Glycaemia, cognition, and type 2 diabetes

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Due to policy boundaries, the full paper cannot be shown. Instead, this paper provides an explicatory background and a short discussion on previous literature concerning outcomes and pathophysiological theory.

Background/Relevance
Cognitive impairment is common in the elderly, with an estimated prevalence ranging from 1% to 29%(1, 2). This prevalence is expected to increase dramatically over the next decades(1). Dementia, the most profound form of cognitive deterioration, is one of ten leading causes of reduction in disability-adjusted life years (DALYs) and increased mortality(3).

Cognition and glucose
Cognition reflects various mechanisms that animals, and thereby humans, use to exploit information from the environment including acquisition, processing, storing and acting on environmental stimuli(4). These mechanisms are generally known as, inter alia, learning, memory, and perception. Note that cognition does not equal intelligence, as cognition is a more fundamental behavioral aspect whilst intelligence is the ‘cleverness’ of the behavior as compared to the pre-specified goal(4).
Cognitive functioning is divided along several networks; a spatial attention network (e.g. eyes), a language network (e.g. Wernicke’s and Broca’s areas for speech and language), a memory-emotion network (e.g. hippocampus and amygdala), an executive function network (e.g. frontal cortex) and an identification network (e.g. temporal cortex)(5). When these cognitive functions are no longer properly executed, we refer to it as cognitive impairment. Cognitive impairment is the transitional phase between normal cognitive functioning and frank dementia, including Alzheimer’s Disease(6, 7). Compared to people with dementia, people with (mild) cognitive impairment have a preserved basic functionality(7-9). Importantly, cognitive impairment is a change in cognitive performance rather than a bad score as compared to a population’s mean(7).
Despite former research, the aetiology of cognitive impairment is rather unknown but thought to be multifactorial\(^{10-13}\). A possible role may be reserved for glucose, as the above-mentioned brain structures utilize high doses of glucose compared to other brain structures\(^{14}\). Glucose is the primary fuel source for the brain, and brain glucose consumption comprises 25% of the body’s total consumption\(^{13, 15, 16}\). As such, glucose may influence brain function through various mechanisms. For example, glucose is known to be involved in the glycolytic and oxidative metabolism, essential for neuronal function and survival\(^{16}\). In addition, cerebral glucose plays a role in the synthesis of neurotransmitters that are involved in cognitive functioning (e.g. via acetyl-CoA as a precursor), and particularly in memory function (e.g. γ-aminobutyric acid, glutamate or acetylcholine)\(^{16-18}\). Additionally, adenosine triphosphate (ATP; generated from glucose), is involved in storing, releasing and re-uptake of neurotransmitters (e.g. glutamate), and also regulates their functioning\(^{16}\). Indeed, previous research has shown that glucose consumption can improve memory function\(^{17, 19, 20}\) and is able to reduce cognitive deficits associated with ageing\(^{17}\).

**Hypoglycaemia and hyperglycaemia**

Although glucose levels within a normal range might enhance cognitive functioning, abnormal levels may differentially affect brain function. Glucose levels are considered normal when they are within a range that has a low risk for development of diabetes and/or cardiovascular disease\(^{21}\). Hyperglycaemia (a state of high levels of glucose) is known to be glucotoxic to neurons as complete oxidation of carbohydrates yields the production of deleterious radicals, presenting as reactive oxygen species (ROS)\(^{22, 23}\). Apart from ROS production in energy metabolism, glucose also undergoes auto-oxidation in the presence of metal ions\(^{24}\). Although the brain has several mechanisms to clear ROS (e.g. glutathione), increased glucose and ROS levels deplete these mechanisms, ultimately leading to oxidized, and dysfunctions proteins\(^{24}\). This oxidation also induces lipid peroxidation, a self-maintaining process of oxidation of membrane lipids, and eventually proteins\(^{24}\). High levels of glucose also increase the production of advanced glycosylation end products (AGEs)\(^{22}\). AGEs may interfere with functional proteins (e.g. tubulin and Na\(^{+}/\)K\(^{-}\)-ATPase) that are essential for memory (in terms of synaptic plasticity) and general neuronal function\(^{24}\). Both ROS and AGEs negatively influence brain function and are even interrelated\(^{22, 24}\). Apart from hyperglycaemia, hypoglycaemia (a state of low levels of glucose) might also give reason for cognitive deterioration as it conveys necrosis due to energy starvation (e.g. ATP is needed for neurotransmitter re-uptake and synthesis), and alkalosis (due to reduced production of lactate via glycolysis)\(^{25}\). In the absence of
energy (i.e. ATP) glutamate will induce excitotoxicity as a result of sustained receptor stimulation(26). This causes ROS (e.g. peroxynitrite) accumulation, DNA damage, and induction of apoptosis through PARP and AIF pathways(26). Mentionable, neuronal cell death is prevented with PARP inhibitors(27).

**Type 2 Diabetes Mellitus**

Taking the above into account, both normal and abnormal glucose levels can be linked to cognitive functioning. Importantly, cerebral effects of glucose might differ with the presence of type 2 diabetes mellitus (T2DM). In people without T2DM, the pancreas is able to maintain glycaemic homeostasis and it thus keeps glucose levels within normal range. Therefore, glucose could have the proposed positive effects on cognitive functioning in people without T2DM. In case of T2DM, however, the pancreas is no longer able to counteract for insulin resistance with sufficient insulin secretion. This causes elevated glucose levels with possible damaging effects to the brain. Moreover, recent research has shown that the brain is sensitive to insulin(28). As such, insulin resistance in people with T2DM might alter the cerebral availability of both insulin and glucose(24). Therefore, the extent to which glucose influences cognitive functioning can differ with glucose metabolism status, as glucose and insulin functions are interrelated.

**Influential factors**

Several cardiovascular risk factors are known to be associated with cognitive functioning, and are more prevalent in people with T2DM(23, 29, 30). These factors, including hypertension, dyslipidaemia and central obesity(23, 30-32), are important to take into account when investigating the relation between markers of glycaemia and brain function. Obesity increases the risk of glucose intolerance (linking it to diabetes), and cognitive decline, but it is also correlated with hypertension and dyslipidaemia(29). Hypertension is associated with glycaemic markers, and cognitive functioning through pathologic microvascular changes(33). Dyslipidaemia co-exists with other confounders within obesity and T2DM, and is thought to influence memory function possibly due to interaction with the NMDA-mediated long term potentiation process(34, 35). Even so, the presence of depressive symptoms might confound the link between glucose and cognition as depression is associated with both a decline in cognitive functioning and hyperglycaemia, possibly due to cortisol abnormalities, and weight gain(36-38).
Goal and hypothesis
The goal of this thesis is to investigate the relation between markers of glycaemia (i.e. HbA1c, fasting glucose, post-load glucose), and cognitive functioning. Former research has been done concerning this question, but mainly focused on either people with or without T2DM(32, 39, 40). In addition, these studies did often not adequately adjust for potential confounders and/or did not consider the possibility of non-linearity.

The following research questions were postulated: [1] What is the relation between markers of glycaemia and cognitive functioning in the absence and presence of T2DM, while taking in account the possibility of non-linearity? [2] Is this relation, if present, independent of vascular risk factors?

We hypothesized that measures of glycaemia are related to cognitive functioning, and that this relation differs with the presence of T2DM. In people without T2DM, the relationship between glucose-related variables and cognitive functioning was expected to be positive, flattening into a plateau for higher glucose levels (in the normal range)(41). In people with T2DM, we expected that the relationship between glucose-related variables and cognitive functioning might resemble an inverted U-shape(42). Finally, the relation between measures of glycaemia and cognitive functioning was expected to be, at least partly, independent of cardiovascular risk factors (e.g. hypertension and hypercholesterolemia).

Previous literature and pathophysiology
Previous studies on this subject were inconclusive. Some studies found HbA1c to be significantly correlated to memory in a linear fashion(32, 43), while others were not able to detect such a relationship(40). A statistically significant relationship between fasting glucose and memory function has been reported previously, but in a negative linear fashion(44). Other studies also examined the relationship between markers of glycaemia and memory in a linear fashion but found no significant relationship(32, 40).

The possibility of a non-linear patterns between markers of glycaemia and cognitive functioning has been investigated by a few studies(45, 46). These studies primarily focussed on processing speed and fluid intelligence, but not on the cognitive domains examined in the present study. Nonetheless, these studies did find significant non-linear (inverted U-shaped) relationships between fasting glucose levels and processing speed(45), and fluid intelligence(46).

From a pathophysiological point of view previous findings indicate a link between glucose levels and cognitive functioning. As highlighted in the introduction section, cognitive functions are executed in various structures within the human brain. These structures, reaching from cortex regions to the more centrally positioned hippocampus, all have
a notable glucose consumption. Glucose is of great importance for these structures as it is involved in both their energy supply through ATP production, and more functional aspects through neurotransmitter synthesis, and re-uptake. When retained within the proposed normal range, glucose can be beneficial in terms of increasing survival and function of neurons. But when, in case of T2DM, glucose levels are dysregulated, hypo- and hyperglycaemia may impose the more deleterious character of glucose. Hence, as described before, extreme low levels of glucose may cause excitotoxicity and energy deprivation, whilst extreme high levels cause neuronal damage through radicals and glycosylation products. The observed relationships between glucose levels and cognitive functions were prominent for memory function. Because the hippocampus is the most important structure for memory, and requires high glucose levels for normal functioning, deleterious effects of glucose in the brain might be most obvious in this structure. Indeed, previous research has shown an association between hippocampal volume and glucose levels, where higher levels of glucose were associated with decreased hippocampal volumes(43).

Future recommendations
In the future, a study on a population with a large sample size, containing both people with and without type 2 diabetes, can adequately assess the possibility of a relation between markers of glycaemia and cognitive performance. Also, a longitudinal study is recommended, as a cross-sectional study does not allow conclusions about causality.

Role of the student
Danny Claessens was an undergraduate student in Biomedical Science who performed this research project at the Maastricht Study of the Maastricht University Medical Center under the supervision of S. Geijselaers and S. Sep.

References


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