Project title: Exploring the Biological Pathways Linking Type 2 Diabetes and "Type 3 Diabetes"

BACKGROUND

With global population aging, the prevalence of Alzheimer's disease (AD) is on the rise.[1] While significant progress has been made in understanding AD, the precise physiological changes that trigger its onset remain elusive. Evidence from both human and animal studies strongly suggest that AD-type neurodegeneration may be mediated by insulin deficiency and resistance.[2] For this reason, AD has sometimes been conceptualized as ***"brain diabetes"*** or ***"type 3 diabetes"*** — given its shared molecular and biochemical features with both type 1 and type 2 diabetes (T2DM).[3,4]

Epidemiological studies have demonstrated the association between T2DM, cognitive decline, and AD.[5–8] However, the biological mechanisms underlying this association are poorly understood.[9] Both T2DM and AD are heritable diseases, with emerging evidence pointing to shared genetic factors, such as the insulin-degrading enzyme (IDE) gene, as potential contributors.[10] Beyond genetics, metabolic alterations—including glucose dysregulation, insulin resistance, cholesterol imbalance, and oxidative stress—and inflammatory mediators, such as C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α), also play crucial roles in the pathophysiological connection between T2DM and AD.[11] Despite progress in identifying individual biomarkers, these are insufficient to fully characterize the complex biological interactions underlying "type 3 diabetes." Metabolomic technologies offer a transformative approach by enabling the measurement of thousands of metabolites in biological samples, creating unique metabolic fingerprints for individuals.[12] This holds promise for discovering novel biomarkers to predict AD risk among T2DM patients.[13] However, the genetic, metabolomic, and inflammatory profiles that underpin the prediction and progression of "type 3 diabetes" remain largely unexplored.

Recent studies have highlighted the potential cognitive benefits of antidiabetic medications – especially metformin, a very widely used drug that is considered first-line therapy for T2DM.[14] People whose diabetes is managed with antidiabetic medication have demonstrated significantly slower cognitive decline compared to untreated individuals, with combined therapies yielding better outcomes than monotherapy.[15] Although epidemiological studies have provided valuable insights into the association between T2DM and AD, there remains a significant gap in our understanding of how genetic, metabolic, and inflammatory signatures contribute to "type 3 diabetes."

OBJECTIVES

The overarching goal of this 2-year project is to advance the understanding of the genetic, metabolic, and inflammatory pathways linking T2DM and AD. This project seeks to identify novel biological mechanisms underlying this association and provide insights for potential therapeutic interventions.

Aim 1: Identify shared genetic factors and pinpoint key genes or genomic regions contributing to the co-occurrence of T2DM and AD.

Aim 2: Discover key metabolic and inflammatory signatures contributing to the shared pathophysiology of T2DM and AD which can predict AD risk in those with T2DM.

Aim 3: Assess whether and to what extent metformin therapy can attenuate the association between T2DM and AD, and explore the potential mechanisms underlying its potential protective effect.

METHODOLOGY

This study will be based on data from three large population-based cohort studies of mid- and older-aged adults in Sweden and UK.[16-18]

Identification of T2DM. In all studies was ascertained based on medical records, self-reported medical history, and/or use of glucose-lowering medications. In SNAC-K and UKB, as-of-yet undiagnosed T2DM could also be identified if HbA1c measured from blood samples collected at baseline was ≥6.5%.

Metformin therapy. Among people with T2DM, metformin use was determined via self-reported medical history and linkage with medical records.

Diagnosis of AD. AD was diagnosed by trained neurologists according to standard *DSM-IV* and *NINCDS/ADRDA* criteria or based on medical records.

Genetic data. About 130,000 SNPs including candidate genes related to neurodegeneration, cognitive functioning, and vascular and metabolic disorders were genotyped. Moreover, GWAS data with respect to 900,000 genetic variations are available. DNA was extracted from blood samples collected at baseline and genotyped across the whole genome.

Metabolomics. Blood-based metabolites were measured from baseline blood samples. A high-throughput serum nuclear magnetic resonance spectroscopy platform quantified 236 metabolites, and a panel of 249 metabolites is available. These biomarkers cover multiple metabolic pathways, including lipoproteins, inflammatory cytokines, low molecular weight metabolites, liver function surrogates, and hormones.

Statistical Analysis. To identify biomarkers with high discriminative ability for T2DM and AD, data reduction techniques such as Principal Component Analysis and Partial Least Squares Discriminant Analysis will be applied. Depending on the study design and the nature of the outcomes, appropriate statistical models will be employed, including linear regression, logistic regression, Cox proportional hazards models, Poisson regression, or mixed-effect models for repeated measures. Drug target Mendelian randomization (MR) analysis will be conducted to assess the causal effects of metformin on cognitive decline and AD risk, focusing on whether these effects are mediated by its glucose-lowering properties. Interaction analyses will be performed to evaluate the extent and direction of interactions between key factors, while mediation modeling will explore pathways linking T2DM, biomarkers, and cognitive outcomes. To address missing data, multiple imputation methods will be used, ensuring robust and unbiased estimates.

WORK PLAN

All tasks in this 2-year project will be completed by the postdoctoral fellow under supervision. The first 3 months will focus on data organization, including updating datasets and preparing it for analysis. The following 3 months will involve skill development through targeted courses and workshops on MR methodologies and integrative omics analysis. Studies 1 and 2 will be conducted over the next 10 months, with two manuscripts prepared and submitted for peer-reviewed publication. The subsequent 6 months will focus on completing Study 3 and submitting it for publication. Finally, the last 2 months will be dedicated to disseminating findings at conferences and preparing a comprehensive final project report.

RELEVANCE

By examining genetic, metabolic, and inflammatory biomarkers, the study aims to uncover novel insights into the shared pathophysiology of these conditions. This approach has the potential to elucidate mechanisms such as insulin resistance, chronic inflammation, and metabolic dysregulation that contribute to cognitive decline in T2DM patients.

Ultimately, the findings from this research could lay the groundwork for developing integrated therapeutic strategies that simultaneously address the overlapping pathways of T2DM and AD. Such advancements would not only deepen the understanding of this dual disease burden but also open doors for innovative prevention and treatment approaches, improving outcomes for individuals affected by both conditions.

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