



REVIEW ARTICLE

Alzheimer disease and cognitive impairment associated with diabetes mellitus type 2: associations and a hypothesis[☆]

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KEYWORDS

Diabetes mellitus type 2;
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Hypoglycaemic drugs

Abstract

Introduction: Epidemiological studies have demonstrated that patients with diabetes mellitus have an increased risk of developing Alzheimer disease, but the relationship between the 2 entities is not clear.

Development: Both diseases exhibit similar metabolic abnormalities: disordered glucose metabolism, abnormal insulin receptor signalling and insulin resistance, oxidative stress, and structural abnormalities in proteins and β -amyloid deposits. Different hypotheses have emerged from experimental work in the last two decades. One of the most comprehensive relates the microvascular damage in diabetic polyneuropathy with the central nervous system changes occurring in Alzheimer disease. Another hypothesis considers that cognitive impairment in both diabetes and Alzheimer disease is linked to a state of systemic oxidative stress. Recently, attenuation of cognitive impairment and normalisation of values in biochemical markers for oxidative stress were found in patients with Alzheimer disease and concomitant diabetes. Antidiabetic drugs may have a beneficial effect on glycolysis and its end products, and on other metabolic alterations.

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PALABRAS CLAVE

Diabetes mellitus de tipo 2;
Enfermedad de Alzheimer;
Metabolismo cerebral de la glucosa;
Resistencia a la insulina;
Estrés oxidativo;
Fármacos hipoglucémicos

Conclusions: Diabetic patients are at increased risk for developing Alzheimer disease, but paradoxically, their biochemical alterations and cognitive impairment are less pronounced than in groups of dementia patients without diabetes. A deeper understanding of interactions between the pathogenic processes of both entities may lead to new therapeutic strategies that would slow or halt the progression of impairment.

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Enfermedad de Alzheimer y deterioro cognitivo asociado a la diabetes mellitus de tipo 2: relaciones e hipótesis

Resumen

Introducción: Varios estudios epidemiológicos han demostrado que los pacientes de diabetes mellitus de tipo 2 presentan un aumento de riesgo para adquirir enfermedad de Alzheimer, pero las relaciones entre ellas no están aclaradas.

Desarrollo: Ambas enfermedades presentan similares anormalidades metabólicas: Alteraciones en el metabolismo de la glucosa, irregularidades en los receptores para la señalización de la insulina, estrés oxidativo, anomalías en la conformación de proteínas y depósitos de β -amiloide. A través del desarrollo de investigaciones experimentales en las últimas 2 décadas, han sido postuladas diversas hipótesis. Una de las más llamativas relaciona los daños microvasculares de la polineuritis diabética con los cambios que se producen en el sistema nervioso central en la enfermedad de Alzheimer. Otra hipótesis considera que en ambas enfermedades la evolución del deterioro cognitivo está vinculada con el estado de estrés oxidativo sistémico. Más recientemente, en pacientes con enfermedad de Alzheimer con diabetes mellitus de tipo 2 concomitante, se ha comprobado la existencia de atenuación en el deterioro cognitivo y la normalización en los valores de variables bioquímicas marcadoras del estrés oxidativo. Los fármacos antidiabéticos podrían ejercer un efecto favorable sobre la glucólisis, sus productos finales y otras alteraciones metabólicas.

Conclusiones: Los pacientes diabéticos presentan mayor riesgo para desarrollar Alzheimer, pero, paradójicamente, las alteraciones bioquímicas y el deterioro cognitivo resultan menores que en los grupos de pacientes dementes sin diabetes mellitus. La mejor comprensión de las patogenias que interactúan en estas enfermedades quizás sustente nuevas estrategias terapéuticas conducentes a disminuir o detener la progresión de los deterioros.

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Introduction

Patients with diabetes mellitus type 2 have an elevated risk of cerebral complications, including cerebrovascular accident,¹ cognitive impairment,² and dementia.³ These risks are added to an array of systemic complications, including retinopathy, kidney disease, and peripheral nerve disease, which accompany anomalies in microcirculation and the development of macrovascular lesions in different systemic arteries.⁴ Doctors must also consider the effect of other variables that are frequently associated with diabetes mellitus (DM), such as arterial hypertension, obesity, and components of metabolic syndrome.⁵

The pathogenic mechanisms by which DM type 2 causes cognitive impairment have not been clearly established. A number of explanations for the link between diabetes and dementia have been proposed, including vascular lesions,⁶ inflammation,⁷ oxidative stress,⁸ elevated levels of end products of glycolysis, insulin resistance and abnormal insulin receptor signalling, and insulin degradation and insulin's relationship with β -amyloid protein deposits.^{9,10}

The purpose of this review is to examine original general, biochemical, and clinical studies of patients with Alzheimer disease, DM type 2, or both diseases presenting concomitantly. The relationship between Alzheimer disease and diabetes has not yet been made clear, and our review will present the most significant hypotheses proposed to date.

Vascular damage

Ischaemic cerebrovascular events are very likely to cause dementia in diabetic patients. Alzheimer disease in the elderly is frequently accompanied by DM type 2. Brains affected by cerebral infarcts show fewer amyloid plaques than brains with no vascular lesions. The hypotheses arising from these findings suggest that vascular lesions seem to decrease the formation of amyloid protein, which itself is the cause of progressive dementia.¹¹

One type of cerebral ischaemic lesion occurs in white matter, but its pathogenesis is poorly understood. This chronic ischaemic lesion, which is clearly visible by brain computed tomography and magnetic resonance imaging, is

usually known as leukoaraiosis.¹² Chronic arterial hypertension and DM type 2 are the main risk factors for developing chronic ischaemia in white matter.¹³ Microvascular disease is frequent in diabetes^{14,15}; it contributes to cognitive impairment and causes clinical manifestations similar to those of Alzheimer disease. There have been fewer studies of diabetes mellitus type 1, and its links to cognitive impairment are still not universally accepted.¹⁶

Diabetes is correlated with an increased risk of developing dementia, which is in fact 63% greater than that in healthy controls. A recent study of subjects monitored for 7 years found the most pronounced cognitive impairment in patients whose imaging studies revealed signs of vascular lesions. Ischaemia was identified as the main factor inducing dementia.¹⁷

Insulin resistance and dementia

Numerous articles support the hypothesis that Alzheimer disease follows a pathogenic process based on changes in neuronal energy use that are caused by deficient glucose metabolism.¹⁸ Metabolic anomalies are related to cerebral insulin growth factor, which regulates energy production and insulin resistance.¹⁹

Furthermore, Alzheimer patients were found to be more insulin-resistant than control subjects without dementia; patients with Alzheimer disease had higher levels of hyperglycaemia and more abundant neurofibrillary tangles.²⁰ Insulin resistance and hyperinsulinaemia cause arterial wall thickening and features associated with the changes in vascular permeability that accompany tissue ischaemia.²¹ New research on diabetes and brain insulin resistance will be very helpful in determining whether Alzheimer disease may be linked to peripheral insulin resistance.

The link between diabetes and polyneuropathy and cognitive decline

Two of the hypotheses about the pathogenic process causing diabetic neuropathy are based on microangiopathic changes²² and metabolic anomalies related to insulin and glucose.²³ There is also a third multifactorial hypothesis involving oxidative stress.²⁴ In addition, employing the brain evoked potential technique in diabetic patients let us identify subclinical impairment in the form of altered central latency.²⁵ This condition also indicates presence of microangiopathy.

One unanswered question about diabetes is whether there are connections between cognitive deficit and the co-presence of microcirculatory changes and hypoglycaemia.²⁶ Comparison of cognitive function between subjects with diabetes mellitus types 1 or 2 found that those with type 2 displayed more profound alterations in the cerebral cortex and more circulatory changes in deep cerebral white matter.¹⁷

Another hypothesis regarding diabetes and cognitive decline points to metabolic changes in subjects who develop sporadic Alzheimer disease. Anomalies have to do with

neuronal insulin receptors and dysfunctional signalling. This neuronal situation gives rise to increased oxidative stress and abnormal tau protein phosphorylation, as well as to more abundant neurofibrillary tangles.²⁷

Another hypothesis explains the combined pathogenic process as the result of microcirculatory changes in the central nervous system as well as those causing peripheral diabetic neuropathy. An anatomical pathology study in diabetic patients showed that microvascular lesions were frequently present at both locations.²⁸ Nevertheless, this presence of vascular lesions in the retina, kidneys, and peripheral nerves of diabetic patients was not associated with significant dementia and cerebral changes.²⁹

Whereas disease pathogenesis supports either of 2 possible pathways (metabolic and microcirculatory), subclinical electrophysiological and neuropsychological findings may offer predictive data about the potential abnormal brain condition which, in turn, may progress towards clinical cognitive impairment.

Antidiabetic drugs and their link to Alzheimer disease

Throughout the last decade, different articles have pointed to a possible, and paradoxical, protective effect of diabetes in patients with concomitant Alzheimer disease. This effect manifests through an improvement in oxidative stress and other peripheral markers of dementia that show a significantly better state when both entities are present.^{30–33} In 2009, this hypothesis arose from a basic study that increased our understanding of the protection offered by diabetes against Alzheimer disease. In this study of mature hippocampal neurons, researchers observed that loss of insulin receptors and poor diffusion of related ligands was mitigated and normalised by the action of insulin.³⁴

Different glycaemia-lowering drugs prevent the reduction in insulin function, which lessens the pathological anomalies observed in Alzheimer disease. Research into whether or not antidiabetic drugs might prevent or improve dementia, or slow the development of Alzheimer disease, has not yet delivered any definite answers. Nevertheless, results of using intranasal insulin and oral glycaemia-lowering agents (metformin, rosiglitazone, pioglitazone, and glibenclamide) in controlled studies all show that these drugs have a favourable effect on cognitive function.^{34–39} These treatments and new research projects are promising and may be helpful for improving the daily lives of patients and close family members.

Dementia and increases in end-products of glycolysis

Advanced glycation end-products (AGEs), and the end-products of lipid and protein oxidation, accumulate in the organs and tissues affected by chronic diabetes. AGEs activate specific receptors called RAGE, which are a subtype of immunoglobulin receptor. This activation produces oxygen reactive species and an inflammatory response mediated

by the enzyme myeloperoxidase. Advanced glycation end-products interact with RAGE to increase the synthesis of the superoxide anion, which in turn decreases the activity of the antioxidant enzymes catalase and superoxide dismutase and also activates protein kinase C.^{23,40} Hyperglycaemia and tissue damage occur by means of 4 mechanisms: (a) activation of protein kinase C and de novo synthesis of the lipid diacylglycerol; (b) overactivity of the hexosamine pathway; (c) formation of AGEs, and (d) increased flux through the polyol pathway. AGE precursors are dicarbonyls, highly reactive intracellular compounds that react with the amino groups of intra- and extracellular proteins to form AGEs,⁴¹ which are able to cross membranes and cause mitochondrial dysfunction.

Reactive oxygen species are active participants in the relationship between oxidative stress and the damage caused by diabetes.⁴² There may be an imbalance between production of AGE precursors and scavengers of reactive oxygen species, which leads to carbonyl stress and impaired glycolysis. This cumulative process attracts inflammatory cells, which will continue to promote inflammation and increased AGE production. AGEs contribute to disease progression by accelerating the deposition of β -amyloid in different areas of the brain.⁴³ These events indicate that the factor in common between diabetes and Alzheimer disease is RAGE, which have an affinity for AGE ligands seen in diabetes and for the β -amyloid protein typical of Alzheimer disease.

Relationship between oxidative stress, diabetes mellitus type 2, and dementia

The last few years have seen abundant publications on the significant associations found between different severe neurological diseases and oxidative stress/damage. These links have been established using the usual peripheral markers of oxidative stress and damage.^{30,31,33,44,45} The following signs are already widely accepted by scientists as markers of oxidative stress. (a) Substances that react to thiobarbituric acid: an increase in these substances is caused by abnormal systemic and neuronal levels of hydroperoxides that cause an increase in lipid peroxidation; and (b) chemiluminescence triggered by tert-butyl hydroperoxide: high levels of luminescence point to oxidative stress in erythrocyte membranes. Other signs, however, are regarded as protective markers. (c) Plasma antioxidant capacity: decreased capacity indicates lower levels of water-soluble plasma antioxidants (for example, uric acid, ascorbic acid, and bilirubin); and (d) the Cu/Zn superoxide dismutase enzyme (SOD), an increase in which has been linked to systemic oxidative stress; enzymatic overregulation is an adaptive response to an increase in oxidative species.

It is therefore appropriate to follow the simple balance model proposed by Sies⁴⁶ and visualise the oxidative stress/damage situation as an imbalance in which intracellular oxidative species (damage) outweigh damage-reducing protective factors. This concept involves recognising physiological production of oxidants (free radical oxidants and related species) and the presence of active antioxidant defence mechanisms. The imbalance scenario recognises

the physiological effectiveness of antioxidant defence mechanisms in maintaining both oxidative stress and cell damage to a minimum level for physiological conditions.

In the mid-1990s, scientists began observing that concomitant presence of diabetes mellitus type 2 in patients with Alzheimer disease was unexpectedly accompanied by significant improvements in the normal measurements of oxidative stress. This group exhibited values that were much closer to normal values from healthy controls.^{30,31,33} Their results for homocysteine, vitamin B₁₂, and folic acid levels were also similar.³¹ Glycated haemoglobin and insulin levels also followed this pattern; levels were inversely related between patients with and without dementia (those with diabetes only and healthy controls).³³ The global analysis of peripheral markers for different diseases showed significant linear correlations between pro-oxidant species and antioxidant defence species.³⁵

Decreases in peripheral markers may be attributed to the following: (a) the known action of sulphonylureas, which decrease values of species reactive to thiobarbituric acid and SOD; (b) a protective effect of diabetes that attenuates systemic oxidative stress due to diabetes complications and tissue damage and (c) the protective effect of insulin on oxidative stress.³⁴

Perhaps the most surprising result of the 'protective effect' of diabetes is its association with survival times and metastasis in patients with malignant tumours, such as lung or prostate cancer.^{47,48}

Alzheimer disease, type 2 diabetes mellitus, and lower level of cognitive impairment

The effect of diabetes mellitus type 2 on cognitive impairment in patients simultaneously affected by Alzheimer disease has not yet been determined. Unfortunately, due to limitations of performing long-term follow-up on elderly patients (4 to 6 years or longer), very few studies examine this effect. The prospective longitudinal study by Sanz et al.⁴⁹ evidenced the typical difficulties of following up on elderly subjects. Researchers began a follow-up study of more than 600 patients with probable Alzheimer disease, 60 of whom also had diabetes, but due to deaths or other events, less than half of the patients were finally included in the study. However, this pioneer study was able to show that presence of diabetes is associated with a lower rate of cognitive impairment among patients with Alzheimer disease.

Current evidence is insufficient to draw firm conclusions about the associations between Alzheimer disease and concomitant diabetes mellitus type 2, but results published in recent years indicate that glycaemia-lowering drugs may play a beneficial role. Antidiabetes drugs (glibenclamide and pioglitazone) exert a significantly beneficial effect on spatial cognition, learning, and memory. They also significantly decrease levels of hyperphosphorylated tau protein and galanine.⁵⁰ In addition, we must consider insulin's demonstrated protective effect in preventing the neurotoxic union of β -amyloid oligomers, the attenuation of cerebral structural changes characteristic of Alzheimer disease, and that metformin ameliorates neuronal insulin resistance.^{34,37,38}

Based on results obtained in the clinical study,⁴⁹ researchers designed a pilot study to evaluate cognitive performance in a homogeneous population of 101 subjects divided into 4 study groups: Alzheimer disease, DM type 2 without dementia, patients with both diseases and similar progression times, and healthy controls.⁵¹ The degree of cognitive impairment was measured using the Alzheimer Disease Assessment Scale-Cognitive and the Mini-Mental State Examination; dementia progression was measured with the Clinical Dementia Rating scale. Results demonstrated the following: (a) the degree of cognitive impairment in patients with Alzheimer disease and diabetes mellitus type 2 was significantly lower than in patients with probable Alzheimer disease and no diabetes with the same progression time for cognitive impairment; and (b) there were no significant differences between patients with diabetes only and healthy controls.

Further experimental and clinical studies are needed, with larger study populations and longer follow-up times.

Conclusions

1. Diabetes mellitus type 2 is associated with an elevated risk of cognitive impairment.
2. There are several hypotheses linking Alzheimer disease to diabetes, including microcirculatory lesions, common metabolic changes that lead to formation of neurofibrillary tangles and β -amyloid deposits in brain tissue, alterations in insulin function (insulin resistance and dysfunctional insulin signalling), and oxidant/antioxidant imbalance. Although the 2 diseases appear in a context of systemic oxidative stress mediated by free radicals, their metabolic pathways and action mechanisms are different.
3. When both diseases are present, systemic oxidative stress is lower than for either disease in isolation, and cognitive impairment is less pronounced.
4. A key challenge for future treatment protocols will be to gain additional knowledge about the metabolic pathways of different diseases, and the links between them.

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Conflicts of interest

The authors declare that they have no conflicts of interest involving specific companies. All of the authors are familiar with the content of the manuscript and have given their permission to publish it.

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