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Cajsa Tonoli

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Vrije Universiteit Brussel

FACULTY OF PHYSICAL EDUCATION AND PHYSIOTHERAPY  
DEPARTMENT OF HUMAN PHYSIOLOGY AND SPORTS MEDICINE



# Diabetes-Associated Cognitive Decline, Is There a Role for Exercise?

A study on the effects of physical activity and exercise on neurotrophic markers and cognitive function in type 1 diabetes

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Cajsa Tonoli

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Doctoral dissertation submitted in fulfilment of the requirements for the degree of Doctor in Rehabilitation Sciences and Physiotherapy - 2014

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## List of Abbreviations

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AGE = advanced glycation end products

AD = alzheimer disease

BBB = blood-brain barrier

BDNF = brain-derived neurotrophic factor

BMI = body mass index

CBF = cerebral blood flow

CI = confidence interval

CNS = central nervous system

CME = continuous moderate Exercise

DA = dietary advice before/during or after exercise

DACD = diabetes-associated cognitive decline

ECG = electrocardiogram

ELISA = enzyme-linked immunosorbent assay

EOD = early onset disease

ES = effect size

GC = glycaemic control

GH = growth hormone

HbA<sub>1c</sub> = glycaeted haemoglobin

HIE = high intensity intermittent exercise

IGF-I = insulin-like growth factor-I

IL = inter leukine

IQ = intelgence quotient

IR = insulin receptor

iv = intra-venous

LOD = late onset disease

MRI = magnetic resonance imaging

NF- $\kappa$ B = nuclear factor  $\kappa$ B

NGF = nerve growth factor

NMDA = N-methyl-D-aspartate

NO = nitric Oxide

NOS = nitric oxide synthases

PA = physical activity

RAGE = receptor of Advanced Glycation End Products

RIA = radio immunoassay

ROS = reactive oxygen species

RPE = rates of perceived exertion

SD = standard deviation

SEM = standard error of the mean

SIGN = scottish intercollegiate guidelines network checklists

SMT = spatial memory task

STZ = streptozotocin

T1D = type 1 diabetes

T2D = type 2 diabetes

TMT A/B = trail making test part A/B

TNF- $\alpha$  = tumor necrosis factor alfa

VEGF = vascular endothelial growth factor

VO<sub>2max</sub> = maximal oxygen uptake

VO<sub>2peak</sub> = peak oxygen uptake

W<sub>max</sub> = maximal power output (Watt)

LIST OF ABBREVIATIONS

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CHAPTER 1.  
GENERAL INTRODUCTION

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Partly based on:



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**Review Article**

**Open Access**

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

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## 1.1 When diabetes meets the brain...

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Type 1 Diabetes (T1D) is a chronic autoimmune disease in which destruction or damage of the beta-cells in the islets of Langerhans is followed by insulin deficiency (Alberti and Zimmet, 1998, van Belle et al. 2011). It occurs very likely as a result of a trigger; e.g. viral infections, bacterias, genes, etc. (van Belle et al. 2011). T1D is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action, or both.

The long-term effects of T1D include progressive development of specific microvascular and macrovascular complications. Microvascular complications include retinopathy with potential blindness, nephropathy that may lead to renal failure, peripheral neuropathy with risk of foot ulcers, amputation and features of autonomic neuropathy, including sexual dysfunction (Alberti and Zimmet, 1998). Macrovascular complications include cardiovascular, peripheral vascular and cerebrovascular disease (Alberti and Zimmet, 1998). Furthermore, T1D can negatively influence brain structure and function (Brands et al. 2005), leading the cognitive dysfunction, a complication that is less regularly assessed in clinical follow-up of these patients. As different terms for cognitive dysfunction are used in literature (e.g. cerebral impairment, central neuropathy, cognitive dysfunctions), the term 'diabetes-associated cognitive decline' (DACD) was proposed to include all terms (Mijnhout et al. 2006). This term is not suggestive of a particular pathogenesis, but merely describes a state of mild to moderate cognitive impairment (Mijnhout et al. 2006). Although many studies concerning the cognitive performance in T1D exist, several questions on its mechanisms of action remain to be answered and as a consequence, this issue remains controversial.

The clearest evidence of a DACD has been shown by a meta-analysis of the existing literature in children (Gaudieri et al. 2008, Blasetti et al. 2011) and adults (Brands et al. 2005). However, none of these studies compared the differences between a DACD in children and adults with T1D. Therefore we performed a meta-analysis of the literature to (1) make an update of the existing literature and (2) compare differences in children and adults with T1D (see chapter 2).

## 1.2 Mechanisms of Diabetes Associated Cognitive Decline

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As glucose is the major fuel for brain function and brain glucose utilization accounts for 25% of the total glucose utilization (van der Heide et al. 2003, Watson and Craft, 2004), it is not inconceivable that disturbances of glucose levels and/or disturbances in the transport of glucose affect brain function in T1D. Glucose crosses the blood brain barrier (BBB) through several glucose transporters: facilitative sodium independent transporters (GLUT) and sodium dependent glucose co-transporters (van der Heide et al. 2003). The GLUT1 transporter (insulin insensitive), localized on BBB endothelial cells and cortical membranes, is the major transporter of glucose across the BBB (van der Heide et al. 2003, Watson and Craft, 2004). The GLUT3 transporter (insulin insensitive) is considered as the main neuronal glucose transporter since it is located on neurons (van der Heide et al. 2003, Watson and Craft, 2004). Finally, the insulin sensitive GLUT4 and GLUTx1 (also known as GLUT8) transporters are expressed in the cerebellum, sensorimotor cortex, hippocampus, pituitary, and hypothalamus of rats (Watson and Craft, 2004). Three possible causes of a DACD are described in literature: severe episodes of hypoglycaemia, chronic hyperglycaemia and C-peptide/ insulin deficiencies, as shown in figure 1.



## Mechanisms of Cognitive Decline in T1DM

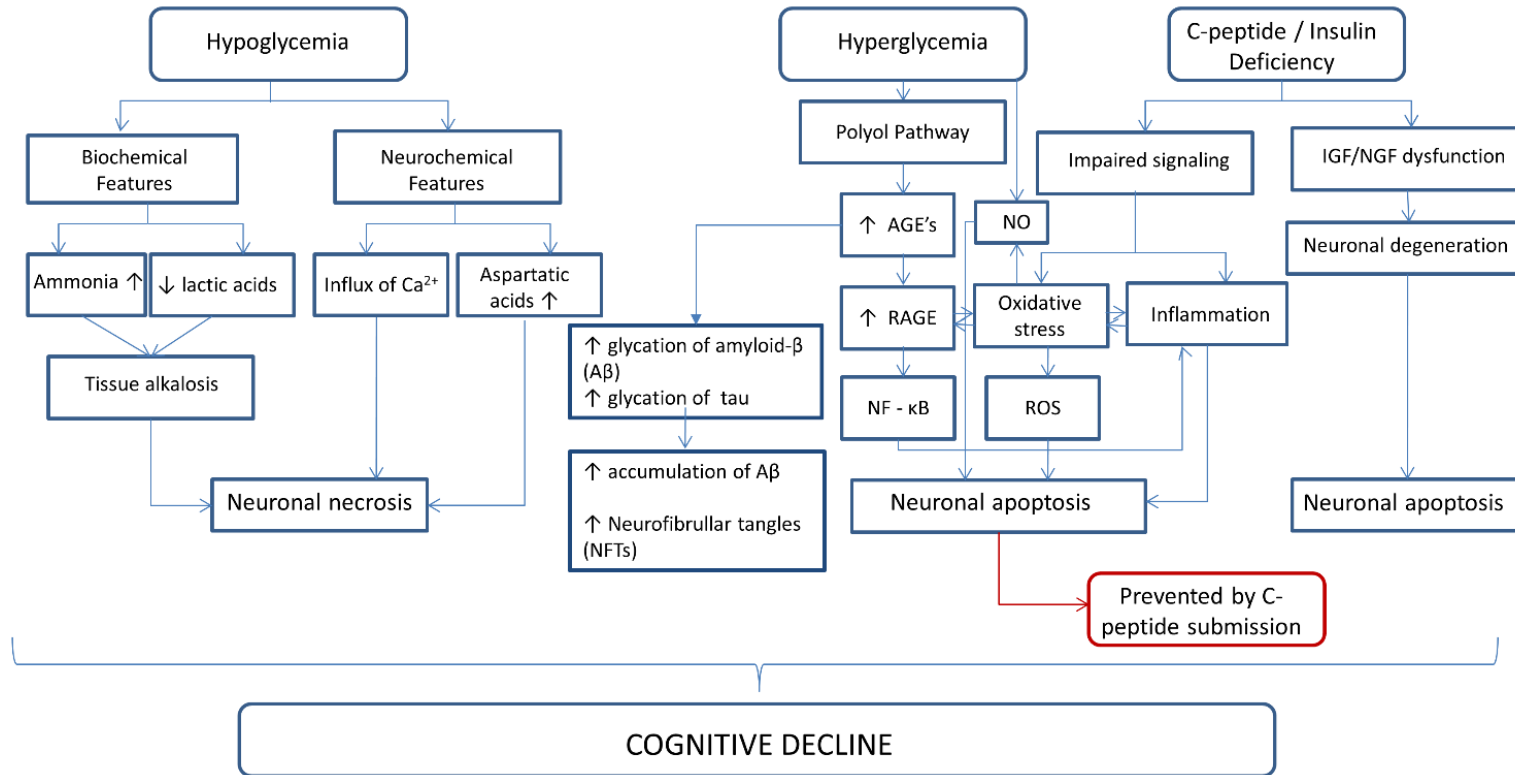


Figure 1 Mechanisms of a DACD

### 1.2.1 HYPOGLYCAEMIA

Chronic hypoglycaemia increases the expression of GLUT1 mRNA and protein at the BBB (Kenner et al. 1995) and the insulin sensitive GLUT4 transporter in the brain (van der Heide et al. 2003), suggesting a compensatory mechanism to increase glucose transport over the BBB when experiencing chronic hypoglycaemia (Kenner et al. 1995). Nonetheless, when the brain becomes hypoglycaemic, it can cause neuronal necrosis through 2 different pathways: a neurochemical and biochemical pathway. At the neurochemical level, low blood glucose levels will alter ion pump activity and disturb cellular homeostasis (Auer, 2004, Ryan et al. 2005, Brands et al. 2004), 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, what may lead to mitochondrial damage and eventually cell death (Auer, 2004, Ryan et al. 2005, Brands et al. 2004). At the same time the decreased flux of glucose to the brain results in a fourfold increase in amino acid concentrations (mostly aspartate) (Auer, 2004), thereby activating neuronal necrosis (Ryan et al. 2005). In the biochemical pathway, the cell catabolizes proteins and deaminates amino acids, what causes increased ammonia production. Ammonia, 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) (Auer, 2004). However, due to a reduced production of lactate during hypoglycaemia, it is impossible to lower tissue pH, what may reinforce alkalosis (Auer, 2004). This alkalosis might in turn explain why selective neuronal necrosis occurs during hypoglycaemia (Auer, 2004).

#### 1.2.1.1 Alterations in cerebral vasoreactivity to hypoglycaemia and microvascular complications in T1D

It is known that structural microvascular abnormalities in T1D, lead to decreased vasoreactivity (Johnson et al. 1982). However, this vasoreactivity is an important compensatory mechanism to limit neuronal damage during hypoglycaemia (Johnson et al. 1982). 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 a bigger risk for

sustaining a DACD. Consequently this can explain why T1D patients suffering from diabetic complication(s) show a decreased performance in several cognitive domains compared to T1D subjects without complications (Ryan et al. 1993, Ferguson et al. 2003).

### *1.2.2 HYPERGLYCAEMIA*

In non-diabetic subjects hyperglycaemia down-regulates glucose transport over the BBB. The results in diabetic animals, however, are inconsistent, with no significant changes in glucose uptake and GLUT1 expression (Heidenreich and Kummer, 1996, Lustig et al. 1999), or decreased mRNA and protein expression of GLUT1 and GLUT3 in streptozotocin (STZ)-induced diabetic rats (van der Heide et al. 2003). There are, however, 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. These different pathways are explained more in detail below.

In the polyol pathway, the excess amount of glucose is converted to sorbitol, which oxidizes NADPH to NADP<sup>+</sup> (Malone et al. 2008). Sorbitol may glycate nitrogens on 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 (Bermon et al. 1999). Additionally, AGEs increase proinflammatory mechanisms by the activation of the receptor of AGE (RAGE) in the vessels, resulting in increased oxidative stress and the dysregulation of proinflammatory cytokines (Hoffman et al. 2008). 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, and this is accompanied by an up-regulation of inflammatory factors such as Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), Inter Leukin (IL)-1 $\beta$ , IL-2, and IL-6 (Sima et al. 2009b). These inflammatory factors can, in turn, also enhance oxidative stress and promote apoptosis (Sima et al. 2009b). This increase in oxidative stress also leads to AGE accumulation and thus creates an unremitting cycle (Bermon et al. 1999). Poor glycaemic control may thus lead to cellular and molecular damage through inflammation and is therefore identified as a potential contributor to a DACD (Goh and Cooper, 2008).

Increased oxidative stress is also associated with the activation of nitric oxide synthases (NOS) in the brain.

The activity of NOS produces Nitric Oxide (NO), that has diverse biological activities including modulation of neurotransmission, promotion of synaptogenesis and synaptic remodelling (Love, 1999, Kaminski et al. 2002). But, the activation of NO also causes ischemia (Love, 1999), a condition in which pro-inflammatory cytokines and leukocytes are activated (Kaminski et al. 2002). Restoration of blood flow to the ischemic area results in excessive production of reactive oxygen species (ROS) (Kaminski et al. 2002), 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.

*1.2.3 INSULIN, INUSLIN-LIKE GROWTH FACTOR-I (IGF-I) AND COGNITIVE DECLINE IN T1D, A POSSIBLE LINK WITH ALZHEIMER'S DISEASE (AD)?*

Another suggested pathway by which brain function is influenced in T1D is through c-peptide/insulin deficiency. Emerging evidence suggests that insulin and IGF-I have important functions in the brain. Insulin and IGF-I are both transported across the BBB into the brain and possibly even produced locally (Frystyk et al. 2010, Park, 2001). Both insulin and IGF-I, have been shown to stimulate motor, sensory and sympathetic neuron proliferation and differentiation, enhance motor neuron sprouting, increase myelination and inhibit demyelination, reduce neuron apoptosis during normal development, enhance axonal regeneration after injury and protect neurons from toxicity induced by chemicals (Thraikill, 2000). However, T1D is associated with reduced levels of IGF-I.

AD and T1D have several shared molecular processes underlying degenerative developments in the brain, including insulin deficiency. These degenerative developments in the brain could consequently cause cognitive dysfunction in both, T1D and AD. Potential mediators of impaired insulin responsiveness in AD are reduced local central nervous system (CNS) levels of insulin, impaired insulin or IGF-I responsiveness binding to its receptor due to lowered affinity or decreased receptor expression or, impaired signaling through insulin stimulated pathways (Krankel et al. 2002). To our knowledge, there is currently no proof of reduced insulin sensitivity nor a decrease in insulin receptor affinity in the brain in patients with T1D. Furthermore, an increased saturable transport of insulin across the BBB was detected in STZ-induced diabetic rats (Widdowson et al. 2009). This is in contrast to the inhibited insulin transport seen in an obese T2D rat model; the Zucker rat (Widdowson et al. 2009).

Nonetheless, we might assume that T1D and AD have some similar mechanisms. The AD-affected brain reveals neuronal loss and accumulation of neurofibrillary tangles and neuritic plaques in which insulin and IGF-I play their role, surrounded by a tract of neuroinflammation (Gasparini and Xu, 2003). The latter can be associated with cognitive dysfunctions in AD (Gasparini and Xu, 2003).

#### 1.2.3.1 Neurofibrillary Tangles

Insulin and IGF-I promote their function via phosphorylation of subunit proteins (Krankel et al. 2002). Phosphorylation of *tau* is a normal physiological process required for cytoskeleton assembly and stabilization (Krankel et al. 2002). In vitro experiments demonstrated that *tau* phosphorylation is normally regulated by insulin and IGF-I, through the inhibition of the activity of glycogen synthase kinase-3 (GSK) - 3 $\beta$  (Schulze et al. 2002). Impaired insulin or IGF-I signaling results in increased GSK- 3 $\beta$  activity, which leads to hyperphosphorylation of tau (Schulze et al. 2002). Hyperphosphorylated tau forms abnormal filaments and aggregates into neurofibrillary tangles (NFTs) (Gasparini and Xu, 2003). Hyperphosphorylated tau fails to be transported into axons and instead promotes oxidative stress that can cause cell death, mitochondrial dysfunction or necrosis (Krankel et al. 2002).

#### 1.2.3.2 Neuritic plaques.

The major factor leading to increased brain levels of Amyloid  $\beta$  (A $\beta$ ) in AD patients is increased tissue accumulation rather than overproduction (Stokes et al. 2010), forming neuritic plaques (Gregory et al. 2013). While A $\beta$  peptides impair neuronal activity, including the impairment of synaptic function and the induction of cell death, the neuritic plaques are linked to the induction of inflammatory processes that cause neurotoxicity (for review see: Gregory et al. (2013)). Insulin and IGF-I have a direct effect on the metabolism and clearance of A $\beta$  from neurons (Stokes et al. 2010, Gasparini and Xu, 2003). Insulin has the potential to regulate brain A $\beta$  levels by at least 2 different pathways: (1) a direct stimulatory action of insulin on cellular clearance of A $\beta$  (Hambrecht et al. 2002) and (2) through the inhibition of A $\beta$  breakdown through the insulin-degrading enzyme.

Carro and colleagues (2001) showed that subcutaneous chronic infusion of IGF-I to aged rats decreased the levels of A $\beta$  in hippocampus and cortex to the levels found in young rats, while increasing the

cerebrospinal fluid content of A $\beta$ . IGF-I appears to stimulate brain amyloid elimination through a compound process that includes stimulation of neuronal A $\beta$  release and its subsequent clearance from the brain parenchyma (Hambrecht et al. 2002). Conversely, mice with a liver-specific depletion of the IGF-I gene showed prematurely increased cerebral levels of A $\beta$  compared with control mice (Stokes et al. 2010).

### 1.2.3.3 Type 1 Diabetes, is there a link with Alzheimer Disease?

Hoyer (2002, 2004) was among the first to suggest that reduced levels of brain insulin may precipitate a cascade resulting in disturbances in cellular glucose, impaired membrane function, accumulation of amyloidogenic derivatives and hyperphosphorylation of *tau*, i.e. that AD may represent a brain form of diabetes (Krankel et al. 2002).

Patients with T1D exhibit increased secretion of GH but have complex tissue-specific changes of IGF binding proteins (IGF-BP) and decreased circulating levels of IGF-I (Thraillkill, 2000, Janssen et al. 1997, Chatzigeorgiou et al. 2009). Reduced mRNA levels of IGF-I, IGF-II, IGF-IR, and IR were found in hippocampi of 2-month diabetic BB/Wor rats compared to age-matched control rats (Li et al. 2002a). In humans, decreased expression of IGF-I in the hippocampus, cerebellum, pons and basal ganglia was seen postmortem in two patients with early onset of diabetes. This finding was associated with severe neuronal loss in the hippocampus and frontal cortex (Hoffman et al. 2008). Furthermore, reduced levels of IGF-I in the brain may cause reduced clearance of A $\beta$ , which consequently increases NFTs in the diabetic brain. Further research is needed to confirm last mentioned hypothesis.

Chronic hyperglycaemia contributes to higher levels of AGEs and consequently RAGEs, and thus may lead to an increase in glycation of A $\beta$  and increased glycated *tau*. This will in turn cause neuronal apoptosis and consequently a cognitive decline. However, the replacement of C-peptide, a product of pro-insulin cleavage, generated in pancreatic beta-cells as a part of normal insulin production, prevents the up regulation of RAGE and NF- $\kappa$ B. Indeed, it was shown by a study of Sima and colleagues (2009a) that after the replacement of C-peptide, the levels of TNF- $\alpha$  as well as the pro- and anti-inflammatory interleukins normalized in the hippocampus of diabetic BB/Wor rats.

In summary, several mechanisms are described concerning the effects of severe hypoglycaemia on brain function in T1D including through a neurochemical and biochemical pathway, and chronic hyperglycaemia through the polyol pathway. Furthermore, hyperglycaemia will increase AGEs, which in turn increase the glycation of  $A\beta$  and *tau*, leading to NFT's and neuritic plaques. NFT's and neuritic plaques are known as degenerative developments in the brain of AD, leading to difficulties in cognitive function. Insulin and IGF-I are associated with clearance of these products, however are both reduced (except with exogenous insulin) in T1D and reduced or insensitive in AD. Therefore, T1D can indeed be linked to AD through insulin and/or IGF-I deficiencies (see figure 2 for a more schematic illustration).

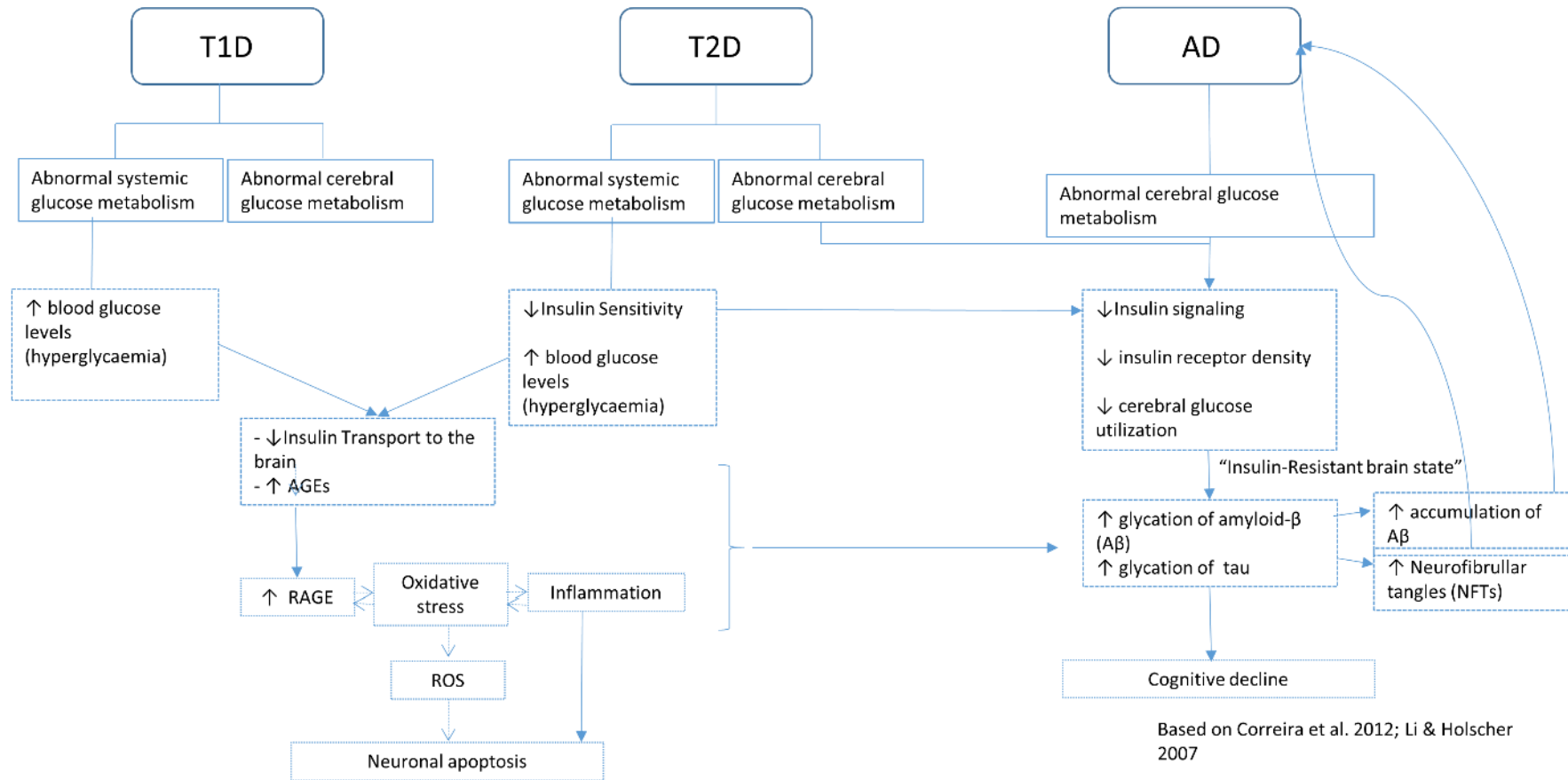


Figure 2 Schematic illustration of the pathological mechanisms linking diabetes and AD



## 1.4 Cognitive Decline, Is there a role for exercise?

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Research indicated that higher levels of physical activity (PA) are effective in maintaining and enhancing physical but also cognitive functioning in healthy adults. PA may enhance cognitive vitality and is able to delay the onset of AD and dementia in elderly (Hillman et al. 2008, Dall et al. 2001, Dregan and Gulliford, 2013, Yaffe et al. 2001, Podewils et al. 2005).

### 1.4.1 LINK BETWEEN EXERCISE AND COGNITIVE FUNCTION IN NON-DIABETIC POPULATIONS.

#### 1.4.1.1 Effects of acute exercise on cognitive performance in non diabetic subjects

Acute exercise leads to small improvements in cognitive task performance (Lambourne and Tomporowski, 2010, Hillman et al. 2011, Netz et al. 2007). Most research on acute exercise has focused on changes in cognition as a result of the exercise mode, stimulus, including exercise intensity, duration and type, with the assesment of cognitive function pre and post exercise. Improved cognitive performance due to exercise was found in several studies in which participants exercised at 40 – 60% of the  $VO_{2max}$  (Brisswalter et al. 2002). In aerobically fit individuals, however, significant improvements in cognitive performance have also been observed for higher intensities ( $> 80\% VO_{2max}$ ). The latter can be addressed to better capacities to adapt to exercise at higher intensities than untrained subjects (Brisswalter et al. 2002). The ideal *exercise intensity* necessary for optimal cognitive performance depends consequently on the characteristics of the population that exercises. Furthermore, the meta-anaysis of Lambourne and Tomporowski (2010) showed that *exercise modes* significantly influence cognitive performance, with smaller effects from studies that involved a running or treadmill modality compared to the studies in which subjects had to cycle.

Furthermore, an interaction between the *type of the cognitive* task and exercise intensity has been identified. Smaller effects of exercise are observed on tasks measuring processing speed compared to tasks measuring memory functions (Lambourne and Tomporowski, 2010). Besides, decreases in cognitive performance are observed during all ranges of intensities in simple tasks (e.g. perceptual tasks), while increases in cognitive performance are detected for more complex tasks at moderate and high intensities (Brisswalter et al. 2002).

1.4.1.2 Effects of chronic exercise (training) on cognitive performance in non diabetic subjects

Cross-sectional, longitudinal training, and neuroimaging studies support a positive association between PA level, aerobic fitness or training and enhanced performance in cognitive tasks (Voss et al. 2011, Hillman et al. 2008, van Praag, 2008, Lambourne and Tomporowski, 2010, Kramer et al. 2006, Stroth et al. 2009, Kamijo et al. 2010, Themanson et al. 2008), especially in children and elderly with and without symptoms of AD or depression (Voss et al. 2011, Colcombe and Kramer, 2003a, Hillman et al. 2008, Kramer et al. 2006).

In the meta-analysis of Colcombe & Kramer (2003a), examining training effects on the cognitive function, the largest positive effects were observed for executive control processes (such as planning, scheduling, working memory, inhibitory processes and multitasking), but also improved spatial memory, and speed tasks (Colcombe and Kramer, 2003a, Hillman et al. 2008). The combination of strength and aerobic training, especially for periods longer than 6 months, improves cognitive functioning to a greater degree than aerobic training alone (Colcombe and Kramer, 2003a). In some studies, a smaller effect of training is found on cognitive function in young adults. This might be explained by the fact that young adulthood (i.e., 18–35 yr) is characterized by a peak in cognitive performance (Voss et al. 2011).

It is important to note that some studies have failed to confirm this positive relationship between chronic exercise and cognitive function (Yamada et al. 2003, Wilson et al. 2002). Kramer et al. (2006) suggested that the failure to (1) distinguish between aerobic and non-aerobic activities, (2) to assess a correct duration / intensity and/or frequency, (3) the difficulty of eliminating participants with signs of dementia, (4) the collection of self-report activity data, and (5) statistical power, might explain these inconsistent associations observed over studies.

In summary, both epidemiological and experimental studies linked the effects of both acute and chronic exercise with improvements in cognitive function in (non-diabetic) children, young and older adults with accumulating evidence supporting a positive relationship between acute and chronic exercise and cognitive function. The effects of exercise (acute or training) are, to our knowledge, not yet examined in T1D.

Several mechanisms such as the acute increase of neurotransmitters in the brain, increased angiogenesis,

neurogenesis, synaptogenesis (Lista and Sorrentino, 2010) and neuroinflammatory processes (van Praag, 2008) are put forward as possible mechanisms by which exercise influences cognitive processes in the brain. Some of these processes are discussed more in detail below.

#### *1.4.2 NEUROGENESIS AND NEUROPLASTICITY*

Adult neurogenesis represents a developing process including the birth of new neurons from adult neural stem cells along with the capacity of plasticity. This includes their differentiation, maturation, migration and incorporation into the mature nervous system (Ge et al. 2008). New neurons are generated from a local population of progenitor cells located in the subgranular zone (Heidenreich, 1993). Adult neurogenesis mainly occurs in both the hippocampal dentate gyrus and olfactory bulb and has also been detected in other brain regions including neocortex and striatum (Christie et al. 2008). An integration of new adult neurons into the existing circuitry (Ge et al. 2008) is essential for specific brain functions, such as learning, memory and mood regulation (Zhao et al. 2008, Jun et al. 2012). Trophic factors that seem to influence adult neurogenesis, include basic fibroblast growth factor, epidermal growth factor, Brain-Derived Neurotrophic Factor (BDNF), IGF-I and Vascular Endothelial Growth Factor (VEGF) (van Praag, 2008).

Exercise is one of the aspects inducing and highlighting the plasticity and regenerative capacity of the adult brain (Ge et al. 2008). Animal research previously showed that voluntary wheel running (Rasmussen et al. 2009, Adlard et al. 2004, Oliff et al. 1998) and treadmill running (Liu et al. 2009, O'Callaghan et al. 2007, Huang et al. 2005) enhances neurogenesis and brain plasticity in the hippocampus (van Praag et al. 2005, Lou et al. 2008, van Praag et al. 1999, Rhodes et al. 2003, Trejo et al. 2001). A key intervention for this increased neurogenesis and neuroplasticity might be the processes in which neurotrophins (including NGF, BDNF, neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) (Donovan et al. 1995)) mediate neural plasticity (van Praag, 2008, van Praag, 2009, Cotman et al. 2007a, Dishman et al. 2006, Vaynman et al. 2004, Neeper et al. 1996). Neuroplasticity, is the capacity that enables the neuronal systems to achieve new functions by modifying the constitutive elements of their internal milieu and/ or connectivity (Vaynman, 2005), it is vital in normal development of neurons (Lou et al. 2008). Indeed, BDNF protein and mRNA are upregulated in the hippocampus after treadmill and voluntary running (van Praag et al. 2005,

van Praag et al. 1999).

#### 1.4.2.1 BDNF

BDNF, a 119-amino-acid, constructing a basic dimeric protein (Chan et al. 2008), is the neurotrophin that is most susceptible to PA (Vaynman and Gomez-Pinilla, 2005, Knaepen et al. 2010). BDNF is initially synthesized from the precursor pro-BDNF and is proteolytically cleaved to produce mature BDNF (Rosenfeld et al. 1995). BDNF acts by binding on 2 receptors: the p75 neurotrophin receptor and the tyrosine kinase B receptor (TrkB), with the highest affinity for the TrkB receptor (Huang and Reichardt, 2001, Donovan et al. 1995). BDNF has many effects on the nervous system such as neuronal growth, differentiation and repair (Huang and Reichardt, 2001).

Indirect evidence suggests that the brain is the main, but not sole source of BDNF (Rasmussen et al. 2009). BDNF can cross the BBB bi-directly (Fujimura et al. 2002, Nakahashi et al. 2000, Pan et al. 1998, Chan et al. 2008). In the periphery BDNF is expressed in tissues that are important for the regulation of energy homeostasis and metabolism (Noble et al. 2011) such as the liver, (Unger et al. 1991a) adipose tissue, skeletal and smooth muscle (Matthews et al. 2009, Unger et al. 1991b). From the moment that BDNF is synthesized, BDNF is stored in secretory granules and released in response to extracellular cues (Vaynman, 2005, Gomez-Pinilla, 2002, Neeper et al. 1996). In blood, BDNF is mostly stored in the platelets, and only a small fraction circulates in blood plasma (Lommatzsch et al. 2005, Fujimura et al. 2002). Rosenfeld and colleagues (1995) showed that serum consists of a 200-fold greater amount of BDNF compared to plasma (Rosenfeld et al. 1995). Positive correlations between blood BDNF levels and hippocampal BDNF levels were shown in rats, suggesting that blood BDNF concentrations reflect brain-tissue BDNF levels (Klein et al. 2010).

#### *Mechanisms of BDNF on brain function*

Molteni and colleagues (2002) were among the first to show that faster learning animals had higher levels of BDNF in their hippocampus. Higher peripheral levels of BDNF would be related to better brain health and decreased levels of BDNF have been related to various mental disorders such as depression, schizophrenia, AD, dementia, Huntington's disease, Parkinson disease (Aydemir et al. 2006). BDNF indeed induces neurogenesis (through neurotransmitters) and triggers neuroplasticity (long-term potentiation

(LTP)) in order to preserve essential functions such as learning and memory (Tyler, 2002, Castellano and White, 2008). The potential mechanisms are explained more in detail below.

One of the phenomena underlying synaptic plasticity is the modulation of synaptic strength due to an increase in signal transmission between 2 neurons, as exemplified by LTP (van Praag, 2008). As memories are thought to be encoded by modification of synaptic strength, LTP is widely considered as one of the major cellular mechanisms that underly learning and memory (Bliss and Collingridge, 1993). LTP is triggered by an increased release of BDNF and is induced in the exact same region of the hippocampus in which neurogenesis is stimulated (van Praag et al. 1999, Jun et al. 2012). Furthermore, transgenic animals with diminished BDNF expression lose their ability to induce LTP (Patterson et al. 1996).

The induction of LTP requires calcium influx into the postsynaptic neuron and the subsequent activation of the calcium-sensitive kinase CAMKII. Exercise leads to an increase in calcium that activates the transcriptional regulator CAMPKII (Akiyama and Sutoo, 1999, Vaynman et al. 2004). On top of that, BDNF activates CAMPKII and signal transduction cascades (MAP kinase) through binding to TrkB. This will in turn activate CREB (Vaynman and Gomez-Pinilla, 2006), leading to changes in structural proteins, enzymes, ion channels, and neurotransmitters, consequently inducing changes in the structure and function of neuronal circuitry (Vaynman, 2005). Therefore, CREB is believed to have functions in activity dependent long-term neuronal plasticity and to mediate long term memory (see figure 3 for an illustration of the mechanisms).

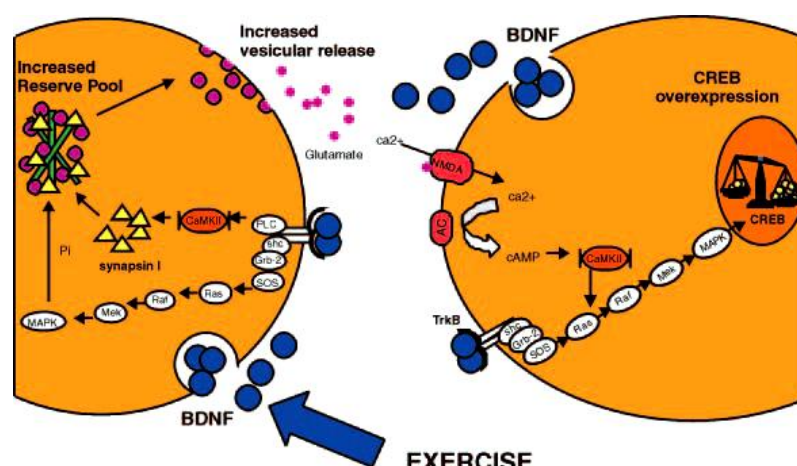


Figure 3 Potential mechanisms through which BDNF may enhance learning and memory under the action of exercise (Vaynman et al. 2004)

Besides the activation of CREB, BDNF also regulates the release of synapsin I (Vaynman et al. 2004, Cotman et al. 2007b), a presynaptic phosphoprotein that has been shown to regulate neurotransmitter release, neurite development, new presynaptic formation and axonal elongation (Vaynman, 2005). Blocking BDNF action prevents the exercise-induced increase in synapsin I, confirming that synapsin I expression depends on BDNF action during exercise (Vaynman et al. 2004). As the neurotransmitter binds to the N-methyl-d-aspartate (NMDA) receptor, a calcium permeable ion channel, LTP occurs with associated depolarization of the postsynaptic membrane (Soule et al. 2006).

LTP is divided into two phases, early LTP (which lasts for 1-2h) and late-LTP (which last for many hours). Early-LTP can be induced by a single burst of high-frequency stimulation, designed to mimic a physiological burst of neuronal activity in the hippocampus. Late-LTP, which lasts many hours, requires repeated bursts of stimulation (Allen and Dawbarn, 2006). Therefore, it is suggested that repeated episodes of increased BDNF are beneficial for long term memory function, as provided by repeated bouts of acute exercise.

*The influence of acute and chronic exercise on levels of BDNF*

In humans, a growing body of evidence suggests that a single bout of aerobic exercise increases serum (Erickson et al. 2011, Schulz et al. 2004, Ferris et al. 2007a, Gold et al. 2003b, Huang et al. 2005, Sharman et al. 2007) and plasma (Baker et al. 2010, Zoladz et al. 2008, Gustafsson et al. 2009) BDNF levels. However, some studies did not find an increase in serum or plasma BDNF levels due to aerobic exercise (Goekint et al. 2010b, Schiffer et al. 2009) or strength exercise (Goekint et al. 2010a, Correia et al. 2010, Levinger et al. 2008). Most studies concluded that peripheral BDNF increases following an acute exercise protocol, with the tendency for acute high-intensity exercise protocols to induce larger increases in BDNF concentrations than acute low-intensity exercise protocols, in both healthy subjects and persons with a chronic disease or disability (Gold et al. 2003a, Winter et al. 2007, Bekinschtein et al. 2011, Berchtold et al. 2005, Ferris et al. 2007b, Knaepen et al. 2010, Griffin et al. 2011). According to Rasmussen and colleagues (2009) the increase in peripheral BDNF after exercise is due to an enhanced release of BDNF from the brain.

BDNF concentration returns to baseline levels within 10–60 minutes post-exercise (Griffin et al. 2011), meaning there is a fast disappearance rate of circulating BDNF after the termination of exercise. This

indicates that BDNF is used or stored elsewhere and/or reflecting a reduction of BDNF release by the brain after exercise (Rasmussen et al. 2009). Both, an increased muscle uptake of BDNF after exercise (Rasmussen et al. 2009), and an increased transport to the brain are suggested (Berchtold et al. 2005).

Less clear results are found concerning the effects of training on the release of BDNF levels. Basal serum and/or plasma BDNF levels are not found to be consistently elevated after strength (Schiffer et al. 2009, Goekint et al. 2010a, Yarrow et al. 2010) or endurance training programs (Schiffer et al. 2009, Zoladz et al. 2008). In contrast to acute exercise, an inverse relationship exists between resting serum BDNF concentrations and measurements of  $VO_{2max}$  (Currie et al. 2009) and long term PA (Currie et al. 2009, Ramsbottom et al. 2010, Nofuji et al. 2008). These reduced levels of serum BDNF in more physically active individuals could reflect a more efficient uptake of serum BDNF into the CNS (Currie et al. 2009). However, experimental evidence supporting this hypotheses is lacking.

#### *BDNF, food intake & glucose/energy metabolism*

BDNF also influences multiple parameters of energy metabolism and homeostasis (Krabbe et al. 2007, Yamanaka et al. 2008b). It has been shown to induce appetite suppression (Krabbe et al. 2007), and change insulin sensitivity (Pelleymounter et al. 1995, Nakagawa et al. 2002), glucose metabolism (Nakagawa et al. 2002, Blackman et al. 1992, Ono et al. 1997, Ono et al. 2000), and lipid metabolism (Tsuchida et al. 2002).

BDNF is a major participant in the regulation of food intake, and can thus be linked to eating disorders. Reduced levels of BDNF are found in patients with bulimia nervosa and anorexia nervosa (Gamero-Villaruel et al. 2013, Perantie et al. 2008), and after hyper caloric diets (high fat and/or sugar) (Chaytor and Schmitter-Edgecombe, 2003, Molteni et al. 2002, Dhillon, 2007). BDNF-mutant mice develop mature onset obesity, characterized by a dramatic increase in body weight, increased linear growth and elevated serum levels of leptin, insulin, glucose, and cholesterol (Rios et al. 2001). Increased levels of BDNF, however, induce appetite suppression and reduced weight gain (Li et al. 2002b, De Palo et al. 2008, Perantie et al. 2008).

Previous rodent studies focused on the effects of BDNF in diabetic (obese) animals and showed that a peripheral injection of BDNF has hypoglycaemic effects by inducing hypophagia (Nakagawa et al. 2000,

Ono et al. 1997, Yamanaka et al. 2008a). In normal rats and mice, however, no significant changes in blood glucose were detected, suggesting that BDNF does not lower blood glucose levels by enhancing endogenous insulin secretion. BDNF might however ameliorate insulin resistance (Ono et al. 2000, Tonra, 1999, Nakagawa et al. 2000, Ono et al. 1997), and therefore has anti-obesic and anti-diabetic effects (Yamanaka et al. 2008a). To investigate this effect of BDNF on insulin action Nakagawa et al. (2002) injected BDNF subcutaneously to STZ-induced diabetic mice with and without insulin co-administration. The injection of BDNF without the co-administration of insulin did not reduce blood glucose concentration. When administered concomitantly with insulin, BDNF did induce a significant hypoglycaemic effect (Nakagawa et al. 2002), indicating an acute enhancement of insulin sensitivity (Nakagawa et al. 2002). BDNF co-injected with IGF-I show similar effects as the co-injection with insulin, meaning enhanced hypoglycemic actions of IGF-I and thus lowered blood glucose concentration of STZ-treated compared to IGF-I treated mice. Since IGF-I binds to the same receptor as insulin, IGF-I might mimic insulin action and thus activate insulin signaling (Nakagawa et al. 2002). In addition to its actions as a growth factor, the physiological role of IGF-I on glucose metabolism has been clarified by analyzing insulin receptor substrate (IRS) null mice. Therefore one can assume that BDNF enhances IGF-I action through the IGF-I receptor and its downstream signaling, and by this process regulates glucose metabolism in insulin-deficient STZ-treated mice (Nakagawa et al. 2002). This hypothesis needs further investigation. Tonra et al. (1999) showed that when BDNF was administered once or twice a week to non insulin-treated obese diabetic mice for three weeks, both blood glucose and HbA<sub>1c</sub> significantly reduced as compared to controls. Furthermore, the administration of BDNF prevented the progression of diabetes in early (prediabetic) db/db mice (Yamanaka et al. 2008b).

#### *BDNF, Diabetes & Cognitive function*

So far, 7 studies have shown differences in (baseline) BDNF levels in non-exercising T2D humans compared to non-diabetic controls. The conclusions of these investigations are inconsistent, reporting either decreased serum and plasma BDNF levels in T2D patients (Krabbe et al. 2007, Fujinami et al. 2008, Zhen et al. 2013, Arentoft et al. 2009) or increased serum and plasma BDNF (Suwa et al. 2006, Liu et al. 2010a, Shin et al. 2012). It has been suggested that systemic increases in BDNF might reflect compensatory



responses in the body (Arentoft et al. 2009). Indeed, increased levels of BDNF were found in newly diagnosed patients with T2D (Suwa et al. 2006), T2D with retinopathy (Liu et al. 2010b) and hemodialysis T2D patients (Shin et al. 2012).

Only one study made the link with BDNF and cognitive function in patients with T2D. Zhen et al. (2013) compared 208 patients with T2D with 212 normal controls on serum BDNF and the '*Repeatable Battery for the Assessment of Neuropsychological Status*' (RBANS). The authors found decreased serum BDNF levels in patients with T2D compared to normal controls. Furthermore, patients with T2D displayed a significantly worse cognitive performance on the RBANS total score and nearly all of its five subscales, except for the attention and visuospatial/constructional index. Moreover, serum BDNF levels were positively correlated with delayed memory and attention index of the RBANS in T2D.

To date, no single study examined the levels of serum/plasma BDNF in humans with T1D.

#### 1.4.2.2 IGF-I

IGF-I is a peptide with a tertiary structure that consists of 70 amino acid residues and has a molecular mass of 7649 Da (Stokes et al. 2010). The release of IGF-I is a result of stimulation by Growth Hormone (GH) and it is mainly secreted by the liver in an endocrine fashion. Besides the liver, IGF-I can also be produced locally (e.g. in skeletal muscle and the brain). This locally produced IGF-I is also released into the circulation (Widdowson et al. 2009). The effects of IGFs (and insulin) are mediated through binding to their own specific receptors: IR and IGF-IR (Gielen et al. 2002, Schulze et al. 2002). In the circulation, free IGF-I accounts for only a minor fraction (less than 1~2%) of the total circulating amount of IGF-I (Gielen et al. 2002, Widdowson et al. 2009). Most of the IGF-I is bound with a high affinity to a family of six specific IGF Binding Proteins (IGFBP1-6). There are several studies that indicate the importance of free vs total IGF-I (Gielen et al. 2002). For example, during oral or intravenous glucose tolerance testing, total IGF-I does not change, while IGFBP-1 increases. Increased IGFBP results in a significant reduction in free IGF-I. During hyperinsulinaemic clamping, total IGF-I stays unaltered while free IGF-I increases, indicating that IGFBP-1 and free IGF-I might play a role in glucose regulation (Gielen et al. 2002).

IGFs (both IGF-I and IGF-II) stimulate the uptake of glucose and amino acids by the cells (e.g. skeletal muscle cells), a similar action to insulin, what led to its name; IGF (Stokes et al. 2010, Lenk et al. 2002,

Gielen et al. 2002). Besides the metabolic effect, IGF-I has a neurotrophic and neuromodulatory effect (Gasparini and Xu, 2003). Diabetes, protein deficiency, physical exercise and energy restriction all influence the action of IGF-I (Stokes et al. 2010). Patients with T1D exhibit increased secretion of GH but also have complex tissue-specific changes in IGF binding proteins (IGFBPs) and reduced levels of IGF-I (Thraillkill, 2000, Janssen et al. 1997, Chatzigeorgiou et al. 2009).

Levels of IGF-I decline with age (Gielen et al. 2002) and are altered in a remarkable variety of neurodegenerative conditions (Trejo et al. 2004). A reduction in learning and memory and deficits in LTP were shown in liver-specific IGF-I knockout mice (Trejo et al. 2007). In the past decades, extensive research has determined that the reduction of IGF-I is an important component of the age-related decline in cognitive function in healthy humans (Sonntag et al. 2013). Van Dam and Aleman (2004) concluded in their review on IGF-I and cognitive functioning that the available data indicate that higher plasma levels of IGF-I in healthy elderly are associated with better cognitive performance (van Dam and Aleman, 2004). Deficiency in circulating total IGF-I has been associated with decreased perceptual motor performance, reduced information processing speed (Aleman et al. 1999, Dik et al. 2003), fluid intelligence (Aleman et al. 2001) and deficiencies in spatial and working memory (Sonntag et al. 2013) in healthy fit older adults.

#### *The influence of acute and chronic exercise on IGF-I in healthy humans*

It is well recognized that exercise has a significant impact on GH/IGF release. The quantification of (total and free) IGF-I levels, however, has yielded conflicting reports regarding the acute and chronic effects of exercise on circulating IGF concentrations (Stokes et al. 2010, Wallace et al. 1999, De Palo et al. 2001, Nguyen et al. 1998, Griffin et al. 2011), with increased levels of total and free IGF-I (Schwarz et al. 1996) (Copeland and Heggie, 2008), no influence on total and free IGF-I (Wallace et al. 1999, Stokes et al. 2010) (Wahl et al. 2010) or even a decrease in free IGF-I (Dall et al. 2001, De Palo et al. 2008) during aerobic exercise. Strength exercise showed similar conflicting results with increased levels of free IGF-I (Bermon et al. 1999) and decreased levels of IGF-I (Gregory et al. 2013). Comparing different types of exercise and intensities; Schwartz et al. (1996) and Copeland et al. (2008) concluded that IGF-I induces a more pronounced increase in total IGF-I and IGFBP-3 after a high-intensity exercise than after a low-intensity exercise. However, Wahl and colleagues (2010) did not find increases in total serum IGF-I after a high and

a moderate intensity exercise of 1h (Wahl et al. 2010).

Exercise training gives similar inconsistent results with increased total IGF-I (Chicharro et al. 2001, Baker et al. 2010), no influence on total IGF-I (Vitiello et al. 1997, Grandys et al. 2008) or decreased total IGF-I (Nishida et al. 2010, Chicharro et al. 2001) after aerobic exercise training protocols of 3 to 6 months. Strength training programs gave increased total (Roelen et al. 1997, 2009) or decreased total (Schiffer et al. 2009) levels of IGF-I. Resistance training combined with endurance training increased total IGF-I and reduced IGFBP-1 concentrations significantly (Gregory et al. 2013), while Sillanpaa et al. (2010) determined significantly higher levels of serum total IGF-I in a combined (strength + endurance) training group compared to endurance or strength training separately.

Long-term PA,  $VO_{2max}$  and  $VO_{2peak}$  are all related with levels of total plasma and/or serum IGF-I (Glaser et al. 2010, Poehlman et al. 1994, Roelen et al. 1997, Whiteman et al. 2014). When compared with other physiological variables (body composition, body fat distribution, nutritional status, and age), reduced  $VO_{2max}$  levels are the best predictor of the decline in plasma total IGF-I in older men (Poehlman et al. 1994, Rubin et al. 2005).

The discrepancy in the results found in literature may be explained by the influence of different exercise protocols with different duration, types and intensities of exercise (Gatti et al. 2012) or due to differences in total/free IGF-I. It is suggested that increases in IGF-I might be related to the stimulus of GH release in short-duration, high intensity exercise (HIE), while less intensive exercises are not influencing GH release and therefore may not influence total IGF-I plasma levels (Nguyen et al. 1998). But even after intense exercise, IGF-I is not consistently increased. Several hypothesis are proposed to explain differences in total and free IGF-I after exercise. For example, decreased levels of venous free IGF-I with no changes in arterial IGF-I could indicate an increased uptake or reduced release of free IGF-I by exercising muscles (Lenk et al. 2002). An alternative hypothesis of the differences found in free versus total IGF-I is that free IGF-I concentrations negatively correlate to IGFBP. Since IGFBP also increase after exercise, free IGF-I will bind to its protein, and therefore a reduction in free IGF-I may be found after acute exercise (Gregory et al. 2013). Increased total IGF-I concentrations in response to exercise may be attributed to the IGF-I release from the muscle, vascular endothelium or extracellular matrix (Gregory et al. 2013). Furthermore, an increased uptake of circulating IGF-I by target organs as muscle and brain may cause unaltered IGF-I

concentrations in the (Carro et al. 2001).

In T1D specific, only one acute exercise trial (in children) examined the effects of a 30 min exercise trial at 80%  $VO_{2max}$  on levels of IGF-I and did not report increased IGF-I after exercise (Galassetti et al. 2006).

*Mechanisms of IGF-I on brain function*

Peripheral administration of IGF-I results in increased neurogenesis in the hippocampus of rats (Aberg et al. 2000, Aberg et al. 2003), and therefore it is speculated that circulating IGF-I might be mediating the stimulatory effects of exercise on neurogenesis in normal adult rats. To investigate the effects of exercise induced changes in IGF-I on neurogenesis, Carro and colleagues (2001) injected labeled IGF-I in running rats compared to non-running rats. The treadmill running group had increased labeled IGF-I in the brain, whereas non-exercising control rats did not show these exercise-induced benefits. Cetinkaya and colleagues (2013) recently confirmed these effects and showed that learning and memory functioning were positively correlated with exercise in rats, while increased IGF-I levels were detected in hippocampus and blood serum (Cetinkaya et al. 2013). Subsequently, blocking the uptake of IGF-I in the brain showed reduced exercise-induced neurogenesis in the hippocampus and impaired spatial learning (Trejo et al. 2008, Trejo et al. 2001), abolished the exercise-induced increase in IGF-I (Ding et al. 2006), altered the exercise-induced effect on learning and memory retention (Ding et al. 2006), and prevented protection of brain damage through increased uptake of circulating IGF-I into the brain (Carro et al. 2001). Administration of exogenous IGF-I restored hippocampal neurogenesis and ameliorated spatial memory in mice (Trejo et al. 2008).

Besides the direct effects of IGF-I on neurogenesis, IGF-I exerts its effects on the brain by interacting with the pathway of BDNF-induced neuroplasticity. It has been proposed that IGF-I may regulate the induction of BDNF with exercise (Carro et al. 2001). IGF-I binding to its receptor activates its downstream signaling mechanism, incorporating p-CAMPKII and p-MAPKII signaling cascades. Both signaling cascades are involved in the regulation of BDNF mRNA expression (Ding et al. 2006), suggesting that (part of) the effects of IGF-I may be accomplished by modulating the precursor to the mature BDNF. A study of Ding and colleagues (2006) demonstrated that IGF-I receptor blockade during exercise abolishes the effects of the exercise-induced increase in hippocampal BDNF mRNA, protein and pro-BDNF protein, and attenuates the

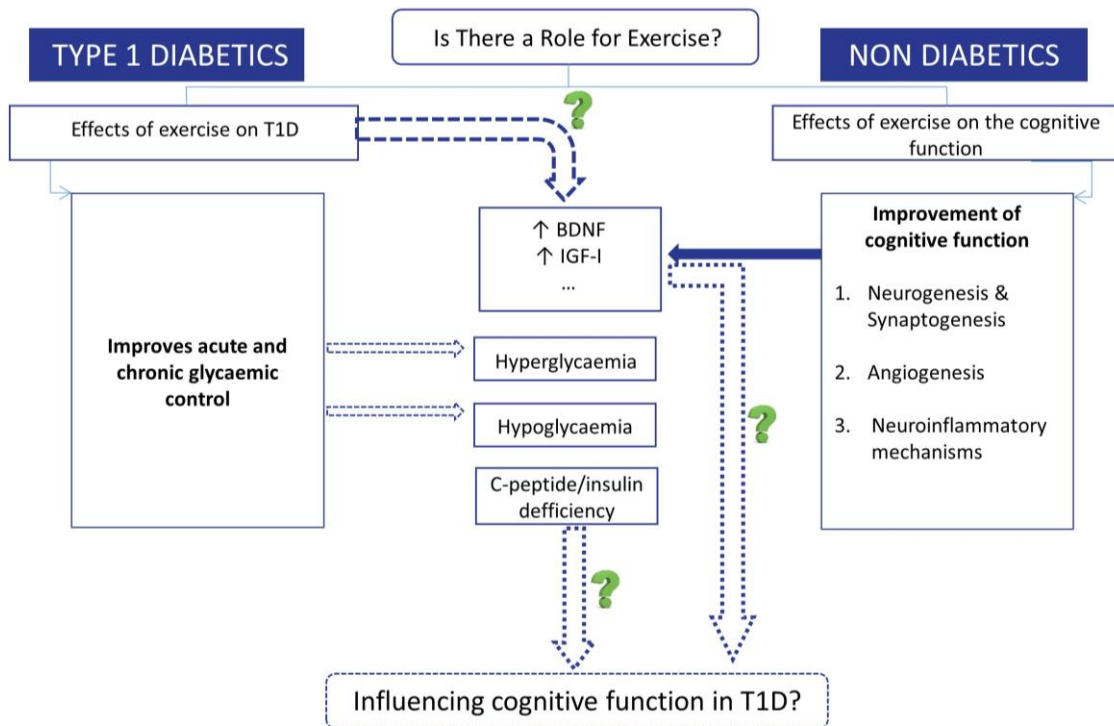
exercise dependent induction of synapsin I, a synaptic protein.

*1.4.3 OTHER PROPOSED MECHANISMS: NEUROINFLAMMATORY PROCESSES & ANGIOGENESIS*

Another potential pathway through which brain 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. Furthermore, vigorous exercise leads to increased levels of pro-inflammatory cytokines (IL-1, IL-10, IL-6 and TNF- $\alpha$ ) (Northoff et al. 1994, Pedersen et al. 1998), but simultaneously cytokine inhibitors and anti-inflammatory cytokines restrict the magnitude and duration of the inflammatory response to exercise (Foster et al. 2011). 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 (Foster et al. 2011).

The effects of exercise on the brain are partly induced by increasing regional cerebral blood flow (CBF), vascular function and angiogenesis, which might facilitate synaptic plasticity via multiple mechanisms (Lista and Sorrentino, 2010, van Praag et al. 2005, Trejo et al. 2001). Increased CBF and angiogenesis may lead to improved physiological functioning of the brain parenchyma (Christie et al. 2008). Two main growth factors inducing angiogenesis are IGF-I and VEGF (Gatti et al. 2012). Fabel et al. (2003) showed that blocking peripheral VEGF abolished the exercise-induced neurogenesis but had no effect on baseline neurogenesis, suggesting VEGF is an important element in exercise-induced angiogenesis and neurogenesis.

## 1.5 Purpose of this PhD: DACD, is there a role for exercise?



**Figure 4 Hypothetical effects of exercise on the cognitive function in T1D. (BDNF = Brain- derived Neurotrophic Factor, IGF-I: Insulin-Like Growth Factor-I.) (figure from Tonoli et al. 2013; Journal of Diabetes & Metabolism)**

An increasing number of studies (in children and adults) have been published on the CNS changes associated with T1D, more precisely on the cognitive function in T1D. As shown previously in this introduction, a DACD can be caused by episodes of severe hypoglycaemia (biochemical and neurochemical features), chronic hyperglycaemia (via the polyol pathway and increased oxidative stress) and C-peptide/IGF-I deficiency. The latter may even link diabetes to AD. Exercise has been generally accepted and recommended for the management of T1D and has been shown to improve acute and chronic glycaemic control, a pathway by which cognitive function is influenced in T1D. However, until today there are no studies exploring the effects of exercise on cognitive function or on neurotrophic markers such as BDNF in T1D.

Recently, strategies to fight or prevent the development of cognitive 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 cognitive decline because it supports brain plasticity, neurogenesis and angiogenesis in different populations, both healthy and diseased (Cassilhas et al. 2012, Heyman et al. 2011, Colcombe and Kramer, 2003b), and therefore it could be a tool to prevent or 'slow down' a DACD. Figure 4 gives an overview of hypothetical pathways by which exercise could have beneficial effects on markers of neurogenesis and the cognitive function in T1D.

To date, no studies have looked into the effects of exercise on a DACD, nor on levels of BDNF in T1D. Only one study examined the effects of exercise in T1D children on levels of IGF-1. Therefore, the **purpose** of this work is to identify the effects of PA and acute exercise on the levels of BDNF, IGF-I, free insulin, glucose and cognitive performance in subjects with T1D. Different research questions raised:

1. What are the effects of T1D on cognitive function in children and adults? Are there differences between these two populations?
2. Are associated contributing factors (hypoglycemia, hyperglycemia, age of onset, diabetes duration, and complications on the cognitive function) related to this cognitive decline?
3. Can we quantify the effects of different types of acute and chronic exercise on (acute and chronic) glycaemic control in T1D?
4. Is the level of PA, serum BDNF and serum IGF-I related to cognitive performance in T1D?
5. Are levels of IGF-I and BDNF altered in T1D patients compared to non-diabetic subjects?
6. Are levels of BDNF, IGF-I, insulin, glucose and cognitive function influenced by acute exercise in T1D patients? Do these patients react similar to exercise compared to non-diabetic controls?
7. Do different types of exercise intensities induce different effects on factors of neurogenesis and neuroplasticity?

The present dissertation aimed at addressing all above listed research questions in 5 studies. Additionally, one validation study needed to be performed in order to be able to address the validity and reliability of the questionnaires used.

A detailed description of the work that has been performed is listed here below.

**Chapter 1** was the general introduction, in which we have tried to situate the research problem combining:

- ✓ The cognitive decline in T1D and the subsequent possible mechanism of this cognitive decline
- ✓ The effects of exercise on cognitive function and neurotrophic markers in non-diabetic and diabetic subjects
- ✓ Combining all those aspects.

To provide clear evidence of the existing literature concerning the effects of T1D on the brain and the effects of exercise on glycaemic control in T1D, meta-analyses were performed. They are presented in **chapter 2 & 3**. In **chapter 2** we give a clear answer on the first two research questions of this PhD by performing a *meta-analysis* of the existing literature on the cognitive function in patients with T1D.

Since impaired acute and chronic glycaemic control underly a DACD, and it is well known that PA can improve acute and chronic glycaemic control in T1D, we have quantified (in a second meta-analysis) the effect of acute and chronic exercise on glycaemic control (Research Question 3). This study is addressed in **chapter 3**.

A cross sectional study in a T1D population investigates whether the self-reported level of PA contributes to a DACD and can predict a DACD, and if baseline levels of BDNF and total IGF-I play a central role in this DACD (Research question 4). This study can be found in **chapter 4**.

In **chapter 5** we aimed to address research questions 5 & 6. This study describes the effects of an acute high intensity exercise on the cognitive performance, levels of serum BDNF, total IGF-I, free insulin and glucose in T1D subjects and their matched controls.

The intensity of acute exercise differentially increases levels of neurotrophins in healthy subjects and also differentially affects glycaemic control in T1D patients (Research Question 7). An acute exercise-induced increase of neurotrophins is crucial for obtaining an improved cognitive function with chronic exercise in healthy subjects. Therefore, the aim of this study – presented in **chapter 6** - was to elaborate on the effects of different exercise intensities (continuous moderate exercise vs. HIE) on levels of serum BDNF and total IGF-I, free insulin and blood glucose in a T1D population.

**Chapter 7** contains the general discussion of the results from the different studies in this research project. In this chapter, the most important results are highlighted, and we tried to clarify those results by linking them to the existing literature. Furthermore, the clinical relevance of our findings and guidelines for



further research in this area are suggested.

**Chapter 8** contains the general conclusion of this dissertation.

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## 1.6 References

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## CHAPTER 1. GENERAL INTRODUCTION

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CHAPTER 2. TYPE 1 DIABETES-ASSOCIATED COGNITIVE DECLINE: A  
META-ANALYSIS AND UPDATE OF THE CURRENT LITERATURE

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ORIGINAL ARTICLE

**Type 1 diabetes-associated cognitive decline: A meta-analysis and update of the current literature**

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## 2.1 Abstract

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**Background:** Type 1 diabetes (T1D) can have a significant impact on brain structure and function, which is referred to as T1D-associated cognitive decline (T1DACD). Diabetes duration, early onset disease, and diabetes-associated complications are all proposed as factors contributing to T1DACD. However, there have been no comparisons in T1DACD between children and adults with T1D. To obtain a better insight into the occurrence and effects of T1DACD in T1D, the aim of the present meta-analysis was to investigate differences between children and adults and to analyze factors contributing T1DACD. **Methods:** Two electronic databases were consulted: PubMed and ISI Web of Knowledge. Literature published up until the end of 2013 was included in the analysis. Effect sizes (Cohen's *d*), which are standardized differences between experimental and control groups, were calculated. **Results:** There was a small to modest decrease in cognitive performance in T1D patients compared with non-diabetic controls. Children with T1D performed worse while testing for executive function, full intelligence quotient (IQ), and motor speed, whereas adults with T1D performed worse while testing the full, verbal and performance IQ, part of the executive function, memory, spatial memory, and motor speed. Episodes of severe hypoglycemia, chronic hyperglycemia, and age of onset can be significant factors influencing cognitive function in T1D. **Conclusions:** The findings in the literature suggest that T1DACD is more severe in adults than children, indicating that age and diabetes duration contribute to this T1DACD.

### *2.1.1 SIGNIFICANT FINDINGS OF THE STUDY:*

- ✓ T1D patients have a small to modest decrease in cognitive performance compared with non-diabetic controls
- ✓ Children with T1D performed worse while testing for executive function, full IQ and motor speed
- ✓ adults with T1D performed worse while testing the full, verbal and performance IQ, part of the executive function, memory, spatial memory, and motor speed
- ✓ Episodes of severe hypoglycemia, chronic hyperglycemia, and age of onset can be significant factors influencing cognitive function in T1D.

## 2.2 Introduction

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Type 1 diabetes (T1D) can have a significant impact on brain structure and function (Brands et al. 2005). The effects of diabetes on the brain were recognized by Miles and Roots as early as 1922 (Miles and Root, 1922). Because different terms are used in literature (e.g. cognitive dysfunction, cerebral impairment, central neuropathy), Mijnhout et al. (2006) proposed a new term, namely diabetes-associated cognitive decline (T1DACD), to include all these terms. The term DACD is not suggestive of a particular pathogenesis, but merely describes a state of mild to moderate cognitive impairment (Mijnhout et al. 2006). Although many studies have evaluated cognitive performance in T1D, several questions regarding how T1D affects cognitive performance remain to be answered; consequently, this issue remains contentious. The clearest evidence of T1DACD has been shown by meta-analyses of the existing literature in children (Gaudieri et al. 2008, Blasetti et al. 2011) and adults (Brands et al. 2005). A large body of literature has been published and diabetes duration, early onset disease (EOD), and diabetes-associated complications are all proposed as factors contributing to T1DACD. However, none of these studies compared differences between DACD children and adults with T1D.

The pathophysiological basis for T1DACD remains poorly understood. Three possible causes of T1DACD are described in the literature: (i) hypoglycemic episodes (Auer, 2004); (ii) hyperglycaemia (Malone et al. 2008, Wrighten et al. 2009); and (iii) deficiencies in C-peptide and/or insulin (Li et al. 2005, Li et al. 2002, Sima et al. 2004). Because the brain cannot synthesize or store glucose, it requires a continuous supply. Therefore, it is not inconceivable that disruption of the glucose supply as a result of hypo- or hyperglycemia will cause disturbances to cognitive function. However, T1D is characterized by chronic hyperglycemia and T1D patients are therefore in need of insulin-replacement therapy. Because administration of exogenous insulin is required in either a conventional or an intensive manner of insulin therapy, this can result in alternation between hypoglycemic and hyperglycemic episodes (Perantie et al. 2007), suggesting that diabetes itself and medical management are potentially risk factors for T1DACD. Other diabetes-associated contributing factors, such as EOD, diabetes duration, and complications, have been debated extensively but no clear-cut results have been reported in the literature.

Type 2 diabetes (T2D) is characterized by high blood sugar and is also related to cognitive impairment (e.g. in memory, psychomotor speed, and executive functions). However, there are both similarities and differences in

the pathophysiology of T2D and T1D. The main hypotheses regarding T2DACD implicate hyperglycemia, hypoglycemia, microvascular disease, insulin resistance, hyperinsulinism, hyperphosphorylation of tau protein, amyloid- $\beta$  deposition and elevated adiposity caused by T2D, as well as vascular risk factors (Stargardt et al. 2009). Furthermore, T2D patients have diminished lipoprotein-related proteins (LRP), a therapeutic candidate for the treatment of late onset Alzheimer's disease. Because the pathophysiology differs in T1D and T2D, the present study only focuses on T1DACD.

The assessment of a DACD in T1D patients is usually based on neuropsychological tests. It is widely agreed that the historical purpose of clinical neuropsychology is to assist in the diagnosis of brain pathology, and neuropsychological tests are successful in doing so (Chaytor and Schmitter-Edgecombe, 2003). However, we have to be careful when using cognitive tests for different cognitive domains. For example, for almost every possible cognitive test, 'attention' is needed. But, when the test becomes more difficult than, for example, a simple reaction time test, the purpose of the test may shift to another cognitive domain (e.g. executive function). Consequently, investigators who are not educated in the area of cognitive research possibly ascribe cognitive tests to the wrong cognitive domain, which can result in a self-perpetuating loop in the existing literature by reading and using the wrong tests for specific cognitive domains. It is therefore important to be critical as to the cognitive tests used and the linked cognitive domains, particularly when performing a meta-analysis dealing with cognitive function.

### *2.2.1 PURPOSE*

The purpose of the present meta-analysis was to evaluate the current literature investigating differences between children and adults with T1D and possible factors contributing to T1DACD. The following two primary research questions were put investigated: (i) what are the effects of T1D on cognitive function in children and adults; and (ii) what are the effects of diabetes-associated contributing factors (hypoglycemia, hyperglycemia, age of onset, diabetes duration, and complications on the cognitive function) to this cognitive decline?

## 2.3 Methods

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### *2.3.1 DATA SOURCES*

The present meta-analysis consists of two parts. The first part analyzes which cognitive domains are affected in children and adults with T1D. The second part determines the putative role of hypoglycemia, chronic hyperglycemia, duration of diabetes, EOD, and diabetes-associated complications on T1DACD. Two electronic databases were consulted: PubMed and ISI Web of Knowledge. The databases were searched systematically by filling in all relevant participants, interventions, comparisons, outcomes and study design (PICOS) key word combinations. Key terms (and synonyms searched on the MeSH database) included and combined as per the different parts of this meta-analysis were: 'diabetes mellitus type 1', 'insulin-dependent diabetes mellitus', 'IDDM', 'cognition', 'cognitive function', 'cognitive performance', 'cognitive decline', 'diabetic encephalopathy', 'diabetes-associated cognitive decline' and 'mechanisms'.

### *2.3.2 STUDY SELECTION*

Studies in this meta-analysis needed to fulfill the following criteria to be included in the analysis: P, T1D humans; I, cognitive performance; C, comparison with diabetics or non-diabetics; O, original data on cognitive performance with sufficient information for calculation of effect sizes (ES; group means, SD, or SEM); S, original data, and published before the end of 2013. Articles were included or excluded by applying these criteria to the title, abstract, and/or full text. Brief reports and reviews were excluded from analysis. University libraries, hand searches, electronic databases, and contact with the authors by mail were used to obtain more details for the papers if necessary. Figure 5 shows the progress of the literature screening and the reasons for inclusion or exclusion. Study characteristics for the selected articles are given in tables 1–4.



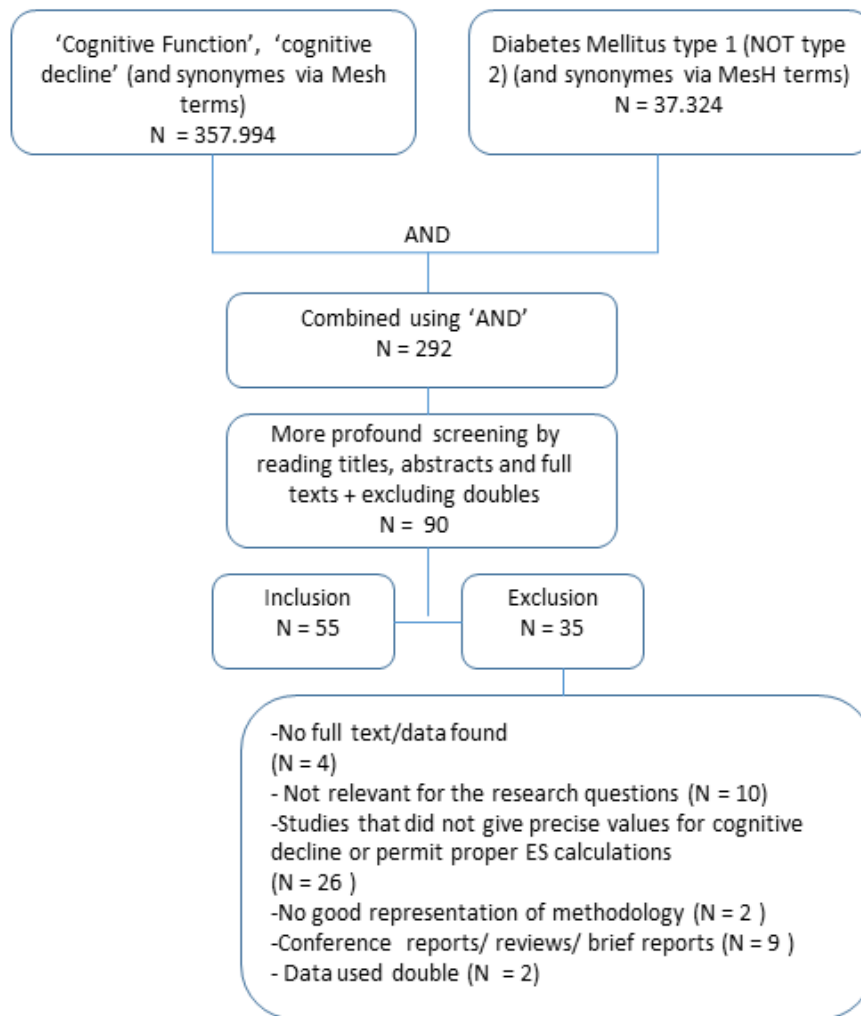


Figure 5 Flow diagram illustrating selection of the included studies

### 2.3.3 DATA EXTRACTION, SYNTHESIS, AND REPORT

In the first part of the analysis, meta-analyses were performed separately for T1D subjects compared to non-diabetic subjects. In the second part of the analysis, T1D groups with a particular diabetes-associated factor (e.g. hyperglycemia) were compared against a control T1D group without this diabetes-associated factor to determine the possible contribution of different diabetes-associated factors.

### 2.3.4 CHILDREN VERSUS ADULTS

During development, many changes take place in the brain, mostly before and during adolescence. Two of the brain regions that have consistently been shown to undergo development during adolescence are the prefrontal cortex and parietal cortex (Blakemore and Choudhury, 2006). Therefore, it may be expected that

cognitive abilities that rely on the functioning of the developing brain also change during this period. The Tanner scale of physical development in children, adolescents, and adults (Marshall and Tanner, 1970) defines physical measurements of development based on external primary and secondary sex characteristics because of large individual differences (which cannot be based on the age of the participants). Because this scale was not used in the papers included in the meta-analysis, and the changes are occurring before and during adolescence compared with adulthood, we could not use this to distinguish between children and adolescents, so we classified our groups into children and adolescents (Group 1) and adults (post-puberty, >18 years of age; Group 2).

#### *2.3.5 CREATION OF A CONSISTENT CLASSIFICATION OF COGNITIVE DOMAINS*

To make a classification, all the cognitive tests used were ordered following the cognitive domain the study itself attributed the test. Subsequently, all the tests were classified according to Lezak et al. (2004) and Strauss et al. (2006) and a professor in neuropsychology (N.P.) to the cognitive domain they suggested. The classification comprised six cognitive areas: attention, intelligence quotient (IQ; full IQ, verbal IQ, and performance IQ), memory (with the subdomain 'spatial memory'), executive function, motor function, and psychomotor speed.

#### *2.3.6 STATISTICAL ANALYSES*

Cohen's *d* statistic was used to calculate the ES, weighted by the sample size of the study. Cohen (1988) defined distinct ES (*d*) for means as small  $d = 0.3$ , medium  $d = 0.5$ , and large  $d = 0.8$ . Ninety-five percent confidence intervals (CI) were used to establish the significance of our findings. The standardized mean difference was considered significant at the 5% level ( $P < 0.05$ ) when zero was not included within the 95% CI. For every cognitive subdomain a meta-analysis was performed when a minimum of three studies had assessed the same subdomain. Negative effects indicate a decrease in the dependent variable (e.g. the performance of the T1D group is worse than that of the control group), whereas positive effects indicate an increase, except for the cognitive tasks measuring duration. In these tasks, a positive ES means a longer time needed to fulfill the cognitive test and is subsequently a sign of altered function in those areas. Both fixed and random effect models were included for to calculate ES.

### 2.3.7 QUALITY ASSESSMENT

Methodological quality was assessed using different assessment tools of the Scottish Intercollegiate Guidelines Network (SIGN) checklist. This checklist assesses the randomization, concealment method, blinding of subjects and/or investigators, drop-out, intention-to-treat-analysis, eligibility criteria, and follow-up.

### 2.3.8 DEFINITION USED FOR ASSOCIATED DISEASE RISK FACTORS

An EOD was set as before 4 years of age (Perantie et al. 2008). For this reason, we could not include the study of Hershey et al. (Hershey et al. 2004) because these authors set an EOD of  $\leq 4.7$  years and a late age of onset of  $\geq 7$  years.

The term 'severe' hypoglycemia was described by the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study as episodes in which the patient was sufficiently incapacitated to require the assistance of another person (The-Diabetes-Control-and-Complications-Trial-Research-Group, 1993).

## 2.4 Results

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First, this meta-analysis looked at the effects of T1D on all domains of cognitive function. Second, a separate meta-analysis was completed for each of the different possible contributing diabetes-associated factors. This included analysis of the duration of diabetes, hypoglycemia, hyperglycemia, age of onset, and complications of diabetes.

### 2.4.1 DIABETES-ASSOCIATED COGNITIVE DECLINE IN T1D PATIENTS VERSUS HEALTHY SUBJECTS

After performing the search as described above, 55 original studies were included in the analysis to determine the diabetes-associated cognitive decline in T1D patients (32 adults, 23 children) (tables 1–4 displays these studies and their characteristics).

**Table 1 Characteristics of studies comparing type 1 diabetes children and non-diabetic controls**

Reference	No. subjects in	No. males in	Age (years)	Age of	Duration of	HbA1c (%)	SH	Complications		
	Group	Group		onset	diabetes			Neuropathy	Nephropathy	Retinopathy
	1/Group	1/Group		(years)	(years)					
	2/Group3	2/Group3								
Aye et al. 2011	27/18	48/61		3.5 ± 1.9	3.6 ± 1.9	7.6 ± 0.9	Yes	–	–	–
Crawford et al. 1995	27	40		>5	–	–	–	–	–	–
Hannonen et al. 2003	11/10/10	45/40/50	14.4 ±	3.23 ±	6.16 ±	8.3 ± 1.9/8.4 ±	Yes/no/no	No	No	No
	(SH/no SH/no D)		2.6/15.1 ±	1.45/5.4 ±	2.52/3.7 ±	2.0/–				
Hannonen et al. 2012	37/26/92	43/62/56	9.9 ±	2.9 ±	7.2 ± 1/6.7	8.31 ± 0.8/8.23 ±	–	–	–	–
	(SH/no SH/no D)		0.25/9.8 ±	1.25/3.3 ±	± 1/–	0.63/–				
Hershey et al. 1999	12 (IT)/13 (CT)		14.3 ±	11.9 ±	2.4 ±	–	14.4 episodes	–	–	–
			2.7/13.9 ±	2.8/11.7 ±	0.5/2.2 ±					
Hershey et al. 2003	16/18/16		2.8	2.8	0.7		4.75/1.39/0	–	–	–
	(SH/no SH/no D)			4.7 ± 3.3/7.	7/4.5/3.1					
Hershey et al. 2004	42/25	45/60	11.3 ± 2.7	6.4 ±	4.9/4.7/–	8.5 ± 1.0/8.5 ±	2.7 ± 1.3/2.4 ±	No	No	No
			(SH)/11.7 ±	3.7/7.0 ±	No	1.5/–	3.0/–			
			2.6 (No	3.4/–	duration					

Reference	No. subjects in Group 1/Group 2/Group3	No. males in Group 1/Group 2/Group3	Age (years)	Age of onset (years)	Duration of diabetes (years)	HbA1c (%)	SH	Complications		
								Neuropathy	Nephropathy	Retinopathy
			SH)/11.9 ± 2.8 (controls		reported					
Hershey et al. 2005	40 (0 SH)/38 (1–2 SH)/25 (≥3 SH)	–	13.4 ± 2.8/12.8 ± 2.2/12.0 ± 3.0	10.2 ± 3.6/8.0 ± 2.7/5.7 ± 3.7	3.3/4.8/5.7	8.1 ± 1.1/8.4 ± 1.5/8.9 ± 2.3	–/1.2 ± 0.5/6.6 ± 9.4	No	No	No
Holmes et al. 1992	95/97	56/44	12.6 ± 2.5/12.6 ± 2.5	7.3 ± 3.3	4.9 ± 3.6	9.1 ± 2.62	–	–	–	–
Kaufman et al. 1999	55/15	51	7.9 ± 1.6	4.5	2.6 ± 2.0	7.8 ± 1.1	18 (#)	–	–	–
Northam et al. 2001	90/84	50/47	(6–17)	–	6	–	–	–	–	–
Ohmann et al. 2010	70 (non GC + GC)/20 (non- D)	–	15.6 ± 1.9/14.0 ± 2.5/15.1	18.2%/20 % <6	7.5 ± 3.2/6.9 ± 0.5/–	9.3 ± 0.4/6.9 ± 0.5/–	–	–	–	–
Patino-Fernandez et al. 2010	36/32	41/53	4.7 ± 1.5/4.1 ± 1.2	2.8 ± 1.7/–	2	8.4	–	–	–	–
Perantie et al. 2008	117 T1D/58 non-D	51/55	12.1 ± 2.9/11.4 ± 3.2	–	6.8 ± 3.3/–	8.3 ± 0.9/–	0→3+	No	No	No

Reference	No. subjects in	No. males in	Age (years)	Age of	Duration of	HbA <sub>1c</sub> (%)	SH	Complications		
	Group 1/Group 2/Group3	Group 1/Group 2/Group3		onset (years)	diabetes (years)			Neuropathy	Nephropathy	Retinopathy
Rovet et al. 1988	27 EOD/24 LOD	51	9.8 ± 2.4/9.8 ± 2.4	<4/>4	7.5 (1.9 – 11.9)/3.7 (1.0 – 8.0)	(10.8 – 11.8)/(10.2 – 11.8)	–	–	–	–
Ryan et al. 1985	46/79/83	53.2/53.8/48. 2		2.9 ± 1.26/7.77 ± 2.06/–	11.4 ± 2.9/7.5 ± 2/–	–/–/–	–	–	–	–
Shehata & Eltayeb, 2010	40/40	45/50	11.7 ± 2.3/10.7 ± 2.7	–	–	–	17.5%	–	–	–

Unless indicated otherwise data are given as the mean ± SD. Group 1: Diabetics; Group 2: controls (unless otherwise described in text); CT, conventional therapy; EOD, Early onset Disease; D, Diabetic; GC, Glycaemic control; HbA<sub>1c</sub>, Glycaeted Hemoglobin (%); IT, Intensive Therapy; LOD, Late Onset Disease; n, number; SH, Severe Hypoglycaemia; T1D, Type 1 Diabetes; y, year(s).

**Table 2 Characteristics of studies comparing type 1 diabetic adults and non-diabetic controls**

Reference	No. subjects in Group 1/Group 2	No. males in Group 1/Group 2	Age (years)	Age of onset (years)	Duration of diabetes (years)	HbA1c (%)	SH	Complications		
								Neuropath y	Nephropathy	Retinopath y
Blackman et al. 1992	14/10	42/50		11.7	15 ± 2	11 ± 0.5	Yes	No	No	No
Brands et al. 2006	40/40	57/40		27.6	34 ± 13	8 ± 1/5.5 ± 0.4	Yes = 75	45	–	58
Deary et al. 1992	100/100	–	40.2 ± 6.7/40.9 ± 8.8	27.3 ± 5.9	14.4	–	Yes	No	No	No
Franceschi et al. 1984	37/26	43/42	25.8 ± 5	18.2	7.6 ± 5.5	12.7 ± 2.5	–	6/–	–/–	6/–
Geddes et al. 2008	16/20	50/45	40 (36–42.8)		15 (6–25)	8.2 ± 0.6		No	No	no
Kramer et al.	53/55	45/–	34 ± 12/38 ± 12	23 ± 6/21 ± 7	10.8 ± 10.6/17.6 ± 11.6	6.9 ± 1.3/7.0 ± 1.6	55 patients	4 (no SH)/6 (SH)	24 (no SH)/88 (SH)	0.3 (no SH)/0.7 (SH)
Lawson et al. 1984	48/40	26/19	38.3 ± 14.6/38.7 ± 12.8	5–60	13 ± 11	–	–	33/0	–	–
Ly et al. 2011	33/34	45/46	19.3 ± 0.5/19.5 ± 0.5	–	16 ± 0.5	8.8 ± 0.3	60%	–	–	–
Maran et al. 1995	18/–	66/–		20/15	16/17	7.7/10.1	Yes	–	–	–

Reference	No. subjects in Group 1/Group 2	No. males in Group 1/Group 2	Age (years)	Age of onset (years)	Duration of diabetes (years)	HbA1c (%)	SH	Complications		
								Neuropath y	Nephropathy	Retinopath y
Ryan et al. 1992	75/75	45/25	355 ±	9.5 ± 3.7/-	26.6 ± 6.7/-	10.3 ± 1.7/-	42%/-	56%/-	-	18%
			5.6/36.2 ±	6.8						
Ryan et al. 1993a	82/82	50/50	33.4 ±	8.4 ± 4/-	26.2 ± 6/-	10.8 ± 1.9/-	41.5%	45%	-	39%
Ryan et al. 1993	142/100	51/47	5.5/33.4 ±							
			5.2	30.7 ±	10.2 ±	20.05 ±	10.7 ±	No/43 (%)	No/52	-
			5.6/34.3 ±	3.4/8.3 ±	5.8/25.9 ±	1.9/10.6 ± 1.7				No/20%
			5.4	4.3	5.6					advanced/4 1% proliferativ e
Sachon et al. 1992	25(aware hypo)/30 (unaware hypo)/25 controls	76/60/48	34 ± 10/41 ±	-	14.11/17.3/ -	8.6 ± 1.9/7.1 ± 1.2/-	Yes/yes/-	2/2/-	3/2/-	4/2/-
Wright et al. 2009	16/-	7/-	28 (25 - 37.5)	-	10 (4.2 - 19)	7.91 ± 0.92	Yes, eu- vs hypo	No	no	no



Reference	No. subjects in Group 1/Group 2	No. males in Group 1/Group 2	Age (years)	Age of onset (years)	Duration of diabetes (years)	HbA1c (%)	SH	Complications		
								Neuropath	Nephropathy	Retinopath
								y		y
Wessels et al. 2007	25/9	40/33	42.3 ± 5.3/40.9 ± 8.5	–	32.4 ± 7.6/–	8.0 ± 1.2/–	–/–	–	–	Yes (10/25)/–

Unless indicated otherwise data are given as the mean ± SD. Group 1: Diabetics; Group 2: controls; CT, conventional therapy; EOD, Early onset Disease; D, Diabetic; GC, Glycaemic control; HbA1c, Glycaeted Hemoglobin (%); IT, Intensive Therapy; LOD, Late Onset Disease; n, number; SH, Severe Hypoglycaemia; T1D, Type 1 Diabetes; y, year(s).

**Table 3 Characteristics of studies investigating factors contributing to a cognitive decline in children with type 1 diabetes**

Reference	No. subjects in Group 1/Group 2/Group 3	No. males in Group 1/Group 2/Group 3	Age (years)	Age of onset (years)	Duration of diabetes (years)	HbA1c (%)	SH	Complications (total diabetic population)		
								Neuropathy	Nephropathy	Retinopathy
Jacobson et al. 2007	588/-/-	51/-/-		21	6	9.0	Yes	9%	–	52%
Jacobson et al. 2007	556/-/-	55/-/-		21	6	9.0	Yes	14%	–	50%
Hannonen et al. 2003	11/10/10	45/40/50	14.4 ± 2.6/15.1 ± 2.9/14.8 ± 2.5	3.23 ± 1.45/5.4 ± 2.38/–	6.16 ± 2.52/3.7 ± 1.63/–	8.3 ± 1.9/8.4 ± 2.0/–	Yes/no/no	No	No	No
Hershey et al. 1999	12/13/-	-/-/-	14.3 ± 2.7/13.9 ± 2.8	11.9 ± 2.8/11.7 ± 2.8	2.4 ± 0.5/2.2 ± 0.7	–	14.4 (#)	–	–	–
Kelly et al. 2010	27/-/-	55/-/-	11.4 ± 1.9	–	1–13	–	Clamp	–	–	–
Knight et al. 2009	32/-/-	57/-/-	6–16	9.6	3.25	8.23 ± 0	–	–	–	–
Northam et al. 2001	90/-/84	50/-/47	6–17	–	6/-	–	–	–	–	–
Ohmann et al.	70/-/-	-/-/-	15.6 ±	18.2%/20% < 6	7.5 ± 3.2/6.9 ±	9.3 ± 0.4/6.9 ±	–	–	–	–

2010			1.9/14.0 ± 2.5		0.5	0.5				
Rovet et al.	27/24/-	51/-/-	9.8 ± 2.4/9.8 ± 2.4	<4/>4	7.5 (1.9 – 11.9)/3.7 (1.0 – 8.0)	(10.8 – 11.8)/(10.2 – 11.8)	-	-	-	-
1988										
Ryan et al.	46/79/83	53.2/53.8/48.2		2.9 ± 1.26/7.77 ± 2.06/-	11.4 ± 2.9/7.5 ± 2/-	-/-/-	-	-	-	-
1985										

Unless indicated otherwise data are given as the mean ± SD. Group 1, Diabetics Early age of Onset; Group 2, Diabetics late age of onset; Group 3, Non diabetics; HbA1c , Glycaeted Hemoglobin (%); n , number; SH , Severe Hypoglycaemia; T1D , Type 1 Diabetes; y , year(s).

**Table 4 Characteristics of studies investigating factors contributing to a cognitive decline in adults with type 1 diabetes**

Reference	No. subjects in Group 1/Group 2	No. males in Group 1/Group 2	Age (years)	Age of onset (years)	Duration of diabetes (years)	HbA1c (%)	SH	Complications		
								Neuropathy	Nephropathy	Retinopathy
DCCT 1996	730/711	54.1/51.5	26.5 ± 7.1/27.1 ± 7.1	21/21.3	5.5 ± 4.1/5.8 ± 4.2	9.1 ± 1.6/9.1 ± 1.6	Yes (%) = 5.3/4.9	Yes	Yes	Yes
Draeos et al. 1995	42/-	47/-	29 ± 8	20.3	8.7 ± 3.2	10.0 ± 2.0	Clamp	No	No	No
Ewing et al. 1998	16/-	75/-	26.9 (18–47)	18.1	8.8 (2–17)	8.5 ± 1.3	Clamp	No	No	No
Geddes et al. 2008	16/-	50/45	40 (36–42.8)	–	15 (6–25)	8.2 ± 0.6	–	No	No	No
Gold et al. 1995	23/-	56/-	–	–	–	–	–	–	–	–
Howorka et al. 2000	13/14	45/36	36.1 ± 10.2/36.1 ± 10.2	–	16.7 ± 3.4/15.6 ± 8.6	7.6 ± 10/7.3 ± 1.2	18 ± 5/0	–	–	2/3
Jacobson et al. 2007	588/556	51/55	–	21	24	7.8/7.6	Yes	30/30	–	89/97
Maran et al. 1995	18/-	66/-	–	20/15	16/17	7.7/10.1	Yes	–	–	–
McAulay et al. 2005	16/-	–	25.5 (18 – 39)	–	8 (2.5 – 15)	7.7 ± 1.0	Clamp	No	No	No
McCrimmon et al. 1997	16/-	100/-	32.5 (20–45)	–	3 (0.5–4.5)	9.7 (8.7 – 10.5)	Clamp	No	No	No
Musen et al. 2008	175/-	43/-	36 ± 3/36 ± 3	–	25 ± 4/24 ± 4	7.8 ± 1.5/7.9 ± 1.6	Yes	17/33	–	11/23
Reichard et al. 1996	43/48	–	31 ± 7/31 ± 7	–	17 ± 6/17 ±	9.5 ± 1.4/9.4	Yes	14/32	110/109	33/63

Reference	No. subjects in Group 1/Group 2	No. males in Group 1/Group 2	Age (years)	Age of onset (years)	Duration of diabetes (years)	HbA1c (%)	SH	Complications		
								Neuropathy	Nephropathy	Retinopathy
Sommerfield et al. 2003	16/-	56/-	28.5 (20.0 – 38.2)	–	4.5 (1.2 – 8.4)	8.2 (6.9 – 8.7)	Clamp	No	No	No
Strachan et al. 2003	15/-	73/-	23.5 ± 9.1	–	11.1 ± 6.6	8.8 ± 2.0	Clamp	No	No	No
Wessels et al. 2007	15/10	45/30	42.1 ± 4.5/42.3 ± 5.3	–	26.4 ± 8.1/32.4 ± 7.6	7.8 ± 1.1	8.0 ± 1.2	–	–	Yes/no
Wredling et al. 1990	17/17	47/-	49 ± 18/48 ± 17	20 ± 17/19 ± 15	28 ± 18/29 ± 13	7.9 ± 1.6/8.8 ± 1.6	Yes/no	Yes	–	Yes
Wright et al. 2009	16/-	–	28 (25 – 37.5)	–	10 (4.2 – 19)	7.91 ± 0.92	Yes, eu– vs hypo	No	No	No

Unless indicated otherwise data are given as the mean ± SD. Group 1, Diabetics; Group 2, non-diabetics SH, DCCT; The Diabetes Control and Complications Trial; HbA1c , Glycaeted Hemoglobin (%);n , number; SH , Severe Hypoglycaemia; T1D , Type 1 Diabetes; vs , versus; y , year(s)

## 2.4.1 DIABETES-ASSOCIATED COGNITIVE DECLINE IN CHILDREN AND ADOLESCENTS WITH T1D

Table 5 gives estimates of the size of the T1DACD in T1D children compared with non-diabetic children. Nineteen studies were included to calculate an ES for T1DACD in T1D children compared with non-diabetic controls (<18 years) (Ohmann et al. 2009, Hannonen et al. 2012, Hershey et al. 2005, Hershey et al. 2003, Hershey et al. 2004, Crawford et al. 1995, Rovet et al. 1988, Northam and Lin, 2010, Ryan et al. 1985, Ryan and Williams, 1993b, Ryan et al. 1993, Ryan et al. 1992, Kaufman et al. 1999, Shehata and Eltayeb, 2010, Patino-Fernandez et al. 2010, Aye et al. 2011, Holmes et al. 1992, Perantie et al. 2008, Wysocki et al. 2003, Northam et al. 2001). Compared with non-diabetic children, T1D children exhibited significantly lower performance on the full IQ and motor speed tests (table 5). No significant differences in cognitive function were found for verbal IQ, performance IQ, executive function, memory, and motor function.

**Table 5** Estimates of the size of the diabetes-associated cognitive decline in children with type 1 diabetes compared with non-diabetic children

Cognitive domain	Cohen's d	95% CI	No. studies	No. subjects
Attention	–	–	–	–
Executive function	–0.06	–0.3, 0.17	3	295
General IQ	–0.4*	–0.52, –0.27	10	1008
Full IQ	–0.4*	–0.52, –0.27	10	1008
Verbal IQ	–0.11	–0.23, 0.01	9	1153
Performance IQ	–0.05	–0.2, 0.11	6	645
Memory	–0.11	–0.22, 0.00	13	1285
Spatial memory	0.0	–0.13, 0.14	9	894
Motor function	0.1	–0.08, 0.28	7	515
Motor speed (s)	0.38*	0.55, 0.19	3	472

\* $P < 0.05$  for type 1 diabetic compared with non-diabetic children. IQ, intelligent quotient; CI, confidence interval.

## 2.4.2 DIABETES-ASSOCIATED COGNITIVE DECLINE IN ADULTS WITH T1D

Table 6 gives estimates of the size of the T1DACD in T1D adults compared with non-diabetic adults. Eighteen studies (Perantie et al. 2008, Wessels et al. 2007, Brands et al. 2006, Deary et al. 1993, Franceschi et al. 1984, Clausen et al. 2011, Ly et al. 2011, Lawson et al. 1984, Kramer et al. 1998, Sachon et al. 1992, Geddes et al.

2008, Maran et al. 1995, Blackman et al. 1992, Wright et al. 2009, Ryan and Williams, 1993b, Ryan et al. 1993, Ryan et al. 1992) were included to calculate the ES for T1DACD in T1D adults (>18 years) compared with non-diabetic controls. Adults with T1D demonstrated a significantly lower performance in the following cognitive domains: executive function (Trail Making Test), general IQ (full, verbal, and performance IQ), spatial memory, and motor speed.

**Table 6 Estimates of the size of the diabetes-associated cognitive decline in adults with type 1 diabetes compared with non-diabetic adults**

Cognitive domain	Cohen's d	95% CI	No. studies	No. subjects
Attention	-0.03	-0.19, 0.13	5	634
Executive function	-0.06	-0.22, 0.11	7	584
TMT (s)	0.69*	0.52, 0.86	7	584
General IQ	-0.42*	-0.57, -0.26	5	686
Full IQ	-0.42*	-0.57, -0.26	5	686
Verbal IQ	-0.32*	-0.44, -0.19	7	1018
Performance IQ	-0.31*	-0.47, -0.16	6	639
Memory	-0.19*	-0.32, -0.06	9	916
Spatial memory	-0.29*	-0.5, -0.07	3	356
Motor function	0.75	0.93, 0.00	4	510
Motor speed (s)	0.5*	0.32, 0.68	6	509

\* $P < 0.05$  for type 1 diabetic compared with non-diabetic adults. IQ, intelligent quotient; CI, confidence interval; TMT, trail making test.

### 2.4.3 FACTORS INFLUENCING T1DACD

#### 2.4.3.1 Age of diabetes onset

Although EOD was most prominent as one of the main risk factors for developing T1DACD, we could only find four studies that included the age of onset in their analysis.(Hershey et al. 2003, Shehata and Eltayeb, 2010, Patino-Fernandez et al. 2010, Gschwend et al. 1995) Independent of diabetes duration, T1D children with an EOD only showed mild, albeit significant, effects of T1DACD in verbal IQ, memory, and executive function, and moderate but significant effects on spatial memory (table 7). No studies were found that compared T1DACD between T1D adults with an EOD and those with late-onset disease (LOD).

#### 2.4.3.2 Role of hypoglycemia

Eight studies in children (Hannonen et al. 2012, Hershey et al. 2003, Hershey et al. 2004, Crawford et al. 1995, Rovet et al. 1988, Kelly et al. 2010, Draelos et al. 1995, Fanelli et al. 2003) and 11 studies in adults (Geddes et al. 2008, Blackman et al. 1992, Wysocki et al. 2003, Wredling et al. 1990, McAulay et al. 2005, Sommerfield et al. 2003, Ewing et al. 1998, Strachan et al. 2003, Gold et al. 1995, McCrimmon and Frier, 1997, Jacobson et al. 2007, Group, 1996) provided results for the calculation of ES. Our data identified no significant differences in general IQ, memory (and spatial memory), executive function, motor function, and motor speed in relation to a history of severe hypoglycemic episodes in children. In adults, executive function and memory were both significantly affected by severe hypoglycemia. Other cognitive domains did not reveal any significant results, or there was an insufficient number of studies to calculate the ES.



**Table 7 Factors influencing diabetes-associated cognitive decline in children and adults with type 1 diabetes**

Cognitive domain	EOD vs LOD		SH vs no SH		Intensive vs conventional therapy		Poor GC vs good GC	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults
Attention	0.06 (−0.4, 0.53)		–	–	−0.1 (−0.35, 0.15)		–	–
Executive function	−0.07 (−0.38, −0.23)*		−0.14 (−0.34, 0.06)	−0.8 (−1.04, −0.54)*	0.09 (−0.17, 0.34)		−0.03 (−0.24, 0.18)	–
General IQ			−0.04 (−0.25, 0.17)	–	–		−0.15 (−0.49, 0.19)	–
Full IQ			–	–	–		–	–
Verbal IQ	−0.26 (−0.4, −0.11)*		–	–	–		–	–
Performance IQ	−0.1 (−0.39, 0.19)		–	–	–		–	–
Memory	−0.25 (−0.45, −0.05)*		−0.07 (−0.36, 0.22)	−1.02 (−1.28, −0.76)*	0.03 (−0.21, 0.27)		−0.24 (−0.42, −0.04)*	−0.4 (−0.2, −0.03)*
Spatial memory	−0.52 (−0.81, −0.23)*		−0.08 (−0.42, 0.26)	–	–		–	–
Motor function	–		0.00 (−0.5, 0.5)	–	–		–	–
Motor speed	–		−0.08 (−0.42, 0.26)	1.99 (1.49, 2.47)*	−0.16 (−0.43, 0.11)		–	0.03 (−0.05, 0.11)

Data show Cohen's *d*, with 95% confidence intervals in parentheses. \**P* < 0.05 for type 1 diabetic compared with non-diabetic individuals. IQ, intelligent quotient; EOD, early onset of diabetes; LOD, late onset of diabetes; SH, severe hypoglycemia; GC, glycemic control.

2.4.3.3 Are single or recurrent episodes of severe hypoglycemia associated with neurocognitive sequelae?

Only two studies (Crawford et al. 1995, Northam and Lin, 2010) provided results in terms of the number of hypoglycemic episodes; therefore, we did not pool the data from these studies. However, the authors of both studies found a significant correlation between the frequency of severe hypoglycemia (three or more vs one or two episodes) and delay on spatial memory and timing in T1D children (Crawford et al. 1995, Northam and Lin, 2010).

2.4.3.4 Role of intensive versus conventional therapy

Four studies in adults (Howorka et al. 2000, Reichard et al. 1996, Knight et al. 2009, Jacobson et al. 2010) and three studies in children (Ohmann et al. 2009, Wessels et al. 2007, Musen et al. 2008) investigated the effects of different therapies on cognitive function. The results of the present meta-analysis show no significant differences in any of the cognitive domains T1DACD using different forms of medical management (either conventional or intensive treatment).

2.4.3.5 Role of poor glycemic control in T1D subjects

Six studies were used to calculate the ES for T1DACD in poorly controlled T1D adults (Geddes et al. 2008, Wright et al. 2009, Wredling et al. 1990, Howorka et al. 2000, The-Diabetes-Control-and-Complications-Trial-Research-Group, 1993, Wessels et al. 2008) and four studies (Wessels et al. 2007, Howorka et al. 2000, Fanelli et al. 2003, Hershey et al. 2005) were used to calculate the ES in poorly controlled children (HbA1c >8%) compared with T1D subjects with adequate glycemic control (HbA1c ≤8%). Poor glycemic control causes a moderate but significant decline in the memory function of children and adults compared with children and adults with adequate glycemic control, respectively (table 7).

2.4.3.6 Role of complications

The primary predictor of cognitive dysfunction may not be having diabetes per se, but having clinically

significant complications (retinopathy) of diabetes, which may have the same trigger as T1DACD (Ferguson et al. 2003, Ryan et al. 1993). Because only two studies were found that provided data for good ES calculation, pooling of the data was not possible. However, the findings of these two studies suggest that patients suffering from diabetic complication(s) perform significantly worse than controls and T1D subjects without complications, especially on tasks that require sustained attention (Ferguson et al. 2003, Ryan et al. 1993), spatial memory (Ryan et al. 1993), hand–eye coordination (Ryan et al. 1993), fluid intelligence (Ferguson et al. 2003), information processing (Ferguson et al. 2003), and the ability to concentrate (Ferguson et al. 2003).

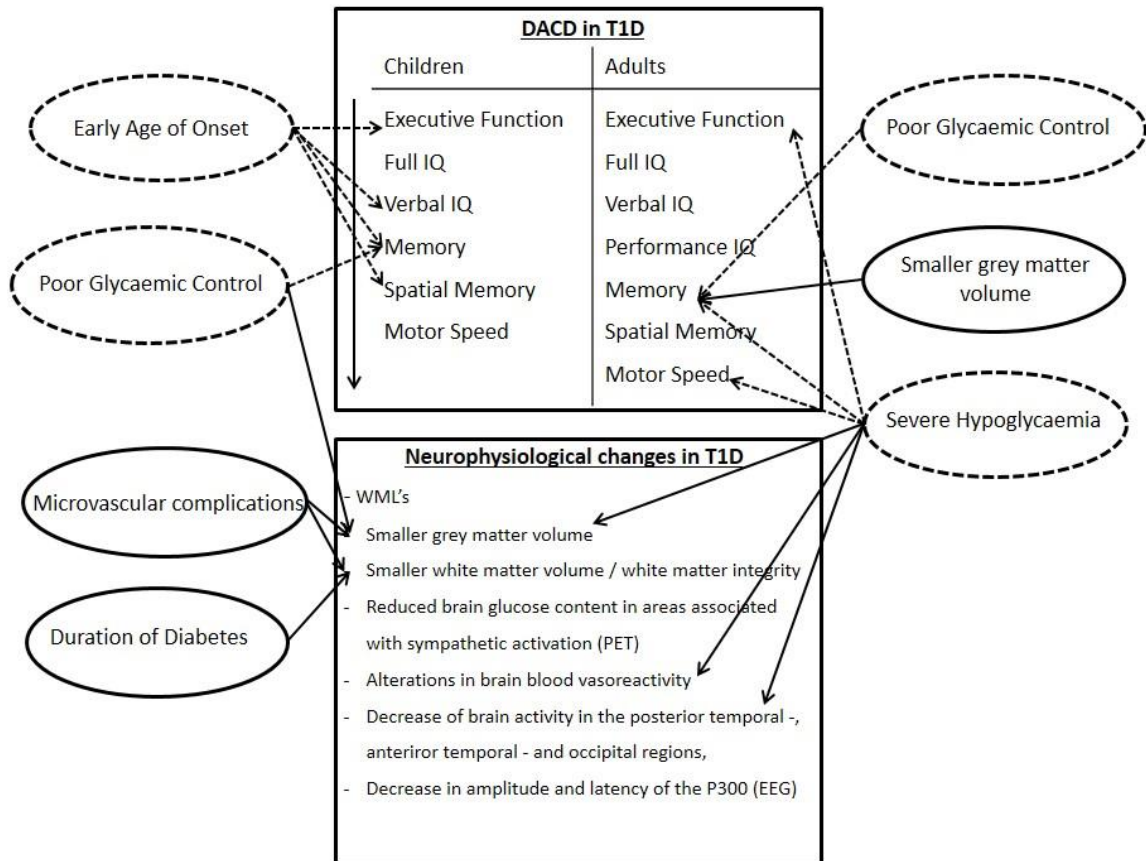
#### 2.4.3.7 Role of C-peptide and/or insulin deficiency

Although C-peptide and/or insulin deficiency is a potential factor involved in a T1DACD as suggested by studies in animals (Li et al. 2005) there have been no studies about the specific effects of C-peptide and/or insulin deficiency on T1DACD in humans with T1D.

## 2.5 Discussion

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Our study strongly supports the hypothesis that T1D has a significant effect on cognitive function. Overall, there is a significant small to modest decrease in cognitive performance in T1D patients compared to non-diabetic controls. Children with T1D performed worse while testing for the executive function, full IQ and motor speed while T1D adults performed worse testing the full and verbal and performance IQ, part of the executive function, memory, spatial memory and motor speed. Motor function and attention were not affected due to diabetes in children and adults. Episodes of hypoglycaemia and chronic hyperglycaemia significantly affected the executive function, memory and motor speed. This meta-analysis could not confirm a negative effect of the different forms of medical treatment, as in line with the DCCT (Group, 1996). Furthermore, we showed that age of onset significantly affects the neurocognitive functioning of T1D children.



**Figure 6 Diabetes-associated cognitive decline (DACD), neurophysiological changes, and their possible causes in type 1 diabetes (T1D).**

Circles indicate T1D-associated factors influencing DACD or neurophysiological changes; arrows reflect correlations or cause-effect relationships; dashed lines, data obtained from the present meta-analysis; solid lines, data obtained through review of the literature (hypothesis only, because a meta-analysis was not possible). IQ, intelligence quotient; PET, positron emission tomography; P300, an event-related potential component elicited in the process of decision making; EEG, electroencephalography.

### 2.5.1 DIABETES-ASSOCIATED COGNITIVE DECLINE IN T1D CHILDREN AND ADULTS

Although executive function, full IQ and motor speed are worse in T1D children, T1D adults exhibit cognitive decline in all but one (attention) cognitive domains. This could indicate that the duration of T1D may play a role in the cognitive decline of T1D patients. Figure 6 shows the possible links between T1DACD and the possible causes in children and adults. Because almost all cognitive domains are affected by T1DACD, the quality of life of patients with T1D may be severely affected. Aggressive glucose management, such as glycemic control, avoiding hypoglycemic episodes, and other diabetes-associated complications, could be a tool to prevent T1DACD.

*2.5.2 EFFECT OF HYPOGLYCEMIC EPISODES ON T1DACD*

The controversy whether a T1DACD in T1D can be caused by hypoglycaemic episodes still exists and the reported cognitive decline varies widely (Li and Sima, 2004, Kramer et al. 1998). 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 2.7-2.9 mmol/L (Warren et al. 2004). However during brain imaging studies, hypoglycaemic-associated changes were only seen when plasma glucose was lowered to 2.5 mmol/L (Kramer et al. 1998) or even at a blood glucose concentration of 2.3 mmol/L (Pramming et al. 1988). This might demonstrate the importance of episodes of severe hypoglycaemia. In an animal study (Puente et al. 2010), rats were subjected to 3 consecutive days of recurrent moderate (1.4 – 2.2 mmol/mol) hypoglycaemia or saline injections. On the fourth day, rats were subjected to a hyperinsulinemic severe hypoglycaemic (0.6 mmol/mol) 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 (Puente et al. 2010).

This meta-analysis showed that only memory and executive function are affected in T1D adults due to severe hypoglycaemia. Indeed, the study of Auer et al. (2004) indicates that the hippocampus is the most vulnerable to hypoglycaemic episodes in the brain. It has also been shown that increases in oxidative stress (which often occur in the mechanisms of DCAD) in the rat hippocampus are associated with decreases in behavioral performance in hippocampal-dependent learning and memory paradigms (Wrighten et al. 2009). We should also note that a high number of insulin receptors are present in the hippocampus (which is critical for memory function) (Faraco et al. 2011) and that glucose facilitates memory function (Park, 2001). During hypoglycaemia, an insulin-stimulated glucose uptake in the hippocampus cannot take place which makes the memory function sensitive to deterioration during hypoglycaemia (Park, 2001). These results are also in line with the results of a study of Musen et al. (2006) who found that hypoglycaemic events (< 40 mg/dl) were associated with lower density of grey matter in brain regions responsible for language processing and memory. Single episodes of severe hypoglycaemia might not be so harmful because it seems that neurobehavioural test performance returns to

prehypoglycaemic baseline levels following restoration of the euglycaemic state (Hershey et al. 2003, 2005).

### *2.5.3 HYPERGLYCEMIA*

Uncontrolled diabetes markedly alters hippocampal gene expression, particularly genes which are involved in synaptic function, plasticity and neurogenesis, all required for normal cognitive function (Thomas et al. 2013). Thomas et al. (2013) evaluated gene expression changes in the hippocampus of STZ mice and found perturbed expression for a number of histone related genes required for various forms of hippocampal-dependent learning and memory and synaptic plasticity (Lubin et al. 2011).

Hippocampal brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, induces neurogenesis and neuroplasticity through diverse roles that include regulation of axonal and dendritic branching and modelling, synaptogenesis in arborizing axon terminals, and synaptic transmission efficiency (Castellano and White, 2008). However, research is needed to establish the role of BDNF in T1DADC in humans with T1D.

### *2.5.4 EFFECT OF HYPERGLYCEMIA ON T1DADC*

In this meta-analysis, poor glycaemic control was found to have negative effects on the memory function of T1D children and adults. Indeed, higher HbA<sub>1c</sub> levels were also associated with lower activation of the brain while lower HbA<sub>1c</sub> levels results in hyperactivation of the brain in a fMRI study (Bolo et al. 2011). Hypoactivation is correlated with a lowered cognitive performance (Sanchez-Carrion et al. 2008) while hyperactivation is thought to permit the subject to compensate for reduced efficiency of their white matter (Bolo et al. 2011). The latter could reflect an upregulation of glucose transport in the brain, as seen in patients with good glycaemic control (Bolo et al. 2011). In the DCCT trial (1993), T1D patients with higher levels of HbA<sub>1c</sub> performed worse on motor speed and psychomotor efficiency, but we could not pool those data to give consistent results on motor speed and motor function because not full data was provided for the calculation of effect sizes.

As a long-term, integrated average of tissue exposure to hyperglycemia, HbA<sub>1c</sub> is the best reflection of average glucose concentrations of diabetes, but fails to capture glycemic variability and the risks

associated with extremes of hypoglycemia and hyperglycemia. Glycemic variability is significantly associated with changes in white matter structure in young T1D children (Barnea-Goraly et al. 2014), and may consequently contribute to T1DACD. Nonetheless, this aspect is not often studied in relation to cognitive function. Gonder-Frederick et al. (2009) investigated found that deteriorations in mental efficiency is associated with episodes of hypo- and hyperglycemia in T1D children. This finding has important implications, but should be included in further research before general conclusions are made.

#### *2.5.5 AGE OF DIABETES ONSET*

The present meta-analyses found that children with EOD showed reductions in executive function, verbal IQ, performance IQ, memory, and spatial memory, which are in line with the results reported by Gaudieri et al. (2008) but contrast with those of Brands et al. (2005) We have to note that Brands et al. (2005) considered <15 years as an upper limit for the measurement of EOD, whereas we considered <7 years as the upper limit. Lower attention and executive function abilities have been identified in children with learning disabilities and these may impact on learning in the classroom (Gaudieri et al. 2008). Children with an EOD have significantly more severe episodes of hypoglycemia than children with LOD. Therefore, the literature assumed that episodes of severe hypoglycemia could be linked to the deteriorated cognitive function in T1D children. However, our meta-analysis did not confirm this because episodes of severe hypoglycemia did not have any significant effect on cognitive decline in children in any domain. In brain imaging studies, results from MRI scans showed that an EOD was associated with higher rates of mild-to-moderate ventricular atrophy (61% vs. 20%) and higher rates of white matter lesions within the hippocampus (14% vs. 2%) (Wessels et al. 2006). Following the study of Ryan et al. (2008) correlational analyses revealed relationships between brain volume and performance on cognitive tasks, providing strong support for the view that an EOD may affect normal brain development, and this eventuates into T1DACD.

#### *2.5.6 SUPPLEMENTARY INFORMATION PROVIDED BY NEUROIMAGING*

Brain imaging techniques are often used in diabetes research. Although MRI techniques are used to assess

white and grey matter, a newer and more sensitive technique (diffusion tensor imaging [DTI]) has been developed that enables evaluations of the integrity of white matter tracts (Musen 2008). It is well known that whole grey and white matter volume is closely related to neuropsychological performance (DCCT, 1996; Marshall et al. 1970), and therefore measures of brain atrophy are well correlated with and predictive of cognitive impairment. White matter atrophy has been shown to be the best predictor of mental processing speed and working memory, whereas grey matter atrophy is associated with verbal memory, euphoria, and disinhibition (Musen et al. 2008). In T1D patients, smaller white matter volumes are significantly associated with microvascular complications (Musen et al. 2008; Warren et al. 2004) and it has been reported that smaller white matter volume is associated with worse performance in the domains of speed of information processing, attention, and executive function (Wysocki et al. 2003).

The magnitude and directionality of water diffusion in the white matter tracts (called fractional anisotropy [FA]) are measured by DTI, and this may permit identification of tissue injury (Kodl et al. 2008). Previous studies have shown that reduced FA correlates to cognitive dysfunction in a variety of conditions, including schizophrenia and depression (Kodl et al. 2008). In T1D patients, reduced FA was correlated with poorer performance on executive function and motor function (Kodl et al. 2008), both of which are believed to assess white matter function. These results indicate that atrophy of both grey and white matter plays a noticeable role in cognitive performances and consequently has possible functional consequences in T1D.

#### *2.5.7 ECOLOGICAL VALIDITY*

It is assumed that impaired brain processes, which lead to poor performance on neuropsychological tests, will also lead to poor performance in a 'real life context', which implies that neuropsychological tests have ecological validity. Surprisingly, there has been very little research investigating the ecological validity of neuropsychological tests (Chaytor et al. 2006). Thus, in practice, poor performance that is observed only in the context of a neuropsychological test could be of limited clinical relevance, or vice versa. In this way, caution is needed when interpreting or translating results into clinical practice. By subjecting a greater amount of data to meta-analysis, we tried to eliminate some of these biases.



*2.5.8 LITERATURE WEAKNESSES AND LIMITATIONS*

The diversity of the methodology used in studies often makes generalization of results difficult. There is some controversy as to whether T1DACD may or may not occur during hypoglycemic periods. (Li and Sima, 2004, Kramer et al. 1998) Although the DCCT trial (The-Diabetes-Control-and-Complications-Trial-Research-Group, 1993) provided a comprehensive definition of severe hypoglycemia, not all studies use the same definition and, furthermore, not all studies define severe hypoglycemia. In addition, different terms (e.g. choice reaction time and complex reaction time) are used in conjunction with what are essentially equivalent definitions. Finally, different authors use diverse definitions for the same term (e.g. hypoglycemia), which can also complicate the generalization of results.

The present meta-analysis shows that diabetes duration and its related diabetic complications may have a strong influence on T1DACD, but proper ES calculations could not be performed because most of the studies did not subdivide their subject groups into 'duration' groups. Furthermore, the factor 'diabetes duration' is associated with an increased risk of episodes of hypoglycemia, hyperglycemia, diabetes-associated complications. Therefore, ES calculations on episodes of hypoglycemia, chronic hyperglycemia, glycemic variations, complications etc., may provide more information with regard to the causes of the cognitive decline rather than diabetes duration itself. For example, Rajashree et al. (2011) performed a study to determine the effects of different 'durations' of diabetes on cognitive parameters in young streptozotocin-diabetic rats and observed cognitive deficits in rats that had been diabetic for 20 days compared with their 10-day counterparts. However, because the rats in that experiment had very high glucose levels (at least 2.5-fold higher than the control group), these authors probably measured the effects of hyperglycemia on cognitive function rather than the effects of diabetes duration on cognitive function.

Furthermore, autonomic neuropathy, an under-recognized complication of diabetes, was only addressed in two studies included in the present meta-analysis, without further details on cognitive performance in subjects with or without autonomic neuropathy. Because this nerve disorder affects autonomic nerves and consequently disrupts signals between the brain and portions of the autonomic nervous system, it is not inconceivable that diabetes-associated cognitive decline is associated with autonomic neuropathy (Tang et al. 2013). This topic should be addressed in future studies.

## 2.6 Conclusions

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Overall, it was demonstrated that T1D has an effect on cognitive function. Episodes of severe hypoglycemia, chronic hyperglycemia, and age of onset are factors influencing cognitive function in T1D. Understanding the mechanisms that contribute to the pathophysiology of T1DACD could be helpful in detecting changes in cognitive function before they occur. Future research should focus on the prevention of T1DACD.

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CHAPTER 3. EFFECTS OF DIFFERENT TYPES OF ACUTE AND  
CHRONIC (TRAINING) EXERCISE ON GLYCAEMIC CONTROL IN TYPE 1  
DIABETES MELLITUS

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# Effects of Different Types of Acute and Chronic (Training) Exercise on Glycaemic Control in Type 1 Diabetes Mellitus

## A Meta-Analysis

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### 3.1 Abstract

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**Objective:** Exercise has been accepted and generally recommended for the management of type 1 diabetes mellitus (T1D) and for improving the overall quality of life in affected individuals. This meta-analysis was conducted to determine the overall effects of exercise (acute bouts of exercise and chronic exercise [or training]) on acute and chronic glycaemic control in patients with T1D, the effects of different types of exercise on glycaemic control and which conditions are required to obtain these positive effects. **Methods:** PubMed, ISI Web of Knowledge and SPORTDiscus™ were consulted to identify studies on T1D and exercise. Cohen's *d* statistics were used for calculating effect sizes (ES) (*d*) for means as small *d* = 0.3, medium *d* = 0.5 and large *d* = 0.8). Ninety-five percent confidence intervals (95% CIs) were used to establish the significance of our findings.

**Results:** From a total of 937 studies, 33 that met the inclusion criteria were selected. Nine studies were used to calculate the ES of a single bout of aerobic exercise; 13 studies to calculate the ES of aerobic training; 2 studies to calculate the ES of strength training; 4 studies to calculate the ES of combined (aerobic and strength) training and 6 studies to calculate the ES of high-intensity exercise (HIE) and training. ES for exercise on acute glycaemic control were large, while they were small for chronic glycaemic control. Aerobic exercise, resistance exercise, mixed exercise (aerobic combined with resistance training) and HIE acutely decreased blood glucose levels. To prevent late-onset hypoglycaemic episodes, the use of single bouts of sprints into an aerobic exercise can be recommended. This meta-analysis also showed that a regular exercise training program has a significant effect on acute and chronic glycaemic control, although not all exercise forms showed significant results. Specifically, aerobic training is a favourable tool for decreasing chronic glycaemic control, while resistance training, mixed and HIE did not significantly improve chronic glycaemic control. Although, this meta-analysis showed there was a tendency for improvement in glycaemic control due to resistance training or resistance training combined with endurance training, there were not enough studies and/or subjects to confirm this statistically.

**Conclusions:** Based on this meta-analysis, we can conclude that the addition of brief bouts of high-intensity, sprint-type exercise to aerobic exercise can minimize the risk of sustaining a hypoglycaemic episode. We can also conclude that only regular aerobic training will improve the glycated haemoglobin level of a patient with T1D.

## 3.2 Introduction

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Exercise has been accepted and generally recommended for the management of T1D and for improving the overall quality of life in affected individuals. In addition to increasing aerobic fitness, reducing cardiovascular risk factors, and reducing body weight and body fat, physical activity develops and maintains chronic glycaemic control by enhancing insulin sensitivity and stimulating muscle glucose uptake. The American College of Sports Medicine (ACSM) has published a guideline for exercise testing and prescription in T1D (Medicine, 2000). This guideline recommends that individuals with T1D need to work out 20-45 minutes at an intensity of 40-60% of their  $VO_{2max}$  (maximal oxygen uptake) for 5-7 days/week, or daily at low to moderate intensity. The ACSM guidelines also advocate strength training as an integral part of the training program. Both the American Diabetes Association and the ACSM recommend patients with T1D to keep blood glucose levels before, during and after exercise above 5.5 mmol/L and below 13.8 - 16.7 mmol/L. If these criteria are not met, it is recommended to delay exercise to determine as to whether or not ketones are present.

Unfortunately, due to the complexity of regulating exogenous insulin in a physiologic manner during exercise, physical activity often results in episodes of hypoglycaemia or hyperglycaemia shortly following or even long after completing exercise (MacDonald, 1987). Owing to the persistent increase of 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, exercise could affect the blood glucose values 24h following intense prolonged exercise and so late onset of hypoglycaemia can occur regardless of appropriate insulin reduction (Graveling and Frier, 2010, MacDonald, 1987). Besides this, previous exercise and the occurrence of previous hypoglycaemic episodes or poor glycaemic control, can affect the hypoglycaemic counter-regulatory mechanisms, which may cause a severe hypoglycaemia (Toni et al. 2006). Moreover, T1D athletes with higher levels of physical activity tend to have an impaired glucose counter-regulatory hormone response to hypoglycaemia (Aussedat et al. 2000). On the other hand, the opposite effect can occur in patients with poor glycaemic control. Patients with poor glycaemic control can easily develop hyperglycemia (with or without ketosis) as a consequence of exercise. Even in well controlled T1D patients with adequate insulinization, acute high intensity exercise may cause hyperglycemia due to an increase in catecholamines and sympathetic nervous system activation of hepatic glucose production which exceeds the rate of glucose use (Toni et al. 2006). Since circulating endogenous insulin levels cannot increase after exercise in T1D patients, even slight

hyperglycaemic episodes should need small doses of supplemental insulin injection in order to prevent higher levels of blood glucose in the post-exercise phase. Chronic glycaemic control, expressed as glycaeted haemoglobin levels (HbA<sub>1c</sub>), represents a measurement to identify the average plasma glucose on haemoglobin. As red blood cells, which contains the haemoglobin, survives up to 120 days - in which a non-enzymatic glycaetion pathway is formed with plasma glucose - it is assumed that HbA<sub>1c</sub> levels are a good marker for average blood glucose levels over the previous months. HbA<sub>1c</sub> was traditionally expressed as % HbA<sub>1c</sub> (to the total amount of haemoglobin), but recently, it is also expressed as mmol/mol (HbA<sub>1c</sub>/total Hb).

Although the current guidelines are well-established, questions remain concerning the exact effect of training on glycaemic control in T1D. While a large body of literature exists, full comparison across individual studies are largely qualitative and hampered by a wide range of study characteristics, including subject population demographics and exercise modalities. For example, most existing exercise and T1D studies have focused on the effects of aerobic exercise (acute and training) on acute and chronic glycaemic control. In contrast, a relatively smaller subset of studies have been published determining the effects of an acute bout of strength exercise or strength training (Durak et al. 1990, Ramalho et al. 2006), combined strength and aerobic exercise or training (Heyman et al. 2007b) and high intensity (or sprint) exercise or training (Guelfi et al. 2005, Guelfi et al. 2007, Harmer et al. 2008, Bussau et al. 2006). Thereby, lots of aspects concerning the optimal mode and amount of exercise per week remain unclear. Furthermore, studies vary widely in terms of insulin or dietary advice during exercise, or changes in VO<sub>2max</sub> levels through training. One approach to provide a more precise and quantitative comparisons across such a large and heterogeneous body of literature is via a meta-analysis, which tends to be more objective and consistent than a narrative review because of its mathematical nature (Pilcher et al. 2002). Meta-analyses have been successfully employed in a number of topics in exercise science, including the effects of thermal stress on cognition, (Pilcher et al. 2002) where wide heterogeneity existed in the degree of thermal stress and also the type of cognitive testing. To the best of our knowledge this is the first meta-analysis on the effects of exercise and training on acute or chronic glycaemic control in T1D individuals. Therefore our hypothesis is that exercise will have beneficial effects on acute and chronic glycaemic control. For the purpose of this article we defined acute exercise as ‘exercise’ while chronic exercise is defined as ‘training’. This second meta-analysis consisted of three primary research questions:

1. The effect across all different forms of acute exercise on acute glycaemic control.

2. The effects of different types of (chronic) training (endurance, strength, combined, or high-intensity training) to determine whether different types of exercise have different effects on chronic glycaemic control.
3. The nature of exercise training (e.g. frequency, duration) and modifying factors (e.g. dietary or insulin advice) required to provide a threshold for improved glycaemic control.

### 3.3 Materials & Methods

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#### 3.3.1 DATA SOURCES

The overall goal of the current study was to examine whether the blood glucose values of subjects with T1D are influenced by physical activity. Three electronic databases were consulted: *Pubmed*, *ISI Web of Knowledge* and *SPORTDiscus*. Key terms (and synonyms searched by MeSH database) that were included and combined were: 'Type 1 Diabetes Mellitus', 'blood glucose', 'humans', 'HbA<sub>1c</sub>', 'metabolic control', 'glycaemic control', 'physical activity' and 'exercise'.

#### 3.3.2 STUDY SELECTION

Studies in this meta-analysis needed to fulfill the following inclusion criteria: 1) subjects diagnosed with T1D, 2) original data reported with sufficient information to allow calculation for Effect Sizes (ES) (group means, standard deviation (SD), or standard *error* of the mean (*SEM*) which were recalculated to SD), 3) no severe methodological flaws, 4) published before the end of 2011. In- or exclusion of articles was performed by applying the above criteria on the title, abstract and/or full text. Case studies and reviews were excluded, although the latter's bibliographies were consulted. The university's library, hand searches, electronically databases and contact with the authors (by mail) were used for the extraction of more details of the manuscripts if necessary. Figure 7 shows the progress of the literature screening and the reasons for in- or exclusion.

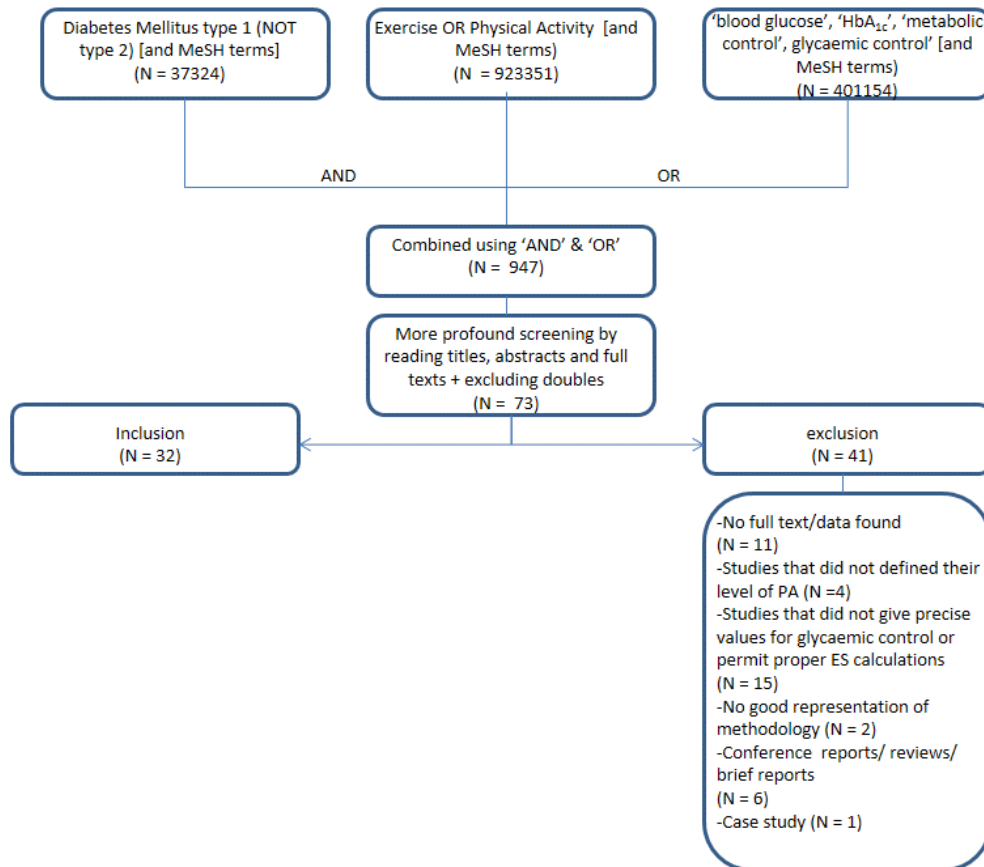


Figure 7 Flow diagram illustrating selection of the included studies

### 3.3.3 DATA EXTRACTION, SYNTHESIS AND REPORT

Effects of exercise (i.e. single bout of exercise) and ‘training’ (i.e. chronic exercise) were distinguished in the analyses. Differences in exercise modes were classified into aerobic exercise, resistance exercise, combined studies (both aerobic and resistance training) and high-intensity exercise. The dependent variables were HbA<sub>1c</sub> as a key marker of chronic glycaemic control and different values for capillary glucose levels or interstitial glucose levels or venous plasma glucose levels, as well as glucosuria as determinants of acute glycaemic control (depending on the displayed value in the studies). All glucose levels not displayed in mmol/L were recalculated in mmol/L to be able to compare all results. Study characteristics from the selected articles are shown in tables 8-12. Cohen’s *d* statistics were used for calculating ES, weighted by the sample size of the study. Cohen (1988) defined effect sizes (*d*) for means as small *d* = 0.3, medium *d* = 0.5 and large *d* = 0.8. Ninety-five percent confidence intervals (95% CI) were used to establish the significance of our findings. Positive effects indicate an

increase in the dependent variable while negative effects indicate a decrease. Both fixed and random effect models were included for calculating ESs. To display effects of exercise and training on (acute & chronic) glycaemic control in patients with T1D, the heterogeneity of the studies must be taken into account. The studies should be comparable in population, type of exercise, duration of exercise and age of subjects. Only if these conditions were met, a data pooling could be performed. Differences in exercise forms were classified into acute aerobic exercise, acute high intensity exercise, chronic aerobic training, chronic strength training, combined (aerobic + strength) training or chronic high intensity training. High Intensity exercise (acute bout) or training (chronic) (also called 'High Intensity intermittent exercise', 'High-Intensity interval training' or 'sprint interval training') was defined as an exercise form including brief bouts of high-intensity, sprint-type exercise (Gibala, 2007) and so have alternating periods of short intense anaerobic exercise near 100%  $VO_{2peak}$  and less-intense recovery periods. Nine studies were used to calculate the ES of a single bout of aerobic exercise; 13 studies to calculate the ES of aerobic training; 2 studies to calculate the ES of strength training; 4 studies to calculate the ES of combined (aerobic and strength) training and 6 studies to calculate the ES of high intensity exercise and training.

#### 3.3.4 *QUALITY ASSESSMENT*

Depending on the article, the methodological quality was assessed using different assessment tools of 'SIGN' (Scottish Intercollegiate Guidelines Network) checklists (Harbour, 2001). This checklist assesses the randomization, concealment method, blinding of subjects and/or investigators, drop-out, intention-to-treat-analysis, eligibility criteria and follow-up. Two papers (research letters) were excluded because they did not provide enough methodological data for meta-analyzing their results (Perrone et al. 2005, Raile et al. 1999).

Table 8 Effects of a single bout of aerobic exercise on blood glucose levels in T1D patients

Reference	N° of Subjects (males)	Age (ys)	HbA <sub>1c</sub> (%)	Characteristics Glucose levels (mmol/L) pre/post	Insulin doses/day	Intervention	Outcome
Heyman et al. 2005	7 T1D (7) 7 CG	10.5 ± 0.3 10.3 ± 0.3	7.7 ± 0.7	[C] 15.4 ± 1.6 → 9.2 ± 1.8	0.92 ± 0.2 IU.kg <sup>-1</sup> .day <sup>-1</sup>	Evaluating aerobic fitness during an incremental maximal test and Aerobic power PWC <sub>170</sub> . [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	50 T1D (NA)	14.8 ± 1.7	7.8 ± 0.8	[V(serum)] 8.8 ± 3.4 → 6.2 ± 3.2	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	19 T1D (0) 19 CG	15.9 ± 0.3 16.6 ± 1.1	8.1 ± 0.3	[VP] 13.8 ± 1.0 → 12.2 ± 0.3	68.3 ± 3.1 IU.day <sup>-1</sup>	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	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	[VP] Good GC: 9.5 ± 4.5 → 8.4 ± 3.0 Poor GC: 14.4 ± 6.5 → 13.9 ± 5.09	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	7 T1D (4)	21.6 ± 4	7.4 ± 1.5	[C] 11.0 ± 2.3 → 6.6 ± 1.2	14.8 ± 7.5 IU.day <sup>-1</sup>	A 30-min session of moderate continuous training (40% of VO <sub>2max</sub> ). [IA -, DA-]. [PP].	- Capillary glucose level significant ↓
West et al. 2011	7 T1D (7)	31 ± 2	8.3 ± 0.1	[V] 30 min: 12.2 0.6 → 8.5 ± 0.4 120 min: 12.0 ± 0.8 → 5.6 ± 0.3	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 <sub>2max</sub> ). [IA+, DA+]. [PP]. Insulin injection 30, 60, 90 and 120 min prior to the exercise.  30 minutes of walking (< 50% of their VO <sub>2max</sub> ) 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.	- 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	6 T1D (3)	42.7 ± 13.6	7.4 ± 0.9	[P] 15.3 ± 3.0 → 11.0 ± 0.7	27.2 ± 9.4 IU.day <sup>-1</sup>	45 min at 50% of VO <sub>2max</sub> . [IA infusion, DA NA] 2 groups: 1 group continuous insulin infusion, 1 group received one-third of usual intermediate acting	- Blood glucose values significant ↓ when exercise is performed after breakfast, but not when exercise is performed before breakfast.
Zinman et al. 1977	16 T1D (10)	30 (22-43)	NA	[P] 12.6 ± 0.9 → 8.7 ± 1	NA		- Rapid ↓ in glucose in subjects receiving one third of usual insulin. [P] glucose during exercise is constant in subjects with iv insulin infusion.

Reference	N° of Subjects (males)	Age (ys)	HbA <sub>1c</sub> (%)	Characteristics Glucose levels (mmol/L) pre/post	Insulin doses/day	Intervention	Outcome
Zinman et al. 1984	13 T1D (7)	30.0 ± 1.8	10.7 ± 0.3 → 10.3 ± 0.8	[P] 12.5 ± 0.9 → 8.2 ± 0.9	37.6 ± 3.2 IU.day <sup>-1</sup>	insulin by subcutaneous injection. [FS]. Exercise ~ 1h after insulin injection. A 45-min session of aerobic exercise (60-85% of their VO <sub>2max</sub> ). [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; T1D = Type 1 Diabetes; 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<sub>1c</sub> = glycaeted haemoglobin; VO<sub>2max</sub> = maximal oxygen uptake; PWC = Physical Working Capacity.



Table 9 Effects of aerobic training on glycaemic control in T1D patients

Reference	N° of Subjects (males)	Age (ys)	HbA <sub>1c</sub> (%) (pre/post)	Characteristics Glucose levels (mmol/L) (pre/post)	Insulin doses/day	Intervention	Outcome
Huttunen et al. 1989	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	[V, P, C = NA] 13.4 ± 5.2 → 14.0 ± 5.3	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 <sub>1c</sub> levels ↑ significant - VO <sub>2max</sub> (pre → post exercise): 40.0 ± 7.2 → 43.8 ± 8.6 ml.min <sup>-1</sup> .kg <sup>-1</sup>
Rowland et al. 1985	14 T1D (7)	9-14	9.9 ± 1.4 → 10.1 ± 1.1	[P] FGL: 15.1 ± 5.0 → 16.5 ± 6.5	NA	1h, 3/wk, 12 wk aerobic (running/walking) exercise. [DA+, IA-]. [PAS, PP, FS = NA].	- VO <sub>2max</sub> ↑ sign (38.4 ± 4.6 → 41.9 ± 6.0 ml.min <sup>-1</sup> .kg <sup>-1</sup> ) - HbA <sub>1c</sub> , fasting blood glucose and glucosuria (24h) did not change significant
Wong et al. 2011	12 EG (4) 11 CG (2)	12.3 ± 2.07	CG: 8.1 ± 1.1 EG: 8.2 ± 1.4	NA	NA	12 wks, 3d/wk aerobic (40-60% VO <sub>2max</sub> ), 30 min. [IA/DA NA]. [PAS, PP, FS = NA].	- 9 month FU → aerobic exercise group had lower HbA <sub>1c</sub> levels than self-directed group. - No changes in VO <sub>2max</sub> .
Bernardini et al. 2004	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	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 <sub>1c</sub> . (60 min significant with 120-360 min and 360-480 min).
Marrero et al. 1988	10 T1D (6)	13.3 (12-14)	Pre → post : 10.1 ± 1.9 → 9.2 ± 2.2	NA	NA	Non-supervised aerobic home exercise protocol: 45 min, 3/wk, 12 wks (heart rate 160 bpm). [IA-, DA+]. [PAS, PP, FS = NA].	- HbA <sub>1c</sub> levels ↓ significant - VO <sub>2max</sub> ↑ significant (40.4 ± 8.8 → 44.9 ± 12.9 ml.min <sup>-1</sup> .kg <sup>-1</sup> )
Michaliszyn et al. 2011	12 T1D	12-19	9.4 ± 1.8 → 9.4 ± 2.0	NA	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 <sub>1c</sub> did not change significant No measurement of VO <sub>2max</sub> .
Ruzic et al. 2007	20 T1D (NA)	12.8 ± 2.1 (9-16)	Pre → post: 8.3 ± 1.3 → 7.9 ± 1.4	[C] 6.24 → 5.9	3.6 ± 0.6 IU.day <sup>-1</sup> 0.9 ± 0.2 IU.kg <sup>-1</sup> .day <sup>-1</sup>	High volume, low intensity program → 60 min, <75% of HR <sub>max</sub> , 2 x 5 days, 3x/day, exercise camp for children. [IA/DA-]. [PP]	- HbA <sub>1c</sub> sign ↓ 10 days after camp, but significant ↑ 2 months after training - Blood glucose values ↓ significant the last days of training session - No VO <sub>2max</sub> levels were shown.
Sideraviciute et al. 2006	19 T1D (0)	14-19	8.5 ± 0.4 → 7.8 ± 0.3	[P] FGL: 9.6 ± 0.5 → 9.0 ± 0.8 Pre → post exercise: 9.0 ± 0.8 → 6.3 ±	Short term: 26.4 ± 1.8 IU.day <sup>-1</sup> → 25.0 ± 7.8 IU.day <sup>-1</sup>	Long term swim (aerobic) training: 45 min, 2/wk, 14 wks. [IA/DA NA]. [PAS, PP, FS = NA].	- HbA <sub>1c</sub> ↓ significant - Daily short acting insulin dose ↓ significant after exercise program.

Reference	N° of Subjects (males)	Age (ys)	HbA <sub>1c</sub> (%) (pre/post)	Characteristics Glucose levels (mmol/L) (pre/post)	Insulin doses/day	Intervention	Outcome
				0.9			- No VO <sub>2max</sub> levels were shown.
Laaksonen et al. 1999	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	[P] 10.5 ± 6.0 → 12.1 ± 6.0 CG→EG: 12.1 ± 6.0 → 11.9 ± 5.8	Pre→post training: 0.7 ± 0.2 → 0.7 ± 0.2 IU.kg <sup>-1</sup> .day <sup>-1</sup> CG→EG: 0.7 ± 0.2 → 0.7 ± 0.2 IU.kg <sup>-1</sup> .day <sup>-1</sup>	1 wk, 20-30 min, 50-60% VO <sub>2peak</sub> gradually increased to 12-16 wks, 30-60 min, 3-5/wk, 60-80% VO <sub>2peak</sub> aerobic training program. [IA/DA NA]. [PAS, PP, FS = NA].	- VO <sub>2max</sub> significant ↑ in training group (43.4 ± 8.0 → 46.1 ± 6.6 ml.min <sup>-1</sup> .kg <sup>-1</sup> ) - HbA <sub>1c</sub> ↓ with training and compared to control group
Lehmann et al. 1997	20 T1D (13)	33 ± 7.7 (22-48)	7.6 ± 4.4 → 7.5 ± 4.0	[V] 7.9 ± 1.7 → 7.5 ± 1.6	48.4 ± 15.1 → 40.4 ± 13 IU.day <sup>-1</sup>	3 x /wk, min 45 min, 3 months of regular endurance exercise, 50- 70 % VO <sub>2max</sub> . [IA/DA NA]. [PAS, PP, FS = NA]. 40 min run or walk, first 2 wks: 60-70% HR <sub>max</sub> , 3-6 <sup>th</sup> week= 70-80% HR <sub>max</sub> , 7-12 <sup>th</sup> weeks= 70-90% HR <sub>max</sub> , 3/wk, 12 wks, aerobic training. [IA+, DA+]. [PAS, PP, FS = NA].	- Total insulin (IU/day) ↓ significant - HbA <sub>1c</sub> did not ↓ significant - VO <sub>2max</sub> increased significant (2914 ± 924 → 3092 ± 905 ml/min). - No difference in lipid profile or fasting blood glucose before and after the exercise program, while the HbA <sub>1c</sub> increased.
Ramalho et al. 2006	7 T1D (2)	19.8 ± 5.1	8.7 ± 1.6 → 9.8 ± 1.8	[C] FGL 12.76 ± 6.5 → 15 ± 6.0	0.95 ± 0.3 → 0.79 ± 0.3 IU.kg <sup>-1</sup> .day <sup>-1</sup>	45 min aerobic exercise, 3/wk, 12 wks (60-85% of their VO <sub>2max</sub> ). [IA-DA- (daily routines)]. Exercise ~ 45 -135 min after insulin injection.	- Self-monitored blood glucose levels, measured before and after each session, showed a significant ↓ post compared to pre exercise training.
Wallberg – Henrikson, 1986	6 EG (NA) 7 CG (NA)	63 ± 2 35 ± 2	10.4 ± 1.5 10.6 ± 1.6	NA	32 ± 2 IU.day <sup>-1</sup> 43 ± 5 IU.day <sup>-1</sup>	20 min of daily bicycle exercise during 5 months vs. non training. [IA/DA NA]. [PAS, PP, FS = NA].	- VO <sub>2max</sub> ↑ significant (pre→post training: 30.2 ± 2.1 → 32.7 ± 2.1 ml.min <sup>-1</sup> .kg <sup>-1</sup> ) - HbA <sub>1c</sub> did not change significant after training
Zinman et al. 1984	13 T1D	30.0 ± 1.8	10.7 ± 0.3 → 10.3 ± 0.8	[P]FGL: 10.8 ± 1.5 → 11.2 ± 1.7	37.6 ± 3.2 IU.day <sup>-1</sup>		- VO <sub>2max</sub> increased sign (33.8 ± 1.7 → 40.0 ± 4.0 ml.min <sup>-1</sup> .kg <sup>-1</sup> ) - [P] FGL and HbA <sub>1c</sub> did not significant change

Data are 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; 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<sub>1c</sub> = glycaeted haemoglobin; VO<sub>2max</sub> = maximal oxygen uptake; VO<sub>2peak</sub> = peak oxygen uptake; HR<sub>max</sub> = maximum heart rate.

Table 10 Effects of strength training on blood glucose levels in T1D patients

Reference	N° of Subjects (males)	Age (ys)	Characteristics			Intervention	Outcome
			HbA <sub>1c</sub> (%)	Glucose levels (mmol/L) (pre/post)	Insulin doses/day		
Durak et al. 1990	8 T1D (8)	31 ± 3.5	6.9 ± 1.4 → 5.8 ± 0.9	[C] 7.8 ± 3.1 → 7.0 ± 2.9	46.2 ± 15 → 41.6 ± 16 IU.day <sup>-1</sup>	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 <sub>1c</sub> and glucose levels ↓ significant
Ramalho et al. 2006	6 T1D (1)	20.8 ± 4.7	8.2 ± 2.9 → 7.6 ± 1.6	[C] FGL (capillary) 7.7 ± 6.5 → 10.0 ± 4.8	0.95 ± 0.3 → 0.79 ± 0.28 IU.day <sup>-1</sup>	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; 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] = Post absorptive state (5-11h after last meal); [PP] = Post prandial (during 4h after meal); [FS] = Fasting state (> 12h after meal); HbA<sub>1c</sub> = glycaeted haemoglobin.

Table 11 Effects of combined (aerobic and strength) training program on glycaemic control in T1D patients

Reference	N° of Subjects (males)	Age (ys)	Characteristics		Intervention	Outcome	
			HbA <sub>1c</sub> (%)	Glucose levels (mmol/L) (pre/post)			Insulin doses/day
Bernardini et al. 2004	90 T1D	14.8 ± 2.7	60 min exercise/wk: 8.9 ± 0.5 Mixed: 7.4 ± 0.6	NA	NA	Prospective cohort study: aerobic activity defined as: walking, cycling, skating and swimming. Mixed defined as: soccer, volleyball, tennis, basketball. No intensity/quantity shown. [DA/IA NA]	- Significant lower HbA <sub>1c</sub> levels in children performing > 360 min (mixed training) of exercise compared to children < 60 min/wk (aerobic training)
D'Hooge et al. 2011	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	[C] 8.5 → 8.2	0.96 → 0.9 IU.kg <sup>-1</sup> .day <sup>-1</sup>	20 wks, 2/wk, 70 min, aerobic and strength group. Aerobic part: 60-75% of HR <sub>peak</sub> . 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 <sub>1c</sub> not significant ↓ - EG: Daily insulin doses: significant ↓ - EG: VO <sub>2peak</sub> ↓ not significant (1478 → 1425 (mL/min))
Heyman et al. 2007b	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	Pre → post EG: [P] 9.6 ± 1.2 → 7.6 ± 0.9 FPGL EG: 10.4 ± 1.2 CG: 15.3 ± 1.5	EG: 1.0 ± 0.1 U.kg <sup>-1</sup> .day <sup>-1</sup> CG: 1.1 ± 0.1 U.kg <sup>-1</sup> .day <sup>-1</sup>	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 - HbA <sub>1c</sub> ↓ not significant in EG compared with CG - [P]FGL were significant ↓ in EG compared with CG. - PWC <sub>170</sub> was not significant ↑ in watts/kg.
Mosher et al. 1998	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	NA	1.02 ± 0.12 IU.kg <sup>-1</sup> .day <sup>-1</sup>	45 min, 3/wk; 12 wks. Aerobic circuit training + strength training. [IA-/DA NA]. [PAS, PP, FS = NA].	- HbA <sub>1c</sub> ↓ 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<sub>1c</sub> = glycaeted haemoglobin; VO<sub>2peak</sub> = peak oxygen uptake; PWC = Physical Working Capacity; HR<sub>peak</sub> = Heart Rate Peak.

Table 12 Effects of HIE exercise and training on glycaemic control in T1D patients

Reference	N° of Subjects (males)	Age (ys)	HbA <sub>1c</sub> (%)	Characteristics Glucose levels (pre/post) mmol/L	Insulin doses/day	Intervention	Outcome
Bussau et al. 2006	7 T1D (7)	21 ± 3.5	7.4 ± 0.8	[C] Mod: 11.9 ± 1.1 → 3.1 ± 1.3 Mod + Sprint (further fall in 120 min): 11.2 ± 1.1 → 3.6 ± 1.3	NA	40% VO <sub>2peak</sub> 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	7 T1D (4)	21.6 ± 4	7.4 ± 1.5	[C] MOD: 11.0 ± 2.3 → 6.6 ± 1.2 [C] MOD + IHE: 11.6 ± 1 → 8.6 ± 2.1	14.8 ± 7.5 IU.day <sup>-1</sup>	30 min continuous cycling exercise at 40% VO <sub>2peak</sub> , interspersed with 16x 4-s maximal sprint efforts [IA -, DA-] compared to 30min continuous cycling at 40% VO <sub>2peak</sub> . [PP]. Exercise ~ 3.5h after insulin injection.	- Glucose production = ↑ in MOD+HIE vs MOD - Glucose utilization = ↓ MOD vs MOD+HIE
Guelfi et al. 2007	9 T1D (5)	22.6 ± 5.7	7.7 ± 0.8	NA	NA	30 min continuous cycling exercise at 40% VO <sub>2peak</sub> , 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	5 T1D (4)	35.2 ± 3.0	7.0 ± 0.2	[IS] 9.0 ± 2.0 → 7.3 ± 1.6	38.8 ± 5.1 IU.day <sup>-1</sup>	60 min exercise spinning class (high intensity). [IA-, DA-]. [PP].	- Blood glucose levels ↓ significant
Iscoe & Riddell 2011	11 T1D (5)	35.1 ± 11.6 (18-51)	7.8 ± 0.4	[IS] absolute fall pre/post MOD → HIE: -5.1 ± 0.7 → -5.0 ± 0.5 [P] absolute fall pre/post MOD → HIE: -5.1 ± 0.6 → -4.4 ± 0.5	34 ± 5 IU.day <sup>-1</sup>	- 45 min of continuous moderate-intensity cycling exercise at 55% of their VO <sub>2peak</sub> (MOD) or continuous exercise at 50% of their VO <sub>2peak</sub> with the addition of 9x 15s bouts of 100% VO <sub>2peak</sub> , 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	7 T1D (5)	25 ± 4	8.6 ± 2.3 → 8.1 ± 1.6	[M] pre training: 3.8 ± 1.8 → 4.9 ± 1.6, [M] post training: 2.9 ± 0.8 → 6.2 ± 2.9	52.4 ± 3.8 IU.day <sup>-1</sup> → 51.2 ± 4.6 IU.day <sup>-1</sup>	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 <sub>1c</sub> levels were not significant influenced.

\*Data presented as mean ± SD; N° 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),

## 3.4 Results

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First, this meta-analysis looked at all different forms of exercise to provide an overall estimation of the effect of exercise on acute and chronic glycaemic control. Second, a separate meta-analysis for each of the different exercise forms was completed. This included an analysis of the effect of aerobic, resistance, mixed (aerobic + resistance) and acute High Intensity Exercise (HIE) and Training (HIT). The third level of the meta-analysis encompasses the changes in  $VO_{2max}$ , number of training sessions per week, duration of training protocol, dietary advice or insulin advice.

### *3.4.1 STUDY CHARACTERISTICS*

An initial raw screening using the listed search terms resulted in a selection of 947 articles. A more detailed screening of titles, abstracts and full-text articles resulted in a selection of 73 studies. Thirty-two studies ultimately met our in- and exclusion criteria for determining the effects of exercise on glycaemic control in T1D. Subject characteristics from these selected studies are shown in tables 8-12. Sixteen additional studies were excluded because insufficient data were presented to perform proper meta-analysis (Aman et al. 2009, Michaliszyn et al. 2009, Costill et al. 1979, Wallymahmed et al. 2007, Kelly, 2010, Ludvigsson, 1980, Nermoen et al. 1998, Roberts et al. 2002, Sonnenberg et al. 1990, Valerio et al. 2007, Vanelli et al. 2006, Fayolle et al. 2006, Meinders et al. 1988, Herbst et al. 2007). Four studies were excluded because they did not define the level of physical activity (Faulkner et al. Herbst et al. 2007, Ligtenberg et al. 1999, Dahl-Jorgensen et al. 1980). Eleven studies were excluded because no full text/data were found (Nugent et al. 1997, Clarke et al. 1997, Szmigiel et al. 1996, McCargar et al. 1991, Stratton et al. 1987, Jensen and Miles, 1986, Hubinger et al. 1985, Schiffrin et al. 1984, Sills and Cerny, 1983, Guler et al. 1982, Zander et al. 1985), and six conference reports, reviews or brief reports and one case study were excluded (Guelfi et al. 2007, Toni et al. 2006, Jette, 1984, Riddell and Iscoe, 2006, Riddell and Milliken, 2011, Steppel and Horton, 2003, Graveling and Frier, 2010).

All studies made a subdivision into children, adolescents and adults. However, studies did not always mention the gender of the population; therefore, no meta-analysis could be performed for gender.

## 3.4.2 EFFECTS OF ACUTE EXERCISE ON GLYCAEMIA /PLASMA GLUCOSE IN T1D

**Table 13 Meta-analytic results for a single bout of acute exercise for aerobic exercise and HIE**

	Cohen's d	95% CI LL	95% CI UL	Studies	Subjects
Overall					
Venous BGL (plasma + whole blood)	-4.17*	-4.57	-3.76	10	147
Interstitial GL	-0.94	-2.23	0.35	1	5
Aerobic exercise	-4.35*	-4.77	-3.92	9	140
Children					
Venous BGL (plasma + whole blood)	-3.64*	-5.27	-2.01	1	7
Adolescents					
Venous BGL (plasma + whole blood)	-1.02*	-1.32	-0.71	3	92
Adults					
Venous BGL (plasma + whole blood)	-6.00*	-6.87	-5.14	5	56
Capillary GL	-2.4*	-3.73	-1.06	1	7
HIE					
Adults					
Venous BGL (plasma + whole blood)	-4.53*	-6.41	-2.65	1	7
Capillary GL	-0.93	-2.02	0.17	1	7
Interstitial GL	-0.94	-2.23	0.35	1	5

LL = Lower limit; UL = Upper limit; (B)GL = (Blood) Glucose Levels; HIE = high intensity exercise

The results from the first and second stage of the statistical analysis on acute glycaemic control are presented in table 13. Exercise, including aerobic (Heyman et al. 2007a, Heyman et al. 2005, Tansey et al. 2006, Poortmans et al. 1986, Guelfi et al. 2005, West et al. 2011) and acute high intensity exercise (Iscoe et al. 2006, Bussau et al. 2006, Guelfi et al. 2005, Guelfi et al. 2007, Harmer et al. 2008, Iscoe and Riddell, 2011), resulted in an overall effect size of -4.17 [-4.57; -3.76]). This indicates that the venous blood glucose values decreased significantly from performing exercise. This meta-analysis clearly shows that aerobic exercise contributes to a larger decrease in venous blood glucose values in adults (-6. [-6.86; -5.14]) compared to acute high intensity exercise (-4.35 [-4.77; -3.92]). Only one study explored the effects of an incremental exercise test on blood glucose concentrations in pre-pubertal children (Heyman et al. 2005), while no studies were found that involved HIE in children or adolescents. West et al. (2011) 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 (ES -10.6 [-14.4; -6.8]) compared to 30 min before exercise (ES -7.26 [-9.97; -4.55]).

3.4.3 EFFECTS OF TRAINING ON FASTING PLASMA GLUCOSE AND HBA<sub>1c</sub> IN T1D.**Table 14 Meta-analytic results for overall exercise training (stage 1) and different types of training (second stage) on chronic glycaemic control**

	Cohen's d	95% CI LL	95% CI UL	Studies	Subjects
Overall (pre/post training)	-0.27*	-0.47	-0.08	16	202
Aerobic training (pre/post training)	-0.23*	-0.44	-0.02	12	171
Children	0.23	-0.28	0.73	2	30
Adolescents	-0.66*	-0.99	-0.34	5	75
Adults	0.08	-0.32	0.36	5	66
Aerobic training (CG vs. EG training)	-0.23*	-0.44	-0.02	12	171
Children	0.21	-0.32	0.74	2	28
Adolescents	-1.03*	-1.56	-0.49	2	30
Resistance training (Adults) (pre/post training)	-0.6	-1.35	0.16	2	14
Mixed (aerobic + resistance training) (Adolescents) (pre/post)	-0.2	-0.87	0.48	2	17
Mixed (aerobic + resistance training) (Adolescents) (CG vs. EG)	-0.2	-0.87	0.48	2	17
High Intensity Training (HIT) (Adults) (pre/post training)	-0.25	-1.3	0.8	1	7

LL = Lower limit; UL = Upper limit; CG = control group; EG = Exercise group. \*p < .05

Tables 9-11 show descriptive data of the studies included in the present meta-analysis for the effects of training on chronic glycaemic control. The results from the first and second stage of our statistical analysis on chronic glycaemic control are presented in table 14. Exercise training resulted in a small, although significant, decrease in levels of HbA<sub>1c</sub> (-0.27 [-0.47; -0.08]). Most of the individual studies on exercise training could not show significant results on glycaemic control; however, since our calculations were weighted based on sample sizes and standard deviations, we could find a significant overall decrease in HbA<sub>1c</sub>.

Twelve studies (Laaksonen et al. 2000, Lehmann et al. 1997, Ramalho et al. 2006, Wallberg-Henriksson et al. 1986, Zinman et al. 1984, Marrero et al. 1988, Michaliszyn and Faulkner, 2011, Ruzic et al. 2008, Sideraviciute et al. 2006, Dahl-Jorgensen et al. 1980, Huttunen et al. 1989, Smith et al. 1985) were used for the estimation of the effect size of aerobic training on chronic glycaemic control in a total population of 171 T1D adults, adolescents and children. Overall effect size of performing aerobic training is small, but significant (-0.23 [-0.44; -0.02]). Chronic aerobic exercise had no significant effect (0.23 [-0.28; 0.73]) in a group of 30 poorly-controlled T1D children (mean age 11.5 y). (Huttunen et al. 1989, Smith et al. 1985) When the effects of exercise training are compared to no training in T1D (Huttunen et al. 1989, Wong et al. 2010), similar results were shown (0.21 [-0.27; 0.32]) (Huttunen et al. 1989, Wong et al. 2010). Chronic aerobic training significantly decreased (-0.66 [-0.99; 0.34]) HbA<sub>1c</sub> levels in a group of 61 poorly-controlled



T1D adolescents (mean age of 13.8 years) (Marrero et al. 1988, Dahl-Jorgensen et al. 1980, Michaliszyn and Faulkner, 2011, Ruzic et al. 2008, Sideraviciute et al. 2006). When comparing the effects of aerobic training with a no exercise group, a significant decrease (-1.03 [-1.56; 0.49]) in HbA<sub>1c</sub> levels was found (Bernardini et al. 2004, Marrero et al. 1988). No significant changes were observed for HbA<sub>1c</sub> levels in 66 poor and good controlled T1D adults (mean age 35.4ys) performing an aerobic training protocol (0.02 [-0.32; 0.36]).

Only 2 studies (Ramalho et al. 2006, Durak et al. 1990) reported data on strength training. Although there seems to be a trend for significant changes with a large effect size, this was not statistically confirmed (-0.6 [-1.35; 0.16]).

The effects of aerobic training combined with strength training were determined in 4 studies (D'Hooge et al. 2011, Bernardini et al. 2004, Mosher et al. 1998, Heyman et al. 2007b) using an adolescent population (10-18 years). The estimation of the size of decrease in HbA<sub>1c</sub> in the exercise group compared to the control T1D non-exercising group is -1.48 [-2.07; -0.89]. HbA<sub>1c</sub> levels comparing pre and post training status in T1D adolescents showed a slightly decreasing effect -0.2 [-1.12; 0.73]. We found no studies evaluating the effect of a combined exercise training program on glycaemic control in T1D adults or children (< 10 years). To determine the effects of sprint training on glycaemic control, Harmer et al. (2008) performed a sprint training study. They concluded that HbA<sub>1c</sub> levels were not influenced by long term HIE training.

Fasting blood glucose levels were shown in 4 studies (Smith et al. 1985, Zinman et al. 1984, Ramalho et al. 2006, Sideraviciute et al. 2006). Fasting blood glucose levels decreased after an aerobic exercise program in T1D adults (-0.16 [-0.52; 0.19]).

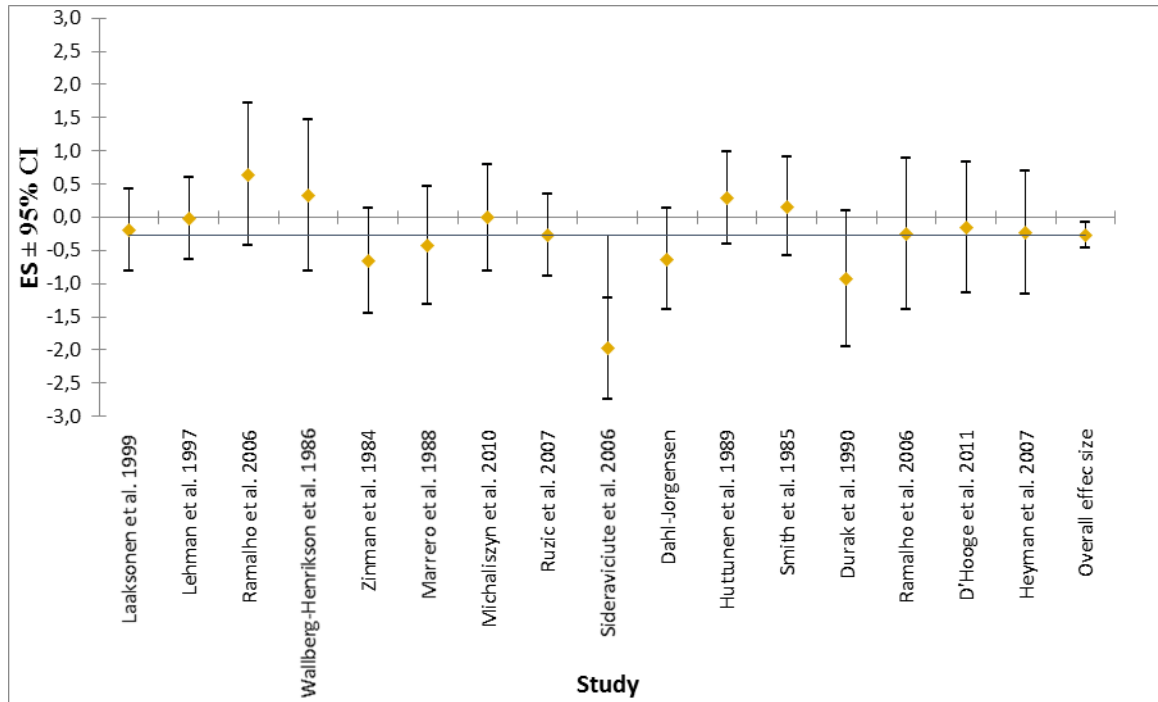


Figure 8 Overall estimates of the size of changes in glycaemic control due to aerobic exercise training in T1D

3.4.4 ARE THERE SPECIFIC THRESHOLDS TO GAIN SIGNIFICANT IMPROVEMENTS IN CHRONIC GLYCAEMIC CONTROL DURING EXERCISE TRAINING?

**Table 15 Meta-analytic results for specific thresholds (volume, duration, intensity; additional recommendations; baseline glycaemic control) to gain significant improvement in HbA<sub>1c</sub>**

	Cohen's d	95% CI LL	95% CI UL	Studies	Subjects
Overall					
< 3 months of training	-0.49	-0.96	0.00	3	35
= 3 months of training	0.06	-0.26	0.39	6	73
> 3 months of training	-0.75*	-1.03	-0.47	8	108
< 3 x/wk training	-0.34*	-0.65	-0.02	5	79
≥ 3 x/wk training	-0.06	-0.33	0.21	10	106
Poor baseline glycaemic control (> 8% HbA <sub>1c</sub> )	-0.25*	-0.48	-0.02	11	151
Adequate baseline glycaemic control (< 8% HbA <sub>1c</sub> )	-0.02	-0.64	0.6	1	20
Increased VO <sub>2max</sub> due to training program	-0.43	-1.31	0.46	1	10
No changes in VO <sub>2max</sub> due to training program	-0.63	-1.39	0.13	1	14
Aerobic training					
< 3 months of training	-0.27	-0.9	0.35	1	20
= 3 months of training	0.13	-0.21	0.47	5	67
> 3 months of training	-0.43*	-0.83	-0.16	5	71
Poor baseline glycaemic control (> 8% HbA <sub>1c</sub> )	-0.25*	-0.48	-0.02	11	151
Adequate baseline glycaemic control (< 8% HbA <sub>1c</sub> )	-0.02	-0.64	0.6	1	20
< 3 x/wk training	-0.63*	-0.97	-0.29	5	69
≥ 3 x/wk training	0.00	-0.3	0.31	7	82
Increased VO <sub>2max</sub> due to training program	-0.43	-1.31	0.46	1	10
No changes in VO <sub>2max</sub> due to training program	-0.63	-1.39	0.13	1	14
Dietary Advice	0.65	-0.43	1.72	1	7
No Dietary Advice	-0.66	-1.45	0.13	1	13
Resistance training					
< 3 months of training	-0.93	-1.96	0.09	1	8
= 3 months of training	-0.26	-1.39	0.88	1	6
Mixed training					
Insulin and dietary advice	-0.6*	-1.14	-0.82	1	8
No insulin and dietary advice	-0.23	-1.16	0.69	1	9
< 3d/wk	0.82	-0.09	1.73	1	10
= 3d/wk	-0.2	-0.87	0.48	2	17

LL = Lower limit; UL = Upper limit; d = days; wk = weeks; VO<sub>2max</sub> = maximal oxygen uptake. \*p < .05

The meta-analytic results from the third stage of analysis examining specific thresholds to gain significant improvements in glycaemic control are reported in table 15. Chronic glycaemic control improved when training is performed more than three months, training 1 - 3 times a week and having dietary or insulin advice. HbA<sub>1c</sub> did not change in subjects with adequate glycaemic control, while the remaining 11 studies (with poor controlled (> 8% HbA<sub>1c</sub>) T1D subjects had a significant decrease in HbA<sub>1c</sub> (ES -0.25 [-0.48; -0.02]) by performing aerobic exercise.

## 3.5 Discussion

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The major findings of this meta-analysis show that exercise has a significant effect on acute and chronic glycaemic control (Figure 8). Prolonged steady-state aerobic exercise has long been known to cause an acute decrease in blood glucose levels in individuals with T1D and may decrease even long after completion of the exercise. HIE gave a smaller decrease in blood glucose values compared to aerobic exercise. Aerobic training seems to be a favorable tool for improving the chronic glycaemic control. There was a tendency for improvement in long-term glycaemic control due to resistance training or resistance combined with endurance training, but there were not enough studies and/or subjects to confirm this statistically.

### *3.5.1 CHANGES IN BLOOD GLUCOSE VALUES 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 (Rabasa-Lhoret et al. 2001, Riddell and Perkins, 2009, Guelfi et al. 2007), nutritional status (Jimenez et al. 2009), time of insulin injection (Iafusco, 2006), or pre-exercise glycaemia level (Zander et al. 1983). After performing moderate, aerobic exercise, all studies found a decrease in blood glucose values (Guelfi et al. 2005, Bussau et al. 2006, Poortmans et al. 1986, West et al. 2011, Yamanouchi et al. 2002, Zinman et al. 1977, Zinman et al. 1984, Tansey et al. 2006, Heyman et al. 2005, Heyman et al. 2007a). The blood glucose-lowering effect of moderate intensity exercise can increase the risk of developing an episode of hypoglycaemia during and after exercising. MacDonald et al. (1987) followed 300 patients with T1D prospectively over 2 years. Sixteen percent developed late-onset (6–15 hours after vigorous exercise) hypoglycaemia. As previously described, through the persistent increase of insulin sensitivity and the required repletion of muscle glycogen stores, exercise could affect the blood glucose values the morning after exercise and so late onset of hypoglycaemia can occur regardless of appropriate insulin reduction (MacDonald, 1987). However, from this meta-analysis, it seems that this risk can be minimized by appropriate insulin reduction and carbohydrate (CHO) ingestion before and during exercise. Perrone et al. (2005) studied whether ingestion

of a drink containing sufficient carbohydrates (CHO 8 or 10%) can avoid the exercise-induced hypoglycemia in T1D adolescents. The authors concluded that supplementation of a CHO drink before and during exercise was in most cases enough to maintain the blood glucose concentrations during moderate exercise. West et al. (2008) concluded that the ingestion of 75 g CHO in T1D patients 30 min before exercise resulted in less hypoglycaemic episodes during exercise and induced higher venous blood glucose levels after exercise compared to the ingestion of 75 g CHO 60, 90 or 120 minutes before exercise.

Although it was not possible to perform a 'meta'-analysis for the effects of HIE due to the methodological differences in all studies (effects on venous, plasma and capillary glucose values before and after HIE+moderate exercise versus moderate exercise [table 13]), we can make some general observations. One has to be careful when interpreting table 12 because of the different protocols used. Therefore, more standardization of protocols is needed for the evaluation of the effects of HIE in T1D. While aerobic exercise elicits marked falls in glycaemia, which can often result in episodes of hypoglycaemia, this meta-analysis revealed that there was a smaller fall of blood glucose levels due to an acute bout of HIE compared with 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. It is even demonstrated that glucose production was higher in HIE+moderate versus moderate exercise alone and that glucose utilization was greater and occurred faster in HIE+moderate compared with moderate exercise. This hypothesis was confirmed by the studies of Iscoe and Riddell and the studies of Bussau et al. (Iscoe and Riddell, 2011, Bussau et al. 2007) who found a more pronounced catecholamine response in HIE+moderate compared with the continuous moderate-intensity exercise trial. Harmer et al. (2007) found that muscle free glucose values increased significantly after HIE. Most recently, Iscoe and Riddell (2011) 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. (2001) observed that blood glucose levels decreased more in moderate continuous and/or longer exercise (periods ranging from 30 to 60 minutes and from 25% to 75% of  $Vo_{2max}$ ) modes than in intense exercise forms. On the other hand, Iscoe and Riddell (2011) did not find any difference in interstitial or plasma glucose levels during exercise between an intermittent high-intensity and a continuous moderate exercise in T1D patients. In this study, the effects

of two different types of exercise with a total equivalent mechanical load were studied: a continuous moderate exercise of 45 minutes at 55% of  $\dot{V}O_{2max}$  and 45 minutes at 50% in which nine sequences of 15-second high-intensity sprints were incorporated. The bouts of intense exercise ( $100\% \dot{V}O_{2peak}$ ) represented only 5% of the total duration of the high-intensity intermittent exercise, which could contribute to the absence of differences in the change in blood glucose levels during exercise. 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.

### *3.5.2 CHANGES IN GLYCAEMIC CONTROL DUE TO TRAINING*

The individual studies on aerobic training demonstrated no significant results on glycaemic control. However, when viewed 'in total', our meta-analysis of the grouped studies successfully demonstrated a reduction in HbA<sub>1c</sub> from aerobic training. Aerobic exercise is well known to enhance insulin action 24h following (Baldi et al. 2011) both acute exercise and training. Therefore, it is recommended that exercise is performed frequently in order to maintain a constant increase in insulin sensitivity and thus improve HbA<sub>1c</sub>. Thus, training once a week might not be enough to improve HbA<sub>1c</sub> levels. For example, Huttunen et al. (1989) performed an exercise intervention of 45 minutes, 1 time per week during 12 weeks and HbA<sub>1c</sub> levels were not affected by the intervention program. The duration of the training period is also an important influencing factor for decreasing HbA<sub>1c</sub>. HbA<sub>1c</sub> levels decreased significantly only in training studies that lasted for more than 3 months. While HbA<sub>1c</sub> levels are inversely correlated with the duration (min) of the exercise training, the amount (times/week) of training per week can also influence the HbA<sub>1c</sub> levels. Besides this, baseline glycaemic control is also an important predictor of HbA<sub>1c</sub> improvement due to training. HbA<sub>1c</sub> decreases significantly more in T1D individuals with poor glycaemic (> 8% HbA<sub>1c</sub>) control compared to individuals with good glycaemic control (<8% HbA<sub>1c</sub>). Lehman et al. (1997) demonstrated only a slight decrease in HbA<sub>1c</sub> in well-controlled subjects who performed exercise training. This might suggest that exercise can be beneficial in order to maintain a good glycaemic control in T1D subjects. In our meta-analysis, the effect size of a decrease in HbA<sub>1c</sub> with training appeared more marked when training was not associated with an improvement in  $\dot{V}O_{2max}$ . This strange result might in fact be explained by the fact that studies where  $\dot{V}O_{2max}$  was not changed probably included more poor-controlled patients.

In line of the later statement, a study of Baldi et al. (2011) demonstrated that despite similar training volumes, subjects with type I diabetes with high HbA<sub>1c</sub> had lower peak workload, VO<sub>2peak</sub>, and peak cardiac output than those with low HbA<sub>1c</sub>. Pulmonary function measures were also lower in the high HbA<sub>1c</sub> group during peak exercise. These data suggest that cardiopulmonary training adaptations are greater in patients with type I diabetes who maintain good glycaemic control (Baldi et al. 2011). The mechanism through which poor glycaemic control influenced cardiac and pulmonary responses to exercise is an interesting area for further study. Several studies reported a blunted sympathoadrenal response to exercise in subjects with T1D (Heyman et al. 2007a, Khoharo et al. 2009). The blunted sympathoadrenal response may be more obvious in those with poor glycaemic control (Khoharo et al. 2009). The autonomic dysfunction can therefore influence the hemodynamic exercise response.

Aerobic training and strength training have different actions in the body and can therefore influence glycaemic control through different pathways. For example, fat mass decrease after a period of aerobic training (Ismail et al. 2012). A prospective study of Svensson et al. (2011) indicates that the change in the amount of body fat contributes to the change in insulin resistance over time in T1D patients. On the other hand, strength training has enhanced insulin sensitivity and improved glucose tolerance (Tresierras and Balady, 2009). A meta-analysis of 9 randomized controlled trials evaluated 372 subjects with type 2 diabetes (Irvine and Taylor, 2009). When compared to not exercising, progressive resistance training led to a small but statistically significant absolute reduction of 0.3% in HbA<sub>1c</sub>, indicating that resistance training is a reasonable option in the management of glycaemic control in diabetic subjects (Sundell). 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) (Heymsfield et al. 2002). A greater muscle mass would thus consume more glucose and therefore could affect glycaemic control. Out of our meta-analysis, strength training (Ramalho et al. 2006, Durak et al. 1990) seems to have a decreasing effect on long term HbA<sub>1c</sub>. However, this effect is only shown in a small sample size and may, for this reason, not be applied generally. Combined training (a combination of strength and aerobic training) showed, compared to a no exercise group, a significant improvement in chronic glycaemic control. A possible explanation for this is the combined effect of a greater use of glucose, caused by an increased muscle mass and the decreased insulin resistance (Heymsfield et al. 2002, Svensson and Eriksson, 2011). We have

to mention that these results are processed from only 2 studies (Bernardini et al. 2004, Heyman et al. 2007b). The study of Heyman et al. (2007b) did not show a significant decrease of HbA<sub>1c</sub> levels, while the study of Bernardini et al. (2004) did show a large, significant decrease in HbA<sub>1c</sub>. This might depend on the type of intervention: et al. (2004) defined his 'combined training' as 'soccer, volleyball, tennis, basketball'. Thus they did not improve their glucose levels due to specific aerobic or strength training programs, but due to the combined effect in different sports. On the other side, children who are very active during this study, are often children who are active during their lifetime (during several precedent years). In the study of Heyman et al. children only benefit from the training during 6 months. Moreover, in a cross sectional study, subjects with poor glycaemic control could be less motivated to involve in physical activity.

The relative difficulty of improving HbA<sub>1c</sub> 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 important and various glycaemic variations depending of a large amount of factors (duration since the last meal or insulin dose, insulin absorption, initial glycaemia, hour of the day...). So 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 of their insulin dose, what in turn can induce slight hyperglycaemia and prevent improvement in HbA<sub>1c</sub>.

### *3.5.3 LIMITATIONS OF THE LITERATURE*

Pooling of data on the effects of acute exercise on glycaemia in T1D populations is difficult. A great variability of glycaemic responses exists according to factors like pre-exercise glycaemia and pre-exercise insulinaemia (Brun et al. in press) depends on numerous factors like time since the last insulin dose or meal, insulin dose, factors modifying insulin absorption (e.g., location of injection, ambient temperature), etc. There are only few studies providing information on the use of the insulin pump, insulin injections or continuous glucose measurement system (CGMS). Small sample studies were included, meaning that the power of these studies might not be satisfactory, but those studies present the advantage to often test novel interventions. In analyzing our cohort of studies, little information on glycaemia or insulin regimes were presented, along with the presence of potential long term micro or macrovascular complications as well as acute diabetic complications, reflecting markers such as ketonuria or glucosuria. To enable better



cross-comparison, future studies should include a standardized set of T1D subject characteristics.

#### 3.5.4 LITERATURE WEAKNESSES

Not all studies met our in- and exclusion criteria. Three cross-sectional studies were excluded because not enough data were presented to be included in this meta-analysis, or else physical activity level was not defined (Herbst et al. 2007, Ligtenberg et al. 1999, Michaliszyn and Faulkner, 2011). The study of Herbst et al. (2007) (a study performed in a population of 23251 T1D subjects) concluded that physically active T1D subjects have significantly lower HbA<sub>1c</sub> levels compared to sedentary T1D subjects. The cross-sectional study of Ligtenberg et al. (1999) found no correlations between long-term physical activity and HbA<sub>1c</sub>. However, we have to be careful with interpreting cross sectional studies because some biases may appear. For example, subjects can 'over-report' their level of physical activity. Therefore, the level of physical activity must be verified (e.g. in a small sample) with more objective measurement systems (e.g. accelerometers). In addition, positive correlations in cross sectional studies give not the sense of the cause-effect relationships and thus they cannot conclude whether this indicates that poor controlled patients might be less motivated to practice (Brazeau et al. 2008) and/or physical activity may have positive effects on glycaemic control).

Mostly only studies where a significant difference is found are published, this implies that some completed studies are not published and therefore cannot be considered in the meta-analysis. It should be therefore mentioned that it is possible that a publication bias occurred. Funnel plots (plots of effect estimates against sample size) is an effective and relatively powerful tests for evaluating the existence of publication bias in a Meta-analysis (Duval and Tweedie, 2000, Song and Gilbody, 1998). It assumes that the largest studies will be near the average, and small studies will be spread on both sides of the average (because of their larger/smaller sample sizes and standard errors). Variation from this assumption can indicate publication bias. A symmetric inverted funnel shape arises from a 'well-behaved' data set, in which publication bias is unlikely, which we detected in our funnel plot.

A major issue is that there are no data available on the exact (or minimum) amount of studies needed to perform a meta-analysis. In this meta-analysis some analysis were made on 2 or 3 studies, which is probably not enough to make uniform conclusions. Furthermore, a common criticism of the meta-analysis

technique is that it focuses on the summary effect and ignores the fact that the treatment effect may vary from study to study. The goal of a meta-analysis should be to synthesize the effect sizes (random model effect), and not simply (or necessarily) to report a summary effect (fixed model effect). If the effects are consistent, then the analysis shows that the effect is robust across the range of included studies. If there is modest dispersion, then this dispersion should serve to place the mean effect in context. If there is substantial dispersion, then the focus should shift from the summary effect to the dispersion itself. By ignoring the heterogeneity of the studies, one also misses the point of the synthesis. Overall, meta-analyzing 2-3 studies might be enough to be able to give directions for further research.

### 3.6 Conclusion and Directions for Future Research

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Some limitations were found in the existing literature concerning the effects of exercise on glycaemic control in T1D. While aspects such as micro- and macrovascular complications, insulin advice and dietary advice are very important in interpreting results emanating from exercise, these aspects are not systematically displayed in the literature. Also, little research is done concerning the effects of resistance training, combined training, or the implementation of HIT in a moderate exercise training program. Due to the few data in these topics, we had to calculate ESs on only two or three papers. Therefore, we have to be careful interpreting these results.

We can conclude that exercise has an overall beneficial lowering effect on acute and chronic glycaemic control in T1D. Exercise can clearly help subjects with poor glycaemic control to decrease their HbA1c and can help to sustain good glycaemic control in T1D subjects. Therefore, T1D subjects should integrate exercise into their lifestyle and should try to exercise every second day. To avoid excessive fluctuation in blood glucose levels during and after exercising, subjects with T1D might need to adjust their insulin doses. Depending on the form of exercise, T1D subjects should ingest some carbohydrate for preventing hypoglycaemic episodes.

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### 3.7 References

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CHAPTER 4. CAN THE LEVEL OF PHYSICAL ACTIVITY PREDICT A  
TYPE 1 DIABETES ASSOCIATED COGNITIVE DECLINE?

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**REFERENCE:**

**TONOLI C., HEYMAN E., ROELANDS B., BUYL R., BUYSE L., PIACENTINI MF., PATTYN N., KEYMEULEN B., UNUANE D., MEEUSEN R.** Can The Level of Physical Activity predict a Type 1 Diabetes Associated Cognitive Decline? [**Submitted**]

## 4.1 Abstract

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**Background.** Type 1 diabetes can have a significant influence on brain structure and function. It is known that physical activity has a positive effect on brain function. Therefore, the **purpose** of this study is to evaluate if the level of PA influences the cognitive function in type 1 diabetes. Furthermore, the relationship between the cognitive function, BDNF and IGF-I are investigated. **Material & Methods.** 103 patients with type 1 diabetes (18-60 years) participated in a cross-sectional study. Participants filled out questionnaires, performed several cognitive tests (attention, cognitive flexibility, executive function, working memory and spatial memory), and blood samples were collected. Multiple regression analyses were performed to discover the individual contribution of each predictor (significances when  $p < 0.05$  was achieved). **Results.** Several factors can predict a cognitive functioning in type 1 diabetes including level of PA, education, glycaemic control, level of BDNF, diabetes duration and episodes of hypoglycaemia. **Conclusions.** It is known that regular PA will help to achieve and minimize the development of several diabetes-associated complications, this paper demonstrates similar results on brain function.

## 4.2 Introduction

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Long-term effects of diabetes include progressive development of specific microvascular/macrovascular complications (Alberti and Zimmet, 1998) and an impact on brain structure and function (Brands et al. 2005, Tonoli et al. 2014b), a complication that is less regularly assessed in clinical follow-up of these patients. A recent meta-analysis showed that compared with non-diabetic subjects, type 1 diabetes (T1D) adults perform worse on tests of IQ, executive function, memory, spatial memory and motor speed (Tonoli et al. 2014c). This cognitive decline is ascribed to episodes of hypoglycaemia (Auer, 2004), hyperglycaemia (Bermon et al. 1999) and C-peptide and/or insulin deficiencies (De Palo et al. 2008). Other proposed diabetes, and non-diabetes associated contributing factors are age of onset disease (Kaufman et al. 1999) and diabetes duration (Ryan et al. 1985).

Research has indicated that physical activity (PA) enhances multiple aspects of physical and cognitive functioning in healthy adults and may delay the onset of Alzheimer Disease (AD) (Hillman et al. 2008, Yaffe et al. 2001). PA seems to be the key intervention to trigger the processes through which neurotrophins as Brain-Derived Neurotrophic Factor (BDNF) and Insulin Like Growth Factor-I (IGF-I) mediate neurogenesis, neural plasticity and consequently long-term potentiation (LTP), a physiological model of learning and memory (Vaynman et al. 2004).

In humans, a growing body of evidence suggests that a single bout of exercise increases serum and plasma BDNF levels (for review see (Knaepen et al. 2010)). According to Rasmussen and colleagues (Rasmussen et al. 2009) the increase in BDNF reported after exercise in the periphery, is due to an enhanced release of BDNF from the brain. Long term PA results in less clear effects; showing even decreased levels of BDNF, which can be attributed to better uptake of BDNF into the brain (for review see (Knaepen et al. 2010)). On the other hand, higher basal levels of BDNF were related to better brain health and associated with a slower rate of cognitive decline in AD patients (Laske et al. 2011). Decreased levels of BDNF, on the other hand, have been related to various mental disorders such as decreased cognitive functioning, depression, schizophrenia, AD, dementia, Huntington's disease, Parkinson disease (Aydemir et al. 2006).

IGF-I is related to the proliferation of progenitor cells (neurogenesis), it participates in brain angiogenesis

(Trejo et al. 2004), and is associated with the effects of BDNF in LTP (Vaynman et al. 2004). In the past decades, extensive research has determined that the reduction of IGF-I in non-diabetic humans is an important component of the age-related cognitive decline (Sonntag et al. 2013) as demonstrated by decreased perceptual motor performance, reduced information processing speed (Aleman et al. 2001), fluid intelligence (Aleman et al. 2001) and deficiencies in spatial and working memory (Sonntag et al. 2013).

Exercise has been accepted and generally recommended for the management of T1D by improving chronic glycaemic control (Tonoli et al. 2012), and therefore could prevent cognitive decline. Whether an active physical lifestyle influences cognitive functioning in T1D is not yet known. The purpose of this study was to detect possible contributing factors to cognitive functioning in T1D and to advance the understanding of the origin of the cognitive deficits in T1D. Therefore, a multiple regression analysis was used to distinguish how cognitive function was affected by diabetes-, demographic-, and education-related contributors, and additionally the self-reported level of PA, baseline levels of BDNF and IGF-I were taken into account. We hypothesize that level of PA, serum BDNF and IGF-I will be associated with cognitive function in T1D.

### 4.3 Materials & Methods

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We performed a cross-sectional study after approval by UZ Brussels ethical committee (B.U.N. 143201111786). The relationship between PA and cognitive function was assessed during a single research appointment. Participants were asked to fill out questionnaires, to perform several cognitive tests, and blood samples were collected to determine the levels of serum BDNF, IGF-I and HbA<sub>1c</sub> (Figure 9).

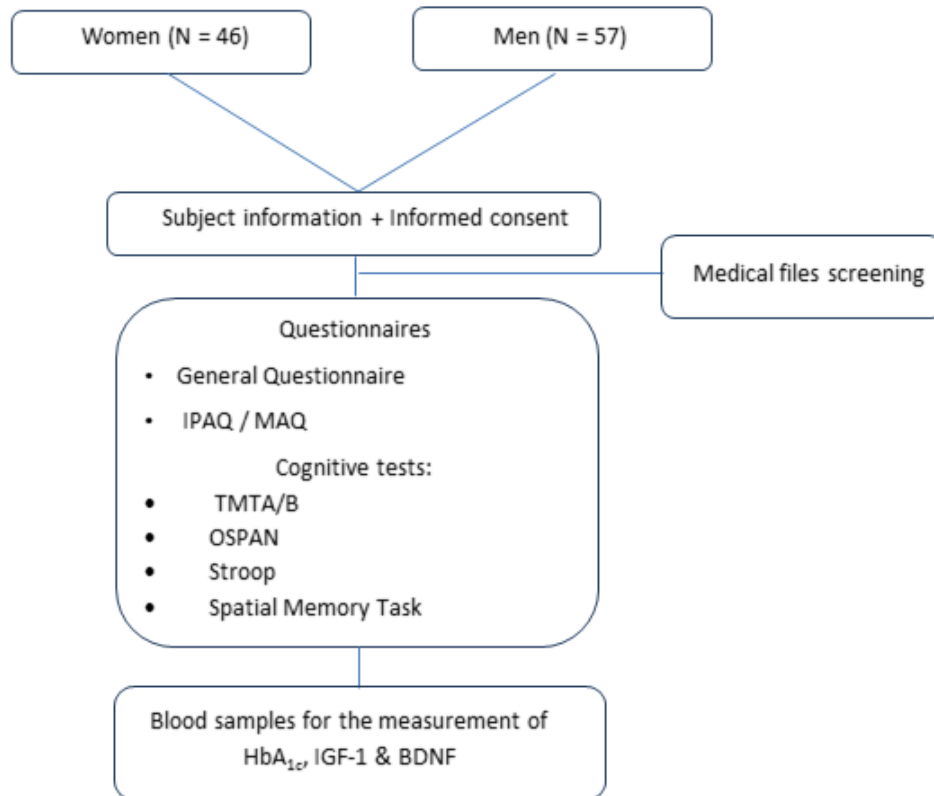


Figure 9. Study Protocol

#### 4.3.1 SUBJECTS

Patients were recruited from the database of the Diabetes Centre of the UZ Brussels. Patients' medical files were carefully screened by the endocrinologist to exclude patients who met one of the following criteria: 1) <18 - >60 years, 2) a history of severe head injuries, 3) other metabolic disorder besides diabetes, 4) neurological, psychological (comorbidities such as AD, dementia, depression...) 5) medication influencing cognitive function. All subjects were informed about the nature and the purpose of this study and gave written informed consent before participating. They were instructed to withhold from caffeine, alcohol and vigorous activity 24 hours before the research appointment.

#### 4.3.2 NEUROPSYCHOLOGICAL ASSESSMENT

The assessment of the cognitive function in T1D is usually based on neuropsychological tests. Since exercise has beneficial effects on cognitive function, especially for tasks related to working and spatial memory and the executive function, the neuropsychological assessment was chosen in function of these cognitive domains with the following tests: Trail Making Test A & B (TMTA/B), the Stroop test, the

Operation Span (OSPAN) task and the Spatial Memory Task (SMT) assessing (divided) attention, speed of information processing, cognitive flexibility/executive functioning, working/spatial memory and attentional capacities. The tests were performed in a fixed order and took approximately 45-60 minutes to prevent cognitive fatigue. Validity and reliability data of these tests have been reported previously (Strauss et al. 2006). Capillary blood glucose level was measured before the cognitive tests. If glucose value was lower than 4.4mmol/L, a carbohydrate drink or snack was provided and cognitive testing was performed as soon as glycaemia achieved a stable level (5-10 mmol/L).

TMTA/B: This test measures speed of information processing and divided attention. TMTB is closely related to tests of executive functioning (Strauss et al. 2006). In this test, the subject had to connect an alternating series of randomly placed numbers (1 to 25) (TMTA) and a combination of numbers and letters (A-L/1 to 12) (TMTB) correctly in their respective order as quickly as possible. The time to complete the task was recorded, meaning high values on the TMTA/B reflect delayed reaction times.

Stroop Color and Word Test: The Stroop effect is a demonstration of interference in the reaction time of a task and measures selective attention, processing speed, working memory and cognitive flexibility. This assesses the ease with which a person can maintain a goal in mind and suppress a habitual response in favour of less familiar ones (25). In this test, subjects read the color name and must press a colored button on the keyboard in which the color names are printed, disregarding their reading content. The presented words/nouns could be classified under different conditions, namely "congruent" (word and color are the same) and incongruent (e.g. word and color are different; or the interference effect).

OSPAN: The OSPAN has related mathematical processing to assess working memory capacity. This computer based test contains 66 mathematical operations and 66 letters to remember and is developed for the evaluation of the working memory (Lezak et al. 2004). During the task, subjects are presented operations and letters to be recalled. Each operation requires the subject to multiply or divide two integers and then add or subtract a third integer, e.g. " $(1*2)+1=3$ ". The number of operations and letters per series varied from 2 to 6. Five parameters were calculated in this test (Lezak et al. 2004): OSPAN score, total number correct, math errors, accuracy errors and speed errors.

SMT: Is assessed to measure spatial attention/memory. In this computerized test, one, two or

three black dots appear at random locations on the screen for 500ms. The dots are removed from the display for 3s. During this time, participants are instructed to try and remember the locations of the previously presented black dots. At the end of the 3s delay, one or more red dots appear on the screen in either one of the same locations as the target dots (match condition) or at a different location (non-match condition). Participants have 2s to respond to the numbers of red dots by pressing one of two keys on a standard keyboard. Forty trials are presented for each set size (one, two, or three dots), with 20 trials as match trials and 20 trials as non-match trials (Erickson et al. 2011).

#### *4.3.3 'GENERAL' AND DIABETES SPECIFIC ASSUMED PREDICTORS OF COGNITIVE FUNCTION IN T1D*

Age, gender and educational level were acquired through a general questionnaire and included in the multiple regression as these parameters influence cognitive function (Brismar et al. 2007). Initially, educational level was divided into: primary, secondary, bachelor and university degree. However, since only a few participants had a primary degree or a bachelor degree, multiple regression was performed with binary levels ("primary + secondary degree" and "bachelor + university degree"). Specific diabetes-associated factors as severe hypoglycaemia, HbA<sub>1c</sub>, age of onset, diabetes duration, blood glucose during the cognitive tests and complications (assessed by a medical doctor) were included. Severe hypoglycaemia (over lifetime) was defined as episodes in which the patient had an incapacity sufficient to require the assistance of another person, according to the definition in the Diabetes Control and Complications Trial (DCCT, 1996). Glaciated haemoglobin (HbA<sub>1c</sub>) is a measurement to identify the chronic glycaemic control.

#### *4.3.4 LAST WEEK AND LAST YEAR PA*

The IPAQ is an instrument designed primarily for population surveillance of PA over the previous 7 days among adults. IPAQ comprises a comprehensive set of 4 questionnaires including: leisure time PA, domestic and gardening activities, work-related PA and transport-related PA. Validity and reliability were previously described (Lamers et al. 2006). The Modifiable Activity Questionnaire (MAQ), measuring level of PA over a longer time-period (1 year), consists of an examination of PA in leisure time (including gardening, sports ...), of non-sporting leisure (TV, computer), and of occupational activities during the past week and past year. Validity and reliability were previously described (Tonoli et al. 2013). The total PA time (total hours/week), (relative and vigorous activities) was calculated with the corresponding metabolic



equivalents (MET-value). Sedentary tasks (watching TV, sitting) were not included for the calculation of the PA level in both questionnaires.

#### *4.3.5 BLOOD ANALYSES*

HbA<sub>1c</sub> was measured in whole blood by chromatography with ion exchange (Tosoh G7). The remaining blood samples were stored at ambient temperature for 1 hour before being centrifuged (4000tr, 4°C, 10 min). The resulting serum was stored in a -80° freezer until analyses of serum BDNF (commercially ELISA kit – CYT306, ChemiKine®, Millipore®, Billerica, MA, USA) and serum (total) IGF-I (commercially IRMA kit, using an Immulite 2000, Siemens for reading) were performed.

#### *4.3.6 STATISTICAL ANALYSES*

Statistical analysis were performed using the IBM SPSS Statistics 22 software. Normality of data was checked with a Kolmogorov-Smirnov Goodness of Fit test. After checking the correlations for multicollinearity ( $r > .6$ ) and lack of autocorrelation with the Durbin Watson test, a forward stepwise multiple regression analysis was performed to find out the individual contribution of each predictor for each cognitive test used in this study. Independent contributing predictors were: education, age, gender, diabetes duration, early age of onset, complications, BMI, episodes of severe hypoglycemia, HbA<sub>1c</sub> during the study and a mean over the past 9 months, capillary glucose level before starting the cognitive tests, level of PA measured over the last week (using the IPAQ) and over the last year (using the MAQ), levels of BDNF, IGF-I and cortisol. The regression model was significant when  $p < 0.05$  was achieved for the F-values. The same method was used to look at possible predictors of levels of serum BDNF and IGF-I.

Due to multicollinearity ( $r > .6$ ) between the two PA questionnaires, we performed the multiple regression with the results of the MAQ, since this questionnaire evaluates levels of PA over 1 year, which is in line with the research question of this study.

**Table 16. Demographics and clinical characteristics**

	Male	Female	Total
<b>Demographic Data</b>			
N (%)	N = 57 (55)	N = 46 (45)	N = 103 (100)
Age (yrs)	36.7 ± 14.4	36.0 ± 13.6	36.4 ± 14.0
Height (m)	1.79 ± 0.1	1.66 ± 0.1	1.73 ± 0.1
Weight (kg)	79.70 ± 12.4	69.79 ± 12.3	75.17 ± 13.3
BMI (kg/m <sup>2</sup> )	24.80 ± 3.8	25.35 ± 3.8	25.05 ± 3.8
<b>Diabetes-Associated factors</b>			
HbA <sub>1c</sub> the day of the research appointment (mmol/mol)	57.17 ± 25.1	66.17 ± 22.7	61.19 ± 24.4
Blood glucose before cognitive tests (mmol/L)	8.88 ± 3.7	8.10 ± 2.7	8.55 ± 3.3
Age of onset (years)	17.60 ± 9.1	15.61 ± 10.2	16.70 ± 9.6
Diabetes duration (years)	19.70 ± 11.9	20.70 ± 11.3	20.16 ± 11.6
Severe hypoglycaemia (N/lifetime)	2.56 ± 3.7	3.42 ± 4.8	2.95 ± 4.4
Number of subjects with retinopathy (%)	5.00 (8.8)	5.00 (10.9)	10.00 (9.7)
Number of subjects with neuropathy (%)	2.00 (3.5)	5.00 (10.9)	7.00 (6.8)
<b>Blood molecules in link with neuroplasticity</b>			
Levels of serum IGF-I (µg/L)	160.72 ± 8.0	173.00 ± 11.4	166.45 ± 6.8
Levels of serum BDNF (ng/mL)	30.44 ± 2.0	27.50 ± 2.3	29.08 ± 1.5
<b>Cognitive Function</b>			
Trail Making Test a	24.1 ± 1.5	24.2 ± 2.1	24.1 ± 1.3
Trail Making Test b	54.3 ± 6.6	46.4 ± 2.5	50.2 ± 3.4
OSPAN Absolute	29.6 ± 3.9	35.4 ± 3.5	32.6 ± 2.6
OSPAN correct	47.1 ± 3.9	53.1 ± 3.1	50.2 ± 2.5
OSPAN Math Errors	6.8 ± 9	6.7 ± 8	6.7 ± 6
OSPAN Speed Errors	1.8 ± 4	1.5 ± 2.3	1.6 ± 2
OSPAN Accuracy Errors	5 ± 9	5.3 ± 8	5.1 ± 6
Spatial Memory Test Reaction Time	962.5 ± 45.9	908.4 ± 31.8	934.5 ± 27.6
STROOP Reaction time congruent trials	1123.3 ± 47.0	981.6 ± 45.7	1049.8 ± 33.9
STROOP Reaction time incongruent trials	1158.6 ± 49.1	1020.5 ± 48.5	1086.9 ± 35.5
<b>Level of Physical Activity (MET/min/wk)</b>			
IPAQ	161.6 ± 108.2	125.8 ± 73.4	145.5 ± 95.3
MAQ	166.1 ± 107.0	110.6 ± 61.6	141.5 ± 93.5

N = Number, BDNF = Brain-derived Neurotrophic Factor; IGF-I: Insulin-like Growth Factor 1, MET = Metabolic Equivalent of Task, IPAQ = International Physical Activity Questionnaire, MAQ = Modifiable Activity Questionnaire

## 4.4 Results

### 4.4.1 DEMOGRAPHIC AND CLINICAL PROPERTIES OF OUR STUDY POPULATION

Demographic and PA data from 103 patients with T1D included in this study are summarized in table 16.

Only 11 (i.e. 10.7% of the total sample) participants were diagnosed before the age of 7. Seventeen patients had good glycaemic control (HbA<sub>1c</sub> < 53 mmol/mol or 7%) and 66 had a poor glycaemic control (HbA<sub>1c</sub> > 64 mmol/mol or 8%). Twenty patients had a glycaemic control between 7-8%. Thirty-two (31.1%) patients never experienced an episode of severe hypoglycaemia during their lifetime.

*4.4.2 CORRELATIONS BETWEEN NEUROTROPHIC FACTORS, DEMOGRAPHICAL FACTORS AND COGNITIVE FUNCTIONS*

Serum BDNF correlated with IGF-I ( $r = -.3, p < .01$ ), age ( $r = .2, p < .05$ ), diabetes duration ( $r = .4, p < .01$ ) and performance in the executive function ( $r = .4; p < .001$ ). In patients with T1D, total IGF-I correlated with BDNF, age ( $r = -.6, p < .001$ ) and onset of diabetes ( $r = -.3; p < .01$ ), diabetes duration ( $r = -.5, p < .001$ ), severe hypoglycaemia ( $r = -.2; p < .05$ ), performance in the executive function (congruent trials:  $r = -.23; p = 0.04$ ; incongruent trials:  $r = -.32; p = .004$ ), and making “speed errors” during the working memory trial ( $r = .3; p = .02$ ).

*4.4.3 INDEPENDENT PREDICTORS OF THE COGNITIVE FUNCTION IN SUBJECTS WITH T1D*

Results of the multiple regression analysis per cognitive domain are presented in table 17. This multiple regression analysis showed that chronic hyperglycaemia ( $\beta = .128; p = .03$ ), age ( $\beta = .238, p < .004$ ) and educational level ( $\beta = -5.223, p = .016$ ) are associated with attention and speed of information processing (table 17). Episodes of severe hypoglycaemia over the whole lifetime ( $\beta = 1.4; p = .007$ ) are associated with speed of information processing and divided attention.

The strongest predictors for cognitive performance in the executive function in T1D are: serum BDNF (Congruent trials  $\beta = 6.25, p = .001$ ; incongruent trials  $\beta = 7.396, p < .001$ ), chronic glycaemic control (incongruent trials  $\beta = 2.123, p = .02$ ), levels of PA (congruent trials  $\beta = -.677, p = .008$ ; incongruent trials  $\beta = -.648, p = .017$ ), age ( $\beta = 5.327, p = .01$ ), and diabetes duration ( $\beta = 6.666, p = .008$ ) (table 17).

Working memory performance was associated with age ( $\beta = -.4, p = .009$ ), errors on the working memory were associated with education ( $\beta = -1.7, p < .001$ ), PA over the last year (MAQ) ( $\beta = .02, p = .002$ ) and poor glycaemic control ( $\beta = 0.5, p = .013$ ) (table 17).

Finally, this study showed that diabetes duration ( $\beta = 9.6, p < .001$ ) was the only predictor for the spatial memory/attention task (table 17).

*4.4.4 PREDICTORS OF THE LEVEL OF SERUM NEUROTROPHINS IN SUBJECTS WITH T1D*

Diabetes duration ( $\beta = .5; p < .001$ ) was found to be a positive strong predictor of serum BDNF levels. Having complications ( $\beta = -8.265; p < .05$ ) negatively predicts levels of BDNF. Levels of IGF-I were associated with diabetes duration ( $\beta = -3.128, p < .001$ ) and age of onset of diabetes ( $\beta = -1.805, p = .007$ ) (table 18).

CHAPTER 4. Can the level of physical activity predict a DACD?

**Table 17. Step-wise Forward Multiple Regression analysis of demographic, diabetes-associated and physical activity parameters on cognitive function in subjects with type 1 diabetes**

Cognitive Domain	Dependent	F	Predictor	B	S.E.	Beta	R <sup>2</sup>	
Attention / speed of information processing / Divided attention	TMTA	7.2 ( p<.001)	(constant)	11.1	5.0			
			HbA <sub>1c</sub>	.1	.06	.2		
			Age	.2	.07	.4		
	TMTB	7.8 (p<.01)	(Constant)	45.7	2.1			
			Education	-5.6	2.2	-.3	0.23	
			Episodes of severe hypoglycaemia	1.4	.2	.3	0.1	
Executive Function / cognitive flexibility	Stroop test CONG	11.2 (p<.001)	(constant)	757.1	64.2			
			Levels of serum BDNF	6.2	1.8	.4		
			Diabetes Duration	6.7	2.4	.3		
			Level of PA (MAQ)	-.7	.25	-.3	.35	
	Stroop test INCONG	10.17 (p<.001)	(constant)	679.8	86.6			
			Levels of serum BDNF	7.4	1.8	.4		
			Age	5.3	2.0	.3		
			Level of PA (MAQ)	-.6	.3	-.3		
	Working memory	OSPAN Absolute	6.3 (p=.015)	(Constant)	46.4	5.8		
				Age	-.4	.15	-.3	.1
		OSPAN Correct	7.3 (p<.01)	(Constant)	64.9	5.2		
				Age	-.4	.1	-.3	.1
OSPAN Accuracy Error		8.9 (p<.001)	(Constant)	13.54	2.5			
			Education	-1.7	.6	-.3		
			PA over last year (MAQ)	0.16	.01	.3	.29	
OSPAN Math Error		10.6 (p = .002)	(Constant)	3.7	1.1			
	PA over last year (MAQ)		.02	.01	.4	.1		
OSPAN Speed Error	6.6 (p=.01)	Constant	-1.5	1.3				
		HbA <sub>1c</sub>	.05	0.02	.3	.1		
Spatial Memory	SMT	17.3 (p<.001)	(constant)	710.5	49.2			
			Diabetes Duration	9.6	2.3	.5	.2	

\*P < 0.05, TMTA/B = Trail Making test part A/B, OSPAN: Operation Span Test, SMT = Spatial Memory Task, RT: reaction times, INCON: incongruent words, CON: congruent words

**Table 18. Step-wise Forward Multiple Regression analysis of serum neurotrophins and their predictors in type 1**

diabetes						
Dependent	F	Predictor	B	S.E.	Beta	Adj. R <sup>2</sup>
BDNF	8.334 (p = 0.001)	(constant)	19.2	2.7		
		Complications (binary)	-8.3	4.1	-.2	
		Long Diabetes Duration	.5	.1	.4	.171
IGF-I	19.337 (p = 0.000)	(constant)	259.3	16.442		
		Long Diabetes Duration	-3.2	.5	-.5	
		Age of Onset	-1.8	.6	-.2	.31

BDNF = Brain-derived Neurotrophic Factor; IGF-I: Insulin-like Growth Factor 1

## 4.5 Discussion

This study showed that level of PA and serum BDNF are indeed associated to cognitive performance. Furthermore, poor glycaemic control, age, education, episodes of severe hypoglycaemia during lifetime, and diabetes duration can predict cognitive performance in T1D.

### 4.5.1 POOR GLYCAEMIC CONTROL AND LEVEL OF PA AS A PREDICTING FACTOR FOR THE COGNITIVE PERFORMANCE

The current study demonstrated for the first time in this specific population that PA is an independent predictor for performance in the executive tasks. Each decrease of 0.65 MET/h/week increases reaction times needed to perform the Stroop Color Word Test. Previous studies showed that aerobically trained individuals outperformed non-aerobic control subjects on a variety of cognitive tasks (Hillman et al. 2008), supporting a positive association between PA level and enhanced performance in cognitive tasks (Hillman et al. 2008, Kramer et al. 2006). However, this has never been shown in T1D. The meta-analysis of Colcombe & Kramer (2003), demonstrated that the largest positive effects of PA were found for executive control processes such as planning, scheduling, working memory, inhibitory processes and multitasking, but also improved spatial memory, and speed tasks (Colcombe and Kramer, 2003, Hillman et al. 2008), which is in line with the results in this study.

In addition, attention, working memory, but especially the executive function is negatively influenced by poor glycaemic control. We found that each 2.2 mmol/mol increase in HbA<sub>1c</sub> will prolong total reaction time and thus decrease the performance in the executive function and attention. Thereby, each rise in HbA<sub>1c</sub> (0.05 mmol/mol) increases the number of errors made during mathematical tasks (working memory). Indeed, executive function, memory and motor speed are significantly impaired by a DACD,

especially in patients with chronic hyperglycaemia (Tonoli et al. 2014b).

From a clinical perspective, it seems worthwhile to take the exercise-induced effects on cognitive function and glycaemic control in T1D patients into consideration. Especially aerobic training improves chronic glycaemic control, when performed at least 3 months (Tonoli et al. 2012). Nevertheless, the combination of strength and aerobic training, improves cognitive functioning to a greater extent than does aerobic training alone in non-diabetic patients (2003). Presumably, the combination of aerobic and strength training, performed for at least 6 months, will increase cognitive functioning in T1D. Further research is needed to test this hypothesis.

#### *4.5.2 CIRCULATING NEUROTROPHINS IN T1D; IS THERE A LINK WITH THE COGNITIVE PERFORMANCE?*

Several possible explanations for the mechanisms of the therapeutic effects of PA on cognitive functioning are suggested, (for review see (Lista and Sorrentino, 2010)). To our knowledge, no previous studies looked at the link between basal serum BDNF, total IGF-I, habitual PA level and cognitive function in T1D.

The present study showed that serum BDNF was correlated with IGF-I, age, diabetes duration, and performance on the executive function ( $r=.4$ ;  $p<.001$ ). Diabetes duration and diabetic-associated complications were significant predictors of the level of serum BDNF and serum level of BDNF predicted the performances in the executive function. Habitual levels of PA were not correlated to levels of serum BDNF. Additionally, we showed that high baseline BDNF levels in patients with T1D were a predicting factor for a delayed performance in the executive function.

Surprisingly, we observed that higher levels of BDNF were associated with poorer performance in the executive function in T1D, while previous studies related higher BDNF levels to better brain health, and were associated with slower rate of cognitive decline in AD patients (Laske et al. 2011). These results might reflect that peripheral BDNF levels may be increased as a compensatory mechanism in the pathogenesis of metabolic disorders (Suwa et al. 2006). This hypothesis is supported by the fact that diabetes duration and complications predicted the serum BDNF level in our study. Another plausible hypothesis is that BDNF has a decreased brain uptake efficiency in T1D, and consequently higher circulating levels of BDNF. The latter is supported by a study of Thomas et al. (2013), who showed an upregulation of the BDNF binding receptor (TrkB) in the hippocampi of STZ mice (Thomas et al. 2013).

TrkB.TK+ overexpressing mice show impaired TrkB signalling and specific behavioural changes (Koponen et al. 2004), which can result in lower uptake of BDNF in the brain. Consistently with this hypothesis, a previous study of our lab (Tonoli et al. 2014a) showed increased levels of serum BDNF in humans with T1D compared to non-diabetic controls. If serum BDNF is not 'absorbed' by the brain, it might not be involved in the synaptic plasticity in T1D. However, this hypothesis needs further investigation.

Additionally, the present study did not reveal an inverse relationship between the level of PA and basal serum level of BDNF, as suggested by the majority of cross-sectional studies (Knaepen et al. 2010). The inverse relationship previously seen in literature has been dedicated to an increased uptake efficiency of circulating BDNF into the brain in physical active individuals, resulting in decreased levels of circulating BDNF (Griffin et al. 2011). Since we did not find a correlation between PA level and peripheral BDNF. This could indicate the strong influence of T1D on this parameter.

As mentioned in the introduction, deficiency in circulating total IGF-I has been associated with decreased perceptual motor performance, reduced information processing speed (Dik et al. 2003), fluid intelligence (Aleman et al. 2001) and deficiencies in spatial and working memory (Sonntag et al. 2013) in healthy fit older adults. This study showed that levels of IGF-I were correlated with improved executive functioning and working memory, however IGF-I was not seen as a predictor of cognitive performance in type 1 diabetic subjects. Therefore, more research is needed to examine the exact link between IGF-I, T1D and cognitive function.

This study showed that the diabetes duration, is a strong predictor for cognitive function, and serum levels of BDNF & IGF-I. Ryan et al. (1993) suggested that it is not 'diabetes duration' per sé that appeared to influence the cognitive function, but the duration of diabetes may interact with several aspects of diabetes associated complications and therefore affects cognitive functioning, as shown in this study.

#### *4.5.3 SEVERE HYPOGLYCAEMIA AS A CONTRIBUTING FACTOR?*

Whether episodes of hypoglycemia are harmful to the brain remains controversial. An animal study showed that moderate hypoglycemia preconditioned the brain and markedly limited the extent of subsequent severe hypoglycemia-induced neuronal damage and associated cognitive impairment (Puente et al. 2010). However, irreversible brain damage occurred after a period of at least one hour of flat

electro-encephalogram. These data, in combination with the results of our study, suggest that severe hypoglycemia, at least if duration is long and severity is 'intense' enough, can affect brain function.

#### *4.5.4 LIMITATIONS OF THE STUDY*

The setting of the cross-sectional study did not allow us to determine the causal direction of associations. However it is important to collect large scale cross sectional data for the examination of the influence of PA in patients with T1D. Subsequently, longitudinal data can be collected to investigate the effects of exercise on the cognitive function in this population. Patients often overestimate their level of PA which could influence the correlations between real-life exercise and the patients' personal estimations of their level of PA. With the use of 2 validated questionnaires, we tried to minimize this problem as much as possible. We limited our neuropsychological testing to a maximum of 1 hour, because we wanted to avoid neuropsychological fatigue during neurocognitive testing.

#### *4.5.5 CONCLUSIONS AND GUIDELINES FOR FURTHER RESEARCH*

Several factors can predict cognitive function in T1D including the level of PA, level of education, lower levels of HbA<sub>1c</sub>, positively predicted the cognitive performance and long diabetes duration and episodes of severe hypoglycaemia negatively predicted the cognitive performance in T1D. Furthermore, levels of serum BDNF were positively predicted by T1D duration and inversely predicted cognitive function. Achieving good glycaemic control by regular PA can thus minimize the development and severity of diabetes-associated complications, including complications on brain function.

BDNF and IGF-I are believed to play a key role in exercise-induced positive cognitive effects, but basal levels of BDNF and IGF-I were not influenced by the level of PA in T1D. To elucidate the association between acute exercise and increments of these factors in T1D, further examination of the effects of different types of (acute and chronic) exercise on cognitive function and diabetes-associated influence are needed.

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CHAPTER 5. NEUROTROPHINS AND COGNITIVE FUNCTIONS IN T1D  
COMPARED TO HEALTHY CONTROLS: BENEFICIAL EFFECTS OF A HIGH-  
INTENSITY EXERCISE

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**ARTICLE**

Neurotrophins and cognitive functions in T1D compared with  
healthy controls: effects of a high-intensity exercise

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Nathalie Pattyn, Serge Berthoin, and Romain Meeusen

## 5.1 Abstract

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**Purpose.** Exercise is known to have beneficial effects on cognitive function. This effect is greatly favored by an exercise-induced increase in neurotrophic factors such as Brain-derived Neurotrophic Factor (BDNF) and Insulin-like Growth Factor (IGF-I), especially with high intensity exercises (HIE). As a complication of Type 1 Diabetes (T1D), a cognitive decline may occur, mostly ascribed to hypoglycaemia and chronic hyperglycaemia. Therefore, the purpose of this study is to examine the effects of acute HIE on cognitive function and neurotrophins in T1D and matched controls. **Methods.** Ten trained T1D (8 males, 2 females) participants and their matched (by age, gender, fitness level) controls were evaluated on 2 occasions after familiarization: a maximal test to exhaustion and a HIE bout (10 x [60s 90%Wmax, 60s 50W]). Cognitive tests and analyses of serum BDNF, IGF-1, and free insulin were performed before and after HIE and following 30min recovery. **Results.** At baseline, cognitive performance was better in the controls compared to the T1D participants ( $p < 0.05$ ). After exercise, no significant differences in cognitive performance were detected. BDNF levels were significantly higher and IGF-I levels significantly lower in T1D compared to the control group ( $p < 0.05$ ) at all-time points. Exercise increased BDNF and IGF-I levels in a comparable percentage in both groups ( $p < 0.05$ ). **Conclusion.** Although resting levels of serum BDNF and IGF-I were altered by T1D, comparable increasing effects on BDNF and IGF-I in T1D and healthy participants was found. Therefore, regularly repeating acute HIE could be a promising strategy for brain health in T1D.

## 5.2 Introduction

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One of the complications of individuals with Type 1 diabetes (T1D) is the impact on brain structure and function. A recent meta-analysis showed that T1D adults perform worse on tests of full/verbal and performance IQ, executive function, memory, spatial memory and motor speed (Tonoli et al. 2014). This cognitive decline has been ascribed to episodes of hypoglycaemia (Auer, 2004), hyperglycaemia (Wrighten et al. 2009) and C-peptide and/or insulin deficiencies (Li et al. 2005) as a pathophysiological basis.

Over the last several decades much research in non-diabetic subjects has been carried out to identify the influence of acute and chronic physical exercise on cognitive function. Acute exercise leads to an increased arousal. As arousal increases, attention narrows and an optimal level is reached when only relevant cues are processed (Brisswalter et al. 2002). Consequently, acute exercise improves cognitive task performance in several domains of cognitive function right after exercise (Lambourne and Tomporowski, 2010). Chronic exercise, on the other hand, improves executive function (Colcombe and Kramer, 2003) and spatial memory (Erickson et al. 2011). Acute exercise and training seem to be key interventions that trigger the processes through which neurotrophins mediate neural plasticity and energy metabolism (van Praag, 2008, Vaynman et al. 2004, Neeper et al. 1996).

Brain-derived neurotrophic factor (BDNF) is the neurotrophin that is most susceptible to physical activity (Vaynman and Gomez-Pinilla, 2005, Knaepen et al. 2010). Previous research consistently shows BDNF is released into the blood circulation as a result of a physical stimulus in a dose response manner (Knaepen et al. 2010). As BDNF influences energy and glucose metabolism (Nakagawa et al. 2002, Blackman et al. 1992, Ono et al. 1997, Ono et al. 2000) in diabetic and non-diabetic rodent studies, it is not inconceivable that the release of BDNF is related to remaining circulating levels of insulin. Besides, insulin is emerging as a substance with widespread effects on the brain with additionally increased saturable transport across the blood-brain barrier in T1D-induced diabetic animals (Banks, 2004).

Furthermore, Insulin Like Growth Factor-I (IGF-I) is also believed to play key role in these exercise-induced effects on the cognitive function and is involved in brain growth and development, myelination and brain plasticity (Aberg, 2010). While the impact of exercise on the GH/IGF system is well recognized, the impact of

acute and chronic (training) exercise on circulating IGF is unclear (Stokes et al. 2010, Wallace et al. 1999, De Palo et al. 2001, Nguyen et al. 1998, Griffin et al. 2011). In general, there appears to be a tendency for larger increases in circulating IGF after exercise at higher intensities as compared to exercise at moderate intensities (Copeland and Heggie, 2008, Schwarz et al. 1996). The acute release of neurotransmitters and increased levels of neurotrophic factors may enhance neurogenesis, neuronal plasticity, learning ability and memory (Knaepen et al. 2010).

Exercise has emerged as a promising low-cost treatment in non-diabetics suffering from a cognitive decline (Colcombe and Kramer, 2003) and acutely increases the release of neurotrophins in a dose response matter. The effect of acute exercise on the release of neurotrophins and cognitive function in T1D subjects has yet to be examined. Therefore, the aim of this study was to evaluate if there are differences between in serum levels of BDNF between subjects with T1D and their matched controls. Subsequently, to elucidate the effects of HIE on cognitive function, levels of BDNF, IGF-I and free insulin in T1D adults compared to non-diabetic controls. It is hypothesized that an acute HIE might have a beneficial effect on neurotrophic factors and on cognitive function in T1D participants. Several research questions are being addressed by this investigation: (1) Is there a difference among T1D and matched non-diabetic controls in baseline levels of BDNF? (2) Are levels of serum BDNF and IGF-I influenced by a HIE? (3) Is cognitive function influenced by exercise in T1D subjects? (4) Is there a difference in cognitive performance after exercise between a diabetic and a non-diabetic group.

## 5.3 Materials & Methods

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A non-randomized control group pretest-posttest design was performed to study the effects of a HIE on cognitive function and markers of neurogenesis. The study was approved by the local ethics committee.

### *5.3.1 PARTICIPANTS*

Ten trained T1D participants (T1D group), aged 18-44 years, were recruited to participate in this study. Matched controls were recruited one by one matching the characteristics of the T1D participants (CONT group, matched by age, gender, BMI and training level, see table 19). All T1D participants had been diagnosed with T1D for at least 1 year, according to the WHO criteria (Expert Committee on the and Classification of Diabetes, 2003). Exclusion criteria were (1) psychological problems, (2) neurological abnormalities, (3) physical

disabilities, (4) head injuries, (5) metabolic conditions other than T1D, and (6) the use of medications which might alter cognitive function. All T1D participants were free from micro-and macrovascular complications since these complications might influence cognitive function. All volunteers were informed about the nature and the risks of the experimental procedures before their written informed consent was obtained.

### *5.3.2 PROTOCOL*

Approximately 1 week prior to the start of the intervention period all participants performed a familiarization trial of the cognitive tests and got a full explanation on the study. Afterwards, the participants were evaluated on 2 occasions.

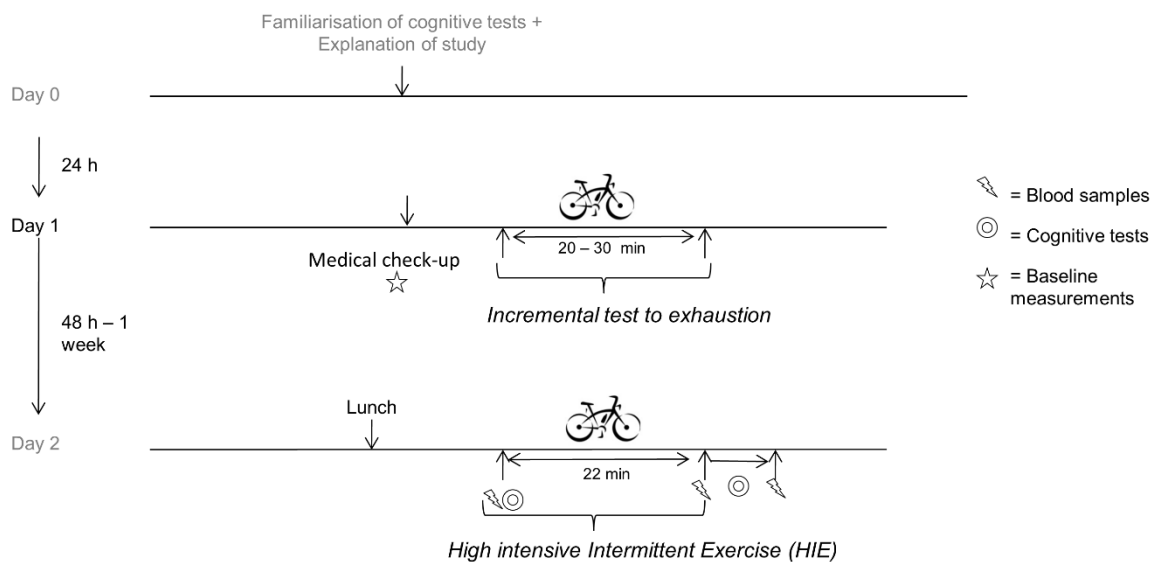
First, participants underwent a complete medical check-up (including collection of anthropometrical baseline data) in which the absence of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (high blood pressure, coronary disease, peripheral arteriopathy) complications were checked by a clinician. Afterwards, participants performed an incremental test to exhaustion on a bicycle ergometer at a constant pedal rate between 80-100 rpm. They started pedaling for 5 minutes at 50 Watts and thereafter the workload increased by 25 Watts every minute. The test was terminated at the point when the desired pedaling rate (80-100 rpm) could no longer be sustained and a heart rate  $> 90\%$  of the theoretical maximal heart rate ( $210 - 0.65 * \text{age}$ ) (Astrand et al. 2003).  $\text{VO}_{2\text{max}}$  was measured using the METALYZER CORTEX (Biophysik GmbH, Germany). The maximal wattage was determined as the highest workload sustained during the last step of this test (see figure 10).

Secondly, participants performed a High Intensity Exercise (HIE) bout. The HIE protocol used in the present study, is based on the study of Little et al. (2010) in T2D subjects. HIE was performed on a bicycle ergometer and subjects started with a warming-up session of 2 minutes at 100 Watt, followed by an effort of 1 minute at 90% of the maximum wattage cycled during the Max-test, at a rate between 80-100 rpm. This effort was repeated 10 times, with 1 minute of cycling at a very low intensity (50 Watt) between each effort. This resulted in a total exercise time of 22 minutes.

Participants were asked to refrain from vigorous physical activity ( $> 6$  METs; such as running, cycling etc. at intensities corresponding to high percentage of their maximal aerobic power) and should not have severe



hypoglycaemic episodes for 48h before the test. All HIE were performed between 13h30 and 14h30. A standardized meal was consumed approximately 2 hours before the HIE. Meal composition was identical for each subject and was based on current recommendations for T1D to achieve a neutral energy balance with 60% of calories from carbohydrates, 20% from protein and 20% from fat (Iscoe and Riddell, 2011). T1D participants injected their insulin as they usually would do before their training sessions. When glycaemia levels reached stable values (between 1-1.8 g/L), the exercise protocol started. If glycaemia was below 1g/L, supplementations of carbohydrates were provided until achievement of the targeted stable blood glucose value. Immediately before and immediately after the HIE, blood samples were collected and cognitive tests were performed. Furthermore, a third blood sample was collected after 30 minutes of recovery.



**Figure 10: Protocol of the study**

### 5.3.3 BLOOD MEASUREMENTS

Venous blood samples were collected immediately before and after exercise and after recuperation, through a catheter placed 30 min before the first blood sampling.

**HbA<sub>1c</sub> and Blood Glucose Levels:** HbA<sub>1c</sub> and blood glucose were measured in whole blood. HbA<sub>1c</sub> was measured using chromatography with ion exchange (Tosoh G7). Blood glucose was measured using a photometrical method (using the hexokinase Roche).

The additive free blood samples were stored at ambient temperature for 1 hour before being centrifuged, and

the resulting serum was stored in a -80°C freezer until analyses of BDNF (commercially ELISA kit – CYT306, ChemiKine®, Millipore®, Billerica, MA, USA), total IGF-I (commercially IRMA kit, using an Immulite 2000, Siemens for reading) and serum free insulin levels (non-competitive radio immunoassay (IRMA) using the BI INS IRMA kit from Cis Bio Bioassays (Codolet, France) were performed. Results of serum free insulin levels were expressed in mUI/L in terms of WHO 66/304 insulin reference preparation.

#### *5.3.4 NEUROCOGNITIVE ASSESSMENT*

The assessment of a DACD in T1D patients is usually based on neuropsychological tests. Since exercise has beneficial effects on cognitive function, especially for tasks related to the executive function (Colcombe and Kramer, 2003) and spatial memory (Erickson et al. 2011), the neuropsychological assessment was chosen to assess these different cognitive domains with the following tests: The Stroop test and the Spatial Memory Task (SMT), respectively. The tests were performed in a fixed order and took together less than 20 minutes. Validity and reliability data of these tests have been reported previously (Strauss et al. 2006).

**Stroop Test:** This measure of selective attention and cognitive flexibility (executive functions) assesses the ease with which a person can maintain a goal in mind and suppress a habitual response in favor of less familiar ones (25). In this study we used a computerized Stroop test in which the participants read the color name and must press a colored button on the keyboard in which the color names are printed and disregard their reading content. The presented words/nouns could be classified under different conditions, namely “congruent” (word and color are the same [e.g. the word red displayed in a red color]) and incongruent (e.g. word a color are not the same).

**SMT:** In this computerized test one, two or three black dots appear at random locations on the screen for 500ms. The dots are removed from the display for 3s. During this time, participants are instructed to try and remember the locations of the previously presented black dots. At the end of the 3s delay, one or more red dots appear on the screen in either one of the same locations as the target dots (match condition) or at a different location (non-match condition). Participants have 2 seconds to respond to the number and location of red dots by pressing keys on a standard keyboard. Forty trials are presented for each set size (one, two, or three dots), with 20 trials as match trials and 20 trials as non-match trials. Participants are instructed to respond as quickly and accurately as possible (Erickson

et al. 2011).

### 5.3.5 STATISTICAL ANALYSIS

All analyses were carried out via IBM SPSS Statistics 22 software and considered significant at  $\alpha = .05$ . Normality of the data was tested using Kolmogorov-Smirnov Goodness of Fit test. Accuracy data of the cognitive tests and free insulin levels were log-transformed because normality was violated. Since outliers influence statistical analysis, outliers were excluded when a S.D. of  $>3$  or  $<-3$  was reached (1 subject for BDNF). Paired sample t-test and the nonparametric variant (i.e. Related-Samples Wilcoxon Signed Rank Test) were used for the determination of differences in characteristics between the matched groups at baseline. Correlations between blood glucose, serum IGF-I, serum BDNF and serum free insulin were analysed using Pearson and Spearman's rho correlations, depending on the normality of the data. After adjusting for differences in cognitive performance during the pre-exercise test, Analysis of Covariance (ANCOVA – Group \* time) was performed to estimate the differences between the groups on cognitive performances after HIE. Changes in blood glucose, serum BDNF, serum IGF-I and serum free insulin over the three different time points (pre/post ex and after recovery) were determined and compared between groups using a two-way analysis of variance (ANOVA) (group \* time) with repeated measures on time. Post-hoc analyses were performed using the Sidak correction. Differences were considered significant when  $p < 0.05$ .

## 5.4 Results

### 5.4.1 DEMOGRAPHIC AND CLINICAL PROPERTIES OF THE STUDY POPULATION

**Table 19. Demographic and clinical characteristics.**

	Mean ( $\pm$ SD)	
	T1D	Controls
Demographic and medical characteristics		
N	10	10
Age (yrs)	30.6 (2.3)	31.0 (2.4)
Height (m)	1.80 (0.1)	1.8 (0.03)
Body Mass (kg)	77.0 (2.7)	73.8 (4.3)
BMI (kg/m <sup>2</sup> )	23.5 (0.8)	22.9 (0.8)
HbA <sub>1c</sub> (mmol/mol)	53.4 (4.4)	31.0 (0.9)*
Diabetes Duration (yrs)	8.2 (1.5)	N.A
Aerobic Fitness		
VO <sub>2max</sub> (ml/kg/min)	52.5 (2.7)	55.7 (2.4)
W <sub>max</sub>	338.9 (22.1)	365 (22.4)

\* =  $p < 0.05$

The characteristics of the study population are shown in table 19. According to recently published guidelines to classify subject groups in sport-science research, these athletes fall in the “trained” category (Performance level 3) (De Pauw et al. 2013). Participants with T1D had a significantly higher level of HbA<sub>1c</sub> ( $53.44 \pm 4.4$  mmol/mol vs  $31.02 \pm 0.9$  mmol/mol) compared to their matched non-diabetic controls. No other significant differences were observed between the two groups.

#### *5.4.2 CHANGES IN BLOOD GLUCOSE, SERUM BDNF, SERUM IGF-I AND SERUM FREE INSULIN AFTER A HIE IN T1D PARTICIPANTS AND THEIR MATCHED CONTROLS*

##### 5.4.2.1 Changes in serum BDNF concentrations

Significantly higher levels of BDNF were found in the T1D group compared to the control group ( $F = 7.8$ ;  $p < 0.05$ , post-hoc corrections =  $p = 0.01$ ) at all-time points and BDNF significantly changed over time during the HIE trial ( $F = 11.5$ ;  $p < 0.05$ ). No interaction effect (time \* group) was observed ( $F = 1.25$ ;  $p > 0.05$ ). After a post hoc Sidak correction, BDNF levels significantly increased post exercise compared to pre-exercise ( $p = 0.01$ ) in both groups, and returned to baseline levels after recovery in both groups ( $p = 0.02$ ) (table 20, figure 11).

##### 5.4.2.2 Changes in serum IGF-I concentrations

Levels of IGF-I were significantly lower in the T1D group compared to the control group at all time-points ( $F = 9.23$ ;  $p = 0.014$ ) and a significant effect was found over the three time points (pre, post-HIE and after recuperation) ( $F = 18.7$ ;  $p = 0.00$ ). However, no interaction effect was observed ( $F = 0.405$ ;  $p > 0.05$ ). After a post hoc Sidak correction, IGF-I levels increased post exercise compared to pre-exercise ( $p = 0.002$ ), and decreased back to baseline levels compared to post-exercise in both groups ( $p = 0.001$ ) (table 20, figure 11).

##### 5.4.2.3 Changes in blood glucose

Levels of blood glucose were significant higher in the T1D group compared to the control group ( $F(1,20) = 6.8$ ;  $p = 0.03$ ) and a significant effect was found over time ( $F(2,20) = 6.2$ ;  $p = 0.01$ ). No interaction effect was observed ( $F = (2,20) 0.3$ ;  $p > 0.05$ ). After a post hoc Sidak correction, post blood glucose levels significantly decreased after exercise compared to pre-exercise ( $p = 0.004$ ) in the T1D group. No significant differences were found in the control group. No differences were found after the short resting period compared to the end of

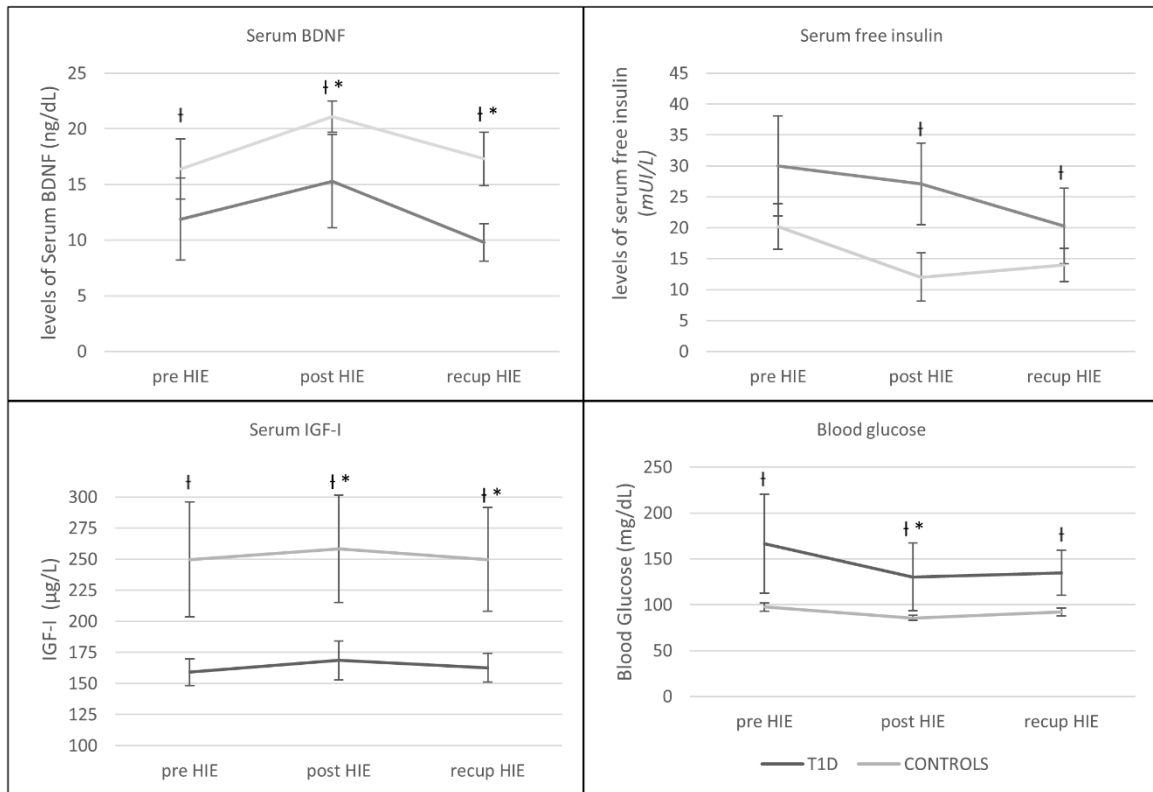
exercise in both groups (table 20, figure 11).

#### 5.4.2.4 Changes in serum free insulin levels

The change in serum free insulin levels over time was significantly different between both groups ( $F(2,20) = 8.7$ ;  $p < 0.01$ ). Post hoc Sidak correction demonstrated that free insulin levels increased after the short recuperation in the non-diabetic control group ( $p < 0.05$ ). No difference in free serum insulin levels was found between both groups ( $F(1,20) = 3.5$ ;  $p > 0.05$ ) and no interaction effect was observed ( $F(2,20) = 2.6$ ;  $p > 0.05$ ) (table 20, figure 11).

#### 5.4.3 *CORRELATIONS BETWEEN SERUM IGF-I, BDNF, FREE INSULIN AND BLOOD GLUCOSE*

Serum free insulin was correlated to serum BDNF and negatively correlated to serum IGF-I in the diabetic population (respectively  $r = .5$   $p < 0.01$ ;  $r = -.38$   $p < 0.05$ ). In the non-diabetic group; serum free insulin is correlated to IGF-I and blood glucose (respectively  $r = .44$   $p < 0.05$ ;  $r = .8$   $p < .001$ ) and negatively to BDNF ( $r = -.52$   $p < 0.01$ ). Furthermore, levels of serum BDNF were inversely correlated to blood glucose levels in the non-diabetic control group ( $r = -.47$   $p = 0.01$ ).



**Figure 11: Serum BDNF, serum IGF-I, serum free insulin and venous glucose levels over time (pre, post-ex and after recuperation) after a HIE in T1D and their matched controls**

BDNF = Brain-derived Neurotrophic Factor. IGF-I = Insulin Like Growth Factor. T1D = Type 1 Diabetes. HIE = High Intensity Exercise. † = significant ( $p < .05$ ) between groups, \* = significant ( $p < .05$ ) in time

**Table 20. Changes in Venous Glucose Level, serum BDNF, serum IGF-I during and after a Max test and a HIE in T1D subjects and their matched controls.**

	T1D			Controls			Repeated Measures ANOVA (group * time)
	Pre -ex	Post-ex	After recup	Pre -ex	Post-ex	After recup	
Serum BDNF <sup>1</sup> (ng/mL)	16.4 (2.7)	21.1 (1.4)	17.3 (2.4)	11.88 (3.7)	15.3 (4.2)	9.8 (1.7)	Group: p<.05 Time: p<.05 Interaction: NS
Serum IGF-I (µg/L)	159.0 (10.8)	168.5 (15.7)	162.7 (11.7)	249.8 (46.3)	258.4 (43.27)	249.8 (41.57)	Group: p<.05 Time: p<.01 Interaction: NS
Venous Glucose (mg/dL)	166.5 (54.0)	130.2 (36.9)	134.7 (24.6)	97.6 (4.5)	85.4 (2.8)	92.0 (4.4)	Group: p<.05 Time: p<.01 Interaction: NS
Serum Free insulin levels ( <i>mUI/L</i> )	30.0 (8.1)	27.1 (6.6)	20.3 (6.1)	20.2 (3.7)	12.0 (3.9)	14.0 (2.7)	Group: NS Time: p<.05 Interaction: NS

Data expressed as Mean (SE). T1D = Type 1 Diabetes, ex = exercise, recup = recuperation, BDNF = Brain derived Neurotrophic Factor, IGF-I = Insulin-like Growth Factor, NS = Not significant. <sup>1</sup> Analyses were only performed in male subjects due to possible differential effects in males and females of BDNF

#### 5.4.4 DIFFERENCES IN COGNITIVE FUNCTION

At baseline, the T1D group performed significantly worse compared to the control group during the Stroop test (reaction times) ( $t = -2.452$ ,  $p = 0.037$ ). No other differences were observed for cognitive performance at baseline between the two groups. After HIE both groups performed better in the congruent and incongruent parts of the Stroop test (reaction times decreased) compared to pre-exercise ( $p < 0.05$ ). The T1D group performed significantly better on the SMT after exercise compared to pre-exercise (reaction times decreased) ( $p < 0.05$ ). No significant differences were observed in accuracy for both congruent and incongruent trials during the Stroop and during the SMT after exercise in both groups (table 21).

To reveal the effects of exercise on cognitive performance, an ANCOVA with pre-test values as a confounding factor was used. Out of our results, it is clear that pre-exercise values are significantly related to post exercise cognitive performance (SMT:  $F(1,18) = 133.82$ ,  $p < 0.001$ . Stroop incongruent:  $F(1,18) = 33.42$ ,  $p < 0.05$ ; Stroop congruent:  $F(1,18) = 50.24$ ,  $p < 0.001$ ). However, when pre-exercise cognitive performance data were excluded (covariate), no significant differences were found between diabetics and non-diabetic patients (SMT:  $F(1,18) = 0.46$ ,  $p > 0.05$ ; Stroop incongruent:  $F(1,18) = 0.94$ ,  $p > 0.05$ ; Stroop congruent:  $F(1,18) = 1.15$ ,  $p > 0.05$ ).



**Table 21. Differences in cognitive function after a HIE between T1D group and their matched controls**

	High Intermittent Intensity Exercise					
	T1D			Controls		
	Pre – Ex	Post - Ex	p - value	Pre – Ex	Post - Ex	p - value
<b>Spatial Memory</b>						
SMT RT (ms)	645.0 (31.2)	621.2 (31.6)	.02*	591.9 (44.0)	564.3 (35.9)	.11
SMT Accuracy	0.94 (.01)	0.93 (0.01)	.62	0.92 (.01)	0.92 (.01)	.23
<b>Executive function</b>						
Stroop RT cong (ms)	703.9 (26.5)	664.5 (23.5)	.00*	734.5 (25.3)	670.7 (21.7)	.004*
Stroop RT incong (ms)	722.1 (31.3)	684.9 (29.4)	.005*	759.3 (24.0)	712.1 (22.2)	.047*
Stroop Accuracy cong	.97 (.01)	.97 (.01)	.41	.99 (.01)	.98 (.01)	.23
Stroop Accuracy incong	.99 (.01)	.99 (.01)	.91	.97 (.03)	.98 (.01)	.60

Data are presented as Mean  $\pm$  SD. \*  $p < 0.05$ . RT = Reaction Time

## 5.5 Discussion

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The present study examined differences in blood glucose, serum levels of BDNF, IGF-I, free insulin and cognitive performance in executive and spatial memory function between a T1D group and their non-diabetic matched controls at baseline and after a single acute HIE. This study found that, at all-time points, levels of serum BDNF were significantly higher and levels of IGF-I were significantly lower in T1D compared to the control group. Serum free insulin was positively correlated to serum BDNF and negatively correlated to serum IGF-I in the diabetic population, while in the control group serum BDNF was inversely correlated to blood glucose and serum free insulin. HIE significantly increased serum BDNF and serum IGF-I levels after exercise in both groups with the same percentage. These levels decreased significantly after a short period of recovery in both subject groups. At baseline T1D subjects performed significantly worse on executive function tests. After HIE, the performance on the executive function improved in both groups. However, since we did not use a control resting session, we cannot exclude that this result might be due to a short-term learning effect.

A remarkable result of the present study was that the BDNF levels were higher (at all-time points) in T1D participants compared to their matched controls. Previously, 7 studies have shown differences in (baseline) BDNF levels in non-exercising T2D humans compared to non-diabetic controls. The conclusions of these investigations are inconsistent reporting either decreased serum and plasma BDNF levels in T2D patients (Krabbe et al. 2007, Fujinami et al. 2008, Zhen et al. 2013, Arentoft et al. 2009) or increased serum and plasma BDNF (Suwa et al. 2006, Liu et al. 2010a, Shin et al. 2012). It has been suggested that systemic increases in BDNF might reflect compensatory responses in the body (Arentoft et al. 2009). Indeed, increased levels of BDNF were found in newly diagnosed patients with T2D (Suwa et al. 2006), T2D with retinopathy (Liu et al. 2010b) and hemodialysis T2D patients (Shin et al. 2012). The consistent higher levels of BDNF in T1D found in this present study could consequently reflect compensatory responses in T1D; suggesting that many other factors including glucose metabolism, pathological disorders, insulin, etc. can influence the serum BDNF level in T1D. Hence, blood glucose and serum free insulin were analyzed considering that they may be altered by both diabetes and exercise and that they might influence

neurotrophic factors and/or cognitive performance. Indeed, levels of BDNF were positively correlated to the levels of serum free insulin in T1D, while inversely correlated to free insulin levels in the non-diabetic control group. Previous work by Banks (2004) has shown that insulin transport across the blood-brain barrier is increased in rats with STZ-induced diabetes. When this finding is considered along with the higher levels of BDNF in the periphery of T1D subjects found in this investigation, it seems possible that there could be a link between insulin and BDNF in the brain in patients with diabetes. However, further investigation into this phenomenon needs to be completed before a substantive conclusion is made.

Furthermore, these findings supports the hypotheses that BDNF is linked to multiple parameters of energy metabolism and homeostasis in diabetes (Yamanaka et al. 2008, Krabbe et al. 2007). Nakagawa and colleagues (Nakagawa et al. 2002) injected BDNF subcutaneously ino STZ-induced diabetic mice with or without insulin administration. In this study, reduced blood glucose concentration was found two hours after co-injection of BDNF and insulin compared with mice which were given insulin alone (Nakagawa et al. 2002). This shows that co-administration of BDNF with insulin potentiates the hypoglycemic action of insulin in STZ mice, indicating an acute enhancement of insulin sensitivity (Nakagawa et al. 2002). The efficacy of BDNF in regulating glucose and energy metabolism was reproduced through intra-cerebroventricular administration of small portions of BDNF in db/db mice, suggesting that BDNF acted directly on the hypothalamus, a region where the insulin receptor is widely expressed (Unger et al. 1991, Banks et al. 2012). This effect of BDNF on glucose is illustrated in our study by the inverse correlation between BDNF and glucose levels in the healthy control group, which is in line with results out of previous studies. On the contrary, in the T1D group, serum BDNF was positively correlated to free insulin levels which might suggest an increase in serum BDNF to compensate hyperinsulinemia, reflecting back to the 'compensatory hypotheses' of BDNF (Arentoft et al. 2009).

It is not inconceivable that levels of BDNF, which are higher in the periphery of T1D participants, will also consistently be higher in the diabetic brain. One study so far has shown that *chronic* overexpression of BDNF in the brain resulted in significant impairments in both short and longterm memory formation in BDNF transgenic mice (Cunha et al. 2009). The hypothesis these authors tend to favor is that an excess of BDNF may act on inhibitory interneurons, leading to a general alteration of the inhibitory tone of the synaptic circuitry underlying learning. Whether this might be the case in T1D obviously needs further

research and such notion remains to be experimentally evaluated.

As a consequence of insulin deficiency, patients with T1D have shown reduced levels of total and free levels of IGF-I (Thraillkill, 2000), which is consistent with our results at all-time points. IGF-I is important for nervous system growth and differentiation and is therefore characterized as a neurotrophin (Park, 2001). Consequently, lower IGF-I levels could be a possible cause of cognitive impairments. The production of IGF-I leads to angiogenesis and synaptogenesis through a downstream signaling cascade at the presynaptic and the postsynaptic level. Angiogenesis is enhanced by vascular endothelial growth factor that is directed by IGF-I and several energy dependent mechanisms such as cellular hypoxia and glucose deficit. IGF-I, necessary for normal insulin sensitivity, binds to insulin receptors to stimulate glucose transport, inhibit glucose release from the liver and lower blood glucose while simultaneously suppressing insulin secretion (Clemmons, 2004). Decreased IGF-I levels could thus contribute to diminished angiogenesis and synaptogenesis in the diabetic brain and the homeostasis of glucose metabolism.

Another remarkable result is that serum BDNF and IGF-I increased immediately after the HIE in T1D and their matched controls and the increment was similar in both groups. Serum BDNF levels decreased significantly after a short recovery period in both groups compared to the post-exercise levels, similar to what has been observed in other studies (For review see: Knaepen et al. 2010, Rojas Vega et al. 2006). The percentage increase in BDNF after exercise was comparable in both groups (28.6 % increase of serum BDNF in the T1D group vs. 28.5% increase of serum BDNF in the control group), suggesting that exercise had the same effect on BDNF in the T1D group as in the control group. After a short period of recuperation, serum BDNF of the controls decreased almost twice as much (35.8%) as compared to the diabetic group (18%), but this difference was not significant.

Several studies have confirmed that brief bouts of (intense) aerobic exercise result in a transient increase in circulating IGF-I and BDNF. Gene expression and secretion of BDNF in the brain is mainly regulated in an activity-dependent manner which might explain why BDNF, among all neurotrophins, is most consistently up regulated with exercise (Allen et al. 2013). The mechanisms/stimuli responsible for this exercise-induced increase have not yet been clearly established, but some hypotheses are proposed in literature. BDNF gene expression is stimulated by neuronal activity (Murer et al. 2001), which is increased by exercise

(Foley et al. 2012). Acute exercise also leads to an increase in serum calcium and consequently increased cerebral calcium level that activates CREB, which is a prominent regulator of BDNF transcription and consequently influences BDNF gene expression (Akiyama and Sutoo, 1999). It has been shown that at rest and during exercise, the brain contributes 70-80% of circulating BDNF, suggesting that the brain is a major but not the sole contributor to circulating BDNF (Rasmussen et al. 2009). IGF-I, on the other hand, is believed to increase due to an increased release of GH during exercise. GH is believed to be the major hormonal regulator of hepatic syntheses and of release of IGF-I together with its binding proteins (IGFBP1-6) (De Palo et al. 2001). Besides being mostly derived from the liver, circulating IGF-I is also produced in many other tissues including brain and skeletal muscle. Therefore, it has also been proposed that the exercise-induced increase in IGF-I is partly due to an increased influx from locally produced IGF-I, such as an increased production from exercising muscle or the brain themselves (Dall et al. 2001).

It is well established that exercise has a positive effect on a wide range of cognitive functions (Berchtold et al. 2010, Knaepen et al. 2010). Generally, acute exercise has been claimed to have an inverted U-effect on the cognitive performance in non-diabetic participants (Brisswalter et al. 2002). With the hypothesis that HIE might have protective effects on the cognitive function in T1D, this type of exercise was chosen in this study. Our results demonstrated a faster reaction time in the Stroop test (executive function) and spatial memory task for T1D patients and their matched controls after exercise. To our knowledge, this is the first study investigating the effects of HIE on the cognitive function in T1D. However we cannot conclude that the cognitive function improved solely as a result of the exercise intervention because a non-exercise control session was not used and therefore at least some of this effect could be a consequence of a short-term learning effect. The lack of difference in the improvement in cognitive function following exercise between the T1D group and their matched controls also suggest that the presence of T1D does not influence how the brain responds to exercise. When considering this finding, along with the similar responses to exercise in BDNF and IGF-I, it seems reasonable to conclude that the neurophysiologic and neurocognitive effects of exercise in T1D patients is similar to people without diabetes.

### 5.5.1 LIMITATIONS OF THE STUDY

This study was performed in well trained participants. Exercise can decrease blood glucose levels depending on the intensity of the exercise. However, the implementation of a HIE can prevent an episode of hypoglycemia due to a smaller decrease in blood glucose after HIE. For example, blood glucose levels may drop less if the intensity of the exercise is sufficiently high enough to increase catecholamines in patients with T1D. Since this study tested a novel protocol of HIE, which was already previously tested in subjects with Type 2 diabetes, well-trained T1D patients were included because it was believed they would be able to respond more quickly and more safely to changes in blood glucose levels. This might complicate the generalization of these results from this specific population to an untrained population with T1D. Untrained (sedentary), or recreationally trained participants can react (in cognitive performance and blood glucose levels) differently to high intensity exercises. However, with proper precautions present to monitor blood glucose control, this protocol should be able to be used in further studies in untrained populations with T1D. It is also possible that the training status of the T1D subjects included in this investigation prevented any negative impact of their disease process on cognitive function. As a consequence, further studies need to be performed to determine the effects of different types of exercise with the inclusion of a control non-exercise trial on cognitive function in untrained T1D patients, including a control, untrained group.

## 5.6 Conclusions and guidelines for further research

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This study showed that, at all time points, serum BDNF levels were significantly higher, and serum IGF-I levels were significantly lower in T1D compared to the control group. The consistent higher levels of BDNF in T1D could consequently reflect compensatory responses in T1D, suggesting that BDNF is influenced by the pathological disorder of T1D, as shown by the positive correlation between serum free insulin and serum BDNF in T1D patients. This study showed that HIE had comparable increasing effects on BDNF and IGF-I in T1D and healthy participants. Similar improvements in cognitive function were seen after a HIE in trained T1D participants and their matched controls, suggesting that there was no difference in how their brain responded to HIE. An appropriately designed, large-scale study is necessary to further explore these findings, and additional research on other types of acute exercise and training, with the inclusion of a non-

exercise control trial, are needed. Further research is also warranted to establish the metabotropic action of BDNF and its link with insulin in T1D.

## 5.7 Acknowledgments and Conflict of Interest

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CHAPTER 6. BDNF, IGF-I, GLUCOSE AND INSULIN DURING  
CONTINUOUS AND INTERVAL EXERCISE IN TYPE 1 DIABETES

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**REFERENCE:**

**TONOLI C., HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., BAILEY S., PATTYN N., BERTHOIN S., MEEUSEN R.** BDNF, IGF-I, glucose and insulin during continuous and interval exercise in Type 1 Diabetes. [Submitted in International Journal of Sports Medicine]

## 6.1 Abstract

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**Introduction.** Type 1 Diabetes (T1D) can have a significant impact on brain function, mostly ascribed to episodes of hypoglycaemia and chronic hyperglycaemia. Exercise has positive effects on acute and chronic glycaemic control in T1D, and has beneficial effects on cognitive function by increasing neurotrophins as BDNF and IGF-I in non-diabetic humans. The present study **examines** the effects of different types of exercise intensities on neurotrophins in T1D. **Methods.** Ten participants with type 1 diabetes were evaluated on 3 occasions: a high intensity (10 x [60s 90%Wmax, 60s 50W]) and continuous (22 min, 70% VO<sub>2max</sub>) exercise and a control session. Blood glucose, serum free insulin, serum BDNF and IGF-I were assessed pre/post all the trials and after recovery. **Results.** Blood glucose significantly decreased after both exercise intensities and BDNF levels increased, with a dose-response effect for exercise intensity on BDNF. IGF-I changed over time, but without a difference between the different exercise protocols. **Conclusion.** Both exercise intensities changes neurotrophins in T1D, but with a dose response effect for BDNF. The intensity-dependent findings may aid in designing exercise prescriptions for maintaining or improving neurological health in T1D, but both types of exercise can be implemented.

## 6.2 Introduction

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Research has indicated physical activity or exercise enhances multiple aspects of physical and cognitive functioning in healthy adults (Hillman et al. 2008). It has been hypothesized that Type 1 Diabetes (T1D) is associated with an increased risk of cognitive decline in domains such as IQ, executive function, memory, spatial memory and motor speed (Tonoli et al. 2014b). It is believed that these deficits are precipitated by repetitive episodes of severe hypoglycemia, chronic hyperglycemia and C-peptide/insulin deficiencies (Tonoli et al. 2014b).

Acute exercise and life time physical activity have been reported to be associated with better performance in memory and executive functioning in the mid-adult years (Dregan and Gulliford, 2013). PA seems to be the key intervention to trigger the processes through which neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF) and Insulin Like Growth Factor-I (IGF-I) mediate neural growth and development, survival, plasticity and long term potentiation (Vaynman et al. 2004, Rasmussen et al. 2009). While BDNF is mostly produced in the brain, circulating IGF-I is mostly derived from the liver but can also be produced in the brain, both are able to cross the blood-brain barrier (Carro et al. 2001, Rasmussen et al. 2009).

A wealth of evidence exists demonstrating that a single bout of aerobic exercise increases serum and plasma BDNF levels in non-diabetic humans (Knaepen et al. 2010). The quantification of (total and free) IGF-I levels after acute and chronic exercise has yielded conflicting reports (Copeland and Heggie, 2008, Nguyen et al. 1998, Griffin et al. 2011). Both, IGF-I and BDNF might influence the brain by independent mechanisms (Cassilhas et al. 2012), but there is evidence that IGF-I is involved in the modulation of BDNF (Vaynman et al. 2004). Besides, insulin signaling contributes also to synaptogenesis and synaptic remodeling (Abbott et al. 1999). Furthermore, we recently showed that diabetes does not influence how the brain responds to acute HIE exercise in terms of release in BDNF, IGF-I and cognitive functioning (Schwarz et al. 1996). Different types of exercise intensities in T1D are, however, not yet established.

Considering the inverse relationship between exercise intensity and patient compliance, the preference for implementing different intensities clinical relevance. Having the ability to switch between various forms of exercise intensities, such as HIE and moderate continuous exercise equally may increase patient compliance. Therefore, the aim of this study is to examine the effects of continuous and HIE on glycaemia, insulin and

neurotrophic markers (BDNF, IGF-I) in T1D participants.

## 6.3 Material & Methods

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### 6.3.1 PARTICIPANTS

Ten T1D men were recruited to participate in this randomized cross over design which was approved by the local ethics committee (table 22). All participants had been diagnosed with T1D for at least 1 year and were between 24-46 years old. Exclusion criteria were 1) <18 - >60 years, 2) a history of severe head injuries, 3) other metabolic disorder besides diabetes, 4) neurological, psychological (comorbidities such as Alzheimer disease, dementia, depression...) or physical disabilities. All volunteers were informed about the nature and the risks of the experimental procedures before their written informed consent was obtained.

### 6.3.2 PROTOCOL

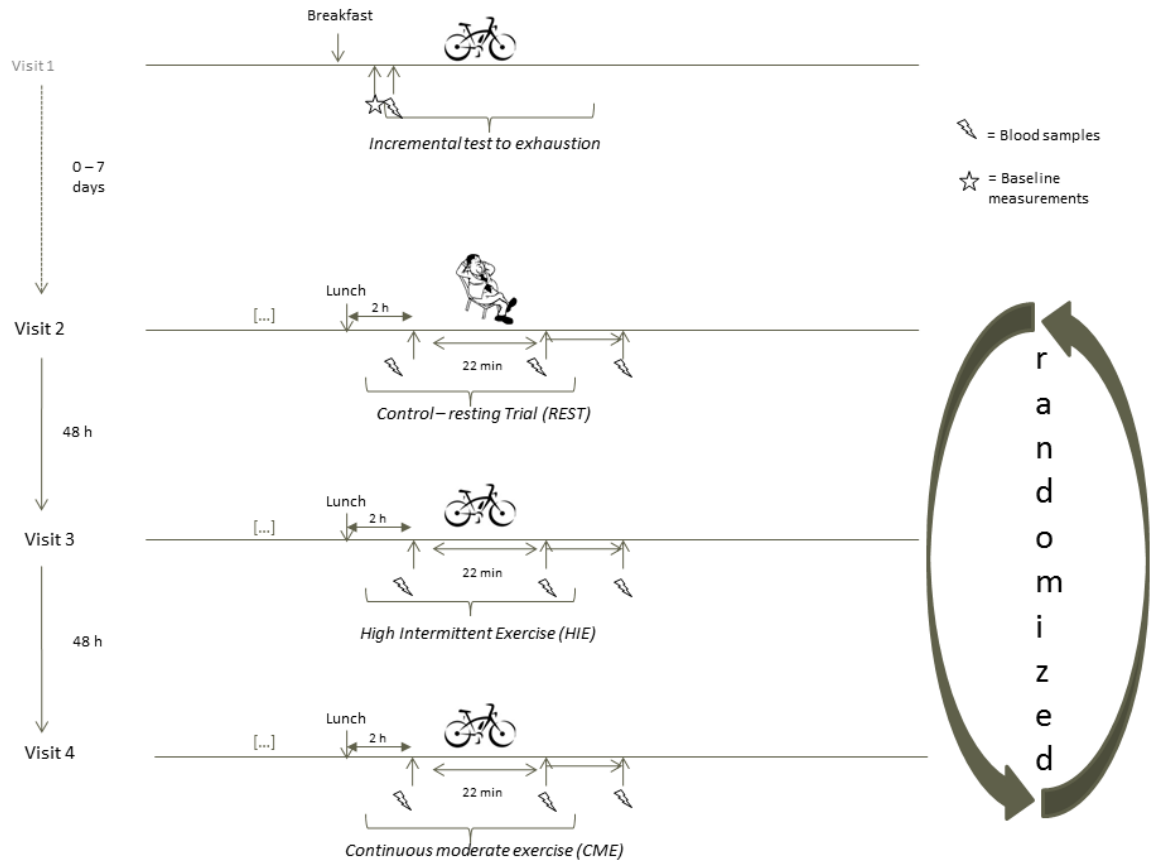
Participants visited the laboratory on four occasions (figure 12). The test was terminated when the pedaling rate (80-100 rpm) and a heart rate > 90% of the theoretical maximal heart rate ( $210 - 0.65 * \text{age}$ ) (Alemany et al. 2008) could no longer be sustained.  $\text{VO}_2\text{max}$  was measured using the METALYZER CORTEX (Biophysik GmbH, Germany). Maximal workload ( $W_{\text{max}}$ ) was determined as the highest workload sustained during the last stage of the test.

The following three visits were separated by at least 48 hours. During these three visits, subjects completed three exercise conditions; HIE, Continuous Moderate-intensity Exercise (CME) and Resting Control (REST). All trials were completed between 13:00 and 14:00 PM and exercise conditions were applied in a randomized order.

The 22-min HIE protocol is based on the protocol of Little et al. (2011). After a warming-up of 2 minutes, 10 times repeated effort of 1 minute at a resistance of 90% of the participants'  $W_{\text{max}}$ , interspersed with 1 minute of cycling at a very low intensity (50W) followed. In order to exercise the same time as the HIE, the CME started with a warming-up of 2 minutes at 100 Watt, followed by 20min of continuous cycling at an intensity of 70%  $W_{\text{max}}$ . During the control session each participant sat for 22 min in a chair next to the cycle ergometer.

Participants were asked to refrain from vigorous activity (> 6 MET) and to avoid severe hypoglycaemic episodes for 48h before the test. A standardized meal with 60% of calories from carbohydrates, 20% from protein and

20% from fat, was consumed approximately 2 hours before the exercise trials. Participants injected their insulin as they usually would do before exercising. When the glycaemia levels reached stable values (between 5.5-10 mmol/L), the exercise protocol started.



**Figure 12 Protocol of the study**

### 6.3.3 BLOOD ANALYSES

HbA<sub>1c</sub> and blood glucose were measured in whole blood using chromatography with ion exchange and photometrical method respectively. The additive blood samples were stored at ambient temperature for 1 hour before being centrifuged (4000tr, 4°C, 10 min). The resulting serum was stored in a -80°C freezer until analyses of serum BDNF (commercially ELISA kit – CYT306, ChemiKine®, Millipore®), serum total IGF-I (commercially IRMA kit, using an Immulite 2000, Siemens for reading) and serum free insulin levels (non-competitive radio immunoassay using the BI INS IRMA kit from Cis Bio Bioassays) were performed.

### 6.3.4 STATISTICS

All analyses were carried out via IBM SPSS Statistics 22 software and considered significant at  $\alpha < .05$ . Normality



of the data was tested using Kolmogorov-Smirnov Goodness of Fit test. The effect of 3 trials (REST, HIE, CME) on changes (3 times) in neurotrophins, glucose and insulin was examined using two-way (trial x time) analysis of variance (ANOVA) with repeated measures on both factors. If significant main effects were observed with ANOVA, post-hoc Sidak corrections were applied to examine specific pairwise differences. Further 2-way (2 trials \* 3 times) ANOVA's were performed using separately HIE vs. REST, CME vs. REST and HIE v. CME. Data are presented as means  $\pm$  SD except when otherwise indicated.

## 6.4 Results

### 6.4.1 DEMOGRAPHIC AND CLINICAL PROPERTIES OF THE STUDY POPULATION

Sample size calculations were completed using G\*Power, with a power of 80%,  $\alpha = 0.05$  and medium ES (ES = 0.26) based on a recent study of Griffin et al. (2011) and Tonoli et al. (2014a). A total of 10 T1D males with good glycaemic control ((Mean HbA<sub>1c</sub> = 7.2%), an average of 9.5 years of diabetes, and a good level of physical activity (VO<sub>2max</sub> = 53.34), participated in the study to have a power of 80% (table 22).

**Table 22. Demographic and clinical characteristics.**

	Mean ( SD)
N	10
Age (years)	33.8 (12.0)
Body Mass Weight (kg)	78.9 (6.6)
BMI (kg/m <sup>2</sup> )	23.7 (2.4)
Diabetes duration (yr)	9.5 (4.8)
Baseline HbA <sub>1c</sub> (mmol/mol)	54.9 (11.9)
Baseline Levels of serum IGF-I (pre Max-test) ( $\mu$ g/L)	142.6 (45.6)
Baseline Levels of serum BDNF (pre Max-test) (ng/ml)	14.7 (5.2)
VO <sub>2max</sub> (ml/min/kg)	53.34 (7.1)
Max Wattage at the end of Max test (W)	355.0 (45.3)

### 6.4.2 LEVELS OF BLOOD GLUCOSE, SERUM BDNF, SERUM IGF-I AND FREE INSULIN AT DIFFERENT TIME POINTS (PRE/POST/RECOVERY) ACCORDING TO THE TYPE OF EXERCISE.

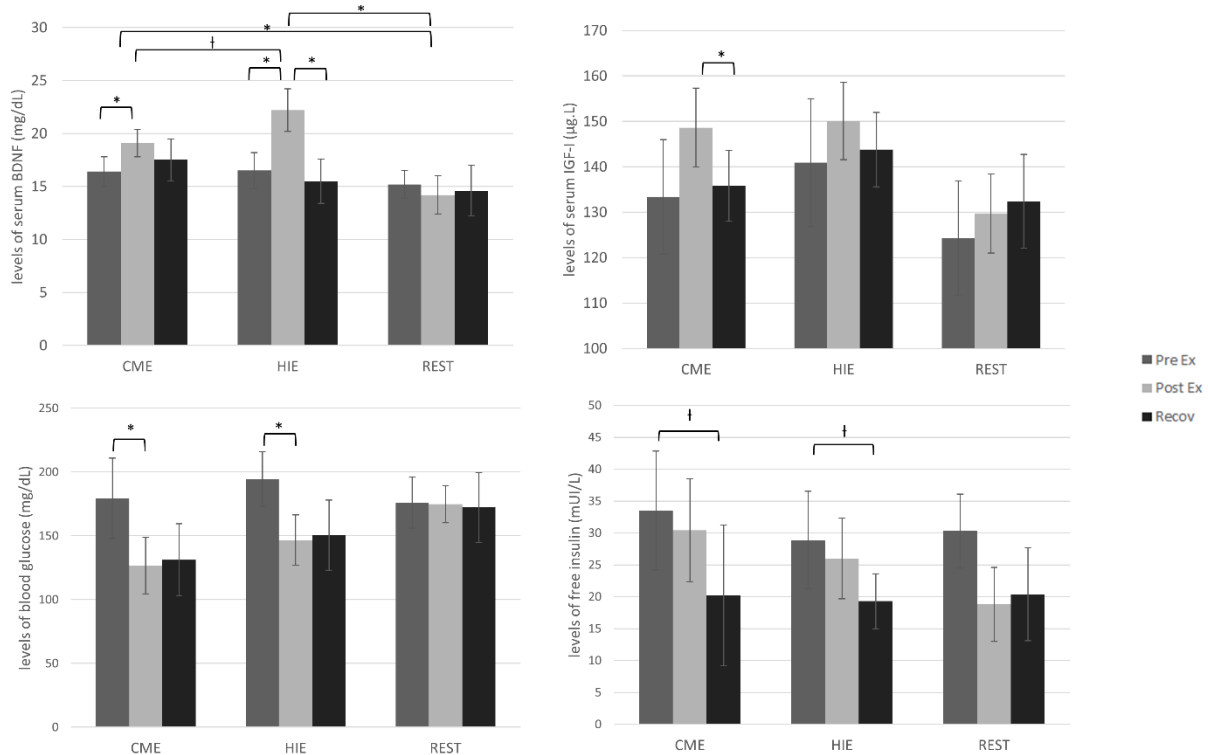
Depending on the performed trial (HIE vs. REST and CME vs. REST) ( $F = 3.4$ ;  $p = .02$ ), blood glucose significantly decreased over time ( $F = 21.5$ ;  $p < .01$ ) (table 23; figure 13). Further analyses between the 2 exercise types and the control session (i.e. HIE vs. REST and CME vs. REST) demonstrated significant trial x time interactions underlining a significant decrease in blood glucose with both types of exercise while blood glucose remained constant during REST. Comparing the 2 exercise types, blood glucose decreased post-exercise compared to pre-

exercise in both exercise types ( $F=9.6$ ; post-hoc  $p=.01$ ) without any difference in the rate of decrease according to exercise type (table 23). After a short recovery period, blood glucose levels were still decreased compared to pre-exercise levels during the HIE trial (post-hoc  $p<.05$ ). The control session did not show differences over time (figure 13).

Levels of BDNF significantly changed between the three trials ( $F = 4.05$ ;  $p=.04$ ), over time ( $F= 10.9$ ;  $p<.01$ ) and showed an interaction effect ( $F= 7.51$ ;  $p<.01$ ) (table 23). Both exercises, HIE and CME, induced increased levels of BDNF post-exercise compared to pre-exercise ( $F=5.3$ ; post-hoc  $p<.01$  CME; post-hoc  $p<.01$  HIE), with a dose-response effect between exercise intensity and level of BDNF, while BDNF remained constant during REST (HIE vs. REST and CME vs. REST in table 23; figure 13). Significant higher post exercise BDNF levels in the HIE compared to CME ( $p=.02$ ), in the CME compared to REST ( $p=.04$ ) and HIE compared to REST ( $p=.001$ ). After recovery, BDNF levels decreased significantly during the HIE compared to post-exercise levels ( $p=.01$ ) (figure 13). The REST trial did not induce changes in serum BDNF over time (figure 13). Levels of serum BDNF correlated with serum IGF-I ( $r = 0.53$ ;  $p < .001$ ), however not with blood glucose.

IGF-I significantly changed over time ( $F = 16.1$ ;  $p<.02$ ), but without any differences between the three trials conditions (interaction NS, table 23). In the CME trial, recovery caused decreased levels of IGF-I compared to post-exercise levels (post-hoc  $p<.01$ ; figure 13).

Free insulin significantly changed over time ( $F = 5.4$ ;  $p<.02$ ) without any significant difference between 3 trials. Free insulin decreased significantly during the HIE and CME after the recuperation compared with pre-exercise levels in both exercise trials (post hoc  $p< .005$ ), while it did not change significantly during the REST trial (table 23, figure 13).



**Figure 13 Comparison of the blood glucose, serum level of BDNF and IGF-I between the 3 different trials over time**  
 Data expressed as Mean (SE). T1D = Type 1 Diabetes, ex = exercise, recup = recuperation, BDNF = Brain derived Neurotrophic Factor, IGF-I = Insulin-like Growth Factor. \*post hoc  $p < .01$ , † post hoc  $p < .05$ .

## 6.5 Discussion

This study examined the effects of different types of exercise on serum BDNF, total IGF-I, free insulin and blood glucose in T1D. Exercise increased BDNF levels in T1D subjects after both HIE and CME, with a dose-response effect for exercise intensity in BDNF in participants with T1D. Serum levels of total IGF-I and free insulin changed over time, without an interaction effect nor a trial effect. Blood glucose levels significantly decreased after exercise in the CME and HIE trial. However, no differences were observed between the two types of exercise. Finally, serum BDNF correlated positively with serum total IGF-I and free insulin levels.

The findings of the increase in BDNF after both exercises intensities may be important with respect to recent findings of beneficial effect of exercise on brain health. Rasmussen and colleagues (Rasmussen et al. 2009) showed that the peripheral increase in BDNF after exercise is due to an enhanced release of BDNF from the brain. Our results are in line with previous evidence suggesting that a single bout of aerobic exercise increases serum BDNF levels in non-diabetic humans (Schulz et al. 2004, Ferris et al. 2007a), with the tendency of acute high-intensity exercise protocols having larger increases in BDNF concentrations than acute low or moderate

intensity exercise protocols (Ferris et al. 2007b, Knaepen et al. 2010, Griffin et al. 2011). This suggests that T1D patients are reacting in a similar way as healthy subjects to the acute effects of exercise intensity regarding BDNF release.

Comparing different types of exercise and intensities, contradictory findings are reported on the IGF-I response to acute exercise with increased (Copeland and Heggie, 2008) in levels of total IGF-I after high but not moderate intensity exercise and no differences between a high and a moderate intensity exercise (Wahl et al. 2010) were found, as in line with our results. In T1D specific, a 30 min exercise trial at 80% VO<sub>2</sub>max did not report increased IGF-I after exercise (Galassetti et al. 2006), while a HIE (bouts of 90%WMax) demonstrated increased levels of total IGF-I (Tonoli et al. 2014a). The discrepancy in results might be explained by the influence of different exercise protocols in which GH release is not influenced by short or less intensive exercises and therefore may not influence total IGF-I levels (Nguyen et al. 1998).

The intensity-dependent findings of increased levels of BDNF may aid in designing exercise prescriptions for maintaining or improving neurological health in T1D. Besides the effects on BDNF, HIE is characterized with substantial lower time commitment and reduced total exercise volume (Gibala et al. 2012), and therefore has recently become more popular. However, in our study both types of exercise caused an increase in BDNF after exercise and could therefore be alternatively used in training programs in order to improve patients' compliance, and consequently motivation to exercise.

This study was performed in well trained participants which can complicate the generalization of the results to an untrained population with T1D. However, with proper precautions present to monitor blood glucose control, these exercise intensities can be used in future studies including non-trained subjects with T1D.

In summary, glucose decreased while BDNF increased after exercise in both types of exercise with an exercise intensity dose response effect for BDNF. The intensity-dependent findings may aid in designing exercise prescriptions for maintaining or improving neurological health in T1D, but both types of exercise can be implemented. Further longitudinal studies should be performed to establish the effects of exercise and training on cognitive function in the long term in T1D.

**Table 23. Main effects by ANOVA regarding results from blood glucose BDNF and IGF-I**

Variable	HIE vs. CME vs. REST	HIE vs. CME	HIE vs. REST	CME vs. REST
<b>Main effects by ANOVA</b>				
BGL	Trial: NS Time: p<.01 Interaction: p=.02	Trial: NS Time: p<.01 Interaction: NS	Trial: NS Time: p= .01 Interaction: p=.01	Trial: NS Time: p<.01 Interaction: p<.01
BDNF	Trial: p=.04 Time: p<.01 Interaction: p<.01	Trial: NS Time: p<.01 Interaction: p=.01	Trial: P <0.0001 Group: p<.01 Interaction: p<.01	Trial: NS Time: NS Interaction: p<.01
IGF-I	Trial: NS Time: p<.001 Interaction: NS			
Free insulin	Trial: NS Time: p=.01 Interaction: NS			

BGL = Blood Glucose Levels; BDNF = Brain-derived Neurotrophic Factor, IGF-I = Insulin-Like Growth Factor, NS = not significant

## 6.6 References

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CHAPTER 7. GENERAL DISCUSSION AND FUTURE PERSPECTIVES

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## 7.1 General discussion

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Despite of extensive research efforts examining the effects of exercise on cognitive performance in both, health and disease, this remains a challenging topic. Patients with T1D show a cognitive decline when compared with non-diabetic subjects (Brands et al. 2005), the so called DACD. Mainly episodes of severe hypoglycaemia and chronic hyperglycaemia are pointed out as potential causes of this DACD. An emerging body of multidisciplinary literature has recognized the beneficial influence of PA and exercise on brain function in non-diabetic humans (Hillman et al. 2008). These positive effects are accomplished through a cascade of molecular and cellular processes (Cotman and Berchtold, 2007). The role of neurotrophic factors such as BDNF, IGF-I and even insulin in mediating hippocampal synaptic plasticity are well established (Erickson et al. 2011, Gorski et al. 2003, Vaynman et al. 2004). Indeed, recently insulin has been named as an influencing factor in brain functioning, especially in AD, a disease hypothesized as 'Type 3' Diabetes due to lack of cerebral insulin (Wiwanitkit, 2008).

Exercise is commonly used as an intervention to promote general health (Vaynman, 2005). In T1D specifically, exercise can have a significant effect on the acute and chronic glycaemic control (Tonoli et al. 2012), both involved in the etiology of a cognitive decline in T1D. Since exercise can attenuate these effects of diabetes, it is of great clinical relevance. Additionally, it is known that exercise mediates the effects of neurotrophic factors in the brain of non-diabetic patients (Aberg, 2010, Aberg et al. 2003, Åberg et al. 2006, Aleman and Torres-Alemán, 2009, Aleman et al. 1999, Ding et al. 2006, Griffin et al. 2011), but the effects of exercise on neurotrophic markers are not yet established in T1D.

This dissertation consists of several studies that have been performed in order to answer our research questions, suggested in the introduction. We aimed to examine the effects of a physical active life-style and acute exercise on the cognitive performance, BDNF, IGF-I, blood glucose and (free) insulin in T1D.

### *7.1.1 COGNITIVE FUNCTION IN T1D, GLYCAEMIC CONTROL AND PHYSICAL ACTIVITY*

Our first meta-analysis (Tonoli et al. 2014b) showed a significant decrease in cognitive performance in T1D patients compared to non-diabetic controls. Children with T1D performed worse while testing for the executive function, full IQ and motor speed, while T1D adults performed worse testing the IQ, executive function, memory, spatial memory and motor speed. Episodes of hypoglycaemia and chronic hyperglycaemia

significantly affected executive function, memory and motor speed; suggesting that good glycaemic control might be essential for the prevention of a DACD. Better performance and better glycaemic control can at least partly be achieved, by regular PA (Tonoli et al. 2012). The purpose of the cross-sectional study (Tonoli et al. 2014 - Submitted-b) was to evaluate if the self-reported level of PA, measured using the MAQ, could predict cognitive functioning in a T1D population. We also wanted to explore the possible relationship between cognitive functioning and basal levels of serum BDNF and total IGF-I. We showed that several factors can predict cognitive function in T1D, including a low level of PA, poor glycaemic control, education, age, serum levels of BDNF, and episodes of severe hypoglycaemia (Tonoli et al. 2014 - Submitted-b).

#### 7.1.1.1 PA, chronic hyperglycaemia & cognitive function in T1D

Our cross-sectional study showed that attention, working memory, and certainly the executive function are negatively influenced by chronic hyperglycaemia (poor glycaemic control). We found that each 2.2 mmol/mol increase in HbA<sub>1c</sub> will increase reaction time and thus decrease the performance in executive function and attention. Furthermore, small rises in HbA<sub>1c</sub> (each .05 mmol/mol) will increase the errors made during mathematical tasks required during the OSPAN (working memory). Indeed, executive function and memory were seen as significantly impaired by the DACD, especially in patients with severe hypoglycaemic episodes and chronic hyperglycaemia (Tonoli et al. 2014b). In the introduction of this dissertation, several possible pathways to explain the interaction between high glucose levels and cognitive decline in T1D were summarized (Tonoli et al. 2013). For example, hyperglycaemia causes oxidative stress via the polyol pathway, enhanced advanced glycation end products (AGEs) and increased vascular tone and permeability of the endothelial cell monolayer in the brain. All these factors might influence cognitive functioning in T1D. From a clinical point of view, improving glycaemic control (or decreasing chronic hyperglycaemia) is thus important, not only to decrease diabetes-associated complications as micro- or macrovascular complications, but also to decrease negative effects on the brain.

PA has been shown to improve chronic glycaemic control (Tonoli et al. 2012). Aerobic training and strength training have different actions in the body and can therefore influence glycaemic control through different pathways (see figure 14 for a schematic illustration of these effects). For example, fat mass decreases after a period of aerobic training (Ismail et al. 2012). A prospective study of Svensson et al. (2011) indicates that the

change in the amount of body fat contributes to the change in insulin resistance over time in T1D patients. On the other hand, strength training has enhanced insulin sensitivity, improved glucose tolerance (Tresierras and Balady, 2009), and results in 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) (Heymsfield et al. 2002). A greater muscle mass would thus consume more glucose and therefore could affect glycaemic control.

It is recommended that exercise is performed frequently in order to maintain a constant increase in insulin sensitivity and thus improve HbA<sub>1c</sub>. Chronic glycaemic control improves only if the training period is long enough (three months) and frequency is adequate (1-3 times a week), and dietary or insulin advice is followed. Furthermore, there is a tendency for improvement in long-term glycaemic control due to resistance training or resistance combined with endurance training, but there were not enough studies were found to confirm this statistically (Tonoli et al. 2012).

Besides the effects of PA on glycaemic control in T1D, we demonstrated in our cross sectional study that PA positively influences cognitive function in T1D. Each decrease of 0.65 MET/h/week prolongs reaction times needed to perform the Stroop Color Word Test. Consequently lower levels of PA predict decreased performance in executive function. Over the past several decades, both cross-sectional and longitudinal training studies support a positive association between PA level, aerobic fitness or training and enhanced performance on cognitive tasks (Voss et al. 2011, Hillman et al. 2008, van Praag, 2008, Lambourne and Tomporowski, 2010, Kramer et al. 2006, Stroth et al. 2009), especially in children and elderly with and without symptoms of AD or depression (Voss et al. 2011, Colcombe and Kramer, 2003, Hillman et al. 2008, Kramer et al. 2006). The meta-analysis of Colcombe & Kramer (2003) screened the literature on training effects on cognitive function in elderly. They observed the largest positive effects for executive control processes such as planning, scheduling, working memory, inhibitory processes and multitasking, but also improved spatial memory, and speed tasks were found (Colcombe and Kramer, 2003, Hillman et al. 2008). Our results are in line with the existing literature.

On the long term, PA leads thus to improved glycaemic control and positively influences cognitive function in T1D.

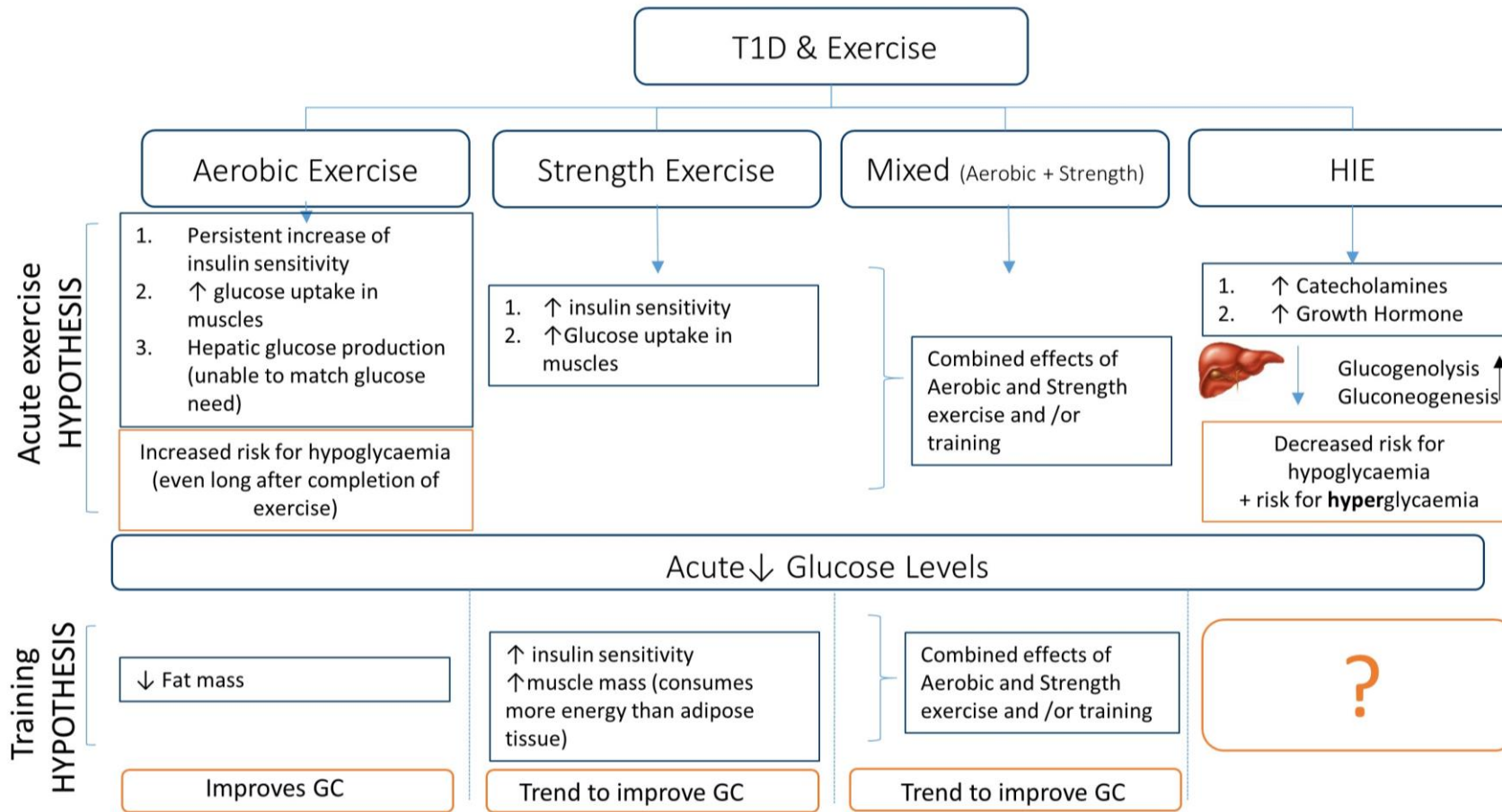
In terms of acute glycaemic control, our studies demonstrated that acute exercise results in significantly decreased blood glucose levels after exercise at different intensities (Tonoli et al. 2014, 2014 submitted-a). Glycaemia during exercise can vary inter- as well as intra-individually given that it depends on various factors such as exercise modality and intensity, (Rabasa-Lhoret et al. 2001, Riddell and Perkins, 2009, Guelfi et al. 2007) nutritional status, (Jimenez et al. 2009) time of insulin injection (Iafusco, 2006), pre-exercise glycaemia level (Zander et al. 1983). After performing moderate, aerobic exercise, all studies found a decrease in blood glucose values (Guelfi et al. 2005, Bussau et al. 2006, Poortmans et al. 1986, West et al. 2011, Yamanouchi et al. 2002, Zinman et al. 1977, Zinman et al. 1984, Tansey et al. 2006, Heyman et al. 2005, Heyman et al. 2007). However, acute exercise may also lead to hypoglycaemia.

While aerobic exercise elicits marked falls in glycaemia, which can often result in episodes of hypoglycaemia, our meta-analysis (Tonoli et al. 2012 – see figure 14) revealed that there was a smaller fall of blood glucose levels due to an acute bout of HIE compared with 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. It is even demonstrated that glucose production was higher in HIE+moderate versus moderate exercise alone and that glucose utilization was greater and occurred faster in HIE+moderate compared with moderate exercise (Iscoe and Riddell, 2011, Bussau et al. 2007).

Furthermore, we also found improvements in cognitive function after an acute HIE in trained T1D participants and their matched controls, suggesting that there is no difference in how their brain responded to acute HIE (Tonoli et al. 2014a). However, we could not conclude that HIE increases cognitive performance, because no sedentary control condition was added in this study and consequently, this effect might be attributed to a learning effect.

When examining the existing literature in a meta-analysis, it was demonstrated that executive function and memory function are both significantly affected by episodes of severe hypoglycaemia in T1D (Tonoli et al. 2014b). Our cross-sectional study, however only showed associations between severe hypoglycaemia, attention and cognitive flexibility. Whether episodes of hypoglycemia are harmful to the brain remains controversial. An animal study showed that moderate hypoglycemia preconditioned the brain and markedly

limited the extent of subsequent severe hypoglycemia-induced neuronal damage and associated cognitive impairment (Puente et al. 2010). However, irreversible brain damage occurred after a period of at least one hour of electro-encephalogram. These data, in combination with the results of our study, suggest that severe hypoglycemia, at least if duration is long and severity is 'intense' enough, can affect brain function.



Legend: ↓ = decrease, ↑ = increase, T1D = Type 1 Diabetes, HIE = High Intensity Exercise, GC = Glycaemic control

Figure 14 Effects of exercise on glycaemic control in T1D. (Figure from Tonoli et al. 2013b)

*7.1.2 EXERCISE, NEUROTROPHIC FACTORS & THE BRAIN IN T1D*

An acute exercise-induced increase of neurotrophins might be crucial for improving cognitive function with chronic exercise in healthy subjects. Exploring the effect of different modalities and intensities of an exercise training program on the levels of BDNF and IGF-I, has a strong clinical relevance (van Praag, 2008, van Praag, 2009, Cotman et al. 2007, Dishman et al. 2006, Vaynman et al. 2004, Neeper et al. 1996). Furthermore, changing exercise modality and intensity can increase patient compliance, and thus their motivation to exercise. Therefore, the aim of the first acute exercise study was to investigate whether exercise has the same beneficial effects on cognitive function, levels of serum BDNF, serum total IGF-I and free insulin in T1D patients compared to their non-diabetic matched controls (Tonoli et al. 2014a). In the last study the effects of different exercise intensities (HIE vs continuous moderate exercise) on serum levels of BDNF, IGF-I, blood glucose and free insulin in T1D participants were determined (Tonoli et al. 2014 - Submitted-a).

7.1.2.1 T1D, serum BDNF & exercise

BDNF is the neurotrophin that is most susceptible to exercise (Vaynman and Gomez-Pinilla, 2005, Knaepen et al. 2010). We demonstrated that HIE increases BDNF in both T1D and healthy participants in a comparable way. Acute exercise raised BDNF in a dose-response manner in both studies (Tonoli et al. 2014 & submitted-a), with higher post exercise BDNF levels after the HIE compared to after the continuous moderate exercise trial (Tonoli et al. submitted-a). Furthermore, BDNF levels rapidly returned to basal levels (after 30 min) during the recovery period following both exercises, which suggests a fast disappearance rate of the circulating BDNF (Griffin et al. 2011). All these observations are similar to those found in a non-diabetic population, suggesting that there is no difference between T1D patients and healthy controls in how the brain releases serum BDNF during and after exercise (Tonoli et al. 2014a).

Given the importance of BDNF for synaptic plasticity and learning and memory, it has been proposed that these exercise-induced increases might, on the long term, trigger the ability of exercise to enhance cognitive function (Vaynman et al. 2004). However, more research is needed to confirm this hypothesis.

Physically active subjects show decreased basal levels of BDNF compared to non-physical active subjects.

It is suggested that these decreased levels of BDNF are due to an increased or more efficient uptake mechanism of serum BDNF into the CNS (Currie et al. 2009). Our studies showed that subjects with T1D had significantly higher levels of baseline serum BDNF compared to non-diabetic controls. Surprisingly, high levels of serum BDNF independently predicted a decreased performance on the executive function. Long diabetes duration was found to be a significant predictor of high levels of serum BDNF and low levels of serum IGF-I. On the one hand, the consistent higher levels of BDNF in T1D could reflect compensatory responses, suggesting that BDNF is influenced by the pathology. On the other hand, this can point to a reduced uptake or less efficient uptake mechanism of BDNF in patients with T1D with concomitant higher circulating levels of BDNF.

The mode of dendritic growth can be modulated by neurotrophins but also by TrkB receptors (Tolwani et al. 2002). Chronic BDNF overexpression appears to induce structural instability of newly formed dendrites. Therefore, it has been hypothesized that 'chronic' excessive BDNF might deteriorate neuronal survival or neurite outgrowth (Nakajo et al. 2008). Chronic overexpression of BDNF might also have diverging actions on the TrkB receptors, compared to short-term elevations of BDNF (as obtained by acute exercise) (Tolwani et al. 2002). To date, only a few animal studies exist examining the effects of chronic overexpression of BDNF/TrkB. In non-diabetic animals, Cunha et al. (2009) studied the effects of overexpression of BDNF (in the forebrain) on a battery of cognitive tests and showed learning and short-term memory impairments. In diabetic animals, Thomas et al. (2013) mentioned unpublished results showing significant increase in expression of TrkB receptor in diabetic hippocampi in STZ 'stable' diabetic mice compared to non-diabetic mice. The upregulation of TrkB in the hippocampi of STZ mice might be induced by changes in gene expression that are associated with a lack of insulin (related to hyperglycemia) (Thomas et al. 2013). However, Koponen et al. (2004) showed that TrkB.TK+ overexpressing mice showed altered TrkB signaling and specific behavioral changes. It is also demonstrated that the overexpression of the full-length TrkB receptor is accompanied by alterations in genes (such as c-fos,  $\alpha$ -CaMKII, GAP-43 and NPY) that are suggested to play a role in neural remodeling and regulation of cognitive functions (Koponen et al. 2004).

#### 7.1.2.2 BDNF, T1D & glucose metabolism



Since BDNF can originate from peripheral sources (i.e. liver and muscles) and serve a peripheral purpose, our results need to be interpreted with precaution. Peripheral BDNF changes play a role in energy metabolism and consequently in diabetes. The latter was also confirmed by the positive correlation between serum free insulin and serum BDNF in T1D patients (Tonoli et al. 2014a). However, we could not find any significant correlation between glucose and serum BDNF in T1D subjects.

The efficacy of BDNF in regulating glucose and energy metabolism was reproduced through intracerebroventricular administration of small portions of BDNF in *db/db* mice (T2D mice), suggesting that BDNF acted directly on the hypothalamus. Because the BDNF receptor (TrkB) is expressed in the hypothalamus, BDNF may regulate glucose metabolism by modulating the autonomic function in this region (Nakagawa et al. 2000). As previously written, Thomas et al (2013) showed an upregulation of TrkB in STZ mice and it has been demonstrated that this causes altered trkB signaling (Koponen et al. 2004), which might affect glucose metabolism. However, animal models of diabetes differ greatly from humans with insulin-treated T1D, and these results require further investigation.

#### 7.1.2.3 T1D, total IGF-I, insulin & exercise

Previous literature shows that a deficiency in circulating IGF-I is associated with decreased perceptual motor performance, reduced information processing speed (Aleman et al. 1999, Dik et al. 2003), fluid intelligence (Aleman et al. 2001) and deficiencies in spatial and working memory (Sonntag et al. 2013) in healthy fit older adults.

Although reduced levels of total IGF-I in T1D compared to non-diabetic subjects were shown (Tonoli et al. 2014a), in our cross-sectional study (Tonoli et al. Submitted-b) lower levels of IGF-I were not correlated to cognitive performance. Further, total IGF-I seemed to be increased after acute exercise in both, T1D and non diabetic humans (Tonoli et al. 2014), however this result was not reproducible in our subsequent research in which we compared different types of exercise intensities with no exercise (Tonoli et al. Submitted-a), indicating the importance of including a non-exercise trial/control group in each acute exercise research. The response of IGF-I to physical exercise is not consistent in studies investigating non-diabetic subjects. Some groups observed acute increments, while others showed no variations (Wallace et al. 1999, De Palo et al. 2001, Nguyen et al. 1998, Griffin et al. 2011). It is known that exercise has a

significant impact on GH/IGF release by stimulating GH mRNA synthesis, which in turn induces an increase in IGF-I. Increased total IGF-I concentrations in response to exercise may be attributed to the IGF-I release from within the muscle, vascular endothelium, extracellular matrix (Gregory et al. 2013), or by increased GH stimulated IGF-I from the liver. Differences in exercise induced increase in IGF-I might be attributed to a delay in IGF-I release. GH stimulated mRNA synthesis reaches peak values after 16-28h post stimulation (Kelly et al. 2010). Consequently IGF-I might have delayed secretions until the GH stimulated synthesis from the liver can take place, i.e. 3-9h after stimulation (Kelly et al. 2010).

Furthermore, the relevance of measuring total and free levels of IGF-I has been discussed. While increasing levels of total IGF-I are found, reduced levels of free IGF-I are detected. This might indicate an increased uptake or reduced release of free IGF-I by exercising muscles or an increased binding of free IGF-I to its binding protein, IGFBP (Gregory et al. 2013).

As we did not find that lower levels of IGF-I are a predictor of cognitive functioning in T1D, and IGF-I is not increasing after exercise in T1D, we suggest that the link between IGF-I, cognitive functioning and T1D needs further research to establish the role of IGF-I in a DACD.

### *7.1.3 LINK BETWEEN T1D – EXERCISE – BDNF - IGF-I - INSULIN AND BRAIN FUNCTION*

It seems that in T1D each factor (exercise, BDNF, IGF-I & Insulin) plays its role on cognitive functioning, and may be interrelated (figure 15). BDNF, IGF-I and insulin are all associated with synaptic plasticity, which can be modulated by exercise. IGF-I may regulate the induction of BDNF with exercise (Carro et al. 2001) as brain uptake of IGF-I is a prerequisite for the elevation in BDNF mRNA expression (Siwak-Tapp et al. 2007, McCusker et al. 2006). Furthermore, BDNF influences LTP, which occurs with associated depolarization of the postsynaptic membrane, in conjunction with the binding of the excitatory neurotransmitter glutamate to the NMDA receptor, a calcium permeable ion channel (Soule et al. 2006). Insulin augments the induction of LTP by influencing cell membrane expression of NMDA receptors (Cholerton et al. 2013).

However we found that levels of peripheral serum BDNF were elevated in a T1D population compared to non-diabetic controls, and that poorer cognitive performance was associated with higher levels of serum BDNF (Tonoli et al. 2014a). The latter could be due to less (efficient) uptake of BDNF into the brain, and

consequently increased levels of circulating BDNF. The transient increase in serum BDNF after acute exercise in T1D disappeared after 30 minutes, suggesting an increased uptake after exercise. This might be of great clinical relevance, since exercise might increase the release, but more importantly also the uptake of BDNF into the brain. However, further research is needed to explore this hypothesis.

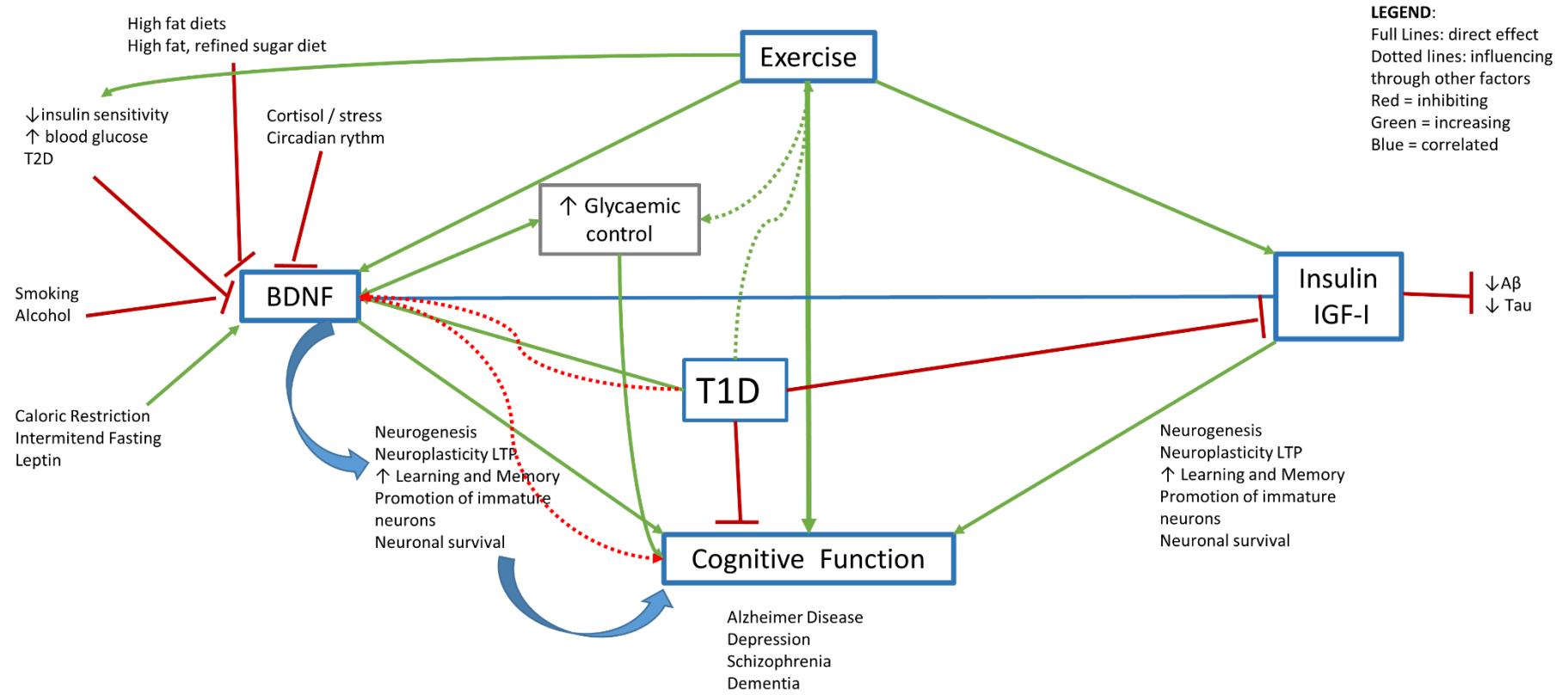


Figure 15. Schematic illustration of all the influencing factors and the link between the cognitive function, BDNF, IGF-I and insulin in T1D

#### *7.1.4 STUDY LIMITATIONS*

Limitations in our studies are discussed within each chapter. In chapter 5, a cross-sectional design was used. Although our results clearly indicate several predicting factors (including level of PA) associated with cognitive function in T1D, these results were based on cross-sectional data. This set-up does not allow exploring the cause of cognitive decline over time, or the causality of the associations between risk factors and outcome measures. Of course, the causality issue can only be addressed by a longitudinal design. Furthermore, we did not measure free insulin levels in that cross-sectional trial, which could have given explanatory results concerning the effects of insulin on brain function in T1D.

Furthermore, the present project only established the effects of acute forms of physical exercise on cognitive function in T1D. Since long term aerobic training results in a small, though significant, improvement of glycaemic control in T1D patients, the relation between chronic exercise (training) and the cognitive function in T1D patients remains to be established.

## **7.2 Guidelines for further research**

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We demonstrated that exercise has beneficial lowering effects on acute and chronic glycaemic control in T1D. Therefore, T1D subjects should integrate exercise into their lifestyle. To increase insulin sensitivity, these patients should try to exercise every second day. To avoid excessive fluctuation in blood glucose levels during and after exercising, subjects with T1D might need to adjust their insulin doses. Depending on the form of exercise, T1D subjects should ingest some carbohydrates to prevent hypoglycaemic episodes. However, little research is done concerning the effects of resistance training, combined training, or the implementation of high intensity training in a moderate exercise training program on the glycaemic control in T1D. Therefore, further research should focus on these types of exercise in T1D. Additionally, further research is needed to investigate the effects of nutritional interventions in combination with exercise interventions on the glycaemic control of T1D patients.

Our study showed consistently higher serum BDNF levels in T1D subjects compared to their matched controls. This might suggest that peripheral BDNF levels of T1D patients are influenced by the pathology of

T1D. Whether overproduction of BDNF and altered trkB signaling are present in the brain, and can have negative effects on brain function, has not yet been established. This topic needs further investigation.

Further research should also focus on the 'long term' effects of exercise (exercise training) on cognitive functioning and underlying mechanisms in T1D. Any manipulation that increases brain vascularity or plasticity can be an effective strategy to minimize or delay the cognitive decline associated with diabetes. Research focusing on the prevention of DACD can be helpful. Therefore, more mechanistic research into the development of new neurons and their function in T1D is needed.

A last point we want to highlight is that future research aiming to reduce or prevent or delay a cognitive decline should also focus on the combined effects of exercise and certain nutritional interventions, such as high polyphenol diets. For example, flavonoids are powerful antioxidants involved in creating several effects within the brain related to the ability to interact with intracellular neuronal and glial signaling pathways. This includes neuroprotective properties against neurotoxins (Williams and Spencer, 2012, Vauzour, 2012) and the ability to suppress neuroinflammation (decreases in oxidative/inflammatory stress signaling). Besides, flavonoids increase protective signaling leading to the expression of genes that encode antioxidant enzymes, enhancing neuronal function by stimulating neurogenesis, neurotrophic factors, cytoprotective proteins (Williams and Spencer, 2012, Vauzour, 2012), and hence promote memory, learning, and cognitive function (Vauzour, 2012, Spencer, 2007, Spencer, 2008, Macready et al. 2009). The combination of the effects of nutritional and exercise interventions could give even more beneficial and protective effects on the brain.

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## 7.3 References

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- TONOLI, C., HEYMAN, E., BUYSE, L., ROELANDS, B., PIACENTINI, F., BAILEY, S., PATTYN, N. & MEEUSEN, R. 2014 - Submitted-a. BDNF, IGF-I, glucose and insulin during continuous and interval exercise in Type 1 Diabetes. *Int J Sports Med*.

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CHAPTER 8. GENERAL CONCLUSIONS: IS THERE A ROLE FOR  
EXERCISE?

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The purpose of this work was to unravel the influence of physical activity and different types of acute exercise intensities on levels of BDNF, IGF-I, glucose, free insulin and cognitive function in subjects with T1D.

Following results were obtained:

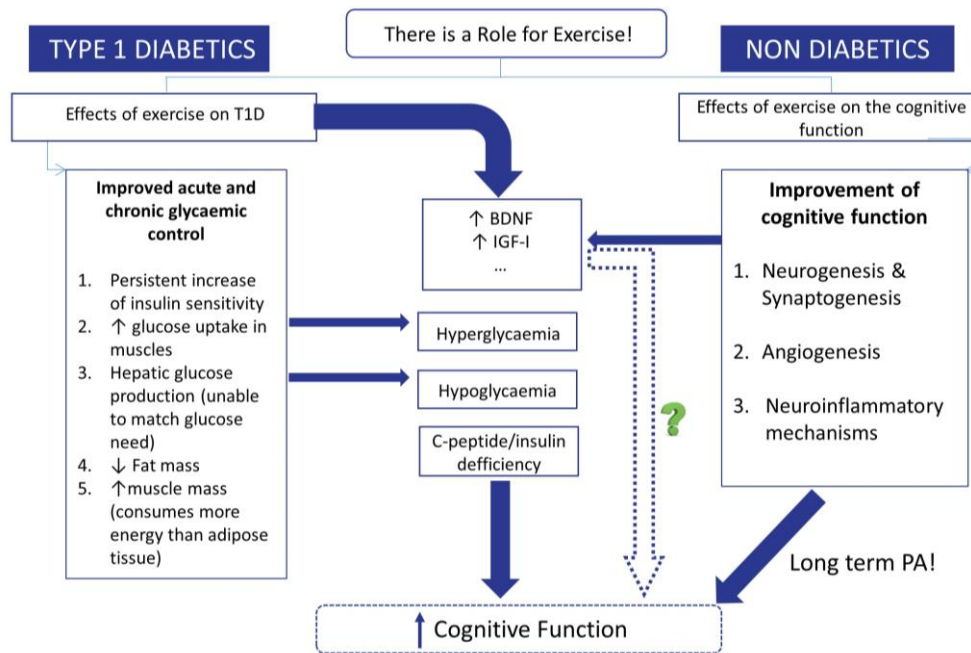
- ✓ A decrease in cognitive performance in T1D patients compared with non-diabetic controls: Children with T1D performed worse while testing for executive function, full intelligence quotient (IQ), and motor speed, whereas adults with T1D performed worse while testing the full, verbal and performance IQ, executive function, memory, spatial memory, and motor speed.
- ✓ Episodes of severe hypoglycemia, chronic hyperglycemia, and age of onset can significantly influence cognitive function in T1D.
- ✓ A regular exercise training program has a significant effect on acute and chronic glycaemic control
- ✓ Specifically, aerobic training is a favourable tool for decreasing chronic glycaemic control, while resistance training, mixed and HIE did not significantly improve chronic glycaemic control.
- ✓ Higher levels of PA can predict a cognitive functioning in type 1 diabetes.
- ✓ Other predictors of cognitive functioning are: education, glycaemic control, level of BDNF, diabetes duration and episodes of hypoglycaemia.
- ✓ Basal level of serum BDNF and total IGF-I were not associated to levels of PA.
- ✓ Humans with T1D have higher BDNF levels and lower total IGF-I levels compared to non-diabetic controls.
- ✓ HIE had comparable effects on the increase in BDNF and IGF-I and cognitive function in T1D and non-diabetic participants.
- ✓ Continuous and high intensity exercise changes neurotrophins in T1D, with a dose response effect for BDNF.

#### **So, is there a role for exercise in a T1 DACD?**

An emerging body of multidisciplinary literature has recognized the beneficial influence of PA and exercise on brain function (Hillman et al. 2008) through a cascade of molecular and cellular processes that support brain health (Cotman and Berchtold, 2007). Furthermore, physical exercise is commonly used as an intervention to promote general health (Vaynman, 2005).

The cognitive deficits found in T1D are small to modest, nonetheless, this can affect patients' daily living and their QOL. As hypo- and hyperglycaemia are associated with the etiology of a DACD, improving glycaemic control must be the 'center' for the prevention of a DACD. We showed that exercise can influence both, acute and chronic glycaemic control (both triggers of the DACD), cognitive performance and neurotrophic factors in humans with T1D.

Any manipulation that increases brain vascularity or plasticity can be an effective strategy to minimize or delay the cognitive decline associated with diabetes. Exercise is one of the possible candidates to prevent or minimize a cognitive decline in the diabetic population. The intensity-dependent findings may aid in designing exercise prescriptions for maintaining or improving neurological health in T1D, but both types of exercise can be implemented.





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LIST OF PUBLICATIONS – Scientific CV

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## 1. Articles in international journals peer-reviewed (Reference 2-8 = PhD)

1. **TONOLI C.**, CUMPS E., AERTS I., VERHAGEN E., MEEUSEN R., Incidence, risk factors and prevention of running related injuries in long-distance running: a systematic review. *Injury, location and type, Sport en Geneeskunde*, 2010: 5: 12 – 18.
2. **TONOLI C.**, HEYMAN E., ROELANDS B., BUYSE L., CHUENG SS., BERTHOIN S., MEEUSEN R., 2012. Effects of different types of acute and chronic exercise on glycaemic control in Type 1 Diabetes – A meta-analysis. *Sports Medicine*, 2012 Dec 1;42(12):1059-80.
3. **TONOLI C.**, HEYMAN E., ROELANDS B., PIACENTINI F., BUYSE L., PATTYN N., BERTHOIN S., MEEUSEN R., Type 1 Diabetes-Associated Cognitive Decline: A Meta-Analysis and update of the current literature. *J of Diabetes*. Accepted 2014 June 29, Epub ahead of print: 2014 Jul 7. doi: 10.1111/1753-0407.12193.
4. **TONOLI C.**, HEYMAN E., ROELANDS B., PIACENTINI MF., BUYSE L., BERTHOIN S., MEEUSEN R., Diabetes-Associated Cognitive Decline, Is there a Role for Exercise? *J Diabetes Metab* 2013, *S10:006*. doi: 10.4172/2155-6156.S10-006
5. **TONOLI C.**, HEYMAN E., ROELANDS B., BAQUET G., BERTHOIN S., MEEUSEN R. Validation and reliability of the Dutch Language Version of The Modifiable Activity Questionnaire in healthy subjects. *Sport Sciences for Health*. December 2013, Volume 9, Issue 3, pp 139-144.
6. **TONOLI C.**, HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., KEYMEULEN B., UNUANE D., BERTHOIN S., MEEUSEN R. Can The Level of Physical Activity predict a Type 1 Diabetes Associated Cognitive Decline? [**Submitted** in *Journal of Clinical Endocrinology & Metabolism*]
7. **TONOLI C.**, HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., BERTHOIN S., MEEUSEN R. Neurotrophins and cognitive functions in T1D compared to healthy controls: effects of a high-intensity exercise. Accepted 20 August 2014 - *Applied Physiology and Nutrition*.
8. **TONOLI C.**, HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., BERTHOIN S., MEEUSEN R. BDNF, IGF-I, glucose and insulin during continuous and interval exercise in Type 1 Diabetes. [**Submitted** in *International Journal of Sports Medicine*]

## 2. Articles in national journals

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1. **TONOLI C.**, CUMPS E., AERTS I., VERHAGEN E., MEEUSEN R., Incidentie, risicofactoren en preventie van loongerelateerde letsels bij lange afstandslopers: een systematische review. *Vlaamse Trainerschool*. 01/01/2013.

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2. **TONOLI C.**, HEYMAN E., ROELANDS B., BUYSE L., BERTHOIN S., MEEUSEN R., 2013. Effecten van verschillende vormen van fysieke inspanning en training op de glycemische controle in type 1 diabetes. Wetenschappelijk tijdschrift van de Vlaamse Diabetes Vereniging, April/mei 2013.
  3. **TONOLI C.**, BUYSE L., ROELANDS B., HEYMAN E., MEEUSEN R., 2013. Type 1 Diabetes-geassocieerde cognitieve achteruitgang. Wetenschappelijk tijdschrift van de Vlaamse Diabetes Vereniging, oktober 2014.

### 3. Abstracts

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1. SPALC congress May 2011, Rome, Italy: **TONOLI C.**, CUMPS E., AERTS I., VERHAGEN E., MEEUSEN R., Incidence, risk factors and prevention of running related injuries in long-distance running.
2. Annual Meeting ECSS Congress June 2011, Liverpool, UK: **TONOLI C.**, HANSEN, D., HEYMAN E., VAN LOON, LJC., MEEUSEN R. Can proteins influence brain-derived neurotrophic factor (BDNF) in type 2 diabetic patients?
3. Dag van de Doctorandi 2011, May, VUB, Belgium: **TONOLI C.**, BUYSE L., HEYMAN E., MEEUSEN R., Cognitive decline in type 1 diabetes Mellitus, how can exercise help? (Dag van de Doctorandi, May, VUB, Belgium)
4. Vereniging voor kinesiology 2011, December 16<sup>th</sup>, UGent, Ghent: **TONOLI C.**, HEYMAN E., BUYSE L., BERTHOIN S., MEEUSEN R.: Cognitive decline in type 1 Diabetes patients – A meta-analysis.
5. Annual Meeting ACSM Congress 2012, San Fransisco, US: **TONOLI C.**, HEYMAN E., BUYSE L., BERTHOIN S., MEEUSEN R.: Type 1 Diabetes-Associated Cognitive Decline: nature and magnitude – A meta-analysis.
6. Annual Meeting ECSS Congress, July 2012, Bruges, BE: **TONOLI C.**, HEYMAN E., ROELANDS R., BUYSE L., CHUENG, S., BERTHOIN S., MEEUSEN R.: Effects of different types of acute and chronic (training) exercise on glycaemic control in Type 1 Diabetes – A meta-analysis.
7. 12<sup>ème</sup> Journée André Verbert: Colloque Annuel des Doctorants. September, 11<sup>th</sup>, 2013 Lille, France. Poster Presentation. **TONOLI C.**, HEYMAN E., ROELANDS R., BUYSE L., CHUENG S., BERTHOIN S., MEEUSEN R.: Effects of different types of acute and chronic exercise (training) on glycaemic control in Type 1 Diabetes – A meta-analysis.
8. Annual Meeting ECSS Congress, July 2013, Barcelona, Spain: Is level of Physical Activity a predictor of a Diabetes Associated Cognitive Decline in Type 1 Diabetes Mellitus patients, an epidemiological cross-sectional study?
9. American College of Sports Medicine, ACSM Annual Meeting, 2014. **TONOLI C.**, HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., BERTHOIN S., MEEUSEN R.: Effects of different types of exercise on the Cognitive Function in Type 1 Diabetes.

10. European College of Sports Science, Annual Meeting, 2014. MEEUSEN R, PIACENTINI M.F., TONOLI C., MACDONALD-NETHERCOTT, ROELANDS B., PATTYN N. No effect of exercise on BDNF during long-duration missions in Antarctica.
11. PhD day Centre for Neuroscience. 13/03/2014. Brussels Belgium. TONOLI C., HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., BERTHOIN S., MEEUSEN R. Effects of different types of exercise on BDNF, IGF-I and Cognition in Type 1 Diabetes.

#### 4. Attended congresses

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1. *Coachcongres voor en door coaches*, Oktober 30th 2010, Brussel (Diamant), Belgium.
2. Journée Thématique: *Diabetes and the Brain*, December 3th 2010, Paris, France.
3. VK-symposium, Kinesiology in Flanders: *Motivatie & Transpiratie*, December 10th 2009, Antwerp, Belgium.
4. Congrès de la Société Francophone du diabète 2011, Mars 22-25<sup>th</sup> 2011, Genève, France.
5. SPALC, 2011, May 9-21th, Rome, Italy.
6. American College of Sports Medicine, ACSM Annual Meeting, 2011, May 31th – June 4th, Denver Colorado, USA.
7. European College of Sport Science, ECSS, 2011, July, 6-9, Liverpool, United Kingdom. Poster presentation
8. VK-symposium, Kinesiology in Flanders: 2012, December 16<sup>th</sup>, Ghent, Belgium. Poster presentation.
9. American College of Sports Medicine, ACSM Annual Meeting, 2012, May 31th – June 4th, San Fransisco, Amerika. Poster presentation.
10. European College of Sport Science, ECSS, 2012, July, 3-6, Brugge, Belgium. Poster presentation.
11. ‘Sportief met Diabetes’, Bas Vande Goor Foundation: 2012, April 19th, Arnhem, Netherlands.
12. 12ème Journée André Verbert: Colloque Annuel des Doctorants. September, 11th, Lille, France. Poster Presentation.
13. VK-symposium, Kinesiology in Flanders: Van Bewegingsonderzoek naar Bewegingsbeleid. December 7th 2012, Brussels, Belgium.
14. European College of Sport Science, ECSS, 2013, July, 26-29th june, Barcelona, Spain. Poster presentation.
15. Interuniversity Doctoral School - State of the Art in Exercise Physiology, 12 May 2014, Lueven, Belgium.
16. American College of Sports Medicine, ACSM Annual Meeting, 2014, May 26th-June 1st, Florida, Orlando, USA.

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## 5. Poster presentations

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1. CAN PROTEINS INFLUENCE BRAIN-DERIVED NEUROTHROPIC FACTOR (BDNF) TYPE 2 DIABETIC PATIENTS? TONOLI C., Hansen, D., HEYMAN E., van Loon, LJC., MEEUSEN R. European College of Sport Science, ECSS, 2011, July, 6-9, Liverpool, United Kingdom.
2. Vereniging voor kinesiology, December, UGent, Ghent: **TONOLI C**, HEYMAN E., BUYSE L., BERTHOIN S., MEEUSEN R.: Cognitive decline in type 1 Diabetes patients – A meta-analysis.
3. Annual Meeting ACSM Congress 2012, San Fransisco, US: **TONOLI C**, HEYMAN E., BUYSE L., BERTHOIN S., MEEUSEN R.: Type 1 Diabetes-Associated Cognitive Decline: nature and magnitude – A meta-analysis.
4. 12ème Journée André Verbert: Colloque Annuel des Doctorants. September, 11the, Lille, France. Poster Presentation. **TONOLI C**, HEYMAN E., ROELANDS B., BUYSE L., CHUENG, S., BERTHOIN S., MEEUSEN R.: Effects of different types of acute and chronic exercise (training) on glycaemic control in Type 1 Diabetes – A meta-analysis.
5. Annual Meeting ECSS Congress, July 2013, Barcelona, Spain: **TONOLI C**, HEYMAN E., ROELANDS B., BUYSE L., BERTHOIN S., MEEUSEN R.: Is level of Physical Activity a predictor of a Diabetes Associated Cognitive Decline in Type 1 Diabetes Mellitus patients, an epidemiological cross-sectional study?
6. American College of Sports Medicine, ACSM Annual Meeting, 2014. **TONOLI C**, HEYMAN E., BUSYE, L., ROELANDS B., PIACENTINI MF., PATTYN N., BERTHOIN S., MEEUSEN R.: Effects of different types of exercise on the Cognitive Function in Type 1 Diabetes.

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## 6. Oral sessions for congresses

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1. SPALC, May 2011, Rome, Italy: **TONOLI C.**, CUMPS E., AERTS I., VERHAGEN E., MEEUSEN R., Incidence, risk factors and prevention of running related injuries in long-distance running.
2. Annual Meeting of ECSS Congress 2012, ECSS, July, 3-6, Bruges: **TONOLI C.**, HEYMAN E., ROELANDS B., BUYSE L., CHUENG SS., BERTHOIN S., MEEUSEN R., 2012. Effects of different types of acute and chronic exercise on glycaemic control in Type 1 Diabetes.

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### Thankfulness for making a PhD: A Longitudinal Study

Cajsa TONOLI<sup>1, 2, 3, 4, 5, 6, 7, 8</sup>

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#### Abstract

The interaction between thankfulness over an extended period of time in a variety of locations and with a multitude of additional subjects was measured. Additional tests in the later period of the study, and a summary of the study's results are presented.

#### Introduction

Many people collaborate to realize a PhD. However, it is widely acknowledged that human body interactions during the time period of making a PhD, are poorly understood. Therefore, the aim of this study was to evaluate the interaction between different populations. Furthermore, the interaction between a 4 year-duing PhD project and happiness, confidence and thankfulness were measured.

#### Materials and Methods

A non-Randomized unControlled Trial design has been performed to study the effects of interactions between subjects, correlations between thankfulness, happiness and confidence, during this 4 year PhD period. The study was approved by the local ethics committee.

#### Participants

Two groups participated in this research: (i) 'colleagues related' subjects, and (ii) 'friends and family', although some subjects are floating between the 2 groups. This resulted in an uncountable amount of subjects who participated in this non-randomized uncontrolled trial, aged from 16-94 years. At least one of the following inclusion criteria must have been met: (1) helping, (2) being a great support, (3) being tolerant, (4) having a big shoulder, (5) making the best 'after-work' dinners, cakes and chats, (6) performing lots of parties, (7) making lots of skydive jumps, (10) being an exercise buddy, (8) willing to make (skydive) trips, (9) have fun, (10 – last but not least) give lots of love.

There were no exclusion criteria's to participate in this study.

#### Protocol

Data was collected from October 2010 to November 2014 at several locations: home, Human Physiology Laboratory, 'DZ schaffen/ Moorsele/ Zwartberg (PCV)', 'DZ Skydive Spa/Cerfontaine/ Empuria Brava' with **Les Stunts** and other skydivers, different locations from 'de vriendjes', different locations from 'the MABO'enaars, the 'via' and many more.

Participants were asked to refrain from any proud or sense of dignity and to help each other going through different stages of this study, including having fun, getting through the research design, data collection & analysis, scientific writing, being involved in merenda's, participating congresses... Participants were evaluated on different time occasions (meetings) during this 4 year period study.

#### Results

A total of uncountable people participated in this last research.

Our primary result was the fulfilment of a PhD. The meetings were mostly under 'optimal' conditions, since these years were practically the best years of my life. Especially a high level of compatibility coupled with a high rate of interaction between C. TONOLI, R. MEEUSEN, E. HEYMAN and B. ROELANDS resulted in this full PhD project.

The summary of the findings of this study are presented in figure 1. This study showed that thankfulness is positively correlated with happiness ( $p < .001$ ) and confidence ( $p < .001$ ). Furthermore, this study showed a positive correlation between the PhD and the amount of

subjects helping during this PhD project ( $r=1$ ,  $p<.001$ ).

make a continuation of this study. The subjects response to this proposal can be indicated below:

Yes     No

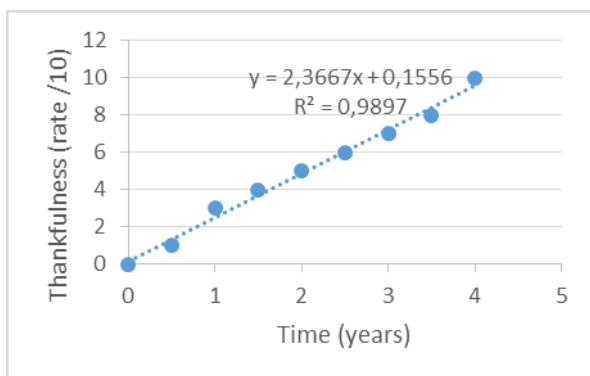
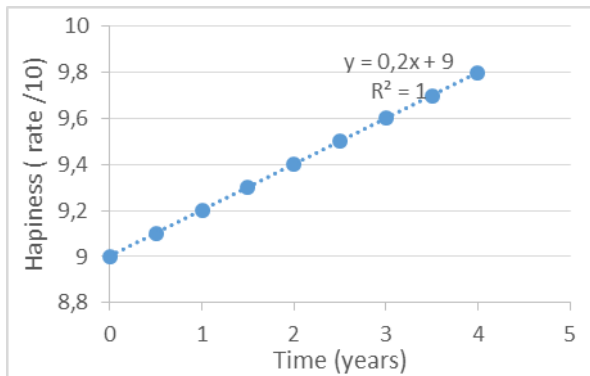
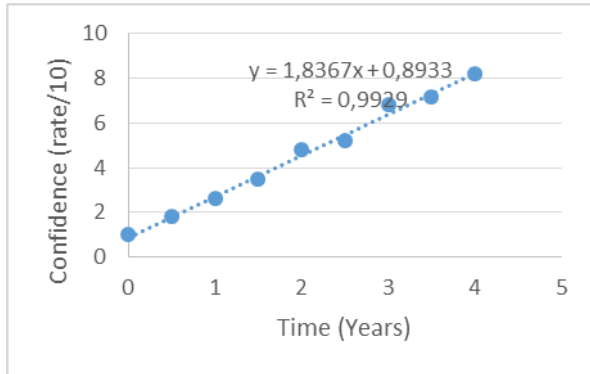


Figure 16-18 Confidence, happiness and thankfulness over time (4 years).

**Conclusions**

The summary of the findings of the study are presented in figure 16-18 and show that the projected confidence, happiness but most of all thankfulness are upward during the 4 years. Taking these results into account, the author wants to truly thank everyone who participated in this project. The author proposes to everybody to

**Acknowledgments**

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Prof. dr. B. de Geus, Prof. dr. B. Roelands (a.k.a. B&B departement), dr. Peacock, dra. K. Knaepen, drs. J. Verschueren, dr I. Bos, drs. J. Vanparijs, dra. T. Torbeyns, dra. M. De Kooning, dr. K. Ickmans, dr. J. Van Oosterwijck, dra. A. Valente, dra. L. Decroix, V. Fontenelle, drs. J. van Cutsem, M. Hanssen, C. Vrambouts and the rest of the MFYS-team contributed to efficient 'Merenda's' for a better working sphericity. Colleagues of Lille who contributed to the same 'Merenda's + gateau's', called coffee breaks. Furthermore I would like to thank dr. K.T. Cumming for the uncountable mails of support & chats we had the last years!

A special contribution goes out to dr. E. Heyman, B. Roelands, and R. Meeusen who helped me through the research part as much as possible. It would not have been possible to bring this project to a successful ending without your cooperation!

dr. E. Cumps, dra. I. Aerts, dr. M. Goekint: Thank you for introducing me into research!

A second special contribution part goes out to my parents, Gilles, friends & colleagues who helped





SUMMARY

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Patients with type 1 diabetes (T1D) show a cognitive decline when compared with non-diabetic subjects, the so called diabetes-associated cognitive decline (DACD). Mainly episodes of severe hypoglycaemia and chronic hyperglycaemia are pointed out as potential causes of this DACD. Exercise is commonly used as an intervention to promote brain function through a cascade of molecular and cellular processes that support brain health. The role of neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF), Insulin-like Growth Factor (IGF-I) and even insulin in mediating hippocampal synaptic plasticity are well established. Additionally, it is known that exercise mediates the effects of neurotrophic factors in the brain of non-diabetic patients, but the effects of exercise on neurotrophic markers are not yet established in T1D. In T1D specific, exercise may be of great clinical relevance to decrease or counteract the effects of diabetes (by influencing acute and chronic glycaemic control) on the brain and the cognitive function. Consequently, this dissertation mainly focused on the effects of long-term physical activity (PA) and acute exercise at different intensities on cognitive functioning, blood glucose, levels BDNF and IGF-I.

Firstly, two systematic literature studies and meta-analysis were performed quantifying the effects of diabetes on the brain (meta-analysis 1), and quantifying the effects of different types of exercise on glycaemic control in T1D.

The first meta-analysis looked at the effects of T1D on all domains of cognitive function. Second, a separate meta-analysis was completed for each of the different possible contributing diabetes-associated factors. This included analysis of the duration of diabetes, hypoglycemia, hyperglycemia, age of onset, and complications of diabetes. A total of 55 original studies were included in the analysis to determine the diabetes-associated cognitive decline in T1D patients (32 adults, 23 children). In this study, a small to modest decrease in cognitive performance in T1D patients compared with non-diabetic controls. Children with T1D performed worse while testing for executive function, full intelligence quotient (IQ), and motor speed, whereas adults with T1D performed worse while testing the full, verbal and performance IQ, executive function, memory, spatial memory, and motor speed. The second part of this study revealed that episodes of severe hypoglycemia, chronic hyperglycemia, and age of onset can be significant factors influencing cognitive function in T1D.

The second meta-analysis was conducted to determine the overall effects of exercise on acute and chronic glycaemic control in patients with T1D, the effects of different types of exercise on glycaemic control and which conditions are required to obtain these positive effects. From a total of 937 studies, 33 met the inclusion criteria for this meta-analysis. ES for exercise on acute glycaemic control were large, while they were small for chronic glycaemic control. Aerobic exercise, resistance exercise, mixed exercise (aerobic combined with resistance training) and HIE acutely decreased blood glucose levels. To prevent late-onset hypoglycaemic episodes, the use of single bouts of sprints into an aerobic exercise can be recommended. This meta-analysis also showed that a regular exercise training program has a significant effect on acute and chronic glycaemic control, although not all exercise forms showed significant results. Specifically, aerobic training is a favourable tool for decreasing chronic glycaemic control, while resistance training, mixed and HIE did not significantly improve chronic glycaemic control.

A cross-sectional study was performed in the diabetes clinic in the UZ of Brussels to determine the impact of long-term PA on cognitive function in T1D. Furthermore, the possible association between basal levels of BDNF and IGF-I, exercise and cognitive function were measured. A total of 103 patients with type 1 diabetes (18-60 years) participated in this study by filling out questionnaires, performed several cognitive tests (attention, cognitive flexibility, executive function, working memory and spatial memory), and collecting blood samples. Multiple regression analyses were performed to discover the individual contribution of each predictor. Several factors can predict a cognitive functioning in type 1 diabetes including level of PA, education, glycaemic control, level of BDNF, diabetes duration and episodes of hypoglycaemia.

Subsequently, the effects of acute HIE on cognitive function and neurotrophins in T1D and matched controls were studied. In this study, Ten trained T1D participants and their matched (by age, gender, fitness level) controls were evaluated on 2 occasions: a maximal test to exhaustion and a HIE bout (10 x [60s 90%Wmax, 60s 50W]). Cognitive tests and analyses of serum BDNF, IGF-1, and free insulin were performed before and after HIE and following 30min recovery. This study demonstrated higher BDNF levels and lower total IGF-I levels in T1D compared to the control group at all-time points. Furthermore,

this study showed that HIE had comparable increasing effects on BDNF and IGF-I in T1D and healthy participants. Similar improvements in cognitive function were seen after a HIE in trained T1D participants and their matched controls, suggesting that there was no difference in how their brain responded to HIE.

In the final study of this dissertation, the effects of different types of exercise intensities on neurotrophins in T1D were examined. Ten participants with type 1 diabetes were evaluated on 3 occasions: a high intensity (10 x [60s 90%Wmax, 60s 50W]) and continuous (22 min, 70% VO<sub>2max</sub>) exercise and a control session. Blood glucose, serum free insulin, serum BDNF and IGF-I were assessed pre/post all the trials and after recovery. This study showed that both exercise intensities changes neurotrophins in T1D, but with a dose response effect for BDNF, which is in line with studies performed in non-diabetic humans.

In conclusion, long term PA is associated with cognitive performance in T1D. Acute exercise (in different exercise intensities) influences neurotrophic factors, especially BDNF, in a dose-response manner. The intensity-dependent findings may aid in designing exercise prescriptions for maintaining or improving neurological health in T1D, but both types of exercise can be implemented.

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SAMENVATTING

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Type 1 diabetes blijkt een significante impact te hebben op de structuur en de functie van het brein. Patiënten met type 1 diabetes vertonen in vergelijking met niet-diabeten een cognitieve achteruitgang, de zogenoemde “diabetes-geassocieerde cognitieve achteruitgang” of DACD. De pathofysiologische basis van deze DACD blijkt nog niet volledig duidelijk, maar 3 mogelijke oorzaken van deze DACD zijn: 1) het ervaren van ernstige hypoglycemie, 2) chronische hyperglycemie of een slechte glycemische controle en 3) C-peptide/insulinedeficiëntie. Verder blijken de diabetesduur, het vroege ontstaan van diabetes en diabetesgerelateerde complicaties bij te dragen tot het ontstaan van een DACD.

Fysieke activiteit wordt vaak gebruikt als interventie ter verbetering van de cognitieve functie van niet-diabeten. Fysieke inspanning ondersteunt een cascade van moleculaire en cellulaire processen die de functie van de hersenen bevorderen. Deze processen worden door neurotrofe factoren zoals Brain-Derived Neurotrophic Factor (BDNF), Insulin-Like Growth Factor I (IGF-I) en insuline beïnvloed. Het is reeds bewezen dat fysieke activiteit een positief effect heeft op neurotrofe factoren in de hersenen van niet-diabeten. De effecten van lichaamsbeweging op neurotrofe factoren in type 1 diabetes werden echter nog niet onderzocht. Daarom is het doel van deze doctoraatsverhandeling de effecten van acute inspanning en regelmatige fysieke activiteit op de cognitieve functie en neurotrofe factoren bij patiënten met type 1 diabetes na te gaan.

Vooreerst werden twee meta-analyses uitgevoerd. In deze onderzoeken werd getracht de effecten van diabetes op de hersenen (meta-analyse 1), en de effecten van verschillende soorten van fysieke activiteit op de glycemische controle in type 1 diabetes te kwantificeren (meta-analyse 2).

In de eerste meta-analyse werden 55 studies weerhouden om de diabetes-geassocieerde cognitieve achteruitgang bij type 1 diabetespatiënten te bepalen. Uit de resultaten blijkt dat er een kleine, doch significante, afname is van de cognitieve prestaties bij type 1 diabetes patiënten in vergelijking met niet-diabeten. Kinderen met type 1 diabetes vertoonden slechtere uitvoerende cognitieve functies, een lagere motorische snelheid en presteerden slechter op IQ-testen. Ook volwassenen met type 1 diabetes presteerden slechter op uitvoerende cognitieve functies, motorische snelheid en alle gebieden van het IQ. Daarenboven werd ook hun (werk)geheugen en ruimtelijk geheugen negatief beïnvloed. Uit het tweede deel van deze studie bleek dat, naast ernstige hypoglycemie en chronische hyperglycemie, de

ontstaansleeftijd van de diabetes en de duur van de ziekte de belangrijkste beïnvloedende factoren van cognitieve functie bij type 1 diabetes zijn.

De tweede meta-analyse werd uitgevoerd om de effecten van fysieke activiteit op de acute en chronische glycemische controle in patiënten met type 1 diabetes te onderzoeken. Uit een totaal van 937 studies, voldeden 33 studies aan onze vooropgestelde inclusiecriteria. Deze meta-analyse toont aan dat sporten een significant positief effect heeft op zowel de acute als de chronische glycemiecontrole. Een acute inspanning aan hoge intensiteit resulteert in een kleinere daling van het bloedglucosegehalte dan aerob sporten. Een aerob trainingsprogramma (in vergelijking met krachttraining of krachttraining gecombineerd met aerob trainen) geeft het beste resultaat om de chronische glycemische controle te verbeteren. Voor het effect van krachttraining of krachttraining gecombineerd met aerob trainen op chronische glycemische controle, werd een trend tot significantie gevonden. Er zijn echter onvoldoende studies om dit statistisch te bevestigen.

Aangezien fysieke inspanning een positief effect heeft op de glycemische controle bij type 1 diabetes, en op cognitief presteren bij niet-diabetes, werd in dit proefschrift onderzoek verricht naar de effecten van éénmalige fysieke inspanningen (aan verschillende intensiteiten) en langdurige, regelmatige fysieke activiteit op de cognitieve functie en neurotrofe factoren bij patiënten met type 1 diabetes.

In de eerste studie, een cross-sectioneel onderzoek, werd uitgevoerd in de diabetes kliniek van het UZ Brussel. We bepaalden het effect van langdurige, regelmatige fysieke activiteit op de cognitieve functie bij patiënten met type 1 diabetes. Bovendien werden mogelijke verbanden tussen basale waarden van BDNF, IGF-I, lichaamsbeweging en cognitieve functies onderzocht. Een totaal van 103 patiënten met type 1 diabetes namen deel aan dit onderzoek. Zij vulden vragenlijsten in en voerden cognitieve tests uit. Deze cognitieve tests maten aandacht, cognitieve flexibiliteit, executieve functie, werkgeheugen en ruimtelijk geheugen. Ook werden bloedstalen genomen. Meervoudige regressieanalyses toonden aan dat verschillende factoren het cognitief functioneren in type 1 diabetes kunnen voorspellen, waaronder fysieke activiteit, educatie, de chronische glycemische controle, basale waarden van BDNF, duur van diabetes en het aantal keer dat de patiënten al een ernstige hypoglycemische ‘aanval’ heeft gehad tijdens zijn of haar leven.



De laatste twee studies bestudeerden de effecten van een éénmalige inspanning aan verschillende intensiteiten op het cognitief presteren en op veranderingen in BDNF, IGF-I, bloedsuikerspiegel en insuline. Hierin werd aangetoond dat mensen met type 1 diabetes significante hogere basale BDNF en lagere basale IGF-I waarden hebben dan niet-diabeten. Verder werd aangetoond dat er geen verschil was in cognitief presteren na een fysieke inspanning tussen mensen met type 1 diabetes en gematchte niet-diabeten. Dit geeft weer dat het brein van mensen met type 1 diabetes op een gelijkaardige manier reageert na een acute inspanning ten opzichte van niet-diabeten. Verder zagen wij dat BDNF-waarden in het bloed zowel na inspanningen aan een continue, matige intensiteit als inspanningen aan een hoge intensiteit significant stijgen, terwijl insuline en de bloedsuikerspiegel significant daalden. Hierbij zagen wij ook dat er een 'dose-response' effect is voor inspanning en BDNF. Dit wil zeggen dat inspanningen aan een hogere intensiteit de BDNF waarden meer doen stijgen in het bloed, dan inspanningen aan matige, continue intensiteit. Tot slot werden er geen verschillen gevonden in IGF-I waarden in het bloed ten gevolge van inspanning in type 1 diabetes.

Uit dit proefschrift kunnen wij besluiten dat fysieke activiteit geassocieerd is met betere cognitieve prestaties bij mensen met type 1 diabetes. Acute fysieke inspanningen (aan diverse trainingsintensiteiten) beïnvloeden de vrijzetting van neurotrofe factoren in het bloed, zoals bijvoorbeeld BDNF. Deze bevindingen kunnen ons in de toekomst helpen om door middel van fysieke inspanning cognitieve functies te verbeteren bij type 1 diabetes.



Nous avons observé, une augmentation significative d'une molécule clé pour la plasticité neuronale, le BDNF, induite par l'exercice intense et prolongé chez l'homme sain. Les perspectives thérapeutiques découlant de ce résultat sont nombreuses, notamment dans le cadre de pathologies associant des troubles du métabolisme du BDNF et des dysfonctions cognitives. Le DT1 au long terme peut engendrer un déclin des fonctions cognitives, certes léger mais significatif. Dans d'autres pathologies métaboliques, comme le diabète de Type 2, plusieurs travaux suggèrent l'existence de modifications du métabolisme du BDNF, probablement en lien avec le fait que, outre ses actions sur la plasticité neuronale, le BDNF est capable d'interagir avec le métabolisme du glucose. Ainsi, en collaboration avec mon laboratoire de post-doctorat, nous nous sommes naturellement tournés vers l'étude des effets de l'exercice aigu et chronique sur le BDNF et les fonctions cognitives des patients DT1.

Dans le projet qui suit, nous cherchons à mieux comprendre la nature et l'origine des dysfonctions cognitives chez le patient DT1 ainsi que l'effet possible de l'exercice aigu et chronique sur ces fonctions cognitives en prenant en compte les mécanismes sous-jacents à ces effets, notamment liés aux facteurs neurotrophiques et aux variations glycémiques.

## 8.1 Contexte scientifique

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### **REFERENCES:**

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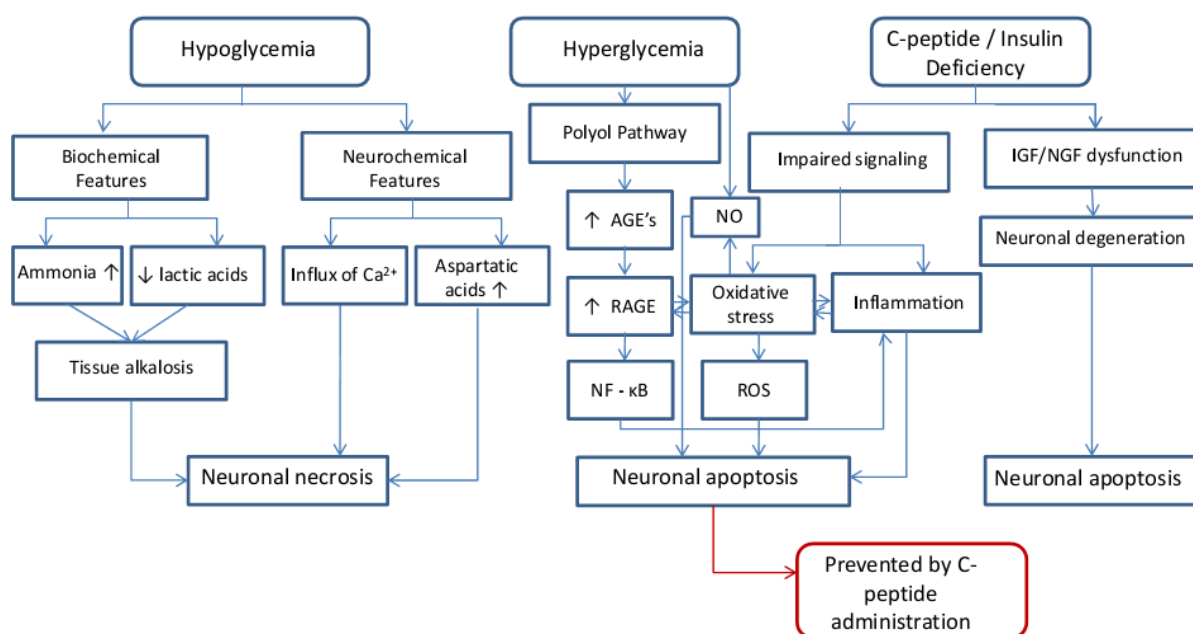
**TONOLI C., HEYMAN E., ROELANDS B., PIACENTINI MF., BUYSE L., BERTHOIN S., MEEUSEN R.,** Diabetes-Associated Cognitive Decline, Is there a Role for Exercise? *J Diabetes Metab* 2013, *S10:006*. doi: 10.4172/2155-6156.S10-006

Les patients DT1 peuvent présenter un déclin léger, progressif, des fonctions cognitives en comparaison

de sujets sains (Brands et coll. 2005 ; Gaudieri et coll. 2008 ; Blasetti et coll. 2011), nommé Déclin Cognitif Associé au Diabète (DACD) (Mijnhout et coll. 2006). Les fonctions cognitives les plus touchées semblent être l'efficacité psychomotrice, l'intelligence, l'attention, la vitesse de traitement des informations, la flexibilité cognitive et la perception visuelle (Brands et coll. 2005). Bien que ce déclin cognitif reste modeste, il peut affecter les activités quotidiennes et la qualité de vie des patients.

Beaucoup de travaux se sont intéressés à la performance cognitive des patients DT1, mais les mécanismes patho-physiologiques conduisant au DACD ne sont pas clairement élucidés (Figure 2). Les épisodes hypoglycémiques, l'hyperglycémie chronique et le déficit en Peptide C/Insuline, sont souvent cités comme délétères pour le cerveau (Tonoli, Heyman et coll. 2013b).

## Mechanisms of Cognitive Decline in T1DM



**Figure 19 : Mécanismes possibles conduisant au déclin cognitif chez les patients DT1** – Figure extraite de Tonoli et coll. Revue de Littérature dans *J Diabetes Metab*, 2013b.

La prise en charge du diabète de Type 1, grâce à un traitement insulinique (par injections ou par débit continu sous-cutané par pompe) adapté à la vie quotidienne (insulinothérapie fonctionnelle) vise à éviter

l'hyperglycémie chronique induite par le diabète, puisque cette hyperglycémie est la cause principale des complications microvasculaires au long terme. Néanmoins, l'insulinothérapie intensive, nécessaire pour atteindre les objectifs stricts de glycémies visés, conduit souvent à un risque accru d'épisodes hypoglycémiques. Ceci implique que les patients doivent gérer des alternances entre épisodes hyperglycémiques et hypoglycémiques, suggérant que le diabète lui-même et la gestion de son traitement (insulinothérapie intensive) (Perantie et coll. 2007) sont 2 risques potentiels pouvant être impliqués dans le développement d'un DACD. Il se peut que l'âge précoce de survenue du diabète soit un facteur de risque de DACD, puisque les enfants sont plus enclins à avoir des épisodes hypoglycémiques sévères en raison de leur moins bonne capacité à percevoir et communiquer leurs symptômes précoces d'hypoglycémie (Northam et coll. 2001 ; Ryan et coll. 2006). Chez l'enfant, il se peut donc que le facteur majeur d'un DACD soit l'hypoglycémie. La durée du diabète et les complications diabétiques sont également cités comme facteurs de risque d'un DACD dans la littérature (Northam et coll. 2001 ; Jacobson et coll. 2007). Néanmoins, aucune méta-analyse n'a comparé les différences en termes de DACD (quelles fonctions touchées, quels facteurs impliqués) entre les enfants et les adultes DT1.

Notre 1<sup>ère</sup> étude vise, par une méta-analyse, à préciser quelles sont les fonctions cognitives touchées par un DACD chez l'enfant et l'adulte DT1 et à analyser l'influence respective des facteurs pouvant y contribuer.

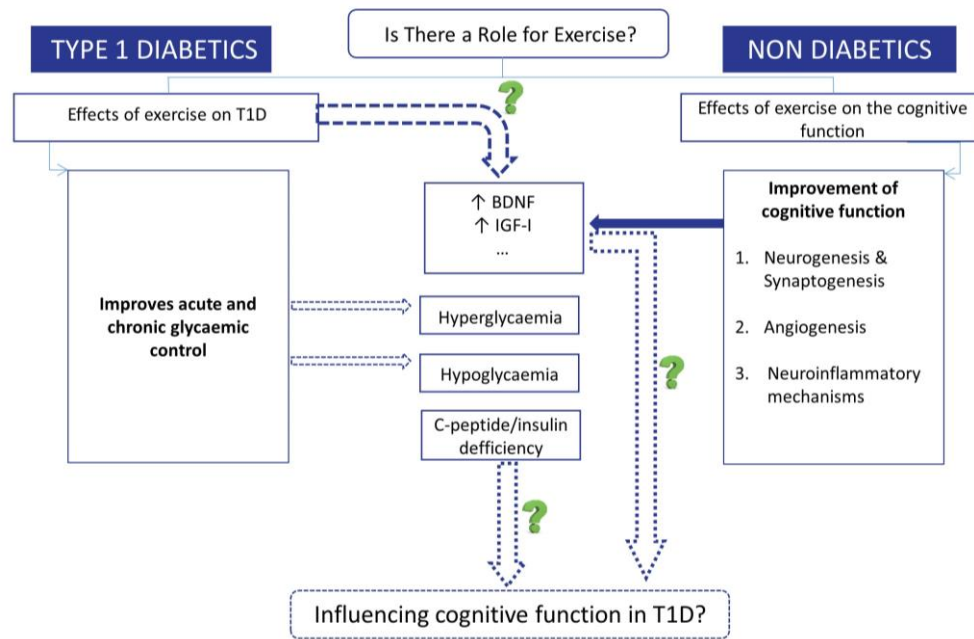
Face à ce déclin progressif des fonctions cognitives, il est important de proposer des mesures préventives aux patients. A ce titre, la pratique d'une activité physique régulière, laquelle est déjà recommandée dans la prise en charge du diabète pour ses effets sur le contrôle glycémique, pourrait s'avérer une stratégie très prometteuse (Tonoli, Heyman et coll. 2013b).

L'effet potentiellement bénéfique préventif de l'activité physique sur le DACD des patients DT1 pourrait alors selon nous passer par :

1/ L'effet bénéfique, bien démontré chez le sujet sain, de l'exercice aigu et chronique sur les facteurs neurotrophiques (comme BDNF et somatomédine C [IGF-I]), et leurs répercussions sur les fonctions cognitives

2/ L'effet de l'exercice aigu et chronique sur le contrôle glycémique des patients DT1 puisqu'un déséquilibre de ce contrôle glycémique (épisodes hypoglycémiques sévères ou hyperglycémiques) est cité

comme l'un des facteurs de DACD (hypothèses avancées dans Tonoli, Heyman et coll. 2013b, figure 3 ci-dessous).



**Figure 20: Effets de l'exercice sur la fonction cognitive des patients DT1, mécanismes et interactions possibles** – Figure extraite de Tonoli, Heyman et coll. Revue de Littérature dans *J Diabetes Metab*, 2013b.

### 8.1.1 L'EFFET DE L'EXERCICE AIGU ET CHRONIQUE SUR LES FACTEURS NEUROTROPHIQUES ET LES FONCTIONS COGNITIVES CHEZ LE SUJET SAIN

#### 8.1.1.1 Exercice et fonctions cognitives

L'exercice régulier semble être une stratégie prometteuse pour améliorer les fonctions cognitives (Cassilhas et coll. 2012) notamment exécutives (Colcombe et coll. 2003).

L'exercice aigu peut améliorer les performances cognitives (Lambourne et coll. 2010), surtout pour les tâches liées aux fonctions exécutives (Colcombe et coll. 2003 ; Tomporowski et coll. 2003) et la mémoire spatiale (Ericksson et coll. 2011). Selon certains auteurs, cette amélioration des performances cognitives pourrait être en partie attribuée à un niveau d'éveil plus important (Brisswalter et coll. 2002). Dans l'analyse des effets de l'exercice aigu sur les fonctions cognitives, il est important de prendre en

considération l'intensité et la modalité d'exercice puisqu'il a été montré, chez le sujet sain, qu'un exercice modéré pouvait améliorer les performances cognitives alors qu'un exercice intermittent de haute intensité les détériorait (Brisswalter et coll. 2002). Il est aussi nécessaire de tenir compte du niveau d'entraînement des sujets puisque lorsque ceux-ci sont entraînés en endurance, l'exercice à haute intensité peut s'avérer au contraire bénéfique sur les fonctions cognitives (Brisswalter et coll. 1997). L'effet bénéfique de l'exercice de haute intensité sur les fonctions cognitives pourrait alors passer par une sécrétion plus importante de catécholamines, lesquelles augmenteraient le niveau d'éveil des sujets (Chmura et coll. 1998).

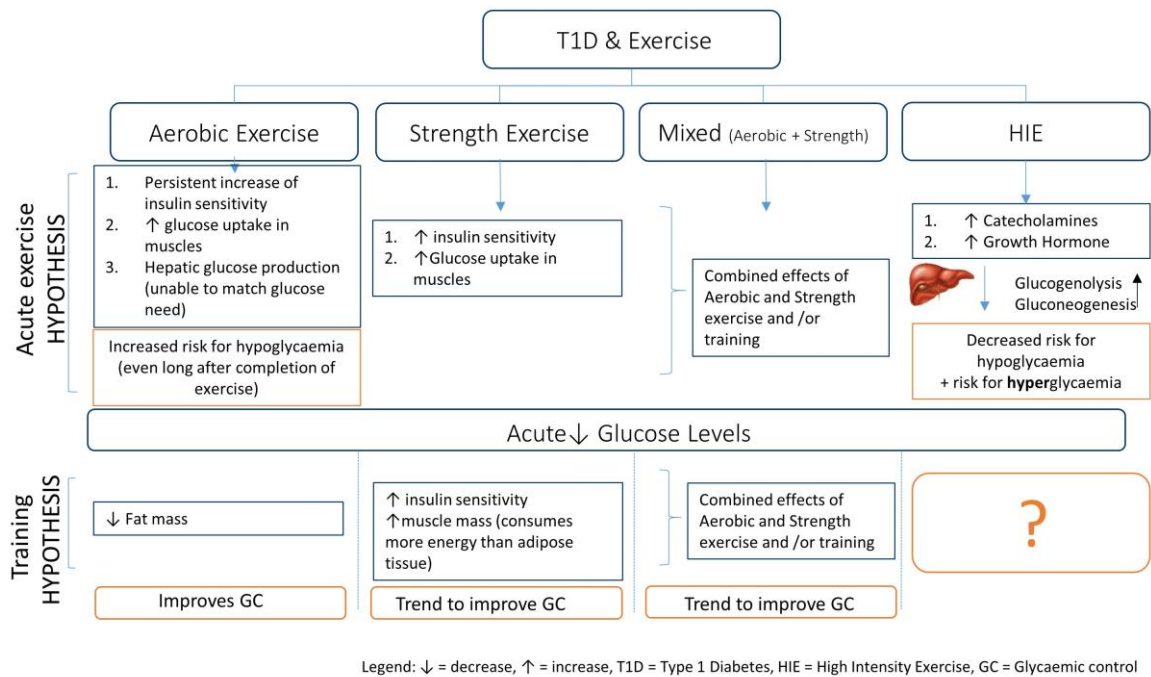
#### 8.1.1.2 Les facteurs neurotrophiques

La libération aigue, induite par une session d'exercice, de neurotransmetteurs et de facteurs neurotrophiques comme le BDNF et l'IGF-I (Heyman et coll. 2011) pourrait avoir un effet bénéfique sur la neurogenèse, la plasticité neuronale, les capacités d'apprentissage et la mémoire (Knaepen et coll. 2010). Le BDNF peut traverser la barrière hémato-encéphalique dans les deux sens et l'augmentation des concentrations de BDNF périphériques est associée à une amélioration des performances cognitives (Pan et coll. 1998). Comme la libération du BDNF dans la circulation sanguine en réponse au stimulus « exercice » semble être dose-dépendant (Knaepen et coll. 2010), notre hypothèse est que des intensités plus élevées d'exercice pourraient susciter des augmentations plus marquées de facteurs neurotrophiques.

Des travaux récents, parfois contradictoires, rapportent des niveaux circulants de BDNF altérés par le diabète ou ses complications (Ola et coll. 2013 ; Liu et coll. 2008 ; Suwa et coll. 2006). De plus, les patients DT1 ont souvent des niveaux circulants d'IGF-I réduits en raison de la déficience en insuline dans la veine porte hépatique (Thraillkill et coll. 2000).

Il serait donc intéressant d'étudier l'effet de l'exercice aigu et chronique sur les facteurs neurotrophiques (BDNF, IGF-I) des patients DT1 et les répercussions possibles sur leurs fonctions cognitives.

## L'effet de l'exercice aigu et chronique sur le contrôle glycémique chez le patient DT1



**Figure 21: Effets de différents types d'exercice sur le contrôle glycémique à court et long terme** – Figure extraite de Tonoli, Heyman et coll. Revue de Littérature dans *J Diabetes Metab*, 2013b.

Notre méta-analyse sur les effets de l'exercice aigu et chronique chez le patient DT1 (Tonoli, Heyman, et coll. 2012) a permis de montrer que :

L'entraînement aérobic pouvait améliorer le contrôle glycémique à long terme (diminuer l'HbA<sub>1c</sub>) : notre hypothèse est donc que l'entraînement pourrait alors jouer un rôle sur les fonctions cognitives des patients puisqu'un des facteurs du DACD est l'hyperglycémie chronique

L'exercice aigu (aérobic, intermittent intense, de force) diminue la glycémie mais cette diminution est atténuée dans le cas de l'exercice intermittent intense. De plus ce dernier permettrait de diminuer le



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risque d'hypoglycémies à la récupération. Comme les épisodes hypoglycémiques sévères sont un des facteurs répertoriés de DACD, il apparaît important de prendre en compte l'intensité et la modalité de l'exercice dans l'étude de l'effet de l'exercice aigu sur les fonctions cognitives du patient DT1.

Notre hypothèse est donc que l'activité physique régulière pourrait réduire ou limiter l'apparition d'un déclin des fonctions cognitives chez les patients DT1 par des mécanismes impliquant une modulation des taux circulants de BDNF et d'IGF-I (**Etude 2 – Exercice chronique & fonctions cognitives du DT1**). Néanmoins, l'exercice physique peut être source de variations importantes de la glycémie chez le patient DT1. Ces variations sont importantes à prendre en considération puisqu'elles pourraient également influencer les fonctions cognitives. La meilleure compréhension des effets possibles de l'activité physique sur la fonction cognitive des patients DT1 en lien avec la glycémie pourrait aider à définir des programmes d'activité physique adaptés pour limiter le déclin des fonctions cognitives (**Etude 3 – Exercices aigus & Fonctions cognitives du DT1**).

## 8.2 Etude 1 – Méta-analyse sur le Déclin Cognitif Associé au Diabète

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REFERENCE :

TONOLI C., HEYMAN E., ROELANDS B., PIACENTINI F., BUYSE L., PATTYN N., BERTHOIN S., MEEUSEN R., Type 1 Diabetes-Associated Cognitive Decline: A Meta-Analysis and update of the current literature. J. of Diabetes. Accepted 2014 June 29, Epub ahead of print: 2014 Jul 7. doi: 10.1111/1753-0407.12193.

### 8.2.1 MÉTHODOLOGIE.

Deux bases de données électroniques ont été consultées jusqu'en 2012 : Pubmed et ISI Web of Knowledge. 55 études (dont 32 chez l'adulte et 23 chez l'enfant) originales de la littérature ont été retenues et nous ont permis de calculer, dans un 1<sup>er</sup> temps, des tailles d'effets observés (le *d* de Cohen) pour estimer la différence standard entre les patients DT1 et les sujets sains. Nous avons ensuite réalisé une 2<sup>ème</sup> méta-analyse pour étudier l'influence relative des différents facteurs de risques d'un DACD cités dans la littérature. La taille des effets (*d*) selon Cohen (1998) vont de léger *d*=0,3 à moyen *d*=0,5 et large *d*=0,8. Un effet négatif indique une diminution de la variable dépendante (par exemple une performance altérée

chez les patients DT1 en comparaison des contrôles sains) alors qu'un effet positif indique une meilleure performance (sauf pour les résultats des tâches cognitives s'exprimant en durée comme le temps de réaction).

8.2.2 RÉSULTATS ET DISCUSSION (FIGURE 5).

Nous avons observé un déclin significatif léger à modéré des performances cognitives des patients DT1 comparés aux sujets sains.

Alors que les enfants DT1 présentaient une altération des fonctions exécutives, du quotient intellectuel général, et de la vitesse motrice, les adultes DT1 avaient un déclin cognitif dans presque tous les domaines (sauf l'attention), c'est-à-dire les fonctions exécutives, le quotient intellectuel général et verbal, la vitesse motrice mais aussi la mémoire générale et la mémoire spatiale.

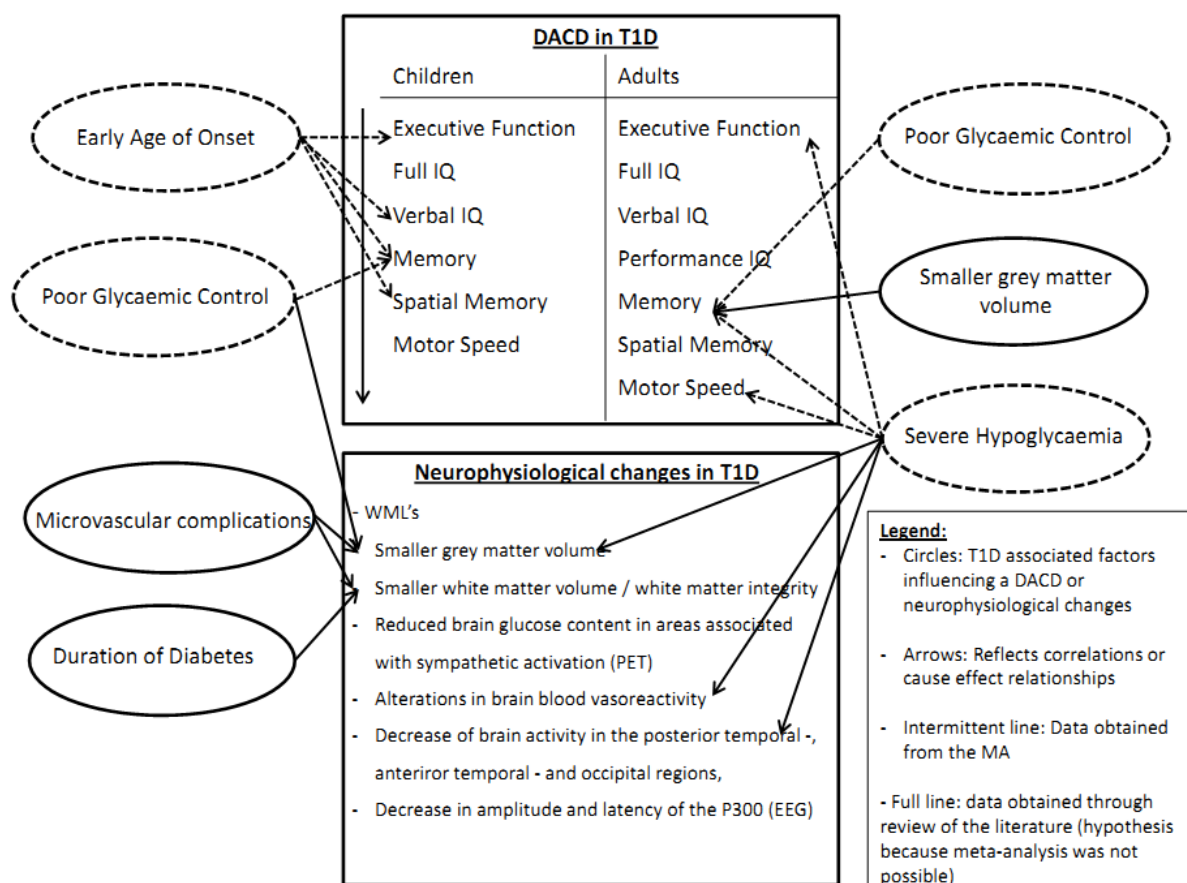


Figure 22: DACD, altérations neurophysiologiques et leurs causes possibles chez le patient DT1 – Figure

extraite de Tonoli, Heyman et coll. Accepté sous réserve de corrections à *Journal of Diabetes*, Fev 2014.

Les facteurs qui influençaient significativement la fonction cognitive des DT1 étaient :

- la répétition d'épisodes hypoglycémiques sévères, avec des effets significatifs sur la mémoire et la fonction exécutive des adultes DT1 ; en effet l'hippocampe pourrait être très vulnérable aux épisodes hypoglycémiques. Contrairement aux hypothèses dans la littérature, cet effet n'était pas retrouvé chez l'enfant DT1 dans notre étude.

- l'hyperglycémie chronique (HbA<sub>1c</sub> >8%) qui affectait significativement les fonctions de mémoire des enfants et adultes DT1 de notre étude. Cet effet délétère de l'hyperglycémie pourrait passer par exemple par l'induction d'un stress oxydant et d'un stress nitrique, par la formation de produits terminaux de glycation et par la dérivation du glucose vers la voie du sorbitol.

- l'âge de début du diabète.

Le DACD était plus sévère chez l'adulte que chez l'enfant, suggérant que l'âge et la durée du diabète pourraient également contribuer au DACD.

Les études futures devraient permettre de définir des stratégies préventives à ce DACD. Nous nous intéresserons ci-après à une stratégie non pharmacologique, l'exercice physique.

### 8.3 Etude 2 – Etude épidémiologique sur les facteurs de DACD chez l'adulte DT1 – Quel rôle de l'activité physique ?

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REFERENCE :

**TONOLI C., HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., KEYMEULEN B., UNUANE D., BERTHOIN S., MEEUSEN R.** Can The Level of Physical Activity predict a Type 1 Diabetes Associated Cognitive Decline? [**Submitted** in *Journal of Clinical Endocrinology & Metabolism*]

#### 8.3.1 OBJECTIF.

Il s'agit de mieux comprendre l'origine des dysfonctions cognitives chez le DT1, notamment de préciser les rôles respectifs de la répétition d'épisodes hypoglycémiques sévères, de l'hyperglycémie chronique, et d'isoler l'impact possible du niveau d'activité physique sur la fonction cérébrale. Ce dernier facteur n'a jamais été pris en compte dans la littérature. Seront alors pris en compte les fonctions cognitives ainsi que

les mécanismes sous-jacents à la santé cérébrale (BDNF, IGF-I, contrôle glycémique), pouvant être influencés par l'exercice.

### *8.3.2 METHODOLOGIE*

103 patients DT1 âgés de 18 à 60 ans ont participé à cette étude épidémiologique transversale. Le niveau d'activité physique habituel était évalué en utilisant la forme courte de l'IPAQ. Celui-ci étant déjà validé en Anglais et en Français, C. Tonoli l'a, dans un premier temps, validé en Néerlandais afin de pouvoir l'utiliser dans notre étude (Tonoli, Heyman et coll. 2013a). Après familiarisation, les sujets ont réalisé les tests cognitifs, en ordre fixe (durée moyenne 45min) pour évaluer les capacités d'attention (Trail Making Test A), les fonctions exécutives (Trail Making Test B et Test de Stroop), la mémoire de travail (Tâche d'Operation Span OPSAN) et la mémoire spatiale (Spatial Memory Task SMT). Un prélèvement sanguin a permis de mesurer le BDNF et l'IGF-I sériques. Nous avons effectué des régressions multiples pour évaluer la contribution respective des différents facteurs sur les fonctions cognitives et sur les niveaux de facteurs neurotrophiques.

### *8.3.3 RÉSULTATS ET DISCUSSION*

Chez les adultes DT1 recrutés, une moindre performance aux tests cognitifs était indépendamment associée à divers facteurs, parmi lesquels :

Le faible niveau d'activité physique (effets sur les fonctions exécutives)

Un niveau faible d'éducation (effets sur l'attention, les fonctions exécutives, la mémoire de travail)

L'hyperglycémie chronique (i.e. niveau d'HbA<sub>1c</sub> au moment de l'étude) (effets sur l'attention, les fonctions exécutives)

La fréquence des épisodes hypoglycémiques antérieurs (effet uniquement sur les fonctions exécutives)

La durée du diabète (effets sur l'attention, les fonctions exécutives, la mémoire de travail, la mémoire spatiale)

Les niveaux élevés de BDNF sériques (effets sur les fonctions exécutives)

Cette dernière relation entre altération des fonctions exécutives et niveaux élevés de BDNF sériques peut

paraître, à 1<sup>ère</sup> vue, contradictoire.

#### 8.3.3.1 Le BDNF sérique : lien avec les fonctions cognitives, l'activité physique, le diabète ?

Chez le sujet sain, la littérature s'accorde sur une augmentation, dose-dépendante, des niveaux de BDNF sériques en réponse à l'exercice aigu (Knaepen et coll. 2010). Par contre, la majorité des études transversales suggèrent une relation inverse entre BDNF périphérique et niveaux habituels d'activité physique. Cette relation inverse, surprenante au 1<sup>er</sup> abord, pourrait avoir plusieurs explications (Huang et coll. 2013). Par exemple, il se peut que les cela traduise une meilleure efficacité du captage de BDNF circulant vers le cerveau chez les sujets plus actifs, résultant en une diminution des niveaux périphériques de BDNF (Currie et coll. 2009).

Néanmoins, chez les patients DT1 de notre étude, les niveaux de BDNF sériques n'étaient pas corrélés au niveau d'activité physique. Le seul facteur qui, finalement, prédisait positivement significativement les niveaux de BDNF sérique était la durée du diabète. Suwa et coll. (2006) suggèrent que, dans le diabète de Type 2, les niveaux de BDNF périphériques pourraient être influencés par la pathophysiologie de la maladie. L'importance fonctionnelle de l'augmentation des niveaux de BDNF circulant observée dans le DT1 reste à élucider.

#### 8.3.3.2 Et l'IGF-I ?

Remarquons que des niveaux faibles d'IGF-I sériques étaient corrélés à une mauvaise performance au Stroop en régression linéaire mais cette corrélation n'était plus significative dans la régression multiple. Ceci nous fait suggérer que la relation entre IGF-I et fonctions cognitives n'est peut être pas directe mais pourrait passer par d'autres mécanismes comme la durée du diabète. En effet, ce facteur prédisait significativement négativement les niveaux d'IGF-I dans notre étude.

#### 8.3.4 CONCLUSION

Un niveau d'activité physique faible pourrait prédire des performances cognitives moindres dans le domaine des fonctions exécutives et de la mémoire de travail. Ces 2 domaines étant parmi ceux touchés

par un DACD chez le patient DT1 (Etude 1, Méta-analyse), il apparaît important de motiver les patients à s'investir dans une pratique physique régulière.

Néanmoins, l'exercice aigu est source de variations glycémiques importantes, lesquelles pourraient également influencer les fonctions cognitives. Cette problématique est intégrée dans l'étude 3 qui suit.

## 8.4 Etude 3 – Effets de différents types d'exercices aigus sur les fonctions cognitives et les facteurs neurotrophiques chez l'adulte DT1

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**TONOLI C., HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., BERTHOIN S., MEEUSEN R.**  
Neurotrophins and cognitive functions in T1D compared to healthy controls: effects of a high-intensity exercise. Accepted 20 August 2014 - Applied Physiology and Nutrition.

**TONOLI C., HEYMAN E., BUYSE L., ROELANDS B., PIACENTINI MF., PATTYN N., BERTHOIN S., MEEUSEN R.**  
BDNF, IGF-I, glucose and insulin during continuous and interval exercise in Type 1 Diabetes. [Submitted – International Journal of Sports Medicine]

### *8.4.1 OBJECTIFS*

Il s'agit d'étudier, les effets respectifs d'un exercice modéré continu et d'un exercice intermittent intense sur les fonctions cognitives d'adultes DT1 en prenant en compte des mécanismes possibles sous-jacents à ces effets comme les variations glycémiques et les niveaux circulants de facteurs neurotrophiques (BDNF, IGF-I). Les effets de l'exercice intermittent intense seront également comparés aux effets d'un tel exercice chez des témoins sains.

### *8.4.2 METHODOLOGIE*

10 sujets DT1 (8 hommes et 2 femmes) ( $HbA_{1c} = 53.44 (4.40)$  mmol/mol) âgés de 18 à 44 ans et 10 sujets sains, appariés sur l'âge, le sexe, l'IMC et le niveau d'entraînement, ont participé à cette étude. Ils ont tous bénéficié, lors d'une 1<sup>ère</sup> visite, d'une familiarisation avec les tests cognitifs utilisés. Lors de leur 2<sup>ème</sup> visite

au laboratoire, ils ont réalisé un exercice triangulaire maximal sur bicyclette ergométrique permettant de déterminer la puissance maximale aérobie ( $P_{max}$ ).

Les 3 visites suivantes, réalisées en ordre randomisé et espacées de 48h chacune, consistaient en une visite « sédentaire » (pas d'exercice mais tests cognitifs et prélèvements sanguins aux mêmes temps que lors des visites « exercice »), une visite pour l'exercice continu modéré (2min d'échauffement à 100 Watts puis 20min à 70%  $P_{max}$ ) et une visite pour l'exercice intermittent de haute intensité (2min d'échauffement à 100 Watts suivies de 10 répétitions de 1min à 90%  $P_{max}$ /1min à 50 Watts). Les 2 exercices duraient au total 22min et les sujets devaient pédaler à 80-100 rpm. Seuls les sujets DT1 ont réalisé l'ensemble des 3 visites, les sujets sains ayant réalisé uniquement la visite « exercice intermittent intense ». Tous les exercices avaient lieu environ 2h après un repas léger standardisé et l'injection d'insuline chez les DT1.

Des prélèvements sanguins étaient effectués au repos et à la fin des exercices et après 30min de récupération pour mesurer le glucose sanguin, le BDNF sérique, l'IGF-I sérique.

Avant et après les exercices ou la période sédentaire de 22min, les fonctions exécutives et la mémoire spatiale ont été testées (par le Stroop et le Spatial Memory Test, respectivement) (durée totale maximale des tests cognitifs, 20min).

#### 8.4.3 RÉSULTATS

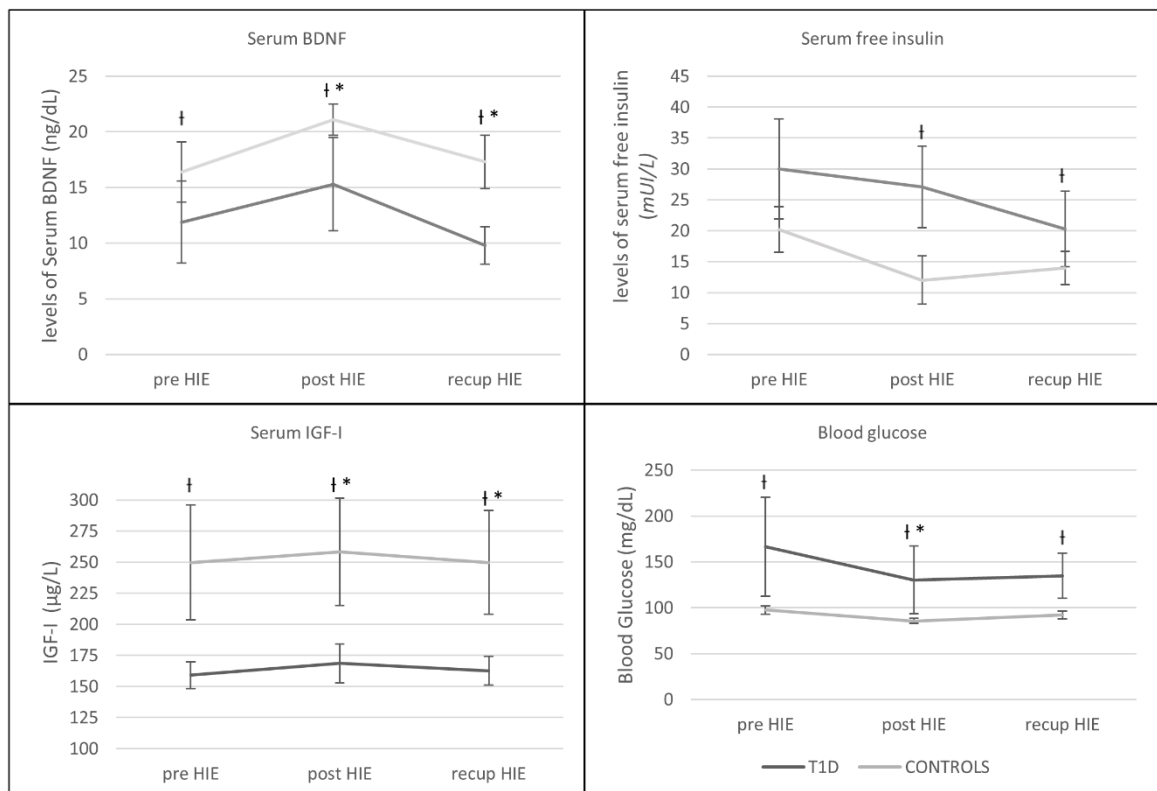
Au repos, les performances cognitives dans le domaine des fonctions exécutives étaient plus faibles chez les sujets DT1 en comparaison des sujets sains. Chez les DT1, les performances liées à la fonction exécutive étaient inversement corrélées aux niveaux d'IGF-I sériques, lesquels étaient diminués chez les DT1 en comparaison des contrôles sains (Figure 6).

Les fonctions exécutives se sont améliorées après l'exercice intermittent intense dans les 2 groupes, sans différences entre les 2 groupes et ceci s'accompagnait d'une augmentation des niveaux d'IGF-I sérique (Figure 6). La mémoire spatiale s'est améliorée significativement avec l'exercice uniquement chez les sujets DT1.

Les niveaux de BDNF étaient plus élevés chez les sujets DT1 en comparaison des contrôles sains à tous les temps, et ils augmentaient à l'exercice dans les 2 groupes (Figure 6). Ces niveaux de BDNF sériques

n'étaient pas corrélés aux performances cognitives.

Enfin, les glycémies étaient plus élevées avant l'effort chez les sujets DT1 en comparaison des sujets sains, puis elles diminuaient à l'exercice (Figure 6). Ces valeurs de glycémies plus élevées chez les DT1 que chez les sujets sains, représentaient en fait des valeurs tout à fait acceptable (< 180 mg/dL) en situation postprandiale dans le cadre de la prise en charge des DT1. En effet, nous avons demandé aux sujets DT1 de gérer leur insuline rapide pour viser une glycémie entre 100 et 150 mg/dL avant l'effort. Finalement, nous trouvons une corrélation entre des niveaux faibles de glycémies de départ avec des mauvaises performances cognitives dans les 2 domaines (fonction exécutive et mémoire spatiale) chez les patients DT1.

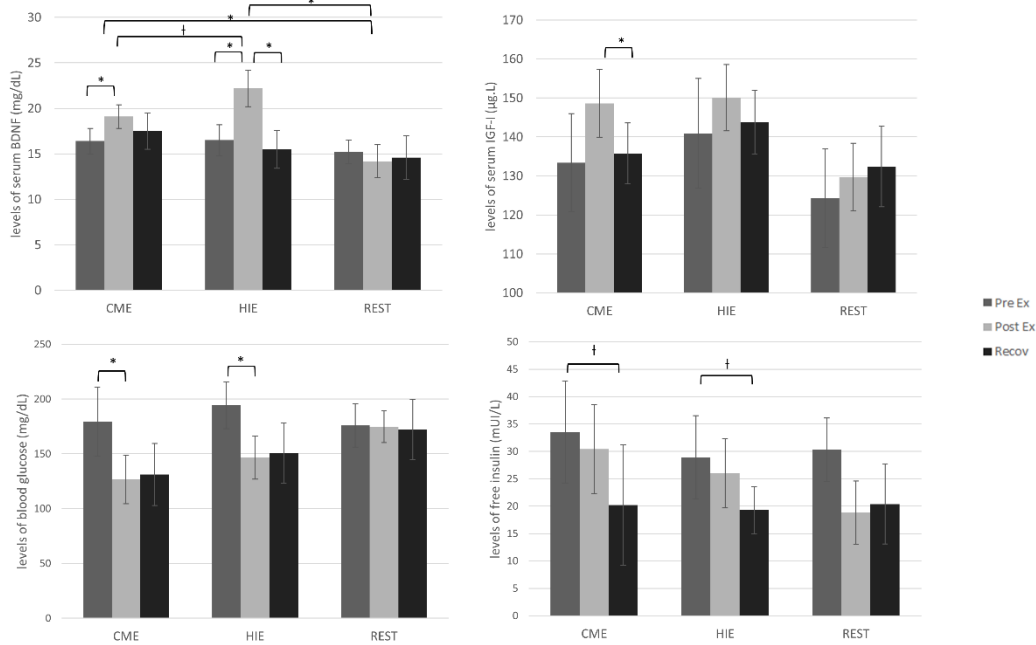


**Figure 23 : Evolution du BDNF, de l'IGF-I sériques, du glucose plasmatique et insuline sérique libre en réponse à l'exercice continu (CME) et à l'exercice intermittent intense ('HIE') et un control trial (REST) chez les patients DT1 et leurs contrôles sains – Figure extraite de l'article Tonoli, Heyman et coll. Soumis en sept. 2014.**

L'évolution du BDNF, de l'IGF-I sériques, du glucose plasmatique ainsi que des performances cognitives (mémoire spatiale, fonctions exécutives) ne différait pas significativement en fonction du type d'exercice chez les patients DT1 (Figure 7). Ceci pourrait éventuellement s'expliquer par le fait que la différence



d'intensité entre l'exercice continu et l'exercice intermittent intense n'était que de 20% de la  $P_{max}$ , ce qui pourrait atténuer les différences de réponses contre-régulatrices hyperglycémiantes escomptées.



**Figure 24: Evolution de l'IGF1, du BDNF sériques et du glucose plasmatique en réponse à l'exercice continu (CONT), l'exercice intermittent intense (HIE) et le repos (REST) chez les sujets DT1 – Figure extraite de l'article Tonoli, Heyman et coll. Soumis en sept. 2014.**

Légende : Pre : repos ; Post : fin d'exercice ; Recov : après 20min de récupération passive.

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## RESUME

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