Introduction

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.
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 with 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 [53,55,72-80].

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 electroencephalogram (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 [7,83] 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 [7,83]. 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
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$_\text{r}$) perform worse on motor speed and psychomotor efficiency [J Diabetes Metab 2013; S10:006. doi:10.4172/2155-6156.S10-006]

Patients with lower HbA$_\text{r}$ levels have a significant smaller white matter (WM) volume than diabetic controls without microvascular complications [66].

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 deregulation of proinflammatory cytokines [92]. The key target of RAGE is nuclear factor $\kappa$B (NF-$\kappa$B), both (RAGE and NF-$\kappa$B) are up-regulated in the hippocampus of rats during hyperglycaemia. Up-regulation of RAGE and NF-$\kappa$B is accompanied by an up-regulation of inflammatory factors such as TNF-$\alpha$, IL-1$\beta$, 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 unmitting 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, using rats [17] showed that c-peptide replacement prevented the up regulations of RAGE and NF-$\kappa$B. Consequently, TNF-$\alpha$ 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 hyperglycaemia 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 hyperglycaemia or even episodes of hypoglycaemia 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 hyperglycaemia 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 VO2max) could assure that blood levels stayed within acceptable ranges. They concluded that venous blood glucose levels decreased more whenCHO 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 hypoglycaemia. 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 VO2max) 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 Hba1c [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 Hba1c. Thus, training once a week might not be adequate to improve Hba1c levels. For example, Huttunen et al. [133] performed an exercise intervention of 45 minutes, 1 time...
per week during 12 weeks and HbA1c levels were not affected by the intervention program. The duration of the training period is also an important influencing factor for decreasing HbA1c. HbA1c levels decreased significantly only in training studies that lasted for more than 3 months. The frequency (times/week) of training will also influence the HbA1c levels [100]. Besides this, baseline glycaemic control is also an important predictor of HbA1c improvement due to training. HbA1c decreases significantly more in T1D individuals with poor glycaemic (> 8% HbA1c) control compared to individuals with good glycaemic control (<8% HbA1c) [100]. Lehman et al. [134] demonstrated only a slight decrease in HbA1c 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 HbA1c, 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 54.4kJ/kg(13.0kcal/kg) per day, which is larger than adipose tissue at 18.8kJ/kg (4.5kcal/kg) [140]. A greater muscle mass would thus consume more glucose and therefore could affect glycaemic control.

![Table 1](https://example.com/table1.png)

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

1. **Reference**
2. **No. of Subjects (males)**
3. **Age (ys)**
4. **HbA1c (%)**
5. **Intervention**
6. **Outcome**

### Example:

| Reference       | No. of Subjects (males) | Age (ys) | HbA1c (%) | Intervention | Outcome |
|-----------------|-------------------------|----------|-----------|--------------|---------|
| Heyman et al.   | 7 T1D (7) 7 CG          | 10.5 ± 0.3 | 0.92 ± 0.2 | Evaluating aerobic fitness during an incremental maximal test and Aerobic power PWC170. [IA-, DA-]. [PP]. Exercise ~ 2.25 h after insulin injection. | - T1D pre-pubertal boys showed a significant ↓ in blood glucose during exercise. |
| Poortmans et al. | 17 T1D (17) 17 CG (17)  | 16.2 ± 0.7 | 68.3 ± 3.1 | 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. |
| Yamanouchi et al. | 6 T1D (3)             | 42.7 ± 13.6 | 14.8 ± 7.5 | A 30-min session of moderate continuous training (40% of VO2max). [IA-, DA-]. [PP]. | - Capillary glucose level significant ↓ |
| Zinman et al.   | 16 T1D (10) 30 (22-43) | NA       | 27.2 ± 9.4 | A 30-min session of moderate continuous training (40% of VO2max). [IA-, DA-]. [PP]. | - Blood glucose levels significant ↓ when exercise is performed before breakfast, but not when exercise is performed before breakfast. |
| Zinman et al.   | 13 T1D (7) 30.0 ± 1.8  | 10.7 ± 0.3 | 37.6 ± 3.2 | A 45-min session of aerobic exercise (60-85% of their VO2max). [IA-, DA- (daily routines)]. [PP]. Exercise ~ 1h 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 meal); [PP]: Post Prandial (during 4h after meal); [FS]: Fasting State (> 12h after meal); HbA1c: Glycaeted Haemoglobin; VO2max: Maximal Oxygen Uptake; PWC: Physical Working Capacity.*
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 HbA1c 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 Bernardini et al. [144] did not show a significant decrease of HbA1c levels, while the study of Bernardini et al. [142] showed a large, significant decrease in HbA1c. 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 HbA1c levels were not influenced by long term High Intensity Training (HITT).

From the above studies, the following guidelines can be for the maintenance of improved chronic glycemic 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 VO2max) 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 HbA1c 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 glycemic 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 glycemic 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 HbA1c (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 dentate gyrus [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-1 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-1 may be partially accomplished by modulating the precursor to the mature BDNF.
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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); HbA1c: Glycaeted Haemoglobin; VO2max: Maximal Oxygen Uptake; VO2peak: Peak Oxygen Uptake; HRmax: Maximum Heart Rate

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

| Reference                        | No. of Subjects (males) | Age (ys) | HbA1c (%) (pre/post) | Insulin doses/day | Intervention                                                                 | Outcome                                                                                                                   |
|----------------------------------|-------------------------|----------|----------------------|-------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Huttunen et al. 1989 [130]       | 34 (20) EG 16 CG        | 11.9     | 9.8 ± 3.2 to 10.5 ± 2.5 | CG 9.4 ± 2.1 to 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]. |
|                                  |                         | (8-17)   |                      |                   |                                                                             | - Blood glucose and glucosuria did not change significant HbA1c levels |                                                                                                                              |
|                                  |                         |          |                      |                   |                                                                             | - VO2max (pre/post exercise): 40.3 ± 7.2 to 43.8 ± 8.6 ml/min.kg⁻¹ |                                                                                                                              |
| Rowland et al. 1985 [131]        | 14 T1D (7)              | 9-14     | 9.9 ± 1.4 to 10.1 ± 1.1 | NA                |                                                                             | 1h, 3/wk, 12 wk aerobic (running/walking) exercise. [DA+, IA-]. [PAS, PP, FS = NA]. | - VO2max ↑sign (38.4 ± 4.6 to 41.9 ± 6.0 ml/min.kg⁻¹) |                                                                                                                              |
|                                  |                         |          |                      |                   |                                                                             | - HbA1c 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 to 8.2 ± 1.4 | NA                | 12 wks, 3/wk aerobic (40-60% VO2max), 30 min. [IA/DA NA]. [PAS, PP, FS = NA]. | - 9 month FU aerobic exercise group had less HbA1c levels than self-directed group. | - No changes in VO2max. |                                                                                                                              |
| Bernardini et al. 2004 [142]     | 91 T1D (50)             | 14.8 ± 2.7 | < 60 min/wk, 8.9 ± 0.5 to 120-360 min/wk, 8.3 ± 0.4 to 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 HbA1c (60 min significant with 120-360 min and 360-480 min). |                                                                                                                              |
| Marrero et al. 1988 [125]        | 10 T1D (6)              | 13.3 ± 2.1 (12-14) | Pre/post: 10.1 ± 1.9 to 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]. | - HbA1c levels ↓ significant | - VO2max ↓significant (40.4 ± 8.8 to 44.9 ± 12.9 ml/min.kg⁻¹) |                                                                                                                              |
| Michaliszyn et al. 2011 [126]    | 12 T1D (6)              | 12.7 ± 2.1 (9-15) | Pre/post: 8.3 ± 1.3 to 7.9 ± 1.4 | 3.6 ± 0.6 IU.day⁻¹ | High volume, low intensity program → 60 min, <75% of HRmax 2 x 5 days, 3/day, exercise camp for children. [IA/DA-]. [PP] | - HbA1c did not change significant No measurement of VO2max. | - HbA1c levels ↓ significant |                                                                                                                              |
| Ruzic et al. 2007 [127]          | 20 T1D (NA)             | 12.8 ± 2.1 (9-16) | Pre/post: 8.3 ± 1.3 to 7.9 ± 1.4 | 0.9 ± 0.2 IU.kg⁻¹. day⁻¹ | High volume, low intensity program → 60 min, <75% of HRmax 2 x 5 days, 3/day, exercise camp for children. [IA/DA-]. [PP] | - HbA1c levels ↓ significant | - VO2max ↓significant (40.4 ± 8.8 to 44.9 ± 12.9 ml/min.kg⁻¹) |                                                                                                                              |
| Sideravicui et al. 2006 [128]    | 19 T1D (0)              | 14-19 | 8.5 ± 0.4 to 7.8 ± 0.3 | Short term: 26.4 ± 1.8 IU.day⁻¹ | Long term swim (aerobic training): 45 min, 2/wk, 14 wks. [IA/DA NA]. [PAS, PP, FS = NA]. | - HbA1c levels ↓ significant | - VO2max increased levels were shown. |                                                                                                                              |
| Laaksonen et al. 1999 [120]      | 20 T1D (20)             | 32 ± 5.7 | Pre/post: 8.2 ± 1.1 to 8.0 ± 1.0 | Pre/post training: 0.7 ± 0.2 to 0.7 ± 0.2 IU.kg⁻¹.day⁻¹ | 1 wk, 20-30 min, 50-60% VO2max gradually increased to 12-16 wks, 30- 60 min, 3-5wk, 60-80% VO2max aerobic training program. [IA/DA NA]. [PAS, PP, FS = NA]. | - VO2max ↑significant (43.4 ± 6.0 to 46.1 ± 6.6 ml/min.kg⁻¹) | - HbA1c ↑with training and compared to control group. |                                                                                                                              |
| Lehmann et al. 1997 [121]        | 20 T1D (13)             | 33 ± 7.7 (22-48) | 7.6 ± 4.4 to 7.5 ± 4.0 | VO2max (pre/post) | VO2max (pre/post exercise) 24h did not change significant | - Total insulin (IU/day) ↓ significant | - HbA1c did not change significant | - VO2max increased significant (2914 ± 924 to 3092 ± 905 mmin/ml). |                                                                                                                              |
| Ramalho et al. 2006 [122]        | 7 T1D (2)               | 19.8 ± 5.1 | 8.7 ± 1.6 to 9.8 ± 1.8 | 0.95 ± 0.3 to 0.75 ± 0.3 IU.kg⁻¹.day⁻¹ | 40 min run or walk, first 2 wks: 60-70% HRmax, 3-6th week= 70-80% HRmax, 7-12 weeks= 70-90% HRmax, 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 HbA1c increased. | - Self-monitored blood glucose levels, measured before and after each session, showed a significant ↓ post compared to pre exercise training. |                                                                                                                              |
| Wollberg – Henrikson, 1986 [123] | 6 EG (NA) 7 CG (NA)     | 63 ± 2.9 (35 ± 2.6) | 10.4 ± 1.5 to 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]. | - VO2max ↑significant (pre/post training: 30.2 ± 2.1 to 32.7 ± 2.1 ml/min.kg⁻¹) | - HbA1c did not change significant after training |                                                                                                                              |
| Zinnan et al. 1984 [124]         | 13 T1D                  | 30.0 ± 1.8 | 10.7 ± 0.3 to 10.3 ± 0.8 | 37.6 ± 3.2 IU.day⁻¹ | 45 min aerobic exercise, 3/wk, 12 wks (60-85% of their VO2max), 2x/day. [IA/DA- (daily routines)]. Exercise → 45 -13 min after insulin injection. | - VO2peak increased sign (33.8 ± 1.7 to 40.0 ± 4.0 ml/min.kg⁻¹) | - VO2max did not significant change |                                                                                                                              |

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. Li et al. [147] 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-a (TNF-a)) [172, 173], but simultaneously cytotoxic 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 impairment targeted at reducing inflammation and promoting (cognitive) recovery have been suggested. Exercise has been found to promote neurogenesis [92] and reduces the severity of hippocampal apoptosis and neuronal loss in T1D rats. They found a significant 63% decrease in the hippocampal system. These changes were preceded and accompanied by a significant 63% down-regulation of the hippocampal IGF system.

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

| Reference            | N° of Subjects (males) | No of Subjects | Age (yr) | Characteristics | Intervention | Outcome                  |
|----------------------|------------------------|----------------|----------|-----------------|--------------|--------------------------|
| Durak et al. 1990    | T1D (8)                | 31 ± 3.3       | 6.9 ± 1.4 | 58.8 ± 0.9      | 3 days, 10 days | HbA1c and glucose levels ↓ significant |
| Ramalho et al. 2006  | T1D (1)                | 20.8 ± 4.7     | 7.2 ± 1.2 | 8.7 ± 0.8       | 2 days, 15 days | HbA1c and glucose levels ↓ 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; [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, PP, FS = NA]. Exercise ~ 5h after insulin injection.**

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

| Reference            | No of Subjects (males) | N° of Subjects | Age (yr) | Characteristics | Intervention | Outcome                  |
|----------------------|------------------------|----------------|----------|-----------------|--------------|--------------------------|
| Bernardini et al. 2004 | T1D (9)                | 34 ± 2.7       | 60 min exercise/ wk: 8.9 ± 0.5 | NA | 20 wks, 2/wk, 70 min, aerobic and strength group. Aerobic part: 60-75% of HRpeak. Strength training: 20 RM ≥ 12 RM, 3 sets, 10 repetitions, 60 sec rest. [IA+, DA+]. [PAS, PP, FS = NA]. |
| D’Hooge et al. 2011 [141] | T1D (8)                | 14.1 ± 0.5     | 7.9 ± 1.3 | 7.2 ± 1.2       | 20 wks, 2/wk, 70 min, aerobic and strength group. Aerobic part: 60-75% of HRpeak. Strength training: 20 RM ≥ 12 RM, 3 sets, 10 repetitions, 60 sec rest. [IA+, DA+]. [PAS, PP, FS = NA]. |
| Heyman et al. 2007 [144] | T1D (9)                | 15.9 ± 0.1     | 7.3 ± 0.9 | 8.7 ± 0.7       | 22 ± 2h + 25x 1 h of training during 6 months of aerobic and strength training in adolescent girls. [IA+ DA+]. [PAS, PP, FS = NA]. |
| Mosher et al. 1998 [142] | T1D (10)               | 17.2 ± 1.2     | Pre – Post EG: 7.7 ± 1.26 | 10.2 ± 0.2 | 45 min, 3/wk, 12 wks. Aerobic circuit training + strength training. [IA-/DA NA]. |

*Data presented as mean ± SD; N° of Subjects (males) = total number of subjects and the number between brackets are the number of males; [P]: Post Absorptive State; [FS]: Fasting State (> 12h after meal); [PP]: Post Prandial (during 4h after meal); [IA]: Insulin Advice before/after Exercise; [DA]: Dietary Advice before/during or after Exercise; ↓: Decrease; [PAS, PP, FS = NA]. Exercise ~ 5h after insulin injection.**

**Table 2: Effects of strength training on blood glucose levels in T1D patients. (Table based on [100]).**

| Reference            | N° of Subjects (males) | N° of Subjects | Age (yr) | Characteristics | Intervention | Outcome                  |
|----------------------|------------------------|----------------|----------|-----------------|--------------|--------------------------|
| Durak et al. 1990    | T1D (8)                | 31 ± 3.3       | 6.9 ± 1.4 | 58.8 ± 0.9      | 3 days, 10 days | HbA1c and glucose levels ↓ significant |
| Ramalho et al. 2006  | T1D (1)                | 20.8 ± 4.7     | 7.2 ± 1.2 | 8.7 ± 0.8       | 2 days, 15 days | HbA1c and glucose levels ↓ significant |

*Data presented as mean ± SD; N° of Subjects (males) = total number of subjects and the number between brackets are the number of males; [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, PP, FS = NA]. Exercise ~ 5h after insulin injection.**

**Table 1: Effects of strength training on blood glucose levels in T1D patients. (Table based on [100]).**

*Data presented as mean ± SD; N° of Subjects (males) = total number of subjects and the number between brackets are the number of males; [P]: Post Absorptive State; [FS]: Fasting State (> 12h after meal); [PP]: Post Prandial (during 4h after meal); [IA]: Insulin Advice before/after Exercise; [DA]: Dietary Advice before/during or after Exercise; ↓: Decrease; [PAS, PP, FS = NA]. Exercise ~ 5h after insulin injection.**

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

**Table 3: Effects of strength training on blood glucose levels 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 angiogenesis in 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, it could prevent or ‘slow down’ a DACD in T1D. Figure 3 gives an overview of the possible pathways and interconnections 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 neurotransmitters 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 HbA1c 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
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 hyperglycemia (biochemical and neurochemical features), chronic hyperglycaemia (via the polyol 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 glycemic control. The addition of brief bouts of high-intensity, sprint-type exercise to aerobic exercise can acutely minimize the risk of sustaining a hypoglycemic episode. On the level of chronic glycemic control; regular aerobic training is a favorable tool for the improvement of glycemic control; regular aerobic training is a favorable tool for the improvement of a Type 1 DACD?

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

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