Editorial

Metformin: good or bad for the brain?

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Although diabetes mellitus seems to be associated with the development of cognitive impairment as well as dementia (1), much can be said regarding hypoglycemia (2,3). Among oral hypoglycemic agents, metformin has the advantage of lower rates of unwanted hypoglycemic events over sulphonylurea class of drugs (4). Hence, metformin treatment can be thought to be a safe option with regards the preservation of cognitive skills both through improvement of fasting plasma glucose and causing less number of hypoglycemic events. However, in an article published several months ago in the journal *Diabetes Care*, Australian scientist Eileen M. Moore and her colleagues found metformin use associated with impaired cognitive performance in a group of people with a mean age of 73.8±8.3 years (5). In their study they pooled participants from two prospective studies: the Prospective Research in Memory (PRIME) clinics study and the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, with the addition of participants from a special center as well as a geriatrician's private office, reaching a total of 1,354 subjects in their final analyses. After basic adjustments, they reported that patients with type 2 diabetes were 1.51 times more likely to display worse cognitive performance than participants without diabetes (P=0.033). Moreover, they observed that the risk of having worse cognitive performance was 2.23 times higher among metformin users (P=0.037). However, after inclusion of vitamin B12 deficiency in the model, the association of metformin use to cognitive impairment disappeared. They found significantly worse cognitive performance in participants with diabetes who had vitamin B12 levels <250 ρmol/L. Their data suggested vitamin B12 deficiency as the primary mediator of cognitive loss in diabetic subjects on metformin treatment. Interestingly, use of calcium supplements was related to better cognitive skills in their participants with diabetes; however, whether combined use of metformin with these supplements reduces the risk of cognitive loss could be discussed by the authors.

In animal experiments metformin was shown to accumulate in the brain (6) and up-regulate blood brain barrier in a protective manner (7). Metformin was shown to induce dephosphorylation of tau in cortical neurons in experimental conditions (8), but in an animal model of insulin resistance it failed to improve cognitive tests despite improvement in metabolic responses (9). Thus, it is currently unknown whether metformin does good both in peripheral tissues and brain. The clinical results are also challenging as long term metformin use was linked to lower rates of cardiovascular disease including stroke and mortality (10), but in a recent case control study on elderly, it was associated with slightly higher risk of Alzheimer's disease while users of sulfonylureas, thiazolidinediones or insulin were not associated with such an outcome (11).

What we already know is the clear evidence of higher risk of vitamin B12 deficiency in metformin users which is thought to impair the natural neuronal protection by this nutrient (12,13). However, numerous points need to be identified in prospectively designed controlled trials as to whether supplementation increases blood vitamin B12 level (13) or improves cognition in subjects with diabetes mellitus (14).

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