Chapter 8

Influence of Glycaemic Control on Cognitive Function in Diabetic Children and Adolescents

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Additional information is available at the end of the chapter

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Abstract

According to the World Health Organisation (WHO), the number of people with diabetes has risen to 422 million in 2014. Poorly managed diabetes leads to chronic hyper and/or hypoglycaemia, which are associated with neurological complications in type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. Therefore, the primary target of diabetic treatment is to achieve a good glycaemic control (GC). In this chapter, we reviewed studies published up to September 2017 about GC and cognitive development in diabetic children and adolescents, as well as the nutritional approaches used for the management of diabetes in childhood, focusing on low glycaemic index (GI) diets. According to different studies, low GI diets effectively improve GC, which may reduce the risk of diabetes-related complications, such as cognitive dysfunction; however, the evidence is not sufficiently robust and the results are inconclusive. Despite the fact that, low GI diets are consistent with healthy eating recommendations and should be encouraged in the prevention and nutritional management of diabetes. Further research is needed in diabetic children and adolescents at risk, especially well-designed long-term randomised controlled trials, with larger sample size, to determine the true value of low GI diets on long-term GC and diabetes prevention and management.

Keywords: diabetes, glycaemic index, blood glucose, neurodevelopment, cognitive performance, brain

1. Introduction

Diabetes mellitus (DM) is a complex, chronic endocrine disorder of carbohydrate metabolism resulting from a defect in insulin secretion, insulin action, or both and characterised by high

plasma glucose levels. Currently, it is a major contributor to morbidity and mortality and is becoming an epidemic together with obesity worldwide. In fact, according to the WHO, the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014; furthermore, WHO projects that diabetes will be the seventh leading cause of death in 2030. However, the most worrying fact is that the number of people who suffer diabetes will reach over half a billion by 2030, becoming a major public health issue [1–5].

Diabetes is classified into four clinical categories, T1DM, T2DM, gestational diabetes mellitus (GDM) and other specific types of diabetes due to other causes, such as genetic defects in β-cell function, genetic defects in insulin action or diseases of the exocrine pancreas, among others [6]. The two primary forms of diabetes are T1DM and T2DM. T1DM or insulin-dependent DM is an autoimmune disorder characterised by insulin deficiency (an absolute or near total loss of insulin secretion) caused by the destruction of the insulin-producing pancreatic β-cells; the onset occurs typically during childhood or early adulthood, between the ages of 8 and 12, although it could happen at early ages. This form of diabetes is fatal in the absence of insulin replacement therapy. T1DM represents approximately 5–10% of all diagnosed cases of diabetes [1, 3, 7–9], whereas T2DM or non-insulin-dependent diabetes, that accounts for 90–95% of all diagnosed cases. T2DM is characterised by decreased insulin sensitivity or insulin resistance in peripheral tissues and relative insulin deficiency; this pathology is commonly associated with other metabolic disturbances like obesity, hypercholesterolemia, hypertension and other features of the metabolic syndrome. The prevalence of this disturbance is increasing and is been diagnosed at increasingly younger ages [1–3, 7, 8, 10].

Cognitive dysfunction is a well-established consequence of diabetes. There is extensive literature which has demonstrated that diabetes, its microvascular complications (nephropathy, neuropathy and retinopathy), and its management with insulin and other drugs can induce mild to moderately severe neurocognitive dysfunction as a consequence of structural and functional changes in the central nervous system (CNS), and it will be especially harmful in infancy and childhood when it is under development. It is known that glycaemic extremes (hyper and hypoglycaemia) affect brain development. The subjects who develop diabetes early in life (6–7 years old) have an elevated risk of mild to moderately severe dysfunction that affects virtually all cognitive domains, including learning and memory. However, if the onset of the diabetes is after this critical period, the neurocognitive dysfunction will be less severe and more restricted. But, although "later onset" subjects show lower scores compared with their healthy siblings on tests of intelligence, sustained attention, visuospatial skills, psychomotor speed and executive functions, they show essentially normal learning and memory skills [9, 11]. Despite the fact that, poorly managed diabetes is associated with neurological complications [4, 12, 13].

Therefore, the primary target of diabetic treatment is to achieve a good GC measured by the glycated haemoglobin A1c (HbA1c). HbA1c reflects average glycaemia during the last 3 months and has strong predictive value for diabetes-related complications. It has to be measured every 3 months in order to determine if patients´ glycaemic targets have been reached and maintained (HbA1c < 7.5% is recommended among all paediatric age-groups according to the American Diabetes Association; a lower goal <7% is recommended if it can be achieved

without excessive risk of hypoglycaemia) [4, 12, 13]. The optimal diet and macronutrient composition for diabetic children or adolescents remain controversial [14]. Initial reports support the use of the GI in diabetic management; GI is defined as *'the incremental area under the blood glucose response curve elicited by a 50 g available carbohydrate of a test food expressed as a percentage of the response elicited by 50 g glucose in the same subject'* [15]. Recent criticisms of the GI focus on its validity, claiming that GI values are inaccurate and imprecise. Although, there are controversial results in this matter and some research groups claim that there is insufficient evidence for the beneficial effects of GI diets, several studies have demonstrated that diets promoting low GI patterns effectively improved GC by reducing the occurrence of glycaemic extremes in subjects with diabetes [2, 4, 10, 14–20].

In this chapter, we reviewed the studies published up to September 2017 about GC and cognitive development in diabetic children and adolescents. Furthermore, it has been performed a review of the nutritional approaches (*Mediterranean diet, low GI diet, high-cereal fibre diet, carbohydrate exchange or low carbohydrate diets, low fat diet or diets rich in antioxidants*) used for the management of diabetes, focused on low GI diets.

2. Early programming of diabetes

Recent studies highlight the importance of the intrauterine environment in women with preexisting diabetes and obesity on the long-term health of the offspring. Thus, an intrauterine environment that exposes the foetus to excess of glucose, lipids, inflammation, growth factors, and cytokines may promote adipogenesis, alter appetite regulation, adversely affect pancreas development, and modify mitochondrial function, resulting in long-term metabolic risk to the offspring. The metabolic intrauterine environment is considered a critical risk factor for the development of adult diabetes and cardiovascular diseases [21]. As a consequence, any harm during critical developmental windows induces permanent adaptive programming in key organs, leading to persistent alterations in gene expression through epigenetic mechanisms. Nutrition constitutes the most significant environmental factor, being both a risk factor and the key in the prevention and protection against different metabolic disorders later in life [22].

In utero programming seems to create a *'metabolic memory'*, considering that physiological anomalies during the gestational period are responsible for the onset of T2DM and obesity associated with metabolic syndrome in the offspring at adulthood [23]. The periconceptional period has also been found as a critical period for nutritional effects on the ability of the foetus to respond to acute and chronic stressors, and for postnatal and adult metabolic health outcomes. It has been suggested that this period constitutes a critical time for nutritional effects on gene expression, with a potential preventive effect of postnatal risks related to prenatal maternal overconsumption and/or overweight, and DM or metabolic syndrome during pregnancy [22].

The association between poor psychosocial health, the risk of obesity and T2DM is well established. DynaHEALTH EU project hypothesises that factors determining glucose metabolism and insulin sensitivity on one hand, and the neuroendocrine response resulting from exposure to psychosocial stress on the other, should be incorporated as a single health indicator,

named *'gluco-psychosocial axis'* (GPA) [24]. It is proposed that long-term GPA status could be established during developmental windows throughout early stages of life, via programming. The metabolic and psychosocial environments in early stages of life play an important role in the structural and functional development of the GPA components. Several studies have demonstrated the importance of the prenatal environment in determining long-term health and the ageing process [24].

Epidemiological evidence suggests impaired glucose metabolism begins much earlier in life [24]. According to clinical studies pre-pregnancy diabetes or GDM, together with maternal obesity, have been associated with higher risk in the offspring of developing obesity, insulin resistance and T2DM later in life [25]. Complications in the offspring might appear even with gestational glucose levels below the thresholds of GDM; even borderline high blood glucose levels increase the risk of infants of being large for gestational age, early adiposity rebound and higher prevalence of metabolic syndrome, especially if they become obese [22]. Infants born from mothers who developed DM before pregnancy had higher risk to develop obesity, higher blood glucose and HbA1c levels, as well as lower HDL cholesterol concentrations and were more prone to DM during childhood, compared to those infants born from mothers who developed DM after pregnancy [25]. Furthermore, different studies have demonstrated that both, GDM or pre-gestational diabetes are related to delayed brain maturation, deficiencies in fine/gross motor development, cognitive deficiencies, and higher risk to develop Attention Deficit Hyperactivity Disease (ADHD) in the offspring, especially when there was a bad control of the maternal illness (HbA1c > 7.5%) during pregnancy [26–28].

T2DM burden is currently increasing in young people; higher maternal body mass index (BMI) during pregnancy is associated with higher all-cause mortality, higher cardiovascular morbidity and mortality, and increased risk of T2DM among offspring [24]. Data from PREOBE project have demonstrated that infants born from obese mothers had significantly higher birth weight and waist circumference, and those born from mothers with GDM had higher waist/height index compared to the healthy controls [29]. Maftei et al. reported that maternal pre-pregnancy BMI is related to offspring's insulin resistance at 9–10 years old, independently of GDM, and gestational weight gain does not appear to affect insulin resistance in children [30]. Other studies, showed that both foetal hyperglycaemia and hyperinsulinaemia in GDM increase the obesity and diabetes rates in the offspring, independently of maternal genetic influence [31]. Additionally, Westermeier et al., found that maternal obesity and neonatal insulin resistance are associated with long-term development of obesity, DM, and increased global cardiovascular risk in the offspring, involving deleterious mechanisms of intrauterine programming [32].

The DynaHEALTH EU project is testing how offspring's diseases later in life and their own GPA status is established in early life in response to metabolic and stress factors and partly related to maternal GPA status in pregnancy [24].

Nevertheless, developmental programming in humans is not limited to the *in utero* environment, the nutritional status during post-natal period has a considerable impact on later life health. As well, gender differences in developmental programming have been largely ignored and it has been suggested that offspring responses to the early metabolic environment are highly

sexually driven. This could be due to inherent gender differences in hypothalamic development, or gender specificity of the adaptive response to environmental challenges. In fact, there is higher risk of T2DM in women who were exposed to high maternal BMI during foetal life. Thus, in the future it will be vital to take into account sex differences for the establishment of recommendations, health guidelines and in the design of new therapeutic interventions [24, 33].

Either pre-existing diabetes (T1DM/T2DM) or GDM are associated with macrosomia in the offspring. Alterations in macrosomic infants persist postnatally, leading to insulin resistance, obesity, diabetes and metabolic syndrome at adulthood [23]. Maternal programming creates a vicious cycle by which maternal diet, weight or glycaemic status can increase offspring susceptibility to metabolic disease. These offspring during their pregnancies will have their own children; also exposed to an adverse *in utero* environment, perpetuating the burden of such conditions to future generations (**Figure 1**) [25, 33].

The molecular mechanisms involved in foetal programming in diabetic women are far from understood [31]. It is essential that all diabetic women receive a proper management, including preconception counselling about weight management and weight loss (if they are overweight),

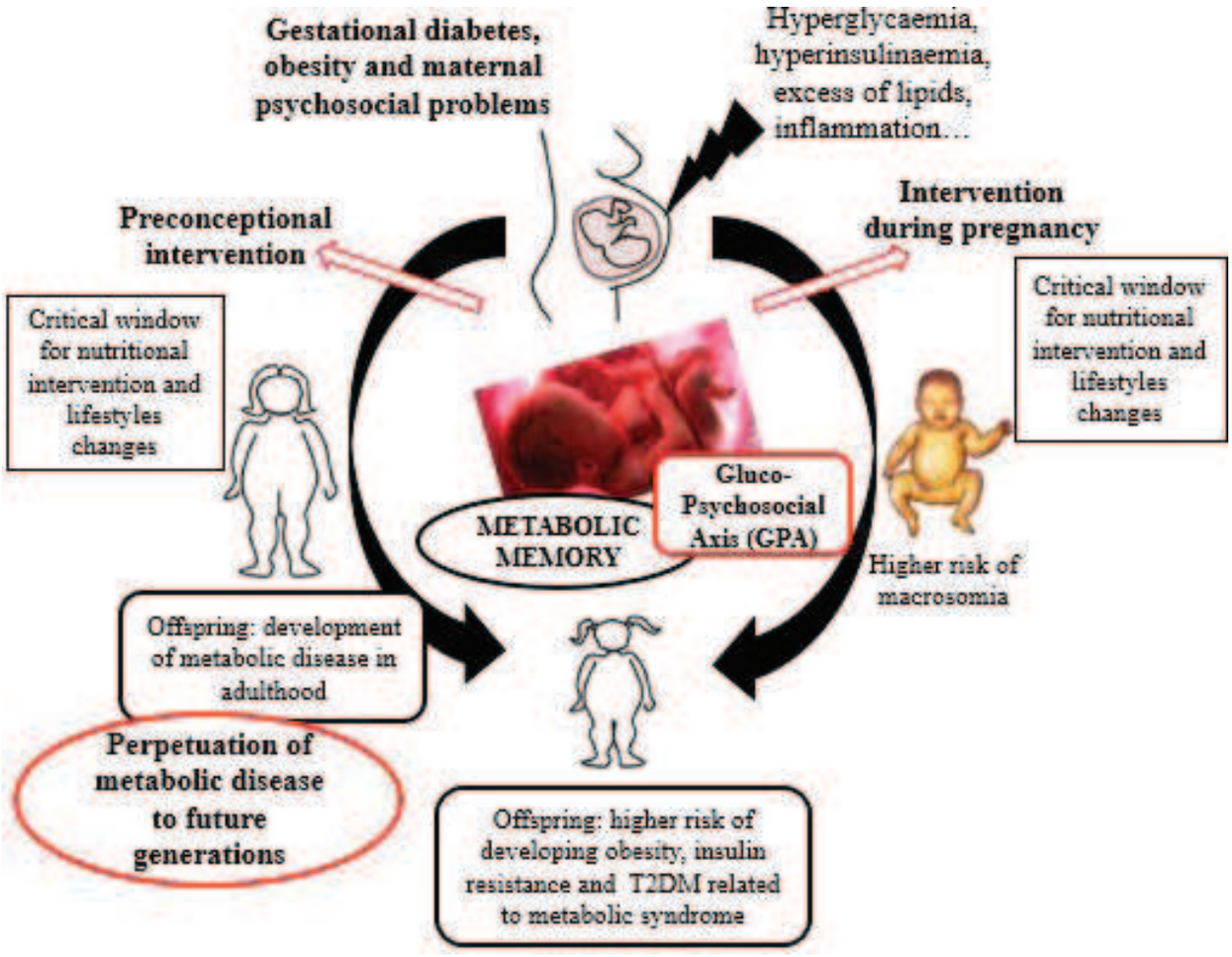

Figure 1. Vicious cycle of metabolic disease perpetuation to future generations and critical windows for intervention. Adapted from Dearden and Ozanne [33].

proper weight gain during pregnancy, the critical importance of optimising GC (HbA1c < 6.5), by self-monitoring blood glucose levels, medication (if needed), medical nutrition therapy (eating a healthy diet) and optimal individualised exercise [21, 31]. Therefore, prevention of foetal programming by tight GC will be essential in order to break the vicious cycle of obesity, diabetes and related-complications in future generations [31]. In order to develop effective intervention strategies, it is important to understand the programming effects of maternal nutrition during pregnancy and the post-natal period both separately and combined, as well as to define clearly the critical developmental periods in order to establish an appropriate time intervention [33].

3. Cognitive dysfunction related to diabetes

The negative effects of DM on retinal, renal, cardiovascular, and peripheral nervous systems are widely acknowledged, but less attention has received its effects on cognitive function and neurodevelopment. T1DM and T2DM are associated with reduced performance on numerous domains of cognitive function. The exact pathophysiology of cognitive dysfunction in diabetic patients is not well understood; nonetheless, vascular disease, hyper or hypoglycaemia, and insulin resistance seem to play significant roles [34].

Subjects with T1DM and T2DM can develop several microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (coronary heart disease, peripheral arterial disease, cerebrovascular disease) complications that will contribute to cognitive dysfunction in adults; however, the major cause of mortality and morbidity in children with T1DM is the diabetic ketoacidosis, which cause cerebral injury along with haemorrhage or cerebral infarction in some cases, leading to cerebral edema (**Table 1**) [7, 8, 35].

Cognitive dysfunction in T1DM and T2DM share many similarities, but important differences do exist [7], specifically in the degree of cognitive dysfunction and in the manifestation of cognitive abnormalities [1]. Poorly managed diabetes due to chronic hyper and hypoglycaemia or elevated postprandial glucose may be common aetiological causes of the neurological complications of T1DM and T2DM or cognitive dysfunction [12, 36].

3.1. Type 1 diabetes

Different studies assessing cognition in children and adolescents with an early onset of diabetes (EOD) (6–7 years) have shown higher risk of developing more severe cognitive deficits, especially impairments in *memory, learning, intelligence* and *verbal fluency/language* [36, 37], as well as in *attention, executive function* [38], *psychomotor speed* [9], *slowing of information processing, problem solving, visuoconstruction, visual perception* and *mental flexibility* [7].

Patients with T1DM often perform within normal cognitive range; however, they may perform more poorly on some cognitive tasks compared to non-diabetic control subjects, such as *executive functions, short-term memory, psychomotor efficiency* and measure of *mental efficiency*, which predispose for more rapid deterioration of cognitive function later in life [1]. Kodl and

Metabolic factors	• Chronic exposure to hyperglycaemia [1] • Acute exposure to hypoglycaemia [11] • Recurrent exposure to hypoglycaemia [1] • Increased plasmatic concentration of AGEs [34]
CV factors	• Microvascular complications (*nephropathy, neuropathy, retinopathy*) [8] • Macrovascular complications (*coronary heart, peripheral arterial and cerebrovascular diseases*) [8] • Endothelial dysfunction [17] • Increased inflammatory markers (*C-reactive protein, α-1-antichymotrypsin, interleukin-6 and intercellular adhesion molecule 1*) [34] • Changes in blood–brain barrier permeability • Reduced fibrinolysis [14] • Dyslipidemia (*increased total cholesterol, LDL-c and triglycerides, and reduced HDL-c*) [14] Hypertension [1]
Endocrine factors	• Insulin resistance [34] • Hyperinsulinaemia • Impaired HPA axis activity [12] • Absence of C-Peptide [34] • Increased antidiuretic hormone Hyperleptinaemia
CNS factors	• Genetic predisposition (*Absence of Apoε4 Allele*) [34] • Amyloid disposition • Increased oxidative stress [11] • Changes in neuronal calcium homeostasis • Depression and anxiety [2, 12] • Disrupted myelination [11] • Increased apoptosis in oligodendrocyte precursor cells [11] • Dysfunctional synaptic plasticity [1]
Disease onset	• Early onset diabetes (6–7 years old) [9]

Advanced glycation end products, AGEs; cardiovascular, CV; central nervous system, CNS; high density lipoprotein cholesterol, HDL-c; hypothalamic-pituitary-adrenal, HPA; low density lipoprotein cholesterol, LDL-c. Adapted from McCrimmon RJ, Ryan CM, Frier BM. Lancet, 2012 [7].

Table 1. Factors that contribute to the development of cognitive dysfunction in diabetic patients.

Seaquist found different cognitive domains negatively affected in T1DM, specifically *information processing*, psychomotor efficiency*, attention*, memory, learning, problem solving, motor speed, vocabulary, general intelligence, visuoconstruction*, visual perception, somatosensory examination, motor strength, mental flexibility** and *executive function*. According to the authors the domains marked by asterisks have strong supporting data [34].

Neuroimaging studies have found morphological abnormalities, cortical atrophy, lower grey matter volume and density in left temporal-occipital junction, white matter hyper-intensities and reduced white matter densities, concretely white matter microstructural deficits, as well as neuroanatomical changes in the hippocampal region. However, other studies did not find volumetric changes in the hippocampus [12, 36, 37]. In fact, Ho et al., have reported that measuring subfields of the hippocampus with high resolution magnetic resonance imaging may provide a way to specifically target the neurogenic regions of the hippocampus and may show different effects of diabetes on different parts of the hippocampus. It should be noted that studies carried out in rodents with T1DM have shown reductions in hippocampal cell proliferation and survival, leading to learning and memory deficits compared to control rodents (**Figure 2**) [3].

Additionally, glycaemic extremes (hyper and hypoglycaemia) affect brain development. Severe hypoglycaemia during a lifetime exposure decreases lateral temporal–parietal-occipital grey matter volume, whereas after 2 years with T1DM showed a greater reduction in the regional white matter volume in the precuneus/cuneus region [11]. Furthermore, severe

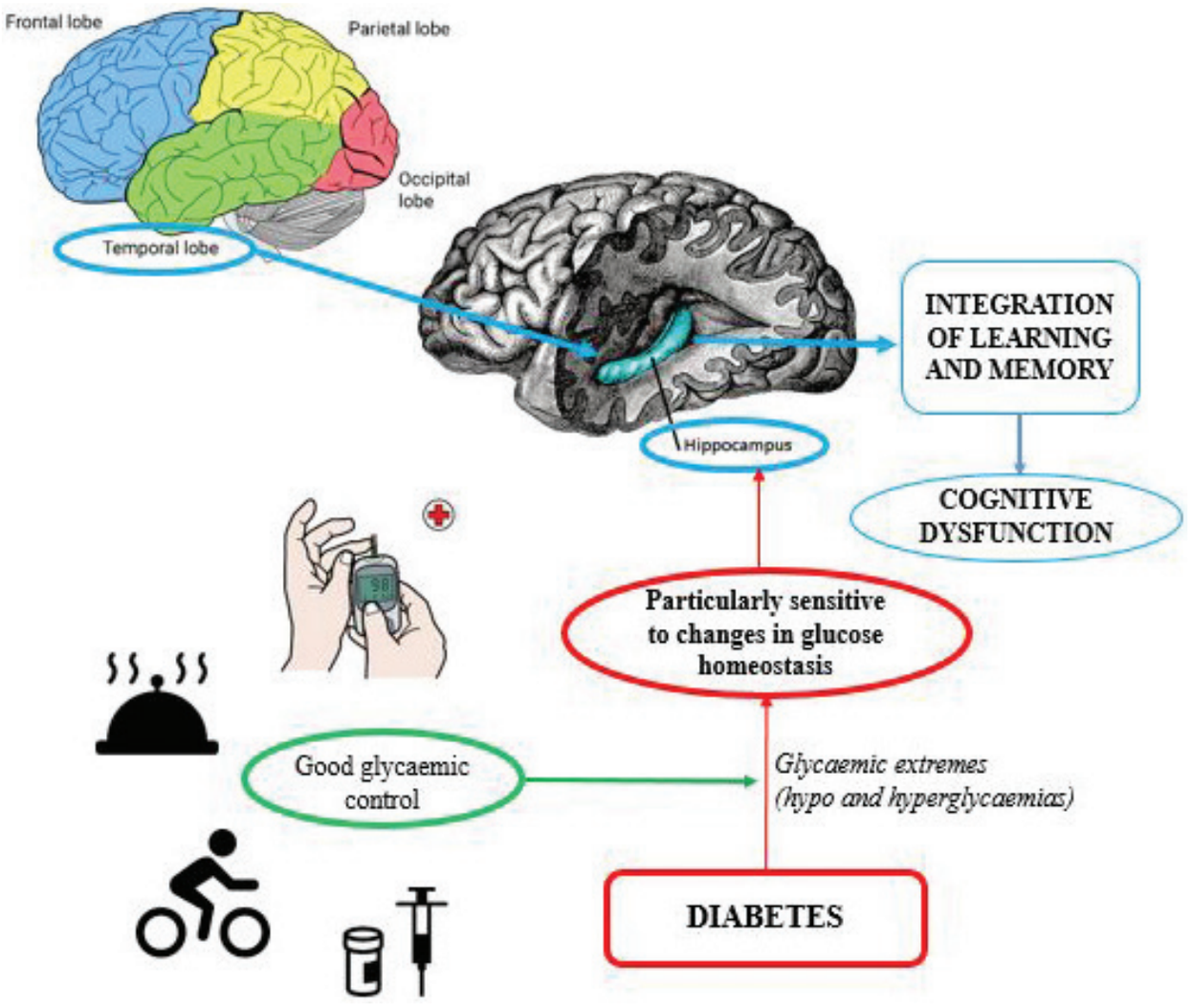

Figure 2. Effect of glycaemic extremes on the development of congestive dysfunction.

hypoglycaemia harms neurons in cerebral cortex, medial temporal region, including hippocampus, basal ganglia and brain stem with unknown individual consequences [36]. Hypoglycaemic episodes in T1DM children lead to significant declines in *verbal abilities, memory skills* and *ability to organise* and *recall information*. Severe hypoglycaemia may result in persistent electroencephalography (EEG) changes, with 80% of EEG abnormalities observed in diabetic children with history of severe hypoglycaemia compared with 30% of abnormalities in diabetic subjects without severe hypoglycaemia and 24% in healthy control children [39]. In presence of severe hypoglycaemia in T1DM, children show mildly reduced intelligence quotient (IQ), as well as adverse effects in general, verbal and performance IQ [40].

Children and adults with T1DM have worse performance in executive function, full IQ and motor speed; in presence of hyperglycaemia negative effects on memory function were observed in children. Moreover, higher HbA1c levels were associated with worse *motor speed* and *psychomotor efficiency* [41]. Additionally, chronic hyperglycaemia has been associated with reductions in grey matter volume and multiple posterior brain regions, including the cerebellum. Adolescents with three or more symptomatic hyperglycaemic episodes showed reductions in white matter integrity, specifically in superior parietal lobule, corpus callosum, posterior limb of the internal capsule, and grey matter integrity, concretely in thalamus and putamen, whereas children (4–10 years old) showed microstructural abnormalities in white matter with lower IQ scores [40]. A lifetime exposure to hyperglycaemia reduces occipital/parietal grey and matter volume; after 2 years with T1DM, a reduction in the whole brain grey matter has been observed [11]. Large effects have been observed in T1DM patients regarding *visuospatial ability, motor speed, writing, sustained attention* and *reading* [40, 42].

It is worth noting that a late onset of diabetes (LOD) entails several cognitive dysfunctions, although these impairments are less severe compared to those subjects with EOD. In subjects with a LOD, it has been found lower *overall cognition, intelligence, visual learning* and *memory, motor speed* and *visual motor integration, sustained attention* and *executive function* compared to their healthy siblings [9, 38].

Finally, several studies have shown that gender influences neurocognitive function in T1DM. In a study with children and adolescents (aged 7–16 years), boys presented decline in *verbal intelligence*, which was correlated with worse GC. This was not seen in girls of similar ages. It should be noted that most human studies do not distinguish between genders when describing results of neurocognitive testing [34].

3.2. Type 2 diabetes

The prevalence of childhood obesity has increased dramatically worldwide, leading to a variety of health problems, including T2DM, which previously was seen only in adults. The Centres for Disease Control (CDC) and Prevention foresee that the prevalence of T2DM in those under 20 years of age will quadruple in 40 years, assuming a 2.3% annual increase [6]. In the United States, up to 1 in 3 new cases of diabetes diagnosed in subjects younger than 18 years old is T2DM, occurring most commonly in children and adolescents between 10 and

19 years of age [43]. It is difficult to distinguish between T1DM and T2DM in children, given the current obesity epidemic worldwide. The rapid emergence of childhood T2DM means that health professionals have to treat a disease in children, which previously was encountered only in adults. This represents several challenges, because most of diabetes education materials are designed and directed to children with T1DM, but not to T2DM and probably obese patients. Another problem is that most medications used for T2DM have been tested for safety and efficacy in subjects older than 18 years old, because ethical reasons. Therefore, there is scarce scientific data for optimal management of children with T2DM [6, 43].

The comorbidities, such as obesity, hypertension and dyslipidaemia, may be present at the time of diagnosis in youth with T2DM, which contribute to the severity of the disease. The cause of diabetes-related cognitive dysfunction is difficult to establish, because of the prevalence of several comorbidities in the same individual, which might affect cognitive function [6, 7].

Lamport et al. [44], performed a systematic review in adults, concluding that T2DM is associated with cognitive impairments. In the present longitudinal review we found many studies relating an accelerated cognitive decline in adults with T2DM; however, it is difficult to conclude that these reported cognitive impairments are independently associated to abnormalities in glucose tolerance or due to the associated comorbidities present in these patients (cerebrovascular and cardiovascular diseases, obesity, hypertension and hypercholesterolemia) [44]. Some studies suggest that cognitive performance does not differ in T2DM subjects in relation to non-diabetic controls when it is taken into account the influence of age, premorbid IQ, BMI and depression [1]. Unlike the studies in T1DM patients, most studies suggest that T2DM subjects experience cognitive decline. T2DM most often is associated with deficits in cognitive domains, *declarative memory*, *attention* and *executive function*, alterations also seen in children and adolescents with Metabolic Syndrome or obesity and glycaemic disorders [45, 46]. The GC, the disease duration and cerebrovascular complications are considered risk factors that influence the magnitude of the cognitive decline [12]. *Learning* and *memory* deficits are the cognitive abnormalities that most clearly differentiate patients with T2DM from T1DM patients [7].

Kodl and Seaquist, established that the cognitive domains that are negatively affected in adults with T2DM are *memory* (verbal memory, visual retention, working memory, immediate recall, delayed recall), psychomotor speed*, executive function*, processing speed, complex motor function, verbal fluency, attention* and it seems to be related with the development of diabetes. According to the authors, the domains marked by asterisks have strong supporting data [34]. Additionally, Sweat et al., in a study carried out in 162 adolescents (aged 19.53 ± 1.53 years), found that obese adolescents showed slower *processing speed* maintaining equivalent *executive functioning* compared with their healthy siblings [46]. Whereas, a recent systematic review performed Barkin et al., showed a consistent inverse association between obesity and *executive function* in children and adolescents, emphasising that in future research is necessary to use a standardised method of *executive function* measurement in order to establish causality with obesity and develop new and more effective intervention strategies [47].

Neuroimaging studies have shown deficits in hippocampal-based cognitive performance, which may be attributed to changes in brain structure and volume, leading to deficits in *attention, learning* and *memory* [1]. T2DM subjects have similar morphological abnormalities than T1DM patients, such as cortical atrophy and white matter lesions. Moreover, it has been shown a reduction in the microstructural integrity of white matter and grey matter. The reductions in grey matter volumes have been observed in the prefrontal cortex, amygdala and hippocampus [12]. Additionally, greater cortical atrophy, more lesions in deep white matter and hippocampal (susceptible to acute metabolic changes, such as hypoglycaemia) atrophy, leading to impairments in *immediate memory*, have been observed (**Figure 2**) [7].

Hippocampal atrophy is one of the neuroanatomical characteristics that differs between people with T1DM and T2DM, both have reduced grey matter density and white matter lesions. Nevertheless, cortical atrophy is more pronounced in T2DM, possibly because the subjects are older on average. Moreover, the hippocampus is more affected in T2DM, is unclear why, because this area is susceptible to acute metabolic change, which is more prominent in T1DM. This suggests that age, sex, the associated comorbidities and the presence of macrovascular disease or insulin resistance might be important risk factors for hippocampal atrophy (**Figure 2**). T2DM subjects perform worse than healthy control on learning and memory tests, unlike those with T1DM, who rarely have deficits in these domains [7]. However, the results are inconclusive, because other studies have found deficits in *learning* and *memory* in T1DM patients, but Kodl and Seaquist confirmed that there is no strong evidence to suggest this [34].

4. Glycaemic index and dietetic management in diabetic children and adolescents

At present, nutritional interventions, physical activity and weight control remain the main pillars of effective diabetes management. Despite modern approaches to intensive insulin therapy and other drugs for the management of diabetes, dietary management remains as the main important action of diabetes treatment [48]. There is not an ideal nutritional intervention for the management of diabetes. A poor GC in subjects with T1DM and T2DM has been related with the onset of diabetes complications. Therefore, it is vital to develop new strategies in order to maintain a good GC. Current standards for diabetes management reflect the need to lower glucose as safely as possible, without increasing the risk or hypoglycaemic episodes. It should receive special consideration the risk of hypoglycaemia in young children (aged <6 years or EOD), because usually they are unable to recognise and/or manage the symptoms. This is called *'hypoglycaemia unawareness'* [6].

There are different dietetic approaches aimed at the improvement of the GC in children and adolescents with T1DM and T2DM, among them it is worth noting low GI diets, diets rich in antioxidants, carbohydrate exchange diets, high-cereal fibre diet, traditional Mediterranean-style dietary pattern, low carbohydrate Mediterranean style diet, low carbohydrate diets and low fat diets.

Although there are no long-term intervention studies looking at the effects of a low GI diet on diabetes prevention, there is a large body of evidence from animal models, clinical trials and epidemiologic studies that demonstrates the benefits of a low GI diet in the prevention and management of diabetes. Low GI diets in subjects with T1DM and T2DM improve blood glucose control to a similar extent as medications, improving GC and reducing the risk of hypoglycaemic events [14].

Derdemezis and Loveg [4], reported in by a systematic review that low GI diets effectively improve GC. They observed that subjects with T2DM presented significant beneficial effects after the consumption of low GI diets; however, in some cases, a low GI diet was associated with significant weight reduction, which makes difficult to establish firm conclusions, because it is not clear if the effect on the improvement of GC is for the low GI diet per se or derived from the weight loss itself. On the other hand, in subjects with T1DM there is insufficient evidence for the beneficial effects of GI control due to different confounding factors (differences in dietary fibre intake and the values used for calculation of dietary GI and weight loss), suggesting that total carbohydrate content adjusting pre-meal insulin infusion might be more important than GI in controlling postprandial glucose levels. However, low GI diets might be used as a treatment in T1DM in order to reduce the insulin infusions. The potential of a low GI diet in preventing diabetes has not been studied to date, but low GI diet may improve GC and reduce the risk of diabetes and its complications [4].

In another study, T1DM subjects (7–17 years old) were provided with four premade test meals, which were consumed at breakfast after a minimum 10 h overnight fast [16]. The low GI test meal had a GI of 48, meanwhile the one with high-GI test meal had a GI of 84. For the measurement of blood glucose, they used a continuous glucose monitoring system. The low GI meal produced significantly lower postprandial glucose excursion (PPGE) for 30–180 minutes, lower area under the blood glucose response curve (AUC), a smaller peak blood glucose excursion, and reduced time to reach baseline blood glucose levels compared with the high GI meal when preprandial ultra-short-acting insulin was administered. Nevertheless, the effect of GI on the postprandial glucose response requires further exploration in children receiving intensive insulin therapy [16].

A systematic review performed by Thomas and Elliott [2] in T1DM and T2DM children and adults, showed that GC in people with diabetes improved significantly with a low GI diet, by decreasing hypoglycaemic episodes, compared to those on higher GI diets or measured carbohydrate exchange diets. It was observed that a low GI diet produces a decrease of 0.5% HbA1c, clinically significant, similar to the reductions produce by the medications given to newly diagnosed T2DM subjects; as a result, it has been confirmed that a low GI diet is associated with a significant reduction in the risk of microvascular complications [2].

In 2010, these authors performed a meta-analysis with evidence that low GI diets significantly improve GC, by lowering HbA1c without any increase in the rate of hypoglycaemic episodes, when compared with a measured carbohydrate exchange diet and a high-cereal fibre diet. In other studies, low GI diet improved HbA1c levels in T1DM children; in contrast, T2DM low GI group presented a significant increase in insulin sensitivity compared to the high GI group.

The effect is sufficiently strong that may benefit diabetic patients by reducing or even avoiding their requirement for medication [10].

It is important to keep in mind that medications that improve blood glucose levels usually are associated with high risk of hypoglycaemia, which is the greatest barrier to achieve an optimal GC, particularly in T1DM. In people with T2DM a reduction in HbA1c levels after the consumption of low GI diets has been observed, whereas in children with T1DM, with both intensive multiple daily injection of insulin or insulin pump therapy, a reduction in postprandial glucose excursions, as well as improvements in insulin sensitivity after 3 to 4 weeks was demonstrated. However, a high GI diet worsens insulin resistance in individuals with and without diabetes and rises blood glucose levels and the need to medication in T2DM and the insulin requirements in T1DM. Therefore, the reduction of the risk of diabetes-related complications with low GI diets is similar to or greater than the diets including a high intake of fibre and whole grains [14].

A low GI diets favours slower and more gradual absorption of glucose from the gastrointestinal tract, avoiding hypoglycaemic episodes; moreover, it produces fewer stimuli for insulin release, reduces free fatty acids levels and oxidative stress, and increases insulin sensitivity [17].

According to the Canadian Diabetes Association, interventions replacing high GI carbohydrates with low GI carbohydrates in mixed meals have shown clinically significant improvements in GC over 2 weeks to 6 months in people with T1DM or T2DM; improvements were observed in cardiovascular risk factors, postprandial glycaemia and high sensitivity C-reactive protein over 1 year in people with T2DM, whereas adults and children with T1DM showed lower hypoglycaemic events over 24 to 52 weeks [20]. In addition, it has been shown that low GI diets sustain improved GC and HDL cholesterol compared with a high-cereal fibre diet over 6 months, and improved β-cell function in comparison with a low carbohydrate, high monounsaturated fat diet over 1 year in people with T2DM [20]. As it has been already mentioned, diets with lower GI result in improvements in HbA1c in the order of 0.5%. [19].

In contrast, a review carried out by Madsbad [49] in subjects with T1DM and T2DM showed different results. Dietary carbohydrate restriction as early therapy in T2DM, and as an adjunct to therapy in T1DM, effectively reduces blood glucose levels. However, longer-term studies (≥6 months) have variable results regarding the relative efficacy of low carbohydrate diets compared to low in fat or low GI diets on weight and HbA1c reductions. While recent meta-analyses suggest that low carbohydrate diets may be no more effective over the longer term than low fat or Low GI diets, in terms of weight and HbA1c changes [49].

It has been observed a reduction in the risk of diabetes with the consumption of low GI diet, whereas high dietary GI and/or glycaemic load increase the risk of T2DM [18]. Observational data suggest that replacing high GI with low GI carbohydrate reduces the risk of metabolic disturbances and T2DM. Nevertheless, some studies show inconclusive results that may be due to methodological differences and confounding parameters that can dramatically modify the post-meal metabolic response, such as the type of carbohydrate and its digestibility, quantity of carbohydrates as compared with other macronutrients, lipids, proteins and fibres [18].

Recent criticisms of the GI claim that GI methodology is not valid, and GI values are inaccurate and imprecise, and GI does not predict what foods are healthy and that whole grain and fibre are better markers of carbohydrate quality than GI. Eating a food as part of a mixed meal affects the glycaemic response, but does not alter the food's GI, because is an intrinsic characteristic of food. However, the glycaemic response of a food or a meal is altered in the presence of other foods depending on the amount and source (GI) of carbohydrate and the amounts and types of fat and protein added. Moreover, it is important to take into account that the relative glycaemic response of a meal is determined by its calculated meal GI and the amounts of available carbohydrates, fat and protein. Therefore, GI is a valid marker of carbohydrate quality because GI methodology is accurate and precise and GI is a property of the food, and is biologically meaningful and influences outcomes in health and disease, especially in the nutritional management of diabetes. Despite the fact that the results are inconclusive, there is no evidence to suggest any negative effect of following low GI diets, which are consistent with healthy eating recommendations aimed at weight control and reducing the risk of diabetes-related complications by improving the GC in people with diabetes (**Table 2**) [14, 15, 17, 49].

It should be noted that a traditional Mediterranean-style dietary pattern improves GC and cardiovascular risk factors, including systolic blood pressure, total cholesterol, HDL cholesterol, the total cholesterol/HDL cholesterol ratio and triglycerides in T2DM. On the other hand, a low carbohydrate Mediterranean-style diet has shown reductions in HbA1c and delays on the need for antihyperglycaemic drug therapy at 4 years of diagnosis, compared with low fat diet in overweight individuals with newly diagnosed T2DM. To sum up, traditional and low carbohydrate Mediterranean-style diets are shown to reduce HbA1c and triglycerides, whereas only the low carbohydrate Mediterranean-style diet improves LDL cholesterol and HDL cholesterol at 1 year of diagnosis in overweight subjects with T2DM [14, 20].

It has been shown that a disrupted balance between oxidative stress and antioxidant cascades contributes to neuroplasticity deficits in experimental models of diabetes; therefore, antioxidants treatments may provide excellent adjunct treatments to traditional approaches to reduce the neurological complications of diabetes. In a review carried out by Reagan, the neuroplasticity deficits were attenuated or eliminated by antioxidants, including melatonin and vitamin E, lycopene, resveratrol, dehydroepiandrosterone (DHEA) and essential fatty acids. T2DM patients supplemented with vitamin E and with increasing serum lycopene levels showed reductions in oxidative stress parameters, whereas DHEA administration showed reductions in plasma oxidative stress measures and lipid peroxidation products and increased antioxidants in T2DM subjects [12].

It is essential to take into account that the nutritional management in children and adolescents is more complex than in adults, because they do not have autonomy or the necessary knowledge to maintain a good GC. In a recent study carried out in 282 T1DM children and adolescents, a greater nutrition knowledge of parents and patients, measured by a type 1 diabetes Nutrition Knowledge Survey (NKS), was associated with both better GC and higher diet quality in their children. Therefore, it is vital an early nutritional education and the role of parents in order to achieve good nutritional management and GC during childhood [48].

	References	Low GI diet
T1DM	Rahelić, et al. [17]	• Lower fasting glucose • Reduction of oxidative stress
	Ryan, et al. [16]	• Lower PPGE • Lower AUC • Lower peak blood glucose excursion • Reduced time to reach baseline blood glucose levels
	Thomas, et al. [2, 10]	Acceptable/ Improved HbA1c levels
	Derdemezis, et al [4]; Dworatzek et al. [20]	Improved glycaemic control
	Thomas, et al. [2]; Marsh et al. [14]; Dworatzek et al. [20]	Lower hypoglycaemic events
	Marsh et al. [14]; Blaak et al. [18]	Reduced postprandial hyperglycaemia
		High GI diet
	Marsh et al. [14]	• Rapid rise in blood glucose and insulin levels • Increased insulin requirements • Increased postprandial glycaemia • Higher hypoglycaemic episodes
	References	**Low GI diet**
T2DM	Rahelić et al. [17]	Lower fasting glucose Reduction of oxidative stress
	Thomas et al. [2]; IDF* [19]	Decrease of 0.5% in HbA1c levels
	Thomas, et al. [10]; Marsh et al. [14]	Increased insulin sensitivity
	Thomas, et al. [10]	• Reduction or avoidance of diabetic medication • Significant reduction in BMI, total fat mass and body mass
	Thomas, et al. [2]; Derdemezis, et al. [2]; Dworatzek et al. [20]	Improved glycaemic control
	Thomas, et al. [10]; Marsh et al. [14]; Dworatzek et al. [20]	Improvement in lipid profiles *(total cholesterol, LDL-c and HDL-c levels)* and C-reactive protein
	Dworatzek et al. [20]	• Improvement in CV risk factors • Improved postprandial glycaemia
	Marsh et al. [14]	Reduced postprandial hyperglycaemia
	Derdemezis, et al. [4]; Thomas, et al. [10]	Significant weight loss in overweight/obese people

References	Low GI diet
	High GI diet
Marsh et al. [14]	• Rapid rise in blood glucose and insulin levels • Increased postprandial glycaemia • Higher need to medication • Fasting hypertriglyceridaemia • Lower HDL-c levels • Reduced fibrinolysis
Marsh et al. [14]; Rahelić et al. [17]	Increased insulin resistance
Marsh et al. [14]; Rahelić et al. [17]; Blaak et al. [18]	Increased risk of T2DM up to 40%

Area under the blood glucose response curve, AUC; body mass index, BMI; cardiovascular, CV; glycated haemoglobin A1c, HbA1c; high density lipoprotein cholesterol, HDL-c; low density lipoprotein cholesterol, LDL-c; postprandial glucose excursion, PPGE; type 1 diabetes mellitus, T1DM; type 2 diabetes mellitus, T2DM'International Diabetes Federation.

Table 2. Main effects of low and high glycaemic index diets on the nutritional management of diabetes in children and adolescents.

The previous nutritional recommendations are aimed to achieve a good GC and nutritional management in the long-term; nonetheless, it is necessary to address the acute dietary complications, meaning the management of hypoglycaemia, because it is the most common acute complication of the treatment of T1DM. In case of hypoglycaemia (<60–70 mg/dl) it is necessary an immediate oral, rapidly absorbed, simple carbohydrate to raise blood glucose up to 100 mg/dl [39].

Finally, the exercise is indispensable in the management of diabetes, especially in T2DM children and adolescents, due to this pathology is commonly associated with obesity. The American Academy of Paediatrics recommends that health care professionals encourage children and adolescents with T2DM to practice moderate to vigorous exercise for at least 60 minutes daily and to limit non-academic '*screen time*', such as watching television or playing computer games, to less than 2 hours per day for the reduction of BMI and the improvement of GC. Physical activity is an integral part of weight management for the prevention and treatment of T2DM. Although there is scarce available data from children and adolescents with T2DM, several well-controlled studies performed in obese children and adolescents at risk of metabolic syndrome and T2DM provide guidelines for physical activity [43].

5. Future prospects

Although, the optimal diet and macronutrient composition in diabetes remain controversial and the evidence is not sufficiently robust to recommend a low GI diet as the primary dietary

strategy for GC, low GI diets are high in fibre and whole-grain products, rich in legumes, fruits and vegetables with balanced fat profile, low saturated fats and high monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). Therefore, this nutritional intervention may have beneficial effects in diabetics and populations at risk, such as children with T1DM [4, 14]. Antioxidant treatments or diets rich in antioxidants may reduce the diabetes-related neurological complications, when they are used together with traditional treatments [12]. Given that there is no optimal diet for the management of GC in subjects with T1DM and T2DM, it would be interesting to study the effects of a low GI diet based in a traditional Mediterranean-diet pattern (rich in vegetables and fruits, high content in antioxidants and fibre), that had demonstrated to improve the GC in these subjects, to evaluate the power for preventing cognitive dysfunctions and to optimise the neurodevelopment in children and youth.

It is vital to perform more long-term studies in children and adolescents, especially in those with T2DM, due to the increased prevalence in this population, considering the scarce evidence for optimal management of children with T2DM [43]. On the other hand, it is essential to develop lifestyle interventions in population at risk during childhood and adolescence (individualised nutritional and exercise programmes), focused on investigating how to prevent the development of glucose tolerance impairment, and diabetes. These interventions could protect against cognitive decline, because they help to achieve GC, reducing hypo and hyperglycaemic episodes [44].

Furthermore, the clinical follow-up of T1DM children must include also a survey of neuropsychological and brain development to prevent long-lasting consequences.

6. Conclusions

Further research is needed in diabetic children and adolescents, especially well-designed long-term randomised controlled trials with larger sample size to determine the true value of low GI diets on overall quality of life, long-term GC and the prevention or management of diabetes-related complications. The results obtained up to the present moment are inconclusive due to discrepancies between the methods of analysis and the diversity in the methodology employed. Therefore, it is difficult to generalise results. It is necessary the use of validated questionnaires for the dietary assessment and standardised the GI databases in order to make the data comparable between different studies. One limitation of all observational studies published to date is that none of the food frequency questionnaires have been specifically designed to assess the GI and until recently, few were validated against another method of dietary assessment, such as 24 h recalls or diet records. Therefore, these questionnaires have poor ability to estimate carbohydrate intake, calling into question the accuracy of any GI or glycaemic load estimation [14]. On the other hand, the studies use different cognitive tests to assess cognitive domains. Therefore, it is difficult to compare results between studies. Brain imaging is becoming essential to clarify the effects of diabetes on brain development, and it will offer us new perspectives for the prevention of neurological disorders and mental health.

Covariates that could affect neurocognitive testing and should be taken into account are, age, education, sex, history of other chronic illnesses, psychiatric and neurological disorders, absence from school, socioeconomic status, and hypo/hyperglycaemia during testing. Most of the studies control for at least some of these covariates, but most fail to control all of them [34].

There is wide criticism and controversies about low GI diet. Some authors state that is easy to follow and effective, whereas other authors think GI is highly variable, not physiological and difficult to learn and follow. Despite this, GI concept is accepted by many diabetes associations around the world as an integral part of the dietary treatment of diabetes. Despite the controversy, there is substantial evidence that a low GI diet can improve the GC in subjects with diabetes. It is vital to carry out further research of the role of GI in the prevention and treatment of diabetes and its complications together with beneficial effects of a low GI diet [17]. One of the major controversies about GI is that different studies state that the GI of food change in the presence of other macronutrients, but the reality is that GI is an intrinsic characteristic of food. Therefore, the GI of food does not change in the presence of other macronutrients, such as lipids, proteins and fibre, is just the glycaemic response. It has been shown that proteins induce greater insulin secretion, while fats reduce gastric emptying and slow down the absorption of carbohydrate. It is essential to study the effects of protein, fat and fibre on the glycaemic response to a carbohydrate meal [15], especially in children and adolescents.

On the other hand, nutritional education and physical activity are essential in order to achieve a good GC of the disease. The main goal of diabetes management is to prevent long-term complications, not only cognitive dysfunction, also micro and macrovascular complications. More studies in cognitive function in diabetic children and adolescents with severe hypoglycaemia are needed, because preventing hypoglycaemia could reduce cognitive dysfunction [36], and improve healthy ageing in the diabetic patients. Long-term interventions will help also to know the impact of disease duration on cognition. More intensive diabetes medical regimes will be associated with less neurocognitive deficits, especially in patients with an EOD because they are more expose through time to glycaemic extremes (hypo and hyperglycaemias). It is vital to identify the factors that are involved in the aetiology and progression of the neurological complications, because currently the pathophysiology of cognitive dysfunction in diabetes is not well understood [1]. Therefore, it is important to understand the pathogenesis of cognitive dysfunction secondary to diabetes in order to establish more efficient treatments and prevent or reverse these cognitive alterations [34]. Thus, further well designed human studies are needed to elucidate the pathophysiology and the mechanisms of action of cognitive dysfunction through neuroimaging [3].

In conclusion, it is necessary to carry out well designed long-term intervention randomised control trials with larger sample size, detailed cognitive assessment combined with neuroimaging [7] and adequate dietetic management. Furthermore, it is essential an early dietetic intervention in order to prevent or reduce diabetes-related complications, especially in children and adolescents with an EOD, because they are exposed through time to glycaemic extremes and are more vulnerable than adults, because their CNS is developing and any damage could be irreversible. Finally, it is important to identify population at risk during early life and childhood in order to develop clear recommendations, prevent the development of diabetes and promote healthy ageing.

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Abbreviations

ADHD	attention deficit hyperactivity disease
AGEs	advanced glycation end products
AUC	area under the blood glucose response curve
BMI	body mass index
CDC	Centres for Disease Control
CNS	central nervous system
DHEA	dehydroepiandrosterone
DM	diabetes mellitus
EEG	electroencephalography
EOD	early onset of diabetes
GC	glycaemic control
GDM	gestational diabetes mellitus
GI	glycaemic index
GPA	gluco-psychosocial axis
HbA1c	glycated haemoglobin A1c
HDL-c	high density lipoprotein cholesterol
HPA	hypothalamic-pituitary-adrenal
IQ	intelligence quotient
LDL-c	low density lipoprotein cholesterol
LOD	late onset of diabetes
MUFAs	monounsaturated fatty acids
NKS	Nutrition Knowledge Survey
PPGE	postprandial glucose excursion
PUFAs	polyunsaturated fatty acids
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WHO	World Health Organisation

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