XXXVII Congreso Nacional FSED
Fundación Sociedad Española de Diabetes
15 a 17 abril 2026
Barceló Sevilla Convention Center
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Impact of Hypoglycemic Therapies on Mitochondrial Function in Type 2 Diabetes and Their Association with Neurocognitive Decline

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Introduction - Cases of **Type 2 Diabetes Mellitus (T2DM)** continue to rise worldwide, and current projections indicate that the condition may reach epidemic levels in the coming years. Hyperglycemia resulting from inadequate glycemic control is linked to several comorbidities, including **neurocognitive impairments**. Recent investigations have aimed to clarify the mechanisms connecting T2DM, a metabolic disorder, to neurocognitive diseases such as Alzheimer's disease (AD) and vascular dementia (VaD). Mitochondria, key components of the insulin–brain axis, have drawn increasing attention due to their central role in cellular energy homeostasis and their suspected involvement in the pathophysiology of AD and VaD. Therapies for T2DM are currently being evaluated for their potential to preserve mitochondrial function. In this study, we assessed redox status and mitochondrial DNA (mtDNA) stability in plasma from a cohort of individuals with T2DM undergoing different hypoglycemic pharmacological regimens. We also explored the relationship between mitochondrial integrity and two neurocognitive risk markers: abnormal intima–media thickness (IMT) and diabetic peripheral neuropathy (DPN).

Longitudinal time-dependent effects

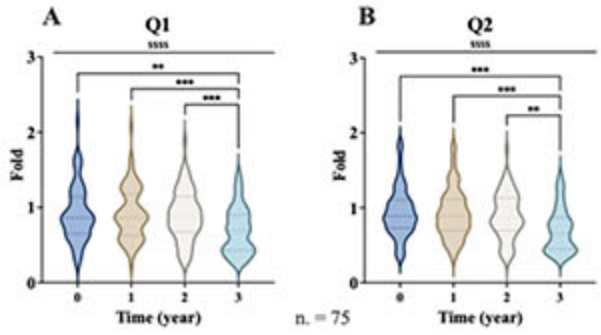

Figure 1. Antioxidant capacity (fold) in subjects' plasma over a 3-year period. *(A) Fast-acting (Q1) and (B) slow-acting (Q2) antioxidants levels across four time points: 0 (baseline), 1-year, 2-years, and 3-years follow-up.*

Longitudinal effects of pharmacological treatment

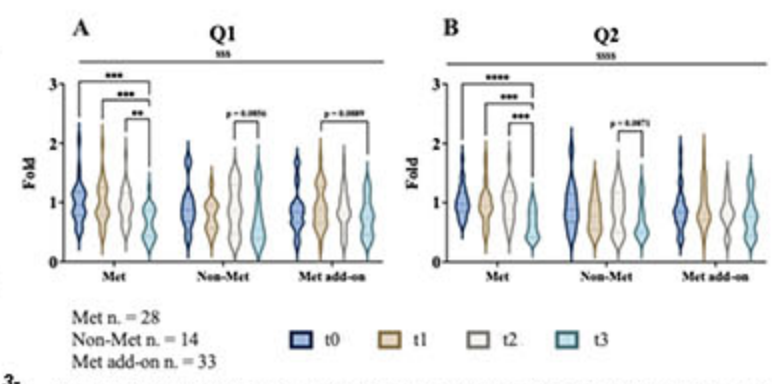

Figure 2. Antioxidant capacity (fold) in plasma of T2DM subjects over a 3-year period, stratified by treatment regimen. *(A) Fast-acting (Q1) and (B) slow-acting (Q2) antioxidants levels across four time points: t0 (baseline), t1 (1-year), t2 (2-years), and t3 (3-years) follow-up; and grouped by treatment type: Met (Metformin therapy), Non-Met (Non-metformin therapy), Met add-on (Metformin therapy with added-on hypoglycemic agents).*

Longitudinal effects of intima media thickness

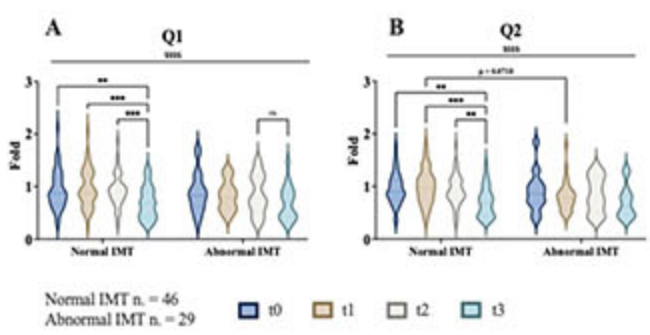

Figure 3. Antioxidant capacity (fold) in plasma of T2DM subjects over a 3-year period, stratified by intima media thickening. *(A) Fast-acting (Q1) and (B) slow-acting (Q2) antioxidants levels across four time points: t0 (baseline), t1 (1-year), t2 (2- year), and t3 (3-year) follow-up; and grouped by intima media thickening (IMT): Normal IMT (IMT ≤ 0.9 mm), Abnormal IMT (IMT ³. 0.9 mm).*

Longitudinal effects of diabetic peripheral neuropathy

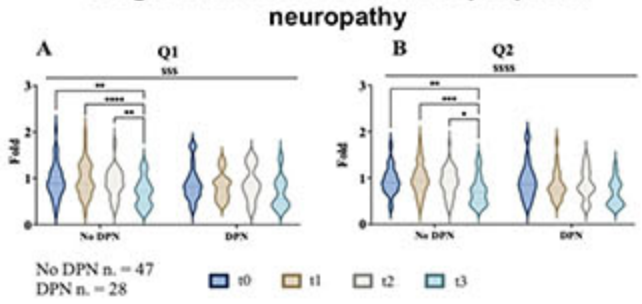

Figure 4. Antioxidant capacity (fold) in plasma of T2DM subjects over a 3-year period, stratified by diabetic neuropathy diagnosis. *(A) Fast-acting (Q1) and (B) slow-acting (Q2) antioxidants levels across four time points: t0 (baseline), t1 (1-year), t2 (2-years), and t3 (3-years) follow-up; and grouped by diabetic peripheral neuropathy (DPN) diagnosis: No DPN (T2DM) subjects not diagnosed with DPN), DPN (T2DM subjects diagnosed with DPN).*

Mitochondrial *ND1* and *ND4* DNA in cell-free plasma

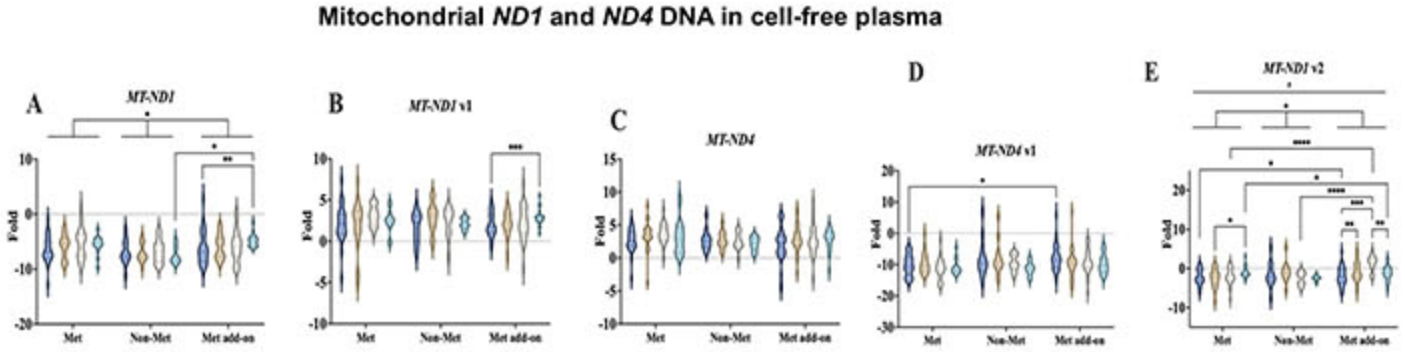

Figure 5. Relative mitochondrial gene load (fold, -ΔΔCt, normalized to mtDNA) in plasma of T2DM subjects over a 3-year follow-up period, stratified by treatment regimen. *Gene expression of mitochondrial genes such as, MT-ND1 (A), MT-ND1 v1 (B), MT-ND4 v1 (C), MT-ND4 v2 (D), MT-ND1 v2 (E); across four time points: t0 (baseline), t1 (1-year), t2 (2-year), and t3 (3-year) follow-up; and grouped by treatment type: Met (Metformin therapy), Non-Met (Non-metformin therapy), Met add-on (Metformin therapy with added-on hypoglycemic agents).*

Longitudinal effects of intima media thickness on relative mitochondrial gene load

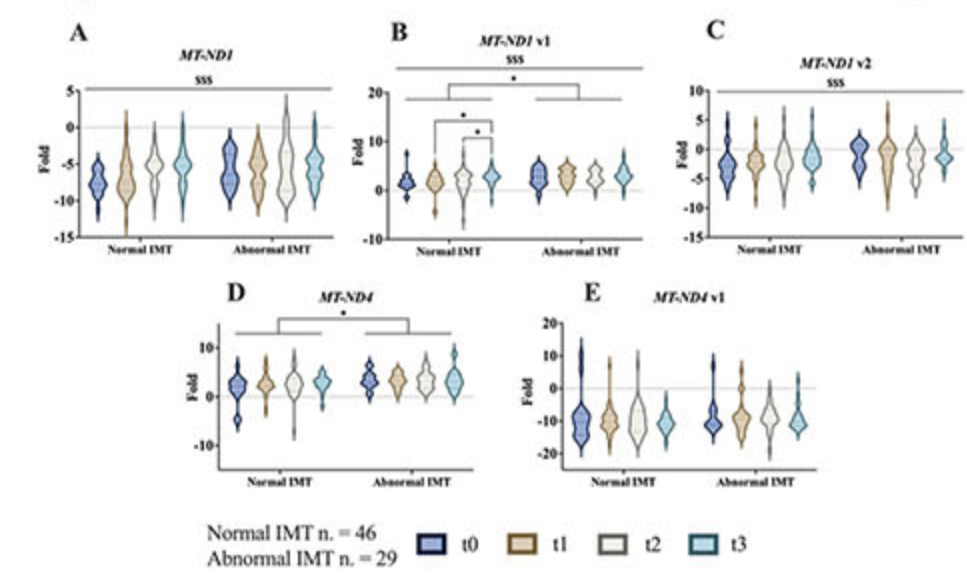

Figure 6. Relative mitochondrial gene load (fold, -ΔΔCt, normalized to mtDNA) in plasma of T2DM subjects over a 3-year follow-up period, stratified by intima media thickness. *Gene expression of mitochondrial genes such as, MT-ND1 (A), MT-ND1 v1 (B), MT-ND1 v2 (C), MT-ND4 (D), MT-ND4 v1 (E); across four time points: t0 (baseline), t1 (1-year), t2 (2-years), and t3 (3-years) follow-up; and grouped by intima media thickening (IMT): Normal IMT (IMT ≤ 0.9 mm), Abnormal IMT (IMT ³ 0.9 mm).*

Longitudinal effects of diabetic peripheral neuropathy on relative mitochondrial gene load

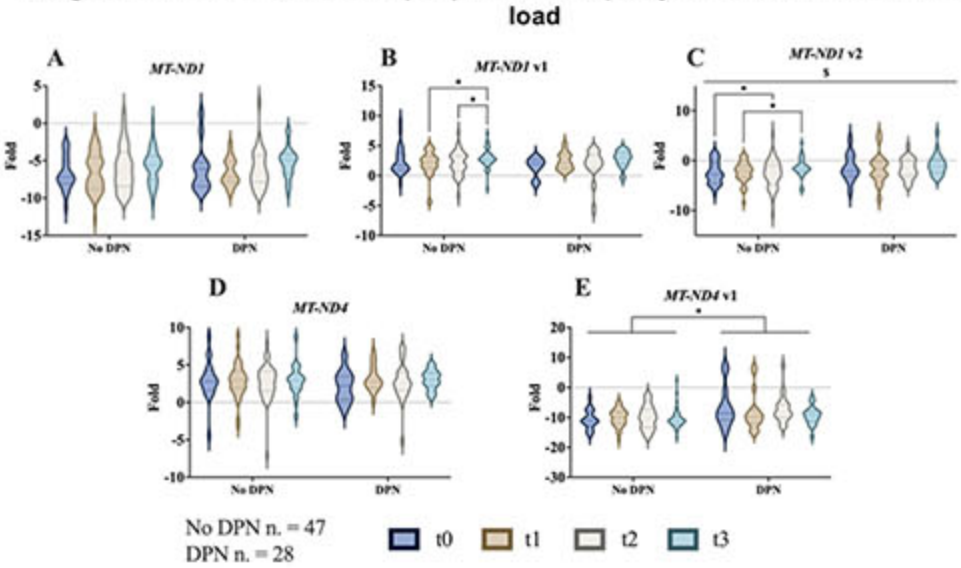

Figure 7. Relative mitochondrial gene load (fold, -ΔΔCt, normalized to mtDNA) in plasma of T2DM subjects over a 3-year period, stratified by diabetic peripheral neuropathy diagnosis. *Gene expression of mitochondrial genes such as, MT-ND1 (A), MT-ND1 v1 (B), MT-ND1 v2 (C), MT-ND4 (D), MT-ND4 v1 (E); across four time points: t0 (baseline), t1 (1-year), t2 (2-years), and t3 (3-years) follow-up; and grouped by diabetic peripheral neuropathy (DPN) diagnosis: No DPN (subjects not diagnosedwith DPN), DPN (subjects diagnosed with DPN).*

Conclusion: The data derived from this study suggests that pharmacological interventions have differential effects on the protection of mitochondrial function. In particular, our study shows that metformin-exclusive treatment has a detrimental impact on both antioxidant capacity and mitochondrial DNA copy number, as well as on mitochondrial genetic instability. Non-metformin agents may offer better mitochondrial protection than metformin, as the detrimental effects regarding redox balance and mitochondrial genetic instability in T2DM subjects receiving non-metformin or metformin with add-on agents appear milder. *MT-ND4* to *MT-ND1* ratio is a reliable plasma biomarker to evaluate the impact of pharmacological interventions on mitochondrial function in T2DM subjects. It was observed that T2DM subjects with abnormal IMT and a DPN diagnosis exhibited lower antioxidant levels, although the study posed some limitations. Further studies are required to extensively investigate the correlation of neurocognitive disorders with adequate mitochondrial function.

Financial support:
GOBIERNO DE ESPAÑA · MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES · AGENCIA ESTATAL DE INVESTIGACIÓN
UAM Universidad Autónoma de Madrid
IIBM Instituto de Investigaciones Biomédicas Sols-Morreale
cost · BenBedPhar
CONMETA
CSIC
DiBaN GA-101162517 European Innovation Council
Funded by the European Union