INTRODUCTION

On 3 November 1906 in Munich, the neuropathologist Alois Alzheimer first reported the presence of (i) neurofibrillary tangles in neurons of the cortex and hippocampus, and (ii) extracellular cerebral deposits of amyloid in “presenile dementia”, later identified as Alzheimer’s disease, a catastrophic brain damage leading to loss or decline in memory and other cognitive abilities. Dementia is a common problem affecting older persons. In the UK alone, it is estimated that nearly 700,000 people have dementia, while worldwide this figure approaches 30 million individuals, including patients with Alzheimer’s disease (1). The direct and indirect costs of Alzheimer’s and other dementias in the United States amount to more than 148 billion dollars each year. Over 2 million of the United Kingdom population are diagnosed with diabetes mellitus, type 2 diabetes being a prominent expression of the disease.

Over the last few years, a large number of articles have drawn attention to the association between dementia and type 2 diabetes mellitus. A causative link between Alzheimer’s disease and diabetes has been suggested based on clinical and epidemiological studies. One hypothesis is that the link is related to the function of insulin-degrading enzyme, an enzyme that degrades not only insulin and pancreatic amylin but also amyloid-beta peptide (Aβ) (2). A systematic review of 25 longitudinal studies of cognitive function changes related to
diabetic status found that compared to non-diabetics, diabetics have both a greater risk and rate of cognitive decline (3). A study of a further 19 case-control studies examining cognitive function in type 2 diabetes came to the cautious conclusion that cognitive decline in diabetics may be due to metabolic abnormalities intrinsic to diabetes (4). A further systematic review of longitudinal population based studies has also found that any form of dementia is more frequent in diabetics and proposed 3 broad potential causes: vascular disease, alterations in glucose and insulin, and alterations in amyloid metabolism (5).

Taken together, these studies give strong support to the observation that cognitive decline is more common in diabetic compared to non-diabetic subjects. Naturally, this makes us ask ourselves; why should this be? Let us look briefly at the 3 potential causes proposed above and one other which may provide a link between all 3 – cholesterol.

**VASCULAR DISEASE**

Diabetes can be considered as a cardiovascular (cardiometabolic) disease, the risk of atherosclerotic disease being higher in diabetic versus non-diabetic patients. Higher than optimum blood glucose levels is a leading cause of cardiovascular mortality in terms of ischaemic heart disease and also stroke (6). Meta-analysis has shown that attempts to improve glycaemic control also reduce macrovascular complications of diabetes (7). Vascular dementia is a common cause of dementia in the elderly, second only to Alzheimer’s disease. It is defined as loss of cognitive function resulting from ischaemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular disease. A large clinical trial is currently under way to assess whether tight glycaemic control reduces the incidence of either Alzheimer’s disease or vascular dementia (8). Vascular dementia and Alzheimer’s disease both give rise to dementia, however they have distinct pathologies. This would suggest that vascular changes alone are not sufficient to explain a link between diabetes and dementia, especially when linked to Alzheimer’s disease.

**HYPOGLYCAEMIA**

Insulin dependant, type 2 diabetics are at an increased risk of periods of hypoglycaemia. This risk increases with tighter glycaemic control regimes, which at the same time reduce the risk of vascular and neuropathic complications of diabetes. An inappropriately high insulin level leads to hypoglycaemia. The brain relies on glucose as a fuel source. The effects of hypoglycaemia upon brain function are profound, reversible and short lived. A large randomised controlled trial, the DCCT/EDIC study looked at the effects of tight glycaemic control and number of hypoglycaemic events upon cognitive function. It was found that the cumulative number of hypoglycaemic events did not influence long term cognitive function. However, a higher glycosylated haemoglobin (HbA1c) value, indicating poorer glycaemic control was associated with a decline in psychomotor function. This study suggests that while acute hypoglycaemia is dangerous, tighter glycaemic control in the long term reduces psychomotor function decline as seen in less well controlled diabetics (9). It would seem, therefore, that hypoglycaemic episodes are not responsible for long term cognitive decline.

**AMYLOID METABOLISM**

Localised progressive amyloidosis is seen in both Alzheimer’s and type 2 diabetes. The formation of neurofibrillary tangles composed of Abeta and abnormally phosphorylated microtubule-associated tau protein has been well studied in Alzheimer’s disease but less so in type 2 diabetes, where amyloid accumulation is found in pancreatic islets. In both cases, misfolding of insoluble proteins leads to an interaction with cell membrane and a loss of normal cell function and ultimately cell mass. Both conditions can be considered to be a low grade inflammatory reaction associated with the elevation of circulating pro-inflammatory cytokines and acute phase proteins including serum amyloid A and C-reactive protein. Recently, another common player, acetylcholine (Ach), has been introduced into diabetes-dementia link (10,11). Acetylcholine is one of the principle neurotransmitters within the human body and its brain deficit is a classical feature of Alzheimer’s disease (1). Acetylcholine is broken down by Ach esterase (AChE), found in high concentrations in nervous tissue. Intriguingly, the activity of AChE has also been implicated in an anti-inflammatory pathway (10-13). Selective inhibition of AChE to increase Ach concentration forms the basis of several anti-dementia drugs currently available.

Acetylcholine is also broken down by the related enzyme butyrylcholine esterase (BChE), which is found in the blood, pancreas, liver and central nervous system (CNS). In the healthy state, AChE predominates over BChE. The enzymes differ in their CNS localisation, AChE being localised to the neurons while BChE is localised to the glia, endothelial cells and neurons. AChE knockout mice are viable, this supports the notion that BChE has a key role and can partly compensate
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Studies of Alzheimer’s brain tissue have localised BChE to neurofibrillary tangles and have shown BChE to attenuate amyloid formation by interaction with the C terminus of Abeta (15). It has also been found that increasing levels of BChE correlate positively with the development of neurofibrillary tangle and plaque formation (11). A particular variant of BChE, the K-variant (G1615A/Ala539Thr) has been associated with Alzheimer’s disease and the development of neurofibrillary tangles and Abeta, when homozygous; no association has been proven with heterozygous allele carriage (16,17). Selective inhibition of BChE in old rats has improved cognitive navigation (18). There have been recent developments in designing specific BChE inhibitors as potential treatment agents for Alzheimer’s disease, however none have yet reached regular clinical use (19-21).

Despite these interesting hypotheses, at present the evidence to support a genetic link between Alzheimer’s disease and type 2 diabetes based upon polymorphisms of the BChE gene is unclear. One study has found a link between the BChE K variant and type 2 diabetes (22), while a larger scale population study found that while the K-variant of BChE was not associated with type 2 diabetes (23).

COULD CHOLESTEROL BE THE MISSING LINK?
The brain content of cholesterol is high, approximately 2% by weight. Circulating cholesterol is tightly bound to lipoproteins and its entry to the brain is tightly regulated and enters cells by receptor-mediated endocytosis using low-density lipoprotein (LDL) receptors. Little cholesterol crosses the blood-brain barrier and almost all of the brain’s cholesterol is synthesised by the brain itself. A complex biochemical pathway is involved in cholesterol synthesis, starting with acetyl co-enzyme A. The rate limiting step in this pathway is the synthesis of mevalonic acid by the enzyme hydroxymethylglutaryl co-enzyme A reductase (HMG-CoA Reductase). This enzyme is said to be the most highly regulated enzyme in nature and is subject to feedback control at both protein and mRNA level from cholesterol. Insulin, acting through the phosphorylation of cAMP-response element protein has been found to increase HMG-CoA reductase activity by 10 fold in rat hepatoma cells. Insulin also acts to down regulate two enzymes involved in cholesterol breakdown, sterol 27-hydroxylase and cholesterol 7α-hydroxylase (24).

Cholesterol is implicated in amyloid formation as cholesterol and cholesteryl esters can directly regulate the generation of β-amyloid and inhibit its clearance (25). Cholesterol also accumulates within amyloid plaques (26) and binds directly to both β-amyloid and its precursor protein (27). A catalytic reaction between β-amyloid and cholesterol produces 7β-hydroxycholesterol which is extremely toxic to hippocampal neurons, the area of the brain responsible for memory (28).

In type 2 diabetes, insulin resistance is seen, leading to higher levels of circulating insulin. Through its interaction with the cholesterol biosynthesis pathway could abnormal patterns of insulin secretion be causing an increase in cholesterol within the brain leading to increased amyloid formation and destruction of hippocampal neurons? If this is the case then could early type 2 diabetes begin a process of amyloid formation in both the brain and pancreas involving cholesterol?

The class of anticholesterol drugs known as the “statins” (e.g. simvastatin, pravastatin, rosuvastatin) inhibit cholesterol synthesis via a competitive inhibition of HMG-CoA reductase. Could they be used in the prevention or treatment of Alzheimer’s disease? At present the evidence is again lacking. Studies are reported to be on going but at present there is no clear evidence for the use of statins as either a therapeutic intervention or preventative measure for Alzheimer’s development (29-31).

In reducing the risk of vascular and atherosclerotic disease a role for statins is recognised. A link between vascular disease and type 2 diabetes may be found via insulin resistance leading to an increase in insulin circulation causing an increase in cholesterol which deposits in atherosclerotic plaques and also encourages amyloid formation.

Glucagon like peptide-1 (GLP-1) regulates insulin secretion and inhibits glucagon release thus regulating both insulin and glucose levels. In addition it is has a role in reducing amyloid and protecting neural cells from apoptosis; GLP-1 has recently been endorsed as a promising new treatment for type 2 diabetes (32,33). Again, we await with interest the results of studies into possible GLP-1 use in dementia patients. Likewise, the body of evidence has to grow and further develop before an opinion can be reached on the suggestion that Alzheimer’s disease can be viewed as type 3 diabetes mellitus (34-37) as well as understanding the association between obesity and dementia (38-40). Further, altered, usually decreased, plasma levels of the neurotrophins nerve growth factor and brain-derived neurotrophic factor are associated with psychiatric disorders, such as depression and dementia, and diabetes including the metabolic syndrome (41-44). Overall these may have important therapeutic and public health implications.
CONCLUSION

From the evidence available, diabetes and a general cognitive decline are associated with each other. Specifically, Alzheimer’s disease appears to be associated with type 2 diabetes. The nature of this association is not yet clear. Both conditions share the pathology of amyloid deposition and loss of cell function, a cholinesterase enzyme, common to both brain and pancreas, is associated with neurofibrillary tangles and a particular variant of this enzyme is associated in homozygotes with the development of amyloid depositions. Cholesterol is associated with the formation of amyloid, and toxicity to hippocampal neurons and the synthesis of cholesterol is increased by insulin. However, conflicting evidence make these difficult to interpret and their relationships remain unclear. Other mechanisms of cognitive decline include vascular complications of diabetes associated with poor glycaemic control. It is possible that both Alzheimer’s and vascular dementia can coexist in a person with one or the other been the predominant form of cognitive decline.

At present we are unable to clearly define the link between Alzheimer’s and diabetes, could we be looking at several mechanisms interacting with each other or have we just examined several small parts of a bigger pathway? Should BchE inhibitors come into clinical use, while evaluating their effect upon cognitive decline, the progression of diabetes or indeed development of diabetes in subjects will be interesting to observe. As studies continue into the use of statins in the prevention and treatment of Alzheimer’s disease we have to wait for the results with cautious optimism. Likewise, we must await other studies involving agonists of peroxisome proliferator-activated receptors gamma, the known insulin sensitizers and anti-inflammatory drugs (37). The clinical use if GLP-1 will also help our understanding into these complex relationships. Research into this topic has generated as many questions as is has answers. Likewise, studies are required to pursue an eventual link between diabetes and other, non-Alzheimer’s types of dementias such as vascular dementia, dementia with Lewy bodies, Parkinson’s disease, mild cognitive impairment, and even Creutzfeldt-Jakob disease (insulin-prion protein association?).

As Robert Frost would tell us, while we dance round in our ring and suppose, the link between diabetes and dementia stays firmly in the middle and knows.

REFERENCES


13. Das UN. Acetylcholinesterase and butyrylcholinesterase as possible markers of low-grade systemic inflammation.
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