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Glucose intolerance and diabetes as risk factors for cognitive impairment in people at high cardiovascular risk: Results from the ONTARGET/TRANSCEND Research Programme☆

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ABSTRACT

Aims: To assess the cross-sectional associations of the measures of glycemia and cognitive function in subjects at high cardiovascular risk.

Methods: Setting and patients: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and concurrent Telmisartan Randomized Assessment Study in ACE intolerant Subjects with Cardiovascular Disease (TRANSCEND) are multi-center, randomized, controlled investigations of different approaches to angiotensin receptor blockade in over 30,000 high CV risk subjects. Baseline data in both trials was used to analyze relationships between measures of glycemic control and cognition.

Outcomes: The univariate and multivariate relationships between diabetes status, fasting plasma glucose (FPG), and scores on the Mini-Mental State Examination (MMSE) were assessed.

Results: In subjects with diabetes, the mean MMSE score was 0.4 units lower than in those without diabetes ($P < 0.0001$). In all subjects, a 1 mmol/L higher FPG value was associated with a MMSE score that was 0.06 units lower ($P < 0.0001$). The association persisted after adjustment for several cardiovascular risk factors.

Conclusions: Dysglycemia is a risk factor for impaired cognitive function in this broadly representative, high-risk study population. Prospective studies can more reliably discern temporal associations, including the effects of glucose lowering in this clinical group.

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1. Introduction

Cognitive impairment, with or without features of overt dementia, is a major cause of disease burden in ageing populations. In Western countries, the prevalence of dementia is estimated at 8% in people over the age of 65 years and 30% in people aged 85 years or older [1,2]. For Alzheimer's disease, the most common form of dementia, the numbers of affected people are estimated to increase from 4.5 million in 2000 to 13.2 million by 2050 in the United States, alone [3]. Mild cognitive impairment, sometimes referred to as 'pre-dementia', is even more prevalent than dementia. The chronic and progressive nature of these disturbances in memory and other cognitive functions often interfere with occupational and/or social performance, and are accompanied by abnormalities of mood, behaviour and personality. Cognitive impairment is associated with deficits in self-care and [4] represents a large and increasing cost to individuals, families and societies around the world.

In addition to stroke and other cardiovascular (CV) risk factors, diabetes has recently emerged as a determinant of cognitive impairment [5]. People with diabetes are approximately 1.5 times more likely to experience both cognitive decline and dementia than people without diabetes [6]. The relationship between 'non-diabetic' degrees of hyperglycemia and cognitive impairment is less well established. Experimental studies in both animals and humans without diabetes have shown that poor glucose regulation following a glucose loading test is associated with poor performance on a variety of cognitive tests, especially with ageing [7]. Conversely, some [8–14] but not all [15–19], cross-sectional epidemiological studies report an inverse association between cognitive function and glucose levels, whilst several prospective studies indicate that people with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) are at increased risk of cognitive decline when compared with those who are normoglycemic [20,21].

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and parallel Telmisartan Randomized Assessment Study in ACE intolerant Subjects with Cardiovascular Disease (TRANSCEND) study, are two large-scale, multi-center, randomized controlled trials being undertaken to assess the effects of angiotensin receptor blockade in people at high risk of CV disease. The primary objectives of ONTARGET ($N = 25{,}620$) are to determine if: (a) the combination of the angiotensin receptor blocker (ARB) telmisartan and angiotensin converting enzyme inhibitor (ACE-I) ramipril is more effective in reducing the composite outcome of cardiovascular death, acute myocardial infarction (AMI), stroke, or hospitalization for congestive heart failure (CHF), than ramipril alone; and (b) whether telmisartan alone is at least as effective as (i.e. 'not inferior' to) ramipril alone. The primary objective of TRANSCEND ($N = 5926$) is to determine if treatment with telmisartan is superior to placebo in people who are intolerant of an ACE-I. An important secondary outcome of both trials, due to be completed in 2008, is to evaluate the treatment effects on cognitive function. The large-scale and wide baseline data available on demographic characteristics, diabetes status, fasting blood glucose levels, together with a measure of cognitive function, provides a unique opportunity to analyze the cross-sectional relationship between measures of glycemic control and cognition in people at high CV risk.

2. Subjects materials and methods

2.1. *Study population*

The design of the ONTARGET and TRANSCEND trials has been described elsewhere [22]. In brief, the study included men and women (aged $\geq$55 years) who are at high risk of a major CV event on the basis of one or more of the following: a history of coronary artery disease, peripheral vascular disease, stroke or transient ischemic attack, and diabetes with end-organ complications. Individuals were excluded if they were unable to discontinue an ARB, had known hypersensitivity or intolerance to an ARB, or were seriously ill. The study protocol was approved by the Research Ethics Board of each participating center, and all participants provided written informed consent.

2.2. *Measures*

Baseline characteristics were obtained by clinical assessment, local measurement of a fasting glucose and lipid profile, and completion of a baseline questionnaire. Diabetes was defined as any self-report of a diagnosis of diabetes and depression was defined as an affirmative answer to the question of whether or not the participant was feeling ''sad, low in spirits or depressed for 2 or more weeks'' and during that time also ''thought a lot about death or required treatment for depression''. Individuals were deemed to have: (a) CV disease if they had a previous myocardial infarction (MI), stroke, transient ischemic attack or angina; (b) a prior revascularization if they had previous coronary artery bypass surgery, percutaneous coronary intervention, atherectomy, carotid enedarterectomy, or peripheral artery surgery; (c) cerebrovascular disease if they reported experiencing a stroke, Transient Ischemic Attack (TIA) or undergoing a carotid endarterectomy; (d) hypertension if they reported a previous hypertension diagnosis. They were deemed to: (a) use tobacco if they reported current use of cigarettes, beedies, pipes, cigars, or sheesa; (b) regularly consume alcohol if they reported three or more drinks a week; (c) be physically active if they reported physical activity at least 2–4 times a week; and (d) consume fruit, vegetables or fish if they reported such intake on a daily basis.

The Mini-Mental State Examination (MMSE) instrument, which provides a maximum score of 30 across seven cognitive domains: orientation to time (5 points), orientation to place (5 points), registration of three words (3 points), attention and calculation (5 points), recall of 3 words (3 points), language (8 points), and visual construction (1 point) [23], was used to measure cognitive function. The MMSE was completed in the participant's native language using validated translated questionnaires, and the scoring was done centrally. The validity of the MMSE as a general screening tool for detecting dementia has been extensively demonstrated [24]. It can also identify changes in cognitive function for non-demented