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EDITORIAL

Type 3 diabetes mellitus. The revival of inhaled insulin?☆

Diabetes mellitus tipo 3. ¿El renacer de la insulina inhalada?

Francesc Formiga[a,*], **Manuel Pérez-Maraver**[b]

[a] *Programa de Geriatría, Servicio de Medicina Interna, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain*

[b] *Servicio de Endocrinología y Nutrición, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain*

Type 2 diabetes mellitus (DM) and dementia are two conditions highly prevalent today and probably interrelated. The term type 3 diabetes has therefore been proposed to try and provide a view integrating the potential pathogenetic mechanisms shared by DM and Alzheimer disease (AD).[1–3]

Significant epidemiological evidence relating DM and dementia has accumulated in the past decade.[1–3] According to a recent complete meta-analysis, patients with DM have a relative risk of 1.46[4] of suffering AD. A greater impact of diabetes on dementia has been reported in people who also have a genetic predisposition, and also when diabetes is diagnosed earlier in life. Impact is lower in older groups, but diabetes continues to be a risk factor even in people aged 85 years.[5] It should be noted that current epidemiological studies were not especially designed to assess the relationship between diabetes and dementia, and have therefore some limitations which are expected to be solved with future evidence from the Edinburgh Type 2 Diabetes Study.[6]

Various hypotheses have been proposed to explain the relationship between DM and dementia, from the effect of acute hyperglycemia itself (which may affect working memory and attention) to the effect of chronic hyperglycemia, which may cause and aggravate macrovascular disease, more related to vascular dementia, and microvascular disease.[1–3] Chronic hyperglycemia may also involve increased oxidative stress, mitochondrial dysfunction, and production of advanced glycation end-products.[2]

A very interesting theory considers hyperinsulinemia and insulin resistance as a potential risk factor for AD, because they may cause neuron apoptosis and promote formation of extracellular β-amyloid deposits.[1–3] Under normal conditions, excess β-amyloid may be removed through the lipoprotein receptor-related protein 1 (which decreases if insulin resistance exists) or by a degradation process in which insulin-degrading enzyme (IDE) is involved. If chronic peripheral hyperinsulinemia exists, insulin transport across the blood-brain barrier will decrease. This is important because, among other effects in the brain, insulin promotes learning and long-term memory, stimulates acecylcholinesterase expression responsible for acetylcholine, and decreases phosphorylation of tau proteins.[7,8] Insulin activates IDEs and, when effective insulin levels are low, IDE activation may be lower, and a greater harmful accumulation of β-amyloid may therefore occur.[2] Thus, possible diabetes 3 would be defined as the condition occurring when hyperinsulinemia in response to insulin resistance leads to a decrease in cerebral insulin and poor regulation of IDE. β-Amyloid would accumulate due to its decreased degradation by IDE, among other mechanisms.[2,9]

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* Corresponding author.
E-mail address: fformiga@bellvitgehospital.cat (F. Formiga).

As regards the potential leading role of hypoglycemia in cognitive impairment, it should be noted that this is a controversial and usually two-directional issue. Thus, while recurrent hypoglycemia appears to promote cognitive impairment, people who already have cognitive impairment have greater difficulty to achieve stable diabetes control and therefore experience more hypoglycemic episodes.[2]

With regard to DM control, a moderate improvement in learning memory and a less marked improvement in complex motor skills have been reported three weeks after achievement of good glycemic control. By contrast, higher glycosylated hemoglobin levels are associated to poorer cognitive performance and greater difficulty for executive functions.[2] However, the results of the ACCORD-MIND substudy do not support intensive treatment as a strategy to improve cognition.[10]

There is currently no agreement on the drug class to be used for diabetes control in order to achieve potential prevention of AD or to slow cognitive loss when this already exists, but use of drugs not causing hypoglycemia appears logical. Thus, conflicting results have been reported for metformin. Both positive results (metformin may counteract structural changes in tau protein in nerve cells from mice)[11] and negative results (the drug may increase β-amyloid production through dysregulation of β-secretase)[12] have been reported. In population studies, chronic use of metformin have been associated to increased risk of dementia, but a causal relationship between both could not be established.[13] Glitazones, as drugs which decrease insulin resistance, could have a neuroprotective effect, but early interesting results, even in humans, have not been confirmed in the recent ACCORD-MIND study, and rosiglitazone may even be associated to negative results.[14] Incretin agents (GLP-1 analogues and dipeptidylpeptidase-4 inhibitors), because of their characteristics, especially their safety in terms of hypoglycemia, appear to have a clear chance of being beneficial to prevent cognitive loss, but confirmatory studies are needed.[2] Finally, the potential of intranasal insulin to achieve the positive effects attributed to insulin in the central nervous system with no risk of hypoglycemia and prolonged peripheral hyperinsulinemia is being explored. Using this route, insulin directly reaches the central nervous system with no limitation from the blood-brain barrier. The results of a pilot study of daily use of a nasal insulin inhaler for four months, conducted after encouraging results were found in animals, are now known. The drug stabilized or improved cognition, function, and cerebral metabolism of glucose in adults with amnestic mild cognitive impairment and mild to moderate AD.[15] The study showed that treatment with 20 units of insulin improved delayed memory and supports the conduct of future trials with intranasal insulin on a higher number of participants.[15] Moreover, in a recently published study, improved cognition also appeared to be related to insulin capacity to achieve selective vasodilation, thus improving blood flow in given areas of the brain related to cognitive functions. If this mechanism of action is confirmed, this would be a measurable variable to assess and monitor the result.[16] As regards safety of the procedure, nasal insulin does not appear to affect blood glucose or peripheral insulin levels.

Based on the foregoing, it appears reasonable to recommend physicians to specifically assess cognition in patients with DM.[17] Thus, the idea of including the Mini-mental State Examination in annual examination of the patients does not appear to be crazy.[2]

To sum up, an epidemiological association appears to exist between DM and dementia, and although its existence is more evident for vascular dementia, it has also been reported for AD. AD could be conditioned, among other mechanisms, by a cerebral resistance to insulin which could be called type 3 diabetes. Today, the potential contribution of intranasal insulin to counteract this problem is one of the mechanisms which are creating more expectation in the field of future treatments for AD.

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