Diabetes mellitus and hyperglycaemia as risk factors in cognitive impairment, dementia and Alzheimer's disease:

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Abstract: Most research into whether Type-2 diabetes is associated with cognitive impairment (CI) and Alzheimer's disease (AD) is generally accompanied with a preamble describing the inconsistent results in the literature. This is true for both psychological testing and brain imaging results. This review also finds inconsistent findings, but in addition attempts to explain 'between study' variance by examining the definitions of the independent variables themselves. This is achieved by looking at the theoretical relevance and validity of the variables involved, examining how these are operationalised.

The complications associated with Type-2 Diabetes Mellitus (DM) are proportional to blood sugar levels, UKPDS (1998). The resulting hyperglycaemic conditions have damaging effects on non-insulin dependent cells and the vasculature of the body. It is proposed these effects may also occur in the brain, causing cognitive impairment. In the glycation theory of AD sugar concentrations and elapsed time are critical parameters, Takeuchi, (2004). In the vascular theory of AD, it is the accumulated levels of vascular damage Zlokovic (2005). Elapsed time and glucose levels are again critical.

Clearly how DM control and elapsed time are operationalised may result in different associations between DM and cognitive impairment. Diagnosis and treatment type variables are less problematic than DM control and age of onset. However DM

sometimes goes undiagnosed or age of onset is not available, often HbA1c figures are not available.

Studies will be examined to see how these variables are treated and what conclusions were drawn. Generally, in this research, it is concluded that more recent studies are better designed and have a greater reliability but are systematically flawed if DM control and age of onset are not included as independent variables.

Good long term Blood Glucose (BG) control is important and is associated with long term health benefits. The psychological needs of people with diabetes are also increasingly recognised, as are the effects of various psychosocial stressors. The effects of psychosocial stress on BG, compliance, diet and exercise are considered with a view to evaluating therapeutic interventions including the use of hypnosis.

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Diabetes mellitus and hyperglycaemia as risk factors in cognitive impairment, dementia and Alzheimer's disease

Section 1: Introduction

Alzheimer's disease (AD) is a common type of dementia characterised by progressive forgetfulness and memory loss with end stage dependency and death. Normal ageing is often associated with similar if less dramatic cognitive deficits benignly associated with old age. **Type-2 diabetes mellitus (DM)** results from insufficient insulin or insulin resistance, reducing glucose transport into insulin dependent cells such as muscle and fat. Uncontrolled DM is associated with high blood glucose levels.

There are a number of methodologies that describe pathological neural ageing and associations with DM. **Neuropsychological testing** maps the extent and location of impairment to cognitive systems, this will include normal ageing. DM may be associated with selective cognitive deficits including memory and executive function, Yeung et al., (2009). Animal models of diabetes are used to manipulate some of the effects and complications of controlled and uncontrolled diabetes. Gispen and Biessels, (2000).

Epidemiological studies look basic co-morbidity but also take into account the definition and aetiology of DM and often consider mechanisms that will account for associations between DM and neural ageing. DM is associated with increased prevalence of dementia and AD in old age**,** Ott et al., (1996); Akomolafe et al., (2006). The incidence of AD with age shows an increase after age 60 with a step change in the over 80's.

Neuroscience:

The volumetrics and functioning of ageing brains can be imaged using Magnetic Resonance Imaging (MRI) and f-MRI. Comparisons can then be made between controls, Mild Cognitive Impairment (MCI) and AD, Colliot et al., (2008), Jauhiainen et al., (2008). This allows both diagnoses and prediction of conversion rates. Similar measures of brain atrophy and lesions have been studied by Schmidt, et al., (2004) allowing comparisons between DM subjects and controls.

AD is associated with the presence of extracellular β-amyloid peptide (Aβ) deposits known as senile plaques (SP's) and particularly associated with intracellular neurofibrillary tangles (NFT's) comprising tau protein and other cellular debris, (Finch & Cohen, 1997). SP's and NFT's are present in normal ageing but much increased in AD.

Advanced glycation end products (**AGE**'s) are responsible for many of the vascular complications of diabetes and are implicated in neuro-pathogenesis, (Brownlee 1995; Finch & Cohen, 1997; Gispen and Biessels 2000; Takeuchi et al., 2007). AGE's occur independently of SP's and NFT's. They are present in the blood stream, Cerebrospinal Fluid (CSF) and in cells and in the extracellular matrix. They are found in association with SP's and NFT'S (Finch). AGE's are reactive and modify cellular and extracellular proteins by covalent bonding forming insoluble aggregates, damaging collagen and lipids, resulting in narrowing of vasculature typically seen in diabetes. Similar consequences are theorised for long lived neurons and the vascular units of the brain, Takeuchi et al., 2004; Zlokovic, 2005.

Most reviews carry caveats highlighting **inconsistent results** in associations of DM with mild cognitive impairment (MCI) or AD, Ott, (1996);Finch & Cohen,

(1997);Schmidt et al., (2004). Current contradictory results are evidenced in Ott (Rotterdam study, 1996) and Akomolafe et al. (Framlington study, 2006). This may reflect the multivariate contribution of predictors for AD and/or the individual variability of neural ageing, dementia, AD and diabetic aetiology. However there are inherent design weaknesses in many epidemiological studies set up to monitor co-morbidity of diseases of the elderly. The benefits of control over blood sugars in reducing diabetic complications has been extensively raised (Pirart, (1978); DCCT, (1993), UKPDS, (1998)), yet many epidemiological studies do not hold basic control markers such as HbA1c or age of onset.

Hyperglycaemia is a major risk factor in the vascular complications of diabetes and vascular disease is associated with cognitive impairment, dementia and AD. The aim of the review is not only to examine associations between DM, impairment and AD, but also to determine if the diabetes variable is adequately and consistently defined.

Does diabetes per se have significant associations with cognitive impairment and AD or is it moderated by quality of glucose control, one of the risk factors for diabetes complications?

2. Theoretical bases for neural ageing and neurodegenerative disease: protein glycation and vascular diseases.

The prevalence of all forms of dementia in the elderly (>65yrs) in Europe is estimated at 6.4% of which 4.4% AD and 1.6% VaD, van der Flier & Scheltens, (2005). Vascular dementia (VaD) is characterised by vascular disease resulting in large or small vessel infarcts, commonly known as stroke. This causes areas of

neuronal death and loss of function. Alzheimer's disease (AD) is a metabolic disease, associated with SP's, NFT's and massive loss of neurons in the hippocampal area. Both VaD and AD result in serious cognitive impairment, weight loss and end stage death. The incidence of AD and VaD increases with increasing old age.

Diabetes complications are predominantly vascular in nature causing neuropathy, retinopathy, nephropathy, CHD and stroke. UKPDS 1998 recommended tighter control of blood sugars and diet to reduce the long term risk of complications. Risk factors for complications include hypertension, BMI, plasma lipids and HbA1c. HbA1c is a measure of glycated haemoglobin averaged over the previous 120 days and is an independent measure of **diabetes control**. A clinical diagnosis of Type-2 diabetes mellitus or impaired glucose tolerance (IGT) is associated with blood sugars above standard limits of 4.0 – 7.0 mmol/l. Type-1 diabetes, previously known as Insulin Dependent IDDM, results from destruction of pancreatic β cells often from autoimmune disease. Cognitive impairment in DM is generally mild and may be wholly associated with hyperglycaemia itself, (Nilsson et al., 2002; Yeung, 2009)

<u>The glycation theory of AD:</u>

Brownlee, 1995 proposed a role for advance protein 'glycosylation' in neural ageing and DM. Adducts of sugar convert to stable 'Amadori' products in proportion to glucose concentration. These reducing 'Amadori' products modify cellular proteins including those in the epithelium and basement proteins, forming Advanced Glucose End products (AGE's). These insoluble products themselves stimulate immune response and Reactive Oxygen Species (ROS) production which can cause further oxidative damage.

Brownlee proposed the Amadori glucose derived product 3-deoxyglucosone as a precursor to AGE production, see AGE-6 in Fig.1 below, (Takeuchi, 2004). AGE-6 is normally broken down by a reductase enzyme to harmless 3-deoxyfructose. Brownlee also proposed possible genetic factors might be involved in the ability to break down AGE-s and that this might account for the variation in diabetes complications.

The accumulation of AGE is proportionate to glucose concentration and elapsed time: a 10-45 times increase in non-insulin gated cells was observed in diabetic rats after 5-20 weeks of diabetes. Glyceraldehyde derived from glyceraldehyde-3-phosphate (G3P), see AGE-2 in Fig. 1 below is much more reactive than glucose, resulting faster rates of intracellular AGE accumulation: a 13.8 fold increase was observed in glucose rich cultured endothelial cells. Age inhibitors such as aminogaunidine react with G3P to prevent AGE formation and complications in DM rodents.

AGE's are involved in the pathology of the complications of DM causing narrowing the vasculature and ischemia. AGE production in hyperglycaemic diabetes can take place over relatively short time periods. Brownlee proposes the same mechanisms for long lived neurons and vasculature in the brain on the basis that AGE modified Aβ, precursor of SP's, and AGE modified tau, precursor of NFT'S are present in AD brains. Sasaki, N, (1998) cited by Takeuchi et al., (2004) has confirmed AGE's are present in SP's and NFT's in patients with AD and they are also present in primitive SP's suggesting a role for glycation in AD.

The rationale for association between DM and AD is the propensity for AGE formation in hyperglycaemic conditions and the damage caused to non-insulin dependent cells in DM. AGE's are present in SP's and NFT's in AD brains. Takeuchi (2007), Fig. 1 below), describes a family of AGE's circulating in the serum of diabetic patients on haemodialysis. Breakdown protein products and AGE's may contribute to 'abnormal tau protein and the deposition of Aβ' in the brains of such patients.

However the results remain inconclusive.

Glucose derived AGE, AGE Receptors (RAGE) and Aβ have been found in the hippocampal area of AD and DM patients. In AD brains 70-80% of astrocytes were AGE-1 and RAGE positive and 20-30% Aβ positive. Intracellular glucose derived AGE-1 was 'very rare' in DM and controls, suggesting a role for glycated Aβ in AD, Takeuchi et al., (2004).

Choie, Sasaki,Takeuchi et al., (2004) suggest that glucose derived AGE although widespread in the AD brain has no pathological role in AD. AGE-1 is found in SP's and this may be responsible for Aβ glycation. Glycer-AGE (AGE-2) and glycol-AGE (AGE-3) are both more toxic to rat neurons and AGE-2 has been found in the cytostol of hippocampal neurons in AD patients but not in SP's or astrocytes suggesting a limited role for glycated Aβ. Only small amounts of AGE-3 were found in AD or control brains suggesting no specific role in controls or AD.

It has also been proposed Finch & Cohen 1997;Takeuchi et al., (2004) that the decreased metabolic activity of glyceraldehydes-3-phoshhate dehydrogenase (GAPDH) observed in AD patients, and in normal ageing (Finch & Cohen, pp84) may be sufficient to disrupt the glycolytic pathway in favour of glyceraldehyde and AGE-2

production see Choie et al., (2004, Fig.3 below). AGE-2 is present in the blood of diabetic patients on haemodialysis contributing to damage to non-insulin dependent cells such as kidney, neurons, retina and red blood cells. The hyperglycaemic route to AGE-2 production may render DM patients particularly susceptible to neuronal damage.

RAGE's are also implicated in AD. a) Double transgenic mice that over-express RAGE and mutant Amyloid Precursor Protein (APP) show spatial learning deficits compared to m-APP only mice, Takeuchi, (2007). b) Clearance of AGE's depends on scavenger RAGE's on the surface of astrocytes. Synaptic plasticity may account for increased levels of RAGE, responding to increased levels of AGE, Gispen 2000. Increased neuropathy may be due to the affinity of AGE-2 for RAGE and the corresponding increase of these receptors. c) RAGE is also a receptor for Aβ and increased receptors and may contribute to increased Aβ uptake into the cell maintaining a role for both AGE-2 and Aβ in AD.

Taken together these results show:

Glucose AGE (AGE-1) is present in SP's and NFT's. Increased SP's and NFT's are present in the AD brain. However AGE-1 may have no pathological role.

Production of neuro-toxic AGE-2 is considerably more likely in glycaemic conditions leading to a vicious circle of reduced GADPH metabolism and the polypol pathway.

Increased AGE leads to neuronal plasticity, more RAGE, greater uptake of AB and AGE including AGE-2. AGE-2 damage to non-insulin dependent cells, including

peripheral neuropathy, occurs in hyperglycaemic conditions such as diabetes. A similar, if delayed process is proposed for long lived neurons in the brain.

AGE-2 damage to hippocampal neurons occurs in AD. This may be associated with metabolic changes in GAPDH activity that increase AGE-2 levels. However these changes in GAPDH activity occur in normal ageing.

Only small amounts of AGE-3 were found in AD or control brains suggesting no specific role in controls or AD.

Figure 1. Takeuchi et al., (2007, pp.1360)

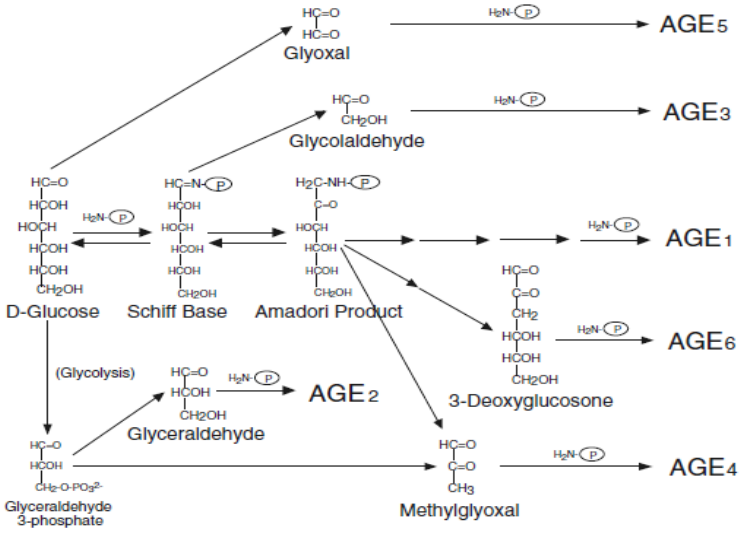

Figure 1 Alternative routes for the formation of AGEs *in vivo*. AGE-1, glucose-derived AGEs; AGE-2, glyceraldehyde-derived AGEs; AGE-3, glycolaldehyde-derived AGEs; AGE-4, methylglyoxal-derived AGEs; AGE-5, glyoxal-derived AGEs; and AGE-6, 3-deoxyglucosone-derived AGEs. P-NH_2, free amino residue of protein.

Figure 3. Choie, Sasaki, Takeuchi et al., (2004, pp.192)

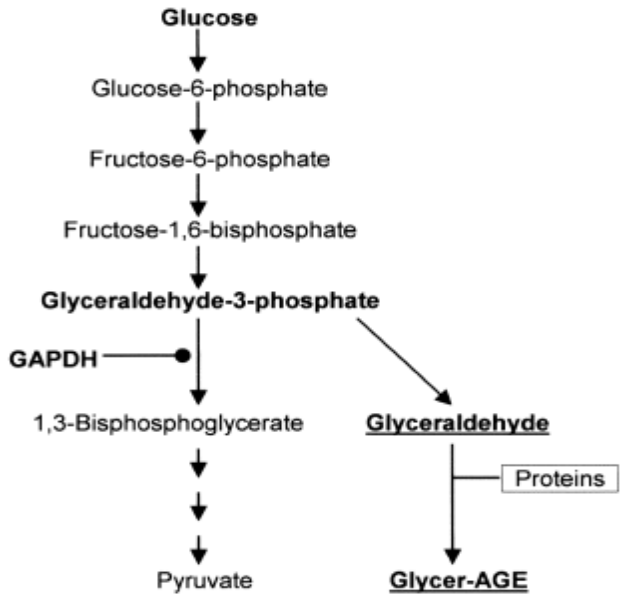

Fig. 3 The glycolytic pathway and glycer-AGE generation (*GAPDH* glyceraldehyde-3-phosphate dehydrogenase)

The vascular theory of AD:

Zlokovic (2005) proposes that neuronal and vascular lesions define AD. Neuronal loss is the result of vascular disease in the brain with the accumulated dysregulation of the neurovascular units causing MCI, dementia and AD. The theory describes the effects of vascular senescence in brain capillaries and cerebral arteries leading to hypo-perfusion, stroke and cell death. In addition an increasingly leaky BBB contributes to an imbalance of Aβ aggregates and increased RAGE expression leading to further cell death.

The Blood Brain Barrier (BBB) allows Aβ transport, however when the vasculature is 'leaky' this leads to an imbalance of Aβ in the brain, increased aggregation into Aβ oligomers and their deposition in SP's. Increased Aβ in brain up-regulates RAGE (see Gispen above) and low-density lipoprotein receptor-related protein (LRP), involved in Aβ clearance from the brain.

Neuro-vasculature remodelling is part of normal ageing and occurs in degenerative disorders such as stroke. However brain capillary endothelial cells do not work as a repair system in presence of Aβ rich in β sheets which is anti-angiogenic.

AD is co-morbid with cerebo-vascular disease and atherosclerosis and is associated with reduced capillaries in the hippocampal area CA1 and increased dementia ratings. Diabetes accelerates vascular ageing and has negative effects on the normal Blood Brain Barrier (BBB).

In summary the vascular theory of AD Fig.2 below has a specific role for DM vascular complications and deposition of Aβ, as with the pathogenesis of AD. This is not incompatible with the additional processes associated with Advanced Glucose End products, see glycation model above.

Figure 2, Zlokovic (2005, pp.206)

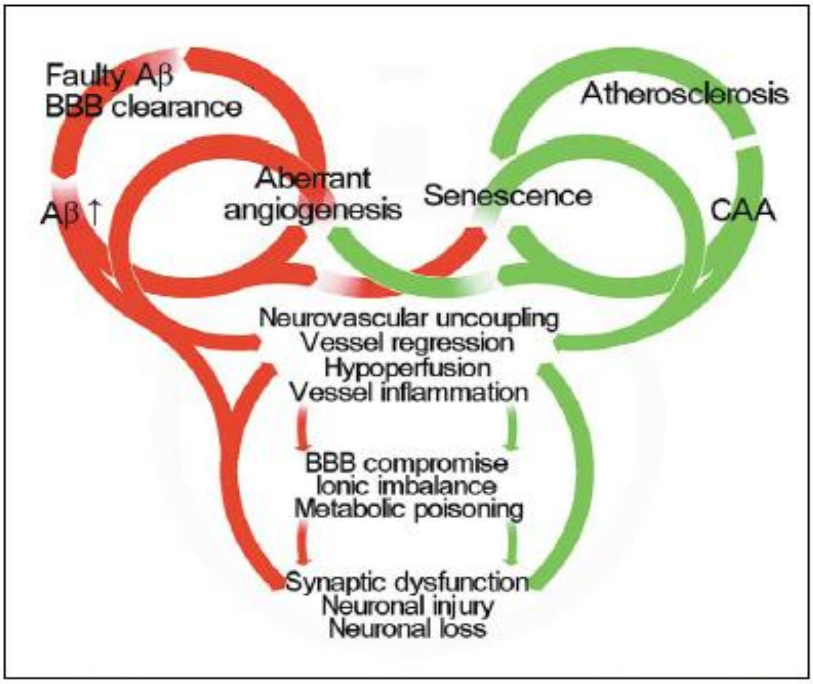

Figure 2. Neurovascular model of Alzheimer's disease. Multiple pathogenic cascades originating from altered cerebral arteries (green) or altered brain capillaries (red) can initiate disintegration of the neurovascular unit, including aberrant angiogenesis, cerebral amyloid angiopathy (CAA), senescence and faulty clearance of Aβ across the BBB, resulting in increased Aβ levels. Both sets of cascades can initiate neurovascular uncoupling and hypoperfusion, although only aberrant angiogenesis and accumulation of amyloid result in vessel regression and inflammation. This leads to the BBB compromise and reduced control of the chemical composition of brain interstitial fluid, which can result in, or amplify, synaptic and/or neuronal and oligodendroglial dysfunction, neuronal injury and loss.

3. Neuroscience: brain imaging results

The pathology in Alzheimer's disease (AD) occurs, at least initially, mainly in the Hippocampus and related cortical areas of the limbic system. This results in severe degeneration of the hippocampus, entorhinal cortex and the neocortex especially the frontal temporal lobes. Morris, (1999, pp.1172) reports 'abundant' Aβ plaques in the neocortex in pre-clinical AD with 32% loss of neurons in the entorhinal cortex.

This percentage loss has been demonstrated using automated volumetrics and MR imaging. Colliot et al., (2008) found similar levels of hippocampal atrophy, 32% in AD and 19% in MCI, concurrently demonstrating an association between smaller baseline hippocampal volumes and progression to AD.

Lind, Larson et al., 2006 demonstrate a possible confound with smaller hippocampal volume in carriers of APOE e4, while Rodriguez et al., 2002 in the Honolulu study demonstrated a 3-fold increase in SP's and NFT''s in post mortem diabetic carriers of this allele.

Schmidt et al., (2004), in the CASCADE study, report associations between diabetes and MRI volumes of the brain. The study has the hallmarks of a well run study especially validity of design and methodology. It is a large study (n=1252) randomly selected from ongoing community based studies with disease data collected ≥5yrs previously. It includes cardiovascular disease (CVD) data and DM risk factors such as BMI and hypertension. The diabetes variable itself is well defined as having a 'diagnosis by a physician' with details of diabetes treatment, diet, tablets or insulin, although like many studies it does not report duration of DM, as suggested by Finch & Cohen, 1997. Mini Mental Status Examination (MMSE values < 15) excluded participants with probable dementia or MCI.

There were no significant differences in brain lesions between diabetes and the non diabetes control group. Significant differences between groups were seen in severe cortical atrophy (p=0.003) and the sub-cortical ventricle to brain ratio (p=0.03). The added design value of the CASCADE study lies in the capture of biological and medical predictor variables. Multiple regression controlling for 'sex, age, study, education and CVD risk factors hypertension, CHD, smoking status, BMI and total cholesterol' redefined group differences to a non-significant trend towards more pronounced cortical atrophy, (β= 0.44, 95%CI:(- 0.4 to 0.92, p=0.07).

Additionally some interesting interaction terms are included in the model, namely the interaction of treatment type and hypertension as predictive of cortical atrophy. Table 4) below highlights the differences between 'untreated': no treatment or diet and 'treated' diabetics: tablets or insulin. Overall, diabetics with hypertension have a significant association with increased cortical atrophy β = 1.19, 95%CI (0.22-2.15), p=0.02 but 'treated' diabetics with hypertension showed no significant increased risk of cortical atrophy β=0.10, 95%CI (1.24-1.44), p=ns.

The overall odds ratios for DM versus non diabetic patients for severe cortical atrophy were [OR] 1.73, 95%CI (1.06-2.81), reducing to [OR]: 1.25, 95% CI (0.64–2.45) for normotensive diabetics. Schmidt cautions that brain atrophy does not necessarily map to dementia or AD but may relate to the hydrating effects of glucose.

TABLE 4
Results from linear regression analyses: interactions of diabetes and hypertension on cortical atrophy

Interaction term	ß	95% CI	P*
Total diabetes × hypertension†	1.19	0.22–2.15	0.02
Untreated diabetes × hypertension†	2.20	0.88–3.51	0.001
Treated diabetes × hypertension†	0.10	−1.24 to 1.44	0.88

*Adjusted for age, sex, study, years of education, smoking status, coronary heart disease, BMI, and cholesterol level; †reference group is nondiabetic normotensive participants.

In summary: the better designed CASCADE study does not find significant effects after controlling for important risk factors including treatment regime. Again the literature search revealed little consensus. Schmidt et al., found only 6 of 19 previous population based imaging studies with positive associations between diabetes and small vessel disease and 3 with positive associations to cortical atrophy.

The interaction between hypertension and treatment should be matter of increasing interest.

4. Epidemiological results: an analysis of the treatment of the diabetes variable.

It is common for studies to make reference to the inconsistent findings in the literature. This section proposes that this is due to the treatment of the diabetes variable. There is a general trend towards a more comprehensive concept of the diabetes variable that includes treatment, control/HbA1c, age of onset and medical diagnosis. This section seeks to demonstrate a trend towards increased design validity that will give increased validity to associations between DM and AD.

1) Finch and Cohen 1997 raise the problem of inconsistent correlation between DM and AD with a summary of studies between 1983 and 1997 showing 5 without any association, 6 with significant negative associations and only 2 with significant positive associations, namely Ott et al., 1996; Leibson et al., in press (2009). More significantly Finch points out that they are not aware of any studies with data on HbA1c.

The Leibson study is well designed and uses a proper diagnosis of diabetes according to NDDG criteria. It reports a > 2-fold increased ($p<0.05$) risk for males only. Risk of AD for Adult Onset DM was elevated (for men, RR = 2.27, 95% CI 1.55-3.31; for women, RR = 1.37, 95% CI 0.94-2.01). Ott's diagnostic procedures, sufficient for epidemiological studies, do not conform to clinical standards for symptomless diabetes which require both the random and oral load to exceed 11.1 mmol/l, WHO 1999.

2) Schmidt 2004 in the CASCADE study raises the inconsistency in previous radiological studies. The *population validity* of previous samples is also questioned by Schmidt, subjects belonging to highly selective groups for radiological procedures. Six out of 19 studies found associations with small vessel disease and 3 with brain atrophy. The interaction of diabetes and hypertension is known from the UKDPS and this interaction is reported by Schmidt. In the CASCADE study only 22 of the 114 diabetic participants relied on one random or one oral load for a diagnosis of DM, more in line with current standards, WHO 1999.

No data is available for HbA1c although the participants were dichotomised into 'treated' and 'untreated' diabetes demonstrating a powerful interaction with hypertension in relation to brain atrophy.

3) Again in the CASCADE study Schmidt et al.2004 correctly excluded participants not clinically diagnosed with DM and or without treatment information. This excluded 92 potential participants, 13 from the Rotterdam study and 21 from the Whitehall II study.

In the Rotterdam blood glucose measuring data did not start until July 1990. Ott, et al., 1996, found an overall increased association between DM and AD [OR] 1.3, 95%CI (1.0-1.9), treatment data was available but no HbA1c or age of onset. Ott, et al.,1999, (abstract), found [OR] 1.9 95%CI (1.2-3.1). These two studies associating DM and AD are much cited: Ott, et al.,1996 cited 229 times; Ott, et al., 1999 cited 480 times, www.SCOPUS.com 27.09.08:18.45.

4) Akomolafe et al., 2006 in the Framlington community based study account for the variability in previous results by positing possible population differences and confounders such as definitions of DM, dementia and AD. They found no significant association between DM and AD and no effect from 'treatment type' but found significant associations in a low risk sub-group.

The study includes both 'treatment type' and risk factors for DM in its regression models, but still no mention of HbA1. The finding of differential sub-groups raises doubts as to the *design validity* of previous studies.

5) Nilsson (2006) describes the approach of the Betula study combining longitudinal and cross-sectional design so controlling for age, cohort and time of testing. The benefits of the Betula design include multiple testing domains; multidisciplinary teams and the indivisibility of cognitive testing in detecting early MCI leading to dementia. HbA1c levels are part of the study and the results showed a **main effect**

with HbA1C rather than DM per se, Nilsson Nilsson, Wahlin, Fastbom, and Nilsson (2002) and Nilsson, Wahlin, and Nilsson (2005). This study incorporates good design features, a multi-domain approach to MCI and dementia.

6) Finally, Yeung et al., 2009 in their literature search of almost exclusively post 2000 papers again find no consistency in associations between DM cognitive functioning. After controlling for hypertension Yeung found only two significant measures ($p < 0.05$) out of 20 tested and no interaction between diabetes and age groups 53-70yrs, m=72.5yrs and 71-90yrs, m=77.6yrs. This differs from Hassing 2004 who found significant effects of diabetes on nearly all measures in an elderly sub-group 80-93; m=82.8.

Both studies had diabetes duration and hypertension data although only Yeung controls for hypertension. Neither study included glucose control status as a variable although Yeung tellingly refers to study participants having 'mild' diabetes. However Yeung et al., (2009) highlight their Victoria Longitudinal Study has sampling validity. It is taken from the wider community rather than relying on selective samples from sheltered care and nursing homes.

Additionally epidemiological studies often use Oral Glucose Tolerance Testing at 2hrs. This may not be diagnostic particularly in the elderly WHO section 2.3.2.

In summary: while more recent studies have better design many studies still fail the test of good research set out by Sapsford, 2007.

The diabetes variable is inconsistently diagnosed and ill defined in terms of treatment options failing *validity of measurement*. The populations are often not randomly sampled and may be drawn from clinical or non community based

populations, failing the *validity of population* test. The failure to include pertinent variables such as diabetes control, treatment or known risk factors such as hypertension means conclusions may fail the test of *validity of design*.

5. Neuropsychology: normal ageing and psychopathology

Associations with memory deficit and diabetes are widely reported but evidence is weak for progression to AD.

Diabetes associations with dementia, VaD and AD:

The aim of psychological testing is to determine early signs of MCI and dementia. The memory impairments reported in DM may be an effect of glycaemia, diabetic neural ageing or diabetic neuropathy.

The increased risk of vascular dementia in diabetes is reported by, Ott (1999), Akomolafe et al., 2006. These results are subject to the same design caveats raised in section 4 above. Given an ostensibly non-demented group Hassing et al., 2002: (abstract) found increased relative risk [RR] 2.54 95%CI (1.35-4.78) of VaD in the very old (m=83yrs) but no association with AD.

The association between diabetes and AD is then still unclear. Ott et al., (1996) found an overall positive association between diabetes and AD with the strongest association in those using insulin therapy [OR] 3.2, 95%CI (1.4-7.5). As above this study does not consider HbA1c or duration of disease.

Akomolafe et al., 2006 Framlington study, fig.1 below report a small increased overall relative risk (RR) of 1.15, 95% CI (0.65-2.05) compared to controls and

conclude that 'DM is a risk factor for AD in the absence of other known major AD risk factors'.

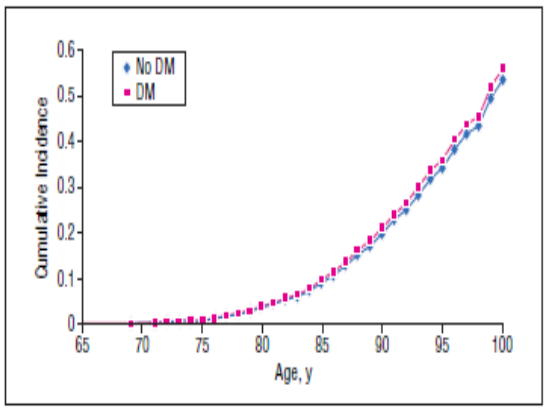

Figure 1. Cumulative incidence of Alzheimer disease in entire sample: comparison of groups with and without diabetes mellitus (DM), adjusted for age and sex.

Akomolafe et al., did not find any interaction effects by treatment type although 26 of the 202 DM subjects were on 'no treatment'. This is in contradiction to the strong interaction effects found by Schmidt et al.,(2004). The interaction found between treatment types as defined in the Rotterdam study, Ott et al., (1996), is instructive, with higher relative risks for dementia and AD for those on insulin treatment. Since Type-2 diabetes may progress from 'no treatment' to tablets to insulin therapy this would support a more complex aetiological analysis than is served by treatment categories alone.

Diabetes and cognitive decline:

Lower cognitive scores are associated with normal ageing and onset of neurological disease such as dementia or AD. The incidence of diabetes increases with age so it

is important to separate out the effects. The goal of psychological testing is earlier diagnosis allowing earlier therapeutic intervention.

1) Verhaeghen et al (2003) Berlin Study using 1990 baseline data performed a multivariate analysis of cognitive tests controlling for age, sex, social educational status and dementia status. Of the remaining major risk factors congestive heart failure, stroke, coronary heart disease, and diabetes mellitus each contributed to overall cognitive impairment. DM was the only risk factor that contributed to decline in memory, however the presence of any one risk factor did not lead to an increased rate of cognitive decline, see Fig.2 below

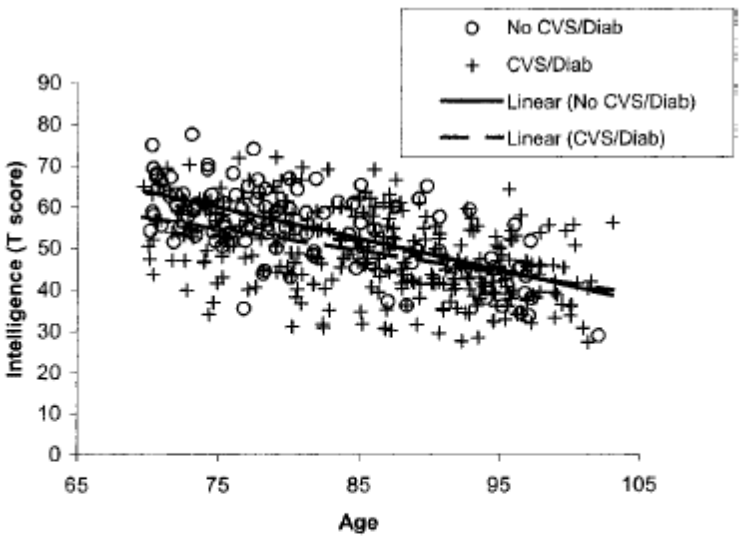

Figure 2. Composite intelligence score as a function of age in the group of participants with at least one of the four cognition-related diagnoses (i.e., diabetes, congestive heart failure, coronary heart disease, or stroke) and the group of participants without any cognition-related diagnosis. CVS = cardiovascular syndrome; Diab = diabetes.

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2) Hassing, et al., (2004) report no differences at baseline 1991 between diabetic and normal in elderly subjects (m=82.8yrs), but shows a significant cognitive decline in MMSE and in 5 out of 10 other cognitive measures over the following 6 years, concluding that diabetes is a risk factor for cognitive decline in elderly subjects..

3) In contrast to many studies Yeung et al., (2009) report no significant contribution of diabetes to episodic memory, verbal fluency, reaction time or perceptual speed. Diabetic impairment was observed in 1 out of 3 tests of executive function and in 1 out of 2 measures of sentence verification, a measure of semantic speed. No significant decline was seen in the other 16 tests. These measures held over both groups Young-old (m=63.6yrs) and Old-old (m=75.6yrs) .

In conclusion there is evidence for selective effects of DM on cognition but little for long term cognitive decline, except in the most elderly subjects Hassing. A possible confound is the effect of hyperglycaemia on cognitive testing Nilsson, Wahlin, and Nilsson (2005) find it is the presence of elevated glucose, hyperglycaemia as measured by blood sugars, rather than diabetes per se that affects memory.

6. Glycaemic control in diabetes

Animal models:

Experimental animal studies are not subject to random control regimes and can demonstrate analogous associations between diabetes and cognition, neuropathy, insulin control and deficits in old age.

STZ-diabetic rats with glucose levels at 20-25mmol/l quickly develop diabetic complications. Young adult rats show learning difficulties unless given insulin treatment. If treatment is withheld until 10 weeks of onset learning is already impaired. After around 12 weeks without insulin treatment, hippocampal areas show

maximum synaptic change that affects Long Term Potentiation (LTP). The effects are dose dependent: at 15mmol/l glucose levels no LTP deficits were observed. Gispen and Biessels 2000. Hyperglycaemia in diabetic rats favours the polypol pathway as evidenced by the levels of sorbitol and fructose: less in diabetic rat brains than in the peripheral nerves. Takeuchi proposes that hyperglycaemia and the polypol pathway are associated with increased AGE-2 production, a neurotoxin.

Control of diabetes, by treatments lowering glucose levels, has positive effects in both rodent and human subjects. Gispen (2000, pp.458) makes this argument citing studies that correlate good metabolic control with enhanced cognitive function. Where diabetic complications are reduced and in rats and cognitive deficits eliminated.

Current control strategies

Holland and Rabbitt (1991) raised the issues of age of onset and diabetes control as important variables when studying cognitive deficit in psychological testing. Although they are rarely collected together in epidemiological studies. Schmidt ,(2004) comments on the dearth of such figures, indeed Yeung et al., (2009) reports that no HbA1c figures, let alone treatment or age of onset, available in their VLS, relying on self report for diabetes control status. They describe their sample as having 'mild diabetes', somewhat of a contradiction of terms.

1) The findings of the US Diabetic Control and Complications Trial (DCCT), 1993 and The UK Prospective Diabetes Study (UKPDS), 1998 have shown that tight control of blood glucose levels reduce the long term complications of DM. This is true of other risk factors BMI, hypertension and cholesterol levels. Diabetic regimes aimed at tight control of blood glucose levels, measured by glycated haemoglobin

(HbA1c), have been shown to change the rate of progress in micro-vascular and macro-vascular complications in type-2 diabetes. HbA_{1c} is used to assess blood glucose control, a range of 6.5 – 7.5% being the aim set by NICE, (2002).

2) There remains unexplained variance with well controlled patients suffering severe complications and poorly controlled patients suffering no ill-effects.

In general however, good control will reduce glucose concentration and reduce the glycation of proteins and production of AGE's. According to the glycation theory AGE-2 is favoured by hyperglycaemic conditions and is implicated in AD.

3) Using UK as a proxy timetable for better glycaemic control, following on from DCCT (1993), UKPDS (1998) and the UK National Services Framework for Diabetes (NSF) 2003 a 10yr plan - we can assume that a reduction in undiagnosed diabetes and the effects from good diabetic control would not begin to show in research much before 2000. Regardless of this if the data are collected they can be controlled for.

More recent results could should show different effect . The Schmidt 2004 CASCADE study and the Akomolafe et al., 2006 Framlington study apply more rigorous definitions of 'diabetes' and have established interesting 'treatment' effects.

7. Psychotherapeutic interventions and hypnosis: John Jeffrey, MSc. Psychology, DHP(NC)

The need for improved emotional and psychological support is recognised in the Department of Health (2008) publication '5 Years On': Delivering the Diabetes National Service Framework. The proposed Improved Access to Psychological

Therapies (IAPT) aimed at improving support above the 38% level of primary care trusts providing psychological support for adults with diabetes. The efficacy of psychological interventions in the general population is not in doubt. However the literature reveals a limited number of well controlled studies of psychological interventions with diabetic patients, Snoek, F. J. & Skinner T. C., (2001).

In the absence of emotional and psychological support people may seek to maximise self control through alternative therapies.

Complementary and Alternative medicine (CAM) is a life style choice for many United States diabetic patients. This does not appear to be a barrier or alternative to conventional medicine. In a sample of 2500 DM patients no negative impact was observed on the take up of preventative care or primary care, Garrow, D, Egede, L (2006a). Using the same 2002 national household survey data sponsored by the "National Center for Health Statistics", Garrow, D, Egede, L (2006b) confirmed a dramatic increase in CAM among DM patients in line with the general population. 48% of DM patients used CAM of which 17% used relaxation therapy. Prayer was significantly higher in diabetic patients (Odds Ratio 1.19, 95% CI 1.05, 1.36). Hypnosis was grouped under 'other' but no conclusions could be drawn given the small sub-sample size.

A review of the CAMEOL project, Pilkington, K., Stenhouse., E, Kirkwood., G, Richardson J (2007), identifies only one study of hypnosis and its affect on Blood Glucose (BG). This same study is cited by Xu, Y and Cardeña, E (2008) in a review of hypnosis as an adjunct to therapy in supporting patients manage their diabetes.

Xu, et al., cite one other case study (n=1) in their review covering BG control. Xu, et al., also review compliance, weight loss and increased peripheral circulation discussed below.

Glucose Control

Pilkington et al., & Xu et al., cite the study measuring the affects of hypnotically induced stress by abreaction on three physiological markers including blood glucose. However the actual study by Vandenbergh, Sussman, and Titus (1966) was poorly controlled and lacks both design and methodological validity. It was a small non random opportunity sample using repeated measures (n=6). It had uncontrolled variables such diabetes type, patient profile, treatment type and level of abreaction. Post priori selection of control day, uncontrolled order effects and simplistic student t-tests mean the results have little relevance to the literature on glucose control or hypnosis.

As a proxy however DM glucose control and stress management were examined by Surwit, S et al., (2002). A controlled study using type-2 DM patients looked at the effects of stress management on glucose control. Stress management training showed positive effects in follow up assessments, 1 year after baseline, on glucose control as measured by HbA1c. The training consisted of 1) Progressive Muscle Relaxation PMR, 2) Cognitive Behavioural Techniques for recognising and dealing with stress, including guided imagery, deep breathing and ‘thought stopping’ and 3) health education on the effects of stress. Training was 5 half-hour sessions, in small groups, the control group were given non directive diabetes education. The

treatment group continued to practice mini stress busting techniques, incorporating these into their daily lives.

Compared to the control group HbA1c was reduced by 0.5% in the treatment group. Although modest this is associated with significant reductions in micro-vascular complications.

Compliance

Diabetes has multiple psychological components and often the resultant effect of psychological stress on BG is idiosyncratic and contingent. This is more so in IDDM than with NIDDM when BG should theoretically rise in response to stress hormones.

Stress and DM can have bi-directional effects. Stress can also affect BG indirectly through poor compliance with BG testing and self- medication, similarly with diet and exercise regimes. Psychological stress can be negative or positive.

Interventions aimed at compliance need to be targeted. Cox, D., J., and Linda Gonder-Frederick, L., (1992) review the complexity of psychological behavioural research in diabetes. Inconsistent results they conclude are due to the high level of uncontrolled diabetes related variables and research would benefit from a more experimental methodology.

Xu, Y et al. cite the Ratner, Gross, Casas, and Castells (1990) with hypnosis leading to improved compliance as evidenced in HbA1c results. However this is a study of 7 Insulin Dependent DM (IDDM) adolescent patients (n=7) and does not necessarily generalise beyond the study to the DM population in general.

Exercise & Diet

Weight reduction and exercise are associated with both short term and long term health benefits for both NIDDM and IDDM patients, UKPDS, (1998), '5 Years On' (2008). There is a large amount of literature relating to healthy exercise and diet regimes in the general population, including CAM and psychological interventions. In this respect, subject to any caveats above, there is no reason to assume any significant differences in the diabetic population per se. Typically evidence on compliance and its positive effects is variable Cox et al., cite Rubin et al. (1990), who found that 'improvements in insulin adjustment and SMBG were maintained after intervention, but changes in diet and exercise were not'.

Increasing Peripheral Circulation

There is an effect here. Xu, et al., cite Grabowska (1971), although the number of studies since remains low.

A literature search of www.PsychINFO.com 07.08.10:11.15 using (ABS(**vasodilation**) AND ABS(**hypnosis**)) gave 10 hits including Grabowska, www.SCOPUS.com 07.08.10 9 hits and www. PubMED. com 07.08.10.18 hits. There is some overlap.

The range of studies are not necessarily directly relevant to the issues of this research, namely glucose control, compliance and lifestyle choices, however they would appear to be a candidate for further analysis and research.

In summary there is evidence in the literature to support psychotherapeutic interventions aimed at compliance, exercise and diet. While there is a lack of controlled studies using hypnosis the content of hypno-psychotherapy sessions is well represented namely progressive relaxation, CBT techniques and self awareness.

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8. Discussion

1) Two themes of the epidemiological research are diseases of the elderly and cognition. Epidemiological studies have included in their remit the explication of the causes of disease, van der Fliers, 2005. Notwithstanding genetic variation, the inconsistent associations between MCI, AD and diabetes may be due to lack of study validity and confounds such as treatment, control and age of onset.

The variables included in studies are those considered valid at the time the studies are set up. These may be amended in the light of new findings although the results may take time to feed through. Treatment, control and age of onset of diabetes are such predictor variables: defined by diagnosis, treatment and medical history.

Ideally diagnosis of should be by a physician, especially when dealing with elderly subjects. Treatment ranges from diet and exercise, tablets to insulin. There are different tablet types and different insulin regimes. Age of onset and control are associated with vascular complications and may be relevant.

2) To properly partial out the effect of diabetes it is necessary to include these predictor variables in multiple regression analyses, including appropriate interaction terms in the model. An example is Schmidt (2004) who included treatment as a dichotomised variable showing hypertensive diabetics are at increased risk of brain atrophy (β=1.19, p=0.02). But when interaction between hypertension and treatment is included the contribution to overall risk for treated diabetes is not significant (β=0.10, p=ns), while untreated diabetes is at increased risk (β=2.2, p=0.001).

Nilsson 2002 included HbA1c levels allowing the separation of diabetes from transitory glucose effects on memory. Hyperglycaemia rather than diabetes is associated with memory deficit. This again supports a role for these variables.

Ott 1996 included treatment details and found no increased risk of dementia with diabetics on oral medication [OR] 1.0: CI 95%(0.6-1.9) after controlling for risk factors including hypertension and treatment for hypertension. Compared to the overall [OR] 1.2: CI 95%(0.8-1.9) and insulin treatment ,[OR] 2.6: CI 95%(1.1- 6.2). The range of OR values for insulin treatment (1.1- 6.2) shows a high level of variation. Unfortunately there are no data available to subdivide this range by level of glucose control (HbA1c).

Lack of appropriate data meant that 13 participants from the Rotterdam and 21 from the Whitehall study were excluded from the CASCADE study due to lack fasting or random glucose levels, Schmidt 2006. Yet both the Rotterdam and Whitehall studies are widely cited. Yeung 2009, investigating the effects of diabetes on cognition included years since onset but no HbA1c detail, which in light of Nilsson's conclusions above emphasises the need for such data.

3) Epidemiological studies are not immune from the effects of International and National Health Policy standards. Diabetes diagnosis, treatment and control in the UK, and elsewhere, have been subject to a number of such changes, DCCT 1993; UKDPS 1998; WHO 1999; NSF for Diabetes (2003).

If age of onset, treatment and glucose control are important predictors of MCI then studies that do not include them will have inherent confounds, secondly if these variables are significant predictors more recent studies that include them should show a change in effect size, e.g. Akalomafe, Yeung.

4) The glycation theory of neural ageing supports the importance of data on treatment and glucose control, Takeuchi, 2004. Glucose concentration and elapsed time determine the production of AGE's and hyperglycaemia particularly favours the

polypol pathway and TAGE. AGE's accumulate in the skin of diabetic animals according to severity of complications but there is no correlation between HbA1c in mammals and accumulation in the dura mater of the brain, Finch and Cohen, 1997.

This is taken to imply different tissue thresholds for accumulation of AGE's and could be a factor in the much increased incidence rates of AD in the over 70's.

The vascular theory of neural ageing Zlokovic (2005) relies on same parameters of glucose concentration and elapsed time as above. It is the quality of prolonged control over blood sugar levels that mainly determine vascular complications in diabetes, namely retinopathy nephropathy, neuropathy, coronary heart disease and stroke. According to Zlokovic (2005) vascular disease is responsible for an increase in Aβ leaking across the BBB and for dysfunction of the neurovascular unit leading to encephalopathy.

Clearly on theoretical grounds treatment, control and age of onset shuld be pertinent data in the analysis of associations between DM, MCI and AD.

5) Psycho-therapeutic interventions aimed at compliance can have an effect on blood glucose control and help to delay or avoid the complications of diabetes. Additionally psychotherapy, counselling and education enable the person with diabetes to assert personal control over their condition. This can have the indirect effects on better control and avoid the spiral of failure that can lead to depression often associated with chronic conditions.

9. Summary/conclusions.

Main effects for DM seen in historic epidemiological studies may be significantly different from more recent findings. This is due to poor design in operationalising key diabetic variables such as treatment, control and duration of illness or from other uncontrolled variables.

It is perhaps a subtle distinction to argue that hyperglycemia rather than diabetes is responsible for cognitive impairment in diabetic patients. But, the distinction being made, it allows the limits of normal functioning to be defined, less than 15mmol/l for rodents, much in the way that blood glucose limits of 4-7mmol/l before meals are optimum levels to reduce diabetic complications. Control within these limits can be assisted using psychotherapeutic interventions.

Glucose control, treatment and duration have theoretical links to neural ageing in both the glycation and vascular theories. Glucose control, treatment and duration all have causative links.

When all sources of variance have been accounted for then results from different studies should converge. Previous results showed little consensus. Policy changes on diabetes have resulted in earlier diagnosis and better control. Glucose control and duration will have different cumulative effects between different cohorts, although this can be controlled for. Any associations between diabetes and AD that do not include as variables glucose control and duration are likely to have uncontrolled variation and results will remain inconsistent. It is also a caution to the practice of citing previous studies in support of a research hypothesis.

In summary the inclusion of both HbA1c and duration of illness would add value to epidemiological studies. Accounting for more variation will result in more consistent findings on the association between diabetes, MCI and AD. The results considered here (1996-2009) are still inconsistent. However more recent studies controlling for glucose control and treatment type do show smaller or non-significant effect sizes and admit to the possibility that together both variables might reduce variability further. In any event psychotherapeutic interventions have their own modest effects

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