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Diabetes in Sports and Exercise Medicine

Edited by
Jason R. Jaggers

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Editor

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About the Editor

Jason R. Jaggers

Dr. Jason R. Jaggers is an Associate Professor of exercise physiology. His research interests are focused on community-based interventions, as well as exercise testing and prescriptions for special populations, with a strong emphasis on HIV and diabetes (Type 1 and 2). As a leading expert in clinical exercise science, Dr. Jaggers would like for his research to help establish the importance of increased fitness among clinical populations as a way to help manage the symptoms and side effects associated with chronic disease.

Preface to "Diabetes in Sports and Exercise Medicine"

The long-term health benefits of daily physical activity and/or routine exercise have been clearly established, with strong evidence suggesting its use as both preventative care and a form of complementary medicine for nearly every clinical population. Even though diabetes mellitus is a serious disease, advances in treatment options have made this condition manageable, giving individuals the opportunity to live full, active lives. However, recommendations regarding the inclusion of physical activity, exercise, and/or competitive sports are minimal due to the lack of research within this population, especially in regard to type 1 diabetes. The available research indicates that exercise training could result in health improvements and long-term adaptations that would suggest someone with diabetes could improve glycemic control and naturally reduce insulin requirements of the body, which in turn may result in a reduction in insulin usage. Therefore, it is important to enhance the current state of research for individuals managing diabetes while being physically active and/or exercising.

What you will see on the pages of this book is a collection of original research findings and novel literature reviews covering a wide range of information related to the positive impacts physical activity can play in the successful management of diabetes for people across all walks of life, while also embracing the concept that Exercise is Medicine for all populations with or without known disease. It was important to not limit this collection to any specific type of diabetes, component of fitness, form of exercise, or type of individuals who are either at risk of developing diabetes or currently working hard to manage their blood glucose following diagnosis. Therefore, you will find research ranging from the glucose response following VO2max testing in young athletes with type 1 diabetes to the impacts of yoga for individuals with type 2 diabetes and everything in between.

This book is not intended to provide specific guidance or recommendations in managing diabetes through exercise or the different types of physical activity but rather to serve as a provider for additional evidence to help expand the literature. The research included within these pages may assist with future adaptations to the current recommendations by providing additional evidence-based approaches when setting such guidelines. As Guest Editor of this first edition, it is also my hope to possibly inspire interest among researchers, scientists, and healthcare specialists to continue exploring this topic while also sparking healthy debate to help push the science forward. By doing so then maybe one day those living with diabetes can reap all the substantial benefits physical activity and exercise offers without fear of extreme disruptions in glycemic control.

Finally, I would like to thank all of the researchers and their study participants for each of their individual contributions to this body of literature. I would also like to thank the reviewers who volunteered their time to provide critical reviews of each published paper and, of course, the readers, who helped make each article a success post-publication.

Jason R. Jaggers
Editor

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Article

Integration of Consumer-Based Activity Monitors into Clinical Practice for Children with Type 1 Diabetes: A Feasibility Study

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Abstract: Current technology commonly utilized in diabetes care includes continuous glucose monitors (CGMs) and insulin pumps. One often overlooked critical component to the human glucose response is daily physical activity habits. Consumer-based activity monitors may be a valid way for clinics to collect physical activity data, but whether or not children with type 1 diabetes (T1D) would wear them or use the associated mobile application is unknown. Therefore, the purpose of this study was to test the feasibility of implementing a consumer-based accelerometer directly into ongoing care for adolescents managing T1D. Methods: Adolescents with T1D were invited to participate in this study and instructed to wear a mobile physical activity monitor while also completing a diet log for a minimum of 3 days. Clinical compliance was defined as the number of participants who were compliant with all measures while also having adequate glucose recordings using either a CGM, insulin pump, or on the diet log. Feasibility was defined as >50% of the total sample reaching clinical compliance. Results: A total of 57 children and teenagers between the ages of 7 and 19 agreed to participate in this study and were included in the final analysis. Chi-square results indicated significant compliance for activity tracking ($p < 0.001$), diet logs ($p = 0.04$), and overall clinical compliance ($p = 0.04$). Conclusion: More than half the children in this study were compliant for both activity monitoring and diet logs. This indicates that it is feasible for children with T1D to wear a consumer-based activity monitor while also recording their diet for a minimum of three days.

Keywords: physical activity; pediatric; clinical exercise; accelerometer; diabetes

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1. Introduction

With overwhelming evidence supporting the value of daily physical activity [1], healthcare providers educate their patients that staying physically active improves cardiovascular health, increases insulin sensitivity, and improves mental health among many other benefits. There have been calls to action for healthcare professionals to include measures of physical activity and exercise in a standard assessment during routine clinical visits for use as a vital sign that is kept as a health indicator in their medical record, similar to blood pressure and weight [1–5]. Unfortunately, obtaining verifiably accurate activity data from patients has been difficult, with most providers relying on self-reported times and individual perceptions of activity degree (i.e., moderate vs. vigorous) [3,5]. Whether or not it would be feasible to incorporate data from a physical activity monitor for patient management into standard practice is unknown. Utilizing this technology would provide healthcare providers with accurate activity data and improve specific time and activity level counseling. Furthermore, to continue to explore the range of activity associated with health in children, studies involving accelerometers could provide valid and reliable measurements for household and sedentary behaviors that often go under-reported when

communicating with healthcare providers [6]. One such clinical population that could benefit from physical activity monitoring is type 1 diabetes (T1D). With the assistance of an exercise physiologist, physicians can incorporate individualized recommendations for increasing physical activity and/or exercise prescriptions into their clinical practices. This ensures the patient's exercise regimen is both safe and effective [2,7].

With all children encouraged to accumulate at least 60 min of play for known health benefits [8], providers caring for children with T1D must determine how best to advise so that participation can be free from fear of diabetes-related complications. This is particularly challenging because children with T1D often have frequent changes in carbohydrate needs and insulin requirements as they grow. This is especially true during periods of more rapid growth and development, as well as acutely with changes in physical activity. During moderate-to-vigorous physical activity, there are significant changes in blood glucose concentration [9–11], and poor glycemic control can lead to the impairment of physical growth and a delay in pubertal development [12]. Utilizing activity monitoring technology could help medical professionals involved in T1D care make more accurate adjustments to insulin therapy and diet recommendations. Children with T1D that maintain good glycemic control do not display signs of impaired muscle function, while children with poor glycemic control can have altered aerobic muscle capacity [11,13]. Hypoglycemia, during or within hours following large bouts of increased activity or planned exercise, can interfere with the activity or even cause potential harm [14]. In fact, many children with T1D are inactive due to the fear of, and possible prior experiences with, hypoglycemia or hyperglycemia [15,16].

The American Diabetes Association's position statement "Type 1 Diabetes through the life span" recommends physical activity and exercise [17,18]. This statement provides examples of reviews that have been published regarding consensus on exercise management for individuals with T1D who exercise regularly, including glucose targets for safe and effective exercise, and nutritional and insulin dose adjustments to protect against exercise-related glucose excursions [7,19]. Unfortunately, these recommendations are relatively general and based primarily on research studies with adults managing type 2 diabetes. Individuals managing T1D need recommendations that are tailored to their individual needs. Providers have been increasingly turning to diabetes technology to better serve their patients, and the use of activity monitoring technology would be another valuable step.

The advancement of diabetes technology, including continuous glucose monitoring (CGM) devices, continuous subcutaneous insulin pumps, and even hybrid closed-loop systems, has demonstrated direct value from increasing data input from the patient. Direct patient activity data are not yet a factor in these technologies yet clearly influence glucose change. This area of research is steadily growing, and, similar to study comparisons between glucose monitoring devices, activity monitoring devices are also being evaluated. In 2018, the American Heart Association investigated the validity and feasibility of wearable activity monitoring devices for patients and healthcare data integration. Accelerometers were scored based on variables regarding the validity, test–retest reliability, and even clinical feasibility among other criteria [3]. With consumer-based activity monitors only improving, it seems ideal to use this form of technology for T1D management. However, wearing or even carrying too many devices (i.e., continuous glucose monitors and insulin pumps) has been reported as a barrier for the adoption of current diabetes technology, which could limit its use.

The relationship between physical activity and glycemic control is complex because the acute and prolonged glucose response experienced is highly variable among patients managing T1D and dependent on both the intensity and duration of physical activity [7,9,13,19]. For example, prolonged aerobic activity causes blood glucose values to decline, whereas brief, intense anaerobic exercises causes blood glucose values to rise. This complexity has become clearer from past studies that utilized accelerometers in this population showing risk of nocturnal and next day hypoglycemia that was identified in children hours after en-

gaging in physical activity durations longer than one hour [9,18,19]. Further risk has been identified when engaging in physical activity during late afternoon or early evening hours, which are common times for many adolescent sporting events or competitions [7,13,19]. Having a reliable tool available, such as accelerometers, would help the patient and their diabetes care team to identify these short and/or prolonged bouts more objectively and take necessary precautionary measures by providing an individualized plan of action before, during, and after said activity, thus allowing for improved glycemic control. Furthermore, to alleviate dysglycemia for those engaging in physical activity, recreationally or during school-based activities such as gym class or recess, knowing the type of activity the patient engaged in, at what intensity level, and for how long provides crucial information that allows for better adjustments to the patient's diabetes treatment regimen.

Another important factor to include that influences both glucose and activity is food intake. Activity and dietary intake data collected and analyzed together provide a more comprehensive view of the influences on glucose for diabetes management. Historically, certified diabetes clinical and educator specialists (CDCES) have relied primarily on written logs from patients to assess carbohydrate intake. However, more robust diet logs or even technologies such as smartphone apps could offer a more in-depth overview of food intakes such as total calories, fat, protein, and fiber intake. However, obtaining information about food intake is time consuming, which is a significant barrier for appropriate analysis of this information. With the availability of more advanced technology and having multiple tools available to record dietary intake, it is just as important to explore more advantageous ways to collect dietary information that a CDCES can analyze quickly for appropriate analysis.

Therefore, the purpose of this investigation was to test the feasibility of integrating a consumer-based physical activity monitor into an established pediatric specialty clinic to collect physical activity data for a minimum of three days. We also sought to determine the feasibility of collecting a complete diet log on the same three days in which the activity monitor was worn since carbohydrate and protein intake directly impact blood glucose, providing further insight for providers to make more informed recommendations for their patient's diabetes management plan. We hypothesized that full compliance in wearing the activity monitor and recording dietary intake for three days as instructed would be reached by >50% of the total sample, indicating feasibility.

2. Materials and Methods

2.1. Study Design

This study is a single cohort design to assess the feasibility of using an activity monitor in combination with diet intake data collection in children with T1D. The primary aim was to determine if children with T1D would wear an activity monitor while also tracking their diet for a minimum of three days using either a smartphone app or paper log. Feasibility was defined as >50% of the total sample reaching clinical compliance, as described below.

2.2. Participants

Children and adolescents aged 7 to 19 with T1D receiving care at the Wendy Novak Diabetes Center at Norton Children's and the University of Louisville were invited to participate in this study. Eligible criteria included individuals with a diagnosis of T1D and who agreed to the following: (1) Willing to wear a physical activity monitor during the study period. (2) Log diet for 3 days using either a paper log or a dietary app on their smartphone. (3) Provide daily glucose values from the same days in which diet was logged and the activity monitor was worn by allowing researchers access to their wireless CGM reports or on a paper log if no CGM is available. The study was approved by the University Institutional Review Board (Approval # 18.0713). Parental consent and child assent were obtained for all participants under 18 years of age.

2.3. Study Procedures

After obtaining assent and/or consent, each participant was provided a Fitbit Charge 2 physical activity monitor and the option to utilize a paper log or a mobile application to collect diet information. Clinical chart data at consent and during the study period were collected, including demographic information, HbA1c measurements on record <1 month in which activity monitor was worn, next available HbA1c measurement on record following retrieval of activity monitor, and if applicable their exported CGM, glucose meter, and insulin pump data covering the same timeframe that the activity monitor was worn.

Each participant was also provided a unique email and password combination to create an account on Fitbit.com. The account was connected to the Fitbit provided to each participant throughout the study duration. Participants were given the associated email/password so that they could log in to the Fitbit.com user account to log their diet if they did not want to turn in a paper copy and use the online dashboard and associated mobile applications. All participants were instructed to log their diet a minimum of 3 days at the same time they wore the activity monitor, insulin pump (if applicable), and CGM. Three days was chosen for clinical feasibility since it was determined by medical staff that having at least 3 days of a complete diet and activity habits to review would be adequate to make informed decisions regarding dietary recommendations and insulin adjustments to improve diabetes management.

Compliance was determined for each introduced measure including the diet log and activity monitor. In order to be compliant with the activity monitor, participants had to have a minimum of 3 days with at least 10 hours or more of wear time while awake. Dietary compliance was determined if participants recorded their diet for a minimum of the 3 days that they also wore the activity monitor. Clinical compliance was defined as the number of participants who were compliant with all measures while also having adequate glucose recordings using either a CGM, insulin pump, or on the diet log. These variables were chosen because they are collected during routine standard of care visits with their diabetes care team due to their known influence on blood glucose.

2.4. Data Analysis

All data were exported into an Excel spreadsheet for analysis using SPSS. Chi-square tests were used for dichotomous variables coded according to compliant (1) or non-compliant (0) with activity monitor only, diet only, or both (clinical compliance). As previously stated, feasibility was defined as >50% of the total sample reaching clinical compliance. Since there was an uneven distribution of sample sizes between groups, a Kruskal–Wallis non-parametric test of independent samples was used to compare average daily glucose for those in compliance with those who were not. A normality test indicated HbA1c was shown to follow a normal distribution, so a paired samples *t*-test was used to test for differences in HbA1c within each group.

3. Results

A total of 57 children and teenagers between the ages of 7 and 19 were enrolled in the study and included in the analysis. Participant demographics for the entire sample as well as comparisons of compliant vs. non-compliant individuals are presented in Table 1. Over the study period, 84% of participants were compliant with activity monitoring and 63% successfully recorded their diet for at least 3 days. When looking at clinical compliance, there were a total of 36 participants (63%) who completed both on the same days in which they wore their CGM, or recorded glucose numbers on the diet log (Table 2). Chi-square results indicated significant compliance for activity tracking ($p < 0.001$), diet logs ($p = 0.04$), and overall clinical compliance ($p = 0.04$). A Kruskal–Wallis non-parametric test of independent samples showed no significant difference in average daily glucose or HbA1c between groups. However, within the compliant group, a paired samples *t*-test indicated a decreasing trend that nearly reached significance ($p = 0.09$) was observed in HbA1c levels, which went from 8.19 $\pm$ 1.25% to 7.84 $\pm$ 1.13% after receiving a summary of

results in the form of daily activity and glucose graphs. Figure 1 shows a single-day graph created using Excel of a compliant participant as an example, with hourly intensity values (orange line) indicated on the left side of the y-axis and glucose measures obtained from the CGM (black line) on the right side of the y-axis.

Table 1. Demographic characteristics for all participants and separated by compliancy.

Characteristics	Enrolled $n = 57$	Compliant $n = 36$	Non-Compliant $n = 21$
Age, years	14 ± 3	13 ± 2.5	14 ± 3.5
HbA1c (%)	8.20 ± 1.30	8.19 ± 1.25	8.21 ± 1.43
Gender	Male: 36 Female 21	Male: 24 Female 12	Male: 12 Female 9
Race/Ethnicity	White: 49 (86%) Black: 5 (9%) Latino: 3 (5%)	White: 32 (88%) Black: 2 (6%) Latino: 2 (6%)	White: 17 (81%) Black: 3 (14%) Latino: 1 (5%)
BMI (Z-Score)	65.95 ± 23.41	65.89 ± 25.03	66.05 ± 18.47
T1D Diagnosis (Months)	52.77 ± 64.26	60.00 ± 73.48	40.86 ± 42.69
Insulin Pump Use	35 (61%)	21 (58%)	14 (67%)
Insurance Type	Private: 49 (84%) Medicare/Medicaid: 6 (12%) None: 2 (4%)	Private: 35 (97%) Medicare/Medicaid: 0 (0%) None: 1 (3%)	Private: 14 (67%) Medicare/Medicaid: 6 (28%) None: 1 (5%)
CGM Use	46 (81%)	27 (75%)	18 (86%)
Glucose (Avg)	185.46 ± 34.03	184.72 ± 32.95	188.20 ± 40.50
Daily Steps	10328.35 ± 3741.44	10752.83 ± 3338.98	9152.29 ± 4631.04 †
Vigorous Activity (mins.)	23.83 ± 22.78	24.34 ± 22.41	22.42 ± 23.88 †
Moderate Activity (mins.)	32.77 ± 20.49	34.74 ± 21.87	27.32 ± 17.74 †
Light Activity (mins.)	235.75 ± 68.51	253.20 ± 65.84	187.51 ± 50.86 †
Sedentary (mins.)	846.48 ± 244.53	794.29 ± 217.97	991.01 ± 267.18 †

†: $n = 13$ (number of participants compliant with activity monitor but not diet log). Abbreviations: HbA1C = glycated hemoglobin; T1D = Type 1 Diabetes; CGM = continuous glucose monitor; BMI = body mass index.

Table 2. Results of compliance.

Compliance Metric	Yes (%)	No (%)
Activity Monitor	48 (84%)	9 (16%)
Diet Record	36 (63%)	21 (37%)
Clinically Compliant	36 (63%)	21 (37%)

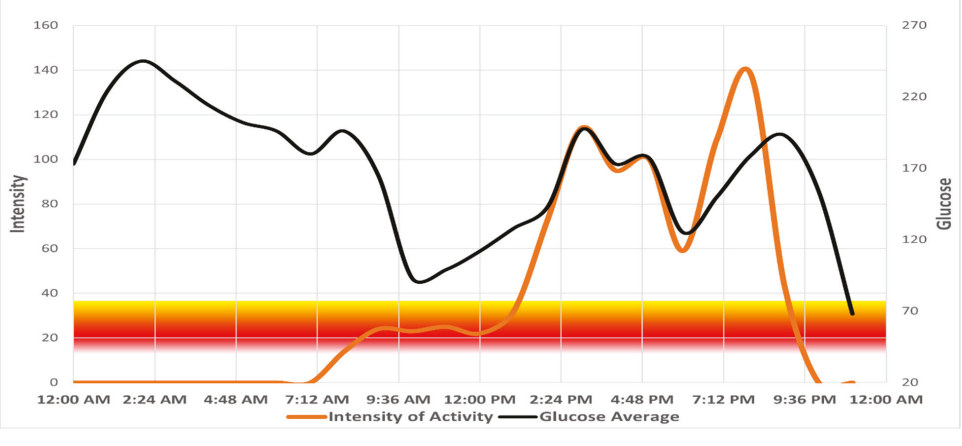

Figure 1. Graph of single day hourly averages of activity monitor and CGM measures. Intensity of activity values indicated on left side of *y*-axis and glucose measures obtained from CGM on right.

4. Discussion

This study sought to test the feasibility of incorporating activity monitors and diet logs as a form of mobile data collection in an established pediatric diabetes specialty clinic. Our intent was not to intervene with current medical recommendations, but simply to establish whether or not a convenience sample of a clinical population would wear an activity monitor during waking hours and also log their diet for a minimum of 3 days either on paper or by using a Fitbit account created specifically for them. We found that in this population gathering diet and physical activity data using wearable technology is feasible and could potentially have clinically relevant effects on improving health outcomes. However, the results also demonstrated that, while monitoring the daily physical activity of pediatric patients was feasible, consistent dietary intake data collection had a lower compliance rate with the children in this study. Given this is a population that typically must monitor diet intake relatively closely, it does raise the question of whether this modality would be successful in children with other health conditions.

The primary reason for those who did not reach clinical compliance was, indeed, due to a lack of dietary logs. Even though 84% of our study sample were compliant with wearing the Fitbit as instructed, only 63% recorded a complete diet for at least three days. Additional investigations regarding this aspect of the protocol may need more validation with research studies looking at reliable ways to collect such information. However, with such a large percentage of the subjects complying with wearing a physical activity monitor, this study would indicate that incorporating a wearable activity monitor as a vital sign in clinical practices to collect additional health information is not only feasible but also practical considering the benefit potential.

A recent study from Coleman et al. examined the validity of an exercise vital sign for use in an outpatient electronic medical record and reported a high discriminate validity when incorporating self-reported measures of weekly moderate-to-vigorous physical activity into patient records during routine clinical visits [1]. However, when compared to other studies with similar demographics using more objective measures, such as accelerometers, the study authors acknowledged that the total minutes being reported by their sample may have been overestimating the total number of minutes spent in moderate-to-vigorous physical activity. If used with more reliable objective measures, this type of exercise vital sign would provide more information regarding physical activity behavior that could assist in the treatment of certain clinical populations, such as T1D, while also helping patients to better understand the impact daily physical activity can have on their body and diabetes management. Prior studies among general populations only investigated physical activity benefits and counseling outside a typical clinical setting, or accumulated amounts using self-reported measures [20,21]. Additionally, studies look at the benefits of physical activity broadly. Therefore, it is important to individualize physical activity counseling to the patient's needs.

To our knowledge, this is the first study to explore the implementation of activity monitoring into standard clinical practice and test whether or not it would be feasible to use with pediatric patients. Prior studies have looked into the feasibility of a physical activity and/or exercise intervention to determine if children with T1D would adhere, but none have included measures that would also serve as a vital sign within medical records such as data from consumer-based physical activity monitors. Marrero and colleagues conducted a 12-week home-based intervention that included unsupervised moderate-to-vigorous physical activity routines using videos. Not only did they find this to be a safe and effective approach in which children would comply, but they also reported a reduction in HbA1c following the intervention [22]. In contrast, another investigation by Wong et al. found no change in HbA1c following 12 weeks of a home-based exercise intervention that also relied on video instruction and was unsupervised [23]. They attributed the lack of significant findings to a small sample size and possible low adherence since all the reported activity was completed in phone interviews in which researchers relied on young children to self-report how much moderate-to-vigorous physical activity they accumulated each

week [23]. Only one study was identified that investigated the use of an accelerometer as a tool included as part of diabetes management. An investigation by Stenerson et al. tested an algorithm created from a simulation study by their group [24] that included data points from an accelerometer combined with a heart rate monitor as a form of threshold-based insulin pump suspension for insulin delivery. After identifying a potential accelerometer-augmented pump suspension algorithm, they further tested its effectiveness in reducing the incidence of exercise-related hypoglycemia in a small sample of 18 children playing soccer. They did not find significant differences in exercise-associated hypoglycemia compared to subjects on their usual basal rates, but acknowledged that a larger sample size may have achieved statistical significance [25]. Further, the algorithm was developed using a sample that was instructed to "go about their everyday activities" and not specific to exercise or large bouts of moderate-to-vigorous activity like what was completed in the effectiveness pilot study to test the same algorithm [24,25].

In a secondary analysis, we compared HbA1c for those who are compliant compared to non-compliant. Surprisingly, we found there to be a decreasing trend for those who were in full compliance with wearing the activity monitor and recording dietary intake. This was unexpected due to the small sample size but shows promise as future studies will look at the impact activity monitors may have in encouraging behavior change and provide additional framework within the recommendations for diabetes management. Doing so would help diabetes providers and staff to provide more informed guidance to their patients when it comes to managing T1D by having more reliable information regarding daily activity habits and intensity levels. It would also assist in the recommendations they would provide for carbohydrate intake and insulin adjustments prior to exercise or participation in recreational sports. The results of this study will allow researchers to further evaluate its possible integration into the health management of children with T1D. Future studies should look into the effectiveness of providing activity monitoring as part of routine medical care and a more holistic team approach when making adjustments to carbohydrate and insulin needs.

When it comes to the potential out of pocket costs to patients, activity monitor price points have a wide variety of ranges depending on not just the specific brand, but also individual models they provide. Smart watches are beginning to explore incorporating glucose monitoring abilities, which may help overcome this obstacle, but if still required to pay out of pocket, some patients may need assistance financially. Some insurers are already utilizing accelerometers within their existing plans offered to employees, as well as strategies to deploy them, but, to our knowledge, most plans are not providing coverage for these devices as part of their plans. Research has also shown that people in general would be more willing to try consumer-based activity monitors if they were provided to them by their primary care doctor's office, helping them to incorporate these devices into their daily lives [26].

Limitations to this study include the lack of a control group, the small sample size, and recruiting a very specific population that included only children with T1D. However, this study demonstrates that it would be feasible to monitor daily physical activity and diet using consumer-based devices instead of relying on patient self-reporting during appointments with their clinician. Other studies have established accelerometer data to be more accurate than self-report measurements of physical activity [3,27]. It is also important to note the added value this tool could offer if used by competitive athletes to improve glycemic control and performance while keeping them safe, which cannot be overstated enough. When used in conjunction with current diabetes management devices and adequate nutrition, ideal metabolic set points could be easier to achieve during sports and competitive activities, which would enhance overall performance while lessening the risk of severe hyper- and/or hypoglycemia. Future studies should investigate the possible incorporation of this technology into the health management of T1D. It is also important that this technology be explored in all clinical populations, including routine annual wellness visits with a primary care physician. More robust investigations are

also needed for validating the use of wearable activity monitors beyond three days, since research suggests a minimum of four days with at least ten hours of wear time during waking hours for the reliable determination of weekly physical activity behaviors. This would be ideal for general populations as a preventative measure and for the management of co-morbidities for patients with chronic disease.

5. Conclusions

This study highlights the feasibility and potential value of obtaining objective activity data that are more reliable and accurate as compared to information that is traditionally obtained by self-report or not at all. Consumer-based devices appear to be a feasible way to obtain physical activity and diet information from children with T1D. There is now overwhelming evidence of the known benefits of physical activity on cardiovascular health, mental health, and insulin sensitivity; therefore, physical activity should be considered a vital sign and be incorporated into patients' medical record just like blood pressure and BMI [2,5]. Future studies need to work on the incorporation of this technology into diabetes care management for people of all ages and expand on these findings by looking into the health benefits of long-term changes in activity behaviors when incorporated in healthcare settings. By doing so, it is possible that diabetes management providers and staff may identify possible trends in glucose levels with real-world data providing feedback to also help make more informed decisions about changes in a patient's care or treatment plan.

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Review

Can Resistance Exercise Be a Tool for Healthy Aging in Post-Menopausal Women with Type 1 Diabetes?

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Abstract: Due to improvements in diabetes care, people with type 1 diabetes (T1D) are living longer. Studies show that post-menopausal T1D women have a substantially elevated cardiovascular risk compared to those without T1D. As T1D may also accelerate age-related bone and muscle loss, the risk of frailty may be considerable for T1D women. Exercise and physical activity may be optimal preventative therapies to maintain health and prevent complications in this population: They are associated with improvements in, or maintenance of, cardiovascular health, bone mineral density, and muscle mass in older adults. Resistance exercise, in particular, may provide important protection against age-related frailty, due to its specific effects on bone and muscle. Fear of hypoglycemia can be a barrier to exercise in those with T1D, and resistance exercise may cause less hypoglycemia than aerobic exercise. There are currently no exercise studies involving older, post-menopausal women with T1D. As such, it is unknown whether current guidelines for insulin adjustment/carbohydrate intake for activity are appropriate for this population. This review focuses on existing knowledge about exercise in older adults and considers potential future directions around resistance exercise as a therapeutic intervention for post-menopausal T1D women.

Keywords: exercise; physical activity; resistance training; menopause; women; type 1 diabetes

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1. Introduction

Menopause can be a difficult transition for women, as it can have an impact on several aspects of physical health, in addition to affecting the quality of life. Several studies show that exercise and physical activity may help manage many of the physical symptoms experienced during and after menopause [1–3]. In addition, being active is known to improve functional fitness (the ability to perform daily activities of living) and ameliorate the quality of life [4,5]. Women with type 1 diabetes (T1D) may experience worse health outcomes with respect to cardiometabolic [6] and musculoskeletal health [7,8] with menopause than women without diabetes; however, they also have greater barriers to exercise due to their condition, such as fear of hypoglycemia [9]. Resistance exercise may be a promising approach for this population due to its specific impact on musculoskeletal [10,11] and cardiometabolic health [12,13] as well as its protection against age-related frailty [14]. In addition, resistance exercise may cause less decline in blood glucose during exercise than aerobic exercise [15]. There are currently no exercise studies involving post-menopausal women with T1D. This review discusses how exercise, and in particular resistance exercise, may be able to improve the physical and mental well-being of women with T1D as they age, and demonstrates the need for more research in this area.

2. Menopause and its Impact on Women's Physical Well-Being

Menopause is the permanent cessation of menstruation, typically occurring naturally in a woman's late 40s or early 50s. It is preceded by a 2–10-year period of perimenopause, during which the ovaries gradually produce less estrogen and progesterone. Menopause occurs when the ovaries stop releasing eggs [16]. These decreases in estrogen and progesterone levels are often associated with a variety of symptoms and conditions [17], the incidence and severity of which are highly variable [18]. In addition to the commonly identified hot flushes experienced by most women, musculoskeletal, metabolic, and cardiovascular complications, among others, have been widely reported after menopause.

A decline in muscle mass and strength, also known as sarcopenia, often occurs along with, and may be partly caused by, the decrease in estrogen that characterizes menopause [19]. In addition, low physical activity and age-related increases in oxidative stress and inflammation are among the greatest contributing factors for sarcopenia in post-menopausal women [19]. Menopause is also a critical period of change in bone mass and strength, which sets the stage for the development of osteopenia and osteoporosis, along with increased susceptibility to fractures [20]. Declines in bone mineral density (BMD) and a rapid phase of bone loss over the menopause transition [21] are well documented. The high prevalence of these musculoskeletal complications in post-menopausal women leads to higher incidences of falls and fractures, frailty, and subsequent morbidity and mortality in this population [8]. It needs to be noted that in addition to menopause, hyperglycemia-induced oxidative stress and accumulation of reactive oxygen species and advanced glycation end products also play roles in bone fragility by compromising bone collagen mineralization and, ultimately, bone strength, increasing marrow adiposity, and releasing inflammatory factors and adipokines from visceral fat which can potentially alter the function of osteocytes [22].

The prevalence of metabolic syndrome also increases with menopause [23]. The metabolic syndrome refers to the co-occurrence of several interconnected factors such as insulin resistance, obesity, atherogenic dyslipidemia, hypertension, and endothelial dysfunction, which increase the risk of developing cardiovascular disease (CVD) [24,25]. Menopause is often associated with changes in weight and body composition such as an increase in visceral abdominal fat deposition [26]. Alterations in lipid levels [27], such as increases in triglycerides and low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL-C), are among other CVD risk factors associated with menopause [23]. Increased risk of insulin resistance [23] and type 2 diabetes [28] as well as hypertension [29] have also been linked to menopause. These metabolic changes that emerge with estrogen deficiency after menopause may explain some of the elevated CVD risks in post-menopausal women [23].

3. Role of Exercise in the Management of Menopausal Symptoms

The pervasive burden of menopausal symptoms and complications across a wide array of health outcomes can have significant impacts on women's quality of life [30–32]. As such, the management of symptoms in this population is essential. Regular exercise and/or physical activity is a safe, non-pharmacological approach to the management of several of these symptoms as it has been shown to decrease or alleviate many of them [3,33,34]. Table 1 provides a detailed summary of the studies examining the effects of physical activity and exercise on the management of musculoskeletal and cardiometabolic symptoms and quality of life in post-menopausal women.

Table 1. Changes in musculoskeletal and cardiometabolic parameters and quality of life in response to physical activity, and aerobic and/or resistance exercise interventions in post-menopausal women.

Study	Number of Participants	Type of Physical Activity/Exercise	Intensity/Frequency	Program Duration	Outcome
STUDIES INVOLVING AEROBIC EXERCISE AND UNSPECIFIED PHYSICAL ACTIVITY					
Juppi et al. 2020 [35]	234	Habitual physical activity (observational data)	At least 150 min of moderate-to-vigorous PA/week, ≈ 21 min/day	Women were followed from peri to early post menopause	While menopausal transition decreased lean body mass and index and appendicular lean mass and index, physical activity was positively associated with maintained lean body mass (r = 0.182) and appendicular lean mass and index (r = 0.235 and r = 0.238, respectively)
Mazurek et al. 2017 [36]	35	Physical activity	2 weeks moderate-intensity physical training program (2.5–5.0 METs, 3 times/day, 40–75 min/session, at 40–60% of MHR) followed by 3 months of organized home-based physical activity targeting all major muscle groups	2 weeks and 3 months	Physical activity reduced systolic and diastolic blood pressure, and reduced BMI, waist-to-hip ratio, and LDL-C as compared to baseline (data provided as figures). Among participants with organized physical activity, 40.6% of women met the baseline criteria of metabolic syndrome. After two weeks of physical exercise, this percentage decreased to 18.7%, mainly due to the reduction in the above-mentioned risk factors
Hagner et al. 2009 [37]	168 (pre-, peri-, and post-menopausal women)	Aerobic exercise	Moderate-intensity Nordic walking program, three 90-minute sessions, average heart rate of 100–140 bpm	12 weeks	Exercise improved VO_2 max, reduced BMI, waist circumference, and total fat mass, increased HDL-C, and deceased LDL-C, cholesterol, and triglycerides after 12 weeks in pre-, peri-, and post-menopausal women (except for HDL level in post-menopausal women)
Mason et al. 2013 [38]	117 (Exercise group) 98 (Control group)	Aerobic exercise	Moderate-to-vigorous intensity, 70–85% MHR, 45 min/day, 5 days/week	12 months	Intervention significantly preserved appendicular lean mass (%Δ: −0.12) and skeletal muscle index (%Δ: 0.4) compared to controls (%Δ: −1.2 and −1.5, respectively), despite no change in total lean mass
Mason et al. 2013 [38]	118 (Reduced-calorie diet group) 117 (Reduced-calorie diet with exercise)	Aerobic exercise	Moderate-to-vigorous intensity, 70–85% MHR, 45 min/day, 5 days/week	12 months	Exercise + diet attenuated the loss of appendicular lean mass and skeletal muscle index (%Δ: −1.4 and −1.0, respectively) as compared to the diet group (%Δ: −2.9 and −3.1, respectively)
Friedenreich et al. 2011 [39]	155 (Exercise group) 156 (Control group)	Aerobic exercise	Moderate-to-vigorous intensity, 45 min at 70–80% of HRR for at least half of the workout time, 5 times/week	12 months	Changes in all measures of adiposity were observed in exercisers relative to controls (the mean difference between groups: −1.8 kg for body weight; −2.0 kg for total body fat; −14.9 cm^2 for intra-abdominal fat area; and −24.1 cm^2 for subcutaneous abdominal fat area). Greater body fat losses were found with increasing volume of exercise (more than 225 min per week)
Gonzalo–Encabo et al. 2019 [40]	200 (High-dose group) 200 (Moderate-dose group)	Aerobic exercise	300 min a week (high dose) compared to 150 min a week (moderate dose) aerobic exercise	12 months 24 months	Significantly higher BMD (0.006 g/cm^2 higher after 12 months and 0.007 g/cm^2 higher after 24 months) in the high-dose exercise group as compared to moderate-dose exercise group
STUDIES INCLUDING RESISTANCE EXERCISE					
Teoman et al. 2004 [41]	41 (Exercise group) 40 (Control group)	Combined aerobic and resistance training program	Aerobic (65–70% MHR) and resistance training program 3 times a week for 6 weeks, starting at 30 min (including warm-up and cool-down) and increasing by 20 min over the training period	6 weeks	Significant improvements in all six markers of quality of life (physical mobility, pain, sleep, energy, social isolation, emotional status) in the exercise group as compared to control at the end of the 6th week of the training program
Villaverde–Gutiérrez et al. 2006 [42]	24 (Exercise group)24 (Control group)	Combined aerobic, resistance, flexibility, and relaxation exercises	2 supervised sessions of 30 to 60 min per week	12 months	The health-related quality of life significantly improved after the intervention in the exercise group (16.58 pre-exercise vs. 18.58 post-exercise), while it became significantly worse in the control group at the end of the study as compared to the beginning (11.96 vs. 14.12, respectively)
Figueroa et al. 2003 [43]	20 and 24 (Exercise groups with and without HRT, respectively) 22 and 28 (Control groups with and without HRT, respectively)	Combined resistance training and weight-bearing and non-weight-bearing aerobic exercise program	Resistance (free-weights with machines at 70–80% of 1-RM, 2 sets/day, 3 days/week). Aerobic (50–80% of MHR, 60–75 min/session, 3 days/week)	12 months	Combined exercise significantly increased total body (11.6%), arm (14.7%), and leg (11.0%) lean soft tissue mass, and decreased percentage of body fat (−22.9%), independent of HRT
Wooten et al. 2011 [44]	9 (Exercise group) 12 (Control group)	Resistance training program	10 exercises for 2 sets at 8-RM and the 3rd set to failure, 3 days/week	12 weeks	Significant reductions in total cholesterol (23.6%), LDL-C (28.5%), non-HDL-C (27.0%), and HDL_3-C (24.1%) in the exercise group as compared to control following 12 weeks of resistance exercise
Ogwumike et al. 2011 [45]	90 (Exercise group) 85 (Control group)	Endurance exercise program	10 stations of circuit training exercises at 60–80% of HRR, 3 days/week	12 weeks	Significant reduction in the waist-to-hip ratio between baseline and end of 12th week in both peri-menopausal (0.86 ± 0.08 vs. 0.71 ± 0.07) and post-menopausal (0.88 ± 0.06 vs. 0.77 ± 0.07) exercise groups, with no significant changes in the control groups
Conceição et al. 2013 [46]	10 (Intervention group)10 (Control group)	Resistance training program	3 sets of 8−10 repetitions at 50–70% of 1-RM, 3 times/week, with a progressive weekly increase in load	16 weeks	Intervention decreased the metabolic syndrome severity Z-score (p = 0.0162) while lowering fasting blood glucose (−13.97%), improving lean body mass (2.46%), decreasing body fat percentage (−6.75%), and increasing muscle strength (41.29% for leg press and 27.23% for bench press) in exercisers as compared to controls
Watson et al. 2018 [47]	43 (High-impact training group) 43 (Control: low-impact training group)	Resistance training program	Supervised twice weekly HiRIT, compared to home-based low impact training of identical frequency and duration	8 months	HiRIT effects were superior to controls for lumbar spine BMD (2.9 ± 2.8% vs. −1.2 ± 2.8%), femoral neck BMD (0.3 ± 2.6% vs. −1.9 ± 2.6%), femoral neck cortical thickness (13.6 ± 16.6% vs. 6.3 ± 16.6%), height (0.2 ± 0.5 cm vs. −0.2 ± 0.5 cm), and all functional performance measures (p < 0.001)
Gómez–Tomás, et al. 2018 [48]	18 (Intervention group) 20 (Control group)	Resistance training program	6 exercises for whole-body training involving major muscle groups, 3 sets of 10 repetitions, 3 days/week	12 months	Exercise decreased weight (1.31 ± 1.49 kg decrease), waist circumference (2.67 ± 2.61 cm decrease), total cholesterol (15.72 ± 46.47 mg/dL decrease), LDL-C (16.77 ± 41.74 mg/dL decrease), and C-reactive protein (0.81 ± 1.78 mg/L decrease). No significant difference was found in HDL-C or triglycerides
Bea et al. 2010 [49]	65 (Exercise group) 32 (Crossovers) 25 (Sedentary controls)	Resistance training program	Supervised 8 exercises targeting major muscle groups, 2 sets of 8 repetitions at 70–80% of 1-RM, 3 times/week, plus progressive weight-bearing activity	6 years	Weight gain occurred in a stepwise fashion over the 6 years with controls gaining the greatest amount of weight (2.1 ± 4.3 kg controls, 0.7 ± 4.4 kg crossovers, 0.4 ± 6.2 kg exercisers). Similar to weight, gain in total body fat was also significant between baseline and 6 years in controls only (1.9 ± 4 for controls, 0.4 ± 3 for crossovers, and 0.3 ± 6 for exercisers)

PA: physical activity; METs: metabolic equivalents; MHR: maximal heart rate; bpm: beats per minute; HRR: heart rate reserve; 1-RM: one-repetition maximum; HRT: hormone replacement therapy; HiRIT: high-intensity resistance and impact training; BMI: body mass index; BMD: bone mineral density; VO_2 max: maximal oxygen consumption; HDL-C: high-density lipoprotein cholesterol; HDL_3-C: high-density lipoprotein 3 cholesterol; LDL-C: low density lipoprotein cholesterol.

3.1. Musculoskeletal Effects of Exercise

While the menopausal transition is associated with decreases in muscle mass at multiple anatomical levels, habitual participation in physical activity can maintain skeletal muscle mass during this transition [35]. For example, one moderate-to-vigorous intensity aerobic exercise program was able to preserve appendicular lean mass and skeletal muscle index (the ratio of skeletal muscle mass to height), despite no change in total lean mass in post-menopausal women [38]. The inclusion of resistance exercise, however, may be essential in increasing, rather than just preserving muscle mass and strength in this population. A training program consisting of both resistance and aerobic exercise significantly increased total body and regional lean soft tissue mass and decreased percentage of body fat in post-menopausal women [43]. A systematic review and meta-analysis, however, demonstrated that muscle strength and muscle function can be improved more than muscle mass by exercise programs such as aerobic training and resistance training in older adults with sarcopenia [50]. Resistance training improves neuromuscular adaptations including increased muscle strength [50], which would be particularly beneficial for post-menopausal women who experience a significant age-related decline in muscle force [51].

Resistance exercise, and in particular high-intensity resistance exercise, can also be an effective method to help prevent and reduce the severity of osteopenia and osteoporosis in aging women. Women are at a significantly higher risk of developing osteopenia and osteoporosis than men, as they have lower peak bone density, along with an earlier onset and faster rate of bone loss [52]. High-intensity resistance and impact training significantly improves bone density, functional performance relevant to falls, and decreases markers of frailty, while increasing lumbar spine and femoral head BMD in post-menopausal women [47].

The volume of exercise performed may also be a key factor in the impact of activity on bone density. While no difference was found in bone mineral content, one study found significantly higher BMD after a year in the post-menopausal women assigned to a higher dose of aerobic exercise as compared to those in a lower dose group [40]. It should be noted that the "low-dose" group was actually performing the recommended 150 min per week of moderate activity, indicating that post-menopausal women may, in fact, require more exercise than what is currently recommended in order to increase BMD.

While many studies vary in the exercise protocol being tested, a review of 43 randomized control trials examining exercise impacts on bone density in post-menopausal women found that the most effective intervention for improved BMD in the spine was a combined resistance and aerobic training program, while the most effective intervention for hip and femur BMD was resistance training [53]. It is important to note, however, that while the relationship between exercise and increased BMD is well established, the link between exercise and maintained whole bone strength is less clear [54]. Existing evidence around this topic relies mostly on a combination of exercise and hormone replacement therapy (HRT) [55], or nutritional supplements [56]. In general, these studies show that the combined effect of exercise and the added intervention (i.e., HRT and/or vitamin D) improve bone density in post-menopausal women and may improve whole bone strength immediately after intervention [55,56]. However, more research is needed on how exercise alone can influence menopause-induced decline in bone strength or metabolically-induced bone fragility, and whether improvements are maintained beyond the intervention period.

3.2. Metabolic and Cardiovascular Effects of Exercise

Regular exercise programs can be used as a means of weight management in post-menopausal women. For example, implementation of a moderate-intensity Nordic walking program resulted in reductions in total body fat, waist circumference, and body mass index (BMI) in pre- to post-menopausal women [37]. Similarly, another intervention study examining the effects of an endurance exercise program on central and abdominal adiposity in peri- and post-menopausal women showed a significant reduction in the waist-to-hip ratio in this population, without having an impact on BMI [45]. A yearlong moderate-

to-vigorous intensity aerobic exercise intervention also produced significant reductions in overall and abdominal adiposity in post-menopausal women, with greater decreases among those with a higher exercise duration [39].

Resistance exercise is also beneficial for weight and adiposity management in this population. In a randomized clinical trial involving sedentary post-menopausal women, a long-term resistance exercise program led to significant weight and body fat losses in this population, especially among those with a higher exercise volume and frequency [49]. Similarly, in addition to a reduction in body fat percentage, one study showed that resistance exercise can decrease the metabolic syndrome severity Z-score with a concomitant lowering of fasting blood glucose and improvement in lean muscle mass in post-menopausal women [46]. The metabolic syndrome severity Z-score is a composite index of the severity of metabolic syndrome, taking into account the contributions of each component of the metabolic syndrome [57].

In addition to improvements in body composition, regular exercise and physical activity are beneficial for lowering other cardiovascular and metabolic risk factors. In an observational study during 458,018 woman-years of follow-up, walking, and total physical activity scores (based on weekly energy expenditure calculated in metabolic equivalents (MET)) were negatively correlated with risk factors for type 2 diabetes, especially BMI, in Caucasian post-menopausal women [58]. Similarly, while diabetes incidence was positively associated with BMI and the waist-to-hip ratio, it was negatively correlated with the frequency of both moderate and vigorous physical activity (self-reported and based on MET) in a cohort of 34,257 post-menopausal women [59]. Likewise, in a cross-sectional study, a lower risk of type 2 diabetes and a more favorable cardiovascular profile were found with higher levels of habitual physical activity (assessed by a digital pedometer), specifically walking, in a population of 292 middle-aged women, regardless of the menopausal status [60].

In line with the above evidence, a moderate-intensity physical training program followed by home-based physical activity targeting all major muscle groups reduced systolic and diastolic blood pressure, in addition to reducing BMI, waist-to-hip ratio, and LDL in sedentary post-menopausal women [36]. Similarly, resistance training led to significant reductions in total cholesterol, LDL-C, and non-HDL-C in this population [44]. Furthermore, a study of progressive resistance training showed that this activity could decrease weight, waist circumference, total cholesterol, LDL-C, and C-reactive protein in post-menopausal women, supporting the anti-inflammatory and the cardiometabolic benefits of exercise and physical activity in this population [48].

Overall, resistance exercise seems to be of particular importance in post-menopausal women as it can increase muscle mass and strength, and hip and femur BMD. This is of high importance due to the loss of skeletal muscle mass and strength with aging, and increased risk of hip injuries and frailty after the menopausal transition. In addition, through affecting the metabolic syndrome risk factors and improving lipid profile [61,62], resistance exercise can be considered an optimal strategy for preventing CVD and subsequent morbidity and mortality in this population.

3.3. Effects of Exercise on the Quality of Life

Menopausal and post-menopausal women who are regularly active have higher health-related quality of life scores than their sedentary counterparts [63]. An exercise intervention consisting of combined resistance and aerobic training found significant improvements in all six markers of quality of life (physical mobility, pain, sleep, energy, social isolation, emotional status) in post-menopausal women [41]. Longer-term interventions have produced similar results, with significant improvements in health-related quality of life in rural post-menopausal women who underwent a year-long customized exercise program of combined resistance, aerobic, flexibility, and relaxation exercises [42]. In addition to enhancing the quality of life directly, resistance training can also allow for a better quality

of life indirectly, through promoting beneficial effects on muscles, bone, and adipose tissues in this population, as discussed earlier [64].

4. Type 1 Diabetes

Type 1 diabetes (T1D) is an auto-immune disorder in which the beta cells of the pancreas are destroyed, resulting in chronic insulin deficiency [65]. The absence or near-absence of endogenous insulin leads to hyperglycemia (high blood glucose), which must be treated by exogenous insulin, either through injections or an insulin pump. It is challenging to maintain continuously the balance of carbohydrate intake, physical activity, and exogenous insulin, and hypoglycemia (low blood glucose) often occurs [65]. People with T1D share many of the same benefits from exercise as their non-diabetic counterparts [66], in addition to the exercise-specific effects in this population such as reduced insulin requirements, reduced insulin resistance, and favorable changes in lipids [66].

4.1. Menopause in Women with T1D

As discussed earlier, menopause is associated with a wide range of symptoms across a wide array of health complications among women without diabetes. Throughout the life course, women with T1D tend to experience more complications related to the menstrual cycle and its cessation, many of which have negative consequences for cardiovascular and overall health. For example, compared to those without diabetes, women with T1D often experience delayed menarche and irregular menstrual cycles [67–69], which have been associated with increased coronary artery calcification (CAC) [70] and increased risk of fatal and non-fatal coronary heart disease (CHD) [71]. Because of such pre-existing conditions, it is reasonable to suspect that menopause would lead to more severe health consequences in women with T1D. There is, however, a need for a great deal more research in this understudied area.

Although T1D per se may not affect the age of onset of menopause [72,73], women with more severe microvascular complications of diabetes (such as retinopathy, neuropathy, and nephropathy [74]) are at greater risk of earlier menopause compared to other women with T1D and their non-diabetic counterparts [72,75]. Of note, lower age of menopause has been correlated with a higher risk of CVD and mortality [76,77]. This premise is also supported by data from a longitudinal study (n = 636) investigating the association between the menopausal transition and subclinical atherosclerosis in women with T1D, where higher CAC volume was found in this group as compared with non-diabetic women [6]. Moreover, differences in CAC volume between those with and without diabetes increased as women transitioned through menopause [6].

Compared to women without diabetes, those with T1D have greater excess risks of all-cause mortality, along with more fatal and non-fatal vascular events. The increase in risk with aging in women with T1D compared to women without diabetes is greater than the increase in risk experienced by T1D men compared to men without diabetes [78]. In particular, females with T1D are generally more insulin resistant [79], have more unfavorable changes in their fat distribution [80], and tend to develop a more atherogenic lipoprotein profile [81] with aging as compared to males with T1D. These metabolic risk factors, independently or together, put females with T1D at a significantly higher risk of developing CVD than their non-diabetic counterparts [82].

In addition to CVD, a significantly high risk of fractures is also reported in women with T1D. In a large (n = 334,266) population-based cohort study, a higher risk of fractures was reported in individuals with T1D compared to those without diabetes, particularly after the age of 40. The risk of hip fractures was greatest in the 80- to 90-year age bracket for both sexes, at 244.5 and 116.1 fractures per 10,000 person-years in women with and without T1D, and 76.7 and 59.6 fractures per 10,000 person-years in men with and without T1D, respectively [83]. Similarly, in another observational study, post-menopausal women with T1D were at least 12 times more likely to report an incident hip fracture than their non-diabetic counterparts [84]. In line with this report, a 15-year longitudinal study

(n = 10,981) showed that women with T1D had more falls, incident fractures, and osteoporosis as compared to non-diabetic women across the menopausal transition [85], which could be attributed to the lower BMD [86] or lower bone quality [87] in this population. Moreover, many of the menopausal conditions discussed above have been shown to negatively impact quality of life [63,88,89], although there is insufficient research directly considering the interaction between T1D and menopause on quality of life. Further research is, therefore, warranted in this area.

With the majority of research in the field focusing on type 2 diabetes, there is limited research on menopause in women with T1D. Further research is strongly needed to determine how T1D affects the presence, severity, and management of menopausal symptoms in this high-risk group. Given the importance of exercise and physical activity in the management of menopausal symptoms in women without T1D, it is reasonable to consider physical activity and exercise as practical strategies for the management of menopausal symptoms in women with T1D.

4.2. Exercise and T1D

Regular exercise (at least 150 min per week) is recommended in both adults with and without T1D to maintain a balanced and healthy lifestyle [90,91], by improving cardiorespiratory fitness, muscular strength [92], mental health [93], and quality of life [94]. In addition, exercise also lowers the risk of a variety of chronic conditions, such as type 2 diabetes [93], CVD [95], hypertension [96], and dementia [97], while slowing age-related decline in physical function [98]. In those with T1D in particular, exercise and physical activity are associated with not only greater longevity [99,100], but also a decrease in the frequency and severity of diabetes-related complications [101–103].

People with T1D who exercise regularly have lower all-cause (hazard ratio 0.66) [104] and cardiovascular mortality. One large (n = 2639) longitudinal study of people with T1D showed that the 10-year cumulative cardiovascular mortality rates were 4.7% in low (<10 MET-h/week), 1.9% in moderate (10–40 MET-h/week), and 1.8% in high (>40 MET-h/week) leisure-time physical activity participants, respectively. In addition, increased frequency of physical activity was associated with a lower risk of cardiovascular mortality, with rates of 5.5% in low (fewer than one session/week), 2.8% in moderate (1–2 session/week), and 2.2% in high (more than 2 sessions/week) exercise frequency groups [105].

Where CVD is concerned, a cross-sectional study on males and females with (n = 105) and without (n = 176) T1D (mean age 39 $\pm$ 14 vs. 38 $\pm$ 12 years, respectively) found that three or more episodes of self-reported vigorous physical activity per week were associated with reduced CVD risk through the preservation of small artery compliance, independent of age, sex, and diabetes status [106]. Greater large artery compliance and pulse rate, however, were significantly associated with the frequency of physical activity only in the T1D group [106]. In addition, a prospective cohort study (n = 2185) of males and females (mean age 32.7 $\pm$ 10.2 years) with T1D found an inverse association between self-reported baseline physical activity and all-cause mortality in both sexes. Incident CVD, however, was inversely correlated with baseline physical activity only in women in the longitudinal analysis (n = 1063). Both walking distance and total physical activity were inversely associated with prevalent CVD in both sexes in the cross-sectional analysis (n = 1690) [104].

Similarly, in a cross-sectional study of 18,028 adults (mean age 33.8 $\pm$ 7.5 years) with T1D, an inverse relationship was found between self-reported physical activity and several CVD factors, including BMI, hypertension, and dyslipidemia [107]. Self-reported physical activity was also negatively correlated with hemoglobin A1c (HbA1c), diabetic ketoacidosis, microalbuminuria, and retinopathy in this population [107]. Another cross-sectional study of 1945 males and females (mean age 38.5 $\pm$ 12.3 years) with T1D showed less leisure-time physical activity as well as low-frequency and low-intensity leisure-time physical activity in those with diabetic nephropathy and proliferative retinopathy than in those without these complications [108]. In particular, low-frequency (one session/week)

and low-intensity physical activity were associated with diabetic nephropathy, while low-intensity physical activity was associated with proliferative retinopathy and CVD in this cohort of T1D participants [108]. It should be noted that although these findings suggest the beneficial role of higher frequency and/or intensity of physical activity in the management of diabetes complications, the hindering impact of these chronic disabling complications on physical activity level in this population should not be overlooked.

Exercise and physical activity are also associated with more favorable body composition, BMI, BMD, and osteopenia in those with T1D. A cross-sectional study on 75 males and females with T1D (mean age 43.5 $\pm$ 10.5 years) and 75 counterparts without diabetes (mean age 40.1 $\pm$ 12.8 years) showed that having an active lifestyle (physical activity level $\geq$ 1.7) was associated with a lower BMI, a lower total and truncal fat mass, as well as a lower waist circumference as compared to those with a more sedentary lifestyle [109]. Similarly, in an intervention study involving 24 males and females with T1D with osteopenia (mean age 17.1 $\pm$ 2) and 38 control individuals without diabetes (mean age 16.9 $\pm$ 1.8), a three-month aerobic exercise program (on ergometer with constant speed and resistance, 70 min including warm-up and rest, 3 times/week) in the T1D group significantly increased BMD and serum procollagen type 1 N-terminal propeptide, reflecting improved bone formation [110].

Being physically active, however, can be challenging for those with T1D. At the onset of moderate-intensity aerobic exercise, uptake of glucose into active muscle cells increases. In people without diabetes, insulin secretion decreases, resulting in an increase in the glucagon:insulin ratio and increased hepatic glucose production, precisely matching the increased glucose utilization by muscles [111]. Although the same increase in muscle glucose uptake occurs in people with T1D, insulin levels are not regulated endogenously, and glucagon secretion is often impaired [112], so the glucagon:insulin ratio cannot increase. This imbalance leads to an insufficient increase in hepatic glucose production to match the increased glucose uptake into the skeletal muscle, subsequently inducing hypoglycemia, particularly during a longer duration of exercise [113]. These hypoglycemic episodes present a considerable barrier to exercise for people with T1D [9].

Catecholamines also play an important role in glucoregulation during exercise, particularly in very intense exercise. The onset of exercise triggers a release of catecholamines [114], which increases in proportion to the intensity and duration of exercise and in turn increases hepatic glucose production. In people with T1D, the increased hepatic glucose production can help override the insufficient change in glucagon:insulin ratio, thus reducing the risk of hypoglycemia during activity. The large catecholamine-induced increase in glucose production during brief, near-maximal intensity exercise can lead to hyperglycemia [115]. In those without T1D, insulin levels rise in response to the excess glucose and return blood glucose to normal. Without an increase in exogenous insulin, however, hyperglycemia can persist for hours after brief, intense exercise in people with T1D [116].

4.2.1. Sex-Related Differences in Response to Exercise

In addition to the differences in response to exercise between those with and without T1D, there may also be sex-related differences in response to exercise. For example, females and males use similar fuel sources for energy at rest [117]. However, during prolonged submaximal exercise, females rely more on lipolysis of myocellular triacylglycerol than males, who rely more on glycogen stores [118]. Furthermore, males transition to using carbohydrates as their main fuel source earlier in anaerobic exercise than females [119]. The lower reliance on carbohydrates for fuel in females is generally reflected in less depletion of hepatic and muscle glycogen after exercise, although this can vary according to the type and duration of exercise, and stage in females' menstrual cycles [120]. Following 60–90 min of isoenergetic moderate and hard-intensity exercise, women maintain blood glucose in a much tighter range than men, likely because of less depleted glycogen stores during exercise [121]. It should be noted, however, that most studies finding differences in fuel selection between males and females were focused on exercise in the fasting state [120].

There are also several hormone-related differences during exercise between females and males. Males tend to have a greater catecholamine response to similar levels of exercise [120]. Prior to menopause, females have a much higher level of estrogen, which contributes to the lower respiratory exchange ratio (i.e., greater reliance on lipids as a fuel source) during exercise [120]. Taken together, these hormonal differences create a reliance on different fuel sources between male and female participants [120]. While some of these differences are well-documented in individuals without T1D, exercise literature involving T1D participants is currently dominated by young fit males, bringing into question whether female participants may experience very different glucose trajectories during various types of exercise [122].

4.2.2. Age-Related Differences in Response to Exercise

In addition to these sex-specific differences, age also has an impact on the effects of, or responses to, exercise. Body composition, hormonal responses, cardiorespiratory fitness, and functional fitness are all affected by aging [123]. Aging causes changes in body composition such as decreases in lean body mass and bone density and increases in body fat and fat redistribution [124]. Hormonal changes such as decreased catecholamine response, and altered responses of growth hormone, cortisol, and glucagon also occur with aging [123]. In addition, aging causes reduced cardiorespiratory fitness, which is related to declines in peak oxygen uptake (VO_2 peak) [125]. Lastly, declines in functional fitness, due to increased body fat percentage, loss of muscle mass in the extremities, as well as loss of flexibility, agility, and endurance also occurs with aging [126], playing potential roles in the effects of exercise in aging adults. In adults with T1D, both aging and longer diabetes duration are associated with greater insulin requirements [127,128], which can make the creation of safety recommendations around excise more challenging in this population. To date, however, there has been a complete lack of studies involving older participants with T1D.

It appears that sex, age, and the presence or absence of T1D all play roles in the effects of, and/or responses to, exercise and physical activity. These physiological factors place post-menopausal women with T1D in a unique position, where the interplay between sex, age, menopausal symptoms, and T1D complications is concerned. Nonetheless, there are currently no exercise studies involving this high-risk population, and as such, their acute blood glucose responses to exercise, as well as their response to longer-term training are essentially unknown. It can be suggested, however, that due to the many benefits of exercise in post-menopausal women it should be prescribed in the management of symptoms in post-menopausal women with T1D. More research is needed in order to ensure that exercise, and in particular resistance exercise, can be used as a therapeutic intervention without compromising blood glucose management in this population.

5. Exercise in Post-Menopausal Women with T1D

Unfortunately, most of the studies examining the effects of exercise and physical activity on T1D complications were conducted with both male and female participants and there is, therefore, a lack of studies with only female participants. Sex-related differences in counter-regulatory hormonal responses such as catecholamines and growth hormone to exercise exist among those without diabetes [120]. This includes a greater catecholamine response to various types of exercise in males, and a different pattern of growth hormone release during exercise such as a more prolonged response in males as compared to a higher, but transient, response in females [120]. In addition to the hormonal differences, being female, by itself, is associated with lower odds of achieving recommended physical activity levels ($\geq$5 days/week) [129]. However, the impact that these factors may have on blood glucose responses to exercise in people with T1D is unclear.

A recent secondary analysis highlighted potential sex-related differences in blood glucose responses to exercise. It examined responses to a program including 7 resistance-based exercises (3 sets of 8 repetition maximum (RM), ~45 min) in individuals with T1D [122]

and found that female participants (mean age 29 ± 8 years) on average did not experience a decline in blood glucose during and after the resistance exercise session compared to male participants (mean age 34 ± 15 years) who experienced significant declines in glycemia. On the other hand, more female participants experienced post-exercise hyperglycemia than males in this secondary analysis [122]. Whether these observations reflect physiological differences in exercise responses or differences in behaviors related to diabetes management around exercise is currently unclear.

Despite such differences, current safety recommendations around exercise for individuals with T1D were developed using evidence from studies involving very few or no female participants, and almost uniquely younger individuals with T1D [123]. As such, the recommendations might not be appropriate for older females with T1D, such as those in the menopausal transition and post-menopause. Following these recommendations which were not developed or tested in studies of older T1D women might result in an increased risk of hypoglycemia, hyperglycemia, or greater fluctuations in blood glucose levels around exercise. Frequent hypoglycemia increases the risk of seizures and loss of consciousness [130], cardiac repolarization [131,132], all-cause mortality, and CVD [133]. Frequent hyperglycemia, on the other hand, can lead to increased HbA1c, and a subsequent increase in the risk of retinopathy and nephropathy [134,135], neuropathy [136], and all-cause morbidity and mortality from CVD and CHD [137]. Finally, greater glycemic variability can result in more endothelial dysfunction [138,139], increased oxidative stress, inflammation, and higher bone fragility [22,140,141], and classic CVD risk markers [142]. These adverse health outcomes underscore the importance of developing specific interventions and safety recommendations for specific populations.

Can Resistance Exercise Be the Answer to Healthy Aging in Post-Menopausal Women with T1D?

As nothing is known about blood glucose changes during exercise in post-menopausal women with T1D, there are no recommendations on how to maintain safe glucose levels in this high-risk population. In addition, as a result of improvements in diabetes care, there are more women with T1D reaching menopause, and living for many years post menopause than ever before. Ensuring equitable access to, and maximal benefits from exercise and physical activity in this population is therefore of high importance.

In this regard, resistance exercise may be a promising preventive therapy to maintain health and mobility, along with preventing frailty in this particular population. As discussed, resistance exercise causes improvements in muscle strength [143], muscle quality [11], and bone density [144]. It has also been argued that resistance training may be as effective or superior to other forms of exercise with respect to treating comorbidities associated with CVD such as sarcopenia, impaired glucose handling, and lipid metabolism [145]. Enhanced vascular condition, reduced resting blood pressure, improved body composition and mobilization of visceral and subcutaneous abdominal fat are among other cardiovascular benefits of resistance training [146]. It is therefore reasonable to consider resistance exercise as suitable for primary and secondary prevention of CVD [145]. In addition, resistance training has been associated with mental health benefits such as improvements in self-rated quality of life [147].

Although individuals with T1D may experience the same health benefits of resistance training as those without T1D, studies are extremely limited regarding the effects of resistance exercise with respect to glycemic variability in this population. While it is reported that aerobic exercise can increase the risk of hypoglycemia in T1D during activity, acute exercise studies indicate that anaerobic forms of exercise may reduce this risk [148]. Studies of resistance exercise in T1D showed that it is associated with greater blood glucose stability [149], and a lower risk of hypoglycemia during exercise [15] compared to aerobic exercise. A study comparing the acute glycemic effects of resistance exercise (3 sets of 7 exercises at 8-RM) and aerobic exercise (45 min of running at 60% of VO_2 peak) in physically fit individuals (mean age 31.8 ± 15.3 years) showed that plasma glucose decreased rapidly during aerobic exercise, while resistance exercise caused less initial decline in

blood glucose during the activity [15]. In addition, performing resistance exercise (3 sets of 7 exercises at 8-RM) prior to aerobic exercise (45 min of running at 60% VO_2 peak) attenuated the decline in blood glucose associated with aerobic exercise and improved glycemic stability throughout the exercise session [149], compared to when these exercises were performed in the reverse order.

The protective effects resistance exercise may offer against hypoglycemia would be mediated in part by catecholamines [150]. Because epinephrine response to exercise tends to diminish with age [150], older women may not benefit as much as others from the protective effect of elevated catecholamines against hypoglycemia. In addition, early evidence that resistance exercise may be associated with higher rates of nocturnal hypoglycemia [15] should be taken into consideration when conducting research with this population.

The Diabetes Canada Clinical Practice Guidelines [151] and the American Diabetes Association's position statement on exercise and physical activity in diabetes [152] both recommend the inclusion of regular resistance exercise for individuals with T1D. When combining aerobic and resistance exercise, the order in which the exercises are performed should also be taken into account as it can affect blood glucose levels in those with T1D [149]. However, as these recommendations are based on relatively young individuals with T1D, the effects of resistance exercise before or after an aerobic exercise session, or alone, in older adults with T1D and especially in post-menopausal women with T1D remain to be examined. Studies examining the acute effects of resistance exercise on blood glucose in this population are essential in order to ascertain its safety prior to implementing any type of long-term training study.

6. Conclusions

Despite the well-documented benefits of exercise, the full range of risks and benefits with respect to the health and wellness of post-menopausal women with T1D have yet to be studied. In addition, the majority of exercise studies were conducted on pre-menopausal women; thus, hormonal differences between pre-menopausal and post-menopausal women, which could play a significant role in fuel utilization and glucose response during exercise, have not been examined. In older adults, and in particular older women with T1D, the acute glycemic effects of exercise are unknown. Ascertaining these effects is essential to removing barriers to exercise and physical activity, such as fear of hypoglycemia and loss of control over blood glucose levels in older women with T1D. A greater understanding of the impacts of age, sex, and gender on the acute and training responses to exercise in post-menopausal women with T1D is necessary to reduce the burden of complications, prevent frailty, and improve quality of life in this high-risk population.

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Maximal Oxygen Uptake, VO_2 Max, Testing Effect on Blood Glucose Level in Adolescents with Type 1 Diabetes Mellitus

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Abstract: Assessing maximal oxygen uptake (VO_2 max) is generally considered safe when performed properly for most adolescents; however, for adolescents with type 1 diabetes mellitus (T1DM), monitoring glucose levels before and after exercise is critical to maintaining euglycemic ranges. Limited guidance exists for glucose level recommendations for the pediatric population; therefore, the purpose of this retrospective clinical chart review study was to determine the effects of VO_2 max testing on blood glucose levels for adolescents with T1DM. A total of 22 adolescents (mean age = 15.6 ± 1.8 years; male = 13, 59.1%) with a diagnosis of T1DM participated in a Bruce protocol for VO_2 max from January 2019 through February 2020. A statistically significant reduction in glucose levels between pretest (<30 min, mean = 191.1 mg/dL ± 61.2) and post-test VO_2 max (<5 min, mean = 166.7 mg/dL ± 57.9); $t(21) = 2.3$, $p < 0.05$) was detected. The results from this current study can help guide health and fitness professionals in formulating glycemic management strategies in preparatory activities prior to exercise testing and during exercise testing.

Keywords: maximal oxygen uptake; VO_2 max; blood glucose; type 1 diabetes mellitus (T1DM); adolescents; exercise testing; pediatric; clinical exercise

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1. Introduction

One of the tenets of the sports medicine field is to advance and integrate scientific research to provide educational and practical applications of exercise science and sports medicine. For individuals engaging in physical activity at any level, whether it is recreational physical activity or competitive sports, there is clear, scientifically based guidance regarding exercise testing and prescription for health and fitness professionals to employ with healthy individuals as well as those living with chronic illnesses [1]. One component of health-related physical fitness is cardiorespiratory fitness (CRF), the body's ability to perform large-muscle, dynamic, moderate-to-vigorous-intensity exercise for prolonged periods of time. Assessing the maximal oxygen uptake (VO_2 max) the body is able to use during exercise is an established exercise test for determining CRF and is more predictive of long-term survival than is any traditional risk factor or other measured physiologic parameter [2]. VO_2 max testing provides a measurement of the relative amount of oxygen consumption per an amount of work. For example, an improved VO_2 may allow one to run longer at the same speed or faster with the same relative effort [3].

The graded exercise test used to elicit VO_2 max is aggressive in nature to achieve a maximal response from the participant. Under stress conditions, the hypothalamus controls many hormone secretions to adjust glucose metabolism and energy production. Glucose secretion and uptake are under the control of nervous and hormonal factors such as catecholamines, cortisol, glucagon, growth hormone, and insulin, and all have an immediate impact [4]. Even though exercise testing is generally considered safe when

performed properly for most individuals, maximal- or vigorous-intensity exercise testing does pose some risk [5–8]. Specifically, for individuals with type 1 diabetes mellitus (T1DM), the risk of hyperglycemia in the initial portion of exercise testing and the risk for hypoglycemia following completion of testing both present themselves. Monitoring glucose levels before and after physical activity is fundamental to maintaining glucose levels in euglycemic ranges during and after exercise [9].

Unfortunately, understanding of safety parameters and the effect of CRF testing on adolescent populations is limited and in need of research [10]. Glucose level recommendations have yet to be established for adolescents diagnosed with T1DM who participate in VO_2 max exercise testing. Although a decrease in glucose may be expected throughout and immediately after exercise testing, a minimal pretest glucose setpoint has not been established to reduce the risk of hypoglycemia. Therefore, the purpose of this study was to examine the impact of VO_2 max testing on blood glucose levels for adolescents with T1DM.

2. Materials and Methods

2.1. Study Design and Setting

This cross-sectional, non-interventional, retrospective chart review study was conducted at a nationally certified pediatric diabetes care and academic medical center located in the Southeast region of the United States. At this center, pediatric endocrinologists, registered nurses, registered dieticians, certified diabetes educators, and clinical exercise physiologists treat pediatric patients diagnosed with T1DM up to 26 years of age. The study was approved by the University Institutional Review board. Retrospective clinical chart reviews were conducted of clinical pediatric sports medicine and physical activity program patients with a diagnosis of T1DM who participated in a Bruce protocol for VO_2 max from January 2019 through February 2020.

2.2. Participant Characteristics

The baseline characteristics of study participants are displayed in Table 1.

Table 1. Characteristics of the Participants, $N = 22$.

Characteristics	Mean ± SD or *n*, %	Range (Minimum–Maximum)
Age, years	15.6 ± 1.8	13–20
Duration of T1DM diagnosis, years	7.1 ± 4.9	>1–16
Height, centimeters	170.9 ± 8.3	157.3–187.4
Weight, kilograms	67.1 ± 13.4	44.6–107.3
BMI percentile, $n = 21$	67th percentile ± 17.7	26–99
HbA1c level, $n = 21$	8.9 ± 1.8	6.1–14.9
Gender	Male, $n = 13$, 59.1% Female, $n = 9$, 40.9%	-
Ethnicity	Non-Hispanic, $n = 20$, 90.1%	-
Race	White, $n = 17$, 77.3% Black or African American, $n = 3$, 13.6% Unknown or Not Reported, $n = 2$, 9.1%	-
Treatment Plan	CGM only, $n = 2$, 9.1% Insulin pump only, $n = 4$, 18.2% Insulin pump integrated with CGM, $n = 9$, 40.9% MDI, $n = 7$, 31.8%	

Note. Data are presented as mean ± standard deviation (SD) or number of participants (*n*), percent (%); BMI, body mass index percentile; HbA1c, hemoglobin A1c; CGM, continuous glucose monitor; MDI, multiple daily injections.

2.3. Measures

Socio-demographic, anthropometric, diabetes monitoring and treatment plans, and hemoglobin A1c (HbA1c) levels data were retrieved from patients' medical records, maintained in the clinical database, as part of standard practice at each patient's appointment in the diabetes clinic. The socio-demographic and anthropometric characteristics utilized were participant's age, date and duration of T1DM diagnosis, ethnicity, race, gender, insurance type, and body mass index (BMI) percentile. Diabetes monitoring was assessed (including whether the participant used a continuous glucose monitor (CGM)), and the type of treatment plan was recorded. The hemoglobin A1c (HbA1c) level was obtained from that day's clinical lab measures at check-in. HbA1c, the most prevalent and accessible measure in determining glucose control, was used as an indicator of the average blood glucose levels over the past 3 months. Adolescents managing T1DM should strive for HbA1c levels less than 7%, as an elevated HbA1c level is known to increase the risk for diabetes-related complications [11]. Blood glucose levels and VO_2 max data were obtained from sports medicine records collected by clinical exercise physiologists in the sports medicine clinic.

2.4. Preparatory Activities Prior to Exercise Testing

Upon registration for an exercise testing appointment, participants were instructed to not eat a heavy meal two hours prior to testing, to maintain their insulin regimen as they would on a regular day, and to dress in exercise attire (e.g., shorts, t-shirt, athletic shoes). Upon arrival to the sports medicine clinic, participants' blood glucose value was screened by a clinical exercise physiologist. If the blood glucose was >250 mg/dL the clinical exercise physiologist obtained urinary ketones with the next void. If urinary ketones were moderate or large, the participant was excluded from participating in VO_2 max testing at that time. If the blood glucose was >300 g/dL and the participant had no or small ketones, the clinical exercise physiologist instructed the participant to give a conservative insulin correction of 50% their calculated correction dose.

Approximately 30 min prior to VO_2 max testing, a pretest blood glucose sample was taken using a point-of-care glucometer and lancet device. Upon determination that blood glucose levels were in the safe range for physical activity, the clinical exercise physiologist conducted the VO_2 max test. Upon completion of the VO_2 max test, a post-test glucose level check was conducted within 5 min using the same glucometer for all participants.

2.5. Exercise Testing Procedures

A Bruce protocol [12] for VO_2 max tests, a valid and reliable measure for assessing cardiorespiratory fitness, was performed on a Woodway ELG treadmill while the participants were connected to the Parvo Medics metabolic gas exchange analyzer by way of respiratory mask. Participants walked on a treadmill in 3 min bouts, starting at 1.7 mph (45.6 $m \cdot min^{-1}$) and 10% grade. At each stage, the speed was increased by either 0.8 or 0.9 mph (21.4 or 24.1 $m \cdot min^{-1}$) and the grade was increased by 2%. This test lasted approximately 10–20 min.

If following the graded exercise test the participant's blood glucose was found to be <70 mg/dL on the glucometer, the participant was treated for hypoglycemia with 15 g of rapid-acting carbohydrate. Blood glucose was then rechecked at 15 min. This process was repeated until their blood glucose was >70 mg/dL. Blood glucose and VO_2 max data stored within REDCap on a secure server in the sports medicine program data were linked to the clinical database by the researchers utilizing the patients' medical record numbers. All clinical data were retrieved from that same-day appointment for each participant. Once data were collected and merged, the full dataset was de-identified for analysis.

2.6. Data Analysis

All statistical analyses were conducted using IBM SPSS 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics and frequencies for socio-demographic, anthropometric, diabetes monitoring and treatment plans, HbA1c levels, and pre- (<30 min) and post-

test (<5 min) blood glucose levels were calculated. Shapiro–Wilk's test ($p < 0.05$) [13,14], histograms, Norman Q–Q plots, and box plots were employed to test the normality of the distribution of the data. A paired-samples *t*-test was employed to detect differences in blood glucose levels from pretest to post-test. *p*-Values of <0.05 were considered as statistically significant.

3. Results

Retrospective VO_2 max data were analyzed from a total of 22 adolescents ($N = 22$; mean age = 15.6 ± 1.8 years; male = 13, 59.1%) (see Table 1). Most of the participants identified as non-Hispanic ($n = 20$, 90.9%), and over three-quarters identified as White ($n = 17$, 77.3%). Continuous glucose monitors were worn by 13 of the 22 participants (59.1%). Their average HbA1c prior to participating in the VO_2 max test was 8.9% ± 1.8. The average BMI, based on age and sex, was in the 67th percentile ± 17.7. The average VO_2 max peak was 43.4 mL/kg/min ± 6.4 (See Table 2).

Table 2. VO_2 max testing measurements, $N = 22$.

Characteristics	Mean ± SD	Range (Minimum–Maximum)
VO_2 max, mL/kg/min, $n = 21$	43.4 ± 6.4	29.3–50.5
Peak HR bpm, $n = 19$	192.3 ± 21.3	119–212
Glucose, mg/dL pretest, $n = 22$	191.1 ± 61.1	96–296
Glucose, mg/dL post-test, $n = 22$	166.7 ± 57.9	83–297

Note. Data are presented as mean ± standard deviation (SD); Peak HR bpm, heart rate beats per minute.

Pre- and post-test blood glucose measurements were obtained from 22 participants. The results of a Shapiro–Wilk's test indicated that the pre- and post-glucose data were normally distributed, and a visual inspection of their histograms, Norman Q–Q plots, and box plots showed that the glucose scores were normally distributed at pretest with a skewness of 0.107 (SE = 0.49) and a kurtosis of −0.868 (SE = 0.95) and at post-test with a skewness of 0.657 (SE = 0.49) and a kurtosis of −0.015 (SE = 0.95). A paired-samples *t*-test was employed to detect a statistically significant reduction in glucose levels between pretest (<30 min, mean = 191.1 mg/dL ± 61.2) and post-test VO_2 max (<5 min, mean = 166.7 mg/dL ± 57.9); $t(21) = 2.3$, $p < 0.05$).

4. Discussion

It is well established that significant changes in blood glucose concentration during physical activity can lead to hypoglycemia or hyperglycemia and, if not prevented or treated quickly and properly, can lead to a medical emergency [1,9,15–27]. This current study sought to examine if there was a significant drop in blood glucose levels after VO_2 max testing, yet it is unique in that it specialized in a pediatric population of adolescents. Results from a recent retrospective study with adults with T1DM (mean age = 32 years, SD ± 13; range 18–65 years) who participated in VO_2 max exercise testing using a cycle ergometer did not demonstrate statistically significant glucose levels from pretest to post-test [28], which aligned with similar results from other studies [29,30]. The conflicting results from the present study may be attributed to differences in the age of participants (and in body composition and hormones) and possibly the modality used during testing.

Given that individuals with T1DM are recommended to participate in daily moderate-to-vigorous-intensity physical activity [31], and general guidance for glucose targets as well as nutritional and insulin dose adjustments to protect against exercise-related glucose excursions are available [9,20,21,26,27], fear of activity-related hypoglycemia has been regularly cited as a barrier to physical activity [32,33]. Health care providers wishing to prescribe even modest increases in intensity levels of daily activity, such as walking and/or jogging, or sport participation that may include moderate-to-vigorous-intensity

activity to their patients with T1DM may consider VO_2 max testing as a first step in establishing safety precautions and working toward the adoption and maintenance of an active lifestyle. For example, participation in sports is touted as a beneficial means for adolescents to accumulate physical activity [34,35]. However, caution must be taken if prescribing sport only without the engagement in additional physical activity. This is because many adolescents who participate in a single sport often do not meet sufficient physical activity recommendations. A recent study involving 153 children and adolescents diagnosed with T1DM demonstrated this fact [36]. Although almost two-thirds of the participants reported playing one or more sports in the previous year, they were only physically active for at least one hour or more on an average 3.5 days per week, with less than 8% of the children and adolescents in the study meeting the recommended duration of one hour and frequency of seven days per week of physical activity.

The results from this current study may help guide health and fitness professionals in formulating glycemic management strategies in preparatory activities prior to exercise testing and during exercise testing. A pre-exercise glucose level of 90–250 mg/dL is suggested in order to prevent symptoms of hypoglycemia and to minimize hyperglycemia [9,11,26]. Considering that the adolescents in this current study experienced a 24.4 mg/dL drop in glucose levels from pretest to post-test, the implications of these results have clinical and practical importance. These results can and should be used to help inform patients and practitioners in clinical care decision making and the formulation of glycemic management strategies. Similar research findings suggest that patients and clinical care teams understand the glycemic changes that occur during progressive exercise so that nutritional and medicinal preparatory routines are safely established [28]. To ensure safe exercise performance ahead of exercise testing, practitioners, physiologists, and patients should be aware of the interindividual responses to VO_2 max testing and treat each case accordingly. With the assistance of a clinical exercise physiologist, physicians can incorporate individualized recommendations for increasing physical activity and/or exercise prescriptions into their clinical practices [37]. Physicians and medical care teams can prescribe physical activity and sport participation when designing treatment plans and refer their patients to qualified health and fitness professionals such as athletic trainers, strength and conditioning coaches, and physical educators who coach or train adolescent athletes diagnosed with T1DM. These protective measures that are grounded in scientific evidence [9,11,38] suggest that adolescent patients diagnosed with T1DM can complete maximal exercise testing without fear of inducing hypoglycemia if the necessary safety precautions as described in this study are taken.

Limitations and Future Research

Various limitations have been identified in this study. Although all participants were instructed to avoid eating greater than 60 g of carbohydrates prior to exercising, unless hypoglycemic, the study was not controlled for nutrition. Future studies should analyze dietary practices leading into exercise testing. In addition, participants were also instructed to administer insulin per their routine standard of care to create a "real-world" testing situation for this study. Future studies could benefit from more restrictive insulin use parameters.

The data in this study were derived from a retrospective chart review of clinical patients who participated in a pre–post VO_2 max test at a newly established (2018) clinic serving only pediatric patients diagnosed with T1DM up to 26 years of age from January 2019 until February 2020. In March 2020, non-emergency clinical operations were suspended due to COVID-19 safety precautions protocol, and sports medicine programming and study endeavors resumed in August 2021, which further limited our total sample size. At the time of the study, there were no matched control group data available. Next, although the clinic houses the only pediatric endocrinology sports medicine program in the state, the homogeneity of the participants in race and ethnicity does not make the findings generalizable to adolescents in other areas. Future research will benefit from a

more extensive and longitudinal review of the pre- and post-VO_2 max testing windows to further understand what variables influence blood glucose variability

5. Conclusions

The results from this retrospective VO_2 max testing study on blood glucose levels in adolescents with T1DM can add to the scientific literature for sports medicine programs that provide clinical care to individuals and their families through patient-centered and community education as well as clinical research. Regardless of sport or physical activity, care is focused on improving the health, safety, and athletic performance of every child and young adult with T1DM. Knowing that a significant drop in glucose levels during VO_2 max testing may occur with their adolescent patients, health and fitness professionals can discuss and implement preventive glycemic management strategies prior to exercise testing and during exercise testing.

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Physical Activity, Dietary Patterns, and Glycemic Management in Active Individuals with Type 1 Diabetes: An Online Survey

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Abstract: Individuals with type 1 diabetes (T1D) are able to balance their blood glucose levels while engaging in a wide variety of physical activities and sports. However, insulin use forces them to contend with many daily training and performance challenges involved with fine-tuning medication dosing, physical activity levels, and dietary patterns to optimize their participation and performance. The aim of this study was to ascertain which variables related to the diabetes management of physically active individuals with T1D have the greatest impact on overall blood glucose levels (reported as A1C) in a real-world setting. A total of 220 individuals with T1D completed an online survey to self-report information about their glycemic management, physical activity patterns, carbohydrate and dietary intake, use of diabetes technologies, and other variables that impact diabetes management and health. In analyzing many variables affecting glycemic management, the primary significant finding was that A1C values in lower, recommended ranges (<7%) were significantly predicted by a very-low carbohydrate intake dietary pattern, whereas the use of continuous glucose monitoring (CGM) devices had the greatest predictive ability when A1C was above recommended (≥7%). Various aspects of physical activity participation (including type, weekly time, frequency, and intensity) were not significantly associated with A1C for participants in this survey. In conclusion, when individuals with T1D are already physically active, dietary changes and more frequent monitoring of glucose may be most capable of further enhancing glycemic management.

Keywords: type 1 diabetes; A1C; physical activity; exercise; athletes; blood glucose; diet; CGM

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1. Introduction

In 2021, a full century has passed since the 1921 discovery of insulin [1], a hormone that must be replaced in individuals with type 1 diabetes (T1D), all of whom have lost the ability to produce it as the result of primarily autoimmune destruction of the pancreatic β-cells [2]. Since its discovery, replacement insulin has evolved greatly with numerous types and delivery methods now possible, along with use of better glycemic management and tracking tools that can assist individuals in preventing acute and chronic diabetes-related health complications. In fact, most people with T1D can expect to experience near normal longevity with a high quality of life, particularly if glycemic management and cardiovascular health are maintained [3].

When undertaken by individuals of all ages with T1D, physical activity is associated with many well-established health benefits, including improved cardiovascular fitness, lower cardiovascular risk, better quality overall health, and enhanced psychological well-being [4,5]. One of the major factors linked with their long-term survival is the absence of features of the metabolic syndrome and, more specifically, the presence of insulin sensitivity [6]. Physical activity of all types has been associated with greater insulin sensitivity [7–9]. In adults with T1D, being regularly active improves cardiometabolic risk profile [10] and is associated with increased longevity [6,11]. Individuals with T1D of all ages are capable of engaging in a wide variety of physical activities and sports, ranging

from recreational to Olympic-level (12), and many choose to be physically active to achieve unique goals related to athletics and/or health. However, these individuals must contend with the continuous challenges associated with being physically active with T1D, including monitoring glucose levels, managing dietary choices and intake, adjusting insulin doses, and adapting daily regimens to account for other factors that impact glycemia [12–15]. Physical activity acutely can lead to hypoglycemia and hyperglycemia [15–20], either of which may become a medical emergency if not adequately managed.

Numerous physical activity training patterns and regimens are possible with T1D, and each individual must choose to follow the one that works uniquely best, although that may vary with the type, intensity, frequency, and timing of activities, among other variables [18,19,21,22]. High-intensity training as well as competition can substantially increase glucose output from the liver, potentially leading to hyperglycemia both before and during activity [19]. Resistance exercise is associated with less of a decline in blood glucose than aerobic [18,23] and can provide a protective effect against glycemic declines if performed prior to aerobic exercise [24]. Even the timing of exercise can impact outcomes, with exercise before breakfast resulting in less hypoglycemia than the same bout of aerobic or resistance activity undertaken later in the day [18,23,25]. An appropriate dose of rapid-acting insulin can be used to treat hyperglycemia after morning exercise of any type without inducing hypoglycemia post-exercise [26]. In addition, exercise glycemic management strategies often vary within sporting events [27,28] and afterward [20,28].

In addition, nutrition and dietary patterns are one of the more controversial topics related to athletic performance in all individuals, as well as to glycemic management in T1D and overall health [12,13,29–31]. Whether individuals are participating in sports and activities recreationally or aiming for competitive levels of athletic achievement, their performance can be positively or negatively impacted by a number of nutritional factors, such as intake and timing of macronutrients, availability of micronutrients, hydration status and electrolyte balance, and exercise training practices [12–14]. In particular, carbohydrate consumption to fuel the exercise bout and/or for hypoglycemia prevention is an important cornerstone to maintain performance and avoid hypoglycemia [31,32].

Use of some of the insulin delivery systems, glucose monitoring devices, algorithms, other glucose-focused technology and tools may also improve how well activity can be managed [26,33–35]. Recent technological advances, such as insulin pumps and continuous glucose monitoring (CGM) devices, have greatly advanced the ability of individuals to manage glucose levels around physical activity by allowing for almost real-time changes in insulin delivery and feedback on glycemic responses [36,37]. When using continuous subcutaneous insulin infusion (i.e., an insulin pump), active individuals can reduce or suspend basal insulin infusion at the start of exercise [38], or even starting 30–60 min before exercise [39], in order to mitigate declines in blood glucose. Likewise, CGM devices have been shown to improve glycemic management [40–42], even in individuals with T1D with lower A1C (a measure of overall blood glucose over the last 2–3 months) values already [43]. However, CGM measure glucose in interstitial spaces, and a time lag exists between blood glucose (measured via finger stick) and CGM glucose levels (measured via CGM) [36,44,45], making it unclear whether use of such devices can benefit glycemic management with physical activity. Finally, integrated insulin pump and CGM systems have shown promise with regard to ameliorating glycemic management in individuals with T1D [35,46–48], but their successful use around exercise remains more limited [49–54].

Thus, the purpose of this study was to ascertain which variables related to the diabetes management of physically active individuals with T1D have the greatest impact on overall blood glucose levels (via A1C) in a cohort of active adults and adolescents with T1D in a real-world setting. Given the complexity of managing blood glucose levels when exogenous insulin must be precisely balanced with food intake for any physical activity, we hypothesized that both physical activity (total weekly time, frequency, intensity, and/or type) and dietary patterns (particularly carbohydrate intake) would potentially impact

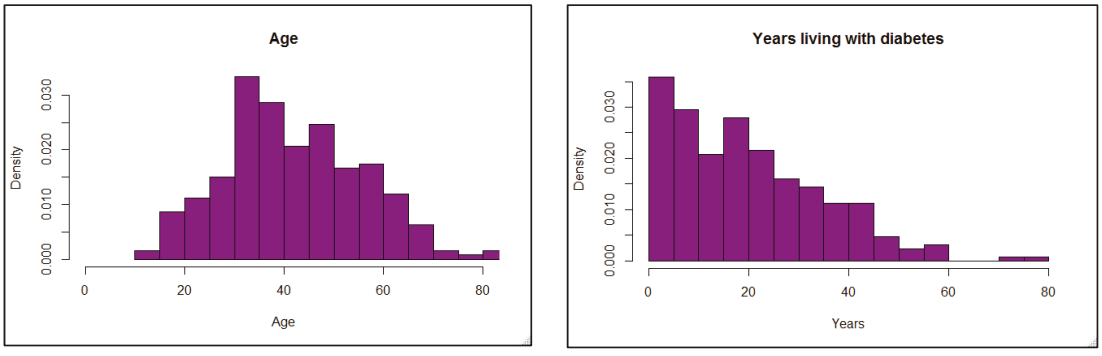
overall blood glucose management in these active individuals, along with the use of the latest diabetes technologies (e.g., insulin pumps and CGM devices).

2. Materials and Methods

2.1. Subject Recruitment

An online survey conducted in English was advertised in 2018 by investigators on diabetes-focused social media platforms and distributed to various professional contacts via email. Participation was completely voluntary with no incentives offered, and the survey was open to all physically active individuals with diabetes of any age during a month-long period. The survey itself was completed through a separate online platform and contained no questions that could be used to identify personal data or characteristics by the investigators. Data collection methods were considered exempt from requiring participant consent by our university due to the online anonymous and voluntary nature in which all survey responses were obtained and recorded.

A total of 220 participants (109 male, 111 female, age range of 13 to 84 years) who had been diagnosed with T1D for varying lengths of time were included in the study. Their distributions by age and years with T1D are shown in Figure 1.



(**a**) (**b**)

Figure 1. Distribution of participants by age (**a**) and years living with type 1 diabetes (**b**).

2.2. Online Survey and Data Collection

The online survey included a broad array of questions that participants could choose to complete with none being mandatory. Self-reported data about each participant included the following variables: age, sex, diabetes type, latest A1C value, usual insulin regimen (including insulin pumps), use of other medications, glucose self-monitoring practices (i.e., frequency and use of CGM devices), typical dietary patterns and estimated carbohydrate intake, physical activity patterns, target blood glucose ranges for exercise, regimen changes for physical activity, and typical treatments for exercise-related hypoglycemia or hyperglycemia. Any A1C values that were reported in mmol/mol (all coming from respondents outside the United States) were converted to equivalent % values before analysis, and only self-reported insulin users were included in the analyses.

2.2.1. Physical Activity Participation and Categorization

Physical activity participation was assessed with questions about typical frequency, intensity, time, and type. Their usual intensity was self-categorized as light, moderate, vigorous (hard), very hard, or maximal using drop-down selections found in the survey. Total physical activity time per week was calculated as a product of self-reported days of activity per week and the typical amount of time spent exercising per day regardless of the activities undertaken. Additional open-ended responses related to participants'

individualized diabetes regimen changes were collected for over 165 different sports and activities, which were largely used for other purposes [55]. Responses to these physical activity and other related, open-ended questions were not directly analyzed and only included in terms of whether participants reported engaging in various activities.

Participants' self-reported activities were placed into one or more of five categories: fitness, endurance, endurance-power, power, and outdoor. The designation of each sport was determined by the investigators and primarily based on the energy systems engaged during the activity itself (aerobic vs. anaerobic ones) [56], although some overlap among categories exists for certain sports and activities. Once participants answered "yes" for a category, numerous examples of activities and sports in each category were provided in the survey as drop-down selections to steer them to select representative ones. Some examples of selections in each category included, but were not limited to, the following:

- Fitness activities: fitness walking, aerobic conditioning machines, resistance training, aerobics classes, Pilates, kettle ball training, dancing, agility training, balance training, stretching, yoga, indoor climbing, martial arts, tai chi, physical activity classes;
- Endurance activities/sports: running and jogging, swimming, cycling, marathons, biathlons, triathlons, cross-country running or skiing, ultra endurance training;
- Endurance-power sports: basketball, soccer, golf, tennis, hockey, football, tennis, indoor racquet sports, intermediate-distance track events, CrossFit, high-intensity interval training;
- Power sports: baseball, bodybuilding, Olympic weight lifting or power lifting, sprinting, field events (shot put, pole vault, high jump, etc.), volleyball or beach volleyball;
- Outdoor activities/sports: kayaking, downhill skiing, curling, waterskiing or wakeboarding, kiteboarding, hiking and backpacking, horseback riding, rock or ice climbing, adventure racing, trail running, hunting, fishing, gardening, etc.

2.2.2. Dietary Patterns and Carbohydrate Intake

The usual dietary patterns of participants were assessed with specific questions about whether they ingested carbohydrate for physical activity, their preferred sport-specific carbohydrate choices, and their usual dietary treatments for hypoglycemia, along with more open-ended questions about their typical dietary patterns. Some responded with definitive dietary patterns from which carbohydrate intake could be easily estimated, such as "keto diet" [57] or "Dr. Bernstein diet" [58,59], whereas others gave actual daily carbohydrate estimates or stated that they were vegan or vegetarian, ate a meat-based diet, consumed a plant-based whole foods diet, or avoided/limited their intake of starches or other food categories. These carbohydrate intake/dietary pattern data have been reported for a larger cohort of individuals with T1D or type 2 diabetes previously [12,13]. All of their responses to nutrition-related or dietary questions were considered together by the investigators, along with typical calorie requirements for active adults and adolescents [60], when estimating participants' generalized daily carbohydrate intake and placing them into one of four categories for analyses:

- Normal (unrestricted): >200 g/day;
- Moderate: 100–200 g/day;
- Low-carbohydrate: 40–99 g/day;
- Very low-carbohydrate: <40 g/day.

2.3. Statistical Analyses

For this study, descriptive variables are presented as mean, standard error of the mean (SE), median, minimum, and maximum. A generalized linear model (GLM) approach was used to measure and quantify association between A1C and predictor variables. Using GLM, the equation for these associations was formulated as:

$$y_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \ldots + \beta_p x_{pi} + e_i,$$

where y_i represents the response of the ith participant's A1C, for $i = 1, \ldots, n$, with $x_1, x_2, \ldots, x_p$ representing other predictors like biological sex, usual carbohydrate intake, use of CGM devices, and other collected variables. Predictor variables were either discrete or continuous. In the model equation, the term β_0 served as the model intercept and β_i referred to the slope associated with the i^{th} predictor variable, with the errors e_i independent and identically distributed $\sim N(0, \sigma^2)$ and σ^2 with the model variance. In order to minimize variance and satisfy model assumptions, a transformation of the A1C to a natural log scale was applied.

Due to a gap in self-reported A1C values, the natural log values (log A1C) were found to be closer to the normal distribution than the A1C itself. Consequently, log A1C values were used for further analyses in the GLM (see Appendix A for a detailed justification of the transformation to natural log and results of statistical tests). Significance for all such analyses was set as $p < 0.05$.

3. Results

3.1. Participant Characteristics and Survey Responses

The demographic factors of participants included their A1C, age, and years living with diabetes, as shown in Table 1, along with responses to other quantifiable and categorical questions from the online survey. The majority of the 220 respondents were from the United States (68%), with others from Europe (13%), Canada (7%), Australia (6%), Eastern Europe (3%), and the rest (3%) from Mexico, South Africa, Iran, India, and the Philippines. Data from another 30 participants with T1D were excluded due to incomplete or missing responses related to A1C and other relevant variables.

Table 1. Participant Characteristics and Survey Question Responses.

Characteristic or Survey Question	*N*	Mean	Median	SE	Min	Max
Latest A1C (%)	220	6.6	6.6	0.1	4.2	10.5
Age (years)	220	42.1	40	1	13	84
Time with T1D (years)	220	21	18	1	1	80
Total weekly physical activity (minutes)	220	498	360	26	30	2520
Total weekly physical activity (hours)	220	8.3	6	0.4	0.5	42
Days per week of physical activity (number)	220	5.2	5	0.1	2	7
Typical duration of physical activity (minutes)	220	93	75	5	15	720
Carbohydrate intake (1 = normal to 4 = very low)	220	2.1	2	0.1	1	4
Ingest carbs if glucose falls with activity (yes/no)	220	1.07	1	0.02	1 (yes)	2 (no)
Insulin pump use (yes/no)	220	1.4	1	0.03	1 (yes)	2 (no)
Noninsulin diabetes medication use (yes/no)	220	1.86	2	0.02	1 (yes)	2 (no)
Statin use to lower blood cholesterol (yes/no)	220	1.71	2	0.03	1 (yes)	2 (no)
Self-monitor blood glucose (yes/no)	220	1.05	1	0.02	1 (yes)	2 (no)
Continuous glucose monitor use (yes/no)	220	1.22	1	0.03	1 (yes)	2 (no)
Fitness activities (yes/no)	220	1.18	1	0.03	1 (yes)	2 (no)
Endurance sports or training (yes/no)	220	1.29	1	0.05	1 (yes)	2 (no)
Endurance-power sports (yes/no)	220	1.75	2	0.03	1 (yes)	2 (no)
Power sports or training (yes/no)	220	1.86	2	0.02	1 (yes)	2 (no)
Outdoor recreational activities (yes/no)	220	1.53	2	0.03	1 (yes)	2 (no)
Exercise-induced low blood glucose (yes/no)	220	1.13	1	0.02	1 (yes)	2 (no)
Exercise-induced high blood glucose (yes/no)	220	1.32	1	0.03	1 (yes)	2 (no)

As a whole, the participants' latest A1C mean and median values (Table 1) were well within commonly recommended ranges of less than 7% [61]. Almost 70% self-reported having an A1C within this recommended range, although values ranged from 4.2% to 10.5%. About 25 individuals reported using a second diabetes medication besides insulin, with the majority of them using either metformin or a sodium-glucose transport protein 2 (SGLT2) inhibitor. As none of these medications impacts exercise-associated blood glucose levels, they were not included in any further analyses.

3.2. AIC and Its Predictors

3.2.1. A1C Prediction with Physical Activity Variables

The total weekly time spent being physically active was estimated based on participant responses to both frequency (number of days per week) and usual time spent exercising on active days. The total hours per week were calculated as a product of the two, and the distribution of participant time is shown in Figure 2. The nature of the survey did not allow for any differentiation among time spent doing different types of activities.

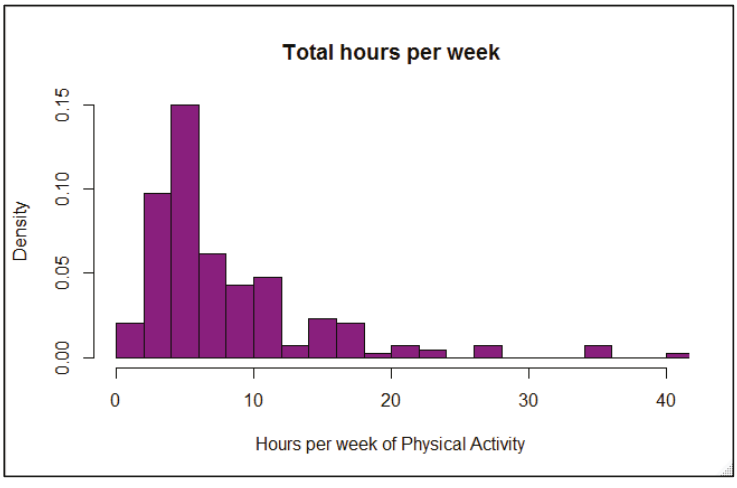


Figure 2. Distribution of participants by total hours per week spent doing all physical activities.

When total physical activity time per week was further categorized into whether participants' met the recommended minimum (at least 150 min, or 2.5 h, of aerobic activity) or engaging in less than 150 min [62,63], total time was not significantly predictive of log A1C values regardless of whether or not participants met weekly physical activity recommendations (Figure 3). Total time, however, included all types of activities in this survey.

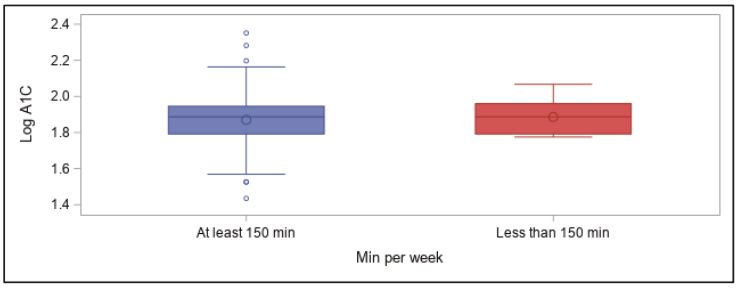


Figure 3. Total physical activity time by recommended amount and association with log A1C values.

The number of days of activity per week ranged from 2 to 7 (Figure 4), demonstrating that all participants were physically active. However, frequency of physical activity was not a significant predictor of A1C.

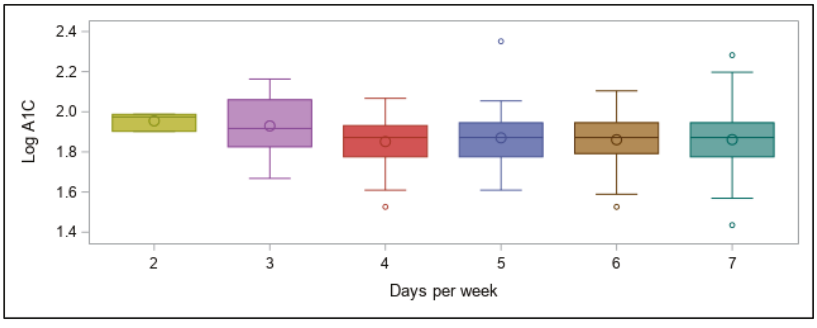


Figure 4. Number of days of physical activity per week and association with log A1C values.

The usual intensity of physical activity engaged in by participants ranged from light to maximal, depending on the sport or activity (Figure 5). However, intensity also failed to predict differences in A1C values.

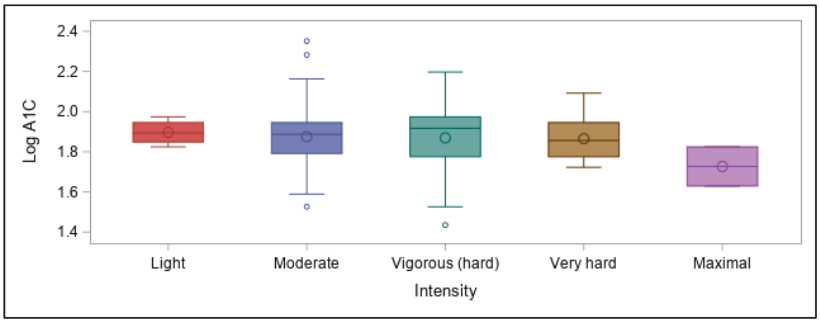


Figure 5. Intensity of physical activity and association with log A1C values.

3.2.2. A1C Prediction with Categorical Responses to Selected Survey Responses

Survey responses related to participation in each category of physical activity or sports and carbohydrate ingestion for activity are shown in Figures 6 and 7. No significant associations were found between these categorical responses and log A1C for any of these.

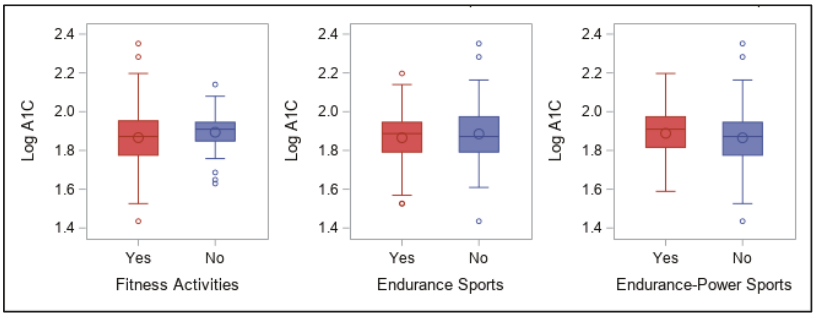


Figure 6. Participation in fitness activities, endurance sports, and endurance-power sports and association with log A1C values.

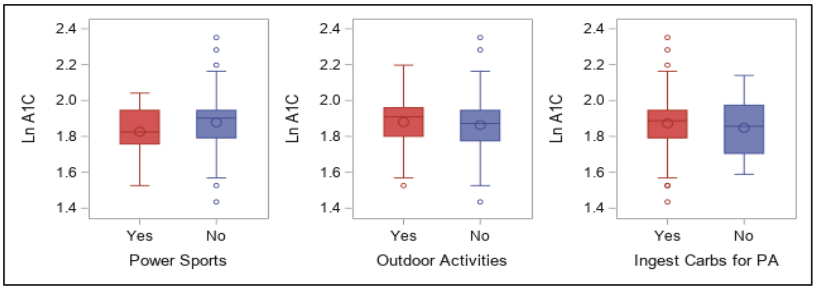


Figure 7. Participation in power sports and outdoor activities and ingestion of carbohydrates for physical activity and association with log A1C values.

3.2.3. A1C Prediction Based on CMG Use and Dietary Patterns

CGM device use and whether participants experience activity-related low and high blood glucose values are shown in Figure 8. No significant associations were found between these yes/no categorical responses and log A1C for these variables.

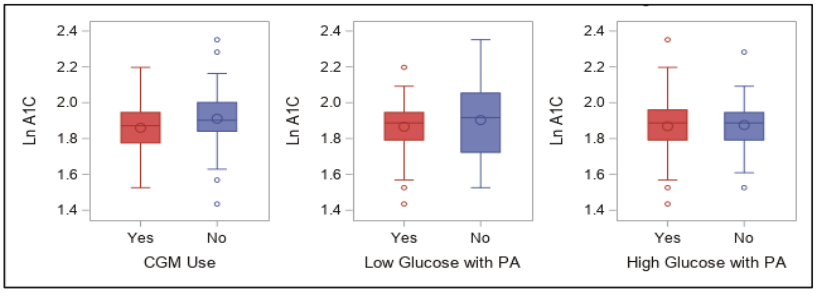


Figure 8. Use of CGM and physical activity-related low and high glucose and association with log A1C values.

With all variables considered within our model, the only significant predictors of participants' log A1C values ended up being their use of CGM devices ($p = 0.02$) and their typical carbohydrate intake ($p < 0.0001$). These associations remained strong when analyzing either A1C or transformed natural log A1C (analyses shown in Appendix A). However, the variance was significantly reduced when the prediction model used log A1C given the gap evident in the distribution of participants' A1C values (see Figure A1). The overall associations between A1C and usual carbohydrate intake categories are shown in Figure 9, and the relative percentages of participants falling into each carbohydrate intake category are shown in Figure 10.

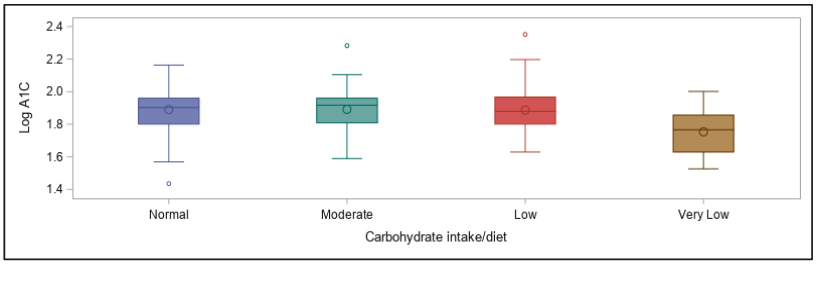


Figure 9. Usual daily carbohydrate intake and association with log A1C values.

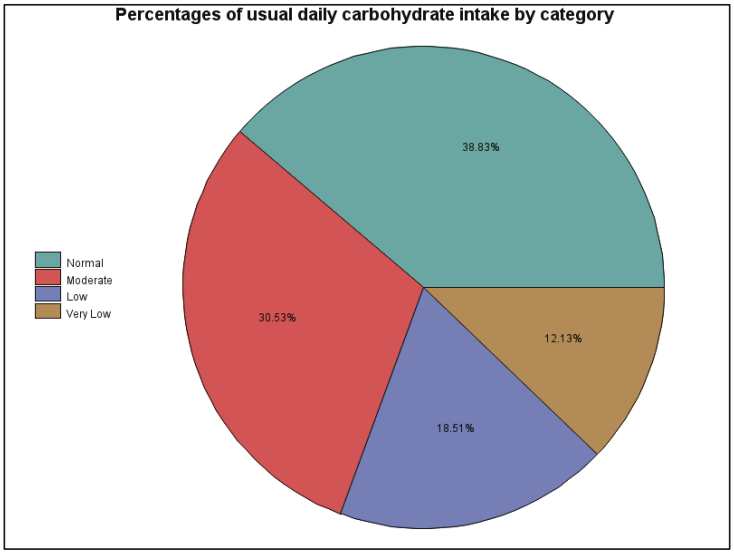


Figure 10. Percentages of usual daily carbohydrate intake by category.

3.2.4. A1C Prediction Based on Attainment of Recommended Ranges

An even more precise prediction emerged when participants were separated into one of two groups based whether their A1C values fell into the recommended range (<7%) or above (≥7%). A very-low carbohydrate intake was significantly associated with the lowest log A1C values when in recommended ranges ($p < 0.0001$), but CGM use was not predictive in that case ($p = 0.90$). When log A1C was in ranges above recommended, the most significant predictor was CGM wear ($p < 0.01$), with users of the devices having significantly lower values even though they failed to meet A1C recommendations, although carbohydrate intake failed to be predictive when A1C was higher ($p = 0.16$).

4. Discussion

As the aim of this online survey study was to ascertain which variables related to the diabetes management have the greatest impact on overall blood glucose levels, the outcomes were focused around achievement of A1C values in a recommended range. The primary findings were that in this cohort of free-living, physically active individuals with T1D of various ages, lower A1C values (within the recommended range of <7%) were best predicted by following a very-low carbohydrate dietary pattern, whereas using a CGM device was associated with better A1C values when A1C was higher than recommended. Contrary to our expectations, participants' self-reported physical activity levels were not predictive of A1C values, even when they engaged in recommended amounts of total weekly activity of any type, and consideration of frequency, intensity, type, or total time did not increase the predictive value. However, most participants were already very active when compared to the population as a whole, which likely impacted these findings.

Reliance on physical activity participation to better manage overall blood glucose in individuals with T1D has shown mixed outcomes, although recent results are more promising (21). Participants in our online survey reported a fairly wide range of A1C values, demonstrating that being physically active alone does not guarantee optimal glycemic management, although the majority of values (70%) fell in the recommended range of <7% and would be considered well-managed. These results concur overall with many other studies showing that unless other glycemic variables are effectively balanced at the same time—such as food intake, insulin doses, and physical or mental stress—

individuals with T1D do not necessarily experience improvements in overall glucose values when regularly active, with some studies demonstrating benefits [64–66] and others finding no improvement in A1C following aerobic or resistance training [67,68]. Our participants were engaging in myriad activities, though, making interpretation more difficult compared to those studies and others in which activities were more controlled and uniform. Moreover, our survey respondents engaged in physical activity 2 to 7 days per week, with over 93% of them reportedly engaging in more than the minimal recommended time. Some were training up to 42 h of weekly as competitive athletes and only five participants were active less than 100 min per week. This level of participation is far more than in the population overall [69,70] and for most with diabetes [71]. While our survey was not capable of discerning time spent in aerobic (as recommended 150 to 300 or more minutes a week) versus other types of activities, others have shown that total exercise volume and time spent being physically active doing any type of activity may matter more to cardiovascular and metabolic health than participation in specific bouts of moderate-to-vigorous aerobic activities by themselves [72–75]. Engaging in muscle-strengthening activity $\geq$2 times/week may provide additional benefits among insufficiently active adults [76]. With these observations in mind, we felt comfortable categorizing our participants as meeting or failing to meet the recommended total activity time with all types of activities considered together, not just aerobic ones.

Being physically active with T1D increases an individual's risk of activity-related hypoglycemia [77–79] and hyperglycemia [80,81], and fear of activity-related hypoglycemia has often been a deterrent of regular participation for insulin users of all ages [82,83]. Conversely, since all of our participants were engaging in regular physical activity, they likely had already adapted their diabetes management strategies to better manage their glycemic variations while minimizing any fear of hypoglycemia associated with being active; in fact, out of 220 participants, only 10 reported A1C values of 8% or higher and only two of those were above 9%. Their regular participation may also at least partly explain why their total activity was not predictive of overall glycemic management since the vast majority were already exceeding recommended levels of activity and had A1C values that were well-managed compared to the majority of individuals with T1D as a whole [41,42]. Thus, it is likely that the glycemic impact of being active was already reflected in their having better A1C values than most individuals with T1D.

Another challenge associated with attempting to achieve better A1C values with physical activity is the unpredictability of glucose responses even to similar bouts of exercise. Active individuals completing our online survey frequently expressed frustrations with maintaining glycemic balance while doing a variety of physical activities under free-living conditions [55]. A recent study conducted on 12 adults with T1D reported that three identical cycling sessions completed on separate days under controlled conditions resulted in varying values for glucose measured either with a finger-stick (capillary blood) blood glucose monitor or a CGM device, even though glucose declined in all three trials [78]; these results indicated low reproducibility at the participant level and remained unchanged after adjustment for baseline glucose values. Likewise, in adolescents with T1D, while greater intrasubject reliability and repeatability of blood glucose responses to prolonged exercise was shown to be possible, this result occurred only when pre-exercise meal, exercise, and insulin regimens were kept constant [84], which is not always feasible in real life. However, recent technological advances, improvements in insulin regimens, newer insulins, and a better understanding of the physiology of various types of exercise may help limit such unpredictability for similar activities and, at the same time, lessen the fear of hypoglycemia by facilitating hypoglycemia prevention [82]. With proper management around activities, athletes with T1D at all levels have been shown to be capable of undertaking and performing well even in long endurance training, high-intensity sports, and other types of events [27,29,85,86].

With regard to dietary patterns, in the current study a very-low carbohydrate intake was surprisingly most predictive of achieving recommended glycemic levels overall (i.e.,

an A1C < 7%), regardless of differing levels and types of physical activity participation. Many endurance athletes with and without T1D have claimed to perform well with a lower, or at least moderate, intake of this macronutrient [57,87] and to maintain a better glycemic balance [31], although the consensus remains that carbohydrates are necessary to perform well at higher intensities and durations of activity [12,88,89]. However, the active individuals in our study who stated that they ingest carbohydrates during physical activity had similar A1C values to those who claimed to refrain from carbohydrate supplementation. In fact, supplementing with carbohydrates has been shown to potentially be superior to bolus insulin reduction for prevention of hypoglycemia during physical activity, as was demonstrated in a group of adults with T1D engaging in moderate-intensity cycling for 45 min in one study [90]. In our survey, however, both strategies (i.e., carbohydrate ingestion and insulin reduction) were used by most participants to prevent hypoglycemia with activity; in many cases, active individuals with T1D must employ a combination of both in order to maintain glycemic balance during and after training or events [12,15,29].

Nowadays, daily carbohydrate intake alone is usually not predictive of A1C values for most with T1D, and consuming carbohydrates can be feasible, which may be reflective of individuals' use of faster-acting insulin analogues for meal boluses. In fact, a single mealtime bolus of insulin has been shown to cover a range of carbohydrate intake without deterioration in postprandial glycemia [91]. Even dietary fat, protein, and the glycemic index of ingested carbohydrates are associated with insulin dosing needs and impact postprandial glucose excursions [92,93], making glycemic predictions and insulin dosing based on grams of carbohydrate intake alone inadequate. Carbohydrate counting is fraught with complications given the complexities in digestion and absorption rates of that macronutrient and challenges related to proper estimation of the amount ingested by individuals [94–96]. With regard to our survey participants, most of whom already had optimal blood glucose management, it may be that they simply were able to tighten it slightly further by restricting their carbohydrate intake. Avoiding greater fluctuations in blood glucose after meals and during activity can improve overall glycemia [97]. In our survey, for individuals with higher-than-recommended A1C values, carbohydrate restriction was not predictive of better glycemic management, suggesting that other variables are impacting glycemia more in their case.

Although trials are undergoing, to date low- and very low-carbohydrate diets have not been extensively studied in the management of T1D [13], with available studies examining glycemic outcomes from such diets being largely cross-sectional and lacking validated dietary data or control subjects [32,98]. Many of the participants in such studies can be described as highly motivated individuals who follow intensive insulin management practices, including frequent blood glucose monitoring and additional insulin corrections to meet tight glycemic targets. While athletes may still perform adequately when following such restricted diets [32,99,100], some potential negative health consequences of ketogenic and other low-carbohydrate diets have been noted [101,102], and longer term studies are needed to determine how feasible these dietary patterns are for most individuals with T1D [103]. Thus, much work remains to be done to fully determine the extent of the impact of dietary carbohydrate restriction on glycemic outcomes and optimal intake levels, particularly in physically active individuals with T1D.

Finally, the use of the latest diabetes technological advances, such as insulin pumps and CGM devices, has greatly advanced the ability to manage glucose levels around physical activity [36,37]. While 60% of our participants used an insulin pump, an even larger percentage (77%) used a CGM. Having access to either one or both devices potentially can allow users to make more informed choices to manage glycemia around exercise [104]. For our survey participants, using a CGM device was predictive of lower A1C values (specifically when above recommended levels) although insulin pump use was not predictive. This is unsurprising given that other studies have shown that CGM can be beneficial for all individuals with T1D [40–42], even for those who have already achieved recommended A1C at <7.0% [43]. Despite the demonstrated time lag between blood glucose (measured

via finger stick) and interstitial glucose levels (measured via CGM) [36,44,45], having closer to real-time feedback on the impact of any activity likely makes glycemic management easier, especially when activities can vary so widely in their effects. For instance, a recent systematic review and meta-analysis that included 12 studies using CGM devices to examine the delayed impact of engaging in various physical activities reported that intermittent exercise (i.e., most endurance-power or power sports) actually increases the time spent in hypoglycemia and lowers mean glycemic values via CGM, with no differences in time spent in hyperglycemia or the number of hypoglycemic events [105]. Hypoglycemia risk was also lower for activities performed in the morning rather than in the afternoon, even with a 50% rapid-acting insulin reduction prior to later-day exercise. While our participants did not indicate their usual time of day for activities, CGM use has the potential to provide feedback that allows users to take corrective actions to manage glycemia in a timelier manner.

Although not a survey question, some of our participants noted employing various exercise strategies with use of hybrid closed-loop systems (i.e., Medtronic 670G), which involve integration of an insulin pump, CGM, and algorithm control system to manage insulin delivery in response to real-time glucose levels with minimal user input. Although some input is usually still required (such as announcement of meals or exercise), hybrid systems have recently been found to improve time-in-range (typically defined as 70–180 mg/dL, or 3.9–10.0 mmol/L) around physical activity [106]. Users of such systems with a lower intake of daily carbohydrates have also experienced better glycemic management [107], likely due to the ability of such systems to make adjustments in response to the slower glucose fluctuations resulting from dietary protein and fat [97,108].

The limitations of this survey research localize mainly around our inability to collect more quantifiable and directly verifiable data, since all of it was self-reported and many of the survey questions were more open-ended. This is particularly an issue for dietary considerations including estimating carbohydrate intake, total calories, macronutrient distribution, and micronutrient adequacy, among other considerations. The authors used their best judgment when placing the participants into dietary categories for carbohydrate intake based on the data collected. However, it is possible that their interpretation of some responses was flawed or that participants failed to report or recognize all the carbohydrate sources in their diets, including those in high-fat, low-carbohydrate foods (e.g., olives, avocados, and nuts); in foods, drinks, or sports supplements taken during activities; and in rapid hypoglycemia treatments. A dietary recall questionnaire would have enhanced the reliability of these data around dietary patterns, total calorie intake, and macronutrient distribution. Likewise, although participants responded to questions around insulin use, types, and delivery methods, our interpretations are limited. More information related to actual dosing, timing, and other insulin-related data, particularly around physical activity and glycemic management would have provided more definitive results. Finally, relying on self-reported data in any research study has its limitations and can be problematic [109,110]; this is particularly true when it comes to data related to physical activity. Our survey participants reported engaging in a wide array of physical activities, many of which have varied glucose responses even within a specific category, especially "outdoor activities and sports". Our data collection and interpretation would have been enhanced by use of a more standardized physical activity questionnaire, quantifiable data that could be converted into objective total exercise volume measures (such as MET-min/week) and, of course, controlled laboratory conditions.

Much remains to be studied related to physical activity in individuals with T1D, especially given the large number of variables that must be simultaneously balanced to maintain normal or near normal glycemic levels. Future research likely should include the potential implications of carbohydrate-restriction and other dietary patterns on physical activity performance and glycemic balance in this population. Another area to pursue is the glycemic benefits of using the latest technologies related to insulin delivery, glucose monitoring, and physical activity trackers and other devices. Such technologies can provide

immediate feedback to users and allow them to make optimal and real-time diabetes regimen adjustments before, during, and after physical activity.

5. Conclusions

In conclusion, when individuals with type 1 diabetes of any age are already physically active and their blood glucose is well-managed, a greater focus on lowering carbohydrate intake may improve glycemic management. In addition, active individuals may benefit from using continuous glucose monitoring to lower overall glycemia, especially when their A1C values are higher than recommended. Nevertheless, all individuals can benefit from being physically active on a regular basis, especially when the myriad variables affecting glucose responses can be adequately managed to prevent hypoglycemia or hyperglycemia.

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Informed Consent Statement: Patient consent was not required due to the anonymous and voluntary nature in which all survey responses were obtained and recorded. This research was considered "exempt" by the Institutional Review Board of Old Dominion University.

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Appendix A

Multiple selection methods used revealed that the participants' usual carbohydrate intake ("CarbIntake") and use of CGM devices ("CGM") factors were strong predictors of their A1C values (Table A1). The corresponding model variance in the case of the parsimonious simplified model (with CarbIntake and CGM use only) showed an estimate of the model variance of $\hat{\sigma}^2 = 0.7098177$ (Table A2).

Table A1. A1C with CGM and CarbIntake as independent variables.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CGM	1	3.92606553	3.92606553	5.53	0.0196
CarbIntake	3	16.96667395	5.6555798	7.97	<0.0001

Table A2. GLM with A1C as dependent variable.

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	22.2315103	5.5578776	7.83	<0.0001
Error	215	152.6108078	0.7098177		
Corrected Total	219	174.8423182			
R-Square	**Coeff Var**	**Root MSE**		**A1C Mean**	
0.127152	12.85111	0.842507		6.555909	

To minimize that variance, a transformation of the A1C to natural log (base e) was considered. When this log A1C was used, the same significant predictors (i.e., CGM and

CarbIntake) were still obtained from the data (Table A3), but the parsimonious model variance was reduced. The variance of the log A1C was $\hat{\sigma}^2 = 0.0162$ (Table A4), which was more than 44 times smaller than the variance of the model with untransformed A1C. With the reduced variance, the model precision increased.

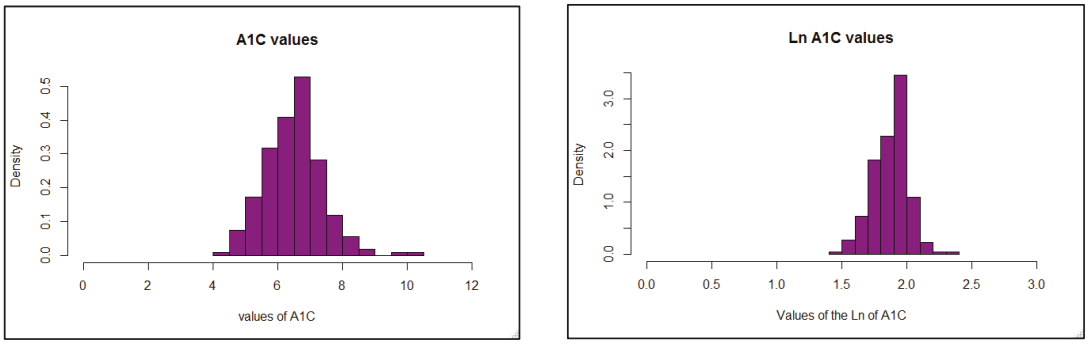
Table A3. Log A1C with CGM and CarbIntake as independent variables.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CGM	1	0.06910170	0.06910170	4.24	0.0407
CarbIntake	3	0.45376179	0.15125393	9.28	<0.0001

Table A4. GLM with log A1C as dependent variable.

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	0.55208798	0.13802199	8.47	<0.0001
Error	215	3.50378520	0.01629668		
Corrected Total	219	4.05587317			
R-Square	**Coeff Var**	**Root MSE**		**Log A1C Mean**	
0.136121	6.822330	0.127658		1.871185	

Thus, the histogram and boxplots of log A1C with respect to the same predictors (e.g., sex, CarbIntake, insulin pump use, CGM, physical activity categories) were created. The histogram plot showed of A1C data exhibited a gap, which led log A1C to have a narrower distribution closer to a normal one than A1C (Figure A1).



(**a**) (**b**)

Figure A1. Histogram plots of A1C (**a**) and log A1C (**b**) distributions.

A classification of the A1C was suggested around current clinical recommendations, leading to equivalent log A1C values to be put into one of two categories: in recommended ranges (low, or <7%) or higher than recommended (high, or ≥7%). At that point, the data were asymmetric, and options were considered. One option was to consider using a regression model to predict A1C based on each category, but the data were mainly limited and exhibited an imbalance with 154 and 148 participants in low A1C and high A1C, respectively. Use of the GLM technique with the transformed, categorized data led to the observation that the imbalanced proportions were not too acute, and the expectation was that the separate models with selected predictor(s) would reduce biases.

We observed that when the A1C was low (<7%), the model variance went from 0.3367 (Table A5) to 0.0101 (Table A6), an almost 33-fold reduction in variance. Moreover, the most significant predictor under GLM for the A1C or its log was CarbIntake (Tables A7 and A8).

Table A5. GLM with A1C < 7% as dependent variable.

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	7.01869591	1.75467398	5.21	0.0006
Error	149	50.16286253	0.33666351		
Corrected Total	153	57.181555844			
R-Square	**Coeff Var**	**Root MSE**		**A1C Mean**	
0.122744	9.453552	0.580227		6.137662	

Table A6. GLM with log A1C < 1.95% (log < 7% equivalent) as dependent variable.

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	0.24412292	0.06103073	6.02	0.0002
Error	161	1.63114020	0.01013131		
Corrected Total	165	1.87526312			
R-Square	**Coeff Var**	**Root MSE**		**Log A1C Mean**	
0.130181	5.533238	0.100654		1.819086	

Table A7. A1C < 7% with CGM and CarbIntake as independent variables.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CGM	1	0.01272245	0.01272245	0.04	0.8461
CarbIntake	3	6.79896805	2.26632268	6.73	0.0003

Table A8. Log A1C < 1.95% with CGM and CarbIntake as independent variables.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CGM	1	0.00018887	0.00018887	0.02	0.8916
CarbIntake	3	0.24281020	0.08093673	7.99	<0.0001

When the A1C was high (≥7%), the model variance went from 0.3440 (Table A9) to 0.0055 (Table A10), a substantial almost 62-fold reduction. Moreover, the most significant predictor under GLM for the A1C or its log was CGM use (Tables A11 and A12, respectively).

Table A9. GLM with A1C ≥ 7% as dependent variable.

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	6.87375483	1.71843871	4.99	0.0015
Error	61	20.98942699	0.34408897		
Corrected Total	65	27.86318182			
R-Square	**Coeff Var**	**Root MSE**		**A1C Mean**	
0.246697	7.788172	0.586591		7.531818	

Table A10. GLM with log A1C ≥ 1.95% (log ≥ 7% equivalent) as dependent variable.

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	0.07311333	0.01827833	3.29	0.0181
Error	49	0.27183879	0.00554773		
Corrected Total	53	0.34495212			
R-Square	**Coeff Var**	**Root MSE**		**Log A1C Mean**	
0.211952	3.666696	0.074483		2.031341	

Table A11. A1C $\geq$ 7% with CGM and CarbIntake as independent variables.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CGM	1	4.27150374	4.27150374	12.41	0.0008
CarbIntake	3	2.88369801	0.96123267	2.79	0.0478

Table A12. Log A1C $\geq$ 1.95% with CGM and CarbIntake as independent variables.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CGM	1	0.05392963	0.05392963	9.72	0.0030
CarbIntake	3	0.031058040	0.01052680	1.90	0.1423

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Association between Physical Activity and Sport Participation on Hemoglobin A1c among Children and Adolescents with Type 1 Diabetes

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Abstract: Purpose: To determine associations between physical activity (PA) and sport participation on HbA1c levels in children with type 1 diabetes (T1D). Method: Pediatric patients with T1D were invited to complete a PA and sport participation survey. Data were linked to their medical records for demographic characteristics, diabetes treatment and monitoring plans, and HbA1c levels. Results: Participants consisted of 71 females and 81 males, were 13 ± 3 years old with an average HbA1c level of 8.75 ± 1.81. Children accumulating 60 min of activity 3 days or more a week had significantly lower HbA1c compared to those who accumulated less than 3 days ($p < 0.01$) of 60 min of activity. However, there was no significant difference in HbA1c values based on sport participation groups. A multiple linear regression model indicated that PA, race, age, duration of diagnosis, and CGM use all significantly predicted HbA1c ($p < 0.05$). Conclusion: This study demonstrated the significant relationship between daily PA and HbA1c. Those in this sample presented with lower HbA1c values even if accumulating less than the recommended number of days of activity. Further, it was shown that sport participation alone may not be adequate enough to impact HbA1c in a similar manner.

Keywords: physical activity; pediatric; clinical exercise; sport medicine; diabetes

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1. Introduction

Children with type 1 diabetes (T1D) should engage in a minimum of 60 min of moderate to vigorous intensity physical activity (PA) per day, the same as children without T1D. However, due to the inability of the body's natural response to control glucose fluctuations, care must be taken to prevent incidents of low blood glucose levels (hypoglycemia) or high blood glucose levels (hyperglycemia) during and after physical activity [1–6]. A continuous, dynamic, and complex balance of insulin administration, nutrition, PA, and monitoring of blood glucose levels are required to manage T1D. Children with T1D can still maintain a healthy and physically active lifestyle through recreational and general play as well as by participating in sports and organized activities as long as necessary safety precautions are taken. Scientific guidance exists regarding glucose targets for safe and effective participation in PA as well as nutritional and insulin dose adjustments to protect against PA-related glucose excursions [7–9].

There have been a number of studies investigating the impacts of sedentary lifestyles compared to physically active lifestyles in patients with T1D outcomes [10–13], however the

majority of studies were conducted with older populations and there is limited information in regards to PA and sports participation available for children with T1D. Participation in sports is an excellent way for children to accumulate PA, while also gaining valuable social and life skills. Furthermore, studies have shown that children who participate in sports were more likely to meet PA guidelines than children who do not participate in sports [14].

There is evidence to suggest that PA in youth with T1D can contribute to decreases in HbA1c [10–13]. For example, among children with T1D, less active children have been known to exhibit poor glycemic control and significantly higher HbA1c levels compared to children who accumulate more physical activity most, if not all, days of the week [15,16]. Although sport participation can be a way for T1D patients to be physically active and perhaps improve HbA1c, no research studies have analyzed the differences in HbA1c levels and sport participation in children with T1D. Therefore, the purpose of this study was to examine the associations between PA and sport participation on HbA1c levels in children with T1D. The influence of sociodemographic characteristics and use of diabetes management tools (e.g., insulin pump) on HbA1c were also explored.

Identifying more direct benefits of increased PA on diabetes management and glucose control may aid diabetes care teams in developing individualized prescriptions to increase daily PA in a safe manner due to their understanding of acute and chronic physiological response for children managing T1D. The most prevalent and accessible measure in determining glucose control is the hemoglobin A1c (HbA1c) test which is an indicator of the average blood glucose levels over the past 3 months. Children managing T1D should strive for HbA1c levels less than 7% as an elevated HbA1c level is known to increase the risk for diabetes related complications [17]. It is important for health professionals, parents, and even teachers to understand children's PA and sport participation behaviors and how they are associated with glucose control in children with T1D.

2. Materials and Methods

2.1. Procedures

This cross-sectional study was conducted at the Wendy Novak Diabetes Center, a nationally certified pediatric diabetes care and academic medical center located in the Southeastern United States. The study was approved by the University Institutional Review Board (IRB #18.0713) and parental/guardian informed consent and child assent were obtained prior to study participation. Patients between the ages of 7 to 17 years old with T1D were invited to participate in this study while in the diabetes care clinic for their regularly scheduled clinic appointment. Interested participants were given an iPad to complete the informed consent/assent process and the PA and sport participation survey which took approximately 10 min to complete. The survey was housed within REDCap [18] on a secure server. Survey data were linked to the clinical database at the Wendy Novak Diabetes Center by the researchers utilizing the patients' medical record numbers to retrieve the measured HbA1c values from that same day appointment for each participant. Once data were collected and merged, the full dataset was de-identified for analysis.

2.2. Demographic Characteristics, Diabetes Monitoring, Treatment Plans and Outcomes

Demographic characteristics utilized were participants' age, duration of T1D diagnosis, ethnicity, race, gender, insurance type, and body composition. Instead of using the more traditional body mass index (BMI) Z score, this study reports children's body composition using the tri-ponderal mass index (TMI) calculation of kg/m^3 as it has been shown to provide better reliability in determining the body composition of growing children [19,20]. Diabetes monitoring was assessed whether a participant used a continuous glucose monitor (CGM), an insulin pump, or relied solely on self-injections and monitoring. The dependent outcome variable HbA1c level, a continuous variable ranging from 6.4 to 14.9%, was obtained from that day's clinical lab measures.

2.3. Physical Activity and Sport Participation

Two survey items from the 2017 Youth Risk Behavior Surveillance System (YRBSS) questionnaire were used in this study [21]. PA participation was assessed by the following item: "During the past 7 days, on how many days were you physically active for a total of at least 60 min per day? (Add up all the time you spend in any kind of physical activity that increased your heart rate and made you breathe hard some of the time)" with response options ranging from 0–7 days. Sport participation was assessed by the following item: "During the past 12 months, on how many sports teams did you play? (Include any teams run by your school or community)" with response items ranging from 0 to 3 or more teams. Both YRBSS items have been shown to be valid and reliable in populations of children of similar ages [22].

2.4. Data Analysis

Survey data and clinical data were imported from REDCap into a spreadsheet for analysis using statistical software SPSS (IBM SPSS Statistics, Version 25.0. Armonk, NY, USA). All variables were tested for normality in which it was discovered that the HbA1c measure did not follow a normal distribution. Therefore, HbA1c was log transformed prior to statistical analysis. PA and sport participation were analyzed individually by separating participants into groups according to number of days per week of PA and sport participation. This was done in an effort to further examine the differences between self-reported weekly PA, sport participation, and HbA1c. For the first analysis participants were grouped into tertiles according to number of days they reported to have accumulated 60 min or more of PA within the past week. Levels of PA were determined by splitting the data into three equal groups, which are as follows: Tertile 1: 0–2 days/week of $\geq$60 min/PA; Tertile 2: 3–4 days/week of $\geq$60 min/PA; Tertile 3: 5–7 days/week of $\geq$60 min/PA. To test the dependent variable HbA1c a one-way ANOVA was used to determine significant differences between groups. Post hoc between-groups comparisons were carried out using Tukey's HSD to account for multiple testing. Due to the unequal distribution of sample sizes for race and ethnicity a Kruskall-Wallis test was used for differences in those groups. For sport participation, participants were separated into two groups based on whether or not they participated in an organized sport within the past year. Since this placed the sample into unevenly distributed groups, the non-parametric independent-samples Mann-Whitney U test was used for analysis.

In the secondary analyses, multiple linear regression models with HbA1c as the dependent variable were employed to examine the association between HbA1c and PA. To examine the relationships between PA and other known covariates on HbA1c independent of one another two multiple regression analyses were run with PA as the independent variable and HbA1c as the dependent variable in all models. The first model adjusted for potential confounding factors that were identified as being significantly associated to HbA1c through a Pearson's correlation analysis. A second regression model also controlled for the independent variables of the other model while including additional sociodemographic and diabetes management variables. To allow for direct comparison across covariates, results of the linear regression analysis also present the standardized beta coefficient. A p-value of < 0.05 was considered statistically significant for all statistical analyses.

3. Results

3.1. Characteristics of the Participants

A total of 153 participants submitted a completed survey. One outlier was identified and removed from the dataset leaving a total of 152 participants in the final analysis. Table 1 shows the sample characteristics and variables of all participants, as well as the separation into groups according to daily PA. Participants consisted of 71 females (46.71%) and 81 males (53.29%), were 13 $\pm$ 3 years of age with an average HbA1c level of 8.75 $\pm$ 1.81. They were, on average, physically active for 60 min or more 3.49 $\pm$ 1.95 days per week. Only

7.9% (n = 12) met the minimal recommendation of daily PA although almost two-thirds played sports (n = 98, 64.1%).

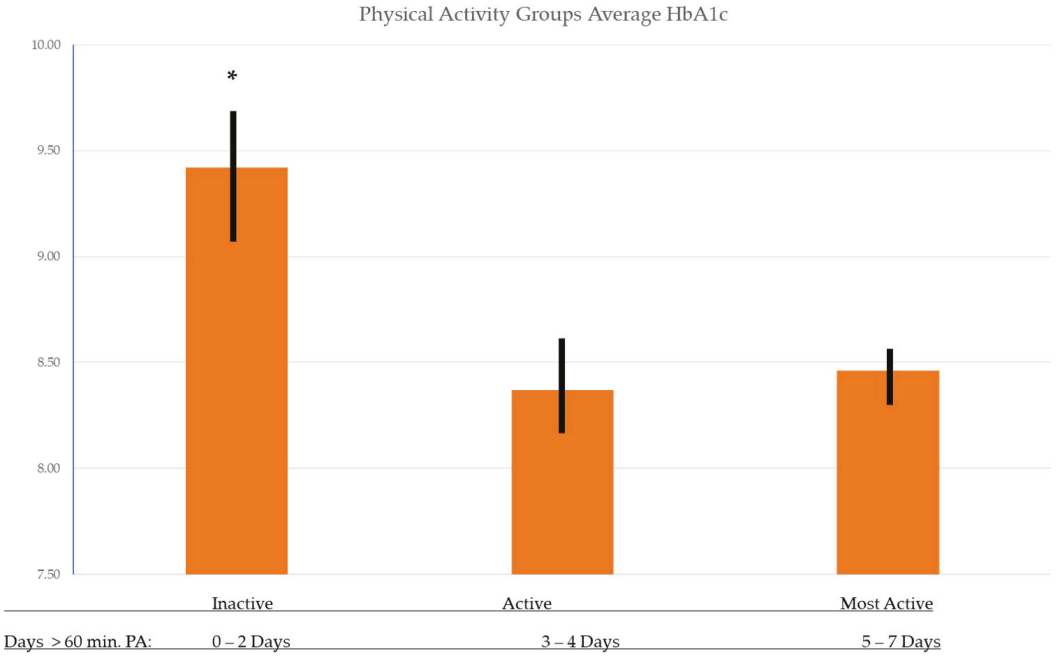
Table 1. Demographic characteristics and diabetes treatment measures for all participants and ANOVA results separated by physical activity group.

Variable	Category	All	Inactive	Active	Most Active	p-Value
Number		152	51 (33.55%)	50 (32.9%)	51 (33.55%)	
Age (avg. yrs)		13 ± 3	14 ± 3	13 ± 3	13 ± 3	0.12
Gender						0.25
	Female	71 (46.71%)	26 (50.98%)	26 (52%)	19 (37.25%)	
	Male	81 (53.29%)	25 (49.02%)	24 (48%)	32 (62.75%)	
Race						0.05
	Black	13 (8.55%)	8 (15.69%)	1 (2%)	4 (7.84%)	
	White	134 (88.16%)	41 (80.39%)	46 (92%)	47 (92.16%)	
	Other	5 (3.29%)	2 (3.92%)	3 (6%)	0	
Ethnicity						0.07
	Hispanic or Latino	5 (3.29%)	4 (7.84%)	1 (2%)	0	
	Not Hispanic or Latino	147 (96.71%)	47 (92.16%)	49 (98%)	51 (100%)	
CGM Use						0.73
	Yes	77 (50.66%)	24 (47.06%)	25 (50%)	28 (54.9%)	
	No	75 (49.34%)	27 (52.94%)	25 (50%)	23 (45.1%)	
Insulin Pump						0.85
	Yes	115 (75.66%)	40 (78.43%)	37 (74%)	38 (74.51%)	
	No	37 (24.34%)	11 (21.57%)	13 (26%)	13 (25.49%)	
Years diagnosed with T1D		4.78 ± 3.91	5.67 ± 4.06	3.84 ± 3.59	4.82 ± 3.91	0.06
Height (m)		156.54 ± 15.60	158.43 ± 14.83	154.32 ± 15.28	157.12 ± 16.67	0.40
Weight (kg)		54.36 ± 16.97	57.30 ± 18.92	53.32 ± 14.99	52.45 ± 16.67	0.31
TMI (kg/m^3)		13.91 ± 2.85	14.09 ± 3.14	14.34 ± 2.75	13.31 ± 2.59	0.16
HbA1c		8.75 ± 1.81	9.42 ± 2.18	8.37 ± 1.70	8.46 ± 1.29	0.007
Sport Participation						<0.001
	Yes	97 (63.82%)	22 (43.14%)	35 (70%)	40 (78.43%)	
	No	55 (36.18%)	29 56.86%)	15 (30%)	11 (21.57%)	
Days of PA		3.49 ± 1.95	1.29 ± 0.83	3.48 ± 0.50	5.69 ± 0.84	<0.001
Insurance Type						
	Private Company	87 (57.24%)	29 (56.86%)	30 (60%)	28 (54.9%)	0.88
	Medicare/Medicaid	122 (80.26%)	46 (90.2%)	39 (78%)	37 (72.55%)	0.07
	None	2 (1.32%)	1 (1.96%)	0	1 (1.96%)	0.61

Abbreviations: HbA1C = glycated hemoglobin; T1D = Type 1 Diabetes; PA = physical activity; CGM = continuous glucose monitor; TMI = Tri-ponderal mass index.

3.2. Associations between Frequency of Physical Activity, Sport Participation and Diabetes Health Measures

A one-way ANOVA showed statistically significant differences between PA groups indicating lower values of HbA1c as daily PA increased ($p < 0.01$) (Table 1). In a Tukey post-hoc analysis of the sub-groups it was further shown that the significant differences were observed between the Inactive and Active groups in terms of HbA1c ($p = 0.01$), as well as the Inactive and Most Active groups ($p = 0.03$) (Figure 1). Comparisons between PA groups Active and Most Active did not have a significant difference in HbA1c ($p = 0.88$). To examine the association between sport participation and HbA1c, an independent-samples Mann-Whitney U test was used and revealed no significant difference between sport participation and HbA1c levels ($p = 0.27$).



* Significant difference between Group 1 and 2 ($p < 0.05$) and Group 1 and 3 ($p < 0.05$), but not Group 2 and 3 ($p = 0.88$).

Figure 1. Differences in HbA1c Across Physical Activity Groups.

Pearson's correlation revealed significant relationships were also observed between HbA1c and age ($r = 0.19$, $p = 0.01$), race ($r = -0.18$, $p = 0.03$), CGM use ($r = -0.22$, $p = 0.006$), and duration of T1D diagnosis ($r = 0.23$, $p = 0.004$). In order to analyze factors influencing HbA1c, multiple regression analyses were performed in the whole population with total days of PA as the independent variable instead of the respective PA groups. Results from the regression analyses indicated that the more days a child engages in 60 min or more of PA the lower their HbA1c compared to less active children from this sample (Table 2). The first model adjusted for variables that had a significant correlation with HbA1c (i.e., disease duration, CGM use, age, and race), in which it was found that in addition to daily PA, other significant predictors of HbA1c included race, CGM use, and disease duration, but not age. After adjustment for all sociodemographic variables (Model 2), the association with daily PA was still statistically significant with a β-coefficient that changed to −0.18 (95% CI: −0.32 to −0.02) indicating an even stronger relationship when taking into consideration other impacts on health like insurance and common medical devices designed to help improve diabetes management as indicated in these models (i.e., CGM use and duration of diagnosis).

Table 2. Adjusted associations of sociodemographic, anthropometric, and physical activity with glycated hemoglobin ($n = 152$).

	Independent Variable HbA1c							
	Model 1 [a]				Model 2 [b]			
Variable	**β (SE)**	**Standardized Beta**	***t***	***p*-Value**	**β (SE)**	**Standardized Beta**	***t***	***p*-Value**
Intercept	11.14 (1.35)		8.23	<0.01	13.2 (2.32)		5.69	<0.001
Days of PA per week	−0.15 (0.07)	−0.16	−2.08	0.03	−0.17 (0.07)	−0.18	−2.26	0.02

Table 2. *Cont.*

Independent Variable HbA1c								
	Model 1 [a]				Model 2 [b]			
Variable	**β (SE)**	**Standardized Beta**	***t***	***p*-Value**	**β (SE)**	**Standardized Beta**	***t***	***p*-Value**
Age	0.06 (0.05)	0.09	1.06	0.29	0.04 (0.05)	0.06	0.72	0.47
Race	−0.66 (0.29)	−0.17	−2.25	0.03	−0.73 (0.34)	−0.19	−2.12	0.04
CGM use	−0.66 (0.28)	−0.18	−2.40	0.02	−0.74 (0.28)	−0.21	−2.69	0.01
Diagnosis Duration	0.08 (0.04)	0.17	2.15	0.03	0.09 (0.04)	0.19	2.30	0.02
Gender					−0.50 (0.29)	−0.14	−1.73	0.09
Ethnicity					−0.27 (0.92)	−0.03	−0.30	0.77
TMI (kg/mt^2)					−0.02 (0.05)	−0.03	−0.30	0.76
Insulin Pump use					0.04 (0.32)	0.01	0.13	0.89
Insurance Type					−0.70 (0.29)	−0.15	−1.94	0.06

Abbreviations: Hb A1C = glycated hemoglobin; PA = physical activity; CGM = continuous glucose monitor; TMI = Tri-ponderal mass index. [a] Model 1 = adjusted for physical activity, age, race, diagnosis duration, and CGM use. [b] Model 2 = adjusted for physical activity, age, race, CGM use, diagnosis duration in years, gender, ethnicity, TMI, insulin pump use, and insurance type.

4. Discussion

This study sought to determine the extent to which PA and sport participation are associated with HbA1c levels in children with T1D as well as explore the strength of relationships among demographics, diabetes treatment, HbA1c, PA, and sport participation characteristics. The results of this study indicated that children's HbA1c improved with PA, but that sport participation alone may not be enough activity to have any positive impact on HbA1c according to this sample. When separated by days of PA, results showed that children who accumulated 60 min of PA at least 3 days or more out of the week presented with lower HbA1c levels when compared to children achieving 60 min of PA only two days out of the week or less. Compared to the Inactive PA group this significant finding was also observed in children who only accumulated 3 to 4 days of PA, which is less than the current recommended amount of 60 min or more of moderate to vigorous physical activity every day of the week (Figure 1). This trend would suggest potential benefit for those children who struggle to meet the current guidelines every single day of the week.

Although almost 2/3 of the children reported playing 1 or more sports in the previous year, they were only physically active for at least 1 h or more on average 3.49 days per week. Of important practical and clinical consideration is that less than 8% of the children in this sample met the recommended duration of one hour and frequency of 7 days per week of PA. Considering that the American Diabetes Association recommends PA as a key behavior in managing T1D effectively, the children in this study were quite sedentary. Results from 2017 YRBSS data indicated that nationally 26.1% (17.5% girls and 35.3% boys) and state-wide 22.0% (12.8% girls and 31.0% boys) were physically active [21]. The sample of children in this study fell far from meeting these PA minimal guidelines.

Sport participation has long been touted as a way for children to increase duration in PA and improve overall health and T1D management [23]. Specifically, previous research has shown PA affected HbA1c levels: the more days active, the lower the child's HbA1c level. Beraki and colleagues [15] found that less active children had an average HbA1c level of 8.8 ± 1.5, while more active children had an average HbA1c level of 7.7, SD ± 1.0. Thus, sport participation, at first glance, appears to be a promising avenue for children with T1D to consider when trying to increase their PA levels. Interestingly 64.4% of the children in this sample played on at least 1 sports team in the past year, more than the national results 54.3% (49.3% girls and 59.7% boys) and statewide results of 48.3% (46.5% girls and 50.5% boys). The findings from this study suggest that daily PA had more of an impact on

reducing HbA1c levels for children with T1D than sport participation alone. These findings would also suggest that children participating in sports is not enough activity by itself to meet current recommended guidelines.

A systematic review of 23 studies with meta-analysis indicated that PA is important for diabetes management but there is a lack of studies promoting sustained PA [24]. There remains a lack of knowledge of how to safely support and promote PA in people with T1D. Results from research on self-management of T1D in the school setting has identified that while some schools have procedures that support the participation of youth with T1D in sports, other schools require that the parents be present in order for their child to participate. A lack of knowledge of T1D among school staff and coaches can be a barrier to PA among youth with T1D [25,26].

Further, results from the exploration into the demographic and PA relationship indicate that there was a negative relationship between physical activity and age, meaning that older children were less active which is concurrent in the research. Recent YRBSS findings indicate that only 35% of high school boys and 18% of high school girls engaged in 60 min of daily PA. Younger children are typically more active than older children. For example, children 6–11 years engaged in 88 min of daily physical activity compared to adolescents aged 12–15 years (33 min), and 16–19 years (26 min) [27].

Children's participation in physical activity may be limited due to lack of access to medically supervised PA opportunities for children managing T1D, and further complicated by logistical or financial reasons, especially among minority or low socioeconomically disadvantaged communities [28]. The participants' demographic characteristics of race, ethnicity, and gender were an approximate reflection of the population in the state and surrounding geographical areas. It is interesting to note that most of the children were enrolled in Medicare/Medicaid which can be indicative of lower socioeconomic status, especially considering that on average, a family with a child with T1D pays extra in medical care coverage, insurance, and expenses per year than a family without T1D. A little over one-half of the sample had additional private insurance and about one-half of the sample used a CGM as well. What is most concerning with the results of the current study is the observation of other significant predictors of HbA1c including race and CGM use which would provide additional evidence in support of racial disparities that exist in healthcare. Even with a smaller sample size, it was found that participants who identified as Black or Other had a significantly higher HbA1c compared to Caucasian participants (10.46 vs. 8.52; $p < 0.001$) after running a separate non-parametric independent samples test.

Although the results from this study did not detect statistical significance in HbA1c outcomes and sport participation, further research is encouraged from the clinical and exercise communities. With strong evidence indicating the importance of daily PA and sport participation on health, proper growth, and motor function for children of all ages recent initiatives have been put in place to help children and youth increase daily PA through sport participation [29]. Thus, hypothetically sport participation can be a way for T1D patients to improve HbA1c, yet more research studies are required to specifically analyze the differences in HbA1c levels and sport participation in children with T1D. For children with T1D, the diligence required to adequately maintain blood glucose levels, while still participating in sports, can be challenging for both the children and their families. For example, children having to stop in the middle of a sport game to treat hypoglycemia and then wait for their blood sugar to return to a safe level before participating again, can be discouraging and frustrating [30].

For children with T1D to safely and confidently participate in PA such as recess, physical education class, or sports, a comprehensive team approach among the child, parents, coaches, and medical providers must ensue. National initiatives, grounded in research, recommend that all children, including those with health conditions, have equal opportunities to participate in sports [21,27–29]. Physicians and medical care teams can prescribe PA and sport participation when designing treatment plans and to refer qualified health and fitness professionals.

This study is not without limitations. The analysis was underpowered and a larger sample size may have helped reach significant findings in areas related to sport participation. The broad range in ages possibly affected the results since some of the participants had either started puberty, or were currently experiencing changes in hormone production while in the middle of puberty. Further, it seems prudent to revisit the research hypothesis with additional participants in the future. Additionally, future research should further investigate potential covariates of the relationship between sport participation, PA, and HbA1c levels that were identified in the present study and other variables not collected here. It would also be necessary to make sure that any measurements related to diabetes management (i.e., HbA1c) are collected within a similar time-frame as sporting seasons, which this study did not do. Some participants may not have been actively participating in a sport within the past 6 months or more prior to the HbA1c reported in this study and we acknowledge this had an impact on our findings.

5. Conclusions

HbA1c levels showed a trending decrease with each day a child engaged in PA, only the number of days a child was active per week was a significant predictor of better HbA1c levels. Clinical applications of this study center around the idea that healthcare providers should be educated about the positive influence that PA and sport participation may have on HbA1c levels in their patients living with T1D.

To develop a truly collaborative clinical and translational research effort in which research and clinical practice work in tandem to help inform each other, it is important for health professionals and researchers to understand children's PA and sport participation characteristics and their impact on the glucose response to ensure safety. Understanding patients' demographic characteristics, physical activity, and sport participation behaviors, and diabetes monitoring, treatment plans, and outcomes may aid sports medicine programs in developing sport-specific programs, identifying specific sports teams in which to partner, and developing sport- and PA-specific recommendations. Since the number of days active per week was a significant predictor of better HbA1c, it behooves diabetes care teams to encourage PA in addition to sport participation alone. Further investigation should address socioecological barriers to PA and sport participation.

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HIIE Protocols Promote Better Acute Effects on Blood Glucose and Pressure Control in People with Type 2 Diabetes than Continuous Exercise

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Abstract: This study compared the acute effects of a session of different high-intensity interval exercise (HIIE) protocols and a session of moderate-intensity continuous exercise (MICE) on blood glucose, blood pressure (BP), and heart rate (HR) in people with Type 2 Diabetes Mellitus (DM2). The trial included 44 participants (age: 55.91 ± 1.25 years; BMI: 28.95 ± 0.67 kg/m^2; Hb1Ac: 9.1 ± 2.3%; 76 mmol/mol) randomized into three exercise protocols based on the velocity at which maximum oxygen consumption was obtained (vVO2 max): long HIIE (2 min at 100% v$\dot{V}$o2peak + 2 min of passive rest); short HIIE (30 s at 100% v$\dot{V}$o2peak + 30 s of passive rest); or MICE (14 min at 70% v$\dot{V}$o2peak) on a treadmill. Capillary blood glucose, BP, and HR measurements were taken at rest, during peak exercise, immediately after the end of exercise, and 10 min after exercise. Long and short HIIE protocols reduced capillary blood glucose by 32.14 mg/dL and 31.40 mg/dL, respectively, and reduced systolic BP by 12.43 mmHg and 8.73 mmHg, respectively. No significant changes were observed for MICE. HIIE was found to promote more acute effects than MICE on glycemia and BP in people with DM2.

Keywords: hyperglycemia; interval training; blood pressure; physical exercise; heart rate

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1. Introduction

Diabetes mellitus type 2 (DM2) is a chronic metabolic condition characterized by high blood glucose levels due to impaired insulin sensitivity and associated with autonomic dysfunction, retinopathy, neuropathy, nephropathy, and cardiovascular diseases, among other complications [1]. In this regard, cardiovascular diseases are the most common cause of death among people with diabetes mellitus [2]. Therefore, controlling risk factors such as blood glucose and blood pressure (BP) is essential for reducing cardiovascular complications during both rest and effort [3].

Non-pharmacological treatments that involve lifestyle changes, such as regular physical exercise, are effective strategies for controlling and preventing DM2, leading to reductions in glycated hemoglobin (HbA1c) levels, blood glycemia [4,5], and BP [6]; increases in insulin sensitivity [7] and cardiorespiratory fitness [8]; and improved lipid profile [9]. However, as DM2 is usually accompanied by other performance-limiting clinical conditions, there is a need for a comprehensive discussion regarding the type, intensity, and duration of exercise for this population, taking cost–benefit analysis into consideration [10].

Although most guidelines recommend moderate-intensity continuous training, some studies have shown that high-intensity interval exercise (HIIE) has positive effects on the cariometabolic risk factors of people with DM2 [11,12]. This type of training can induce similar cardiometabolic adaptations and, in some cases, proves even better than moderate-intensity continuous exercise (MICE), especially in improving glycemic control, glycated hemoglobin, and the cardiorespiratory fitness of people with DM2 [7,10,13,14].

Previous studies have shown that different HIIE protocols have different impacts on acute and chronic responses, which makes it necessary to analyze HIIE considering its specific characteristics, instead of drawing general conclusions [15]. Among the variables that can be manipulated during HIIE, the duration of exercise has been shown to have an important impact on cardiovascular stress [16,17]. Even when the intensity and amount of exercise are kept constant, reducing the duration of this exercise seems to reduce the cardiovascular risk, suggesting that short HIIE (with a duration of 1 min or less) can promote a lower heart rate than MICE, even when it is performed at higher intensities [16,18,19]. However, these studies are limited to young healthy people.

Thus, given the controversies and the scarcity of studies investigating the acute effects of different HIIE and MICE protocols in people with DM2, the objective of this study was to investigate and compare the acute effects of one session of different HIIE protocols and one session of MICE on the capillary blood glucose, blood pressure, and heart rate of people with DM2.

2. Materials and Methods

2.1. Participants and Procedures

Patients were recruited from the 3rd Diabetes Marathon promoted by the Eye Bank Foundation of the State of Goiás, Brazil, in November 2018. The inclusion criteria were patients having been diagnosed with DM2, over 40 years old, and not having participated in any physical training program for at least 6 months. Patients with self-reported infectious disease; self-reported smoking; arrhythmias, angina, and frequent extrasystoles; severe lung diseases; and self-reported musculoskeletal and cardiovascular problems that could impair the evaluation were excluded from the study.

2.2. Data Collection

Data collection took place in three visits. The first involved an interview and blood collection; the second involved anthropometric and hemodynamic evaluations and the cardiopulmonary exercise test; and the third involved physical exercise sessions.

During the first visit, the volunteers completed a questionnaire to capture their personal data, clinical history, disease progression, and the medications they used. Blood collection was then performed after 12 h of fasting. Their fasting blood glucose and HbA1c dosage were evaluated to confirm the diagnosis. Their fasting blood glucose was evaluated according to the enzymatic method using LABTEST kits and the LABMAX PLENNO equipment [20]. A glycated hemoglobin kit was used to measure their HbA1 dosage, using the colorimetric test (Laborclin, Pinhas, Paraná). On a different day, the patients had their cardiac and pulmonary auscultation and resting BP and HR measured using an automated oscillometric sphygmomanometer (Omron HEM-705) following previous recommendations [21]. The patient rested seated for 10 min before each measurement was taken. During measurement, the patient's shoulder was flexed and their elbow was extended to the level of their heart. During the anthropometric assessments, patients remained barefoot and wore light clothing. Their body mass index (BMI) was calculated by dividing their body mass by their height measured in meters squared (kg/m^2) [22]. During the first visit, patients were instructed to avoid radical changes in their diet until the day of the exercise session in order to prevent bias in glycemic control.

A cardiopulmonary exercise test was used to identify possible changes in hemodynamic, ventilatory, and cardiovascular responses to physical exertion using a ramp-type load increment protocol with a treadmill (Micromed®, Centurion 200, Brasília, Brazil)

and gas analyzer (Cortex analyser® Metalyser II, Rome, Italy). The test started with a two-minute warm-up and then the speed was increased by 0.1 km/h every 10, 20, or 30 s until exhaustion, without inclination. The test was followed by a four-minute recovery period. The patients' heart rate was continuously monitored using a heart monitor (Polar v800, Kempele, Finland) and their blood pressure was measured by Korotkoff auscultation with a mercury sphygmomanometer (WanMed, São Paulo, SP, Brazil) and a stethoscope (Littman, São Paulo, MN, USA). The test was supervised by a trained professional and it was interrupted if the patient experienced strige discontinuity or reached their predicted maximum heart rate or a respiratory exchange ratio >1.15 [23].

The velocity at which the volunteers reached peak oxygen consumption (v$\dot{V}$o2peak) was used to determine the amount of exercise they were prescribed.

2.3. Exercise Sessions

The exercise sessions were conducted in a public hospital. The patients were randomized among three protocols adapted from previous studies [16,24,25]. The patients who were assigned the long HIIE protocol carried out five repetitions of 2 min at 100% of v$\dot{V}$o2peak, with 2 min of passive recovery; patients assigned the short HIIE carried out 20 reps of 30 s at 100% vVo2max, with 30 s of passive recovery; and those assigned MICE carried out 14 continuous minutes at 70% of v$\dot{V}$o2peak. All the protocols included a warm-up and a cool-down of 2 min at 50% of v$\dot{V}$o2peak. Familiarization sessions were carried out twice a week during two consecutive weeks, with characteristics similar to those of the data collection.

The testing sessions took place during the third week. Before the evaluation, the patients remained seated for 10 min and had their blood glucose, BP, and HR measured. Then, each patient performed a physical exercise session, and the same measurements were repeated 10 min after the test. Their capillary blood glucose was measured using the AccuCheck Perfoma glucometer, using the index finger. BP and HR were measured using the Omron 7122 automatic sphygmomanometer. Their central ("cardiorespiratory") and peripheral ("muscular") RPE were monitored using the adapted Borg Scale (0 to 10). We opted to separate the RPE because our group had shown that people with high levels of blood glucose might demonstrate an unmatched response between muscular and cardiac responses [26,27]. Figure 1 shows the characteristics of the training protocols and session logistics.

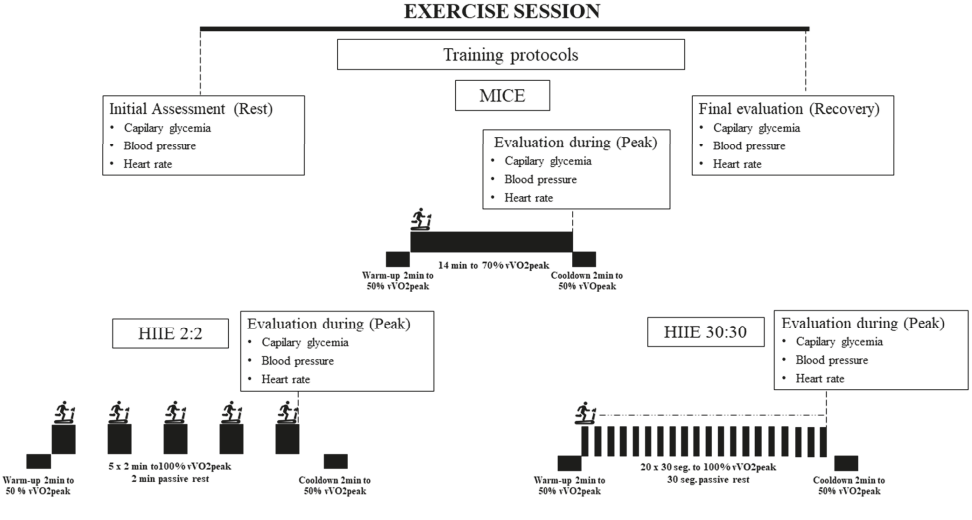

Figure 1. Diagram of training protocols in the session. HIIE: high-intensity interval exercise; MICE: moderate-intensity continuous exercise; vVo2max: velocity relative to the maximum volume of oxygen.

2.4. Data Analysis

Two-way ANOVA with repeated measurements was performed for intra-group and between-group comparisons. Repeated measures were used, with the confidence interval adjusted by the Bonferroni method for post hoc comparisons. The effect size was calculated by η^2. The level of significance was $p \leq 0.05$. Data were analyzed in the Statistical Package for Social Sciences (SPSS—IBM Corp, Armonk, NY, USA), version 2.0.

3. Results

A total of 44 individuals with a mean time of diagnosis of 11.98 ± 6.46 years participated in this study. The medications most commonly used by the participants were biguanide (Metformin—40%; Glifage—17.8%), diuretics (Hydrochlorothiazide—28.9%), angiotensin receptor antagonists (Lozartana—22.2%; Aradois—15.9%), and statins (Simvastatin—6.7%). Most participants were overweight according to BMI classification >25.0 kg/m^2 (n = 35, 79.5%). The other sample characteristics are presented as means ± standard deviations in Table 1. One-way ANOVA showed no significant differences between groups for any variable before evaluation ($p > 0.05$)

Table 1. Characteristics of patients with DM2 classified by group.

	HIIE Long (n = 14)	HIIE Short (n = 15)	MICE (n = 15)	TOTAL (n = 44)
Age (years)	54.64 ± 8.91	55.67 ± 7.44	57.33 ± 8.93	55.91 ± 1.25
Weight (kg)	80.65 ± 14.52	79.45 ± 10.95	76.27 ± 16.91	78.75 ± 21.30
BMI (kg/m^2)	29.44 ± 4.94	28.94 ± 3.64	28.49 ± 4.94	28.95 ± 0.67
Blood glucose (mg/dL)	142.43 ± 59.06	126.47 ± 38.23	133.80 ± 54.84	134.05 ± 7.62
Hb1ac (% mmol/mol)	9.6 ± 2.9; 81	8.9 ± 1.6; 74	9.0 ± 2.4; 75	9.1 ± 2.3; 76
HR (bpm)	75.0 ± 7.38	66.0 ± 9.35	70.75 ± 9.39	71.11 ± 9.07
SBP (mmHg)	143.57 ± 23.65	131.07 ± 14.24	131.0 ± 15.12	135.12 ± 18.62
DBP (mmHg)	90.14 ± 12.24	83.47 ± 9.19	87.50 ± 8.69	86.95 ± 10.28

HIIE: high-intensity interval exercise; MICE: moderate-intensity continuous exercise; BMI: body mass index; Hb1ac: glycated hemoglobin; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

The mean treadmill speed and RPE for each group are presented as mean ± standard deviation in Table 2. RPE was significantly higher for long HIIE than short HIIE and MICE.

Table 2. Mean values of speed and subjective perception of exertion of patients with DM2 organized by group.

	HIIE Long (n = 14)	HIIE Short (n = 15)	MICE (n = 15)	TOTAL (n = 44)
Velocity (km/h)	8.22 ± 0.56	7.32 ± 0.38	5.19 ± 0.43	6.88 ± 2.14
Central SPE	7.5 ± 1.02 *	5.47 ± 2.0	5.33 ± 2.29	6.07 ± 2.07
Peripheral SPE	7.79 ± 1.37 *	5.80 ± 2.37	5.80 ± 1.74	6.43 ± 2.06

* $p < 0.05$, values with significant differences when compared to the other groups.

Comparisons between patients' cardiovascular variables and blood glucose at rest, peak, and recovery are presented as means ± standard deviations along with pre-post variations (Δ) and effect sizes (η^2) in Table 3.

There was an increase in SBP at the peak of the training session in all groups. However, the values reduced beyond the basal state in both HIIE groups, with greater decreases seen for long HIIE ($p < 0.05$). DBP did not show significant changes for any protocol. HR significantly increased at the peak of the exercise in all groups and was higher for both HIIE groups than for MICE.

Blood glucose significantly reduced only at peak exercise for MICE. There was a reduction in blood glucose from post- to pre-test for the HIIE groups, with a greater reduction seen for long HIIE (Δ = 32.14 mg/dL). Effect sizes were large ($\eta^2 > 0.14$) for the HR values in the long HIIE groups, intermediate ($0.06 < \eta^2 < 0.11$) for the SBP values in the HIIE groups, and for HR in the short HIIE and MICE groups.

Table 3. Comparison of cardiovascular variables and blood glucose at rest, peak, and recovery from the evaluation of patients with DM2 organized by group.

		Resting	Peak	Recovery	Δ	η^2
HIIE long	SBP	134.21 ± 19.95	159.93 ± 6.72	121.79 ± 14.68	−12.43 *	0.11
HIIE short		123.60 ± 12.72	154.0 ± 4.96	114.87 ± 9.08	−8.73 *	0.13
MICE		125.33 ± 15.56	155.0 ± 7.22	124.87 ± 17.30	−0.47	0.00
HIIE long	DBP	134.21 ± 19.95	159.93 ± 6.72	121.79 ± 14.68	−12.43 *	0.11
HIIE short		123.60 ± 12.72	154.0 ± 4.96	114.87 ± 9.08	−8.73 *	0.13
MICE		125.33 ± 15.56	155.0 ± 7.22	124.87 ± 17.30	−0.47	0.00
HIIE long	HR	77.57 ± 9.33	133.93 ± 11.70	89.93 ± 12.04	12.35 *	0.24
HIIE short		79.60 ± 10.70	124.53 ± 6.55	92.07 ± 23.41	12.47 *	0.10
MICE		76.6 ± 12.25	105.0 ± 9.30	84.73 ± 13.32	8.13	0.09
HIIE long	Glucose	172.86 ± 77.33	161.29 ± 77.05	140.71 ± 72.61	−32.14 *	0.04
HIIE short		168.67 ± 73.88	152.33 ± 68.12	137.27 ± 69.31	−31.40 *	0.04
MICE		148.13 ± 43.99	126.80 ± 44.0	143.07 ± 56.80	−5.07	0.00

HIIE: high-intensity interval exercise MICE: moderate-intensity continuous exercise; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Δ: rest–recovery variation; η^2: effect size. Values are expressed as means and standard deviations. * $p < 0.05$, values with significant differences.

4. Discussion

The present study aimed to investigate the acute effects of different HIIE and MICE protocols on capillary blood glucose, BP, and HR in people with DM2. Long and short HIIE sessions reduced capillary blood glucose by 32.14 mg/dL and 31.40 mg/dL after exercise, while glycemia significantly decreased during MICE (21.14 mg/dL) and tended to increase during HIIE. This information might be important for glucose monitoring and diet adjustment. For example, if glycemia is low before HIIE, it might be interesting to evaluate the need for glucose ingestion after exercise or to adjust medication dose or timing in exercise days to avoid hypoglycemia. The lowest glucose levels during MICE also might have applications for medication and diet adjustments, since it might be necessary to ingest glucose or to reduce medication dosage before exercise. This might also help to determine the type of exercise best suited to the patient's current state. To avoid hypoglycemia during exercise, HIIE should be chosen; however, to avoid hypoglycemia after exercise, MICE should be chosen.

These results might also have an impact on clinical aspects, since regular exercise sessions might help in glycemic control, which is a critical objective in DM2 treatment as it reduces the incidence of related complications, including the risk of cardiovascular events [13]. In this regard, our study corroborates previous studies which showed reductions of 40 mg/dL immediately after exercise, lasting for up to 6 h after and reaching reductions of 60 mg/dL [28]. In a more prolonged analysis, Gillen et al. showed that a single session of HIIE reduced the mean 24 h glucose and postprandial glucose in people with DM2 [11].

The differences found in glycemic response between exercise modes are in agreement with previous studies and might be related to the physiological impact of different exercise intensities and their interactions with the medications used [29,30]. Lower-intensity activity has a higher dependence on the glucagon/insulin axis for controlling blood glucose, which might be affected by medications such as insulin and biguanides. However, higher-intensity physical activities had a higher impact on the sympathetic system and depended more on catecholamines, which are not affected by the most common hypoglycemic medications.

In patients with DM2, HIIE is usually associated with a transient increase in blood glucose levels, which occurs because, during exercise, there is a greater degradation of hepatic glycogen (glycogenolysis). This degradation makes glucose available to the bloodstream, resulting in an acute increase in capillary blood glucose [30]. However, there was no such increase in blood glucose at peak exercise in the present study, only a progressive reduction, as in the studies by Mendes et al. [14] and Santiago et al. [6]. The hypothesis for

this finding is that the initial glycemic values were already very high, which might have prevented further increases.

After physical exercise, there was a reduction in blood glucose, which might be associated with increased blood flow to the patients' muscle fibers and improvement in their mitochondrial function, increasing tissue sensitivity to insulin and, therefore, glucose uptake in muscles and adipocytes [3]. In addition, there was an increase in the activity of glycolytic and oxidative enzymes [6].

As for cardiovascular stress markers, SBP increased similarly during exercise, but reduced by 12.43 mmHg and 8.73 mmHg during recovery from long and short HIIE, respectively. Although the acute increases might reflect an increased risk, the exercise hypotensive response might have important clinical applications, since it is associated with long-term benefits in BP reduction [31–34]. In this sense, the reduction in SBP has important clinical implications for treating people with DM2 because controlling BP contributes to alleviating microvascular and macrovascular risks. There was also an increase in HR at peak exercise in both HIIE protocols, while the MICE group did not show significant HR changes. Therefore, a single session of HIIE, either long or short, might provide more acute cardiovascular stress than MICE, but have a more pronounced effect on post-exercise hypotension. This information is important for a cost–benefit analysis. If the patient's cardiovascular risk is high, it is recommended to be more conservative and propose MICE; however, it the risk is controlled, then HIIE might be chosen for its potentially higher benefits.

Long HIIE had significantly higher RPE values when compared to short HIIE and MICT. Central RPE is related to respiratory-metabolic effort, and closely related to ventilation, oxygen consumption, and HR, among other physiological mediators. Peripheral SBP, on the other hand, refers to the local effort related to metabolic acidosis, regional blood perfusion, and energy substrates [13,18]. Therefore, the present results showed that long HIIE is the most strenuous, requires the most effort, and results in a high recovery-rest variation, which must also be considered during exercise prescription to avoid attrition, since exercise adherence is associated with the reductions in glycated hemoglobin [35].

This study of the acute responses to different exercise models support the results of different randomized clinical trials that analyzed skeletal muscles [27], the vascular system, respiratory changes [24], cardiac function [36,37], exercise capacity [38], inflammation, quality of life [36], and other physiological markers such as $\dot{V}O2peak$ and endothelial function, with greater improvements seen for the HIIE protocols compared to MICE [8,24,36]. However, it is important to test to chronic adaptation to different protocols in order to see if these acute effects are reflected in long-term changes.

5. Conclusions

Our results provide important information for exercise prescription, taking cost–benefit analysis into consideration. Based on the acute responses, it can be concluded that HIIE, especially long HIIE, might promote the best clinical outcomes; however, it is also associated with higher perceived effort, which can increase the risk of attrition and acute events. On the other hand, although MICE was associated with lower beneficial responses, it was also the exercise type with lower risk factors and lower effort perception. Therefore, MICE could be used during the adaptation phase and for patients at higher risk. On the other hand, HIIE could be used for progression and when the risk factor is controlled to obtain better clinical results. Moreover, during the analysis of acute effects, it might be of clinical importance to adjust a patient's diet and medication. In this regard, it would be important to monitor their blood glucose after HIIT to determine the need to increase glucose ingestion or decrease medication dose when performing protocols that decrease blood sugar.

Limitations

Due to the nature of the study, it was not possible to use a blind methodology. Other limitations were the sample size and the absence of a longer follow-up after the exercise sessions. The present study involved a between-subject comparison; therefore, it cannot account for interindividual differences in exercise responses. For that, it would be necessary to perform each type of exercise and use a within-subject design to evaluate the potential effects in a more rigorous manner. However, we opted for this design in order to avoid the effects of repeated exercise bouts.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee (Opinion No. 2667732, CAAE No. 54522016.6.0000.5083) and duly registered in the registry of clinical trials (TRIAL: RBR-4RJGC3).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available on Google Drive. The data presented in this study are openly available at: https://drive.google.com/drive/folders/1PdUEMd5UlJUwjU1Gi-rq5rVI7Woiy461?usp=sharing (accessed on 12 January 2022) under the title artigo HIIT.

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Comment

Comment on Teles et al. HIIE Protocols Promote Better Acute Effects on Blood Glucose and Pressure Control in People with Type 2 Diabetes than Continuous Exercise. *Int. J. Environ. Res. Public Health* 2022, *19*, 2601

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After a careful appraisal, we are concerned that the article "HIIE Protocols Promote Better Acute Effects on Blood Glucose and Pressure Control in People with Type 2 Diabetes than Continuous Exercise" [1] may have some errors that warrant further review by the editor and authors, and which may impact the original article's conclusions.

Point 1

Regarding the reported statistical description: The article did not note if a normality test was conducted. Additionally, in the supplementary files, the authors highlight those seven variables passed, but eight did not pass in normality. It seems that the authors chose the Kolmogorov–Smirnov test to assume normality, and this test is used with samples up to 100, but the Shapiro–Wilk test is preferred for samples less than 50 [2]. If the assumption of normality is violated, interpretation and inference may not be reliable or valid [2]. More than 50% of the variables do not pass in normality test. The RM ANOVA criteria were violated, and the authors indicate the use of One-Way ANOVA in the results (this is conflicting information). Version 2.0 of SPSS does not exist. The eta squared does not have a reference for interpretation.

Point 2

The entire article needs major revisions regarding terminology. Including the following: The maximal oxygen consumption ($\dot{V}O_{2max}$) and $\dot{V}O_{2peak}$ were not the same terminology and did not present a standard. The medication Losartan was written incorrectly. Glycated hemoglobin (HbA1c) was written incorrectly in various sentences. The RPE (rate of perceived exertion) was described in the methods, and SPE was described in the results (Table 2). Five participants initiated the exercise with blood glucose higher than 250 mg/dL, which is not recommended [3]. The blood glucose data for subject number seven available on Google Drive present a value of 1110 at peak value. This value is wrong, because the Accu-Chek Performa glucometer indicates a maximal value of 600 mg/dL. Different blood pressure monitor types and models were used: an oscillometric sphygmomanometer (OMRON HEM-705 described at data collection and OMROM HEM-7122) and a mercury sphygmomanometer (auscultatory), which violates the internal consistency. It is not clear which arm was measured—both, right, or left arm? It is essential to describe this information according to the guidelines: "measure BP in both arms, preferably simultaneously. If there is a consistent difference between arms > 10 mmHg in repeated measurements, use the arm with the higher BP" [4].

Another critical point is the incremental test protocol. "The test started with a two-minute warm-up, and then the speed was increased by 0.1 km/h every 10, 20, or 30 s until exhaustion, without inclination". How did this increment work? It is not clear. It is necessary to insert the bibliography to determine this protocol. We suggest the authors

insert a reference for the protocol. Since 1996, a 1% treadmill grade most accurately reflects the energetic cost of outdoor running [5].

Point 3

In the discussion section, the authors cited the Santiago et al. (2017) study, which demonstrated reductions in BP and blood glucose after continuous and interval exercise [6]. However, the Santiago study did not cite or analyze glycolytic and oxidative enzymes, as mentioned in the present article: "In addition, there was an increase in the activity of glycolytic and oxidative enzymes" [1].

Point 4

In conclusion, we flag concerns about the data extraction accuracy, its analysis, and procedures that cannot be replicable (one principle of good and clear science). We, therefore, respectfully seek clarification and major revision.

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Conflicts of Interest: The authors declare that the letter was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Article

Diagnosis of Muscle Fatigue Using Surface Electromyography and Analysis of Associated Factors in Type 2 Diabetic Patients with Neuropathy: A Preliminary Study

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Abstract: Diabetic neuropathy (DN) is a major complication associated with diabetes mellitus (DM) and results in fatigue. We investigated whether type 2 diabetic patients with or without neuropathy experienced muscle fatigue and determined the most influencing factor on muscle fatigue. Overall, 15 out of 25 patients with type 2 DM were diagnosed with DN using a nerve conduction study in the upper and lower extremities, and the composite score (CS) was calculated. We obtained the duration of DM and body mass index (BMI) from subjects, and they underwent a series of laboratory tests including HbA1c, fasting plasma glucose, triglycerides, and high- and low-density lipoprotein. To qualify muscle fatigue, this study used surface electromyography (sEMG). Anode and cathode electrodes were attached to the medial gastrocnemius. After 100% isometric maximal voluntary contracture of plantarflexion, the root mean square, median frequency (MDF), and mean power frequency (MNF) were obtained. We showed a correlation among laboratory results, duration of DM, BMI, CS, and parameters of muscle fatigue. The duration of DM was related to fatigue of the muscle and CS ($p < 0.05$). However, CS was not related to fatigue. The MDF and MNF of muscle parameters were positively correlated with HbA1c and fasting plasma glucose ($p < 0.05$). In conclusion, we suggest that the duration of DM and glycemic control play important roles in muscle fatigue in patients with DN. Additionally, sEMG is useful for diagnosing muscle fatigue in patients with DN.

Keywords: type 2 diabetes mellitus; diabetic neuropathy; surface electromyography; fatigue

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1. Introduction

Diabetic neuropathy (DN) is a peripheral nerve dysfunction, and one of the major complications associated with diabetic retinopathy and diabetic nephropathy [1,2]. DN has a high prevalence among diabetic patients [2,3]. In particular, this is more common in patients with type 2 diabetes mellitus (DM) [2]. DN induces symmetrical neuropathic pain which is manifested as a stocking and glove pattern and presents with fatigue and sensory disturbances with motor disturbances being seen in more severe conditions inducing distal weakness and muscle atrophy of the lower legs and feet [2,4,5]. Fatigue is a common complication and leads to an energy imbalance [6,7], in addition to affecting the quality of life and functional status in people with type 2 DM [8,9].

Muscle fatigue is considered a multifaceted phenomenon consisting of physical and chemical changes in muscles which are distinct from alterations in the nervous system efficiency underlying the symptoms, causes, and mechanisms. Muscle fatigue is defined as a decreased maximum capacity to produce force or power output [10]. A range of methods has been used to analyze muscle fatigue, including muscle biopsy, muscle imaging, exercise endurance tests, and isometric strength tests. Due to its non-invasiveness nature, real-time data, and applicability, surface electromyography (sEMG) is a widely used technique to assess muscle fatigue [11,12]. The root mean square (RMS), mean power frequency (MNF),

and median frequency (MDF) obtained from sEMG are useful parameters for assessing muscle fatigue [10,13,14].

A previous study showed that weakness of the ankle plantar and dorsal flexors was progressive and contributed to the severity of neuropathy in patients with symptomatic diabetic neuropathy [4]. The aim of this study was to study the correlation among various parameters, including laboratory studies, duration of diabetes mellitus (DM), body mass index (BMI), nerve conduction studies (NCS), and muscle fatigue (RMS, MDF, and MNF) diagnosed using sEMG in type 2 diabetic patients with and without neuropathy, as well as to investigate the relationship between DN and muscle fatigue and identify its most influencing factors.

2. Materials and Methods

2.1. Participants

Twenty-five patients with type 2 DM who were not previously diagnosed with DN were enrolled in this study. Patients with liver disease, renal disease, chronic alcoholism, and a history of chemotherapy or spine surgery were excluded. Patients with suspected or diagnosed psychological factors related to fatigue [15], spine disease, and vascular, neurological, or metabolic conditions unrelated to DM or DN were also excluded This study was performed retrospectively and in accordance with the Declaration of Helsinki; the study protocol was approved by the Inha University Hospital Institutional Review Board (approval number: 2019-10-018) on 18 November 2019.

Patients with type 2 DM were divided into two groups: with or without DN. Before NCS, all subjects had their history taken, including the duration of DM, and their BMI was assessed. Laboratory tests including HbA1c, fasting plasma glucose (FPG), albumin, creatinine, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were performed. DN examination was performed using NCS. The method of NCS was the same as that reported in a previous study [1,6], using Keypoint electromyography (Dantec, Skovlunde, Denmark), and the temperature of patients during NCS was maintained above 32 °C. This study performed NCS in the upper and lower extremities with more severe sensory or motor symptoms. Examination of motor nerve function used the median, ulnar, posterior tibia, and peroneal nerve. The onset latency, amplitude, velocity, and minimal F-M latency were measured in these nerves. The peak latency and peak-to-peak amplitude were determined from a sensory examination on the median, ulnar, superficial peroneal, and sural nerves. A diagnosis of DN was determined on the basis of abnormal findings, in which a difference of more than two standard deviations above the normal value (Table 1) was observed using the method reported by Dick et al. [16]. DN was said to occur after identifying three or more abnormal findings among the onset latency, amplitude, conduction velocity, and F-latency in more than two of the median, ulnar, peroneal, sural, and tibia nerves. The composite score (CS) has previously been used to quantify NCS [1,6,17]. In previous studies, CS was defined as an objective measure by quantifying the degree of damage to the peripheral nerves in diabetic neuropathy [1]. As in the previous study, we calculated CS using the onset latency, amplitude, and velocity of the peroneal nerve, the distal latency of the tibia nerve and the amplitude of the sural nerve, comparing the results with the normal values of the hospital (Table 1). Additionally, we used the following scores: 0 below the 95th percentile, 1 from the 95th to 99th percentile, 2 from the 99th to 99.9th percentile, and 3 above the 99.9th percentile; all scores were added together and divided by 5. An increase in CS indicates severe neuropathy [1].

Table 1. Electrophysiological criteria for abnormal nerve conduction study.

Median Motor Nerve	Median Sensory Nerve	Ulnar Motor Nerve	Ulnar Sensory Nerve
L > 4.0 ms A < 5.0 mV CV < 49.0 m/s MF > 24.2 ms	L > 3.5 ms A < 10.0 μV	L > 3.8 ms A < 5.0 mV CV < 49.0 m/s MF > 24.8 ms	L > 3.4 ms A < 7.5 μV
Peroneal Motor Nerve	**Superficial Peroneal Sensory Nerve**	**Tibial Motor Nerve**	**Sural Sensory Nerve**
L > 4.5 ms A < 1.0 mV CV < 40.0 m/s MF > 45.0 ms	L > 3.5 ms A < 3.7 μV	L > 5.0 ms A < 5.0 mV CV < 40.0 m/s MF > 45.3 ms	L > 3.5 ms A < 5.0 μV

Note: L, latency; A, amplitude; CV, conduction velocity; MF, minimal F-M latency.

2.2. Exercise Protocol

Participants were placed in the prone position. We used the gastrocnemius medial (GCM) to evaluate muscle fatigue from a previous study [18]. The skin of the subjects was cleaned with alcohol wipes before fixation of the electrodes [10]. The Ag/AgCl surface electrodes (diameter: 30 mm) were placed with the anode attached to the motor point of GCM, and the cathode 2 cm from the anode (Figure 1). To evaluate muscle fatigue, the subjects performed maximal ramp contraction (ramp-up rate: 5% MVC/sec) after a resting time of 10 min. When the isometric maximal voluntary contraction (MVC) was 100%, the participant was asked to sustain it for 30 s. To obtain the MVC of the subjects, they performed maximal plantarflexion for a set time.

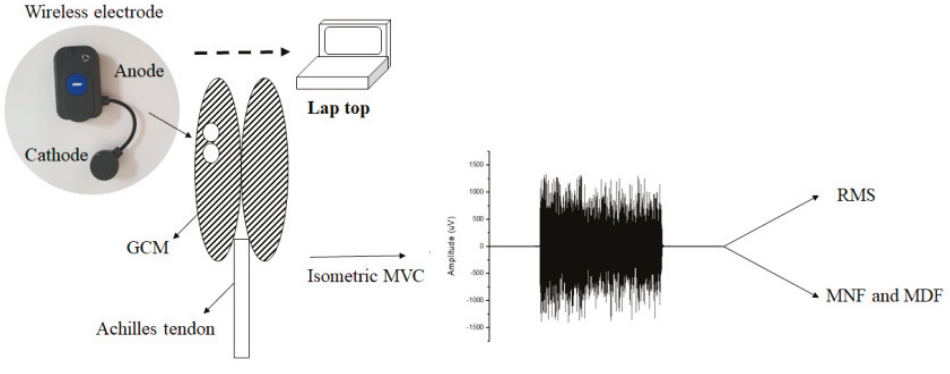

Figure 1. Surface electromyography detection and analysis. This schematic illustration shows the positioning of surface electrodes using wireless electrode devices. Signals obtained during isometric MVC. Note: GCM, medial gastrocnemius; MVC, maximal voluntary contraction; RMS, root mean square; MNF, mean power frequency; MDF = median frequency.

2.3. Signal Processing

The RMS, MDF, and MNF, by plantarflexion in the prone position, were measured using the sEMG system (EMGworks 4.0 Analysis program, Delsys, Germany). The removal of noise generated by the electrocardiogram was performed using 50–500 Hz band-pass filtering, and sampling was set to 1,000 Hz. Using filtering techniques, artifacts were eliminated. To investigate fatigue, the RMS (unit: μV), MDF (unit: Hz) and MNF (unit: Hz) were calculated after the "Fourier transform" and were analyzed using filtered data. Distributions of RMS explain the action potential energies during the contractions, defined as below [10]:

$$\mathrm{RMS} = \sqrt{\frac{\sum_{f=1}^{n} \mathrm{rawData}_f}{n}}$$

where i is the procedure number of the processing sample, rawDdata$_i$ is the value of the i-th sample point, and n is the total number of data points).

The most representative valuable frequency-domain characteristics are MNF and MDF. For the evaluation of muscle fatigue in sEMG signals, MDF and MNF are defined as follows [10]:

$$\int_0^{MDF} P(t,\omega)d\omega = \int_{MDF}^{\infty} P(t,\omega)d\omega$$

$$= \frac{1}{2}\int_{MDF}^{\infty} P(t,\omega)d\omega$$

$$MNF = \frac{\int_0^{\infty} \omega P(t,\omega)d\omega}{\int_0^{\infty} P(t,\omega)d\omega}$$

where (t,ω) is the power spectrum of EMG signals based on wavelet packet transformation.

2.4. Statistical Analysis

Quantitative data are reported as the mean ± standard deviations, and statistical analysis was performed using the SPSS software (version 26.0; SPSS, Chicago, IL, USA). The baseline characteristics in patients with and without DN were compared using an independent sample t-test. To identify a normal distribution, the Kolmogorov–Smirnov test was used on all data. Pearson correlation analyses were also conducted. A p-value of <0.05 was considered statistically significant.

3. Results

Among the 25 subjects with DM, 15 subjects were diagnosed with DN. The comparison between subjects with DN and subjects without DN was investigated using a t-test after verification of a normal distribution using the Kolmogorov–Smirnov test. Subjects with DN had lower albumin levels (Table 2, $p < 0.05$). Although the mean HbA1c and FPG were higher in patients with DN than in patients without DN, the difference was not statistically significant ($p > 0.05$).

Table 2. Clinical characteristics of DM patients with or without DN. (* $p < 0.05$).

Characteristic	DM − DN (n = 10)	DM + DN (n = 15)	p-Value
Sex, men/women	5/5	8/7	
Age (years)	45.67 ± 11.44	48.00 ± 16.24	0.615
Duration of DM, years	5.23 ± 5.89	10.43 ± 6.47	0.066
Height (cm)	165.63 ±11.24	166.16 ± 8.20	0.897
Weight, kg	76.09 ± 18.88	68.99 ± 19.18	0.394
BMI (kg/m$^{2)}$	27.62 ± 5.78	24.73 ± 5.33	0.233
Albumin (g/dL)	4.52 ± 0.35	4.01 ± 0.425	0.007 *
Creatinine (mg/dL)	0.96 ± 0.45	2.09 ± 3.35	0.328
HbA1c (%)	10.29 ± 2.48	10.35 ± 3.30	0.963
FPG (mg/dL)	192.33 ± 61.22	191.57 ± 91.71	0.983
TG (mg/dL)	180.56 ± 70.47	200.50 ± 170.85	0.744
HDL-cholesterol (mg/dL)	46.56 ± 8.23	45.71 ± 14.70	0.878
LDL-cholesterol (mg/dL)	106.00 ± 38.12	105.38 ± 39.71	0.968

Note: DM, diabetic mellitus; DN, diabetic neuropathy; BMI, body mass index; FPG, fasting plasma glucose; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Values are the mean ± standard deviation. * $p < 0.05$.

CS, which indicates the severity of DN, was higher in the subjects with DN (mean ± SD: 0.70 ± 0.45) than those without DN (mean ± SD: 0.07 ± 0.10, $p < 0.05$). The mean MDF ($p = 0.028$) and MNF ($p = 0.027$) in subjects with DN were significantly lower than in the subjects without DN. However, the RMS between groups was not statistically significant ($p > 0.05$, Table 3).

Table 3. NCS and muscle characteristics of DM patients with or without DN. (* $p < 0.05$).

Characteristic	DM − DN (n = 10)	DM + DN (n = 15)	p-Value
CS	0.07 ± 0.10	0.70 ± 0.45	0.000 *
RMS (μV)	191.79 ± 103.79	212.53 ± 86.23	0.608
MDF (Hz)	175.10 ± 37.38	131.99 ± 45.85	0.028 *
MNF (Hz)	190.88 ± 40.48	147.27 ± 44.13	0.027 *

Note: NCS, nerve conduction study; DM, diabetic mellitus; DN, diabetic neuropathy; CS, composite score; RMS, root mean square; MDF, median frequency; MNF, mean power frequency. Values are the mean ± standard deviation. * $p < 0.05$.

The relationship between various parameters in subjects with DN was investigated using Pearson's correlation coefficients after verification of a normal distribution using the Kolmogorov–Smirnov test. CS was correlated with duration ($r = 0.596$, $p < 0.05$) and serum creatinine level ($r = 0.601$, $p < 0.05$) but did not show a significant difference from fatigue parameters obtained using sEMG (Table 4, MDF: $r = -0.354$, MNF: $r = -0.298$, $p > 0.05$). The MDF and MNF were correlated with FPG, HbA1c, and duration. However, RMS was not associated with these measurements. The correlation coefficient between parameters of muscle fatigue (MDF: $r = -0.794$, MNF: $r = -0.813$, $p < 0.05$) and duration was higher than between indicators of muscle fatigue and glycemic control (Table 4, $p < 0.05$).

Table 4. Pearson's correlation coefficient (r) between parameters and CS, RMS, MDF, and MNF using Pearson correlation analysis in patients with DN.

Components	Coefficient	CS	RMS (μV)	MDF (Hz)	MNF (Hz)
BMI	r	−0.334	0.248	−0.061	−0.086
Creatinine	r	0.601 *	0.172	−0.424	−0.418
Albumin	r	−0.447	0.264	−0.229	−0.204
FPG	r	0.134	0.308	0.581 *	0.628 *
TG	r	−0.204	−0.376	0.313	0.324
HDL	r	0.522	−0.015	−0.173	−0.136
LDL	r	0.224	0.239	0.009	0.089
HbA1c	r	0.224	0.118	0.668 *	0.672 *
Duration	r	0.596 *	0.133	−0.794 *	−0.813 *
CS	r	-	−0.265	−0.354	−0.298

Note: DN, diabetic neuropathy; CS, composite score; RMS, root mean square; MDF, median frequency; MNF, mean power frequency; FPG, fasting plasma glucose; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; duration, the duration of DM. Values are the mean ± standard deviation. * $p < 0.05$.

4. Discussion

This study found that in patients with DN there was a high likelihood of muscle fatigue, and the duration of DM and glycemic control were responsible for muscle fatigue. However, there was no correlation between the severity of neuropathy and muscle fatigue. Additionally, the serum albumin level between patients with and without DN was significantly different. This is consistent with a previous study that indicated that albumin changes due to oxidative stress were a representative biomarker for DN [19].

This study showed that CS in patients with DN was related to the duration of DM and serum creatinine level. Several studies have explained the high prevalence of neuropathy in patients as being dependent on age, glucose control, and duration of diabetes [4,20]. The presence of peripheral neuropathy increased with serum creatinine [21]. DN is induced by the progressive degeneration of peripheral nerve axons [22]. The pathophysiology of DN involves increased glucose and lipids which induce vascular dysfunction, causing a decrease in nerve blood flow and an increase in endoneurial hypoxia [23,24]. Our previous study also showed that CS was positively related to the duration of disease, and this indicates that the severity of neuropathy (CS) increases with the increasing duration of DM [1]. However, the evidence that hyperglycemia causes axonal atrophy which leads to DN is inconsistent with our findings, which showed no significant correlation between

CS and HbA1c or FPG [25]. This might be because of the small scale of our study; as such, further evaluation is necessary. Therefore, our findings are consistent with previous evidence suggesting that the duration of DM is responsible for DN.

This study quantified muscle fatigue using sEMG. MDF and MNF showed a significant decrease, but RMS was not significantly different between patients with and without DN. Muscle fatigue is a subjective symptom, which is defined as a decrease in objective performance, as well as a decreased maximum capacity to provoke force or power output, as measured by sEMG [5,10]. Muscle fatigue occurred more rapidly in the absence of glucose. We postulate that the association between low muscle glycogen and impaired contractile function indicates that glycogen is a necessary substrate, the depletion of which causes a decrease in the rate of ATP regeneration [26]. The association between hypoglycemia and fatigue has previously been described in applied physiology studies [14,27]. Another study showed that acute hypoglycemia is related to higher levels of fatigue [5,28]. The present results are consistent with this evidence since MDF and MNF showed a positive correlation with FPG and HbA1c in patients with DN. However, because RMS indicated a low fatigue sensitivity, the RMS was not significantly different [10]. In addition, there were no significant differences between CS and the parameters of muscle fatigue (RMS, MDF, and MNF). We hypothesized that small fibers could not be detected, as our previous study demonstrated a correlation between fatigue and nerve fiber function since NCS detects large nerve fibers. Small nerve fibers or minor defects in peripheral nerves contribute to the pathophysiological mechanism of fatigue in patients with DN [29]. Thus, to illustrate this, further studies are required. In addition, a previous study reported that because MNF is always higher than MDF due to the skewed shape of the EMG power spectrum, MDF estimation is more affected by muscle fatigue than by random noise, particularly noise located in the high-frequency band of the EMG power spectrum [13]. Additionally, in MNF, there are relatively more type 1 muscle fibers, whereas RMS is positively correlated with type 2 muscle fibers [30]. Our findings are consistent with this previous result and suggest that muscle fatigue is influenced by type 1 muscle fibers.

To the best of our knowledge, this is the first study to demonstrate that muscle fatigue, NCS, and parameters of DM are correlated in patients with DN. DN was associated with the duration of DM. Moreover, muscle fatigue and CS in DN patients were greater in those with a longer duration of DM, but CS was not directly related to muscle fatigue.

There were some limitations in this study. Firstly, this study was a preliminary study, and a large-scale study is required to confirm the results. Secondly, as muscle atrophy in patients with DM contributes to protein degradation in the muscle and induces fatigue, a further study of the relationship between fatigue and muscle atrophy is required [7]. Thirdly, muscle fatigue does not represent general fatigue; therefore, a further study of the relationship between isolated muscle fatigue and performance tests (e.g., six-minute walk test) is required [31]. Fourthly, because this study compared and analyzed values between type 2 diabetic patients with and without DN, there was no normalization as a function of the maximal contraction in the movement studied or as a function of the MVC. Fifthly, this study did not consider the effect of BMI. Lastly, despite removing signal artifacts, there remains a question of whether they were completely eliminated. Thus, further evaluation is required.

5. Conclusions

We investigated whether type 2 diabetic patients with or without neuropathy experienced muscle fatigue and determined the most influencing factor on muscle fatigue. In conclusion, we suggest that fatigue in patients with DN is related to the duration of DM and glucose control, and that sEMG is a useful tool to diagnose fatigue in patients with DN.

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Article

Effects of Brain Breaks Video Intervention of Decisional Balance among Malaysians with Type 2 Diabetes Mellitus: A Randomised Controlled Trial

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Abstract: Brain Breaks® are structured physical activity (PA) web-based videos designed to promote an interest in learning and health promotion. The objective of this study was to examine its effects on decision balance (DB) which consists of the perceived benefits (Pros) and perceived barriers (Cons) of exercise in people with type 2 diabetes mellitus (T2DM). A randomised controlled trial was conducted among people with T2DM at Hospital Universiti Sains Malaysia. The intervention group received Brain Breaks videos for a period of four months. The intervention and control groups completed the validated Malay version of DB questionnaire for five times, at pre-intervention, the first month, the second month, the third month, and post-intervention. Multivariate Repeated Measures Analysis of Variance was performed for data analysis. A total of 70 participants were included (male = 39; female = 31) with a mean age of 57.6 years (SD = 8.5). The intervention group showed a significant change in the Pros and Cons factors of DB scores over time. The intervention group showed significantly higher scores for the Pros (p-value < 0.001) and lower scores for the Cons (p-value = 0.008) factors than the control group. In conclusion, the Brain Breaks video is an effective intervention to improve decisional balance in patients with T2DM to help them in deciding on behaviour change to be more physically active.

Keywords: Brain Breaks®; video exercise; decisional balance; diabetes mellitus; physical activity; repeated measures

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1. Introduction

The Centers for Disease Control and Prevention (CDC) [1] defined diabetes as "a chronic (long-lasting) health condition that affects how your body turns food into energy". From a different perspective, diabetes is defined by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [2] as "a disease that occurs when your blood glucose, also called blood sugar, is too high". According to a recent International Diabetes Federation (IDF) [3] report, global diabetes prevalence was 463 million in 2019 and is expected to rise to 578 million in 2030 and 700 million in 2045. From the total of 463 million, 163 million are from the Western Pacific region, 88 million are from the South-East Asia region, 59 million are from Europe, 55 million are from the Middle East and North Africa, 48 million are from North America and the Caribbean, 32 million are from South and Central America, and 19 million are from the Africa region. The IDF also reported that

diabetes affects people of all ages, typically showing higher prevalence with increasing age, up to 60–69 years.

Type 2 diabetes mellitus (T2DM) and its complications have made an enormous contribution worldwide to the burden of death and incapacity. More than 90% of diabetes mellitus cases are T2DM [4]. The early stage of T2DM pathogenesis are insulin resistance and dysfunction of β-cells that leads to insulin release reduction [5]. T2DM comprises a range of hyperglycaemic dysfunctions that are a result of combining insulin resistance, insufficient insulin secretion, and excessive and inadequate glucagon secretion [6]. Khardori [6] added, that worsened T2DM is associated with an array of neuropathic, macrovascular, and microvascular complications.

In the Malaysian population, more than a decade ago, Mustaffa [7] statistically showed the development of diabetes until it became an epidemic in Malaysia. Diabetes prevalence increased from 0.65% in 1960 to 2–4% in the early 1980s [7]. In the same research, it was also stated that in the mid-1990s, the prevalence rose up to 8–12% and the percentage as predicted increased in 1998 with a reported 14% of the prevalence appearing. As we all know, diabetes potentially causes complications for patients if it is not well controlled. According to Mustaffa [7], diabetic patients have been complicated by reported retinopathy (53%), neuropathy (58%), and microalbuminuria (52%). He then added that Malaysian diabetics were at the high potential of suffering from ischaemic heart disease and stroke as complications of macrovascular. The macrovascular complications were due to late diagnosis and poor glycaemic control (mean HbA1c > 9%), and also due to the close relation to obesity (43–52% are either overweight or obese, more in female Malays and Indians), hypertension (10–37%) and hyperlipidaemia (63–76%).

For many years, physical activity (PA) and exercise have been empirically accepted by clinicians and researchers which can improve the health status of patients with any kind of disease. For example, a study conducted by Taylor et al. [8], found that coronary heart disease patients who were given exercise training (intervention group) showed a decrease in the percentage of total and cardiac mortality rates, 20% and 26%, respectively, compared to the regular medical care control group. Other than treating existing diseases, PA could be adopted as a prevention method. Lynch, Neilson and Friedenreich [9] conducted a review of 73 epidemiological studies of PA and breast cancer risk and concluded that the most physically active female group has a 25% lower risk of breast cancer than the least active female group.

Changing lifestyle, including weight loss, increased PA and healthy diet, continues to be one of the top-of-the-line T2DM management strategies [5]. An randomised controlled trial (RCT) was done in the USA on the health benefits of aerobic and resistance training in individual with diabetes, researchers concluded that in the group undertaking combined aerobic and resistance training, after the nine months of training, HbA1c levels were reduced [10]. It indicates that combining both aerobic and strength exercises is more advantageous than performing just one type of exercise if time is limited [11]. In addition, an extra-virgin olive oil enriched Mediterranean diet might prevent diabetic retinopathy, however not diabetic nephropathy [12].

The decisional balance is a Transtheoretical Model psychological construct that comprises benefits (Pros) and drawbacks (Cons) of maintaining current behaviour or beginning a new behaviour [13]. It can also be defined as a multidimensional collection of ideals viewed as advantages and disadvantages correlated with behavioural change [14]. After considering the benefits (Pros) and disadvantages (Cons) of practice, people prefer to change their own practice. According to people who effectively alter new behaviour, their advantages will change rather than drawbacks and their advantages should look more than disadvantages [15]. Benefits for health such as stress relief, better sleep patterns, and more energy and stamina are examples of Pros for exercise, while examples of Cons are injuries, time constraints, and bad weather.

Living in a technologically empowered world, we cannot neglect the use of media influence on education and human development. This effect may be positive as well as

negative. As previously stated, the Brain Breaks video is a web-based structured PA break that promotes an individual's health and learning, and it has recently emerged as a new promising intervention introduced by HopSports [16]. It has been commonly applied among school students as part of their physical education [17–22]. Brain-breaks have always been adopted in research with PA intervention settings where participants are divided into at least two groups.

Although the Brain Breaks intervention has been widely adopted, most of the studies only focus on school students. As the Brain Breaks intervention is categorised as a PA intervention, its use should be applied more among other populations such as university students, healthy adults or patients who are suffering from any kind of disease. For the time being, the researchers only discovered one brain breaks intervention study conducted in people with T2DM, focusing on motives to PA [23]. As one of the PA interventions, the researchers thought it was still relatively new to the Malaysian population. As a result, the researchers decided to use it as an intervention material in the current study at early exposure, and it could benefit the Malaysian population, particularly those suffering from diseases that require PA as part of their self-management.

2. Materials and Methods

2.1. Study Design, Recruitment, and Sampling

A RCT was conducted in the hospital of Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. The present study focuses on people with T2DM, and we employed purposive sampling to recruit participants. The people with T2DM were briefed about the study by the researchers. Participants who agreed to volunteer for the study were randomly allocated to the intervention and control groups using block randomisation [24]. Through block randomisation, the researcher developed a block to similarly assign sample numbers and each group were assigned with block numbers [25]. As the present study have only two groups, intervention and control, hence two blocks (AB and BA) randomisation were applied. Hence, from the 100 participants, both groups were assigned equal numbers of participants, n = 50. The inclusion criteria include 18 years and above Malaysians who were clinically diagnosed with T2DM, can read and understand the Malay language, also, understand and agree the explained information to participants by the researchers. While for exclusion criteria, those who have disabilities that prevent them from being physically active.

2.2. Instruments

There are two sections of the self-administered questionnaire, (1) the demographic details, and (2) the Malay version of Decisional Balance (DB-M) scale. For the demographic details, information such as age (years), gender, and ethnicity were collected from this section.

The Decisional Balance (DB) scale is a questionnaire that consists of 10 items which were initially developed by Plotnikoff et al. (2001) [13]. Each item was measured by using a 5-point Likert scale, from 1 (not at all confident) to 5 (extremely confident). There are two factors in DB, Pros that represent the positive aspect of an individual's behavioural changes, and Cons represent the negative aspect. When it comes to exercise, the decisional balance represents perceived benefits (Pros) and perceived barriers (Cons) [26]. Self-confidence, physical strength, and aerobic ability and cited as perceived benefits of exercise; whereby, physical discomfort and financial concerns are cited as perceived barriers to exercise [26]. The Pros factor consists of five items and there are: physical activity would help me reduce tension or manage stress, I would feel more confident about my health by getting physical activity, I would sleep better, physical activity would help me have a more positive outlook, physical activity would help me control my weight. The Cons factor consists of five items and there are: I am too tired to get physical activity because of my other daily responsibilities, physical activity would take too much of my time, I would have less time for my family and friends if I participated in physical activity, I'd worry about looking

awkward if others saw me being physically active, getting physical activity would cost too much money. The researchers adopted the DB-M scale that has been validated by Kuan, Sabo, Sawang and Kueh [26]. The DB-M scale has good validity and reliability. Based on the confirmatory factor analysis results, the DB-M model fit the data well with acceptable fit indices (CFI = 0.979, TLI = 0.969, RMSEA = 0.047, and SRMR = 0.037). The internal consistency reliability was excellent with a Cronbach's alpha value of 0.86 for both the Pros and Cons subscales. It also showed good test-retest reliability results with an intraclass correlation value of 0.98.

2.3. Sample Size Determination

The sample size was estimated for time (within factor), group (between factor) and interaction (within-between) effects. Using the GPower 3.1, sample size calculation software, with effect size = 0.25 (medium effect) [27], type I error = 0.05, power = 0.8, number of groups = 2, number of measurements = 5, and expected correlation among repeated measure = 0.5, the total sample size calculated was 78 for between factor, 22 for within factor, and 22 within-between interaction. Thus, the largest sample size was 78 for this study with 36 participants per group. However, after a thorough discussion, the researcher decided to recruit 100 participants (50 per group) for this study as a precaution against the high withdrawal rate from the participants.

2.4. Procedure

At baseline or before the intervention started, both groups (intervention and control) were required to answer on the DB-M scale. Then, participants in the intervention group were invited to a WhatsApp group where the Brain Breaks videos were given during the period of the intervention phase. In this period (four months), exercise videos with ten minutes duration specifically designed for diabetes patients were uploaded into the WhatsApp group. All the participants in the intervention group were required to perform the exercise either outdoors or indoors. The videos were uploaded to the WhatsApp group weekly as a regular reminder for the participants. On the first day of each week, different exercise videos were given to avoid participants from getting bored with the same exercise. As part of that, every participant in the intervention group was given an adherence logbook for the purpose of progress monitoring. Participants were required to report to the researcher about their progress of exercise based on the logbook they have noted down. At the end of the intervention, the participants were required to return their adherence logbook to the researcher for assessment. As for the control group, a brochure with the benefits of PA for their health was given to the participants. They did not receive Brain Breaks videos and were not required to perform the exercise. However, they would receive the same intervention videos that were given to the intervention group at the end of the study. Thus, they would get the same benefits similar to the intervention group in the future. The duration of the intervention was four months. At the end of each month, participants in both the intervention and control groups were required to answer the DB-M. The outcome of the study was based on the score of the DB-M.

This study obtained approval from the USM Human Research Ethics Committee (USM/JEPeM/18040201) and was conducted in accordance with the guidelines of the International Declaration of Helsinki. Before the study began, participants were informed that their participation was voluntary and that they could withdraw at any time without incurring any loss or penalty. Written informed consent was obtained from each participant before they participated in the study. This study was registered under the clinical trial of the ISRCTN registry, which is recognized by the World Health Organization (registry number: ISRCTN14952589).

2.5. Data Analysis

The Statistical Package for the Social Sciences (SPSS) version 26.0 was used in conducting the data analysis. The data consisted of two groups (i.e., intervention and control)

with a five-time measurement of the outcome variables (score of the DB-M). The effect of the Brain Breaks video exercises on decisional balance, which consists of Pros and Cons, were investigated using repeated measures multivariate analysis of variance (RM MANOVA). The effects examined consisted of time, group, and interaction (time ∗ group) effects. Mauchly's test of sphericity was used to test whether the sphericity assumption was met. If the assumption is violated, the F-statistic based on Greenhouse-Geisser is reported. A p-value of <0.05 was taken as a significant result.

3. Results

3.1. Participants

The randomisation included 100 T2DM patients. This produced 50 members for each group (intervention and control). In the middle of the intervention period, however, 13 intervention members and 17 control participants withdrew for personal reasons. Therefore, 37 participants in the intervention group and 33 participants in the control group with complete data were obtained at the end of the study. Figure 1 shows the participants' group allocation in this study. Table 1 presents the demographic information for T2DM patients.

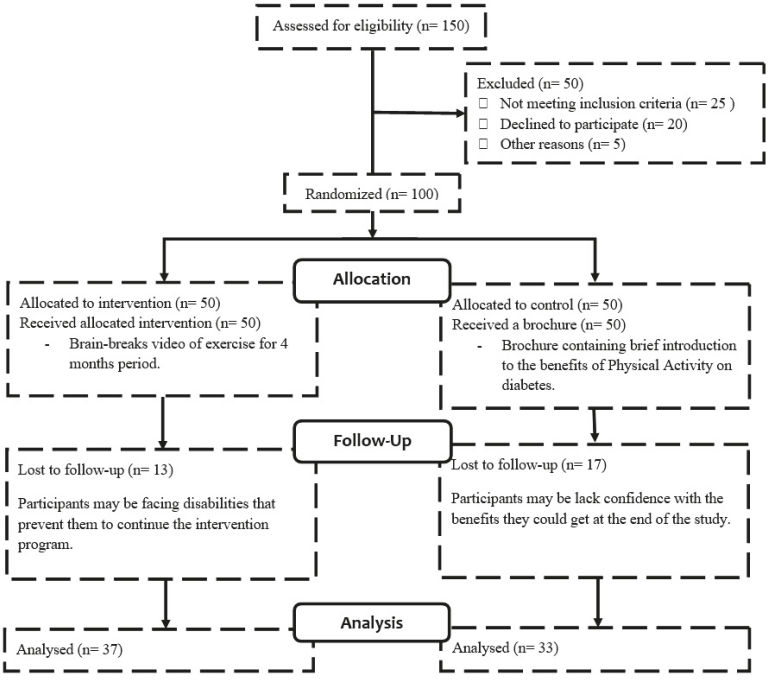

Figure 1. Flow chart of participant's group allocation/randomisation.

Table 1. Participants demographic characteristics.

Characteristics	Intervention				Control				*p*-Value
	Frequencies	Percentage	Median (IQR)	Mean (SD)	Frequencies	Percentage	Median (IQR)	Mean (SD)	
Gender									0.208 [a]
Male	18	48.6%			21	63.6%			
Female	19	51.4%			12	36.4%			
Age			56.00 (10.00)				63.00 (8.00)		<0.001 [c]
Ethnicity									0.242 [b]
Malay	34	91.9%			29	87.9%			
Chinese	3	8.1%			1	3.0%			
Indian	0	0%			1	3.0%			
Others	0	0%			2	6.1%			
HbA1c (*n* = 65)				80.11 (3.74)				76.23 (4.26)	0.529 [d]
BMI			28.06 (5.90)				26.59 (6.19)		0.902 [c]

Note: [a] Pearson Chi-square test, [b] Fisher exact test, [c] Mann-Whitney test, [d] Independent *t*-test.

3.2. Results of RM MANOVA

The researcher started the analysis by checking the assumption of the compound symmetry of the data. Mauchly's test was used to check the compound symmetry assumption. From the result, the *p*-value produced for both factors were significant (*p*-value < 0.05) indicated that the assumption of compound symmetry was not met. Hence, multivariate test statistics result was referred for time effect. The researcher decided to proceed with multivariate test statistics as the assumption has been violated with the Pillai's Trace [F-stat(df) = 7.730 (8, 552), *p*-value < 0.001] and Wilk's Lambda [F-stat(df) = 8.125 (8, 550), *p*-value < 0.001] both produced significant *p*-value.

Then, pairwise comparison with confidence interval adjustment was carried out to determine the differences within the group. Table 2 below show the score comparison within both groups (intervention and control) based on time (Time effect).

The intervention group produced a significant mean score difference in the DB-M scale's Pros and Cons factors, as well as time comparisons. The Intervention group also shows an increasing trend in Pros but a decreasing trend in Cons over time. In the control group, there were a few time comparisons that resulted in a non-significant mean score difference, such as the 3rd month-Post in the Pros factor and the 1st month-2nd month in the Cons factor. There was also a decreasing trend in scores over time in the control group for the Pros and an increasing trend for the Cons.

The overall mean score of both groups (group effect) was compared and the results are in Table 3. Based on the results, the overall mean score of the DB-M scale between both groups was significantly different. Furthermore, the intervention group had a higher mean score for the Pros factor than the control group, and vice versa for the Cons factor.

Based on multivariate test statistics, there was a significant interaction effect between time and group (Time ∗ Group effect), with Pillai's Trace [F-stat(df) = 35.920 (8, 544), *p*-value < 0.001] and Wilk's Lambda [F-stat(df) = 52.750 (8, 542), *p*-value < 0.001] both produced significant *p*-value. The comparison of the mean score for Pros and Cons between the two groups based on within-between groups (Time ∗ Group effect) for each time point are shown in Table 4. For factor Pros, the intervention and control groups showed non-significant differences in the mean score at pre-intervention. However, a significant mean difference between both groups was observed starting from 1st month until post-intervention. For factor Cons, the intervention and control groups showed a non-significant difference in the mean score at pre-intervention and 1st month. However, a significant mean difference between both groups was observed starting from the 2nd month until post-intervention. The changes from pre- to post-intervention among the two groups can be observed in Figure 2.

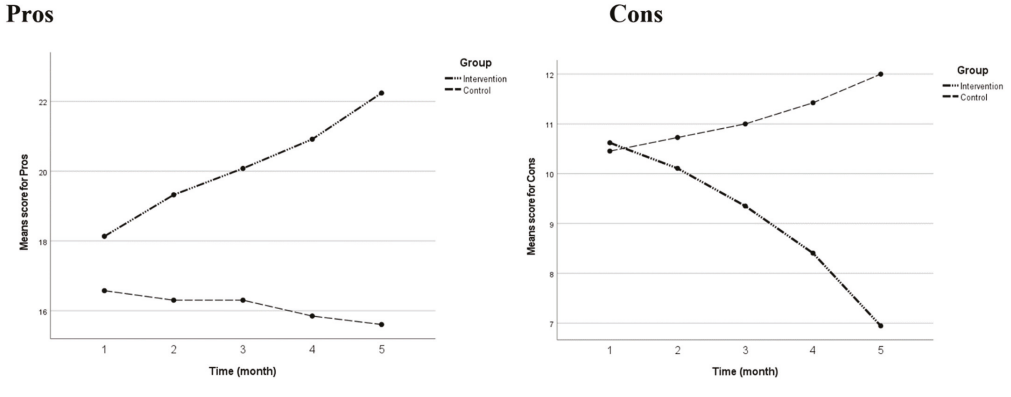

Figure 2. Mean score changes for Pros and Cons of DB-M from pre-intervention to post-intervention. Note the plot shows the mean score of Pros and Cons of DB-M scores (y-axis) for pre-intervention (time 1), 1st month (time 2), 2nd month (time 3), 3rd month (time 4) and post-intervention (time 5; x-axis) for both groups (intervention and control).

Table 2. Comparison of DB-M score within group based on time (Time effect).

Comparison	Intervention Group				Control Group			
	Pros		Cons		Pros		Cons	
	MD (95% CI)	*p*-Value	MD (95% CI)	*p*-Value	MD (95% CI)	*p*-Value	MD (95% CI)	*p*-Value
Pre-1st month	−1.19 (−1.68, −0.70)	<0.001	0.51 (0.14, 0.89)	0.002	0.27 (0.002, 0.54)	0.048	−0.27 (−0.60, 0.06)	0.176
Pre-2nd month	−1.95 (−2.60, −1.29)	<0.001	1.27 (0.65, 1.89)	<0.001	0.27 (0.002, 0.54)	0.048	−0.55 (−1.00, −0.09)	0.010
Pre-3rd month	−2.78 (−3.80, −1.77)	<0.001	2.22 (1.21, 3.23)	<0.001	0.73 (0.11, 1.35)	0.012	−0.97 (−1.52, −0.42)	<0.001
Pre vs. Post intervention	−4.10 (−5.40, −2.81)	<0.001	3.68 (2.10, 5.25)	<0.001	0.97 (0.10, 1.84)	0.019	−1.55 (−2.27, −0.83)	<0.001
1st month–2nd month	−0.76 (−1.05, −0.46)	<0.001	0.76 (0.33, 1.18)	<0.001	-	-	−0.27 (−0.57, 0.03)	0.102
1st month–3rd month	−1.60 (−2.28, −0.91)	<0.001	1.70 (0.90, 2.50)	<0.001	0.46 (−0.06, 0.96)	0.113	−0.70 (−1.14, −0.25)	<0.001
1st month–Post	−2.92 (−3.88, −1.96)	<0.001	3.16 (1.81, 4.51)	<0.001	0.70 (−0.003, 1.40)	0.052	−1.27 (−1.85, −0.70)	<0.001
2nd month–3rd month	−0.84 (−1.36, −0.31)	<0.001	0.95 (0.42, 1.48)	<0.001	0.46 (−0.06, 0.96)	0.113	−0.42 (−0.69, −0.16)	<0.001
2nd month-Post	−2.16 (−2.94, −1.38)	<0.001	2.41 (1.35, 3.46)	<0.001	0.70 (−0.003, 1.40)	0.052	−1.00 (−1.46, −0.55)	<0.001
3rd month-Post	−1.32 (−1.76, −0.89)	<0.001	1.46 (0.75, 2.17)	<0.001	0.24 (−0.17, 0.66)	0.882	−0.58 (−1.03, −0.12)	0.006

Notes. Repeated measure MANOVA between-group analysis with regard to time was applied, 95% CI = 95% confidence interval.

Table 3. Overall mean differences of DB-M score among two groups.

Comparison (Intervention and Control Groups)	Mean Difference (95% CI)	F (df)	*p*-Value
Pros	4.01 (2.63, 5.40)	33.447 (1, 68)	<0.001
Cons	−2.04 (−3.52, −0.55,)	7.489 (1, 68)	0.008

Notes. Repeated measures MANOVA between group was applied, 95% CI = 95% confidence interval.

Table 4. Comparison of the mean score for Pros and Cons from the DB-M scale among two groups based on time (Time ∗ Group effect).

Factor	Time	Group	Mean (95% CI)	*p*-Value
Pros	Pre-intervention	Intervention	18.14 (16.95, 19.32)	0.075
		Control	16.58 (15.32, 17.83)	
	1st month	Intervention	19.32 (18.27, 20.38)	<0.001
		Control	16.30 (15.19, 17.42)	
	2nd month	Intervention	20.08 (19.06, 21.11)	<0.001
		Control	16.30 (15.22, 17.39)	
	3rd month	Intervention	20.92 (20.06, 21.78)	<0.001
		Control	15.85 (14.94, 16.76)	
	Post-intervention	Intervention	22.24 (21.46, 23.03)	<0.001
		Control	15.61 (14.77, 16.44)	
Cons	Pre-intervention	Intervention	10.62 (9.32, 11.92)	0.861
		Control	10.46 (9.08, 11.83)	
	1st month	Intervention	10.11 (8.92, 11.30)	0.478
		Control	10.73 (9.47, 11.99)	
	2nd month	Intervention	9.35 (8.29, 10.42)	0.038
		Control	11.00 (9.87, 12.13)	
	3rd month	Intervention	8.41 (7.48, 9.33)	<0.001
		Control	11.42 (10.45, 12.40)	
	Post-intervention	Intervention	6.95 (6.18, 7.72)	<0.001
		Control	12.00 (11.19, 12.82)	

Note. Repeated measures MANOVA within the group was applied, MD = mean difference, 95% CI = 95% confidence interval.

4. Discussion

The main objective of the present study was to determine the effect of Brain Break exercise videos on the changes in the DB of T2DM patients in terms of perceived Pros and Cons. The effect of Brain Break exercise videos on DB was measured based on three main components, which were time, group, and interaction (time ∗ group). For the time effect, all the measurement time comparisons were significant for both DB components of Pros and Cons in the intervention group. While for the control group, there were no significant differences in the measurement time for both DB components Pros (e.g., 2nd month–3rd month) and Cons (e.g., 1st month–2nd month). For the group effect, results showed a significant overall mean score difference between the two groups on both DB components of Pros and Cons. A significant interaction effect was observed for both DB components of Pros and Cons which indicated that the magnitude and direction of changes from pre- to post-intervention were different between the intervention and the control groups.

Results of the present study displayed similarity with a study conducted by Moeini et al. [28]. Moeini et al. [28] performed a quasi-experimental intervention study among employees of the

defensive industry. The objective of the study was to increase PA among the employees as one of the most effective ways to reduce the risk of non-communicable diseases. A total of 60 employees with the age range from 20 to 57 years old were recruited using simple random sampling. They were divided into intervention and control groups that required them to complete the questionnaires before and three months after the intervention. Only the intervention group received the educational programs during the intervention period. The physical capacity score measured by the Ergo-meter bicycle showed significant improvement in the intervention group (p-value = 0.016) at the end of the study. Total DB scores were also significantly higher in the experimental group (p-value < 0.001) compared to the control group. A conclusion of TTM based educational programs/interventions were beneficial for physical capacity and PA enhancement was made [28].

In addition, PA was also found to be related to DB in a study done by Shtaynberger and Krebs [29], who performed a study of the adult cancer survivorship population in New York. Participants were a total of 86 completed primary treatment of breast/prostate cancer patients. One of the study objectives was to assess the relationship between DB and PA. The findings presented a significant relationship between the Total Metabolic Equivalent of Task units (METs) with both Pros (p-value = 0.012) and Cons (p-value = 0.003).

While the present study shows a positive result, it is necessary to highlight limits and weaknesses. Due to the time constraints facing by the researchers, participants were recruited from only one hospital in Malaysia. The participation of people with T2DM from more hospitals in Malaysia could have contributed to better results in this study. In the future, a multicentre community trial should therefore be used to obtain more responses from different hospitals. Furthermore, the researchers were unable to closely follow the commitment of the participants in the intervention other than with a logbook. Participants may have dishonest or misrepresented their participation in the intervention. This was unavoidable as most patients with T2DM were difficult to assemble in a location where the intervention could be observed every day as a result of logistical and transport constraints. However, we regularly send reminders to the WhatsApp group at daily intervals to ensure the participants adhere to the intervention.

Another limitation is the quantitative methods that need to be used to measures the variables among participants. Respondent bias, acquiescence bias, demand characteristics, extreme responding, and social desirability bias could happen as the participants could answer the questionnaire dishonestly and insincerely. These biases may give a negative impact on the reliability of the completed questionnaire from the participants. However, the researcher had regularly encouraged the participants to answer the questionnaire sincerely and only according to what they were thinking and their current condition.

Another limitation is that only those T2DM patients with internet services on mobile phones were able to participate in the study. This was necessary for the participants to install the WhatsApp application for sharing Brain Breaks videos. We were unable to recruit more participants due to this issue and time constraints. But the researchers believe that this was the best way to get participants involved after taking the logistics and transport restrictions into account. Finally, this study only focuses on a single non-communicable disease (T2DM). Therefore, we urge more kinds of non-communicable diseases to be included in future studies to present broader results.

We believe, however, that the effective design of the study was a community test with block randomisation, which strengthened this study sufficiently to produce good results. Randomisation blocks have been used to reduce selection distortions so that the current study is more confidential for future references. Further, during the trial period (for monitoring purposes), the researchers conducted three repeated measurements and regularly followed up with the participants through WhatsApp to make sure that they adhered to the intervention. The other two repeated measurements (pre- and post-intervention) were conducted through face-to-face meeting with the participants. Finally, RM MANOVA was carried out for this study rather than multiple repeated measures analysis of variance (RM ANOVA). It was due to MANOVA has greater power and improves the chances

of detecting differences between groups than ANOVA [30]. Furthermore, the sphericity assumption in RM MANOVA allows you to control the type of error [31], making them superior to the Paired *t*-test. With proper choice of statistical analysis, the results yielded should be more accurate and more reliable.

5. Conclusions

From the results, the researchers conclude that the brain-breaks intervention is an effective intervention to improve participants' decision-making skills. Participants who were in the intervention group showed significant improvement in the DB mean score compared to participants in the control group. At the end of the study, the intervention group demonstrated superior decision-making abilities, with a higher mean score for both the Pros and Cons of DB than the control group. The intervention with the Brain Breaks videos also helped to demonstrate differences in the trends in the mean scores between the two groups. The intervention group had an uptrend in the Pros factor and a downtrend in the Cons factor. The opposite trends between the two factors indicate that, at the end of the study, the intervention group was more focused on the positive impact and benefits of PA rather than the negative impacts and obstacles of performing PA. In the control group, however, the opposite occurred.

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Institutional Review Board Statement: This study obtained approval from the USM Human Research Ethics Committee (USM/JEPeM/18040201) and was conducted in accordance with the guidelines of the International Declaration of Helsinki. This study was registered under the clinical trial of the ISRCTN registry, which is recognized by the World Health Organization (registry number: ISRCTN14952589).

Informed Consent Statement: Informed consent was obtained from all participants involved in the study. Besides, written informed consent has been obtained from the participants to publish this paper.

Data Availability Statement: The data is available upon request from the authors.

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Conflicts of Interest: The authors declare no conflict of interest.

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The Impact of Nordic Walking on Bone Properties in Postmenopausal Women with Pre-Diabetes and Non-Alcohol Fatty Liver Disease

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Abstract: This study investigated the impact of Nordic walking on bone properties in postmenopausal women with pre-diabetes and non-alcohol fatty liver disease (NAFLD). A total of 63 eligible women randomly participated in the Nordic walking training (AEx, n = 33), or maintained their daily lifestyle (Con, n = 30) during intervention. Bone mineral content (BMC) and density (BMD) of whole body (WB), total femur (TF), femoral neck (FN), and lumbar spine (L2-4) were assessed by dual-energy X-ray absorptiometry. Serum osteocalcin, pentosidine, receptor activator of nuclear factor kappa-B ligand (RANKL) levels were analyzed by ELISA assay. After an 8.6-month intervention, the AEx group maintained their BMC_{TF}, BMD_{TF}, BMC_{L2-4}, and BMD_{L2-4}, and increased their BMC_{FN} ($p = 0.016$), while the Con group decreased their BMC_{TF} ($p = 0.008$), BMD_{TF} ($p = 0.001$), and BMD_{L2-4} ($p = 0.002$). However, no significant group × time interaction was observed, except for BMD_{L2-4} ($p = 0.013$). Decreased pentosidine was correlated with increased BMC_{WB}($r = -0.352$, $p = 0.019$). The intervention has no significant effect on osteocalcin and RANKL. Changing of bone mass was associated with changing of pentosidine, but not with osteocalcin and RANKL. Our results suggest that Nordic walking is effective in preventing bone loss among postmenopausal women with pre-diabetes and NAFLD.

Keywords: Nordic walking; postmenopausal women; fatty liver disease; bone markers; bone mineral density

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1. Introduction

Type 2 diabetes (T2DM) is a widely prevalent chronic disease that affects bone health. Individuals with T2DM are known to have a higher risk for fractures with no change in or higher bone mineral density (BMD) than normal individuals [1]. In addition, studies have shown that non-alcoholic fatty liver disease (NAFLD) is related to decreased BMD in adults [2,3] and that NAFLD is negatively associated with BMD in postmenopausal women [4]. Diabetes, NAFLD, and osteoporosis metabolically alter the biology. Approximately one- to two-thirds of diabetic patients have NAFLD [5], and both diseases are known to be related to insulin resistance and bone metabolism. However, no studies have assessed bone properties in patients with comorbidities; hence, it is important to assess how bone properties would change after exercise intervention.

In humans, bone and glucose metabolism may share similar signaling pathways [6]. Early studies have shown that biomarkers such as osteocalcin (OC), glucose, and adipokines change with age but in a non-commensurate manner [7]. OC is a marker of bone formation and a bone matrix protein that is exclusively produced by osteoblasts and odontoblasts. OC plays a significant role as an endogenous insulin sensitizer [8]. The circulating levels of OC are known to increase with improved glycemic control in type 2 diabetes [8]. Receptor activator of nuclear factor kappa-B ligand (RANKL) is a marker of bone resorption and is accompanied by osteoprotegerin. Recent evidence has shown that RANKL is crucially implicated in the pathogenesis of T2DM [9]. In postmenopausal women with T2DM, the presence of NAFLD and clinically significant fibrosis was strongly associated with low RANKL levels [10]. In addition, pentosidine, a well-known advanced glycation end product (AGE), is an important surrogate marker for total AGE production. There is a negative correlation between serum pentosidine concentration and bone strength [11]. It has been reported that serum or urine levels of pentosidine positively correlate with fracture incidence and prevalence in T2DM [12]. Although the abovementioned biomarkers link both bone and glucose metabolism, the means by which those biomarkers are associated with bone properties in postmenopausal women with prediabetes and NAFLD are largely unknown.

Regular physical exercise has been recommended as an effective and safe non-pharmacological strategy to counter the aging-induced loss of BMD [13]. Nordic walking involves striding with the use of specially designed sticks and is a safe and relatively easy-to-learn form of fitness exercise. It is considered to be effective in patients with different chronic diseases [14], such as cardiovascular disease [15], aging [16], or women with breast cancer [17]. The movement sequences of Nordic walking make this physical activity suitable to support body posture and strengthen the muscles of the spine, shoulders, and hips [18]. Thus, we hypothesized that Nordic walking could be an ideal modality of exercise for postmenopausal women with pre-diabetes and NAFLD. It could help improve their BMD and bone turnover markers. To test our hypothesis, we evaluated the effects of an 8.6-month Nordic walking program on BMD by using dual-energy X-ray densitometry and biomarkers. This was considered to be associated with both bone and glucose metabolism in postmenopausal women with pre-diabetes and NAFLD.

2. Materials and Methods

2.1. Study Design and Participants

The present study is a part of a large interventional study that was published earlier [19,20]. In brief, the participants aged 50–65 years with an impaired fasting glucose level (IFG; between 5.6 and 6.9 mmol/L) or impaired glucose tolerance (IGT; between 7.8 to 11.0 mmol/L 2 h after the intake of 75 g glucose) and NAFLD (hepatic fat content > 5%) were considered eligible. In addition, women with serum follicle-stimulating hormone levels greater than 30 IU/L and last menstruation more than 6 months prior but within 10 years were included in this study. After eligibility was confirmed, the participants were randomly assigned (1:1:1:1) to 4 groups: aerobic exercise (AEx; n = 29), diet intervention (Diet; n = 28), aerobic exercise plus diet intervention (AED; n = 29), or no intervention (NI; n = 29). An intervention was carried out for an on average of 8.6 months (from 6 months to 11 months). For the purpose of this report, we focused on the effects of aerobic exercise on bone properties in postmenopausal women. Thus, we only included postmenopausal women and pooled the groups AEx and AED to form the AEx group (n = 33) and the groups Diet and NI to form the Con group (n = 30). Hence, we could increase the sample size, and the effects of the diet were comparable in both groups.

The protocol of study was approved by the Ethics Committee of Shanghai Institute of Nutrition (No. 2013-003, 6 January 2013). This study conformed to the principles laid down in the world medical association Declaration of Helsinki for medical research involving human participants. Informed consent was obtained from all individual participants included in the study.

2.2. Exercise Intervention

During the 8.6-month intervention, all participants took part in supervised exercise sessions that were conducted 2–3 times per week in a community park that was close to their homes. Exercise sessions consisted of a 5 min warm-up and 5 min cool-down period (such as stretching and group exercises), and supervised progressive Nordic walking. The intensity and duration of exercises were increased from 60% to 75% of the maximum oxygen uptake (estimated from fitness tests) and from 30 to 60 min per session. The exercise intensity was monitored using a heart rate monitor (M5, Suunto, Vantaa, Finland).

2.3. Background Information

Background information regarding lifestyle as well as medical history was collected using questionnaires. Daily physical activity was recorded in an activity diary [19]. In addition, food records were collected to estimate the participant's energy intake and intake of different nutrients during the study. The collected information was evaluated by exercise and nutrition experts.

2.4. Anthropometric and Bone Measurements

Height was determined using a wall-fixed measuring device, and body weight was determined using a calibrated scale, from which BMI was calculated. Dual-energy X-ray absorptiometry (DXA Prodigy, GE Lunar Corp., Madison, WI, USA) was used to assess whole-body lean mass and fat mass, as well as bone mineral content (BMC) and areal BMD of the whole body (WB), total femur (TF), femoral neck (FN), and lumbar spine (L2-4). The coefficient of variation for repeated measurements ranged from 0.9% to 1.3% for BMC and BMD.

2.5. Clinical and Laboratory Measurements

Venous blood samples were taken in standardized fasting conditions between 7:00 a.m. and 8:00 a.m. Plasma samples were used to assess glucose, insulin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and glycated hemoglobin A1c levels as explained previously [19]. The homeostasis model assessment of insulin resistance index was calculated using the formula: (fasting insulin concentration $\times$ fasting glucose concentration)/22.5 [21]. Glucose tolerance tests were performed after overnight fasting, and at 30 min, and 2 h after the intake of 75 g glucose for the assessment of serum insulin and glucose.

The serum concentration of OC as a bone formation marker was assessed by ELISA using Human Osteocalcin Quantikine ELISA kit (produced by R&D Systems, Minneapolis, MN, USA; assay sensitivity 0.898 ng/mL). RANKL was assessed using the Human TNFSF11 ELISA kit (Abcam, Cambridge, MA, USA, assay sensitivity 10 pg/mL). Pentosidine was assessed using the Human Pentosidine ELISA Kit (CUSABIO Technology LLC, Houston, TX, USA; assay sensitivity 7.81 pmol/mL).

2.6. Data Analysis

All analyses were performed using IBM SPSS statistics for Windows, version 25.0 (IBM Corp, Armonk, NY, USA). The Shapiro–Wilk test was used to check all data for normality. If data were not normally distributed, they were transformed by natural logarithm before further analysis. Descriptive statistics were used to present the data as means and 95% confidence intervals (95% CIs) unless otherwise stated. Student's *t*-test was used to compare the differences at the baseline. Paired *t*-tests were used to analyze the changes with time in variables within groups.

Analysis of covariance for repeated measures (group $\times$ time) was used to assess the effects of the interventions by adjusting the corresponding baseline data, "years menopausal", and intervention duration as the covariates. Measures of effect size in the analysis of covariance for repeated measures were shown in partial η^2.

Pearson correlation was used to assess the relationship between bone biomarkers and BMC/BMD at the baseline and post-intervention in the whole samples. Partial correlation coefficients, adjusted for "years menopausal" and intervention duration, were used to evaluate the changes of bone biomarkers with the changes of BMC/BMD from pre-to-post intervention in the whole samples. All tests were two-tailed, and a 5% probability level was considered significant.

3. Results

3.1. Baseline Participant Characteristics

The physical and clinical characteristics of the participants at baseline are summarized in Table 1. No significant difference was observed in any variable among the different groups.

Table 1. Baseline characteristics of the exercise and control group.

	Exercise Group (n = 33)	Control Group (n = 30)
Age (years)	59.8 (58.5, 61.1)	59.7 (58.2, 61.1)
Height (m)	159.6 (157.6, 161.7)	157 (154.5, 159.5)
Weight (kg)	67.1 (64, 70.2)	63.8 (59.5, 68.1)
BMI (kg/m^2)	26.4 (25.2, 27.6)	25.8 (24.4, 27.2)
Age at menopause (years)	49.1 (47.2, 51.0)	51 (49.4, 52.6)
Years post-menopausal (years)	10.6 (8.4, 12.9)	8.7 (6.8, 10.5)
FPG (mmol/L)	5.61 (5.39, 5.83)	5.55 (5.3, 5.81)
2hPG (mmol/L)	8.08 (7.47, 8.7)	8.20 (7.68, 8.72)
HbA1c (%)	6.12 (6, 6.24)	6.21 (6.09, 6.33)
FSH (nmol/L)	50.9 (41.5, 60.4)	50.1 (42.6, 57.5)
Osteocalcin (ng/mL)	236.4 (208.3, 264.4)	225 (189.8, 260.2)
Pentosidine (ng/mL)	13.7 (7.9, 19.4)	11.5 (6.1, 17.0)
RANKL (pg/mL)	46.4 (30.9, 62.0)	42.7 (32.6, 52.8)
Calcium intake (mg)	580.7 (452.2, 709.1)	666.2 (560.5, 771.9)
Physical activity (h/week)	2.45 (1.8, 3.1)	2.45 (1.83, 3.07)
Whole body T-score	−0.13 (−0.47, 0.22)	−0.20 (−0.54, 0.14)
Total femur T-score	−0.07 (−0.45, 0.31)	−0.20 (−0.61, 0.20)
Femoral neck T-score	−0.62 (−0.97, −0.26)	−0.54 (−0.93, −0.15)
Lumbar spine T-score	−0.13 (−0.65, 0.38)	−0.15 (−0.72, 0.42)

Note 1: Data are expressed as mean (95% confidence interval). Note 2: BMI, body mass index; FPG, fasting plasma glucose; 2hPG, 2-h plasma glucose; FSH, follicle-stimulating hormone; RANKL, Receptor Activator of Nuclear Factor-κ B Ligand. Note 3: Student's t-test was used to evaluate the differences between groups at the baseline.

3.2. Change in BMC and BMD after the Intervention

Comparisons of BMC and BMD at the different bone sites before and after intervention are shown in Table 2. After the 8.6-month intervention, the results showed a significant effect of group × time interaction (p = 0.013, partial η^2 = 0.106) on the $BMD_{L2\text{-}4}$. $BMD_{L2\text{-}4}$ levels were significantly lower in the CON group, while the AEx group preserved their earlier levels. Controlling for body weight and duration of the intervention, the results remained the same. No significant group × time interaction was observed in the other BMDs and BMCs. However, BMC_{FN} was increased after intervention within the AEx group (p = 0.016, paired t-tests). In contrast, the CON group showed a decrease in their BMC_{TF} (p = 0.008), BMD_{TF} (p = 0.001) and $BMD_{L2\text{-}4}$ (p = 0.002) values after intervention, respectively (paired t-tests).

Table 2. Pre- and post-intervention values of bone properties for the exercise and control groups.

	Exercise Group			Control Group			Time by Group
	Pre	Post	*p*	Pre	Post	*p*	*p*
Whole-body							
BMC (kg)	2.07 (1.98, 2.16)	2.06 (1.96, 2.16)	0.195	2.00 (1.89, 2.11)	1.99 (1.87, 2.10)	0.589	0.216
BMD (g/cm^2)	1.07 (1.03, 1.11)	1.07 (1.03, 1.12)	0.961	1.07 (1.03, 1.11)	1.06 (1.02, 1.11)	0.756	0.952
Total-femur							
BMC (g)	29.2 (27.5, 30.9)	29.3 (27.6, 31.1)	0.927	28.1 (26.3, 29.9)	27.6 (25.8, 29.3)	0.008	0.587
BMD (g/cm^2)	0.96 (0.91, 1.01)	0.96 (0.91, 1.02)	0.074	0.95 (0.89, 1)	0.93 (0.88, 0.98)	0.001	0.183
Femoral neck							
BMC (g)	4.02 (3.79, 4.25)	4.06 (3.83, 4.29)	0.016	3.98 (3.7, 4.25)	4.27 (3.93, 4.61)	0.131	0.579
BMD (g/cm^2)	0.86 (0.82, 0.91)	0.87 (0.82, 0.92)	0.156	0.87 (0.82, 0.91)	0.86 (0.82, 0.91)	0.606	0.297
Lumbar spine							
BMC (g)	46.0 (43.1, 48.8)	45.8 (42.7, 48.9)	0.821	43.8 (40.5, 47.1)	42.7 (39.3, 46.1)	0.141	0.323
BMD (g/cm^2)	1.12 (1.06, 1.18)	1.12 (1.06, 1.18)	0.592	1.11 (1.05, 1.18)	1.09 (1.02, 1.15)	0.002	0.013

Note 1: Data are shown as mean (95% confidence interval). Note 2: Bone properties were assessed by dual-energy X-ray absorptiometry. Note 3: BMC, bone mineral content; BMD, bone mineral density. Note 4: Paired *t*-tests were used to analyse the changes in variables within groups. Analysis of covariance for repeated measures (group × time) was used to assess the effects of the interventions by adjusting the corresponding baseline data, "years menopausal", and intervention duration as the covariates.

3.3. Change in Bone Turnover Markers after the Intervention

Serum OC, RANKL, and pentosidine levels did not differ significantly between the AEx and CON groups both at the pre- and post-intervention (Figure 1). After the intervention, both the AEx and CON groups had decreased the levels of OC ($p = 0.033$ and 0.001, respectively, paired *t*-test) and pentosidine ($p = 0.035$ and 0.015, respectively, paired *t*-test), but no significant changes were observed in RANKL.

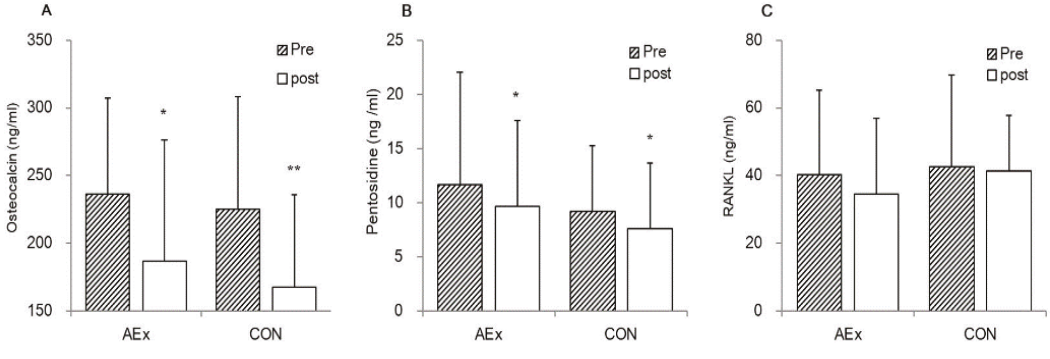

Figure 1. Bone turnover markers in AEx and CON pre-and post-intervention. Note: * $p < 0.05$, ** $p < 0.01$, paired *t*-tests were used to analyze the changes in variables within groups. Data are means ± SD (standard deviation).

3.4. Associations between Biomarkers and BMC/BMD

RANKL displayed a positive correlation with BMC_{WB} ($r = 0.398$, $p = 0.002$), BMC_{TF} ($r = 0.396$, $p = 0.003$), BMC_{FN} ($r = 0.320$, $p = 0.022$), $BMC_{L2\text{-}4}$ ($r = 0.322$, $p = 0.015$), BMD_{WB} ($r = 0.506$, $p < 0.001$), BMD_{TF} ($r = 0.454$, $p < 0.001$), BMD_{FN} ($r = 0.421$, $p = 0.001$), and $BMD_{L2\text{-}4}$ ($r = 0.377$, $p = 0.004$) values in the whole samples at the baseline, while these correlations disappeared after intervention (all $p > 0.05$, data are not shown). No significant associations were found between OC, pentosidine, and BMC/BMD at both pre- and post-intervention (all $p > 0.05$). Decreased pentosidine levels were associated with an increase in BMC_{WB} ($r = -0.352$, $p = 0.019$, Figure 2) values. Even after adjusting for "years menopausal" and intervention duration, the significance remained ($r = -0.369$, $p = 0.032$). No correlations

were observed between changes in OC and RANKL and variations in BMC/BMD at the different bone sites.

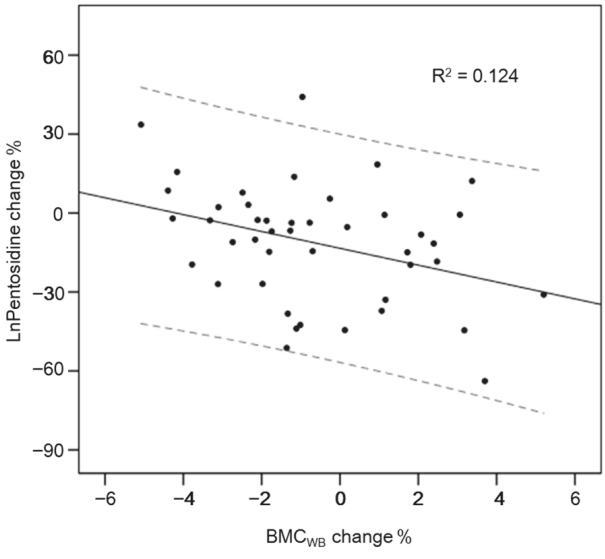

Figure 2. Correlation between pentosidine change and BMC_{WB} change of pre-and post-intervention. Note: BMC_{WB}, bone mineral content of the whole body.

4. Discussion

In this study, we found that an 8.6-month aerobic exercise program that comprised Nordic walking chiefly, was able to maintain bone mass and density in patients with prediabetes and NAFLD. Previous studies have shown that the bone mass of the femur and lumbar spine decreases by approximately 1% annually at midlife and at an accelerated rate of 2% annually during the first few years after menopause in women [22,23]. In the present study, there was a ~0.4% increase in $BMD_{L2\text{-}4}$, and BMD_{TF} was conserved after 8.6 months of the exercise intervention when compared with a 2.6% decrease in the control group, indicating that the osteogenic effects were significant. This positive adaptation occurred in regions where a large portion of the postmenopausal women have osteoporosis or osteopenia.

Previous studies have shown that periodic exercise training in 1-year blocks (4–6-week blocks of high-intensity bone-specific exercise with intermittent moderate-intensity metabolism-specific exercise for 10–12 weeks) positively affected BMD at the lumbar spine that was assessed by peripheral quantitative computed tomography in early post-menopausal women with metabolic syndrome [24]. Skoradal et al. suggested that 30–60 min of soccer training twice a week for 16 weeks could effectively increase BMD (3.9%) in the lumbar spine in individuals 55–70 years of age with pre-diabetes [25]. Chien et al. reported that a 6-month graded treadmill walking program combined with stepping exercises using a 20 cm-high bench attenuated lumbar spine BMD loss in osteopenic postmenopausal women [26]. A 12-month walking program in early ($\leq$6 years) postmenopausal women demonstrated a significant increase in BMD at the lumbar spine [27]. However, some studies also reported that walking did not increase BMD at the lumbar spine [28,29].

Nordic walking has characteristic diagonal movements with contralateral hand-foot coordination such that the swing phase is double (one leg and the pole in the opposite hand). Compared with walking without poles, it has different kinetic variables and involves stronger upper body movements [30]. Studies have shown that Nordic walking enhances muscular strength in healthy participants and in the elderly [14]. It is possible that muscle

tension produces strains in the skeleton, which could induce bone formation [31]. We did not find significant increases in BMD of the lumbar spine and femur in the exercise group; however, there was a decrease in BMD in the control group (meaning amount of bone mass at the measured area of bone sites have changed, with bone becoming less dense). This indicates that our exercise intervention program could help maintain BMD.

OC is one of the bone turnover markers released during bone remodeling by osteoblasts or odontoblasts, which is believed to be associated with an increase in BMD. Studies have reported that exercise programs comprising football training, 40 min of jogging, and 20 min of gymnastics with wrist weights (0.8 kg on each arm) and strength training increased serum OC levels compared to controls [25,32,33]. On the contrary, we found no significant effects of Nordic walking on OC. Shibata et al. and Wochna et al. also demonstrated that exercise training did not increase OC levels while causing favorable changes in bone health [34,35].

RANKL was recently identified as an important cytokine that sustains osteoclast formation and survival [36]. We found that baseline BMC and BMD were associated with RANKL. However, Nordic walking did not change the serum concentration of RANKL. This is supported by previous studies in which there was no significant change in the serum RANKL levels after 8 months of combined exercise intervention in elderly participants [37,38]. In contrast, in one study among middle-aged men, high intensity (70–75% maximal heart rate) walking exercise was instructed for 10 weeks, five times per week. This led to a decrease in the serum concentration of RANKL when compared with moderate-intensity (50–60% maximal heart rate) exercise [39]. This suggested that RANKL signaling factors could be dependent on exercise intensity.

AGEs, especially pentosidine, are considered to affect bone metabolism and contribute to bone fragility in patients with T2DM [40]. AGEs significantly inhibit osteoblast proliferation, differentiation, and mineralization and induce osteoblast apoptosis [41,42]. The formation of bone nodules in human osteoblasts was impaired by pentosidine [43]. In contrast, AGEs led to a decrease in osteoclast-induced bone resorption [44]. In our study, decreases in pentosidine levels were associated with increases in values of BMC of the whole body. Although we do not know the causal relationship, this association indicated that the change of serum pentosidine was correlated with the change of amount of bone mass. This result agreed with previous studies which have shown that pentosidine negatively correlated with bone strength [11] and was positively associated with fracture incidence in T2DM [12].

Our study has some limitations. First, the study only measured BMC/BMD using DXA. Bone quality in individuals with glucose impairment and NAFLD could be more important than BMD [45]. Second, the follow-up period was 8.6 months, which may not be long enough to observe the effects of exercise on BMC/BMD or bone turnover markers due to large individual variations. Third, all participants were from the same community, and the behavior of participants in the no-intervention group could have been influenced by those in the intervention groups, even though we asked them to maintain their existing lifestyle during the intervention. This is reflected by the observation that the fitness level of those in the non-intervention group also increased [20].

5. Conclusions

In conclusion, these findings indicate that brisk Nordic walking for 8.6 months is effective in preventing bone loss in the lumbar spine and femur among postmenopausal women with pre-diabetes. It could help counteract the impairment of bone metabolism in patients with comorbidities of prediabetes, such as NAFLD.

Author Contributions: X.D. (subjects recruitment; exercise intervention; data collection, analysis and interpretation; manuscript drafting). C.Z. (subjects recruitment; exercise intervention; manuscript editing). X.Z. (biomarkers analysis and interpretation; manuscript editing). Z.Q. (biomarkers analysis/interpretation). S.C. (project planning and design; data analysis/interpretation; manuscript reviewing and editing). S.L. (study design; subjects recruitment; data collection, analysis and

interpretation; manuscript editing and reviewing; approved the final manuscript). All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Shanghai Institute of Nutrition (No. 2013–003, 6 January 2013).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Article

Prevalence of Prediabetes and Type 2 Diabetes Mellitus in Football Players: A Novel Multi Football Clubs Cross Sectional Study

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Abstract: Sports offer great benefits, improving health and reducing the risk of illnesses. This study's aim was to investigate the prevalence of prediabetes and type 2 diabetes mellitus in football players compared to population based non-elite athlete control subjects. Initially 1100 male volunteers, (550) football players, and (550) population based non-elite athlete control subjects were interviewed. After socio-demographic and medical history analysis, 756 (378) nonsmoker male football players and (378) nonsmoker male control subjects were recruited. The control subjects were not involved in regular sports activities such as football, volleyball, badminton, cricket, hockey, and swimming. Participants with a known history of anemia, blood diseases, diabetes mellitus, and malignancy were excluded from the study. The mean age of football players was 31.80 ± 5.46 years, Body Mass Index (BMI) was 26.40 ± 2.08 (kg/m^2), and the mean age of control subjects was 32.32 ± 4.37 years, and BMI was 26.66 ± 1.87 (kg/m^2). The selected football players have been playing football for about 2 h a day, 3 days per week, and so the total mean duration of playing football was 1.08 years. American Diabetes Association (ADA) based criteria on Glycated Hemoglobin (HbA1c) was used to investigate prediabetes and type 2 diabetes mellitus. In football players the prevalence of prediabetes was 30 (7.93%) and type 2 diabetes mellitus (T2DM) was 6 (1.59%) compared to population based matched non-elite athlete control subjects where the prediabetes was 71 (18.78%) and T2DM was 89 (23.54%) ($p = 0.001$). Among football players there was a 7-fold decrease in T2DM compared to control subjects. Football recreational activities markedly reduce the prevalence of prediabetes and T2DM. The study findings demonstrate the benefits of football and other such sport activities and emphasize the urgent need for promoting football based physical activities as a physiological preventive strategy against the globally growing diabetes epidemic.

Keywords: football; sports; prevalence; diabetes mellitus

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1. Introduction

Diabetes mellitus (DM) is a global health challenge associated with substantial morbidity, mortality, and economic burden [1]. In spite of advancements in biomedical sciences, DM is an incurable life-long disease [2]. The recent global prevalence of DM is 463 million; 374 million people are suffering from impaired glucose tolerance whereas 232 million people are unaware from the fact that they are suffering from the disease. Diabetes caused 4.2 million deaths in the year 2019, 11,666 people per day, and 8.10 people per minute. Moreover, the world health expenditure on diabetes is 760 billion $ [3].

Currently, diabetes mellitus has a high priority rank on the international health agenda due to being a global pandemic and a deathtrap to human health and worldwide economies [4]. Worldwide, many countries have implemented policies to arbitrate on

risk factors, such as "lifestyle, smoking, diet, physical activity" to minimize the prevalence of diabetes mellitus [5]. Lack of regular physical activities, unhealthy diet, and similar lifestyles account for increasing obesity and diabetes mellitus [6].

Football-based sport has been acknowledged as a potential health promotion strategy to reduce the sedentary behavior. Football improves endurance capacity and has a positive influence on cardiovascular and metabolic health [7]. Football based physiological involvements achieve the primary preventive effects and improvements in human health [8]. In recent years, the evidence for the health benefits of football sport showed that it improves aerobic fitness, muscular performance, metabolic and cardiovascular function, and reduces adiposity [9]. However, literature is extremely lacking to establish an association between playing football and prevalence of prediabetes and type 2 diabetes mellitus (T2DM). This study's aim was to investigate the prevalence of prediabetes and T2DM in football players compared to population based non-elite athlete matched control subjects.

2. Subjects and Methods

2.1. Study Participants

In this study, various schools, colleges, universities, small and large-scale football sport grounds were randomly visited and information about football players was gathered. Initially 1100 volunteer males, (550) football players, and (550) population based non-elite athlete control subjects were interviewed. After socio-demographic, medical history and examination, a total of 756 (378) nonsmoker male football players and (378) nonsmoker control subjects were recruited (Figure 1). Power analysis was used to calculate the sample size. The mean age of football players was 31.80 ± 5.46 years, weight 77.81 ± 6.88 kg, and Body Mass Index (BMI) 26.40 ± 2.08 (kg/m^2). The selected football players have been playing football for about 2 h a day, 3 days per week; the total mean duration of playing football was 12.98 ± 0.47 months (Table 1). It was ensured that these players were involved in football sport only and no other sports allied activities such as volleyball, badminton, cricket, hockey, swimming etc. Moreover, these football players were not involved in working exposure to any industries such as cement, coal, cotton, oil, and flour factories as these industries generate pollution, and pollution increases the prevalence of diabetes mellitus [2,10,11].

Table 1. Sociodemographic and clinical characteristics of football players and matched control subjects (n = 756).

Parameters	Football Players (n = 378)	Control Group (n = 378)	p-Value
Age (years)	31.80 ± 5.46	32.32 ± 4.37	0.148
Height (m)	1.72 ± 0.07	1.69 ± 0.07	0.088
Weight (kg)	77.81 ± 6.88	76.85 ± 6.99	0.060
BMI (kg/m^2)	26.40 ± 2.08	26.66 ± 1.87	0.068

Values are expressed in Mean ± SD.

Similarly, for control group, various schools, colleges, universities were randomly visited and initially, 550 population based non-elite athlete control subjects were interviewed. After socio-demographic and medical history examination, 378 control subjects were selected from schools and universities' clerical staff, technicians, and research assistants. The mean age for the non-elite athlete control subjects was 32.32 ± 4.37 years, weight 76.85 ± 6.99 kg and Body Mass Index 26.66 ± 1.87 (kg/m^2). It was warranted that these control subjects were not involved in regular sports activities such as football, volleyball, badminton, cricket, hockey, swimming, etc. Moreover, these control subjects were not involved in working exposure to any industries such as cement, coal, cotton, oil, and flour factories as these industries generate pollution, and pollution increases the prevalence of

diabetes mellitus [2,10,11]. A verbal consent was obtained from the participants who had voluntarily registered in the research project.

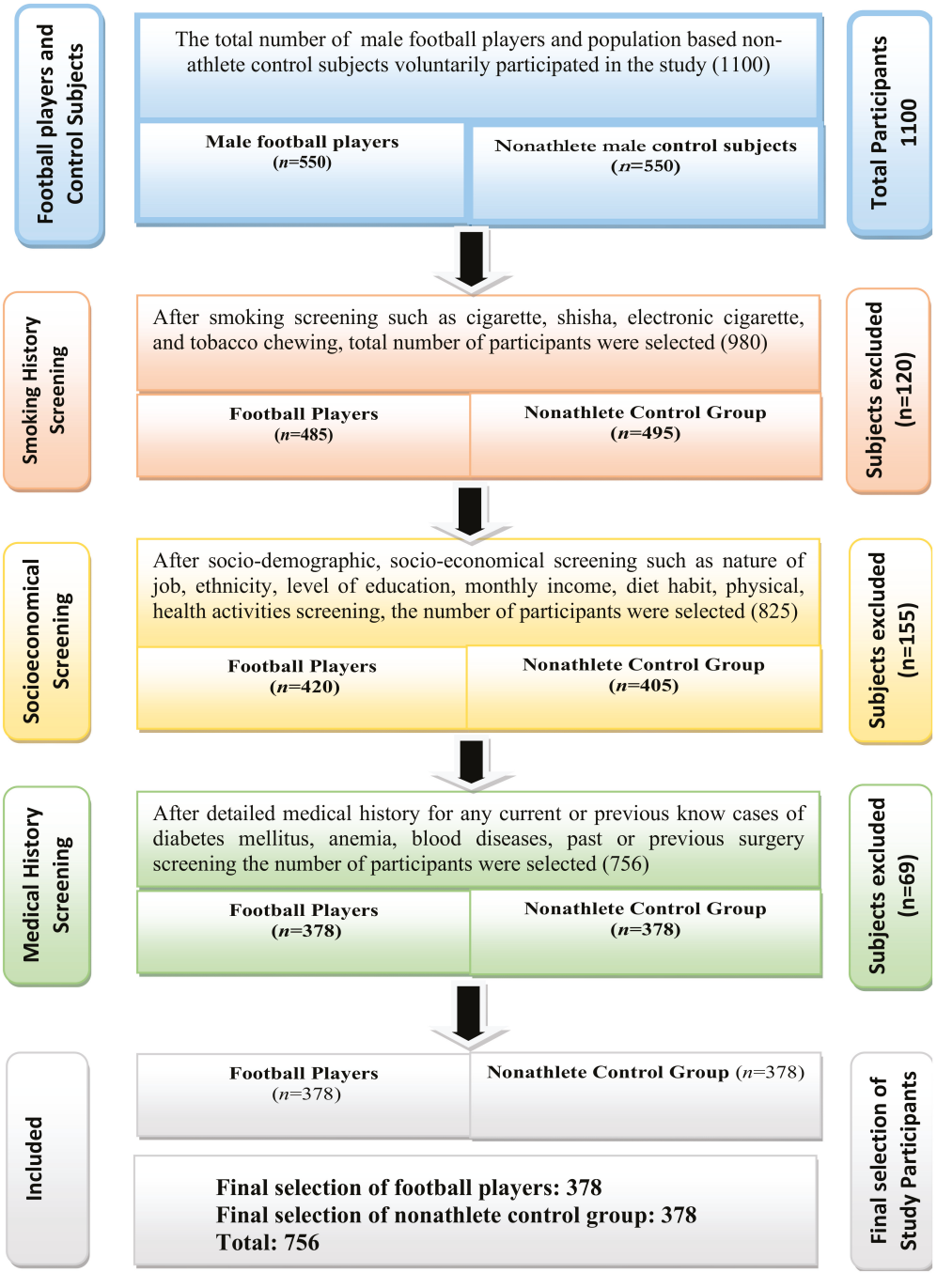

Figure 1. Flow diagram of the selection of football players and population based nonathlete control subjects.

2.2. Clinical History and Socio Demographic Characteristics

Three co-investigators interviewed 550 volunteer male football players and a detailed sociodemographic and medical history was obtained. The information about "age, gender, height, weight, BMI, duration of playing football, demographic characteristics, lifestyle, dietary habit, physical activities and other health-related information" were collected by the use of a questionnaire. Moreover, the "socio-demographic characteristics including residential address, living conditions, education level, marital status, monthly income, lifestyle information, and smoking" were recorded. Other health-related evidence including family history of diabetes mellitus was also taken. Both groups were matched for, "age, weight, BMI, socioeconomical, and dietary habits". After demographic, medical history and examination, a final total of 756, (378) nonsmoker football players, and (378) nonsmoker control subjects were recruited (Figure 1).

2.3. Exclusion Criteria

Participants with a "known history of anemia, blood diseases, blood transfusion, asthma, diabetes mellitus, and malignancy were excluded from the study". Subjects who smoke traditional or electronic cigarette or shisha were also excluded [12]. It was ensured that the football players were only playing football and control group participants were population based non-elite athlete subjects. The participants with a current or previous history of an employment in any industrial plant which produces dust or fumes such as plastic, cement, coal, cotton, and flour factories were also not included in the study [10,11] (Figure 1).

2.4. Measurements of Glycated Hemoglobin (HbA1c)

After detailed interview, the participants were allocated an identification number, and a para-medical staff measured the HbA1c, by using the "Clover A1c system (Inforpia, Kyunggi, Korea), an automated boronate affinity assay for the determination of the percentage of HbA1c % in the whole body's blood" [13]. American Diabetes Association (ADA) [14] based criteria on glycated hemoglobin (HbA1c) was used to diagnose the diabetes mellitus. Subjects with "HbA1c less than 5.7% were considered as non-diabetics; HbA1c 5.7–6.4% as prediabetics; and subjects with HbA1c more than 6.4% were considered diabetics" [14]. HbA1c is a reliable indicator of glycemic measurements for the diagnosis of diabetes mellitus [14,15].

2.5. Ethics Statement

This study was executed in harmony with the "Declaration of Helsinki", and the protocol was approved by the "Ethics Committee, College of Medicine Research Centre, King Saud University (E-19-4494)".

2.6. Statistical Analysis

The continuous variables were expressed as the Mean ± Standard Deviation and descriptive data were expressed as frequency (%). The frequencies and percentages for prevalence of prediabetes and Type 2 Diabetes Mellitus, their association with social-demographics data and duration of playing football was calculated by using chi-square tests of independence. Pearson correlation coefficient regression model was used to identify the independent risk. The level of significance was presumed at $p < 0.05$.

3. Results

The anthropometric characteristics of the football plyers and control subjects are presented in Table 1. The mean age of football payers was 31.80 ± 5.46 years, weight 77.81 ± 6.88 kg, and Body Mass Index 26.40 ± 2.08 (kg/m^2); and the mean age of control subjects was 32.32 ± 4.37 years, weight 76.85 ± 6.99 kg, and Body Mass Index 26.66 ± 1.87 (kg/m^2) (Table 1). The selected football players have been playing football for about 2 h a day, 3 days per week, the mean duration of playing football was

12.98 ± 0.47 months. Both of the groups were matched for age, weight, BMI (Table 1), diet habit, socioeconomic, and educational levels.

In football players the prevalence of prediabetes was 30 (7.93%) and type 2 diabetes mellitus (T2DM) was 6 (1.59%) compared to population based matched non-elite athlete control subjects where the prediabetes was 71 (18.78%) and T2DM was 89 (23.54%) ($p = 0.001$) (Table 2). The prevalence of prediabetes and T2DM among the football players was significantly decreased with duration of playing football (Figure 2). Among football players there was a 7 fold decrease in T2DM compared to control subjects (Table 2).

Table 2. Comparison of prevalence of prediabetes and Type 2 Diabetes Mellitus between football players and matched control subjects ($n = 756$).

Parameters	Football Players ($n = 378$)	Control Group ($n = 378$)	p-Value
Non-diabetic (HbA1c < 5.7%)	342 (90.48%)	218 (57.67%)	0.001
Prediabetic (HbA1c 5.7–6.4%)	30 (7.96%)	71 (18.78%)	0.001
Diabetic (HbA1c > 6.4%)	6 (1.59%)	89 (23.54%)	0.001

Values are expressed in number and percent. HbA1c values are classified as per American Diabetes Association Guidelines [14].

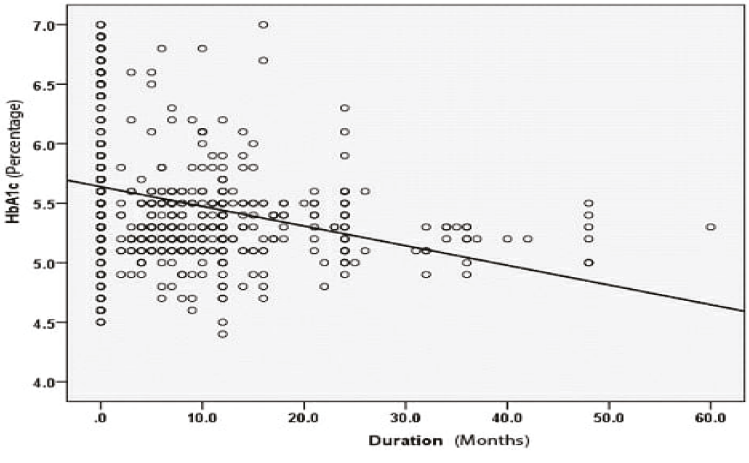

Figure 2. Correlation between duration of playing football and HbA1c.

The correlations between age, BMI, and duration of playing football and level of HbA1c showed that there was a significant association between the duration of playing football and deceased level of HBA1c. However, this association was not established with an age and BMI (Table 3). After adjustment for age, weight, and BMI, based on the findings' analysis for HBA1c between control and football players, it was noticed that HBA1c was significantly lower among the football players compared to control group ($p = 0.001$) (Table 2).

Table 3. Correlations between level of HbA1c and age, Body Mass Index (BMI), and duration of playing football.

Parameters	HBA1C	
	Pearson Correlation Coefficient	*p*-Value
Age (years)	0.026	0.479
BMI (kg/m^2)	−0.008	0.817
Duration (months)	−0.278 **	<0.001

** Correlation is significant at the 0.01 level (2-tailed).

4. Discussion

This is the first study added in the literature to investigate the prevalence of prediabetes and T2DM among football players compared to population based non-elite athlete control subjects. In this study, a significant decreased was found in the prevalence of prediabetes and T2DM in football players compared to control subjects. The findings were interesting from the perspective that the prevalence of T2DM was significantly low in football players in a nation where T2DM is highest across the globe [16].

Meo et al. [17] reported that the prevalence of T2DM in Saudi population with age ranges 29–60 was 32.8%. In another study, Meo et al. [16] identified that in the Arab world nations, highest prevalence of T2DM was in Saudi Arabia (31.6%), followed by Kuwait 25.4%, Bahrain 25.0% and United Arab Emirates 25.0%. As per International Diabetes Federation (IDF) report 2019[3], worldwide total number of diabetic people with age ranges 20–79 years are 463 million (9.3%)[3] the prevalence of diabetes in just one country Saudi Arabia is 18.5% [18]. However, as per World Health Organization the prevalence of diabetes in Saudi Arabia is 14.4% [19]. All these findings suggest that T2DM in Saudi Arabia is highest in the region as well as in the world. However, in the present study we found that the prevalence of T2DM in Saudi adult football players was just 1.59% compared to their matched control group (23.54%). These findings suggest that in football players T2DM is astonishingly almost 7 fold less in football players compared to their age, weight, and BMI matched control subjects.

Football game is packed with a lot of recreational activities, and exercise has been known to positively influence the glucose control [20]. Nieuwoudt et al. [21] determined the changes in beta-cell function after six weeks of high-intensity functional training (HIFT) among 12 sedentary adults with T2DM. After the exercise sessions of 3 days a week, participants showed significant improvements in beta-cell function, while decreasing body fat and preserving lean mass [21]. In another study, Fealy et al. [22] evaluated the effectiveness of their 6-week HIFT intervention for risk factors and reported an increased insulin sensitivity after training. Similarly, Skoradal et al. [1] demonstrated that 16 weeks of football training causes broad-spectrum positive effects on metabolic health profile. It has also been reported that playing football regularly increases insulin sensitivity, positively influencing glycemic control, and potentially providing better tools for the prevention of T2DM [23].

Lao et al. [24] evaluated the impact of habitual leisure-time physical activity (LTPA) on T2DM incidence. The authors reported that high levels of LTPA was associated with a lower risk of diabetes. Sarmento et al. [25] demonstrated the benefits of football sport on diseases, including cardiovascular, bone health, and body composition, as sports allied activities increase the insulin sensitivity, and had a positive impact on glycemic control and T2DM. Krustrup et al. [26] describes the health effects of recreational female football players. The authors found that short-term and medium-term recreational football activities have beneficial impact on metabolic health profiles in women. The authors concluded that regular football sport is an effective tool for the prevention of hypertension and T2DM. In another study, Anderson et al. [27] determined the effects of regular football training on glycemic control in men with T2DM. They found that 1-hr football training session, for a 24-week intervention period, caused a greater reduction in plasma glucose. The present

study findings shows significant decreased prevalence of prediabetes and T2DM among football players compared to population based non-elite athlete control subjects.

4.1. Possible Mechanism-How Football Reduces Diabetes Mellitus

The potential mechanism involved in playing football and decreased insulin resistance and diabetes mellitus is variable. The epidemiological literature acknowledges the fact that football exercise decreases the risk of insulin resistance and ultimately leads to decreased risk of T2DM. Football recreational activities decrease oxidative stress, increase proteins related to mitochondrial biogenesis and improve the antioxidant capabilities along with glucose intake, hence leading to a decrease in T2DM [28] (Figure 3). Moreover, football game improves "insulin sensitivity, enhanced glucose transport into muscle cells [25], and increased production of muscle glycogen to replace the glycogen used during exercise". These are the possible mechanisms in playing football which lead to the decrease in prevalence of prediabetes and T2DM.

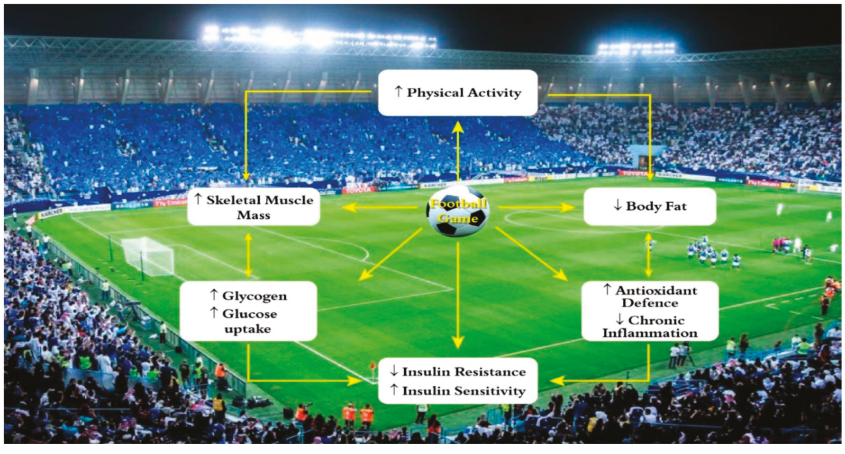

Figure 3. Possible mechanism-how football sport reduces the risk of Type 2 Diabetes Mellitus.

4.2. Study Strengths and Limitations

This is the first study added in the literature to investigate the prevalence of prediabetes and T2DM in football players. The study exclusion criteria were highly standardized and cigarette smokers were excluded. Both groups were matched for age, height, weight, BMI, ethnicity, diet habit, and socio-economic levels to minimize the possible confounding factors. American Diabetes Association diagnosis approach was followed; Glycated Hemoglobin (HbA1c) is a reliable and valid indicator to identify an individual's long-term mean blood glucose levels and therefore its criteria was employed. This study could therefore be the best reference on the prevalence of prediabetes and T2DM among football players. There are some limitations that we would like to point out: despite trying to recruit large number of football players, we excluded cigarette smokers; age, weight, height, and ethnicity matched criteria was employed, hence we excluded large number of participants and finally included 378 football players and 378 control subjects. Moreover, due to cultural limitations we only included the male gender.

5. Conclusions

Football recreational activities significantly decrease the prevalence of prediabetes and T2DM in football players compared to matched control subjects. The decreased prevalence was associated with the duration of football activities. The study findings have significant public health implications, as findings support the extension of diabetes intervention

efforts. Health officials should establish more sport facilities, mainly football grounds, for the public to provide better sports facilities which will help in minimizing the incidence of prediabetes and T2DM. Future prospective studies with large sample sizes are needed to further confirm these findings to get to better conclusions.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of College of Medicine, King Saud University, Riyadh, KSA (E-19-4494, Feb 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data may be provided on reasonable request to corresponding author.

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Conflicts of Interest: The authors declare no competing financial interests.

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Systematic Review

The Effect of Yoga on Health-Related Fitness among Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract: Background: There is a need for a type of physical activity that could address the challenging cycle of physical inactivity, impaired health-related fitness, and type 2 diabetes mellitus (T2DM) conditions. Yoga could be one type of exercise to overcome the barriers to adhere to regular physical activity. The current study aimed to systematically review the effect of yoga on health-related fitness, including cardiorespiratory fitness, muscle strength, body composition, balance, and flexibility, among patients with T2DM. Methods: We systematically searched four databases and two registries (Pubmed, Scopus, Cochrane, Embase, WHO-ITCRP, and Clinicaltrials.gov) in September 2021, following a registered protocol on PROSPERO (CRD42022276225). Study inclusion criteria were T2DM patients with or without complication, yoga intervention as a single component or as a complement compared to other kinds of exercise or an inactive control, health-related fitness, and a randomized, controlled trial or quasi-experimental with control group design. The ROBINS-I tool and ROB 2.0 tool were used to assess the risk of bias in the included studies. A vote-counting analysis and meta-analysis computed using random effects' models were conducted. Results: A total of 10 records from 3 quasi-experimental and 7 randomized, controlled trials with 815 participants in total were included. The meta-analysis favored yoga groups compared to inactive controls in improving muscle strength by 3.42 (95% confidence interval 2.42 to 4.43), repetitions of chair stand test, and improving cardiorespiratory fitness by 6.6% (95% confidence interval 0.4 to 12.8) improvement of baseline forced vital capacity. The quality of evidence for both outcomes was low. Conclusion: Low-quality evidence favored yoga in improving health-related fitness, particularly muscle strength and cardiorespiratory fitness, among patients with T2DM. Funding: All authors in this systematic review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Keywords: cardiorespiratory fitness; diabetes mellitus; exercise; yoga; muscle strength; physical fitness

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1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the largest public health concerns leading to significant premature mortality and serious economic burden [1–4]. Evidence has shown that health-related fitness, such as cardiorespiratory fitness, muscle strength, and body composition, is an independent predictor of reduced quality of life, cardiovascular

risks, and mortality among patients with T2DM [5–9]. Epidemiological studies found that patients with T2DM are frequently found to have low cardiorespiratory fitness and impaired muscle mass and strength as well as altered body composition [6,10–12]. This altered health-related fitness can be attributed to a pathological cycle of increased insulin resistance, vascular alteration, chronic inflammation, and lipid infiltration in patients with T2DM [13–16]. Therefore, intervention and therapy targeting this cycle in patients with T2DM is required to reduce morbidity and mortality, which then can improve their quality of life.

Strong evidence has shown the benefits of physical activity to health-related fitness [17]. However, most patients with T2DM did not adhere to physical activity recommendations [12]. Perceptions that exercise potentially exacerbates diabetes, feelings of inability to do exercise, and lack of facilities for carrying out exercise are among the most mentioned barriers to exercise among patients with T2DM [18]. Yoga is a mind–body exercise that is considered to be a suitable option for physical activity for patients with type 2 diabetes mellitus because of its low cardiovascular demands, low impact, simplicity, and easiness that could address the patients' barriers to physical activity [19,20].

While yoga requires only light intensity during most of its session, it has still been found to provide health benefits for patients with T2DM since several of its poses during a session can result in moderate intensity [20,21]. A recent systematic review also found that yoga provides benefits for certain aspects of health-related fitness, including muscle strength, flexibility, and balance, as well as quality of life among elderly people [22]. However, the results from that review cannot be generalized to patients with T2DM since there are physiological differences among them. Thus, we conducted a systematic review to assess the effectiveness of yoga intervention compared to other exercise interventions and inactive controls on health-related fitness and quality of life for patients with T2DM.

2. Methods

A systematic review was conducted based on a registered protocol on PROSPERO (CRD42022276225), which was developed in advance of the review in accordance with guidelines from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 Statement [23,24].

2.1. Inclusion Criteria

The inclusion criteria for studies were (1) population, studies with adult patients diagnosed with T2DM either with or without complications were included; (2) intervention and comparison, studies comparing yoga to either another exercise intervention or an inactive control or waiting-list control were included. Studies evaluating yoga as a combination with other exercises were included if there were comparators allowing evaluation of yoga as either a single component or a complement. Studies comparing one to another kind of yoga were excluded; (3) outcomes, only studies reporting at least one component of health-related fitness (cardiorespiratory fitness, muscle strength, body composition, balance, or flexibility) were included; and (4) type of study, studies with either a randomized, controlled trial (RCT) or a quasi-experimental with a control group design were included to anticipate insufficient number of RCTs addressing the health-related fitness outcomes. To be included in this review, health-related fitness outcomes must have been able to be assessed using objective measurements. We included studies that objectively measured cardiorespiratory fitness by either direct, indirect, maximal, submaximal, pulmonary functions or functional tests. Studies conducting muscle strength measurements by any instruments, such as the Oxford scale, dynamometer, or functional strength testing, were included. We included studies assessing body composition using magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and anthropometric measurements, including skin fold, waist circumference, hip circumference, or waist-to-hip ratio. Studies assessing flexibility or balance using any objective measurement were included.

2.2. Search Strategy

Four databases (Pubmed, Scopus, Cochrane, and Embase) and two registries (WHO-ICTRP and Clinicaltrials.gov) were searched by RAW and AVI from inception through September 2021. Search strategies were developed based on the population criteria using MeSH terms and free terms related to "Yoga" and "Type 2 Diabetes". The complete search strategy used in each database is presented in the supplementary section (Supplement file S1). The outcome, comparator, and type of study were applied at the screening stage. The reference list of included studies and trial registries found during the database searches were also checked for additional relevant studies [25].

2.3. Study Selection

Having checked and removed duplicates, two reviewers (R.N., H.A.N.) conducted two stages of the screening process using the Rayyan software [26]. First, they screened independently titles and abstracts of all studies by categorizing them into "Yes", "No", and "Maybe". They only categorized studies that explicitly had different populations, types of study, interventions, and comparisons. They did not exclude abstracts that did not report health-related fitness as their outcomes since the majority of abstracts in biomedical research did not fully report all of their research outcomes [27,28]. Finally, they screened the full text of studies included in "Yes" and "Maybe" categories. The third reviewer (R.A.W.) facilitated discussion to resolve any disagreements in the first and second stages of the screening process. The reference list of included studies was checked by R.A.W.

Two reviewers (R.A.W., E.O.) developed and piloted a custom data extraction form (Supplement file S2). Descriptive and outcome data for all included studies were independently extracted by two reviewers (E.O., J.S.). Discussions facilitated by another reviewer (R.A.W.) were conducted to resolve discrepancies.

One reviewer (R.A.W.) assessed the risk of bias using the Cochrane Risk of Bias 2.0 tool for RCT and the risk of bias in non-randomized studies of interventions' assessment (ROBINS-I) tool for quasi-experimental studies [29,30].

2.4. Synthesis Methods

We presented the narrative synthesis based on a vote-counting approach by categorizing the results of each outcome into three categories as follows: (1) statistically significant positive effects favoring yoga group, (2) statistically significant negative effects of the yoga intervention, and (3) no statistically significant difference between groups [31,32]. The results of the vote counting were based on the highest number of votes counted on each outcome. Then, meta-analyses were performed using the RevMan software for cardiorespiratory fitness, muscle strength, and body composition outcome since quantitative data from two or more studies were available and appropriate [32]. We combined groups from multiple intervention groups in one study to avoid double counts of the participants in the yoga group [32]. We multiplied mean values from one set of studies that had a scale with opposite direction to the common scale [32]. Since several studies used more than one instrument to measure an outcome, the most commonly reported outcome measures were included in the meta-analysis. For cardiorespiratory fitness, forced vital capacity (FVC) and a 6-min walk test were included in the meta-analysis, and chair stand tests were included for muscle strength outcome [33–35]. A random effects' model was used since there was clinical heterogeneity resulting from variety in the yoga poses, frequency, session duration, and duration of the intervention [32]. Mean difference of the change of the chair stand test result from baseline between the intervention group and the control group (MD) was used because similar instruments were reported [32]. On the other hand, the standardized mean difference of the change of cardiorespiratory fitness from baseline was used because of the difference in instruments [32]. We obtained standard deviation (SD) of the change from baseline by imputing it from the *p*-value [32]. Meta-analysis of the final values of body composition using the standardized mean difference was conducted since the change scores of the body composition outcomes were not available in the primary studies and

there were variabilities in the measure of body composition outcomes [32]. After that, we used the weighted mean difference and weighted standardized mean difference and then created forest plots to compute the effect size with 95% confidence intervals (CI) [32]. Weighted standardized mean differences were interpreted by expressing them into the most representative measurement instrument [30]. I^2 statistics was used to assess statistical heterogeneity. Substantial heterogeneity was considered if there was I^2 exceeding the threshold of 50% [30]. Subgroup analyses based on study design and duration of the intervention were conducted to explore heterogeneity among study results. Sensitivity analysis was conducted by excluding studies with a high risk of bias. The quality of evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [32].

3. Results

We identified 1117 records through database searches. Having conducted two stages of screening, we included 10 studies in the systematic review (Figure 1). Among the included studies, there were three quasi-experimental studies [36–38] and seven RCTs [39–45]. One quasi-experimental study assessed muscle strength, balance, and fall-related outcomes [37], one quasi-experimental study assessed body composition [36], and another quasi-experimental study assessed body composition and cardiorespiratory fitness [38]. On the other hand, one RCT assessed cardiorespiratory fitness, muscle strength, balance, and quality of life [41], another RCT assessed body composition and quality of life [44], another RCT only assessed cardiorespiratory fitness [39], and the remaining four only assessed body composition [40,42,43,45].

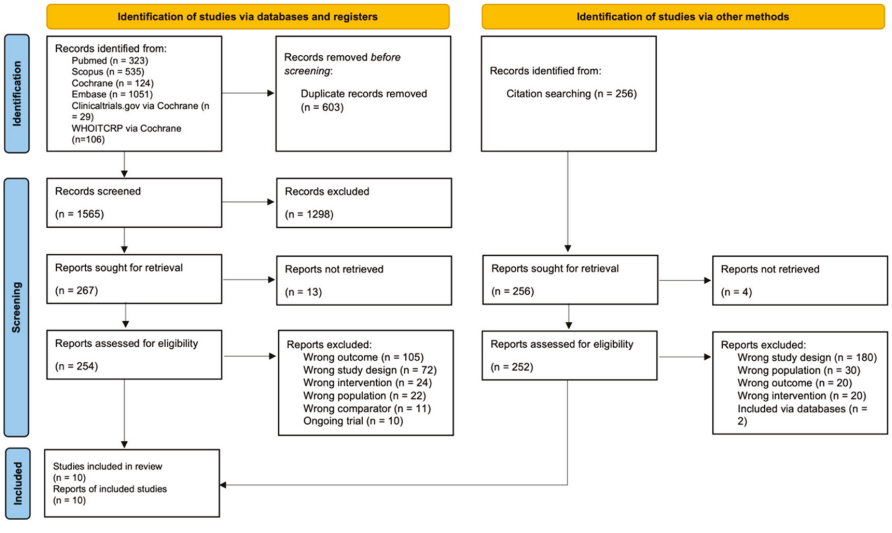

Figure 1. PRISMA flow diagram.

Cardiorespiratory fitness outcomes were measured using lung function tests assessing forced expiratory volume for 1 s (FEV1), FVC, FEV1/FVC ratio, slow vital capacity (SVC), peak expiratory flow rate (PEFR), and maximal voluntary ventilation (MVV); FVC, FEV1, and FEV1/FVC ratio were the most commonly reported measures of lung function. Since FVC ratio represented the degree of restrictive lung disease in patients with T2DM, which resulted in impaired cardiorespiratory fitness, FVC was chosen to be included in the meta-analysis using the standardized mean difference along with the distance in the 6-min walk test [16]. Among included studies, muscle strength was assessed by the chair stand test and the step-up test for lower extremity muscle strength and by the arm curl test for

upper extremity muscle strength. Waist circumference, hip circumference, and waist-to-hip ratio were used to measure body composition among the included studies. Therefore, the standardized mean difference was used in the meta-analysis on body composition outcome. Balance was assessed using the Fullerton Advanced Balance (FAB) Scale, star excursion balance test, and single limb stance test. However, measures of balance were not included in the meta-analysis because of the lack of an included study.

Only two of the included studies were from the USA and UK [41,44]; the rest were from India. The number of participants in the included studies ranged from 18 to 160. The mean age of the participants ranged from 45 years to 60 years. Two studies only recruited female subjects, and another one did not report the proportion of each gender (Table 1).

Table 1. Characteristics of included studies.

Study id Country Funding Source	Study Design	Participants (Number, Mean Age (SD), Gender Proportion, Presence of Diabetic Complication)	Intervention Characteristics (Type, Frequency, Session Duration, Length of Intervention)	Control Group(s)	Outcome Measures
Darimela (2017), India, Funding not stated [36]	Quasi-experimental	*n* = 160, age range 36–48, 100% female, complication not described	Hatha yoga, up to 60–70 min per session, frequency not described, 6 months	1. Active control: exercise 2. Active control: walking exercise 3. Inactive control	Body composition: hip circumference
Kanjirathingal (2021), India, MGM School of Physiotherapy, MGM Institute of Health Sciences, Navi Mumbai, India [37]	Quasi-experimental	*n* = 35, mean age (SD): yoga group = 55.5 (7), mean age (SD): balance exercise group = 58.7 (5.6), mean age (SD): control group = 57.7 (6), 51.4% female, diabetic peripheral neuropathic pain	Hatha yoga, 3 times a week, 1 h per session, 12 weeks	1. Active control: usual care + balance exercise 2. Inactive control: usual care + wait-list control	Muscle strength: chair stand test, step-up test; balance: star excursion balance test, single limb stance test; fall-related outcome: modified fall efficacy scale
Malhotra (2010), India, Funding NA [38]	Quasi-experimental	*n* = 62, age range = 30–60, gender not available, complication not described	Hatha yoga, every day, 30–40 min per session, 40 days	1. Inactive control: usual care + mild exercise advice	Cardiorespiratory fitness: lung function test (slow vital capacity, forced expiratory volume for 1 second, peak expiratory flow rate, maximal voluntary ventilation, forced vital capacity) body composition: waist-to-hip ratio
Balaji (2019) India, Sri Balaji Vidyapeeth funds the CYTER and all of its activities in yoga therapy, education, and research [39]	RCT	*n* = 72, mean age (SD) = 49.6 (5.88), 31.9% female, diabetic lung function	Hatha yoga, thrice a week, 60 min per session, 4 months	1. Inactive control: Usual care + advice on diet	Cardiorespiratory fitness: Lung function test (Forced expiratory volume for 1 second, forced vital capacity, forced expiratory volume for 1 second/forced vital capacity ratio)
Gupta (2020), India Centre for Integrative Medicine and Research, All India Institute of Medical Science [40]	RCT	*n* = 81, mean age (SD) = 50.6 (8.5), 44.4% female, 42% were on blood pressure medication, 44.4% were on lipid-lowering medication	Integrated yoga; 45 min/session; 3 classes/week for the first 2 weeks, 2 classes/week for the next 2 weeks, and 1 class/month for the last 3 months; 4 months	Inactive control: dietary and walking advice	Body composition: waist circumference
Schmid (2018) USA, Colorado State University Prevention Research Center [41]	RCT	*n* = 18, mean age (SD) = 54.95 (9.94), 66.67% female, diabetic peripheral neuropathic pain	Hatha yoga, twice a week, duration not available, 8 weeks	1. Inactive control: usual care + wellness education	Cardiorespiratory fitness: 6-min walk test; muscle strength: upper extremity strength (chair stand test), lower extremity strength (arm curl test); balance: The Fullerton Advanced Balance Scale Quality of life: Rand 36-Item Health Survey

Table 1. *Cont.*

Study id Country Funding Source	Study Design	Participants (Number, Mean Age (SD), Gender Proportion, Presence of Diabetic Complication)	Intervention Characteristics (Type, Frequency, Session Duration, Length of Intervention)	Control Group(s)	Outcome Measures
Shantakumari (2013), India, Funding NA [42]	RCT	*n* = 100, mean age = 45, 48% female, dyslipidemia	1 h/session, daily, 3 months	Inactive control	Body composition: waist-to-hip ratio
Sharma (2020), India, Rajasthan University of Health Sciences [43]	RCT	*n* = 104, age range = 30–65, 45.19% female, dyslipidemia	40 min/session, 5 days/week, 6 months	Inactive control	Body composition: waist-to-hip ratio
Skoro-Kondza (2009), UK, Novo Nordisk Research Foundation [44]	RCT	*n* = 59, mean age (SD) = 60 (10), 61.02% female, type 2 diabetes mellitus without complication	90 min/session, 2 days/week, 12 weeks	Inactive control: lifestyle leaflet and advice + waiting list yoga	Body composition: waist-to-hip ratio; quality of life: audit of diabetes-dependent QoL
Sreedevi (2017) India, Fogarty International Centre, National Institutes of Health [45]	RCT	*n* = 124, mean age (SD)= 51.9 (7.3); 100% female, dyslipidemia	60 min/session, 2 days/week, 3 months	1. Inactive control: standard advice on diet and exercise 2. Inactive control: peer-support on management of diabetes, diet, and exercise	Body composition: waist-to-hip ratio

Based on vote counting, the quasi-experimental studies favored yoga intervention compared to the inactive control in improving cardiorespiratory fitness, muscle strength, body composition, balance, and fall-related outcome (Table 2). While one RCT favored yoga intervention in improving muscle strength [42], the RCTs showed inconsistent effects of yoga intervention on cardiorespiratory fitness, body composition, and quality of life [39–45]. Quasi-experimental studies indicated that yoga provided at least similar benefits compared to other exercise interventions on muscle strength, body composition, balance, and fall-related outcome [36,37].

Two studies (one quasi-experimental and one RCT) assessing muscle strength, three studies (one quasi-experimental and two RCTs) assessing cardiorespiratory fitness, and six studies (two quasi-experimentals and four RCTs) assessing body composition were included in the meta-analyses. Regarding lower extremity muscle strength, yoga was found to be beneficial in improving 3.43 repetitions (95% CI 2.42 to 4.43) of the chair stand test (Figure 2). There was no significant heterogeneity on muscle strength outcome. Regarding cardiorespiratory fitness, yoga was found to be beneficial for improving FVC by 0.26 L (95% CI 0.05 to 0.47) (Figure 2). However, there was substantial heterogeneity. Having conducted subgroup analyses based on study design, we found that yoga still provided benefits without substantial heterogeneity by improving FVC by 0.16 L (95% CI 0.01 to 0.31), which was equivalent to a 6.6% (95% CI 0.4 to 12.8) improvement of the baseline FVC among the yoga group. No significant difference on body composition was found between the yoga and inactive control groups. While there was no heterogeneity among quasi-experimental studies, there were substantial heterogeneities among RCTs even after subgroup analyses based on the duration of the intervention. In sensitivity analysis excluding studies with a high risk of bias, there was still no significant effect of yoga on body composition outcomes (standardized mean difference = 0.14; 95% CI −0.17 to 0.45; $p = 0.38$). However, the heterogeneity was improved from I^2 of 86% to 0%.

Table 2. Vote-counting results.

Study id, Design	Cardiorespiratory Fitness	Muscle Strength		Body Composition		Balance		Fall-Related Outcome		Quality of Life
	vs. Inactive Control	vs. Active Control	vs. Inactive Control	vs. Active Control	vs. Inactive Control	vs. Active Control	vs. Inactive Control	vs. Active Control	vs. Inactive Control	
Darimela (2017), Quasi-experimental [36]				●	▲					
Kanjirathingal (2021), Quasi-experimental [37]		▲	▲			▲	▲	●	▲	
Malhotra (2010), Quasi-experimental [38]	▲				▲					
Balaji (2019), RCT [39]	▲									
Gupta (2020), RCT [40]					●					
Schmid (2018), RCT [41]	●		▲							▲
Shantakumari (2013), RCT [42]					▲					
Sharma (2020), RCT [43]					▲					
Skoro-Kondza (2009), RCT [44]					●					●
Sreedevi (2017), RCT [45]					▼					

▲ statistically significant favoring yoga; ● no statistically significant difference; ▼ statistically significant favoring comparator.

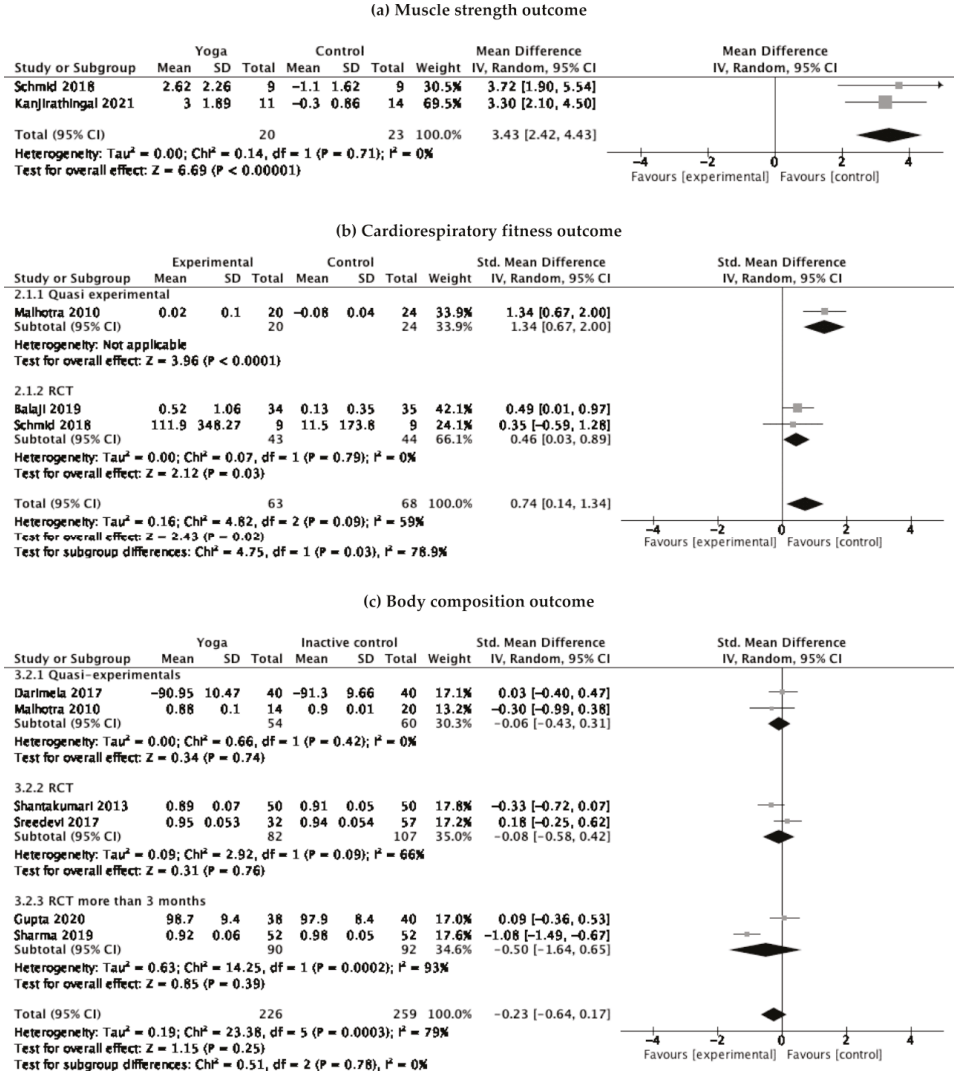

Figure 2. Forest plot for (**a**) muscle strength outcome, (**b**) cardiorespiratory fitness outcome, and (**c**) body composition outcome.

3.1. Risk of Bias

Most of the RCTs had "some concerns" of bias, while two RCTs had a "high risk" of bias and only one RCT had a "low risk" of bias (Table 3). Most of the bias in RCTs resulted from the randomization process, including unreported sequence generation and an allocation concealment process [31,37,40,42]. Most of the RCTS assessing the body composition outcome had bias resulting from the measurement of the outcome since they did not report the blinding process of the anthropometric measurement, which can be influenced by the assessor's knowledge of the intervention received [42–44]. None of the quasi-experimental studies had a low risk of bias. Two quasi-experimental studies had a moderate risk of bias resulting from the imbalance of genders between the groups and the imbalance of the baseline characteristics, which could confound the effect of the

intervention [36,37]. However, those confounders were not controlled using statistical analysis. Malhotra et al. [38] had a serious risk of bias due to several missing pieces of outcome data.

Table 3. Risk of bias assessment.

ROB 2.0	Randomization Process	Deviation from Intended Intervention	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results	Overall Bias		
Balaji 2019 [39]	Some concerns	Low	Low	Low	Low	Some concerns		
Gupta 2020 [40]	Low	Low	Low	Low	Low	Low		
Schmid 2018 [41]	Some concerns	Low	Low	Low	Low	Some concerns		
Shantakumari (2013) [42]	Some concerns	Low	Low	High	Low	High		
Sharma (2020) [43]	High	Low	Low	High	Low	High		
Skoro-Kondza (2009) [44]	Low	Low	Low	Some concerns	Some concerns	Some concerns		
Sreedevi (2017) [45]	Some concerns	Low	Some concerns	Low	Low	Some concerns		
ROBINS-I	**Confounding**	**Selection of participants**	**Classification of intervention**	**Deviation from intended intervention**	**Missing data**	**Measurement of outcome**	**Selection of reported results**	**Overall bias**
Darimela (2017) [36]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate risk of bias
Kanjirathingal (2021) [37]	Moderate	Low	Low	Low	Low	Low	Low	Moderate risk of bias
Malhotra (2010) [38]	Low	Low	Low	Low	Serious	Low	Low	Serious risk of bias

3.2. Quality of Evidence

We used GRADE tools to evaluate the quality of evidence for each outcome. Our meta-analysis on muscle strength had a narrow CI, which did not cross the minimal clinically important difference threshold in the chair stand test [46]. It also had direct evidence on yoga intervention among patients with T2DM, and consistent results reflected the absence of heterogeneity. However, there was a non-randomized study in the meta-analysis on muscle strength, with moderate risks of bias in the included studies. The publication bias could not be examined using a funnel plot because the number of available primary studies was less than 10 [32]. Therefore, the quality of evidence on muscle strength was low since there were two downgrades.

Having conducted a subgroup analysis based on the study design, the meta-analysis on cardiorespiratory fitness resulted from two RCTs that had a low risk of bias. The result was also consistent as reflected by the absence of heterogeneity. However, it did not have direct evidence on the effect of yoga on cardiorespiratory fitness among patients with T2DM since it came from the lung function results, which were not a primary test for cardiorespiratory fitness. In addition, the result was also imprecisely reflected from the wide CI crossing the minimum clinically important difference (MCID) of the FVC percent change [47]. Therefore, the quality of evidence on cardiorespiratory fitness was low. The quality of evidence on body composition was also low even after a subgroup analysis based on the study design. It resulted from four RCTs having some concerns and a high risk of bias.

4. Discussion

We provided low-quality evidence that yoga benefits muscle strength and cardiorespiratory fitness of patients with T2DM compared to the inactive control. In addition, a quasi-experimental study indicated that yoga could provide equal benefits on muscle strength compared to other exercise interventions. However, available evidence failed to show the benefits of yoga on body composition among patients with T2DM.

Yoga could be an alternative type of exercise for patients with T2DM because of the potential superiority of the yoga intervention addition to standard management alone and the equal benefits of yoga to other types of exercise on muscle strength and cardiorespiratory fitness. The improvement of 3.43 repetitions of the chair stand test was above the MCID of muscle strength. On the other hand, the benefit of yoga in improving cardiorespiratory fitness was imprecise since the confidence interval crossing the FVC change of 3% as the MCID. Our meta-analyses also failed to show a significant effect of yoga on body composition outcome. The results of the meta-analyses were in accordance with the findings across all of the included studies, showing a positive effect of yoga on muscle

strength and an inconsistent effect on cardiorespiratory fitness and body composition. While yoga only required low metabolic intensity, the improvement in muscle strength could be caused by the isometric contraction during yoga poses, which could improve muscle strength and induce muscle hypertrophy regardless of intensity [20,48,49]. Forceful inspiration and expiration during yoga could be the cause of cardiorespiratory fitness improvement through the strengthening of respiratory muscle [50]. Therefore, yoga could be one potential type of exercise to address impaired muscle strength and possibly to improve cardiorespiratory fitness among patients with T2DM.

Our results were consistent with previous systematic reviews showing yoga benefits on muscle strength and cardiorespiratory fitness among the general population, elderly, and individuals with overweight or obesity [22,51–53]. Previous meta-analyses found a moderate effect size of yoga on muscle strength but there was heterogeneity [22,51]. The presence of medical conditions could be the source of clinical heterogeneity in the previous studies since our meta-analysis did not find any heterogeneity among patients with T2DM. Regarding the cardiorespiratory fitness outcome, the previous study also found a small effect size with a wide CI from three primary studies [51]. The uncertainty in cardiorespiratory outcome indicated the need to conduct more research on this outcome [54]. Our meta-analyses results were in accordance with previous systematic reviews showing that yoga and low-intensity exercise did not have a significant moderator effect on body fat percentage and waist circumference [43,44]. However, these results had wide CIs, resulting from the small number of primary studies. Therefore, more research should be conducted to examine the effect of yoga and other low-intensity exercise on body composition, particularly body fat percentage and waist circumference.

Having provided evidence systematically in accordance with the PRISMA guideline and fulfilling almost all of the A MeaSurement Tool to Assess Systematic Reviews version 2 (AMSTAR 2) checklist (Supplement file S3) [25], our reviews favored yoga intervention in improving health-related fitness among patients with T2DM. Our systematic review could not examine the publication bias due to the limited number of available studies. To minimize the publication bias, we also searched the Embase database, which covered gray literature such as conference proceedings [55]. To provide a higher quality of evidence, researchers should conduct more RCTs, undertaking and reporting the appropriate randomization and allocation concealment process. The results of our reviews should also be implemented cautiously in populations across genders since the majority of included studies recruited females.

5. Conclusions

A low quality of evidence favored yoga in improving health-related fitness compared to an inactive control, particularly muscle strength and cardiorespiratory fitness. For many patients with T2DM, a challenging cycle exists among a lack of physical activity, impaired health-related fitness, and T2DM conditions. Yoga as a light-intensity physical activity is a potential type of exercise to address T2DM patients' barriers to physical activity. More high-quality RCTs are needed to provide a higher quality of evidence.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/ijerph19074199/s1. Supplementary file S1: Search Strategy; Supplementary file S2: Blank Data Extraction Form SysRev Yoga; Supplementary file S3: PRISMA Checklist.

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