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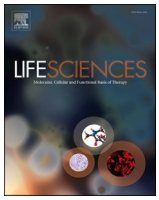

Review article

The association between type 1 diabetes and exercise/physical activity and prolongation of the honeymoon phase in patients

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ABSTRACT

In type 1 diabetes (T1D), pancreatic beta cells are destroyed by the immune system, causing chronic hyperglycemia and micro and macrovascular complications. However, some people experience a 'honeymoon' phase (or partial remission) after being diagnosed with type 1 diabetes. During this phase, a substantial amount of insulin is still produced by the pancreas, helping to reduce blood sugar levels and the requirement for external insulin. The clinical significance of this phase lies in the potential for pharmacological and non-pharmacological interventions during this time frame to either slow down or arrest beta-cell destruction. Clearly, we need to continue researching novel therapies like immunomodulatory agents, but we also need to look at potentially effective therapies with acceptable side effects that can serve as a complement to the medicines currently being studied. Physical activity and exercise, regardless of its type, is one of the factors its impact on the control of diabetes is being investigated and promising results have been achieved. Although there are still limited reports in this regard, there is some evidence to suggest that regular physical exercise could prolong the honeymoon period in both adults and children. In this review, having described the immune base of type 1 diabetes, we outline the benefits of exercise on the general health of individuals with T1D. Moreover, we centered on the honeymoon and current evidence suggesting the effects of physical activity and exercise on this phase duration.

1. Introduction

One of the world's most common and fastest-growing diseases is diabetes, a chronic metabolic disease resulting from absolute or partial insulin deficiency due to β-cell dysfunction, insulin resistance, or both [1]. According to the 10th edition of the IDF Diabetes Atlas, diabetes prevalence globally continues to rise, confirming diabetes as a serious threat to health and well-being worldwide. In 2021, diabetes was estimated to affect 537 million adults aged between 20 and 79 years, worldwide (i.e., 1 out of 10 people). In the same year, every 5 s, one person died due to diabetes. As anticipated, by 2030, there will be 643 million adults with diabetes and 783 million by 2045 (International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org).

Type 1 diabetes mellitus (T1DM), a subtype of diabetes, is characterized by absolute insulin deficiency resulting from β-cell dysfunction in the pancreas. It is estimated that T1DM makes up around 5–10 % of all diabetes cases globally [2]. Reports indicate that the incidence of T1DM varies among different groups of people. The highest rates are reported in Northern Europe, while the lowest rates are observed in Eastern Asia [3]. This disease primarily affects children and adolescents, yet it is possible for anyone to develop it regardless of their age [4]. The etiology of T1DM involves a complex interplay of genetic susceptibility and environmental factors, leading to the autoimmune destruction of β-cells mediated by T lymphocytes [5]. A study analyzing mortality data from 35 countries found that T1DM accounted for a considerable percentage of deaths among individuals aged 20–49 [6]. Furthermore, a study in Sweden found that individuals with T1DM have a mortality ratio of 3.6 compared to the general population [7]. These findings indicate that there is a higher risk of mortality associated with T1DM and emphasize the need for effective management strategies and interventions to improve outcomes in affected individuals.

The honeymoon phase is a temporary period after T1DM diagnosis where some individuals experience improved symptoms, also known as the remission phase. During this phase, there is a partial restoration of endogenous insulin secretion and improved glycemic control, leading to a reduction in exogenous insulin requirements. However, this remission phase is usually incomplete and most people still require a small dose of

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insulin during this phase in order to maintain their blood sugar levels near normal. Based on the present studies, the duration of the honeymoon period varies from case to case. Remission rates in reports have ranged from 25 to 100 %, with remissions lasting one month to 13 years [8].

Recent research has focused on ways to prolong endogenous insulin production during a type 1 diabetes remission. This period is clinically significant because there is a good possibility of applying drug intervention to stop the beta cells destruction development and thereby preserve endogenous insulin secretion. Deterring the β-cell destruction is a fundamental clinical target for improving metabolic control and reducing hypoglycemia incidences and long-lasting difficulties.

There have been a number of clinical and metabolic factors which have been associated with the management of the disease that might directly or indirectly affect the duration and frequency of the honeymoon period. Study results have identified two groups of parameters that can be divided based on the factors reviewed: non-modifiable and modifiable. The patient's gender, age, haemoglobin A1c levels at the diagnosis stage, decompensation level of metabolic dysfunction when diagnosed, and C-peptide level and the presence of autoantibodies are among the factors that cannot be modified [9,10]. And, the modifiable factors include aspects such as medication regimens, insulin dosage adjustments, carbohydrate counting, physical activity, stress management, and lifestyle choices [11,12].

Numerous clinical and metabolic factors have been investigated for their impact on remission rate and honeymoon period duration, but their extent of influence is still unclear [13].

Various medicinal products are currently being investigated for their ability to maintain the beta cell role in T1D patients whose disease has been diagnosed newly. The majority of these drugs are immunomodulatory in nature, in that they suppress the inflammatory autoimmune process that attacks the beta cells. While others act against beta cell antigens directly to modulate the autoimmune response [14–19]. Also, a number of agents suppress the immune system on a broad, non-antigen-specific base [17,20–22]. However, the significant side effects of many of these therapies should be considered. For instance, immunosuppressive therapy can increase the risk of cancer and infection, as well as infection or reactivation of latent infection [23,24]. Moreover, these new therapies haven't yet shown significant and sustained benefits.

It is clear that such novel therapies should be investigated, but it is also imperative to examine new therapies with the lowest side effect profile, which could potentially complement the medicines under consideration. A physical activity and exercise program could play a significant role in this area.

There was a limitation to the amount of exercise T1D patients could do prior to the discovery of insulin because of the known risks of ketosis, dehydration, and having to manage several factors in order to maintain normoglycemia. At the same time, physical activity and exercise has been recognized as an essential part of treating type 2 diabetes mellitus because of its insulin-sensitizing properties and its anti-oxidant and inflammation-reducing properties. Upon introducing insulin therapy, a greater awareness of post-exercise hypoglycemia was achieved. The health benefits of exercise for T1D patients have been discussed in recent studies [25,26]. Based on recent observations, a balanced caloric diet, with physical activity and exercise, improves metabolic control in T1D subjects with residual endocrine pancreatic mass [27].

There is evidence from animal studies that exercise preserves beta cells [28–30]. Park et al. [31] reported that the beta cell mass of rats with insulin-deficient diabetes following an exercise program for eight weeks increased by 31 %, and the staining for beta cells increased by 33 %. Although the precise mechanisms underlying this effect were unclear, they observed the incidence of apoptosis in beta-cell markedly decreased [31]. As an additional benefit of exercise, it is recognized to have anti-inflammatory properties [32], which may thus contribute to the modulation of the autoimmune process.

Here we describe type 1 diabetes and its immune base and outline the physical activity and exercise benefits for the patient's general health. We also reviewed the articles investigating the beneficial effects of exercise and physical activity and exercise, regardless of their type, on T1D patients. This review centered on the effects of exercise on newly diagnosed patients and the impacts of exercise on prolonging the honeymoon phase or/and the partial clinical remission (PCR) phase in the patients.

2. Type 1 and 2 diabetes

Type 1 diabetes (T1D) is defined as an organ-specific autoimmune disease during which the pancreatic β-cells are destroyed by an immune-mediated process, and associated with chronic hyperglycemia and the development of cardiovascular complications. Usually, symptoms of the disease begin in adolescence or develop directly as ketoacidosis. Compared to the general population, people with T1D die almost threefold more often, largely due to premature cardiovascular disease. It has been demonstrated in randomized clinical trials that hyperglycemia contributes to these individuals' high cardiovascular risks [33]. Mounting evidence suggests that the incidence of insulin resistance and related disorders, including systemic hypertension and altered lipid profile, is increasing with diabetes duration, all of which negatively impact diabetic complications. Moreover, type 1 diabetes is associated chiefly with a high rate of cognitive impairment. Elderly people suffering from diabetes are at a greater risk of developing Alzheimer's disease, which can seriously affect their quality of life [34,35].

Diabetes type 2 (T2D) occurs when the body is unable to regulate and use sugar (glucose) effectively for a long time, resulting in too much sugar in the bloodstream. It is mainly the failure of the pancreatic β-cells to properly regulate blood glucose levels that cause type 2 diabetes mellitus. In the long run, high blood sugar levels can lead to circulatory, nervous, and immune system disorders [36]. In recent years, we have gained a better understanding of type 2 diabetes (T2D). Pathogenesis and evolution of this disease are clearly heterogeneous, influenced by both genetic and environmental factors. A polygenic form of diabetes is often inherited from one's parents. In most cases, a genetic predisposition exists at birth, but the abnormally high blood sugar levels which define diabetes only appear slowly over time and become diagnostic in adulthood. There are many environmental factors that affect the expression of diabetes, including the availability of different foods, physical activity and exercise opportunities, and stress from work, family, or other sources [37,38].

Diabetes type 2 is a silent disease that can progress for years without being detected. However, several metabolic malfunctions occur as side effects or independent comorbidities after T2D diagnosis. Fortunately, by interventions, T2D, which accounts for 90–95 % of all types of diabetes, is possible to be prevented or delayed [39].

3. Type 1 diabetes is an autoimmune disease

Diabetes type 1 (T1D) is a condition most commonly associated with childhood, but the disease can affect anyone, even the elderly [40]. There is a subclinical prodrome of variable duration with T1D, an immune-mediated chronic disease. Individuals with genetic susceptibility to this condition experience a selective loss of pancreatic islet cells which are responsible for insulin production. HLA class II, a locus on chromosome 6, has been identified as the most critical gene contributing to disease susceptibility, but ten other genes have also been detected [41]. There is little doubt that clinical T1D represents an advanced state of insulitis, and based on the studies, only 10 to 20 % of the β-cells are still operational when the disease is diagnosed [42]. Fig. 1 represents the variation in the number of β-cells over the disease development [43].

As a consequence of the final phase of cell destruction, type 1 diabetes manifests clinical symptoms. During this phase, there are signs such as inflammatory processes in the islets, increased human leukocyte antigens (HLA) expression, the development of autoantibodies

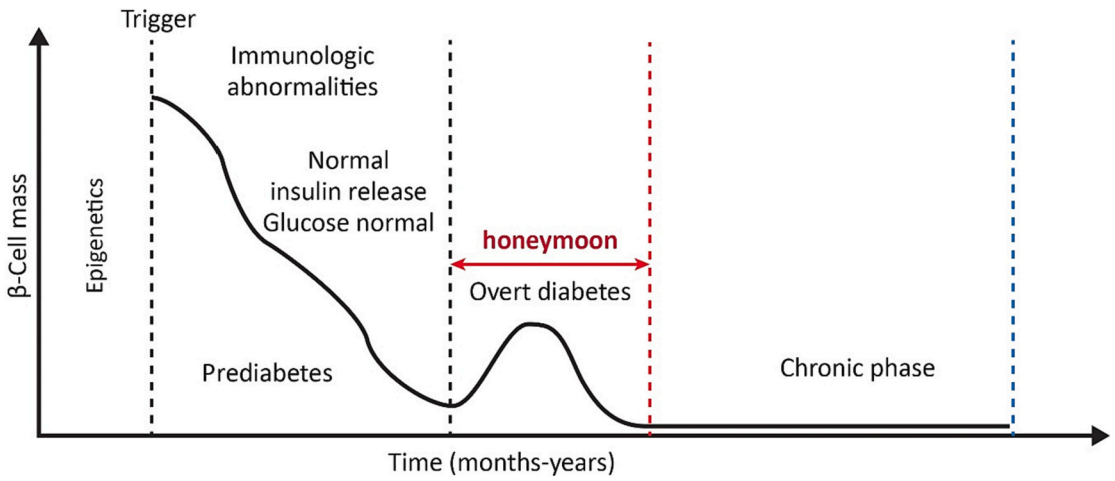

Fig. 1. Changes in the β-cells mass during different phases of the disease. Epigenetics induce diabetes type 1. Initially, the ICA, IAA, GAD, and ZnT8 antibodies are developed followed by the preclinical phase which can long from a few months to years. Next, the disease onset is clinically diagnosed, while accompanying a transient remission called the "honeymoon" phase. Finally, diabetes clinically advances to chronic and acute complications.

(antiGAD, antiIA-2, antiICA or anti-insulin among others) against the islets, and debilitated islets. Mononuclear cells, including CD4+ and CD8 + T-lymphocytes, macrophages, and complement system components infiltrate into the islet tissue [44,45]. The elevated levels of HLA molecules and antigen transporter proteins in the islet tissue suggest a high degree of antigen-presenting activity. Activation of the autoimmune occurs by triggering the autoreactive T-cells. Auto-antigens, in turn, trigger the increase of effector cells and the increased aggressive action against the β-cell [46,47].

Activated T helper (Th) cells are present in the circulation and the infiltrates of islets. They are normally managed by auto-tolerance mechanisms, but under diabetic situations, those mechanisms fail and a series of inflammatory processes are activated, culminating in insulitis. Th1 lymphocytes mediate pathogenic immunity and Th2 lymphocytes provide protection. The production of different types of cytokines characterizes these populations. Pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1β and IL-12, are secreted by the Th1 subset, while anti-inflammatory IL-4, IL-6 and IL-10 cytokines are produced by Th2 lymphocytes [48].

4. Clinical and experimental treatment of type-1 diabetes

In 2022, a century has passed since insulin was administered to the first patient. A revolutionary discovery by Frederick Banting, Charles Best, and James Collip in 1921 led to the cure of millions of people with type 1 diabetes [49].

A human patient first received insulin replacement therapy in 1922, and throughout these years this approach has been approved as the standard treatment for treating Type 1 diabetes. However, by developing different types of insulin, this therapy has become more effective over time. Among the developed therapies, short, intermediate, and long-acting forms and mixed insulin types are currently being used. During the past few years, insulin delivery pens, insulin pumps, glucose sensors, and closed-loop systems or artificial pancreas, have made significant advances in insulin administration. A closed-loop system is equipped with an insulin pump and continuous monitoring of blood glucose levels. Using this technology, hypoglycemic-prone adults with T1D were less likely to experience severe hypoglycemic episodes. T1D patients have been able to control their glucose levels more effectively and live healthier lives thanks to these improvements [50].

While insulin therapy has improved, the ultimate goal is to allow patients to meet their own insulin by maintaining or replacing pancreatic beta cells. So, it seems that the future of treating and preventing T1D lies in immunotherapy and beta cells derived from stem cells. Recent clinical trials are demonstrating that this goal is becoming a reality [51,52].

Considering T1D has a strong genetic base, gene therapy may offer a promising alternative to insulin injections. In gene therapy, faulty genes are modified or replaced in the cell as a therapeutic technique to cure disease and thereby prevent the disease from arising [53].

Medical nutrition therapy (MNT) and exercise training are also essential therapies for diabetes mellitus. Along with its metabolic benefits, exercise also boosts the immune system. T1D management also relies heavily on a healthy lifestyle, including eating patterns, in addition to pharmacotherapy. An effective nutrition therapy intervention could be part of a comprehensive T1D education program or as part of an individualized education program. It should be mentioned that nutritional therapy for T1D patients on multiple insulin doses must be centered around adjusting insulin doses in accordance with carbohydrate intake schedules [54].

5. Exercise and health

5.1. Types of exercise and physical activity

The concept of physical activity and exercise refers to all repetitive, planned, and structured movements aimed at improving health and fitness, whereas exercise refers to a planned and structured physical activity and exercise [55]. At least 10 min of muscles moving in a rhythmic, repetitive, and continuous manner constitute an aerobic exercise [56,57]. Aerobic energy is produced primarily by our bodies during exercises, such as walking, cycling, jogging, and swimming. The term resistance (strength) refers to practices using machines or free weights, elastic resistance bands, or using your own body weight. Flexibility and balance-based exercises relieve joint stiffness and improve the range of motion in order to prevent injury and improve gait [58,59]. Activities like tai chi and yoga are a combination of flexibility, balance, and resistance.

5.2. Effects of exercise/physical activity on general human health

Physical activity and exercise are primarily described as being beneficial in improving general health, heart function, circulatory and respiratory systems as well as the immune system. These are attributed to the fact that physical activity and exercise can counterbalance metabolic disorders, bone, muscle, and joint disorders, as well as neurodegenerative diseases [60,61].

In terms of public health, regular physical activity and exercise plays

a significant role in boosting health. Physical activity and exercise may ameliorate the pathological outcome associated with upper respiratory tract infections (URTI), such as COVID-19 [62]. Furthermore, several studies have shown that physical activity and exercise can contribute to mental well-being and can prevent the development of mental health disorders such as depression and anxiety [63–66].

There is evidence that a reduction in physical activity and exercise levels correlates with worse mental health status. Actually, the benefits of regular physical activity and exercise on psychological well-being are undeniable in medical research. A regular exercise regimen enhances one's sense of well-being and self-esteem. The concept that mental disorders can be prevented by physical activity and exercise is supported by the fact that regular exercises lead to fewer depressive and anxiety symptoms in individuals [67,68]. Researchers have recently suggested a mechanism through which physical activity and exercise induces its anxiolytic effects. They believe regular exercise can modify the hypothalamic-pituitary-adrenal (HPA) axis by mediating the endogenous opioid system, which is responsible for stress reactivity, anxiety, mood, and emotions [69]. In addition, physical activity and exercise can modulate different trophic factors, such as brain-derived neurotrophic factors (BDNF). Following exercise, BDNF levels are upregulated and are thought to contribute to the reduction of anxiety and depression [60,70].

Researchers have found a positive association between physical activity/exercise and health outcomes, regardless of its duration. In light of this, public health recommendations for physical activity and exercise may need a paradigm shift supporting moderate-to-vigorous exercise, regardless of how long it lasts, as an important lifestyle behavior [71].

For subjects with T2D, current guidelines recommend appropriate amounts of exercise (types, duration, intensity) robustly and straightforwardly. However, an extensive and multifactorial strategy has been proposed for exercising patients with T1D, whose therapeutic efficacy ranges widely, due to difficulty controlling glycemic levels and adhering to prescribed regimens. Hence, it is necessary to recommend a personalized omni-comprehensive approach to people with T1D to maximize their exercise benefits [72].

6. Exercise training and the immune system

Exercise immunology is known as an emerging field of research, with 90 % of papers published after 1990. But, more than a century ago, Larrabee reported that the changes in the counts of white blood cells in Boston marathon runners resembled those observed in certain diseases [73]. Also, he has stated that the exertion had gone far beyond physiological limits and the results certainly show that where this is the case we may get a considerable leukocytosis of the inflammatory type 2 [74].

The immune system is positively affected by exercise, in addition to its metabolic benefits. Diabetes subjects exhibited increased expressions of CD19 and CD23 before exercise, according to the results of a study. Following exercise, CD3, CD4 expressions, and CD4/CD8 ratios decreased in both diabetic and control groups; however, natural killer (NK) cell expression increased. Whit regards to the CD8 expression, type 1 diabetic patients were similar to healthy subjects who had a longer acute exercise resulted in an increased CD8 level. Based on the positive impact that submaximal aerobic exercise has on metabolic control and no adverse effects on immunity, this kind of exercise may be considered as safe and suggested for type 1 diabetics [75].

Exercise training and immunosenescence have been the subject of many studies up to now. Several studies have documented how habitual exercise regulates the immune system and delays the onset of immunosenescence [74,76,77].

The effects of exercise on the immune system can be briefly mentioned as follows;

Exercise causes responding to vaccinations more effectively decreases the number of exhausted or senescent T cells, and can increase the capacity of T-cell proliferation. Also, it can decrease the inflammatory cytokines' circulatory levels, such as inflame-aging. The neutrophil phagocytic activity showed an increase following exercise. The inflammatory response to bacterial challenge reduces as a result of exercise. Moreover, the activity of NK cells cytotoxic increases as a result of exercise. Leukocytes with Longer telomere lengths are another result of exercise.

7. Exercise training and diabetes

As previously mentioned, when it comes to general human health, managing non-communicable diseases, also known as chronic diseases, like cardiovascular disease, stroke, diabetes, and certain types of cancer, can take advantage of physical activity and exercise [78,79]. It also improves mental health, delays dementia onset, and improves well-being [80].

To investigate the effects of different types of physical activity and exercise on diabetic patients, many studies have been designed and conducted up to now. These studies focused mainly on the type and characteristics of the activity and its acute or long-lasting effects. Also, the studies have looked at prescribing pharmaceuticals before, during, and after physical activity and exercise [81]. A variety of activities, such as aerobic, anaerobic, and high-intensity interval training, are studied in these subjects.

7.1. Aerobic exercise benefits

Among the benefits of aerobic training is an increase in some features, such as the density of mitochondria, sensitivity to insulin, enzymes involved in the oxidative process, reactivity and compliance properties of blood vessels, the function of the lung, immunity, and cardiac output [82,83]. As Garber et al. (2020) have recently reported, the risk of cardiovascular disease and overall mortality is substantially reduced with moderate to high levels of aerobic activity in both type 1 and type 2 diabetes [84]. Also, it has been revealed that aerobic training improves lipid levels, endothelial function, and cardiorespiratory fitness in type 1 diabetes [85]. Moreover, an exercise involving high-intensity interval training increases the oxidative capacity of skeletal muscle, sensitivity to insulin, and control of glycemic in adults with type 2 diabetes and does not impact glycemic control in patients with type 1 diabetes [86].

7.2. Resistance exercise benefits

A person with diabetes is at greater risk of deteriorating their muscle strength and functional status [87,88]; yet, it is demonstrated that resistance training could be beneficial for all adults' health, especially those with diabetes. This kind of exercise improves the percentages of fat, bone, and muscle in the body. It also boosts the body's strength and improves physical function. Likewise, mental health, sensitivity to insulin, blood pressure, lipid profiles, and cardiovascular health are among the improved features following resistance exercise [89]. According to recent research, resistance training in adults with type 1 diabetes may improve glycemic control when various confounders are taken into account [90]. Likewise, resistance exercise can reduce the risk of hypoglycemia caused by exercise in people with type 1 diabetes [91]. In one exercise session, it was found that starting with resistance exercises resulted in less hypoglycemia than starting with aerobic exercise [92].

7.3. Benefits of other types of physical activity and exercise

Hyperglycemia in older adults with diabetes could accelerate the accumulation of the advanced glycation products occurring due to normal aging, and frequently limits joint mobility. Hence, older adults with diabetes may benefit from flexibility and balance exercises [93]. Stretching improves flexibility and range of motion around joints

without altering blood sugar levels. A balance training program can reduce fall risk by improving balance and gait, even in people with peripheral neuropathy [94]. It has been shown that taking part in group exercise interventions (tai chi classes, balance training) could decrease falls by 28 %–29 % [95].

On the other hand, Kennedy et al. [96] studied attitudes and barriers to exercise among adults with type 1 diabetes who recently had a diagnosis. One of the most interesting results was that about half of the participants reported that their activity levels decreased around diagnosis. Also, some of the participants weren't convinced the exercise was beneficial for their health or were concerned about potential harms such as hypoglycemia [96].

8. Exercise, immune system, and T1D

As mentioned earlier, exercise is recommended to control the metabolisms of type 1 diabetes, not only due to its metabolic effects but also due to its influence on the immune system. In spite of this, since diabetes exercise is not well-defined with regard to its impact on the immune system, more attention needs to be paid to this triad relationship between diabetes exercise and the immune system.

The hyperbolic relationship between b-cell function and insulin sensitivity was described for the first time by Kahn et al. in 1993 [97]. In both type 2 and type 1 diabetes, physical activity and exercise improves insulin sensitivity, allowing better positions on the glucose tolerance curve. In people with T2D with insulin resistance and/or inappropriate insulin secretion, physical exercise has traditionally been prescribed to improve insulin action [83]. In spite of this, oxidative stress and inflammation are involved in the toxicity of b-cells in T1D, and exercise may protect against that toxicity. According to recent research, even low-intensity and short-duration physical activity and exercise may interfere with immune function [72].

An observational and interventional study found that exercise might improve immune function in recipients of b-cell transplants. The quality of life [98], metabolic control, and body composition of active subjects with T1D improved after islet transplantation (IT); that is these people managed their disease more successfully [14]. Moreover, physical exercise reduced diabetic symptoms and minimized the side effects of immunosuppressive drugs and transplant dysfunction in patients undergoing islet transplantation [99,100]. Several factors, such as immunosuppression and chronic inflammation, can contribute to progressive insulin resistance after islet transplantation.

9. The honeymoon phase definition and mechanism

As mentioned earlier, the honeymoon phase, which is also known as the remission phase, is a transient period observed in some individuals with T1DM within a short time after diagnosis. During this phase, there is a partial restoration of endogenous insulin secretion and improved glycemic control, which can result in a decrease in the need for external insulin [13]. The frequency of the honeymoon phase can differ among individuals. It has been reported that approximately 60–80 % of individuals experience it shortly after diagnosis. However, the length and strength of the honeymoon phase can also differ greatly from person to person. Some patients may experience a short-lived and gentle honeymoon stage, while others may have a more prolonged and striking period of improved glycemic control with reduced insulin requirements [9,10].

The precise mechanism behind the honeymoon phase in T1DM is not fully understood. However, several theories have been suggested. One theory proposes that the first autoimmune attack on pancreatic β-cells may not be consistent, resulting in the survival of a few functional β-cells [101]. These remaining β-cells are able to produce insulin for a short period, resulting in the honeymoon phase. The other theory suggests that the honeymoon phase of diabetes occurs because of a reduction in insulin resistance, which enables the remaining β-cells to meet the dropped insulin demands [102]. Additionally, it has been thought that the impermanent remission may occur due to the regeneration or replication of β-cells, although the degree to which this process occurs is still a subject of ongoing discussion [103].

These theories have been backed up by multiple studies. Precise measurements of C-peptide levels have shown a micro-secrete of insulin in 30–80 % of people with long-term type 1 diabetes. These findings support the fact that the quantity and function of endogenous β-cells may decline with increasing disease duration, but they do not disappear completely [104]. Likewise, other studies have found that individuals in the honeymoon phase had higher β-cell mass than those with long-standing T1DM [105].

As previously mentioned, the demolition of pancreatic β-cells is the disease initiator. However, in many cases, remaining activity can still be observed in the β-cell at the onset of diagnosis, facilitating a reasonable control of hyperglycemia over time. In this sense, several cohort studies and a retrospective analysis of the DCCT (Diabetes Control and Complication Trial) by monitoring the C-peptide in circulation indicated the advantages of preserving a residual β-cell function over years [27].

There have been a number of clinical and metabolic factors which have been associated with the duration and frequency of the honeymoon period. Some of these parameters are modifiable; that is, we are able to change them. And others are non-modifiable, which means they are irreversible. For instance, the patient's gender, age, and haemoglobin A1c levels, or degree of metabolic decompensation when diagnosed, are among the fixed features. Moreover, the cases of C-peptide level and the presence of autoantibodies are among the factors that cannot be modified. On the other hand, the nicotinamide, Interleukins (IFNγ, IL-10, IL1-R1), the early introduction of the insulin pump therapy, the diet, and the haemoglobin A1c levels during the disease are features that can be monitored and improved.

10. Physical activity and exercise prolong honeymoon

Interestingly, there are promising reports that introduce physical activity and exercise as one of the most effective factors that can be adopted to influence the honeymoon period. Accordingly, recent studies revealed that people with type 1 diabetes who exercise intensively within a few months of being diagnosed experience a honeymoon period that lasts significantly longer than those who do not exercise.

Results of an epidemiological screening showed that the duration of the honeymoon period could be extended through physical exercise. Based on this investigation, people with T1D who were active, like athletes, had a significantly longer honeymoon. Moreover, it was found that exercise-derived energy expenditure is inversely correlated with autoimmunity markers (GAD, IA) [25,106].

Researchers at the University of Birmingham, to determine how activity level impacts the progression of type 1 diabetes, looked at beta cell preservation and loss as well as how much insulin needed to be changed without exercise as compared to those who were very active soon after diagnosis. They compared 17 newly diagnosed men which had a high activity level with men of the same age, sex, weight, and diagnosis time but without exercising. Specifically focusing on the honeymoon period, it was found that those who participated in physical activity and exercise had a five-fold longer honeymoon than those who did not. Essentially, it allows them to continue producing their own insulin during this time [107].

The assassination between physical activity and exercise and remission phases in adults with type 1 diabetes has recently been investigated by Justyna Flotyńska et al. [108]. In this study, it was recommended that participants exercise 2–3 times a week for one year at a moderate intensity. Research findings revealed that the incidence of remission was significantly higher in the active group (55 % vs. 35 %) after 6 months. Noteworthy, analyses indicated that physical activity and exercise before the diagnosis was the only variable that influenced remission in the 12th month. According to the study, it could be

concluded that physical activity and exercise before the diagnosis of type 1 diabetes is associated with a greater chance of remission in adults [108].

10.1. The association between physical activity and exercise and honeymoon in children

Rydzewska et al. [109] designed a study to describe the course of clinical remission in 82 children (aged 10 ± 3.72 years) with new-onset type 1 diabetes. They compared some intended markers affecting the occurrence of partial clinical remission (CR), focusing on the physical activity and exercise pre- and post-diagnosis process. They found that a higher level of physical activity and exercise was associated with improved biochemical parameters at the time of diagnosis of diabetes and a reduced requirement of insulin over time. It seems that clinical remission is associated with higher physical activity and exercise during the first two years of the disease. In detail, A worse metabolic profile (such as pH, HCO3, and BE) was observed in children who had lower physical activity and exercise before diagnosis, when compared to those who attended additional sports training. The first group had also higher HbA1c ($p = 0.046$) following one year. In contrast, postprandial C-peptide concentrations were significantly higher in children who participated in additional sports classes during diabetes treatment than those who only participated in physical education. A lower demand for insulin was also observed after 3, 6, 12, and 24 months [109].

One prospective study followed 125 children with T1D for two years to see what role regular physical activity and exercise had on partial remission, metabolism, insulin needs per day, and C-peptide secretion. The findings of the study showed that physically active individuals had lower HbA1c after two years, and lower daily insulin requirements after 3, 6, and 24 months. After 2 years, the active group was also found to have a higher partial remission prevalence of 44 % vs. 13 %. Both groups had similar levels of C-peptide after 2 years, but with 79.6 % versus 61.4 %, the prevalence of clinically significant levels was higher in the active group. It has been concluded by these researchers that regular physical activity and exercise may extend partial remission time in pediatric diabetes, and may therefore contribute to improved metabolic control over the long term [110].

10.2. Case reports

In a recent paper, Samson describes a 28-year-old man with diabetic ketoacidosis and features of type 1 diabetes who presented to the emergency department. This patient could stop insulin therapy, in the first three months following diagnosis, even though several types of islet cell autoantibodies were detected. It was determined that the patient maintained glucose at normal levels without insulin therapy by following a low-carbohydrate diet, exercising regularly (weightlifting and cycling), and reducing weight [111].

In another report, Thewjitcharoen described a 24-year-old Thai patient with T1DM who sustained remission without antidiabetic medication for more than 5 years while maintaining a low carbohydrate intake and exercising regularly. A vigorous aerobic exercise program (5–6 times per week) has been undertaken by the patient to maintain a BMI lower than 23 kg/m^2. A period of 6–12 months of repeated mixed meal tolerance tests indicated that the beta-cell preserved their functions. It is interesting to note that repeated pancreatic autoantibodies 5 years after diagnosis still showed positive results for anti-GAD, anti-IA2, and anti-ZnT8 [112].

Silva and Pereira [113] reported a case study about a 33-year-old man who achieved an impressive 6-year complete remission of Type 1 Diabetes (T1D). This is the longest remission duration ever reported in medical literature. The diagnosis of T1D was confirmed through laboratory studies, which included a fasting blood glucose level of 270 mg/dL, an HbA1c level of 10.6 %, and positive anti-glutamic acid decarboxylase. The patient began intensive insulin therapy, but after three months, the disease went into complete remission. Ever since, the patient has been managing the condition with sitagliptin 100 mg daily, a low-carbohydrate diet, and regular aerobic physical activity (specifically, 90 min of walking per day). The authors highlight the importance of these factors in potentially delaying disease progression and preserving pancreatic β-cells when introduced early in the course of the disease [113].

11. Conclusions and future directions

Looking for factors affecting the type 1 diabetes honeymoon phase, which occurs onset of a patient diagnosis, has clinical significance. Knowing the factors offers us a chance to entirely prevent the beta-cells destruction by the immune system, or at least mediate prolonging this phase. There is solid evidence supporting the notion that immunological and metabolic processes interact complexly in type 1 diabetes. Accordingly, it can be concluded that factors affecting these biological features are affecting diabetic patients' health. Among these, physical activity and exercise is of the factors whose promising effects on the prolongation of the honeymoon phase have recently been reported and attracted researchers. However, there are still limited publications in this regard.

We provided a comprehensive literature review on the effects of physical activity and exercise on the honeymoon or the partial remission phase. Overall, it can be concluded that, regardless of their duration and intensity, physical activity and exercise can improve the metabolic and immunologic status of newly diagnosed type 1 diabetes patients. This factor can effectively prolong the honeymoon, in both children and adults. Although there has not yet been known the precise mechanism through which physical activity and exercise can induce its own effect, it seems that regulating the immune system and metabolic processes is one of the main ways. The following lists some related findings that may explain how physical exercise can result in a long-lasting honeymoon phase or even protect the beta cells' function against the immune system attack;

Although the precise mechanisms through which physical activity and exercise contribute to the preservation of β-cell mass are not yet fully understood, two main pathways can be considered. First, physical activity and exercise may promote cell proliferation and increase the presence of growth hormone (GH), insulin-like growth factor-1 (IGF-1), and glucagon-like peptide-1 (GLP-1) in the bloodstream. Second, they may reduce cell death by decreasing levels of inflammatory cytokines such as leptin and TNFa, increasing levels of anti-inflammatory cytokines like adiponectin, modulating innate immunity, and mitigating the destructive response to β-cell function [113,114]. In response to high-intensity exercise, different types of cytokines, such as interleukin-6 (IL-6), modulates immunity and metabolism processes [115]; this agent positively affects glucagon and insulin secretion through the secretion and release of glucagon-like peptide-1 (GLP-1), and subsequent signaling of beta-cells [116]; Insulin secretion from clonal beta-cells and pancreatic islets is improved by mediating the IL-6 [117]; Also, IL-6 can directly influence the beta-cells in the pancreas [118]. Finally, the effects of IL-6 which are activated by exercise, by and large, may reinstate the disparity in the ratio of T helper (Th) 1/Th2 cytokines, which is commonly seen in T1D [119,120]. Exercise can highly likely protect beta-cells from the autoimmune process in this way. Fig. 2 shows how physical activity and exercise can affect the Beta cells' mass and prolong the honeymoon phase.

Reaching a well-described regime for exercising newly diagnosed type 1 diabetes patients to control and prolong the honeymoon phase needs more centered studies on large and different groups of people with a long-term follow-up period. Doing such studies may require great organization and is time and energy-consuming, but it is worth the effort.

CRediT authorship contribution statement

Vazgen Minasian: Supervision. **Maryam Nazari:** Writing – review

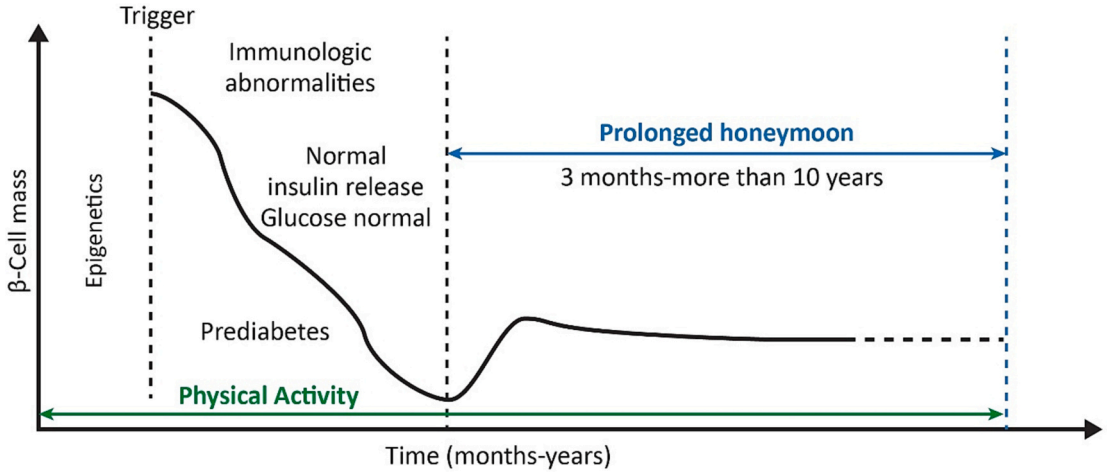

Fig. 2. The effect of physical activity and exercise on the β-cells preservation and prolongation of the honeymoon phase. Physical activity and exercise can cause a prolonged honeymoon for a few months to more than 10 years.

& editing.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Data availability

No data was used for the research described in the article.

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