

Increased Risk of Cognitive Impairment in Patients With Diabetes Is Associated With Metformin

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OBJECTIVE—To investigate the associations of metformin, serum vitamin B₁₂, calcium supplements, and cognitive impairment in patients with diabetes.

RESEARCH DESIGN AND METHODS—Participants were recruited from the Primary Research in Memory (PRIME) clinics study, the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, and the Barwon region of southeastern Australia. Patients with Alzheimer disease (AD) ($n = 480$) or mild cognitive impairment ($n = 187$) and those who were cognitively intact ($n = 687$) were included; patients with stroke or with neurodegenerative diseases other than AD were excluded. Subgroup analyses were performed for participants who had either type 2 diabetes ($n = 104$) or impaired glucose tolerance ($n = 22$).

RESULTS—Participants with diabetes ($n = 126$) had worse cognitive performance than participants who did not have diabetes ($n = 1,228$; adjusted odds ratio 1.51 [95% CI 1.03–2.21]). Among participants with diabetes, worse cognitive performance was associated with metformin use (2.23 [1.05–4.75]). After adjusting for age, sex, level of education, history of depression, serum vitamin B₁₂, and metformin use, participants with diabetes who were taking calcium supplements had better cognitive performance (0.41 [0.19–0.92]).

CONCLUSIONS—Metformin use was associated with impaired cognitive performance. Vitamin B₁₂ and calcium supplements may alleviate metformin-induced vitamin B₁₂ deficiency and were associated with better cognitive outcomes. Prospective trials are warranted to assess the beneficial effects of vitamin B₁₂ and calcium use on cognition in older people with diabetes who are taking metformin.

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In 2010, more than 346 million people had diabetes worldwide. Recent studies from the U.K. (1) and Italy (2) reported that the adult prevalence of diabetes was approximately 4.2%. In the U.S., the prevalence of diabetes in the adult population may be as high as 14% when undiagnosed cases are included (3). The prevalence of diabetes may be higher in some developing nations: in the developing region of southern China it was reported to be 21.7% in 2010 (4). The prevalence of diabetes is more than 20% in some Pacific Island nations, reaching 47% in 22- to 64-year-old American Samoans (5).

In diabetes, hyperglycemia activates the cellular signaling protein kinase C, which induces production of the vasoconstrictor protein endothelin-1. Excess intracellular glucose is converted to sorbitol by the enzyme aldose reductase. When intracellular levels of glucose are high, this process exhausts the energy substrate NADPH, resulting in oxidative stress. High intracellular sorbitol levels cause osmotic stress and cell death. These biochemical changes in hyperglycemia are a proposed mechanism for macrovascular and microvascular complications and neuropathy (6–8). Diabetes is associated with a faster rate of cognitive decline in those with mild cognitive impairment (MCI) (9) and an increased risk for developing Alzheimer disease (AD) (10).

Approximately 90% of patients with diabetes have type 2 diabetes (1). The biguanide metformin is a first-line treatment for type 2 diabetes, increasing glucose uptake in muscle while reducing liver gluconeogenesis (the synthesis of glucose from amino acids). These effects are mediated by activation of the cellular signaling protein AMP-activated protein kinase (11).

Metformin first became available in the U.K. in 1958 and entered the Canadian market in 1971, but it has been available in the U.S. only since 1995. In a survey of 65,000 U.S. war veterans (12), metformin use among those with diabetes increased from 29% in 2000 to 63% in

2005. Among 242 Australian veterans who had diabetes, metformin was used by 75% in 2005 but decreased to 57% in 2009 (13).

The rate of vitamin B₁₂ deficiency among patients who are taking metformin is reported to approach 30% (14–16). A drug interaction between metformin and the cubilin receptor inhibits the uptake of vitamin B₁₂ from the distal ileum, lowering serum vitamin B₁₂ levels. In a long-term, randomized, placebo-controlled trial, metformin therapy in type 2 diabetes was associated with a 19% reduction in serum vitamin B₁₂ concentrations compared with placebo (17). In a case-control study, Wile and Toth (18) reported that metformin use was associated with reduced vitamin B₁₂ levels and more severe peripheral neuropathy in patients with diabetes.

In a prospective trial, calcium supplements were reported to reverse the drug interaction that causes vitamin B₁₂ deficiency induced by metformin (19). The clinical significance of alleviating metformin-induced vitamin B₁₂ malabsorption by calcium supplementation has not been previously investigated. By correcting vitamin B₁₂ levels in patients with diabetes who use metformin, calcium supplements may help to preserve cognitive function. In addition, neuronal signaling in memory and learning involves a calcium-mediated process, so calcium supplementation may also have a direct effect on the brain. Calcium dysregulation is the subject of one proposed theory for age-related cognitive changes and AD (20). The risks and potential benefits of calcium supplementation on cognition and for alleviating vitamin B₁₂ malabsorption merit further investigation.

The amyloid plaques seen in the brains of patients with AD are formed by aggregation of A β peptides. In cell cultures, Chen and colleagues (21) reported that activation of AMP-activated protein kinase by metformin increased the expression of β -secretase, an enzyme that increases the formation of A β peptides. One recent case-control study that included 14,172 participants 65 years of age or older reported that taking metformin over the long term increased the risk of AD (odds ratio [OR] 1.71 [95% CI 1.12–2.60]) (22).

Recent studies of murine models of diabetes indicate that metformin may attenuate irregularities in phosphorylation of tau proteins (23) or may facilitate neuroneogenesis (24) and so may be of

benefit to those with AD. In 25,393 patients older than 50 years with type 2 diabetes, metformin was reported to reduce the risk of dementia by 24% (hazard ratio 0.76 [95% CI 0.58–0.98]) (25). The purpose of our study was to investigate the associations of metformin, serum vitamin B₁₂ levels, and cognition in a sample of patients with diabetes.

RESEARCH DESIGN AND METHODS

Participants and settings

Participants were recruited from two prospective studies: the Prospective Research in Memory (PRIME) clinics study and the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Only data and biochemical measurements pertaining to baseline visits were included in this analysis. The PRIME study recruited 970 participants from 9 sites in Australia, including 3 each in Victoria and New South Wales and 1 each in Queensland, Western Australia, and South Australia. The AIBL study of aging recruited 1,112 participants in Victoria (60%) and Western Australia (40%). The study cohorts and methods of the PRIME and AIBL studies are described elsewhere (26,27).

A further 862 participants who resided in the Barwon region of southeastern Australia between 2001 and 2011 also were recruited through the Cognitive, Dementia and Memory Services clinic at the McKellar Centre, a rehabilitation and aged-care facility. Patients with AD who were seen at a geriatrician's private practice during the same period also were recruited ($n = 935$).

Study design

Participants in the PRIME study were recruited during routine patient care. AIBL participants volunteered after an advertisement on television in late 2006. The Mini-Mental State Examination (MMSE) was used to assess cognitive ability. Subjects were assessed at scheduled visits during the PRIME and AIBL studies or ad hoc during routine patient care. All participants with serum vitamin B₁₂ measurements taken within 6 months of cognitive assessment were included. Participants without serum measurements taken within 6 months of cognitive assessment ($n = 1,015$) were excluded.

The data from records pertaining to subjects who were recruited from more than one source ($n = 566$) were merged. Of the remaining participants, there were

121 with stroke and 566 with diagnoses other than AD, such as frontotemporal dementia, Parkinson disease, dementia with Lewy bodies, or mixed dementias. Participants with other neurodegenerative diseases were excluded to limit confounders. A further 291 participants were excluded because they had incomplete medical histories; information that was missing included dates of birth, medication use, and comorbid conditions.

A subgroup analysis was performed with participants who had diabetes ($n = 104$) or impaired glucose tolerance ($n = 22$). Patients with type 1 diabetes were not specifically excluded, but there were none with serum vitamin B₁₂ measurements taken within 6 months of cognitive assessment.

Ethical approval

Institutional review was performed at each study host site. Reviewing committees included the Barwon Health Human Research Ethics Committee (HREC) (Victoria), Austin Health HREC (Victoria), St. Vincent's Hospital Governance Review Unit (Victoria), Hunter New England HREC (New South Wales), Northern Hospital Network HREC (New South Wales), Northern Sydney Central Coast HREC (New South Wales), Metro North Health Service District HREC (Queensland), South Metropolitan Area Health Service HREC (Western Australia), and The Queen Elizabeth Hospital Ethics of Human Research Committee (South Australia).

Statistical analyses

An ordinal logistic regression model was formed with categories of cognitive performance as the response variable and diabetes as a predictor. Categories were ordered by cognitive performance, including "most impaired" (MMSE <18; $n = 137$), "mildly impaired" (MMSE 18–23; $n = 240$), "minimally impaired" (MMSE 24–27; $n = 295$), and "not impaired" (MMSE 28–30; $n = 682$). The model was adjusted for age, sex, level of education, and depression because these factors were previously reported to affect MMSE testing (28,29).

A subgroup analysis of only patients with diabetes was then performed. The response variable was cognitive performance. Categories were "most impaired" (MMSE <18; $n = 39$), "mildly impaired" (MMSE 18–23; $n = 40$), "minimally impaired" (MMSE 24–27; $n = 32$), and "not impaired" (MMSE 28–30; $n = 15$). The

effect of metformin on the cognitive performance of patients with diabetes was investigated in this model, which then was adjusted for serum vitamin B₁₂ measurements and use of calcium supplements to investigate any possible interactions. There was insufficient information on use of other antidiabetic drugs, the duration of metformin use, and markers for socioeconomic status, diet, or exercise to investigate these variables.

RESULTS—There were 1,354 participants included in this analysis (Fig. 1). Participants were 51–99 years old (mean age \pm SD 73.8 \pm 8.3 years); females outnumbered males (59.5 vs. 40.5%). Just more than half of the participants (50.4%) scored 28–30 on the MMSE and so were considered not impaired; 21.8% were minimally impaired (MMSE 24–27), 17.7% were mildly impaired (MMSE 18–23), and 10.1% scored less than 18 on the MMSE (most impaired).

Participants with diabetes were marginally older than participants without diabetes (75.5 vs. 73.6 years; $P = 0.013$). The number of males was proportionally larger among participants with diabetes (46.8 vs. 39.9%), but this difference was not statistically significant. Prevalence of depression was similar between participants with diabetes and those without diabetes (31.7 vs. 27.3%; $P = 1.000$). The proportion of participants with a tertiary level of education was higher among participants without diabetes than participants with diabetes (39.3 vs. 22.2%; $P < 0.001$). The number of participants who scored below 28 on the MMSE was proportionally higher among participants with diabetes than those without diabetes (69.0 vs. 47.6%; $P = 1.000$).

After adjusting for age, sex, education, and depression, participants with type 2 diabetes had worse cognitive performance than participants without diabetes (adjusted OR 1.51 [95% CI 1.03–2.21]).

Cognitive performance was better in younger participants, those without depression, and those with a higher level of education. The adjusted ORs for each predictor are shown in Table 1.

Among participants with diabetes, cognitive performance was worse in patients who were taking metformin (adjusted OR 2.23 [95% CI 1.05–4.75]). MMSE scores were lower in participants with diabetes who used metformin (mean score \pm SD 22.8 \pm 5.5) than in those who did not use metformin (24.7 \pm 4.4). Participants with diabetes who had vitamin B₁₂ levels <250 μ mol/L also had worse cognitive performance (2.29 [1.12–4.66]). MMSE scores were lower among those with serum vitamin B₁₂ <250 μ mol/L (22.9 \pm 4.7) than those with higher levels (25.0 \pm 4.7).

Each 1-year increase in age was associated with an 8% increased risk of impaired cognitive performance (OR 1.08 [95% CI 1.03–1.13]). A secondary or

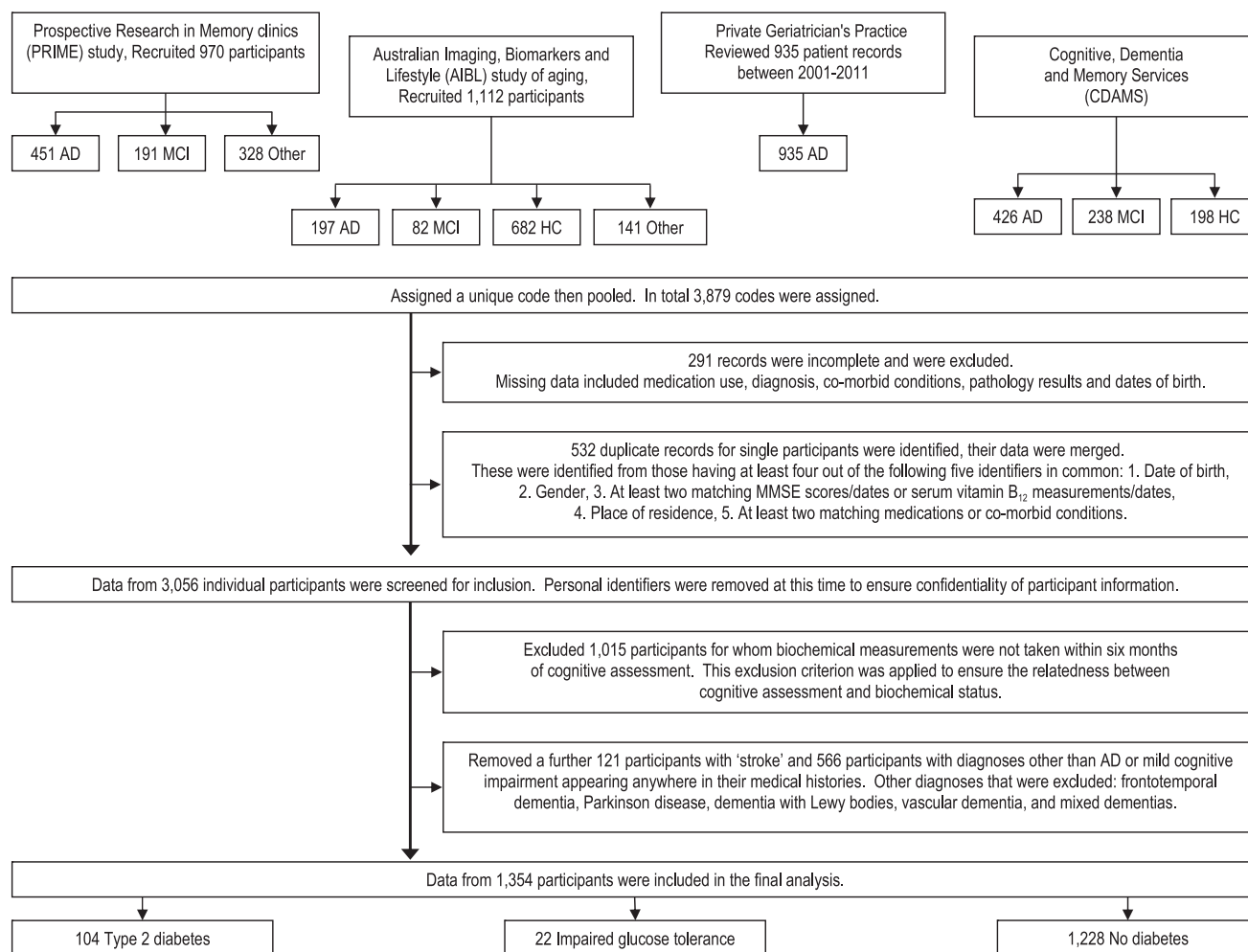


Figure 1—Recruitment, inclusion, and exclusion.

Table 1—Cognitive performance in 1,354 participants who had AD or MCI or were cognitively intact

Categories, by predictor*	Model not adjusted for serum vitamin B ₁₂ levels			Model adjusted for serum vitamin B ₁₂ levels†		
	OR	95% CI	P value	OR	95% CI	P value
Variable						
Diabetes						
Type 2 diabetes (n = 104)	1.51	1.03–2.21	0.033	1.49	1.02–2.19	0.039
Impaired glucose tolerance (n = 22)‡	0.79	0.34–1.85	0.584	0.81	0.34–1.90	0.624
No diabetes (n = 1,228)	—	—	—	—	—	—
Model adjusters						
Age (n = 1,354)	1.11	1.09–1.12	<0.001	1.10	1.09–1.12	<0.001
Sex						
Male (n = 549)	0.88	0.70–1.10	0.257	0.86	0.69–1.08	0.186
Female (n = 805)	—	—	—	—	—	—
Depression						
Yes (n = 375)	1.61	1.27–2.04	<0.001	1.66	1.30–2.10	<0.001
No (n = 979)	—	—	—	—	—	—
Level of education§						
Tertiary (n = 510)	0.12	0.08–0.17	<0.001	0.12	0.08–0.17	<0.001
Secondary (n = 674)	0.36	0.26–0.49	<0.001	0.36	0.26–0.50	<0.001
Primary (n = 170)	—	—	—	—	—	—

All models were adjusted for age, sex, reported history of depression, and level of education. Values obtained in the model that also was adjusted for serum vitamin B₁₂ levels are italicized. *Reference levels for categories were female sex, no reported history of depression, and having attained a primary level of education only (up to 6 years of schooling). †Serum vitamin B₁₂ status was defined as low (serum levels <250 µmol/L) or normal (serum levels >250 µmol/L). The reference level for serum vitamin B₁₂ status was normal. ‡Impaired glucose tolerance was by self-report or review of patient's medical history. §Categories for level of education were tertiary (>13 years of schooling), secondary (6–13 years of schooling), and primary (<6 years of schooling).

tertiary level of education was the strongest predictor of better cognitive performance in patients with diabetes. The adjusted ORs for each variable are shown in Table 2.

CONCLUSIONS—In our series, patients with diabetes who were taking metformin had worse cognitive performance than participants who were not taking metformin. Our observations agree with those previously reported by Imfeld and colleagues (22), in particular that patients who are taking metformin may be at an increased risk for cognitive impairment. This association was weakened after adjusting for serum vitamin B₁₂ levels; thus any effect metformin has on cognitive performance may be at least partially mediated by altering serum vitamin B₁₂ levels.

Alternatively, patients who are prescribed metformin may have worse glycemic control or diabetes-related complications than patients with diabetes who are not prescribed metformin, so there remains the potential for confounding, despite restricting the analysis to only patients with diabetes. However, because metformin is a first-line pharmacotherapy for the treatment of type 2 diabetes, this would seem unlikely (30).

There was insufficient information regarding the duration of metformin use,

the severity of diabetes (e.g., HbA_{1c} levels), duration of diabetes, or use of other anti-diabetic drugs to enable us to investigate these effects in our study, particularly because these findings were based on a small sample. We recommend a larger study to examine the effect of dose and duration of metformin use, and the effects of other anti-diabetic agents using a battery of cognitive assessments and following participants over a number of years.

Calcium supplements have previously been reported to reverse vitamin B₁₂ deficiency induced by metformin. In this study, patients with diabetes who used calcium supplements were less likely to be cognitively impaired. However, calcium supplements have been reported to be associated with an increased risk for myocardial infarction in postmenopausal women and in patients with chronic kidney disease (31–34). In contrast, a recent meta-analysis indicates that supplementation with both vitamin D and calcium is associated with a reduction in mortality compared with vitamin D supplementation alone (35). Because this population already has increased cardiovascular risk (36), the safety of calcium supplementation in patients with diabetes treated with metformin would need to be established before such interventions could be recommended.

Patients with diabetes are at an increased risk for AD (10). In diabetes, amylin aggregation destroys the β-cells of the pancreas (37). By the same mechanism, a protein misfolding disorder may be related to aggregation of amyloid plaques. Metformin is a widely prescribed first-line monotherapy for type 2 diabetes but is associated with vitamin B₁₂ deficiency and peripheral neuropathy. A case-control study of more than 14,000 patients reported that long-term metformin use was associated with an increased risk for AD in those ≥65 years old (22). Metformin at pharmacological doses was reported to increase the expression of β-secretase in cell culture; this may be a possible disease mechanism (21). Alternatively, metformin also impairs absorption of vitamin B₁₂ via a drug interaction that occurs at the distal ileum. Low serum vitamin B₁₂ levels are associated with AD and other neurodegenerative diseases (38).

Cognitive performance of patients with diabetes was measured using the MMSE. The MMSE may be inadequate for detecting differences between higher functioning adults (39). The MMSE is sensitive to age, depression, and level of education, so all models were adjusted for these factors. Most of our subjects were

Table 2—Cognitive performance in 126 patients with either type 2 diabetes or impaired glucose tolerance

Categories, by predictor*	Model not adjusted for serum vitamin B ₁₂ levels			Model adjusted for serum vitamin B ₁₂ levels†		
	OR	95% CI	P value	OR	95% CI	P value
Variables						
Metformin						
Yes (n = 35)	2.23	1.05–4.75	0.037	1.75	0.81–3.78	0.158
No (n = 91)	—	—	—	—	—	—
Calcium supplements						
Yes (n = 44)	0.47	0.22–1.02	0.056	0.41	0.19–0.92	0.030
No (n = 82)	—	—	—	—	—	—
Model adjusters						
Age (n = 1,354)	1.08	1.03–1.13	0.001	1.08	1.03–1.13	0.002
Sex						
Male (n = 59)	0.54	0.27–1.09	0.086	0.49	0.24–1.01	0.052
Female (n = 67)	—	—	—	—	—	—
Depression						
Yes (n = 40)	0.95	0.45–2.00	0.884	0.96	0.45–2.05	0.916
No (n = 86)	—	—	—	—	—	—
Level of education‡						
Tertiary (n = 28)	0.02	0.01–0.08	<0.001	0.03	0.01–0.11	<0.001
Secondary (n = 73)	0.26	0.11–0.63	0.003	0.25	0.10–0.62	0.002
Primary (n = 25)	—	—	—	—	—	—

All models were adjusted for age, sex, reported history of depression, and level of education. Values obtained in the model that also was adjusted for serum vitamin B₁₂ levels are italicized. *Reference levels for categories were “not taking metformin,” female sex, no reported history of depression, and having attained a primary level of education only (up to 6 years of schooling). †Serum vitamin B₁₂ status was defined as low (serum levels <250 µmol/L) or normal (serum levels >250 µmol/L). The reference level for serum vitamin B₁₂ status was normal. ‡Categories for level of education were tertiary (>13 years of schooling), secondary (6–13 years of schooling), and primary (<6 years of schooling).

assessed during routine clinical care by clinicians who use the MMSE as part of their standard assessment. In Australia, documentation of cognitive impairment using an MMSE score and improvement while receiving therapy is required to obtain subsidized antedementia therapies (40). More comprehensive assessment tools may be preferable for use in future investigations of cognitive impairment in at-risk populations such as those we have studied.

Increased monitoring of cognitive ability in patients with diabetes who use metformin is warranted, particularly among older adults (aged older than 50 years). Vitamin B₁₂ supplements are inexpensive and may improve the cognitive outcomes of patients with diabetes. Adequately powered, prospective, controlled trials are warranted to investigate further the association between diabetes, cognitive decline, and the effect of metformin therapy, as well as the possible amelioration using vitamin B₁₂ and/or calcium supplementation.

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E.M.M. reviewed the literature, collected biochemical measurements from study host sites, analyzed and interpreted the data, and drafted the manuscript. A.G.M., M.A.K., R.P.C., and D.A.W. interpreted the data and reviewed the manuscript. D.A. interpreted the data and reviewed the manuscript, collected the PRIME data and managed the PRIME study database, and collected the AIBL data and managed the AIBL database. H.B., M.W., and K.B. interpreted the data and reviewed the manuscript and collected the PRIME data and managed the PRIME study database. K.A.E., A.I.B., N.G.F., R.M., C.S., and C.R. interpreted the data and reviewed the manuscript and collected the AIBL data and managed the AIBL database. E.M.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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