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Diabetes Associated Cognitive Decline, is there a Role for Exercise?

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Abstract

Type 1 Diabetes (T1D) can have a significant impact on brain structure and function. This so-called 'diabetes-associated cognitive decline' (DACD) can be attributed to diverse biochemical and neurochemical pathways which are caused by hyperglycaemia, hypoglycaemia, but also by c-peptide and insulin deficiency. Besides the positive effects of exercise on the acute and chronic glycaemic control in T1D patients, a growing number of studies also documented the beneficial influence of exercise on aspects of cognition and performance. Therefore, the purpose of the present narrative review is to discuss the associative aspects between a DACD and its' proposed mechanisms and the potential beneficial effect of exercise on a DACD.

Introduction

Type 1Diabetes (T1D) is characterized by chronic hyperglycaemia and the patient is therefore in need of insulin replacement therapy [1]. This is set on either a conventional or an intensive manner of treatment. Intensive insulin therapy (with 3 or more daily insulin injections) or continuous subcutaneous insulin infusion [2] is designed to achieve near-normal glucose control and minimizes the development and severity of diabetes associated complications. Because administration of exogenous insulin is required in both manners of insulin therapy, this can result in an alternation of hypoglycaemic and hyperglycaemic episodes [3]. Since glucose is the only energy for the brain, it is not inconceivable that the disruption of the glucose supply caused by hypoglycaemia and/or chronic hyperglycaemia might alter brain functioning. One example is the disturbance of the cognitive functions. Indeed, the effects of diabetes on the brain were already recognized by Miles and Roots in 1922 (cited in [4]). In 1965, Resko-Nielsen stated that the histological pattern observed in diabetes differs from that seen in any other clinical condition and therefore named it diabetic encephalopathy [5]. As different terms (e.g. cognitive dysfunction, cerebral impairment, central neuropathy) are used in literature, Mijnhout et al. [6] proposed a new term: 'diabetes-associated cognitive decline' (DACD), to include all terms and in that way facilitate research in this area [6]. This term is not suggestive of a particular pathogenesis, but merely describes a state of mild to moderate cognitive impairment [6].

The pathophysiological basis for a DACD remains poorly understood. In literature, episodes of hypoglycaemia [7,8], hyperglycaemia [9,10] and C-peptide/ insulin deficiencies [5,11-19] are mostly cited as harmful to the brain and would therefore be triggers for sustaining a DACD.

Exercise has been accepted and generally recommended for the management of T1D. Exercise increases aerobic fitness, reduces cardiovascular risk factors, and decreases body weight and body fat [20]. Physical activity (PA) improves or maintains chronic glycaemic control, a key trigger for DACD, by enhancing insulin sensitivity and stimulating muscle glucose uptake [21]. Therefore, exercise could be a preventive tool for chronic hyperglycaemia and hence presumably also for a DACD. Moreover, PA, especially aerobic exercise, has been shown to exert positive effects on the cognitive function in humans [22,23]. A meta-analysis of Colcombe & Kramer [24] revealed a clear improvement in executive function due to exercise. Their meta-analysis showed that mental control, spatial memory tasks and psychomotor speed were also positively influenced by exercise compared to sedentary controls [24]. Although the role of exercise is clear, it is not that evident to discover which cognitive functions are altered in T1D, and which mechanisms are at the origin of the decreased cognitive function seen in T1D. Other specific questions that can be raised involve the importance of the different exercise intensities and durations on blood glucose levels, and the associated cognitive function in T1D patients. Therefore, in this paper we will review the existing literature on a DACD and the effects of exercise in T1D. Additionally, insights in the mechanisms through which a DACD is caused and how exercise could help will be suggested.

Diabetes Associated Cognitive Decline

To give a clear view on the affected cognitive domains in T1D, a screening of the literature on the electronic databases Pubmed and ISI Web of Knowledge was performed. Fifty-five original studies were found investigating a DACD in T1D patients (32 including adults, 23 including children).

Compared with non-diabetic children (<18 years), T1D children showed significantly decreased performance on full Intelligence Quotient (IQ) and motor speed. No significant differences in cognitive function were found in verbal IQ, performance IQ, executive function, memory and motor function [26-42]. Adults on the other hand showed significantly lowered performance on the executive function, general IQ (full, verbal and performance IQ), spatial memory and motor speed[43-58]compared to non-diabetic adults.

Early onset disease (EOD) has been considered one of the

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most prominent risk factors for sustaining a DACD [29,35,37,59]. Independently of diabetes duration, T1D children with an EOD show a significantly greater DACD for the following domains: verbal IQ, memory and executive function, and a moderate significant DACD for spatial memory. No studies were found comparing the DACD of T1D adults with an EOD versus a late onset disease (LOD). In brain imaging studies, results from magnetic resonance imaging (MRI) scans showed that an EOD was associated with higher rates of ventricular atrophy (61 vs. 20%) and higher rates of white matter lesions within the hippocampus (14 vs. 2%) [60]. According to Ryan [60], brain volume correlates witha performance on cognitive tasks, providing strong support for the view that an EOD may affect normal brain development, and this leads to a DACD [60].

Intensive insulin therapy (with 3 or more daily insulin injections) or continuous subcutaneous insulin infusion [2] is designed to achieve near-normal glucose control, but also increases the risk of hypoglycaemic episodes. Four studies in adults [2,61-63] and 3 studies in children [33,64,65] looked at the effects of different insulin therapies on cognitive function but did not find significant differences in any of the cognitive domains using different forms of medical management (either a conventional or an intensive manner of treatment).

Only two studies suggest that patients suffering from diabetic complications (retinopathy) performed significantly worse than controls (without diabetes) and T1D subjects without complications, especially on tasks that required sustained attention [44,66], spatial memory [44], hand-eye coordination [44], fluid intelligence [66], information processing [66] and concentration ability [66]. This might suggest that the brain can be affected through the same pathways as other diabetes associated complications, such as retinopathy, nephropathy, neuropathy and macrovascular complications.

Mechanisms of a Diabetes Associated Cognitive Decline

Literature describes 3 possible causes of a DACD: hypoglycaemic episodes, chronic hyperglycaemia and C-peptide/ insulin deficiencies (Figure 1).

Hypoglycaemia

The controversy still exists whether a DACD in T1D can be caused by hypoglycaemic episodes [12,53]. When blood glucose levels reach between 3.6-3.8 mmol/L, the release of counter-regulatory hormones (glucagon, adrenaline) starts. Blood glucose levels of 2.9-3.2 mmol/L provide autonomic and neuroglycopenic symptoms, while cognitive dysfunction starts at blood glucose levels of <2.9 mmol/L [67]. However, during brain imaging studies, hypoglycaemic-associated changes were only seen when plasma glucose was lowered to 2.5 mmol/L [53] or 2.3 mmol/L [68]. This might demonstrate the importance of episodes of severe hypoglycaemia.

In children differences in general IQ, memory (and spatial memory), executive function, motor function and motor speed in relation to a history of severe hypoglycaemic episodes were detected [26,28-31,69-71]. In adults, the executive function and memory function were both significantly affected by severe hypoglycaemia [53,55,58,72-80].

On the other hand, moderate episodes of hypoglycaemia might play a protective role against severe hypoglycaemia damages. In an animal study [81], rats were subjected to either 3 consecutive days of recurrent moderate (1.4 – 2.2 mmol/L) hypoglycaemia or saline injections. On the fourth day, rats were subjected to a hyperinsulinemic severe hypoglycaemic (0.6 mmol/L) clamp for 60 or 90 min. In this study, antecedent recurrent moderate hypoglycaemia preconditioned the brain and markedly limited the extent of severe hypoglycaemia-induced neuronal damage and associated cognitive impairment [81].

The findings of the study of Auer et al. [7] suggests that despite the existence of an energy deficit during hypoglycaemia, there still might be a period which is resistant to hypoglycaemia-induced damage. The possibility exists that the brain uses alternative non-glucose fuels such as amino acids and ketone bodies, in order to maintain the cellular energy state for a limited period [82]. In a rat study, irreversible brain damage occurred only after a period of at least one hour of flat electro-encephalogram (EEG), which might indicate that these alternative energy sources could act as a protective mechanism for brain damage.

Single episodes of (severe) hypoglycaemia might not be harmful since cognitive test performance returns to prehypoglycaemic baseline levels following restoration of the euglycaemic state [30,32]. Two studies [30,32] show results in terms of number of hypoglycaemic episodes. They found a significant correlation between severe hypoglycaemia frequency (3 or more compared with 1 or 2 episodes) and a delay on spatial memory and timing in T1D children [30,32].

How would hypoglycaemia be harmful for the brain?: Hypoglycaemia might cause neuronal necrosis through a neurochemical and biochemical pathway. At the neurochemical level, low blood glucose levels will alter ion pump activity and disturb cellular homeostasis [7,8,83] which will cause an influx of calcium into the cells, creating an intracellular alkalosis. Increasing intracellular calcium is also thought to activate a number of proteolytic enzymes, which action may lead to mitochondrial damage and eventually cell death [7,8,83]. On the other hand, the decreased flux of glucose to the brain results in a fourfold increase in amino acid concentrations (mostly aspartate) [7], thereby activating neuronal necrosis [8]. In the biochemical pathway, the cell catabolizes proteins and deaminates amino acids which cause increased ammonia production. Ammonium, which is a strong base, powerfully increases the cellular pH, resulting in an intense tissue alkalosis. Another reason for alkalosis might be lactate deficiency. Lactate tends to pull the tissue pH towards its own pKa (pKa of 3.83) [7]. However, due to a reduced production of lactate during hypoglycaemia, it is impossible to lower tissue pH which may reinforce alkalosis [7]. This alkalosis might explain why selective neuronal necrosis occurs during hypoglycaemia [7].

Alterations in cerebral vasoreactivity to hypoglycaemia and microvascular complications in T1D: Functional alterations in the cerebral vascular system – such as alterations in cerebral blood flow (CBF) have been associated with hypoglycaemic events in T1D. For

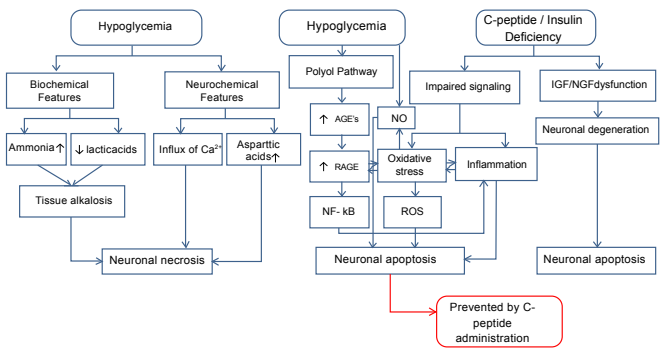

Figure 1: Mechanisms of a DACD.

example, more severe hypoglycaemia was found to be significantly associated with a more pronounced decrease in brain volume and a decreased CBF [84]. According to Wessels et al. [85] vasoreactivity is an important compensatory mechanism in general, especially during hypoglycaemia. It is known that structural microvascular abnormalities include thickening of capillary basement membranes and cause reduced capillary density in diabetes [86], leading to decreased vasoreactivity.

A good vasoreactive response to hypoglycaemia is important in order to limit neuronal damage during hypoglycaemia [86]. Using MRI Wessels et al. [85] discovered that T1D patients with severe diabetic retinopathy (compared with patients without retinopathy) had decreased deactivation in the anterior cingulated gyrus and the orbitofrontal cortex during hypoglycaemia as compared with euglycaemia [85]. They attributed this to microvascular alterations causing regional abnormalities in the regulation of the CBF. In contrast, Tallroth et al. [87] found that CBF was increased when blood glucose levels were lower than 2.0 mmol/L and further increased until 15 min after normalization of blood glucose values. The increase in CBF was correlated with the rate of blood glucose decrease during initiation of hypoglycaemia. These results were supported by the studies of the research group of Macleod et al. [88,89].

Patients with microvascular complications are prone to thickening of the capillary basement membranes and a decreased number of capillaries, making them even more susceptible for alterations in cerebral vasoreactivity and subsequently have a bigger risk for sustaining a DACD. Consequently this can explain why patients suffering from diabetic complication(s) have a decreased performance at several cognitive domains compared to T1D subjects without complications [44,66] and patients with microvascular complications have a significant smaller white matter (WM) volume than diabetic controls without microvascular complications [66].

Hyperglycaemia

Chronic hyperglycaemia (or poor glycaemic control) is another possible cause of a DACD. Poor glycaemic control was found to have negative effects on the memory function of T1D children [27,64,65] and adults [2,72]. T1D patients with higher levels of glycated haemoglobin (HbA_{1c}) perform worse on motor speed and psychomotor efficiency [90]. It was shown by fMRI that higher levels of HbA_{1c} are associated with lower activation in the right para-hippocampalgyrus and amygdala, while lower HbA_{1c}levels resulted in hyperactivation of the brain [91].

How would hyperglycaemia be harmful for the brain?: There are several possible pathways to explain the interaction between high glucose levels and DACD. Hyperglycaemia causes oxidative stress via the polyol pathway, enhances the production of advanced glycation end products (AGEs), and increases vascular tone and permeability of the endothelial cell monolayer.

In the polyol pathway, the excess amount of glucose is converted to sorbitol, which oxidizes NADPH to NADP+ [9]. An increase in sorbitol has been linked to alterations in phosphoinositide and diacylglycerol metabolism. This, in combination with alterations in Ca^{2+}, affects the protein kinases in the brain [9]. Sorbitol may also glycate nitrogens on proteins, called AGEs. The intermolecular collagen cross-linking caused by AGEs on extracellular matrix proteins and basement membrane components leads to diminished arterial and myocardial compliance and increased vascular stiffness [10]. Additionally, AGEs increase proinflammatory mechanisms by the activation of the receptor of AGE (RAGE) in the vessels, resulting in amplification and perpetuation of a loop for oxidative stress and the disregulation of proinflamatory cytokines [92]. The key target of RAGE is nuclear factor κB (NF-κB), both (RAGE and NF-κB) are up-regulated in the hippocampus of rats during hyperglycaemia. Up-regulation of RAGE and NF-κB is accompanied by an up-regulation of inflammatory factors such as TNF-α, IL-1β, IL-2, and IL-6 [18], consequently play a central role in the activation of inflammatory mechanisms [93]. These inflammatory factors can enhance oxidative stress and promote apoptotic stress [18]. This increase in oxidative stress leads also to AGE accumulation and creates thus an unremitting cycle [10]. Poor glycaemic control may thus lead to cellular and molecular damage and is therefore identified as a potential contributor to a DACD [93].

Increased oxidative stress is also associated with the activation of nitric oxide synthases (NOS) in the brain. Nitric Oxide (NO) has diverse biological activities including modulation of neurotransmission, promotion of synaptogenesis and synaptic remodelling, an involvement in long-term potentiation and depression, and is produced by the activity of NOS [94,95]. One of the negative effects is that the activation of NO causes ischemia, leading to neuronal apoptosis [94]. In ischemia, pro-inflammatory cytokines and leukocytes are activated [95].Restoration of blood flow to the ischemic area results in excessive production of reactive oxygen species (ROS) [95], what can result in significant damage to cell structures and even cell apoptosis. Therefore, we can assume that hyperglycaemia can induce, through different pathways, a DACD.

C-peptide and insulin deficiencies

C-peptide is a product of pro insulin cleavage, generated in pancreatic beta-cells as a part of normal insulin production. It is released into the bloodstream in equivalent amounts as insulin in response to various stimuli including elevated blood glucose. In patients with T1D, both insulin and C-peptide are decreased or absent. Insulin plays an important role in the regulation of brain metabolism and has a couple of neuroprotective effects such as preventing neuronal death during stroke and reducing neurological disability [96]. C-peptide has insulinomimetic effects by triggering the insulin receptor (IR) activity and increases glycogen synthesis and amino acid uptake, but has no glucose lowering effects [15]. In 4 months diabetic rats, there was a severe suppression of presynaptic synaptophysin and a marked decrease in presynaptic density. These deficits were fully prevented by the replacement of C-peptide [18]. Interestingly, Sima et al. [17] showed that c-peptide replacement prevented the up regulations of RAGE and NF-κB. Consequently, TNF-α as well as the pro- and anti-inflammatory interleukins normalized in the hippocampus of diabetic BB/Wor rats [17].

The replacement of C-peptide also prevented the suppression of IGF-1, IGF receptor (IGF-IR), IR, NGF and NGF-Tra receptor in peripheral nerves of T1D animals. This resulted in the prevention of structural changes characterizing T1D polyneuropathy [18,19]. Li et al. [13] studied the possible preventive effects of C-peptide replacement on the early abnormalities in the expression of the IGF system in the central nervous system. C-peptide replaced animals showed a partial prevention of hippocampal neuronal loss which was associated with changes in apoptosis related proteins in the hippocampus [13]. These findings might suggest that IGF and insulin action provides anti-apoptotic effects and are in line with earlier studies.

In summary, the data of several studies support the view that insulin/C peptide deficiency plays an important role in type 1 diabetes-induced neuronal apoptosis [12].

Exercise in T1D: Short Term Episodes of Hypoglycaemia, Long Term Prevention of Chronic Hyperglycaemia?

As described above, glycaemic control (prevention of episodes of hypoglycaemia and of chronic hyperglycaemia) is important in the prevention or treatment of a DACD. PA is generally recommended for its positive effects on glycaemic control, insulin sensitivity and stimulation of muscle glucose uptake [97,98]. Unfortunately, due to the complexity of regulating exogenous insulin in a physiologic manner during exercise, PA often results in episodes of hypoglycaemia or even episodes of hyperglycaemia shortly following or even long after completing exercise [99]. It is clear that the type of exercise will influence glycaemic control, possibly inducing or preventing periods of hyper- or hypoglycaemia.

While a large body of literature exists, full comparison across individual studies is largely qualitative and hampered by a wide range of study characteristics, which makes the interpretation of the current literature difficult. One also has to be aware that there is a large difference in acute exercise studies, where the effect of one single exercise bout on glycaemia is examined, and exercise training, in which a systematic exercise program is used. For the purpose of this article we defined acute exercise as 'exercise' while chronic exercise is defined as 'training'. Therefore, questions remain concerning the exact effect of training on glycaemic control in T1D. Subsequently, a screening of the literature resulted in a selection of 32 studies that provide more uniform results concerning the effects of different types of exercise on acute and chronic glycaemic control in T1D [100] (Figure 2).

Changes in blood glucose levels after a single bout of exercise

Glycaemia during exercise can vary inter- as well as intra-individually given that it depends on various factors such as exercise modality and intensity [101-103], nutritional status [104], time of insulin injection [105], or pre-exercise glycaemia level [106]. As expected, aerobic [97,107-111] and to a less important extent, acute high intensity exercise (HIE) [103,110,112-115] results in decreased levels of glucose in the T1D patient, which might cause an episode of hypoglycaemia during or after exercise. The effects of resistance training on acute glycaemia are currently unclear. Jimenez et al. [104] showed that insulin sensitivity remained unaffected after a single bout of resistance exercise, and therefore they suggest that resistance exercise may not cause as severe post-exercise hypoglycaemic episodes as aerobic exercise.

The blood glucose-lowering effect of moderate intensity aerobic exercise can increase the risk of developing an episode of hypoglycaemia during and after exercise. Exercise can acutely affect blood glucose levels, but also influence glycaemia the morning after and exercise bout, this is caused by a persistent increase of peripheral insulin sensitivity and to the required repletion of muscle glycogen stores, in which hepatic glucose production is unable to match the peripheral uptake of glucose by muscle. Consequently, late onset of hypoglycaemia can occur regardless of appropriate insulin reduction [99,116]. MacDonald et al. [114] followed 300 patients with T1D prospectively over 2 years. Sixteen percent developed late-onset (6–15 hours after vigorous exercise) hypoglycaemia. Besides this, previous exercise and the occurrence of previous hypoglycaemic episodes or poor glycaemic control, can affect the hypoglycaemic counter-regulatory mechanisms during subsequent exercise, which may cause even more episodes of severe hypoglycaemia [117]. In well controlled T1D patients with adequate insulinization, acute high intensity exercise may cause a less severe decrease of glucose levels during and after exercise or even prevent an episode of hyperglycemia due to an increase in catecholamines and sympathetic nervous system activation of hepatic glucose production which exceeds the rate of glucose use [117].

One way to prevent these exercise induced hypoglycaemic events is the ingestion of carbohydrates (CHO). West et al. [111] studied whether the ingestion of 75 g of CHO 30 min or 120 min before a 45 min running exercise (at 70% of their VO_{2max}) could assure that blood levels stayed within acceptable ranges. They concluded that venous blood glucose levels decreased more when CHO was ingested 120 min before exercise compared to 30 min before exercise. Another manner to prevent these exercise-associated hypoglycaemic events is by performing an acute bout of high intensity sprint at the end of your moderate exercise. Indeed, studies found a smaller fall of blood glucose levels (or even an increase) due to an acute bout of HIE compared to an acute bout of aerobic exercise. This reaction can be attributed to a greater increase in catecholamines and growth hormone and hence in glucose hepatic production observed during the repeated bouts of HIE during moderate exercise [110,118]. Despite the fact that glucose utilization was greater and occurred faster in HIE + moderate vs. moderate exercise alone, the decrease in plasma glucose was smaller due to a much greater glucose production during HIE + moderate exercise [103,119]. Most recently, Iscoe and Riddell [115] compared moderate exercise with a HIE form with equivalent mechanical load in T1D adults. They showed that HIE provided better protection against nocturnal hypoglycemia. Rabasa-Lhoret et al. [101] observed that blood glucose levels decreased more in moderate continuous and/or longer exercise (periods ranging from 30 to 60 min and from 25 to 75% of VO_{2max}) modes than in intense exercise forms. We could thus hypothesize that the use of high intensity bouts during a moderate form of exercise could successfully limit the risk of hypoglycaemia during and after exercise (Table 1).

Changes in glycaemic control due to exercise training

Twelve studies [120-131] examined the effects of aerobic training on chronic glycaemic control in T1D patients. Aerobic training results in a small, though significant, decrease in levels of HbA_{1c} [100]. Aerobic exercise is known to enhance insulin action 24h following [132] acute exercise. Therefore, it is recommended that exercise is performed frequently in order to maintain a constant increase in insulin sensitivity and thus improve HbA_{1c}. Thus, training once a week might not be adequate to improve HbA_{1c} levels. For example, Huttunen et al. [133] performed an exercise intervention of 45 minutes, 1 time

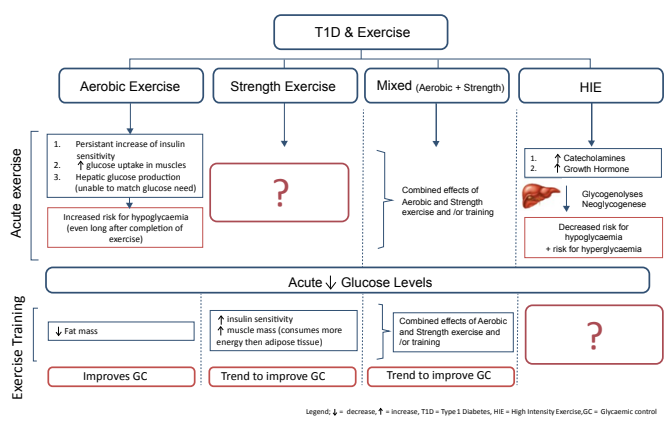

Figure 2: Effects of different types of exercise on acute and chronic glucose levels.

Reference	No. of Subjects (males)	Age (ys)	Characteristics		Intervention	Outcome
			HbA_{1c} (%)	Insulin doses/day		
Heyman et al. 2005 [107]	7 T1D (7) 7 CG	10.5 ± 0.3 10.3 0.3	7.7 ± 0.7	0.92 ± 0.2 $IU.kg^{-1}.day^{-1}$	Evaluating aerobic fitness during an incremental maximal test and Aerobic power $PWC_{170.}$ [IA-,DA-]. [PP]. Exercise ~ 2.25 h after insulin injection.	- T1D pre-pubertal boys showed a significant ↓ in blood glucose during exercise.
Tansey et al. 2006 [108]	50 T1D (NA)	14.8 ± 1.7	7.8 ± 0.8	NA	1 x 75 min aerobic training session, heart rate 140 bpm. [IA+, DA +]. [PP].	- 30% of subjects became hypoglycaemic - Blood glucose level significant ↓
Heyman et al. 2007 [97]	19 T1D (0) 19 CG	15.9 ± 0.3 16.6 ± 1.1	8.1 ± 0.3	68.3 ± 3.1 $IU.day^{-1}$	Maximal incremental exercise test on a bicycle ergometer. [IA-,DA-]. [PP]. Exercise ~ 2.25 h after insulin injection.	- T1D adolescents (girls) showed a significant ↓ in blood glucose during exercise.
Poortmans et al. 1986 [109]	17 T1D (17) 17 CG (17)	16.2 ± 0.7 16.6 ± 1.0	Good GC: 7.3 ± 0.3 Poor GC: 11.4 ± 0.9 Control: 6.3 ± 0.2	NA	Maximal incremental exercise on bicycle ergometer. [IA-, DA-]. [PP].	- Blood glucose levels significant ↓ more in well-controlled T1D compared with poor controlled T1D.
Guelfi et al. 2005 [110]	7 T1D (4)	21.6 ± 4	7.4 ± 1.5	14.8 ± 7.5 $IU.day^{-1}$	A 30-min session of moderate continuous training (40% of $VO_{2max.}$). [IA -, DA-]. [PP].	- Capillary glucose level significant ↓
West et al. 2011 [111]	7 T1D (7)	31 ± 2	8.3 ± 0.1	NA	Ingestion of 75 g CHO 30, 60, 90 and 120 min prior to a single session of 45 min of running exercise (70% of $VO_{2max.}$). [IA+,DA+]. [PP]. Insulin injection 30, 60, 90 and 120 min prior to the exercise.	- 75g CHO 30 min before exercising decreases the incidence of hypoglycemic episodes and augments blood glucose levels after exercise compared to the ingestion of 75 g 60, 90 or 120 minutes before exercise.
Yamanouchi et al. 2002 [25]	6 T1D (3)	42.7 ± 13.6	7.4 ± 0.9	27.2 ± 9.4 $IU.day^{-1}$	30 minutes of walking (< 50% of their VO_{2max}) at a heart rate of 90-110 bpm, before or after breakfast. Subjects had 1 injection of regular insulin 30 min before breakfast: exercise after breakfast is performed while insulinaemia is high (peak of rapid insulin) whereas the exercise before breakfast is performed with low insulinaemia. [IA/DA+]. [FS and PP]. Exercise ~ 1h after insulin injection.	- Blood glucose values significant ↓ when exercise is performed after breakfast, but not when exercise is performed before breakfast.
Zinman et al. 1977 [119]	16 T1D (10)	30 (22-43)	NA	NA	45 min at 50% of $Vo_{2max.}$ [IA infusion, DA NA] 2 groups: 1 group continuous insulin infusion, 1 group received one-third of usual intermediate acting insulin by subcutaneous injection. [FS]. Exercise ~ 1h after insulin injection.	- Rapid ↓ in glucose in subjects receiving one third of usual insulin. [P] glucose during exercise is constant in subjects with iv insulin infusion.
Zinman et al. 1984 [124]	13 T1D (7)	30.0 ± 1.8	10.7 ± 0.3 → 10.3 ± 0.8	37.6 ± 3.2 $IU.day^{-1}$	A 45-min session of aerobic exercise (60-85% of their $VO_{2max.}$). [IA-DA- (daily routines)]. [PAS, PP, FS = NA]. Exercise ~ 45 -135 min after insulin injection.	- Plasma glucose significant ↓

*Data presented as mean ± SD; N° of Subjects (males) = total number of subjects and the number between brackets are the number of males;
T1D: Type 1 Diabetes; GC: Glycaemic Control; NA: Not Applicable; CG: Controls; CHO: Carbohydrates; [VP]: Venous Plasma Glucose; [V]: Venous Whole blood, [P]: Plasma; [C]: Capillary; IA: Insulin Advice before/after Exercise; DA: Dietary Advice before/during or after Exercise; iv: intra-venous; ↓: Decrease; [PAS]: Post Absorptive State (5-11h after last meal); [PP]: Post Prandial (during 4h after meal); [FS]: Fasting State (> 12h after meal); HbA_{1c}: Glycaeted Haemoglobin; VO_{2max}: Maximal Oxygen Uptake; PWC: Physical Working Capacity

Table 1: Effects of a single bout of aerobic exercise on blood glucose levels in T1D patients (Table based on [100]).

per week during 12 weeks and HbA_{1c} levels were not affected by the intervention program. The duration of the training period is also an important influencing factor for decreasing HbA_{1c}. HbA_{1c} levels decreased significantly only in training studies that lasted for more than 3 months. The frequency (times/week) of training will also influence the HbA_{1c} levels [100]. Besides this, baseline glycaemic control is also an important predictor of HbA_{1c} improvement due to training. HbA_{1c} decreases significantly more in T1D individuals with poor glycaemic (> 8% HbA_{1c}) control compared to individuals with good glycaemic control (<8% HbA_{1c}) [100]. Lehman et al. [134] demonstrated only a slight decrease in HbA_{1c} in well-controlled subjects who performed exercise training. This might suggest that exercise can be beneficial in order to improve glycaemic control particularly in poor-controlled T1D subjects.

Only 2studies [122,135] reported data on the effects of resistance training on glycaemic control. Aerobic training and resistance training have different actions in the body and can therefore influence glycaemic control through different pathways. Since fat mass decreases after a period of aerobic training [136], the change in the amount of body fat contributes to the change in insulin resistance over time in T1D patients[133]. On the other hand, resistance training enhances insulin sensitivity [137]. A meta-analysis of 9 randomized controlled trials evaluated 372 subjects with type 2 diabetes (T2D) [138]. When compared to not exercising, progressive resistance training led to a small but statistically significant absolute reduction of 0.3% in HbA_{1c}, indicating that resistance training is a reasonable option in the management of glycaemic control in diabetic subjects [139]. This could be the result of obtaining greater muscle mass. At rest, skeletal muscle consumes 54.4 kJ/kg (13.0 kcal/kg) per day, which is larger than adipose tissue at 18.8 kJ/kg (4.5 kcal/kg) [140]. A greater muscle mass would thus consume more glucose and therefore could affect glycaemic control.

The effects of aerobic training combined with resistance training were determined in 4 studies [141-144] using an adolescent population. There is still no consensus in literature on the combined effect of aerobic and resistance exercise. When comparing pre and post training status levels, there was only a slight decrease of HbA1c. However, the exercise group showed a significant decrease in HbA_{1c} compared to the control T1D non-exercising group. A possible explanation is obviously the combination of both mechanisms of endurance and resistance training, as explained above [133,140]. The study of Heyman et al. [144] did not show a significant decrease of HbA_{1c} levels, while the study of Bernardini et al. [142] showed a large, significant decrease in HbA_{1c}. The contradictory results in literature might be partly explained by the types of interventions. For example, in the cross sectional study of Bernardini et al. [142], they defined 'combined training' as 'soccer, volleyball, tennis, basketball' across lifetime. Their improvement in glucose levels were probably not due to specific aerobic or resistance training programs, but due to the combined effects of different sports and their active lifestyle. In the study of Heyman et al. [144] adolescents only benefit from the training during the study period. This suggests that an active lifestyle (as measured in a cross sectional study) could reflect in good glycaemic control, whereas subjects with poor glycaemic control could be less motivated to engage in PA.

Only one training (7 weeks) study determined the effects of sprint training on glycaemic control [145]. The authors concluded that HbA_{1c} levels were not influenced by long term High Intensity Training (HIT).

From the above studies, the following guidelines can be for the maintenance of improved chronic glycaemic control formulated: training (mostly aerobic) 3 months or more, training at least 2 - 3 times a week and having dietary or insulin advice [100]. For example, West et al. [111] studied whether the ingestion of 75 g of CHO 30 min or 120 min before a 45 min running exercise (70% of their VO_{2max}) could assure that blood levels stayed within acceptable ranges. They found that venous blood glucose levels decreased more when CHO was ingested 120 min before exercise compared to 30 min before exercise. Insulin levels on the other hand, should be adjusted in terms of intensity and duration of the exercise.

The relative difficulty of improving HbA_{1c} with exercise training (all the more when patients do not benefit from specific advice about diet & insulin adaptations) might be partly caused by the difficulty for the patients to manage various important glycaemic variations depending on a large amount of factors (duration since the last meal or insulin dose, insulin absorption, initial glycaemia, hour of the day…). It could be difficult to adapt insulin and diet to these important day-to-day glycaemic variations, resulting in more hypoglycaemic episodes. In response, T1D individuals can consume more CHO or reduce too much their insulin dose that in turn can induce slight hyperglycaemia and prevent improvement in HbA_{1c} (Table 2).

Exercising the Brain

In the last two decades, both epidemiological and experimental studies were published with accumulating evidence supporting a positive relationship between exercise and cognitive function. Results from meta-analysis confirm significant positive effects of exercise on cognitive function [146,147]. The most convincing evidence of exercise-mediated brain changes has been found in the hippocampus (a part in the brain involved in memory forming, organizing, and storing) [148]. In fact, studies show that exercise improves mostly cognitive functions such as tasks mediated by the hippocampus [149].

The exact mechanisms of the therapeutic effects of exercise remain unclear. Some hypotheses are suggested in literature to explain the possible therapeutic effects supporting the relationship between exercise and the brain, including supramolecular mechanisms (e.g. neurogenesis, synaptogenesis and angiogenesis) [150] and the neuroinflammatory processes [147].

Supramolecular mechanisms

Angiogenesis: Enhanced blood flow into the brain might be an effective approach to minimize or delay cognitive decline associated with aging [150]. Exercise enhances angiogenesis and vascular function in several regions, which might facilitate synaptic plasticity via multiple mechanisms [150-152]. These changes may lead to improved physiological functioning of the brain parenchyma [153]. For example, Insulin-Like Growth Factor (IGF-1) and Vascular Endothelial Growth Factor (VEGF), induce the formation of new blood vessels and are up-regulated after exercise [154]. Blockade of IGF-1 in the brain has also shown to prevent exercise-induced neuron proliferation in the dentategyrus [152]. Fabel et al. [155] showed that peripheral blockade of VEGF abolished running-induced neurogenesis but had no effect on baseline neurogenesis, suggesting VEGF is an important element of a somatic regulator of adult neurogenesis.

Synaptogenesis: There is growing evidence that Brain-derived Neurotrophic Factor (BDNF; a member of the neurotrophin family) has a strong modulatory function in synaptic plasticity. Indeed, BDNF induces neurogenesis (directly or through neurotransmitters) and neuroplasticity (such as pre and post-synaptic cascades that induce synaptogenesis) [156]. This includes memory formation (learning and behaviour, synaptic plasticity, synaptic efficacy and neuronal connectivity),promotion of the development of immature neurons and enhancement of adult neurons survival [156]. Decreased levels of BDNF have been related to various mental disorders such as depression, schizophrenia, Alzheimer's disease, dementia, Huntington's disease, Parkinson disease [157] and T2D [158,159] and are associated with an age-related decline in hippocampal volume and elevated memory deficits [160].

There is a growing body of evidence that aerobic exercise training increases serum [161,162] and plasma [163,164] BDNF levels. However, a couple of studies did not find an increase in serum or plasma BDNF levels due to aerobic training [165,166] or strength training [166,167]. It seems that the effects of an endurance training program on (serum) BDNF levels differs from the effects of a single bout of endurance exercise on (serum) BDNF. In addition, Goekint et al. [167] cited that it is clear that an acute exercise bout will increase circulating BDNF levels, but that a longer training period not necessarily increases circulating BDNF concentrations. Furthermore, Ferris, et al. [168] reported that the magnitude of the increase in BDNF levels during exercise is related to exercise intensity. And thus, an increased release of BDNF into the blood circulation is a result of a physical stimulus in a dose-response manner [169]. It seems that only high intensity endurance exercises result into a significant increase of BDNF (Table 3).

Furthermore, exercise activates IGF-1 production, leading to angiogenesis (as described above) and presumably synaptogenesis through a downstream signalling cascade at the presynaptic and the postsynaptic level [150]. Ding et al. showed that blocking the IGF-I receptor significantly reversed an exercise-induced increase in the levels of BDNF mRNA, BDNF protein and pro-BDNF protein. This suggests that the effects of IGF-I may be partially accomplished by modulating the precursor to the mature BDNF.

Reference	No. of Subjects (males)	Age (ys)	HbA_{1c} (%) (pre/post)	Insulin doses/ day	Intervention	Outcome
Huttunen et al. 1989 [130]	34 (20) 16 EG 16 CG	11.9 (8-17)	EG: 9.8 ± 2.3→ 10.5 ± 2.5 CG 9.4 ± 2.1→ 9.7 ± 2.2	NA	45 min, 1/wk, 12 wks, aerobic exercise, heart rate 150 bpm (jogging, running, gymnastics) vs. a non-training group. [IA/ DA NA]. [PAS, PP, FS = NA].	- Blood glucose and glucosuria did not change significant HbA_{1c} levels ↑significant - VO_{2max} (pre→post exercise): 40.0 ± 7.2 → 43.8 ± 8.6 $ml.min^{-1}.kg^{-1}$
Rowland et al. 1985 [131]	14 T1D (7)	9-14	9.9 ± 1.4 → 10.1 ± 1.1	NA	1h, 3/wk, 12 wk aerobic (running/walking) exercise. [DA+, IA-]. [PAS, PP, FS = NA].	- VO_{2max} ↑sign (38.4 ± 4.6 → 41.9 ± 6.0 $ml.min^{-1}.kg^{-1}$) - HbA_{1c}, fasting blood glucose and glucosuria (24h) did not change significant
Wong et al. 2011 [176]	12 EG (4) 11 CG (2)	12.3 ± 2.07	CG: 8.1 ± 1.1 EG: 8.2 ± 1.4	NA	12 wks, 3d/wk aerobic (40-60% VO_{2max}), 30 min. [IA/DA NA]. [PAS, PP, FS = NA].	- 9 month FU → aerobic exercise group had lower HbA_{1c} levels than self-directed group. - No changes in VO_{2max}.
Bernardini et al. 2004 [142]	91 T1D (50)	14.8 ± 2.7	< 60 min/wk: 8.9 ± 0.5 120 -360 min/ wk: 8.3 ± 0.4 360-480 min:wk: 8.0 ± 0.6	NA	Prospective cohort study: aerobic activity defined as: walking, cycling, skating and swimming during the last 6 months. [DA/ IA NA]. [PAS, PP, FS = NA].	- Minutes of exercising is inversely correlated with HbA_{1c}. (60 min significant with 120-360 min and 360-480 min).
Marrero et al. 1988 [125]	10 T1D (6)	13.3 (12-14)	Pre→post : 10.1 ± 1.9 → 9.2 ± 2.2	NA	Non-supervised aerobic home exercise protocol: 45 min, 3/wk, 12 wks (heart rate 160 bpm). [IA-, DA+]. [PAS, PP, FS = NA].	- HbA_{1c} levels ↓ significant - VO_{2max} ↑significant (40.4 ± 8.8 → 44.9 ± 12.9 $ml.min^{-1}.kg^{-1}$)
Michaliszyn et al. 2011 [126]	12 T1D	12-19	9.4 ± 1.8 → 9.4 ± 2.0	NA	60 min, 5 day/wk, 16 wk (60-75% of their predicted peak heart rate) in a home based program. [IA/DA NA].	- HBA_{1c} did not change significant No measurement of VO_{2max}.
Ruzic et al. 2007 [127]	20 T1D (NA)	12.8 ± 2.1 (9-16)	Pre→post: 8.3 ± 1.3 → 7.9 ± 1.4	3.6 ± 0.6 $IU.day^{-1}$ 0.9 ± 0.2 $IU.kg^{-1}.day^{-1}$	High volume, low intensity program → 60 min, <75% of HR_{max}, 2 x 5 days, 3x/day, exercise camp for children. [IA/DA-]. [PP]	- HbA_{1c} sign ↓ 10 days after camp, but significant ↑ 2 months after training - Blood glucose values ↓ significant the last days of training session - No VO_{2max} levels were shown.
Sideraviciute et al. 2006 [128]	19 T1D (0)	14-19	8.5 ± 0.4 → 7.8 ± 0.3	Short term: 26.4 ± 1.8 $IU.day^{-1}$→ 25.0 ± 7.8 $IU.day^{-1}$	Long term swim (aerobic) training: 45 min, 2/wk, 14 wks. [IA/DA NA]. [PAS, PP, FS = NA].	- HbA_{1c} ↓ significant - Daily short acting insulin dose ↓ significant after exercise program. - No VO_{2max} levels were shown.
Laaksonen et al. 1999 [120]	20 T1D (20)	32 ± 5.7	pre→post: 8.2 ± 1.1 → 8.0 ±1.0 CG→EG: 8.5 ± 1.6 → 8.0 ± 1.0	Pre→post training: 0.7 ± 0.2 → 0.7 ± 0.2 $IU.kg^{-1}.day^{-1}$ CG→EG: 0.7 ± 0.2 → 0.7 ± 0.2 $IU.kg^{-1}.day^{-1}$	1 wk, 20-30 min, 50-60% VO_{2peak} gradually increased to 12-16 wks, 30-60 min, 3-5/wk, 60-80% VO_{2peak} aerobic training program. [IA/DA NA]. [PAS, PP, FS = NA].	- VO_{2max} significant ↑in training group (43.4 ± 8.0 → 46.1 ± 6.6 $ml.min^{-1}.kg^{-1}$) - HbA_{1c} ↓ with training and compared to control group
Lehmann et al. 1997 [121]	20 T1D (13)	33 ± 7.7 (22-48)	7.6 ± 4.4 → 7.5 ± 4.0	48.4 ± 15.1 → 40.4 ± 13 $IU.day^{-1}$	3 x /wk, min 45 min, 3 months of regular endurance exercise,. 50- 70 % VO_{2max}. [IA/DA NA]. [PAS, PP, FS = NA].	- Total insulin (IU/day) ↓ significant - HbA_{1c} did not ↓ significant - VO_{2max} increased significant (2914 ± 924→ 3092 ± 905 ml/min).
Ramalho et al. 2006 [122]	7 T1D (2)	19.8 ± 5.1	8.7 ± 1.6 → 9.8 ± 1.8	0.95 ± 0.3 → 0.79 ± 0.3 $IU.kg^{-1}.day^{-1}$	40 min run or walk, first 2 wks: 60-70% HR_{max}, 3-6th week= 70-80% HR_{max}, 7-12thweeks= 70-90% HR_{max}, 3/wk, 12 wks, aerobic training. [IA+, DA+]. [PAS, PP, FS = NA].	- No difference in lipid profile or fasting blood glucose before and after the exercise program, while the HbA_{1c} increased. - Self-monitored blood glucose levels, measured before and after each session, showed a significant ↓ post compared to pre exercise training.
Wallberg – Henrikson, 1986 [123]	6 EG (NA) 7 CG (NA)	63 ± 2 35 ± 2	10.4 ± 1.5 10.6 ± 1.6	32 ± 2 $IU.day^{-1}$ 43 ± 5 $IU.day^{-1}$	20 min of daily bicycle exercise during 5 months vs. non training. [IA/DA NA]. [PAS, PP, FS = NA].	- VO_{2max} ↑significant (pre→post training: 30.2 ±2.1 → 32.7 ± 2.1 $ml.min^{-1}.kg^{-1}$) - HbA_{1c} did not change significant after training
Zinman et al. 1984 [124]	13 T1D	30.0 ± 1.8	10.7 ± 0.3 → 10.3 ± 0.8	37.6 ± 3.2 $IU.day^{-1}$	45 min aerobic exercise, 3/wk, 12 wks (60-85% of their VO_{2max}). [IA-DA- (daily routines)]. Exercise ~ 45 -135 min after insulin injection.	- VO_{2max} increased sign (33.8 ± 1.7 → 40.0 ± 4.0 $ml.min^{-1}.kg^{-1}$) - [P] FGL and HbA_{1c} did not significant change

Data are presented as mean ± SD; No. of Subjects (males) = total number of subjects and the number between brackets are the number of males;[P]FGL: Fasting Glucose Levels; EG: Exercise Group; CG: Control Group; FU: Follow Up; T1D: Type 1 Diabetes; NA: Not Applicable; [VP]: Venous Plasma Glucose; [V]: Venous Whole blood; [P]: Plasma; [C]: Capillary; IA: Insulin Advice before/after Exercise; DA: Dietary Advice before/during or after Exercise; ↓: Decrease; [PAS]: Post Absorptive State (5-11h after last meal); [PP]: Post Prandial (during 4h after meal); [FS]: Fasting State (> 12h after meal); HbA_{1c}: Glycaeted Haemoglobin; VO_{2max}: Maximal Oxygen Uptake; VO_{2peak}: Peak Oxygen Uptake; HR_{max}: Maximum Heart Rate

Table 2: Effects of aerobic training on glycaemic control in T1D patients.(Table based on [100]).

A post-mortem study saw decreased expression of IGF-I in the hippocampus, cerebellum, pons and basal ganglia in two patients with EOD. This finding was associated with severe neuronal loss in the hippocampus and frontal cortex [92]. Li et al. [5,170] studied the possible role of hyperglycaemia vs. impaired insulin action on hippocampal apoptosis and neuronal loss in T1D rats. They found a decreased neuronal density in the hippocampus and a greater neuronal loss in T1D rats. These changes were preceded and accompanied by a significant 63% down-regulation of the hippocampal IGF system.

Neurogenesis: Many substances affect hippocampal neurogenesis. Increased cell genesis is associated with enhanced hippocampal synaptic plasticity and can be exercise-induced. The changes in synaptic plasticity occur in the same regions where neurogenesis was stimulated. This suggests that newborn cells play a functional role in neurogenesis due to exercise [147]. In particular, long-term potentiation -a physiological model of certain forms of learning and memory-is influenced by PA [147].

Neuroinflammatory processes

Another potential pathway through which the cognitive function may be influenced is the link between exercise and inflammation. For example, exercise increases the release of adrenaline, cortisol, growth hormone, and other factors that have immunomodulatory effects [171] and thus reduces the level of systemic inflammation. Furthermore, vigorous exercise leads to increased levels of pro-inflammatory cytokines (IL-1, IL-10, IL-6 and tumor necrosis factor-α (TNF-α)) [172,173], but simultaneously cytokine inhibitors and anti-inflammatory cytokines restrict the magnitude and duration of the inflammatory response to exercise [149]. The release of cytokines such as vascular VEGF and Il-6 are associated with angiogenesis and may therefore contribute to the beneficial effects of exercise (Table 4 and 5).

Diabetes-Associated Cognitive Decline, is there a Role for Exercise?

Recently, strategies to fight or prevent the development of cognitive

Reference	N° of Subjects (males)	Age (ys)	Characteristics		Intervention	Outcome
			HbA_{1c} (%)	Insulin doses/ day		
Durak et al. 1990 [135]	8 T1D (8)	31 ± 3.5	6.9 ± 1.4 → 5.8 ± 0.9	46.2 ± 15 → 41.6 ± 16 $IU.day^{-1}$	3 d/wk; 10 wks, 15 exercises (max 12 reps), 3-6 sets, rest intervals : 30s-2min. [IA/DA NA]. [PAS, PP, FS = NA]. Exercise ~ 5h after insulin injection.	- HbA_{1c} and glucose levels ↓ significant
Ramalho et al. 2006 [122]	6 T1D (1)	20.8 ± 4.7	8.2 ± 2.9 →7.6 ± 1.6	0.95 ± 0.3 → 0.79 ± 0.28 $IU.day^{-1}$	3d/wk , 12 wks, 9 exercises (8-12 reps), 3 sets. [IA+, DA+].	- No significant differences in parameters. - Self-monitored blood glucose levels, measured before and after each training session, show non- significant↑.

Data are presented as mean ± SD; No. of Subjects (males) = total number of subjects and the number between brackets are the number of males;T1D: Type 1 Diabetes; [VP]: Venous Plasma; [C]: Capillary; FGL: Fasting Glycaemic Level; IA: Insulin Advice before/after Exercise; DA: Dietary Advice before/during or after Exercise; ↓: Decrease; [PAS]: Post Absorptive State (5-11h after last meal); [PP]: Post Prandial (during 4h after meal); [FS]: Fasting State (> 12h after meal); HbA_{1c} : Glycaeted Haemoglobin

Table 3: Effects of strength training on blood glucose levels in T1D patients.(Table based on [100]).

Reference	No of Subjects (males)	Age (ys)	Characteristics		Intervention	Outcome
			HbA_{1c} (%)	Insulin doses/day		
Bernardini et al. 2004 [142]	90 T1D	14.8 ± 2.7	60 min exercise/ wk: 8.9 ± 0.5 Mixed: 7.4 ± 0.6	NA	Prospective cohort study: aerobic activity defined as: walking, cycling, skating and swimming. Mixed defined as: soccer, volley- ball, tennis, basketball. No intensity/quantity shown. [DA/IA NA]	- Significant lower HbA_{1c} levels in children performing > 360 min (mixed training) of exercise compared to children < 60 min/wk (aerobic training)
D'Hooge et al. 2011 [141]	16 T1D (NA) 8 EG 8 CG	14.1 (10-18)	EG: 7.9 ± 1.3→ 7.7 ± 1.2 CG: 8.7 ± 0.8→ 8.7 ± 0.9	0.96 → 0.9 $IU.kg^{-1}.day^{-1}$	20 wks, 2/wk, 70 min, aerobic and strength group. Aerobic part: 60-75% of HR_{peak}. Strength training: 20 RM→ 12 RM,3 sets, 10 repetitions, 60 sec rest. [IA+, DA+]. [PAS, PP, FS = NA].	- EG: Capillary glucose significant ↓ after training, HbA_{1c} not significant ↓ - EG: Daily insulin doses: significant ↓ - EG: VO_{2peak} ↓ not significant (1478 → 1425 (mL/min))
Heyman et al. 2007 [144]	16 T1D (0) 9 = EG 7= CG	EG: 15.9 ± 0.5 CG: 16.3 ± 0.4	EG: 7.3 ± 0.9 → 7.1 ± 0.8 CG: 8.5 ± 1.3 → 8.2 ± 1.2	EG: 1.0 ± 0.1 $U.kg^{-1}.day^{-1}$ CG: 1.1 ± 0.1 $U.kg^{-1}.day^{-1}$	22 x 2h + 25x 1 h of training during 6 months of aerobic and strength training in adolescent girls. [IA-,DA-]. [PAS, PP, FS = NA].	- Insulin dose per day ↓ exercise group - HbA1c ↓ not significant in EG compared with CG - [P]FGL were significant ↓ in EG compared with CG. - PWC_{170} was not significant↑ in watts/kg.
Mosher et al. 1998 [142]	10 T1D (10) 11 CG	17.2 ± 1.2	Pre – Post EG : 7.72 ±1.26 → 6.76 ± 1.07 CG vs. EG: 4.47 ± 0.6 vs. 6.76 ± 1.07	1.02 ± 0.12 $IU.kg^{-1}.day^{-1}$	45 min, 3/wk; 12 wks. Aerobic circuit training + strength training. [IA-/DA NA]. [PAS, PP, FS = NA].	- HbA1c ↓ significant - FGL plasma was unchanged

*Data presented as mean ± SD; N° of Subjects (males) = total number of subjects and the number between brackets are the number of males;[P]FGL = fasting glucose levels; EG = exercise group; CG = control Group; T1D = Type 1 Diabetes; NA = not applicable; [VP]: Venous Plasma Glucose; [V]: Venous Whole blood[P]: Plasma; [C]: Capillary; IA: Insulin Advice before/after Exercise; DA: Dietary Advice before/during or after Exercise; ↓: Decrease; [PAS]: Post Absorptive State (5-11h after last meal); [PP]: Post Prandial (during 4h after meal); [FS]: Fasting State (> 12h after meal); HbA_{1c}: Glycaeted Haemoglobin; VO_{2max}: Maximal Oxygen Uptake; VO_{2peak}: Peak Oxygen Uptake; HR_{peak}: Heart Rate Peak

Table 4: Effects of combined (aerobic and strength) training program on glycaemic control in T1D patients.(Table based on [100]).

Reference	No. of Subjects (males)	Age (ys)	Characteristics		Intervention	Outcome
			HbA_{1c} (%)	Insulin doses/ day		
Bussau et al. 2006 [113]	7 T1D (7)	21 ± 3.5	7.4 ± 0.8	NA	40% VO_{2peak} for 20 min on a cycle ergometer then immediately engaged in a maximal 10-s cycling sprint (sprint trial) or rested (control trial). [IA -, DA-]. [PP]. Exercise ~ 109 ± 10 min after insulin injection.	- Moderate intensity resulted in a significant fall in glycaemia in both trials (3.6 mmol/L for sprint training, 3.1 mmol/L for moderate training).
Guelfi et al. 2005 [110]	7 T1D (4)	21.6 ± 4	7.4 ± 1.5	14.8 ± 7.5 $IU.day^{-1}$	30 min continuous cycling exercise at 40% VO_{2peak}, interspersed with 16x 4-s maximal sprint efforts [IA -, DA-] compared to 30min continuous cycling at 40% VO_{2peak}. [PP]. Exercise ~ 3.5h after insulin injection.	- Glucose production = ↑ in MOD+HIE vs MOD - Glucose utilization = ↓ MOD vs MOD+HIE
Guelfi et al. 2007 [103]	9 T1D (5)	22.6 ± 5.7	7.7 ± 0.8	NA	30 min continuous cycling exercise at 40% VO_{2peak}, interspersed with 16x 4-s maximal sprint efforts. [IA/DA: euglycaemic clamp]. [PP].	- High-intensity bouts associated with MOD stimulate a more rapid and greater increment in endogenous glucose production during exercise than MOD alone
Iscoe et al. 2006 [112]	5 T1D (4)	35.2 ± 3.0	7.0 ± 0.2	38.8 ± 5.1 $IU.day^{-1}$	60 min exercise spinning class (high intensity). [IA-, DA-]. [PP].	- Blood glucose levels ↓ significant
Iscoe & Riddell 2011 [115]	11 T1D (5)	35.1 ± 11.6 (18-51)	7.8 ± 0.4	34 ± 5 $IU.day^{-1}$	- 45 min of continuous moderate-intensity cycling exercise at 55% of their VO_{2peak} (MOD) or continuous exercise at 50% of their VO_{2peak} with the addition of 9x 15s bouts of 100% VO_{2peak}, spaced 5 min apart (MOD + HIE). [IA+, DA+]. [PAS]. Exercise ~ 2h after insulin injection.	- MOD and MOD+HIE causes similar reductions in glucose levels during activity - Addition of HIE is associated with less risk for late onset post-exercise hypoglycaemia.
Harmer et al. 2008 [114]	7 T1D (5)	25 ± 4	8.6 ± 2.3 →8.1 ± 1.6	52.4 ± 3.8 $IU.day^{-1}$ 51.2 ± 4.6 $IU.day^{-1}$	7 weeks of sprint training, 3/wk: 4-10, 30s all out sprints, 3-4 min rest). [IA-, DA NA]. [PAS, PP, FS = NA].	- Glucose levels ↑ significant (pre/post training). - HbA_{1c} levels were not significant influenced.

*Data presented as mean ± SD; No. of Subjects (males) = total number of subjects and the number between brackets are the number of males; MOD: Moderate Intensity Training; IHE/HIE: Intermittent High Intensity Exercise; NA: Not Applicable; IA: Insulin Advice before/after Exercise; DA: Dietary Advice before/during or after Exercise; T1D: Type 1 Diabetes; [VP]: Venous Plasma Glucose; [V]: Venous Whole blood; [P]: Plasma; [C]: Capillary; [IS]: Interstitial Glucose Levels; [M]: Free Muscle Glucose; ↓: Decrease; [PAS]: Post Absorptive State (5-11h after last meal); [PP]: Post Prandial (during 4h after meal); [FS]: Fasting State (> 12h after meal); HbA_{1c}: Glycaeted Haemoglobin; VO_{2peak}: Peak Oxygen Uptake

Table 5: Effects of HIE exercise and training on glycaemic control in T1D patients.(Table based on [100]).

impairment have become more and more important. PA, such as aerobic exercise, has emerged as a promising low-cost treatment to slow down or even stop the cognitive decline because it supports brain plasticity, neurogenesis and angiogensisin different populations, both healthy and diseased [24,169,174]. To date no studies reported the effects of exercise on a DACD in subjects with T1D. However, as glycaemic control plays a central role in a DACD, we could hypothesise that, since exercise is linked to synaptic plasticity, neurogenesis and inflammatory and anti-inflammatory processes (in non-diabetic subjects so far),and improves glycaemic control in subjects with T1D,itcould prevent or 'slow down' a DACD in T1D. Figure 3 gives an overview of the possible pathways and interactions of exercise in a DACD.

Hyperglycaemia is associated with neuroinflammation. Vigorous exercise leads to increased levels of pro-inflammatory cytokines (IL-1, IL-10, IL-6 and tumor necrosis factor-α (TNF-α)) [172,173], but simultaneously cytokine inhibitors and anti-inflammatory cytokines restrict the magnitude and duration of the inflammatory response to exercise [149]. Vigorous exercise will lead to increased levels of VEGF and Il-6, which are associated with angiogenesis [149] and thus can influence cognitive function.

PA seems to be a key intervention to trigger the glycaemic control improvement [100]. BDNF triggers the processes through which neurotrophins mediate energy metabolism and in turn neural plasticity [169,178,179]. BDNF levels are inversely associated with fasting plasma glucose and the output of BDNF is inhibited when blood glucose levels are elevated [158]. This suggests that BDNF not only reduces acute blood glucose concentrations but also ameliorates chronic glycaemic control [180], an important cause of a DACD. Until now, no study has looked into the relation between BDNF, exercise and T1D. A vast body of evidence suggests a strong link between circulating BDNF concentrations and cognitive decline [181,182]. Clearly, assumptions can be made that PA can influence the cognitive function in patients with T1D directly through neurogenesis, synaptogenesis and inflammatory responses of exercise, but also through the energy metabolism. Therefore, studies are needed to look at the relationship between PA and cognitive function in T1D.

Another possible mechanism is through energy metabolism. PA and BDNF both trigger the glucose metabolism [158,183]. Previous animal studies focused on the effects of BDNF in diabetic (obese) animals and showed that a peripheral injection of BDNF exhibits hypoglycaemic effects by inducing a hypophagia and reducing plasma insulin levels [184-186]. This indicates that BDNF ameliorates insulin resistance [184,187,188], and therefore has anti-obesity and anti-diabetic effects [186]. Tonra et al. [180] showed that BDNF significantly reduced blood glucose and HbA_{1c} when it was administered once or twice a week to diabetic mice for three weeks as compared with controls. This suggests that BDNF not only reduces acute blood glucose concentrations but also ameliorates chronic glycaemic control [180], an important cause of a DACD. A relationship between BDNF and glucose metabolism is also shown in humans. T2D patients have lower levels of plasma BDNF (independently of obesity) compared to non-diabetic subjects [158,159]. Krabbe and colleagues [158] showed that T2D is associated with lowered levels of plasma BDNF which are in their turn inversely associated with fasting plasma glucose and that the production of BDNF is inhibited when blood glucose levels are elevated [158]. In contrast, another study reported increased levels of serum BDNF in newly diagnosed patients with T2D [189]. We have to

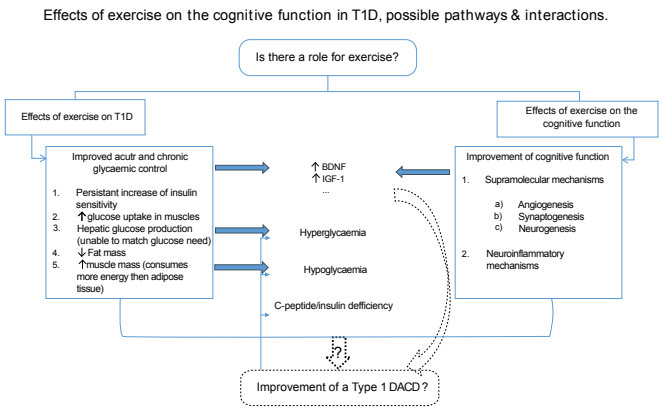

Figure 3: Hypothetical effects of exercise on the cognitive function in T1D. (BDNF = Brain- derived Neurotrophic Factor, IGF-1: Insulin like Growth Factor).

mention that most of the circulating BDNF is stored in the platelets [190], consequently BDNF concentrations are higher in serum [191] than they are in plasma.

Conclusions

An increasing number of studies (in children and adults) have been published on the central nervous system changes associated with T1D in which it was demonstrated that T1D has an effect on cognitive function. A DACD can be caused by episodes of severe hypoglycaemia (biochemical and neurochemical features), chronic hyperglycaemia (via the polyopol pathway and increased oxidative stress) and c-peptide deficiency.Exercise has been accepted and generally recommended for the management of T1D and have been shown to improve acute and chronic glycaemic control. The addition of brief bouts of high-intensity, sprint-type exercise to aerobic exercise can acutely minimize the risk of sustaining a hypoglycaemic episode. On the level of chronic glycaemic control; regular aerobic training is a favorable tool for the improvement ofthe glycaeted haemoglobin level of a patient with T1D.Since exercise is linked to synaptic plasticity, neurogenesis and inflammatory and anti-inflammatory processes, it could be a tool to prevent or 'slow down' a DACD in T1D. However, no studies have been performed to evaluate the effects of exercise on a DACD. Therefore, future research (cross-sectional, longitudinal and interventional studies) is needed for the evaluation of the effects of exercise and training on the cognitive function in T1D patients.

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