines are substantially distinct for T1D and T2D, considering different properties to produce insulin according to both subtypes. People with T1D experience high glycemic instability due to their quick development of acute insulin shortage, which need precise insulin replacement. They also respond poorly to non-insulin based therapies. Individuals with T2D still create a significant portion of their own insulin, which allows them to react to non-insulin therapies and usually have more stable blood sugar levels. [8]The tests listed below are frequently used to distinguish between T1D and T2D:

- Antibodies – While no precise test exists to differentiate between the two types of diabetes, the existence of circulating, islet-specific pancreatic autoantibodies against glutamic acid decarboxylase 65 (GAD65), the 40K fragment of tyrosine phosphatase (IA2), insulin, and/or zinc transporter 8 (ZnT8) suggests T1D. The lack of pancreatic autoantibodies, on the other hand, does not exclude T1D. Up to 30% of people with T2D who have the typical symptoms and presentation have positive autoantibodies and may have a kind of autoimmune diabetes (so called double diabetes) that progresses slowly. [7] The presence of numerous autoantibody reactions is critical for the progression to T1D. Autoantibodies have been found against four islet antigens so far: insulin/proinsulin, GAD 65/67, IA-2 (or ICA 512 or IA-2B or PHOGRIN), and zinc transporter-8 (ZnT8). [3] Zinc transporter 8 was discovered to be an islet cell antigen only a few years ago. The sensitivity of antibody diagnostics in the case of diabetes manifestation could be raised to up to 98% with the help of ZnT8 antibodies. ZnT8 antibodies also play an important role in the prediction of T1D and support risk stratification for future T1D development. [3]
- Values of insulin and C-peptide — T2D is indicated by high fasting insulin and C-peptide values. In T1D, values are abnormally low or normal compared to the contemporaneous plasma glucose concentration. Extreme hyperglycemia and sickness may have lowered insulin and C-peptide values at the time of presentation. Once the patient with the recent diagnosis has recovered from his acute illness, it is usually appropriate to evaluate these levels, but blood glucose should be well controlled at this time. [7]

A small percentage of people with T1D clinical characteristics have no identifiable autoantibodies and are classified as type 1B diabetics. There is no proof of autoimmune beta cell loss in these patients, and no alternative reason has been identified. [7] Additionally, several studies found that the age of diagnosis was the best clinical criterion, with diagnoses made before the age of 30 or before the age of 40 being indicative of T1D. [8]

1.5 Clinical Manifestation Stage of T1D

Children with T1D frequently present with polyuria, polydipsia, and weight loss; around one-third have diabetic ketoacidosis. Adults with T1D may not exhibit the usual signs

found in children. Although symptoms typically appear during childhood or adolescence, they can occasionally appear much later. [9,10]

Symptoms can be broadly classified as follows:

- Symptoms of hyperglycemia and glucosuria with osmotic diuresis: Loss of weight, polydipsia, thirst, and polyuria
- Electrolyte and fluid imbalance symptoms: irregular vision and nocturnal calf cramps
- Unspecific symptoms: reduced performance and fatigue [1]

1.6 Treatment and Management of T1D

Diabetes was once one of a group of diseases that were thought to be fatal. However, after Banting and Best were able to properly isolate insulin from animal pancreata and its effectiveness in treating diabetes was shown, insulin was viewed by the general public and the medical community as a miracle treatment. Although it wasn't a cure for the chronic T1D illness, it was a paradigm shift and meant that T1D was no longer regarded as an immediate and sure death sentence. [11]

1.6.1 Insulin

Insulin is a peptide hormone generated by pancreatic islet beta cells; it is the body's primary anabolic hormone. [12] Beta cells are glucose sensitive, secreting insulin into the circulation in reaction to high glucose levels and inhibiting insulin secretion in response to low glucose levels. Insulin increases glucose uptake and metabolism in cells, lowering blood glucose levels. By absorbing cues from the beta cells, their surrounding alpha cells produce glucagon into the blood in the opposite manner: increased secretion when blood glucose levels are low, and decreased secretion when glucose levels are high. Glucagon raises blood glucose levels via promoting glycogenolysis and gluconeogenesis in the liver. The basic mechanism of glucose homeostasis is the production of insulin and glucagon secreted into the circulation in response to changes of blood glucose levels. [12]
Insulin's actions are mediated by the following mechanisms:

- Membrane impact: This action necessitates the movement of glucose, amino acids, and potassium into muscle and fat cells.

- Metabolic effects: Anabolic metabolic activities (glycogen synthesis, lipid synthesis, protein synthesis) are promoted, while catabolic metabolic processes are reduced (glycogenolysis, lipolysis, proteolysis). [1]

Diabetes makes active glucose absorption into cells more difficult (insulin resistance and/or lack of insulin). Only when blood sugar levels are high enough glucose can enter the cell passively. Because there is a paucity of glucose in the fat depot cells, the formation of glycerol phosphate is inhibited, and fatty acids are not converted into triglycerides and hence exit the fat tissue. Acety1-COA breaks them down in the liver to create ketone bodies (acetoacetic acid, B-hydroxybutyric acid, and acetone). Ketone bodies, which are also used as an energy source by muscle cells, decrease cell permeability to glucose, exacerbating the disturbed mechanisms (insulin antagonistic effect of the ketone bodies). [1]
Insulin secretion can be broken down into two parts:

- basal insulin secretion
- meal-dependent insulin secretion

High blood sugar levels during the fasting phase are caused by glucose release from the liver. This is prevented by basal insulin synthesis. Meal-related insulin secretions, on the other hand, are required for the consumption and storage of glucose obtained from food. [1]
One of the most difficult aspects of insulin substitution in T1D patients is imitating the insulin-action patterns of beta cells — sustaining basal levels while reaching peak levels at mealtimes. The two main drawbacks of external insulin replacement are that it is supplied peripherally, unlike beta cells which secrete insulin in the portal system, and that there is no feedback or reduction of insulin secretion when levels of glucose fall, which raises the risk of hypoglycemia. The introduction of insulin analogues has had a huge impact, allowing intensive insulin therapy to be administered without interfering with regular daily life. When compared to human normal insulin, rapid-acting insulin analogues, especially ultra-rapid-acting insulins, can be utilized right before meals and offer superior coverage of mealtime-induced glucose elevations. Additionally, basal insulin analogues are more trustworthy than human insulin and provide people with T1D with a an improved basal insulin coverage. [13]

- A "typical person's" daily insulin demand is 40 IU insulin (often much more in obese people): approximately 20 IU insulin for food intake and approximately 20 IU insulin for basal requirements.
- One IU of insulin reduces blood sugar levels by 30 to 50 mg/dL (prerequisite: no resistance).
- One CU (carbohydrate unit) equals 10 g of carbohydrates, which raises blood sugar by 30 to 50 mg/dl (prerequisite: no resistance).
- Conclusion: On average, 1 IU insulin neutralizes 1 CU. [1]

Obtaining normoglycemia without hypoglycemia and excessive weight increase in people with T1D remains a challenge, although the introduction of insulin analogues has had a significant impact, allowing intense insulin therapy while not being disruptive to daily routine. When administered immediately before meals, rapid-acting insulin analogues, especially the ultra-rapid-acting insulins, provide superior coverage of mealtime-induced glucose rises than human regular insulin. Additionally, basal insulin analogues become increasingly reliable and offer people with T1D superior basal insulin coverage than human insulin. [14]
However, as the disease progressed into a chronic condition, new types of chronic consequences such as cardiovascular disease, neuropathy, and retinopathy emerged. [11] These difficulties were thought to be a symptom of hyperglycemia that was not physiologically regulated by some medical professionals, but others thought they were a feature of diabetes that was independent of glycemia. [15]
As a result of the Epidemiology of Diabetes Interventions and Complications (EDIC) and the Diabetes Control and Complications Trial (DCCT) demonstrating conclusively that the glucose theory is accurate, all microvascular and cardiovascular complications of diabetes are now safely constrained by an assessment that aims to achieve glycemic control as near to the nondiabetic range as is feasible. [15] Physical activity (PA) seems to be effective in achieving this goal, as an inverse association between physical activity and HbA1c was discovered, resulting in better glycemic management. [16]

1.6.2 Physical activity

According to research, almost everyone benefits from regular physical exercise, including men and women of all racial and ethnic backgrounds, young children to elderly adults,

pregnant or recently delivered women, persons living with a chronic illness or a disability, or those who desire to lower their risk of disease. Thus, the advantages of regular exercise include:

- a decreased chance of dying from any cause
- reduced risk of blood lipid abnormalities
- reduced risk of several types of cancer (bladder, breast, colon, etc.)
- enhanced mental performance and lowered risk of dementia
- enhanced physical performance and quality of life
- less psychological stress, lower chance of depression, and better sleep
- avoided weight gain and protection against weight gain following initial weight loss
- strengthened bone health
- reduced possibility of falling and suffering damage from falls [17]

A healthy weight and regular exercise training both significantly lower the chance of developing T2D, according to extremely good epidemiologic research. Additionally, keeping a higher level of activity is linked to a lower risk of developing cardiovascular disease (CVD) in those with T2D. Furthermore, an increasing number of studies have found that increased cardiorespiratory fitness (CRF) is inversely connected to the progression of the metabolic syndrome. [18,19] Higher CRF is also linked to better survival and a lower occurrence of various comorbidities such as diabetes, heart failure, and atrial fibrillation. [20] All of these are reasons why physical activity (PA) should be generally recommended and encouraged for the general community, including persons with diabetes. However, PA's significance in T1D management cannot be emphasized. In addition to insulin therapy, PA is a non-pharmacologic strategy that is both efficient and affordable for the management of T1D. It ameliorates blood glucose control, physical fitness, endothelial function, insulin sensitivity, well-being, and the body's defense system, among other things. Furthermore, it lowers the blood lipid profile, insulin resistance, the risk of cardiovascular diseases (CVDs), insulin requirements, blood pressure, and mortality associated with T1D. [21] and other researchers have shown that PA and diabetes-related problems and comorbidities, particularly the incidence of microvascular and macrovascular issues, have an antagonistic association. [16,22]

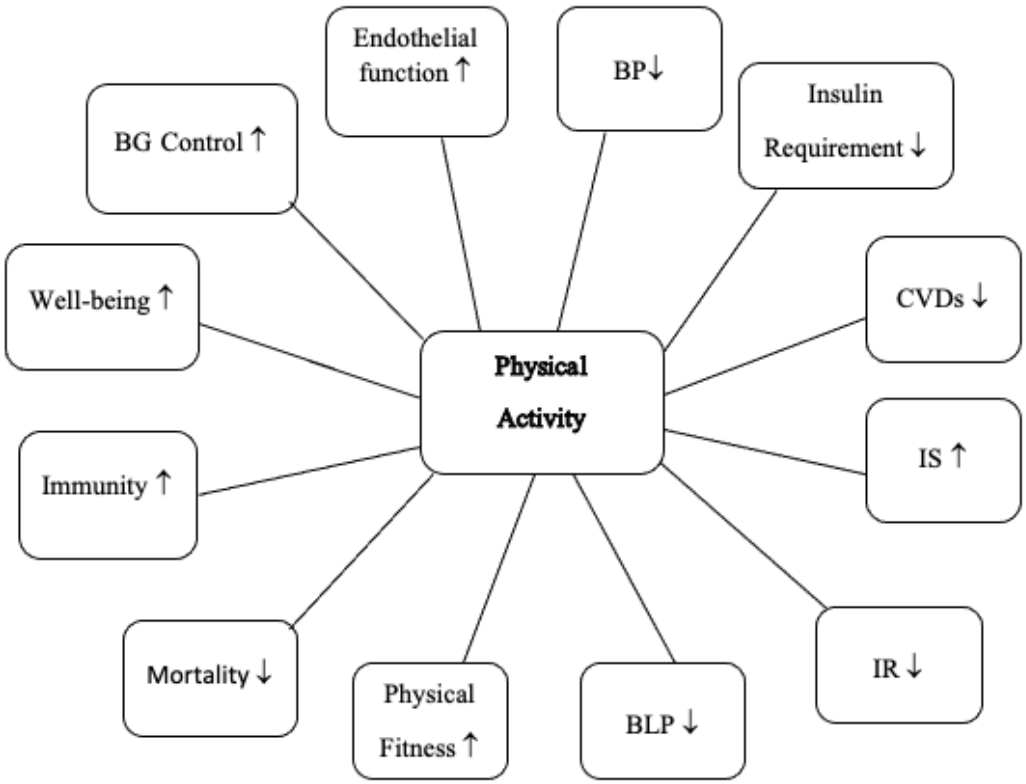

Figure 1: the advantages of exercise for people with type 1 diabetes. IS: Insulin sensitivity; BG: Blood glucose; IR: Insulin resistance; CVDs: Cardiovascular diseases; BP: Blood pressure; BLP: Blood lipid profile. [21]

1.6.2.1 Exercise physiology and glucose

In general, resistance training and endurance exercise increase the glycogen synthase and oxidative (PDH) pathways, GLUT4 protein levels, and insulin-stimulated AS160 phosphorylation in skeletal muscle in healthy older people. [23] Numerous studies have shown that acute exercise promotes the transport of glucose into muscle cells and requires an increase in the absorption of skeletal muscle plasma glucose. Glycolysis stops immediately after exercise, but glucose transport continues to increase due to increased blood flow and membrane capacity for glucose transport; however, 2 hours after exercise finishes, the plasma membrane's glucose transporter level returns to resting levels, implying that improved post-exercise insulin sensitivity may be responsible for the late phase of exercise accelerated glucose uptake. [24] Furthermore, studies have shown that physical activity promotes a redistribution of GLUT-4 (insulin-independent) in human skeletal muscle, which also increases glucose absorption in muscle. [25]

1.6.2.2 Exercise and T1D

According to certain research, people with T1D exhibit dysregulated central and peripheral hemodynamic responses to exercise, resulting in reduced maximum heart rates, stroke volumes, and cardiac output as well as lower VO2max when compared to healthy individuals. These facts may be explained, at least in part, by the catecholamine drop and the sympathetic reaction, a decline in blood volume in circulation, a considerable reduction in lung volume, and aberrant pulmonary diffusing capacity that have been observed in these individuals during exercise. [26-28] Other research, on the other hand, have demonstrated that regular moderate-intensity exercise improves the antioxidant defense system, lowering oxidative stress. [29] Moreover, a 6-week high-intensity interval training program significantly improved health-related quality of life in the physical and social domains, sleep quality, exercise enjoyment, and exercise motivation in previously inactive T1D persons. [30] A randomized experimental, parallel design, open-label trial found that a 6-week High Intensity Interval Training (HIIT) protocol is essential to improve heart rate variability (HRV) and body composition in a previously inactive T1D group without clinical deficits. Its findings also demonstrated an increase in VO2max and a long-term decrease in fasting blood glucose. [31] Another study found that individuals with T1D may benefit from both high-intensity interval exercise (HIIE) and continuous moderate exercise (CON). Short-acting insulin is proposed to be lowered in both exercise types based on mean exercise intensity. [32]

1.6.2.3 Exercise and hypoglycemia

Despite the fact that multiple studies have supported the use of PA for people with T1D, most of people with T1D do not regularly exercise due to a variety of factors. Fear of exercise-induced hypoglycemia, for example, is the most significant impediment to regular PA in individuals with T1D. [21]Physical activity is widely recognized to alter glucose concentrations in people with T1D not only during exercise but also up to 15 hours following exercise, resulting in late evening and overnight hypoglycemia. [33]
A prolonged period of aerobic exercise has been demonstrated to induce an average drop in plasma glucose of around 40% of baseline values. [34] However, compared to aerobic exercise, resistance exercise results in a smaller initial reduction in blood sugar during the activity and prolonged post-exercise glycemia decline. [35] Despite the fact that resistance

training may induce a slight increase in glycemia in some people.[36] Individuals with T1D who are physically fit appear to be more vulnerable to hypoglycemia during exercise. This could be because they have improved insulin sensitivity and exercise at higher work thresholds. As a result, people with type 1 diabetes who are trained or untrained usually need to eat more carbohydrates or take less insulin, or both, before starting an aerobic activity program. [37] Furthermore, research has demonstrated that following antecedent hypoglycemia, exercise-induced blunting of neuroendocrine, autonomic nervous system, and metabolic (lipolysis and glucose kinetics) responses occurs [38] and risky cycles can develop in which one episode of hypoglycemia or exercise might feed back to inhibit the neuroendocrine and autonomic nervous system's reactions to an additional episode of either stress or hypoglycemia. [39]

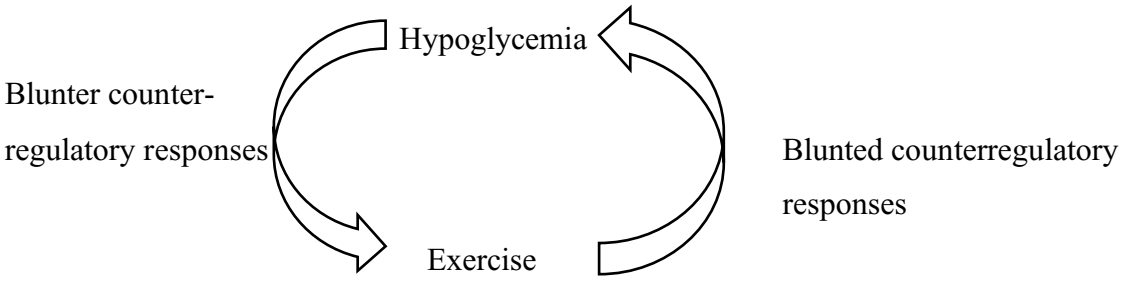

Figure 2: Reciprocal vicious cycles in type 1 diabetes mellitus – Hypoglycemia and Exercise. [39]

1.6.2.4 Recommendation for glycemic management during and after exercise:

Despite the foregoing benefits and drawbacks, the American Diabetes Association recommends that most individuals with diabetes engage in 150 minutes or more of moderate-to-vigorous intensity activity each week, distributed across at least three days per week, with no more than two consecutive days without activity. [40] Safety is key when engaging in physical exercise. The main risks come from the immediate effects of exercise on blood glucose levels, which depend on a number of variables:

- the individual's starting fitness level.
- the kind, intensity, and length of activity.
- how much insulin is circulating in the body.
- the blood glucose level just before physical activity.
- and the ingredients in the most recent snack or meal. [41,42]

In conclusion, fear of hypoglycemia is one of the major barriers to incorporating exercise into a daily practice in people following insulin therapy. However, this could be prevented by altering the insulin dose or consuming more carbohydrates. [43-46] Many studies suggest that increasing the use of technology for persons with T1D, such as continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (insulin pumps), may help reduce barriers to exercise by providing safer and more appropriate activity-related glucose management, as long as we can interpret the values and arrows displayed on those devices. [43,47]

A position statement issued by the European Association for the Study of Diabetes (EASD) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) and supported by the American Diabetes Association (ADA), provides appropriate exercise recommendations in people with T1D, based on the correct interpretation of CGM readings. [43]

1.7 Glucose Monitoring

There are two types of glucose monitoring: invasive blood glucose monitoring and interstitial glucose monitoring.

1.7.1 Invasive Blood Glucose Monitoring

Invasive blood glucose detection method is widely used in hospitals as well as home glucometers. It is based on collecting blood first, then analyzing it in vitro to assess the blood glucose. [48] A home electronic glucometer is typically used for self-monitoring of blood glucose (SMBG), which is the process of keeping track of blood glucose levels at a given moment in time. Home blood glucose monitors mostly employ glucose oxidase biosensors, requiring collection blood from the fingertip using a disposable paper strip, and then calculate the blood glucose concentration using the chemical reaction current of the strip. [48]

Its benefits include:

- portability
- affordability

- ease of use
- the ability to monitor several times each day
- accuracy

Its downsides include:

- Deep punctures will be made in the skin.
- Persons' fingertip wounds have a hard time fully healing due to the increased frequency of blood collection.
- risk of environmental contamination from the outside.
- The person will experience severe discomfort and stress before the blood draw.
- The strip has a short shelf life, and incorrect storage will affect how accurately blood glucose levels are detected. [48]

Additionally, the American Diabetes Association states that SMBG is crucial for people receiving insulin treatment in order to track and prevent asymptomatic hypoglycemia and hyperglycemia. For people receiving repeated insulin injections or insulin pump therapy, SMBG should be performed at least three times per day. [49] Moreover, it has been established that glycated hemoglobin (HbA1c) levels are inversely correlated with measurement frequency. [50]

1.7.2 Interstitial glucose monitoring

It relates to measuring blood glucose in people without harming their tissues. [48] The non-invasive approaches include continuous glucose monitoring systems (CGMs). A sensor, a transmitter, and a receiver are the three parts that make up these gadgets. The sensor, which is embedded in the subcutaneous tissue, continuously measures the interstitial glucose concentration and converts it into an electrical signal. After being processed by particular algorithms, the resultant signal corresponds to a blood glucose level. [51] The glucose oxidation reaction is the mechanism that continuous glucose monitoring (CGM) systems most frequently employ. This approach was put to the test against a variety of glucose-sensing approaches to make sure it complied with all specifications for long-term biosensor use in free-living environments. These CGM systems ignite and catalyze glucose oxidation using a platinum electrode doped with glucose oxidase that is mounted on a

needle and inserted into the subcutaneous tissue. This produces gluconolactone, hydrogen peroxide, and an electrical current signal, which are then converted to a glucose concentration via a calibration procedure utilizing a few self-monitoring blood glucose (SMBG) samples gathered by the patient. [52] Glucose has been discovered in various biofluids such as interstitial fluids (ISF), and its range is the closest to that of actual blood glucose, making it the theoretical basis for the development of an ISF glucose Sensor. [48]

Different CGM systems:

- Retrospective analysis: A blinded, continuous interstitial glucose measurement is systematically analyzed retrospectively (professional CGM) and mainly used for practitioners to analyze glucose profiles from their patients after they returned the device for clinical interpretation.
- Intermittently scanned CGM (isCGM)/Flash glucose monitoring (FGM): This method continuously measures interstitial glucose; the person receives the most recent value and trend through scanning. Another feature is the illustration of retrospective glucose profiles. These systems provide no alarm functions (Consequently, it is not appropriate for people who have chronic severe hypoglycemia or hypoglycemia recognition difficulties)
- Real-time monitoring (rtCGM): Constant measurement of interstitial glucose with readings and trends displayed on the screen of a reader or the mobile phone. When specified limit values are achieved or exceeded, an additional alert function is activated. When goal levels are attained with sensor-supported pumps, insulin delivery may temporarily stop based on the rate at which glucose falls before the target values are attained. [53]

Its benefits include:
In contrast to the concentrated snapshot data supplied by intermittent blood glucose meter testing, CGM data allows 24-hour surveillance of blood glucose readings [54] as well as the direction (glucose trend at that time going up or down) and rate of change in glucose levels. With the use of this knowledge, individuals with diabetes can increase their nutritional intake and physical activity, make informed therapy decisions regarding mealtime and insulin dose correction, and, most critically, respond quickly and proactively to minimize or prevent acute glycemic changes. [55] In addition to being painless, regular

and daily use of the CGM in a clinical care setting has been demonstrated in numerous studies to improve HbA1c and decrease both hypo- and hyperglycemia episodes, which results in better glycemic control. [56-58] This effect is not just for persons with T1D who use multiple insulin injections per day as a therapy, but CGM was also beneficial for those who utilized continuous subcutaneous insulin infusion (CSII, insulin pump therapy), contributing to improved glucose control and a lower incidence of long-term complications. [59] As a result, people with T1D quality of life has improved. [60]

Its Limitations include:
The physiological differences in glucose concentration between the interstitial fluids (ISF) and the related blood sample value could actually be misconstrued for a measurement error [61] and depending on the specific technology, there is a delay of 5 to 15 minutes between blood and interstitial glucose, which affects the accuracy of CGM measurements. [62]
Some rtCGM systems send low or high alerts when hypoglycemia or hyperglycemia occurs or is likely to occur. While isCGM devices provide alarms only while scanning, hypo- or hyperglycemic events may be overlooked if the user does not scan at the proper moment. [63] Although numerous studies indicate that CGM accuracy and precision have significantly increased in recent years [64] , however the issue of those systems being impacted by quickly fluctuating blood glucose concentrations still exists. [65]
Furthermore, the isCGM's performance was hindered by the rate of change in glucose for both rising and falling glucose levels, which resulted in reduced accuracy when the rate of change was high. [66]

1.7.3 CGM and exercise

The main reason why CGM devices were previously not thought for nonadjunctive use was the worry that their accuracy might result in potentially improper treatment and insulin-dosing decisions. Nevertheless, as CGM technology and accuracy advance over time, a number of devices are becoming accepted as the gold standard of care for monitoring T1D and achieving nonadjunctive status, allowing the control of hypoglycemia and insulin dose without the need for confirmatory SMBG. [67]
The performance of CGM sensors has mainly been studied in normal state, where a balance in glucose levels between plasma and interstitial compartments is predicted. Although this isn't usually the case in real life, only a small number of studies have

evaluated the accuracy of CGM under circumstances where the blood glucose steady state is disturbed. One of these scenarios is often during and after physical exercise, when fast occurring glycemic alterations may be captured by sensors with a substantial lag-time. [68] The performance of this sensor and its accuracy may vary based on the type, intensity, and length of exercise, as well as the CGM sensor utilized during the activity. [69]
In spite of significant differences in the metabolic conditions between these two exercise modalities, a study that was published in 2016 comparing the accuracy of CGM during continuous moderate and intermittent high-intensity exercise (IHE) in adults with T1D has found that the CGM system performs well and with comparable accuracy during both types of exercise. [70] But a study published in 2017 examined that three different CGM devices during moderate aerobic activity (50% of VO2max), done by persons with T1D, discovered a high but also variable level of accuracy in all three devices during exercise. However, it was shown that participants' CGM performance was quite reduced when they had hypoglycemia. [71] Another study, published in 2021, investigated the accuracy of modern rt-CGMs in people with T1D during two sessions of physical activity: moderate continuous (CON) and interval exercise (IE), and found that during CON all sensors performed poorly, but from a clinical standpoint, these recent CGMs maintain good clinical reliability, even during exercise, with no changes between the two types of exercises according to Clark error Grid Zones. [68] Since both, physical exercise and CGM accuracy are critical for T1D management, as previously described, it has always been debatable how accurate such devices are, particularly during physical activity. The current study aims to compare the precision of capillary blood glucose measurements with continuous glucose monitoring system (CGM) readings in people with T1D before, after, and during moderate intensity exercise.
We hypothesized that there would be no discernible difference between the two measurements that would influence the clinical choice of insulin dosage or calorie intake.

2 Methods

2.1 Study design

This is a randomized, multi-center, double-blind, four-period, cross-over, twice dose trial in participants with T1D. Each participant was allocated to four periods of one day of twice dosing with either 2 x 50% or 2 x 75% reduced Fiasp®, an ultra- fast acting insulin

analog or 2 x 50% or 2 x 75% NovoRapid®, a fast acting insulin analog (in a randomized sequence). The current study examined a predetermined secondary outcome of a clinical trial that was registered on clinicaltrials.gov (NCT03087773, DRKS00015855). The primary outcome's findings, the effect on blood glucose after the injection of fast-acting insulin aspart (Fiasp®) in comparison to insulin aspart (NovoRapid®) around exercise in participants with T1D, weren't published yet. The study was approved by the relevant regulatory authorities and by the ethics committee of the Medical University of Graz, Austria (EudraCT 2019-001281-14; EK 31-314 ex 18/19).

2.2 Participant characteristics

The inclusion and exclusion criteria will be detailed below. This trial involved eight women and eleven men. Their mean ± SD age was 41.2 ± 13.0 years, BMI 24.2 ± 2.6 kg/m^2, HbA1c 55.7 ± 6.9 mmol/mol diabetes duration 20.2 ± 11.5 years and total daily insulin dose 46.3 ± 28.3 IU. Each one of them was utilizing an isCGM system (FreeStyle Libre 1, Abbott, USA).

	Maximum	Minimum	Range	Mean	Std. Deviation	Std. Error of Mean
Age (Years)	23.40	62.30	38.90	41.23	13.02	2.986
BMI (kg/m2)	19.23	10.09	24.16	24.16	2.583	0.5927
Total daily insulin (IU)	20.00	140.0	120.0	46.32	28.27	6.486
Hba1c (mmol/mol)	43.00	68.00	25.00	55.74	6.854	1.573
Diabetes duration (Years)	49.0	1.00	48.00	21.64	13.90	3.715

Table 1: Participants characteristics – Descriptive Statistics

2.3 Inclusion criteria

- Informed consent obtained
- Male or female between the ages of 18 and 65 (both inclusive)
- Type 1 diabetes mellitus (as diagnosed clinically) ≥ 12 months
- Treated with multiple daily insulin injections ≥ 12 months
- Body mass index between 18.0-29.4 kg/m^2 (both inclusive)
- Participants who, within the three months preceding to screening, engaged in regular physical cardio-respiratory activity in accordance with Department of Health Guidelines.
- HbA1c ≤ 9.5% (80 mmol/mol
- C-peptide ≤ 0.3 nmol/l (≤ 0.91 ng/ml)
- Mass-specific peak oxygen consumption (VO2peak) >20 ml/kg/min

2.4 Exclusion Criteria:

- Known hemoglobin levels of < 8.0 mmol/l (12.8 g/dl) for men or < 6.4 mmol/l (10.3 g/dl) for women
- Oral or intravenous systemic corticosteroids, monoamine oxidase (MAO) inhibitors, non-selective beta-blockers, growth hormone, unusual vitamins, and herbal remedies Thyroid hormones are also prohibited unless their use has been consistent for the previous three months.
- Participant having a heart rate of < 40 beats per minute (bpm) at screening (after resting for 5 min in supine position)
- Cardiac conditions, which include acute myocardial infarction at any time, angina pectoris during the preceding 12 months, and decompensated heart failure (NYHA classes III and IV) at any time.
- Supine blood pressure at screening that is more than 90-140 mmHg for systolic pressure or 50-90 mmHg for diastolic pressure after 5 minutes of resting in the supine position (excluding white-coat hypertension; If white coat hypertension is observed then participants will be measured over 15 - 30 min every 5 min in a separate room and mean blood pressure will be used for eligibility assessment.). This criteria for exclusion also applied to participants who take antihypertensives.
- An aberrant ECG at screening that is clinically significant, as determined by the investigator

- A significant history of drug or alcohol misuse, in the opinion of the investigator.
- Smoker, which is referred to as a participant who smokes more than 5 cigarettes or the equivalent every day.
- Repeated cases of severe hypoglycemia (more than 1 severe hypoglycemic event during the past 12 months)
- Hypoglycemic unawareness, as determined by the investigator, or hospitalization for diabetic ketoacidosis in the prior 6 months
- A female of reproductive capacity who is pregnant, breast-feeding, intends to become pregnant, or is not using adequate contraception methods (adequate contraceptive measures include sterilization, hormonal intrauterine devices, oral contraceptives, sexual abstinence, or vasectomized partner).

2.5 Before screening

Potential participants were given oral and written information about the trial and the processes involved prior to the screening visit, in accordance with local requirements. All of the study's processes, as well as the potential dangers and benefits of participating in the experimental study, were properly explained to participants, along with their obligations and legal rights while taking part in the trial. Participants have had plenty of time to think about participating and have had the chance to ask questions. Before engaging in any trial-related activities, participants were asked to sign an informed consent form if they wanted to take part.

2.6 Screening visit

The screening visit occurred 7-14 or 14-28 days before the first dosing visit. Participants received an isCGM reader, sensors, and a notebook. To achieve a consistent basal therapy, participants were transitioned to the ultralong acting basal insulin degludec (Tresiba®) for a period of 14–28 days following the screening visit. Participants began taking Tresiba® at a dose that was 80% of their prior total daily basal dose. When the participants´ prebreakfast self-measured blood glucose value was between 72 and 126 mg/dl, a stable basal treatment was achieved. Visit 2 was carried out 7–14 days following the screening visit if participants were already on Tresiba®. Participants in the screening visit underwent eligibility screening and underwent a maximum progressive workout on a cycle ergometer

to measure their peak oxygen uptake (VO2peak) and first and second lactate turn points (LTP1 & LTP2) to specify the intensity of the exercise sessions. Throughout this investigation, researchers at the study site provided unblinded isCGM readers and sensors. All of the participants had experience with the isCGM prior to the study's start, thus they all received training on how to use it.

2.7 Trial visits

Participants underwent four trial visits following a screening visit. In the trial visit they spent about 8 hours at the "Forschungszentrum Billrothgasse" where they had 2 standardized meals and 45 minutes of moderate-intensity exercise in between. 70 total blood samples were obtained throughout the visit (venous and capillary sampling). Participants that took part in the trial visits administered their Tresiba® dose in the lateral region of the thigh (basal insulin), completed the International Physical Activity Questionnaire (IPAQ) to monitor their level of physical activity throughout the trial, and were fitted with a small continuous ECG device. The pre-meal Fiasp® or NovoRapid® dose was then reduced by 50% (or 75%) after an overnight fast. Following the bolus insulin injection, participants immediately began eating their meal. The moderate continuous cycle ergometer exercise test's exercise intensity was chosen to be halfway between the LTP1 and LTP2 levels (approximately 65% of VO2peak). Following the exercise test, participants received a second injection of 50% to 75% less pre-meal Fiasp® or NovoRapid® (the same dose). It was decided that the isCGM sensor should be worn for at least 48 hours before the first exercise session. To ensure sensor accuracy, participants were instructed to replace any sensors that were about to expire during the experiment at least two days before the first exercise session. The second treatment session was separated by a 7–14-day wash-out interval, during which the participants resumed their pre-study short-acting insulin medication and Tresiba®.

2.8 Measurements

Cardiopulmonary variables (blood pressure, spirometry readings, and ECG) were continually recorded during the exercise sessions. Capillary blood samples were obtained from the ear lobe and finger before the exercise session (resting value), after the 3-minute warm-up phase, every 5 minutes during the goal workload, and after the 3-minute recovery period to assess glucose concentrations as reference values using a fully enzymatic-

amperometric technique (Biosen S-line; EKF Diagnostics, Barleben, Germany) and Freestyle-Libre (Abbott-USA).
Participants' glucose concentrations were monitored using isCGM (Freestyle-Libre 1, Abott-USA) during exercise to get interstitial glucose concentrations. An isCGM reader scan was done simultaneously with the collection of blood glucose from the finger and earlobe. The isCGM reader's diary was then used to transcribe interstitial glucose data.

Measurement of blood glucose for safety during visits:

- A first aid procedure would have been carried out in the event of unconsciousness (glucose infusion). The ethical review committee would have been informed right away of any unfavorable events. This same committee would have stopped the trial during this period of review.
- If the blood glucose level was <70 mg/dl, a hypoglycemic episode was documented, and oral carbohydrates were given and recorded (type, amount and time).
- A second blood glucose reading was taken.
- With a confirmed blood glucose of 70 mg/dl, the participant was given 10 g of carbohydrate for oral intake, and a new blood glucose value was taken approximately 10 minutes later.
- The carbohydrate administration and blood glucose measurement protocol were repeated if the subsequent blood glucose reading remained at 70 mg/dl.

2.9 Primary objective

To compare the sensor accuracy of the isCGM with blood glucose levels during moderate-intensity exercise

Data were analyzed in the following manner:

- Median absolute relative difference (MARD) is defined as < (sensor glucose - reference blood glucose) / reference blood glucose> expressed as a percentage.
- The median absolute relative difference expresses differences as absolute values, ignoring the direction of the measurement error while expressing the size of the error as a percentage error.
- Clarke Error Grid: The reference blood glucose levels (in mg/dl) are shown on the x-axis, while the results obtained from the intermittent scanned continuous glucose

monitoring system (isCGM) system (mg/dl) are shown on the y-axis. The zones on the grid depict the level of risk brought on by inaccurate measurements: zone A means no effect on clinical action; zone B represents altered clinical action—small or no significant effect on clinical outcome; zone C represents altered clinical action—likely to affect clinical outcome; zone D means altered clinical action—could have significant medical risk; and zone E represents altered clinical action—could have dangerous consequences.

- Bland-Altman: Statistical methods for assessing agreement between two methods of clinical measurement.
- The data presented here were measured during the exercise session.

2.10 Secondary objectives

- Post- exercise comparison between interstitial glucose's level measured by isCGM to the exact blood glucose' level.
- Pre- exercise comparison between interstitial glucose's level measured by isCGM to the exact blood glucose' level.
- isCGM's accuracy based on glucose rate of change.
- isCGM's accuracy based on BMI.
- isCGM's accuracy based on total daily insulin dose.
- isCGM's accuracy based on age
- isCGM's accuracy based on gender

Data were analyzed in the following manner:

- The post-exercise comparative data was gathered through questionnaires that the participants completed.
- Given that the Participants arrived at 7:30 a.m. and the Exercise began at 10:00 a.m., we used the measurement from the morning before to the exercise for the pre-exercise comparison. MARD and the Clark Error Grid were used to analyze both pre- and post-exercise data.
- Using all of the participant's pre, post, and workout data, we generated the individual MARD for each participant in order to evaluate the isCGM's accuracy based on age, BMI, and total daily insulin. The correlation between individual

MARD and each BMI, Total daily insulin, and Age was then looked at using Pearson and Spearman tests.

- To analyze isCGM accuracy based on glucose rate of change, we use the Spearman test to investigate the correlation between ARD (absolute relative difference) and glucose rate of change every 5 minutes during exercise.
- An unpaired T-test for each participant's individual MARD and their gender was used to examine the accuracy of isCGM based on gender.

3 Results

3.1 Primary Outcome

During the study period, 846 scans from the isCGM (FreeStyle Libre, Abbott, USA) were performed, encompassing a glucose range of 105 to 481 mg/dL, and 846 capillary ear lobe samples were collected and analyzed using lab-diagnostic (Biosen S-line device, EKF, GER), covering a glucose range of 98.1 to 513 mg/dL.
The isCGM's accuracy was determined by comparing the two measurements, which were obtained simultaneously every ~ 5 minutes during the workout session.

	Median	**25%**	**75%**	**MAX**	**MIN**	**± SD**
MedDiff	-20.6	-58.0	6.9	102.9	-1685.0	
MAD	30.9	14.8	62.9	168.5	0.0	
MARD	10.3%	4.8%	20.4%	35.1%	0.0%	10.7%

Table 2: Primary Outcome – capillary ear samples analyzed by Biosen S-line device (EKF, GER)

The result reveals a MARD of 10.3% and a median absolute difference (MAD) of 30.9 mg/dL. The greatest absolute difference between the two devices was 168.5 mg/dL, and the two devices agreed on a difference of 0.0 mg/dL in the best situation.

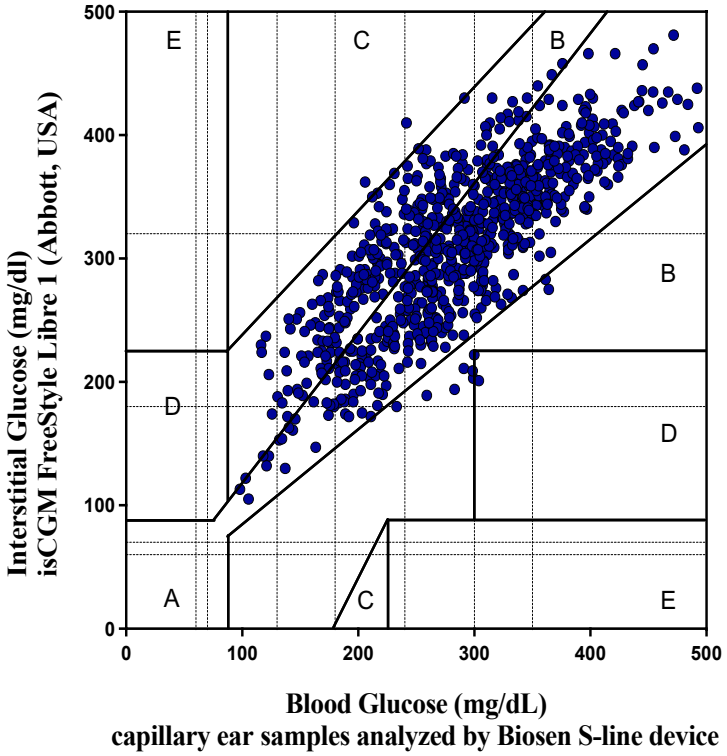

Figure 3: Primary Outcome – Clark Error Grid – Biosen S-line measurements as reference.

According to the Clark Error Grid, zone A contained 70.45% of the data pairs, zone B contained 29.20%, and zones C and D contained less than 0.35%.

3.1.1 isCGM accuracy utilizing capillary finger prick samples analyzed by glucometer (Freestyle Libre, Abbott, USA) as a reference:

During the study period, 846 scans from the isCGM (FreeStyle Libre 1, Abbott, USA) were performed, covering a glucose range of 105 to 481 mg/dL, and 846 capillary finger prick samples covering a glucose range of 109 to 500 mg/dL were taken and analyzed using the glucometer (FreeStyle Libre, Abbott, USA). The two measures, which were taken simultaneously every ~ 5 minutes throughout the workout, were compared to determine the accuracy.

	Median	**25%**	**75%**	**MAX**	**MIN**	**± SD**
MedDiff	-22.5	-52.0	4.0	134.0	-135.0	

MAD	33.0	17.0	59.0	135.0	0.0	
MARD	11.3%	5.5%	19.2%	58.5%	0.0%	9.8%

Table 3: Primary Outcome - capillary finger prick samples analyzed by Freestyle Libre

The results show a MARD of 11.3% and a MAD of 33.0 mg/dl. The two devices' largest absolute difference was 135.0 mg/dl, and in the best-case scenario, they agreed on a difference of 0.0 mg/dl.

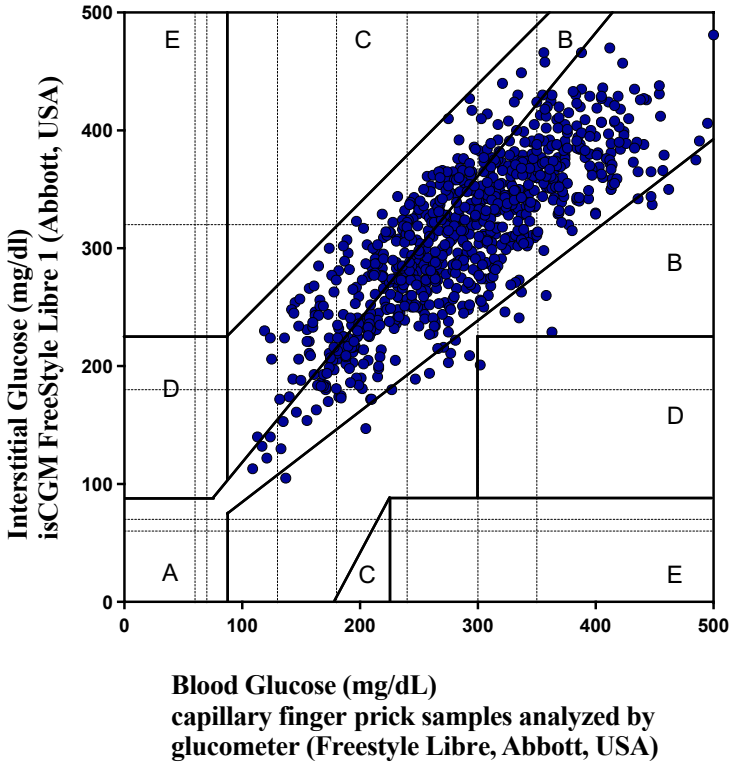

Figure 4 Primary Outcome – Clark Error Grid – Freestyle Libre (Abbott, USA) blood measurements as reference.

Zone A included 72.22% of the data pairs, zone B contained 27.66%, and zone D had less than 0.1%, according to the Clark Error Grid.

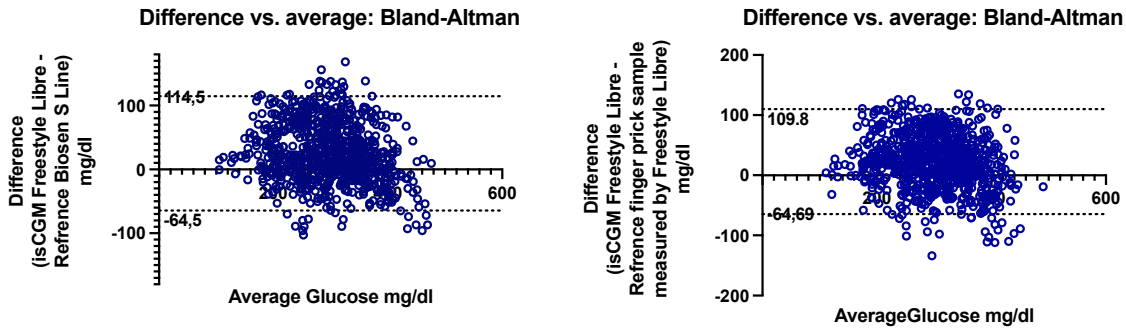

Figure 5:Primary Outcome: Bland-Altman -Comparison

Bland-Altman (Bias and Agreement)	**Bias**	**SD of Bias**	**95% Limits of Agreement:**
Capillary ear lobe sample Measured by lab-diagnostic (Biosen-S-Line, EKF, GER)	24.99	45.67	-64.53 to 114.5
Finger prick sample Measured by glucometer (Freestyle Libre, Abott, USA)	22.56	44.51	-64.69 to 109.8

Table 4:Primary Outcome Bland-Altman Bias and Agreement.

The average of discrepancies (Bias) is not close to zero suggests that the two assay methods (isCGM vs. capillary ear sample analyzed by Biosen-S-line) and (isCGM vs. capillary finger prick sample analyzed by glucometer Freestyle Libre) consistently provide different results. Our findings show that the Bias is 24.99 (Biosen-S-Line) and 22.56 (glucometer Freestyle Libre).

3.2 Secondary Outcomes

Participants	**Individual MARD**	**Age**	**BMI**	**Total daily Insulin**
P01	8	56.2	25.64	40
P02	21.9	32.3	25.96	20
P03	11.5	43.3	21.84	30
P04	8.7	57.1	23.80	38

P05	10.9	39.6	22.15	27
P06	9.4	23.4	21.74	46
P07	8.7	43.8	25.26	40
P08	17.1	42.2	26.00	95
P09	19.3	55.9	29.32	140
P10	16.9	26.4	24.89	62
P11	8.4	59.6	24.96	37
P12	9.3	29.6	24.00	22
P13	8.2	25.3	23.05	38
P14	10.8	43	19.23	28
P15	11.1	30.4	24.78	34
P16	15.3	62.3	22.60	39
P17	16.1	34.1	24.39	60
P18	11.6	53.2	20.37	42
P19	12.8	25.7	29.07	42

Table 5 – Individual MARD/Age/BMI/Total daily Insulin for the secondary outcomes.

3.2.1 Post- exercise isCGM accuracy utilizing capillary finger prick samples analyzed by glucometer (Freestyle Libre, Abbott, USA) as a reference:

During the research site time, 72 scans from the isCGM (FreeStyle Libre 1, Abbott, USA) were performed, covering a glucose range of 65 to 311 mg/dL, and 72 capillary finger prick samples covering a glucose range of 53 to 299 mg/dL were taken and analyzed using the glucometer (FreeStyle Libre, Abbott, USA). Both measurements were taken simultaneously, 24 hours after the exercise session.

	Median	**25%**	**75%**	**MAX**	**MIN**	**± SD**
MedDiff	-6.0	-18.0	5.0	34.0	-77.0	
MAD	13.0	5.5	24.5	77.0	0.0	

MARD	10.2%	4.0%	16.9%	43.0%	0.0%	9.6%

Table 6: Secondary Outcome- Post exercise Accuracy

The findings indicate a MAD of 13.0 mg/dl and a MARD of 10.2%. In the best instance, the two devices agreed on a difference of 0.0 mg/dl, while their biggest absolute difference was 77.0 mg/dl.

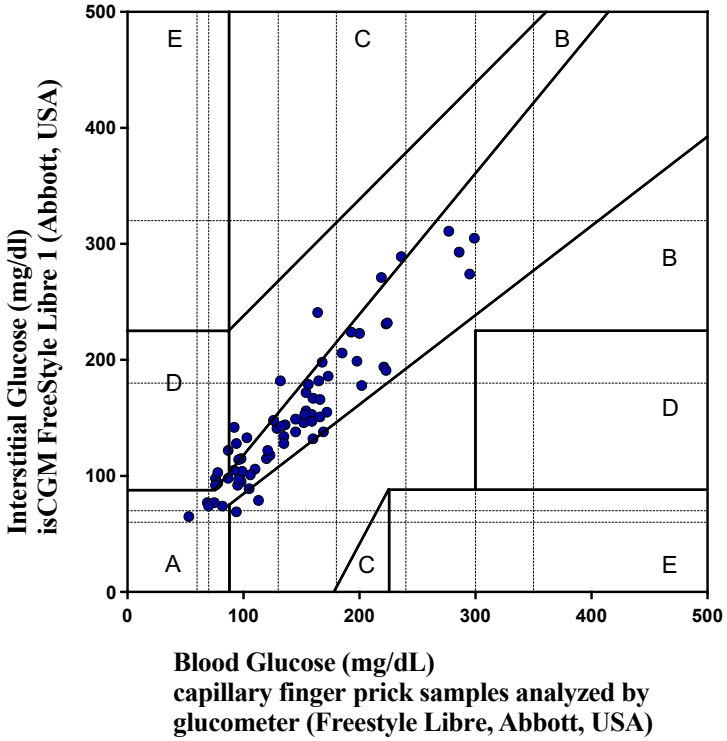

Figure 6: Secondary Outcome – post exercise graph – Clark error grid

According to the Clark Error Grid, zone A contained 77.46% of the data pairs, zone B contained 15.94%, and zone D contained 7.04%.

3.2.2 Pre- exercise isCGM accuracy utilizing capillary finger prick samples analyzed by glucometer (Freestyle Libre, Abbott, USA) as a reference:

During the research site time, 74 isCGM scans (Freestyle Libre, Abott, USA) were done, encompassing a glucose range of 65 to 311 mg/dL, and 74 capillary finger prick samples covering a glucose range of 92 to 327 mg/dL were collected and analyzed using the glucometer (FreeStyle Libre, Abott, USA).

Both measurements were obtained at the same time, at 7:30 a.m., upon the arrival of the participants.

	Median	25%	75%	MAX	MIN	± SD
MedDiff	-5.0	-18.0	11.5	85.0	-40.0	
MAD	17.0	6.3	24.0	85.0	0.0	
MARD	8.6%	4.2%	14.7%	50.0%	0.0%	7.8%

Table 7 Secondary Outcome- Pre exercise Accuracy

The results show a MAD of 17.0 mg/dl and a MARD of 8.6%. The two devices agreed on a difference of 0.0 mg/dl in the best case, whereas their greatest absolute difference was 85.0 mg/dl.

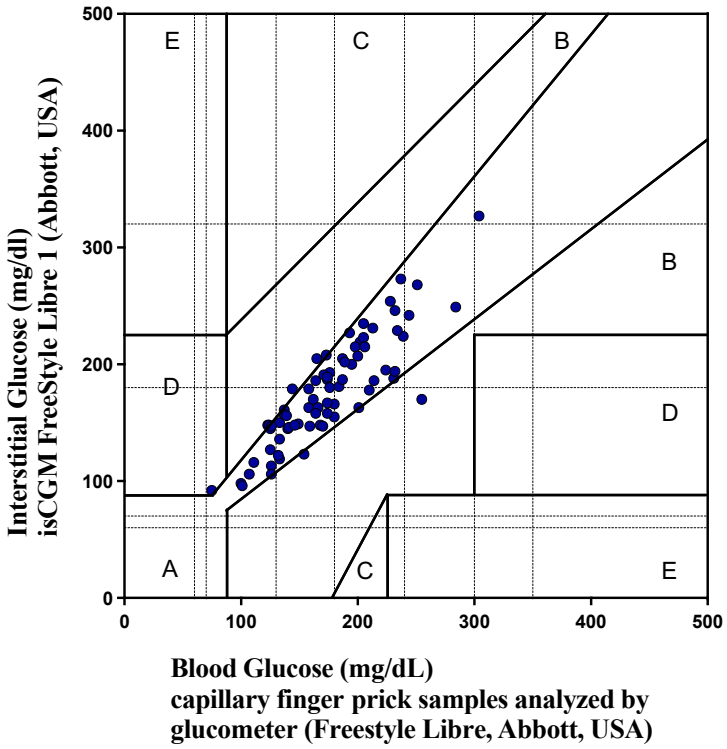

Figure 7 Secondary Outcome – pre-exercise graph – Clark error grid

Zone A included 89.19% of the data pairs, Zone B had 9.46%, and Zone D contained 1.35%, per the Clark Error Grid.

3.2.3 isCGM's accuracy based on glucose rate of change

We used the Spearman rho test to find out the correlation between ARD (absolute relative difference) and glucose rate of change every 5 minutes during exercise because both variables' parameters failed the Shapiro-Wilk test for normal distribution.

Spearman r	r	95% confidence interval	P (two-tailed)	Exact or approximate P value	Significant (alpha = 0.05)	Number of XY Pairs
	0.1282	0.05487 to 0.2001	0.0004	Approximate	Yes	747

Table 8: Secondary Outcome – Spearman tests – Rate of Change

The test shows that the ARD was weak-positively correlated (rho = 0.13, p <0.05) with glucose rate of change, suggesting that the accuracy of the isCGM reduces with an increase in the rate of change.

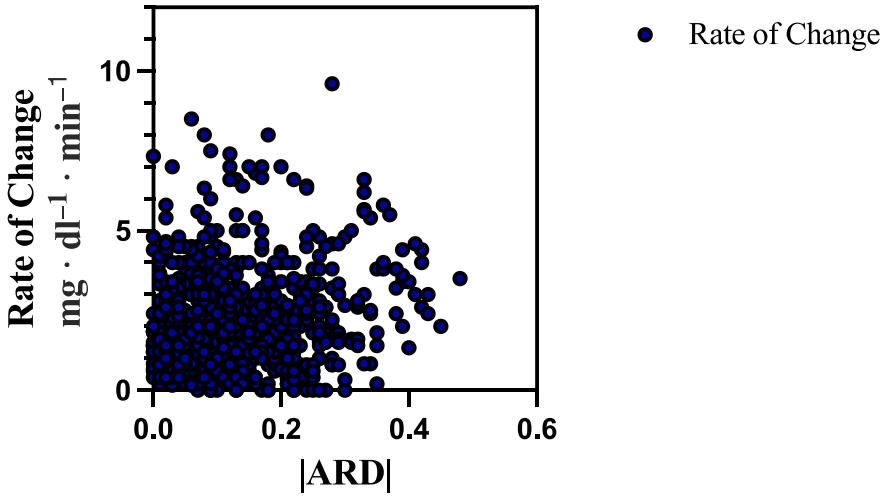

Figure 8: Secondary Outcome – Correlation graph between ARD and Rate of Change

3.2.4 isCGM's accuracy based on BMI

Using all of the participants´ pre, post, and workout data, we determined the individual MARDs. We used capillary finger prick samples analyzed by the glucometer (Freestyle Libre, Abbott, USA) as a blood value reference for the individual MARD.
Shapiro-Wilk test was used to check the values of each person's MARD and BMI for normal distribution; once it was determined that they were, we performed the Pearson test to determine whether there was any correlation between them.

Pearson r	r	95% confidence interval	R squared	P (two-tailed)	Significant? (alpha = 0.05)	Number of XY Pairs
	0.4052	-0.06011 to 0.7258	0.1642	0.0853	No	19

Table 9: Secondary Outcome – Spearman tests – BMI

The Pearson's correlation test shows that there was a moderate-strong positive but insignificant correlation (r = 0.405, p = 0.085) between BMI and individual MARD.

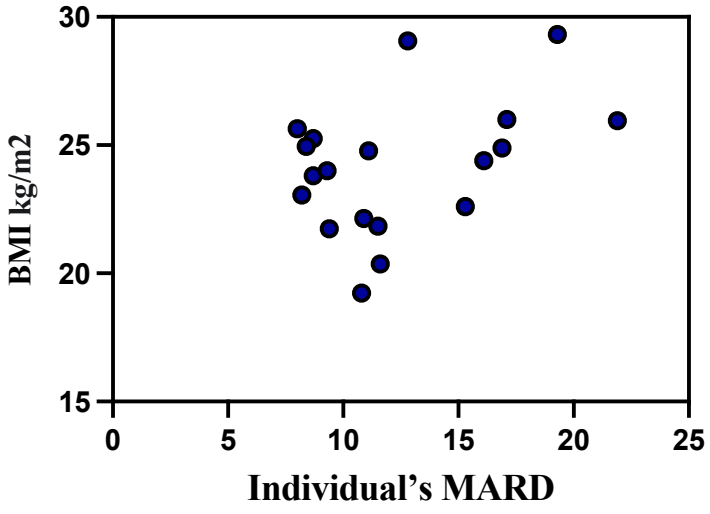

Figure 9: Secondary Outcome – Correlation graph MARD & BMI

3.2.5 isCGM's accuracy based on age

When we used the Shapiro-Wilk test to check for normal distribution in the previously mentioned individuals' MARD and age, they passed, thus we utilized the Pearson test once more to look for correlation between the two of them.

Pearson r	r	95% confidence interval	R squared	P (two-tailed)	Significant? (alpha = 0.05)	Number of XY Pairs
	-0.06811	-0.5066 to 0.3984	0.004638	0.7818	No	19

Table 10: Secondary Outcome – Spearman tests – age

The Pearson's correlation test shows that there was a weak negative but insignificant correlation (r = -0.068, p = 0.085) between age and individual MARD.

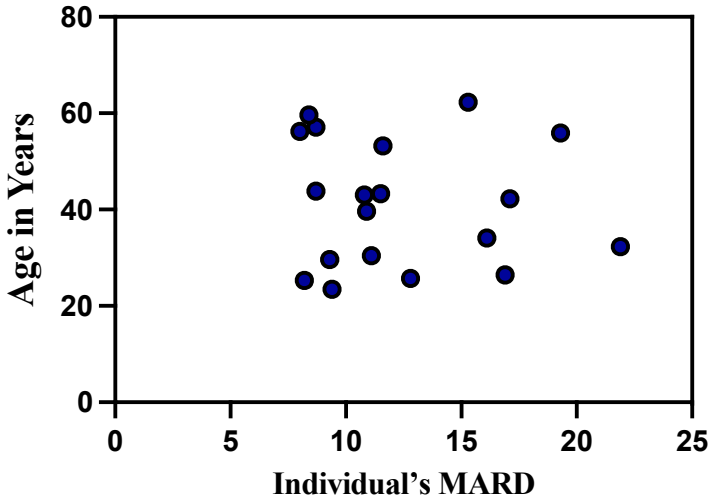

Figure 10: Secondary Outcome – Correlation graph MARD & age

3.2.6 isCGM's accuracy based on total daily insulin

When we used the Shapiro-Wilk test to seek for normal distribution in the previously mentioned persons' MARD and total daily Insulin, they failed, thus we used the Spearman test to look for correlation between the two.

Spearman r	r	95% confidence interval	P (two-tailed)	Exact or approximate P value?	Significant? (alpha = 0.05)	Number of XY Pairs
	0.3286	-0.1617 to 0.6889	0.1695	Approximate	No	19

Table 11 Secondary Outcome – Spearman tests – Total daily insulin

The Spearman's correlation test shows that there was a weak positive but insignificant correlation (r = 0.328, p = 0.169) between the total daily insulin and individual MARD.

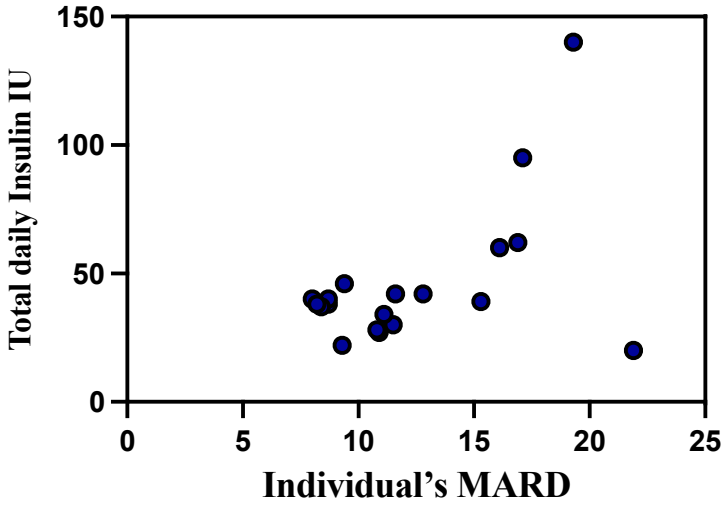

Figure 11 Secondary Outcome – Correlation graph MARD & Total daily insulin

3.2.7 isCGM's accuracy based on gender

Since the values passed the Shapiro-Wilk test for normal distribution, we utilized the unpaired T test to compare the individual MARDs in males and females.

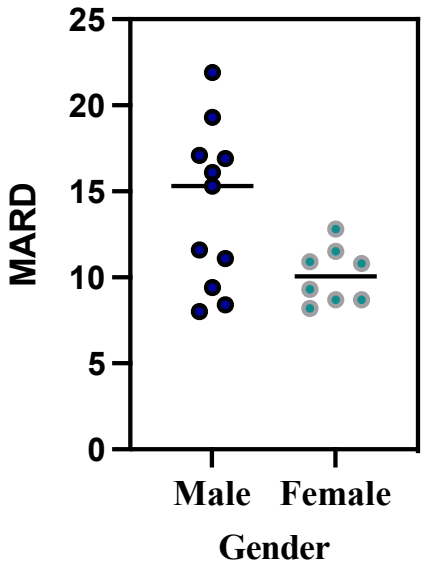

Figure 12 Secondary Outcome Graph – Gender Difference.

The T test shows that males had a significantly higher mean ±SD MARD value (14.10 ± 4.66 vs. 10.11 ± 1.628, p = 0.0208) than females.

4 Discussion

By the fact that blood glucose levels during physical exercise can change quicker than those in the interstitium, and isCGM results can now be used as the sole reference for therapeutic decisions, the accuracy of isCGM devices during physical exercise is becoming increasingly important. This thesis helps to assess if these devices can be utilized as a sole reference for glycemic control during moderate intensity exercise and looks for potential factors that can affect their performance in order to reduce or control them in some ways.

4.1 isCGM accuracy during exercise

The results of the current study revealed that during moderate-intensity exercise, the glucose readings from the isCGM system did not exactly match the capillary glucose values measured by the lab-diagnostic (Biosen-S-line, EKF, GER) or glucometer (Freestyle Libre, Abott, USA) but the MARD values were either 10.3 % (lab-diagnostic) or 11.3% (glucometer), which means that the difference was generally acceptable.
The Clark Error Grid also revealed that 99% of values were in the A and B Zones, which are places where the patient's decision to get treatment is not affected or jeopardized.

Only a small proportion of our measurements and results suggested a bigger ARD, or a greater difference between isCGM and actual blood levels, just as the Clark-error-grid that showed a very small percentage (> 1%) of the measurement in C and D zone, our findings indicate that the isCGM is as precise as it can be when utilized as a sole reference during exercise. But our findings contradict those of a previous study conducted by our research team, which found that isCGM performance is inaccurate during 55 minutes of moderate exercise with a MARD value of 22%, implying that this device should only be used as an addition to blood glucose readings during exercise. [72] These discrepancies in results could be attributable to the prior study's smaller number of participants (n=10). However, the altered blood flow in the interstitium and the greater fluctuations in blood glucose during exercise may be to blame for the lower accuracy and higher MARD values in those two trials compared to non-exercise studies.

4.2 Pre-exercise isCGM accuracy

The pre-exercise MARD 8.6% was obviously lower than the exercise MARD, but we can't state definitively that the isCGM works better without activity based on this study because the pre-exercise data we received for calculating the MARD were considerably less (74 pre-exercise) compared to the exercise Data (846 exercise). The Clark Error Grid revealed that more than 89% of the readings were in zone A, indicating that the discrepancies in measurements between the two devices had no clinical impact in most of the gained glucose values. However, our findings are consistent with the findings of other research, [73,74] implying that isCGM values under resting conditions are accurate compared capillary BG. As a result, this device could be utilized as a sole reference for glycemic control in persons with T1D.

4.3 Post-exercise isCGM accuracy

We collected data for this outcome 24 hours after exercise since it has been observed that the effect of exercise on blood glucose does not end when the exercise is over but can potentially cause late Onset or nighttime hypoglycemia. [75] Here, the Clark Error Grid revealed that only 77% of the values landed in zone A. And the MARD value was 10.2% nearly the same results as the exercise, but we must still consider the fact that our post-exercise data were much smaller (72 pre-exercise) than the exercise Data (846 exercise).

When we compare our pre and post workout results, we can see that the MARD value was lower in the pre-exercise, indicating higher isCGM accuracy. The difference between those two results may be somewhat explained by the post-exercise impact that we previously discussed.

4.4 isCGM accuracy based on glucose rate of change

We discovered a modest correlation between the glucose rate of change during exercise and isCGM accuracy in our investigation, the greater the rate of change, the less accurate the device. This could be explained by the time it takes for a transitory change in blood glucose to be reflected in interstitial fluid glucose and is also related to mass transfer qualities across compartments.

Our results are consistent with research that looked at this factor in two different CGM devices: a functioning CGM system (Dexcom G4, Dexcom, San Diego, CA; system A) and a prototype system (Roche Diagnostics GmbH, Mannheim, Germany; system B). According to the findings of that investigation, MARD outcomes were higher for both systems with quickly variable blood glucose concentrations, just like in our study. [65]

4.5 isCGM's accuracy based on BMI

We also assessed the correlation between BMI and isCGM accuracy as one of our secondary objectives because we hypothesized that differences in subcutaneous fat, potentially influence glucose diffusion, and that could explain differences in isCGM accuracy between those with lower and higher BMI scores. However, we didn't find a statistically significant correlation, which could be explained by our participants' characteristics because most of them were in the normal BMI range (between 18.5 and 25), none of the participants were underweight (18 kg/m^2), and only 6 participants were overweight (> 25 kg/m^2).

However, our findings contradict a study that identified a negative link between body composition and CGM precision, claiming that the Freestyle Libre Pro significantly underestimated average glucose levels in children with higher BMIs. [76]

4.6 isCGM accuracy based on gender

it was interesting to note that there was a gender difference in accuracy, with female individuals having the smaller MARD, implying that their isCGM were more accurate than male participants.
Because our study comprised only 19 participants (8 women and 11 men), which is a small group, and no studies have shown that gender differences affect accuracy, further research should focus on this finding.

4.7 isCGM accuracy based on total daily insulin

We found no statistically significant correlation between the accuracy of the isCGM and the participant's age or total daily insulin intake. Back to our key finding from this secondary outcome analysis, and while the MARD and Clark error provided us with fairly accurate data, we would advise persons with T1D to perform an additional blood measurement to support their treatment decisions during exercise. Particularly when they are about to experience hypoglycemia or inject a large dose of insulin.

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