**Título:** PAPEL DE LA DIABETES MELLITUS TIPO 2 EN LOS PROCESOS NEURODEGENERATIVOS Y DAÑO VASCULAR: IMPLICACIÓN EN LA ENFERMEDAD DE ALZHEIMER

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**El fichero de tesis** no ha sido incorporado al sistema.

**Resumen:** Alzheimer¿s disease (AD) is the most common cause of dementia and has no successful treatment. Vascular Dementia (VaD) is the second common cause of dementia and the borderlines between AD and VaD are blurred in many cases. While age remains the main risk factor to suffer AD, in the last few years epidemiological and clinical studies have identified different metabolic alterations as risk factors to develop AD. Following this idea diabetes mellitus (DM) seems to play a relevant role at this level. Nevertheless, basic science studies are limited and the underlying mechanisms for this relationship (AD-DM) remain largely unknown.
In order to explore the close relationship between both pathologies, we have developed 3 animal models using a classical model of AD, the APPswe/PS1dE9 mouse (APP/PS1) in that we have induced a prediabetic state by administering high fat diet (HFD), type 1 diabetes (T1D) by administering streptozotozin (STZ) and T2D by crossing them with the db/db mouse. While db/db mice have been widely used in metabolic studies, they have not been fully characterized at central level.
We observed that db/db mice per se show vascular damage, brain atrophy and increased tau phosphorylation in an age dependent manner. They also present increased neurogenesis, which decreases as T2D evolves. In our prediabetes-AD model, induced in APP/PS1 mice by long-term HFD treatment, we detected learning and memory impairments. We observed a significant increase in tau hyperphosphorylation and amyloid-ß (Aß) pathology, including Aß levels and amyloid burden. Microglia activation was also significantly increased in prediabetic-AD mice. Our data show that the prediabetic state is enough to worsen central pathology in APP/PS1

mice. On the other hand, we have induced experimental T1D diabetes to APP/PS1 mice by ip STZ injection at 18 weeks of age, when AD pathology is not yet established in this animal model. Cognition was evaluated at 26 weeks of age, and in our hands cognitive impairment was exacerbated in STZ-treated APP/PS1 mice. In this animal model we also observed a shift in soluble/insoluble Aß levels, towards more toxic soluble species. The presence of hemorrhages was significantly higher in APP/PS1-STZ mice and phospho-tau levels were also increased in this group, accompanied by an exacerbated inflammatory process. Finally, we have developed a new model by crossing APP/PS1 mice with db/db mice (APP/PS1xdbdb). We characterized metabolic and cognitive evolution before T2D or AD pathology are present (4 weeks of age), when T2D has debuted but no senile plaques are present (14 weeks of age) and when both pathologies are well established (26 weeks of age). APP/PS1xdb/db mice showed an age-dependent synergistic effect between T2D and AD. Significant brain atrophy and tau pathology were detected in the cortex by 14 weeks, that spread to the hippocampus by 26 weeks of age. Severe cognitive impairment was also detected as soon as at 14 weeks of age. Interestingly, in APP/PS1xdb/db mice we observed a shift in Aß soluble/insoluble levels, and whereas more toxic soluble species were favoured, senile plaque were reduced. An overall increase of microglia activation was observed in APP/PS1xdb/db mice. We also found exacerbated hemorrhagic burden in APP/PS1xdb/db mice, suggesting that blood brain barrier alterations may be responsible, at least in part, for the early pathological features observed. We also observed an early affection of metabolic parameters in APP/PS1xdb/db mice supporting a two-way cross talk between both pathologies. In addition, at cellular level a significant increase of neurite curvature was observed in prediabetic APP/PS1 mice, and this effect was worsened in APP/PS1xdb/db animals. Synaptic density, analysed by array tomography, was reduced in APP/PS1xdb/db mice whereas an intermediate state was observed, once more, in prediabetic-AD mice. Moreover, metabolic parameters predicted many of these alterations, supporting a role for T2D in AD pathology.

Altogether, our data support the relevant role that metabolic alterations play at central level and help to elucidate the implication of prediabetes and diabetes in AD development. These models provide a relevant tool to further explore the relationship between T2D, AD and vascular implications, offering the possibility to assess therapeutic approaches that by improving metabolic control could delay or prevent AD pathology.