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Review

Diabetic central neuropathy: A complication of diabetes that affects cognition

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ABSTRACT

Diabetes mellitus is one of the most prevalent chronic health problems in humans. Its prevalence increases from 10% in people < 65 years to 12% in people < 70 years, and to 15% in people over 80 years of age. People with diabetes are identified by their blood glucose levels being higher than 'normal'. This chronic metabolic abnormality is associated with pathologic changes involving both small and large blood vessels, causing eye, kidney, and myocardial failure, as well as loss of lower limbs. A more subtle complication associated with the hyperglycemia of diabetes mellitus is cognitive dysfunction, which should be termed diabetic central neuropathy, which currently is not generally recognized. It now appears that diabetes, with resulting exposure of the brain to chronic elevated glucose levels, results in slowly evolving neurodegenerative changes. Intelligence is noted to be reduced to the lower end of the average range; psychomotor processing speed, mental flexibility and attention are specific skills that are impaired in subjects with chronic hyperglycemia. The recent recognition of a greater prevalence of silent type 2 diabetes in subjects with Alzheimer's disease has suggested a cause and effect relationship between the two. All Individuals with Down's syndrome are believed to develop Alzheimer's disease. Subjects with trisomy 21 have also been observed to have elevated levels of Inositol in their brains. Laboratory animals as well as humans with chronic hyperglycemia (diabetes) have also been noted to have elevated Inositol levels in the hippocampal region of the brain. This elevated Inositol level has been linked to increased hippocampal amylin production and deposition. Amylin aggregates may be the cause of the dendritic tangles associated with Alzheimer's dementia. This association may be a consequence of chronic hyperglycemia that should not be overlooked when managing older patients with diabetes mellitus. Prevention of Alzheimer's dementia should be added to the list of reasons for prescribing the best metabolic control of diabetes in all patients who have diabetes mellitus, regardless of age.

KEYWORDS: diabetes mellitus, central neuropathy, hyperglycemia, reduced cognition, Alzheimer's disease

INTRODUCTION

The prevalence of diabetes mellitus increases from 10% in people < 65 years to 12% in people < 70 years, and 15% in people over 80 years of age [1]. Clinical diabetes mellitus has been associated with structural and functional damage to the brain [2], but the nature and extent of these abnormalities, or the relevant biomedical risk factors are not currently established. Meta-analytic reviews have documented subtle neurocognitive deficits in pediatric [3] and adult [4] populations with type 1 diabetes mellitus. Basic intelligence, psychomotor processing speed, mental flexibility

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and attention are specific skills that are noted to be reduced [4]. Memory and learning skills in children with early-onset diabetes have been noted to be impaired [5], particularly in those with a history of severe hypoglycemia [6]. Neurophysiologic studies provide further evidence of central nervous system (CNS) changes in type 1 diabetes. Cerebral hypo-perfusion has been documented in adolescents [7] and in young to middle aged adults [8] with no clinical evidence of cerebrovascular degeneration commonly observed in elderly patients with type 1 diabetes. EEG studies have shown increased delta and theta slow-wave and decreased alpha peak frequencies in both adults [9] and children [10] with diabetes. Increased response latencies, suggestive of slow mental processing, have also been found in evoked potential studies [11]. This observation was particularly evident in individuals with early-onset disease and/or a history of severe hypoglycemia [11]. A small number of structural neuro-imaging studies have demonstrated that patients with type 1 diabetes have reductions in brain grey matter, micro structural damage to brain white matter and alterations in levels of brain neuro-metabolites (particularly glutamate). These changes appear to be related to elevated HbA1c levels. A recent clinical report suggests that high levels of glucose (HbA1c) are associated with greater cognitive decline as demonstrated during a 12 year evaluation [12].

Brain dysfunction is also associated with coincident low blood glucose levels. Not only are there modest reductions in cognitive efficiency, but also there is evidence of central brain wave slowing measured using electroencephalography. Reduced evoked potential studies have been attributed to changes in cerebral blood flow that is associated with low blood glucose [10]. These abnormalities are transient and completely resolved with the return of normal blood glucose levels. As with the structural CNS damage, there is little agreement as to which biomedical factors increase the risk of the functional changes. Although a growing body of literature has indicated that patients with higher HbA1c levels are more likely to manifest permanent neurocognitive dysfunction, one cannot yet rule out the possible contributory role of recurrent, moderately severe (subclinical) hypoglycemia.

We have known for a long time that children with diabetes mellitus onset before 5 years of age have permanent neurocognitive dysfunction more commonly than age-matched peers or siblings [13, 14]. One study has shown that children with diabetes onset before the age of 7 have reduced intellectual performance and mild central brain atrophy during adulthood when compared with individuals with similar duration of diabetes but later onset [15]. Because both hyperglycemia and hypoglycemia occur in young children with type 1 diabetes, it is unlikely that hypoglycemia is the only cause of this recognized but little publicized reduction in cognitive function associated with early childhood diabetes. The brains of children and adolescents with type 1 diabetes have a much greater exposure to hyperglycemia (clinically unrecognized) than hypoglycemia (clinically obvious). A recent report indicates that adults (18-50 years of age) with type 1 diabetes of more than 10-year duration have MRI (magnetic resonance imaging) evidence of reduced brain volume [16]. Other reports provide evidence of structural changes in the brains of adults with type 1 diabetes mellitus [17]. Many believe that the critical period for the effect of hyperglycemia is in subjects older than middle age [18]. There is evidence, however, that shows cognitive decline is associated with hyperglycemia during mid-life [19].

Mechanism of brain injury

Hyperglycemia is known to adversely affect peripheral nerve structure and function in younger (3-6 months) but not in older rats [20]. Physical and functional damage to peripheral nerves associated with diabetes is influenced by the level of nerve developmental maturation at the age that hyperglycemia becomes manifest, as well as the increased activity of the polyol pathway [21]. The polyol pathway is a minor pathway of glucose metabolism that increases the intracellular content of the polyol sorbitol in response to increased extracellular glucose concentrations. The increase in intracellular sorbitol has been associated with cellular tissue damage [22]. This damage is believed to be caused by either the increase of intracellular osmolality or the reduction of the cellular redox state. The reduced redox state makes the cells more susceptible to oxidative

damage [23]. Increased intracellular sorbitol elevates the cellular osmolality because it doesn't readily cross cell membranes and accumulates within cells. This situation, however, causes a reduction in intracellular taurine, a common osmole regulator, which is also an important antioxidant [24]. Taurine has also been shown to be an important neurotrophic factor in the retina and brain [25]. Increased activity of the polyol pathway in the peripheral nerve has also been associated with reduced intracellular inositol, a major component of phospholipids which play a major role in regulating neurotransmitters [21]. Moreover, increased activity of the polyol pathway has been reported to reduce the production of nerve growth factor from Schwann cells, which could also be a mechanism for reduced neuronal growth [26]. These observations point toward several mechanisms for brain injury that may be associated with hyperglycemia and its resulting increased activity of the polyol pathway. There are studies, however, that indicate that chronic peripheral hyperglycemia may down-regulate glucose transport across the blood brain barrier and thereby prevent the brain from being exposed to the higher glucose concentrations found around the peripheral nerves of subjects with diabetes [27]. This potential protection of the brain from hyperglycemia could reduce the degree of pathology in the CNS when compared to the peripheral nervous system.

To determine whether the blood brain barrier would protect the brain from peripheral hyperglycemia we made rats hyperglycemic for 2 months following the administration of streptozotocin [28]. It was then demonstrated that the increased peripheral blood glucose concentrations in rats were associated with increased intracellular sorbitol and inositol levels in the rat cerebral cortex and hippocampus [28]. This increase in brain sorbitol level was associated with a reduction in taurine in the cortex and hippocampus (Table 1). This indicated that the blood brain barrier did not protect the brain from elevations of peripheral blood glucose levels. Thus, peripheral hyperglycemia altered the activity of the cerebral polyol pathway sufficiently to increase brain sorbitol content. This resulted in a compensatory reduction in brain taurine to maintain tissue osmotic balance [28]. This reduction in neurotrophic taurine could alter the structure and function of maturing brain neurons. Taurine deficiency causes retinal degeneration and CNS dysfunction [29]. Taurine is believed to be a trophic factor for normal neuronal growth [30]. The reduction in brain taurine may play a role in the neuronal changes that we have noted

Table 1. Brain chemistry.

	Control	**Hypoglycemic**	**Hyperglycemic**
Number of animals	20	20	20
Weight gain/week	17.43 ± 1.2	17.82 ± 1.3	13.2 ± 1.8*
HbA1c (%)	3.5 ± 0.04	3.4 ± 0.04	9.1 ± 0.17*
Cortex			
Sorbitol/protein (μM/mg)	5.84 ± 1.0	5.54 ± 1.0	7.5 ± 1.6*
Inositol/protein (μM/mg)	7.1 ± 1.1	7.5 ± 0.9	9.6 ± 1.4*
Taurine/protein (mg/mg)	1.3 ± 0.09	1.1 ± 0.08	0.65 ± 0.1*
Hippocampus			
Sorbitol/protein (μM/mg)	10.88 ± 1.81	8.13 ± 1.0	17.23 ± 3.25*
Inositol/protein (μM/mg)	28.05 ± 6.3	29.34 ± 3.8	36.43 ± 8.3*
Taurine/protein (mg/mg)	1.15 ± 0.54	1.17 ± 0.42	0.91 ± 0.38*

Results are mean ± SEM.
*Different from control, $p < 0.05$.

and described below. Another unusual biochemical observation in this experiment was the increase in brain inositol level in association with increased levels of sorbitol. It has been frequently reported that peripheral nerve inositol decreases when intracellular sorbitol is increased [21]. This has been attributed to reduced intracellular transport of inositol when extracellular glucose is elevated. Others explain the reduced inositol level as an osmotic response similar to taurine caused by the increase in intracellular sorbitol levels [31]. Thus, the finding in our experiment of increased level of hippocampal inositol was unexpected, but this has been observed by other investigators [32, 33]. The explanation for this difference is increased production of glucose-6-phosphate in the brain with resulting increases in endogenous intracellular inositol production [32]. Since this mechanism is also present for peripheral nerves, something unique to the central nervous system must be in play. Inositol is found primarily in central nervous system glial cells. Increased levels of inositol are thought to reflect gliosis, a known process associated with Alzheimer's disease pathology [34]. The associated elevation of glucose and inositol in the brains of subjects with diabetes may indicate a toxic process with reactive proliferation of glial cells in response to damage in the central nervous system.

Brain structure and function

The clinical management of diabetes is an ongoing battle between blood glucose levels that are too high and those that are too low. This is particularly true when dealing with type 1 diabetes. Current belief is that high glucose levels are more desirable and safer for the brain than low blood glucose levels. It is believed that hypoglycemia damages the brain and hyperglycemia has little significant effect on brain structure and function. We have looked at this question with an animal model of diabetes and hypoglycemia. Structurally our data indicate that the metabolic milieu associated with hyperglycemia is associated with reduced neuronal size [35] and reduced dendritic branching and spines in the brains of 4-week-old Wistar rats exposed to hyperglycemia for an additional 8 weeks [36]. This group of animals was compared to a group of normal littermates exposed to hypoglycemia (2.5 ± 0.21 mmol/L) 3 days each week for 8 weeks. This degree of hypoglycemia was well below that shown to impair cognitive function (3.3-3.6 mmol/L) in humans [37]; it lasted for at least 3 hours each day, and was associated with reduced physical activity but no recognized motor seizures. This is the type of hypoglycemia that clinicians are typically concerned about in patients because it is much more common and less well recognized than hypoglycemia-induced seizures. The hypoglycemic exposure of these study animals was more intense than previously reported [38]. Our animals had a reduction in the ability to solve a water maze while they were hypoglycemic, but they demonstrated normal-to-improved cognitive performance when tested with normal blood glucose levels. No structural abnormalities were noted in the brains of these animals after 8 weeks of intermittent (3X/week) hypoglycemia. The animals in the earlier experiment [38] had their blood glucose lowered to approximately 2.8 mmol/L for 3 hours once a week. Those animals were tested every 3 months for 1 year, and no abnormalities in the structure or function of the brain were noted at the end of that experiment. These studies suggest that recurrent, intermittent subclinical hypoglycemia does not cause long-term permanent damage to the central nervous system.

The dendritic arbor comprises over 95% of the volume of the typical cortical neuron [39, 40], and the vast majority of excitatory synapses are on dendritic spines [39]. Dendritic branch atrophy and spine loss have previously been associated with cognitive dysfunction in humans and rodents [41-43], and this reflects a breakdown or disruption of brain circuitry. The study, evaluating the effects of hyperglycemia and hypoglycemia demonstrated that hyperglycemia, not hypoglycemia, was accompanied by dendritic atrophy and spine loss in the layer II-III pyramids of the parietal cortex, and this could be the underlying neuroanatomical basis for the memory loss observed. In addition, it was found that the M-type, L-type, and N-type spines (but not the D-type spines) showed a reduction in spine density in the diabetic animals. Although the specific functions of the different spine types remain unclear, M-type and L-type spines appear to be more closely related to specific learning and memory functions [44, 45]. Hence, their loss could be regarded as being

particularly related to the impaired memory seen in these hyperglycemic rats. Moreover, it is known that the parietal cortex plays a role (along with hippocampus) in memory functions [45], and there are significant circuits connecting the parietal cortex with the hippocampus [46]. In these studies, the biochemical and physical changes found in animals with hyperglycemia were also associated with reduced long-term spatial memory, an indicator of hippocampal function. Parallel studies failed to demonstrate any biochemical, structural, or functional damage in the brains of Wistar rats exposed to hypoglycemia (glucose 46.1 ± 3.1 mg/dl for 3 hours 3 days a week) for the same 8-week interval. This suggests that chronic hyperglycemia is more damaging than intermittent hypoglycemia to the structure and function of maturing brains in rats between 4 and 12 weeks of life.

Another brain structural measure, neuroimaging, is an Alzheimer's disease biomarker. Neuroimaging has been included in the most recent National Institute of Aging-Alzheimer's Association consensus recommendations on diagnostic guidelines [47]. Atrophy on structural MRI is an accepted biomarker for clinical and neuropathologic progression of Alzheimer's disease [48]. This methodology unfortunately only reveals a manifest process after the occurrence of loss or shrinkage of neurons and synapses. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive neuroimaging technique that quantitatively measures metabolite changes that are associated with Alzheimer's disease type pathology [49]. ^{1}H-MRS has shown that inositol level is increased and is associated with the occurrence of amyloid-β plaques in patients with Alzheimer's disease [50]. Using data from high resolution T-1 weighted magnetic resonance it has been determined that type 1 diabetic subjects have dysfunctional cortical organization that adversely affects memory and emotion [51].

Glucose as a neurotoxic agent

Large amounts of glucose are required to maintain normal neural/glial function in the central nervous system. Glucose is essential for the normal maturation, function and maintenance of the central nervous system. Various toxic agents alter the morphology of neurons in the hippocampus, a region of the brain specializing in long-term memory and spatial navigation [52]. This part of the brain is especially vulnerable to conditions that compromise metabolic efficiency. It has been reported that 10 weeks of excessive glucose (untreated diabetes) causes impaired spatial learning in rats [53]. This impairment was not noted in animals exposed to lower blood glucose levels for the same length of time. It has been noted by McEwen, however, that animal models of type 1 diabetes show accelerated remodeling of neuronal dendrites [54]. Hyperglycemia induced by streptozotocin (STZ) in rats produced retraction and simplification of apical dendrites of hippocampal neurons and exacerbated oxidative damage to neurons of the hippocampus and the neo-cortex [53]. Behaviorally, these changes in the hippocampus and neo-cortex may be reflected as memory deficits. Studies involving behavioral assessment typically reveal a strong correlation between neuronal spines and/or branching atrophy and cognitive dysfunction, further emphasizing the role of these dendritic parameters on learning and memory [55]. Thus, the Golgi impregnation approach for studying dendritic anatomy is invaluable for revealing these changes, specifically as it reveals the soma and dendritic arbor of neurons. Because the dendritic tree makes up about 95% of the volume of the typical neuron, quantitative analysis of dendrites can reveal subtle changes in both dendritic atrophy and neuroplasticity [56]. Such a damaged dendritic anatomy was observed in an animal model of diabetes [56] where the animals were exposed to the same level of hyperglycemia as observed in typical adolescent children with diabetes reported to have the same HbA1c levels [57]. This clinically relevant excessive glucose level has now been shown to damage neurons and glial cells in the central nervous system [56].

Sustained metabolic abnormalities during normal brain development have been accepted as a cause of permanent cognitive dysfunction in children. Following developmental maturation of the brain, metabolic insults appeared to have little long-term effect on CNS function. Adults with chronic hyperglycemia (Diabetes) have not been observed, until recently [58-60], to have any greater

cognitive decline when compared to non-diabetic peers. That concept has now changed with improving clinical evaluations.

Hyperglycemia and aging

Diabetes mellitus is a common condition in older people, with normal brain development and function, affecting about 12% of persons older than 65 years [1]. In cross-sectional studies, diabetes mellitus has been shown to be associated with various adverse health effects, including cognitive impairment. The association of diabetes mellitus with progressive cognitive impairment suggests a relationship with Alzheimer disease. However, very few prospective studies have examined the relationship between diabetes mellitus and the incidence of Alzheimer's disease. The results of these studies have been inconsistent. Some studies [61, 62] have shown that persons with diabetes mellitus are at increased risk for Alzheimer's disease whereas others [63, 64] have not found that association. A longitudinal cohort study evaluated 824 individuals over 55 years with annual clinical evaluations for 9 years and found that those with diabetes had a 65% greater risk of developing Alzheimer's disease compared to those without diabetes mellitus and concluded that diabetes mellitus is associated with increased risk of developing Alzheimer's disease [65].

It has been observed that humans with trisomy 21 have a 100% risk of developing Alzheimer's disease [66]. It has been reported that increased level of hippocampal inositol is associated with reduced cognitive function in adults with Down's syndrome [66]. The elevated inositol level has been linked to increased hippocampal amylin production and deposition. This is a possible mechanism for the dendritic tangles of Alzheimer's dementia. The increased levels of inositol found in subjects with Down syndrome (trisomy 21) have been attributed to increased activity of the sodium/myoinositol co-transporter gene which is localized to chromosome 21 and therefore has greater activity with resulting accumulation of inositol.

Laboratory animals [36] and humans [67] with diabetes mellitus have been noted to have elevated levels of inositol in their brains. This suggests a possible common mechanism and a possible link between diabetes central neuropathology and Alzheimer's disease. The increased availability of glucose to the CNS of diabetics has been cited as a mechanism for the increase of inositol content in the brains of diabetic subjects [30]. The pathogenic mechanisms that cause increased levels of inositol in the brains of individuals with trisomy 21 and those with diabetes (hyperglycemia) appear to be different. The elevated inositol level, as noted above, may reflect either a metabolic or cellular response to some abnormal process in the central nervous system. The elevated levels of inositol in the brain however, have been reported to be a nidus for the polymerization of amyloid-β peptide which enhances plaque formation in the brain [68]. It has also been proposed that amyloid-β peptide causes neurotoxicity linked to the formation of neuronal fibrils associated with the pathology of Alzheimer's disease. Using proton magnetic resonance spectroscopy it has been shown that the myoinositol/creatinine ratio is higher in the gray and white matter of brains in subjects with diabetes than non-diabetic controls of the same age [69]. Another study has shown that there is a negative correlation between brain myoinositol/ creatinine ratios and executive function tests in humans with diabetes [70]. This suggests that increases in the levels of myoinositol can be used as a biomarker of pathologic cognitive decline which can differentiate this impairment from normal aging. These metabolic and functional associations suggest that the hyperglycemia of diabetes mellitus may play a functional role in the pathogenesis of cognitive decline and Alzheimer's dementia.

CONCLUSION

Thus, diabetes mellitus (hyperglycemia) appears to play an important role in permanent structural and functional damage to the central nervous system that results in significant impairment of cognition in the young developing brain. In addition hyperglycemia appears to enhance degeneration in the aging mature brain with resulting Alzheimer's disease. This central diabetic neuropathy is an important cognitive complication of diabetes mellitus at any age. This complication of diabetes reduces productivity and quality of life of many subjects with diabetes mellitus and may contribute

to the basic pathology associated with Alzheimer's disease. Normalization of blood glucose levels is therefore an important goal for patients of all ages trying to prevent diabetic central neuropathy.

CONFLICT OF INTEREST STATEMENT

The author has no affiliations with or involvement in any organization or entity with any financial interest, membership, employment, consultancies, stock ownership, or other equity interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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