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PRE-CLINICAL ALZHEIMER'S DISEASE AND TYPE 2 DIABETES AND OBESITY. EFFECTS OF BARIATRIC SURGERY: A MULTIMODAL STUDY

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1. Abstract

Obesity, type 2 diabetes, and dementia are increasing in epidemic proportions worldwide. Importantly, an association has been suggested in epidemiological studies between T2D and mid-life obesity with increased dementia risk. Alzheimer's Disease (AD) is the most frequent cause of dementia. The mechanisms underlying this association in humans are poorly understood; the potential pathways involved include systemic inflammation and insulin resistance.

Weight loss through bariatric surgery (BS) is associated with significant improvement or even normalization of obese-related metabolic abnormalities, including systemic inflammation and insulin resistance. BS is also related to T2D remission or amelioration in most morbid-obese subjects with T2D. The study of the dynamics and interrelationships (pre- and post-surgery) between AD biomarkers and obesity and T2D related metabolic disturbances, together with the effect of weight loss and glucose normalization on cognition and biochemical and neuroimaging AD and neurodegeneration biomarkers, will provide unique mechanistic insights into the consequences of obesity and T2D on the central nervous system.

This study aimed to explore the impact of obesity and type 2 diabetes on cognitive performance, biochemical biomarkers of AD and neurodegeneration, and on neuroimaging biomarkers. We also examined whether insulin resistance and systemic inflammation mediated the effects of obesity and diabetes in the central nervous system. Finally, we evaluated the effects of weight loss achieved through bariatric surgery on cognitive performance and all the biomarkers mentioned above.

2. Results

1. Patients with obesity, with or without type 2 diabetes, present worse cognitive performance, increased neurodegeneration biomarkers in cerebrospinal fluid, and abnormalities in neuroimaging tests compared with normal-weight healthy controls. These abnormalities are unrelated to Alzheimer's Disease.

We evaluated 60 individuals with obesity (body mass index: 43.6±4.5 Kg/m^2) and 43 normal-weight (24.4±2.7 Kg/m^2) healthy controls matched by age, sex, and education. Participants with obesity showed lower cognitive performance in tests evaluating memory, executive functions, attention capacity, and spatial visual perception. Higher cerebrospinal fluid *Neurofilament light* (Nfl) levels but comparable AD biomarkers were observed in the obese group compared with the control group. NFL is the most abundant component of large myelinated axons, which is released into CSF and systemic circulation when neurodegeneration occurs. Increases in Nfl predict cognitive decline. Overall this data suggests the existence of enhanced amyloid and tau-independent neurodegenerative processes in persons with obesity.

Finally, we observed significant abnormalities in the neuroimaging tests. The obese group compared with the control group showed increased cortical thickness in occipital regions of both hemispheres and frontal areas of the right hemisphere. Obese participants also showed enhanced cortical atrophy in temporal areas (middle and superior).

2. Higher levels of peripheral inflammation and lower insulin sensitivity are related to impaired memory performance, higher Nfl levels, and brain metabolic abnormalities but not to AD biomarkers

In our study cohort higher insulin resistance was associated with lower performance in memory tests and diminished brain glucose metabolism in widespread brain areas. Higher levels of peripheral inflammation were also related to impaired memory, higher cerebrospinal Nfl levels (r: 0.394, p=0.06) and increased brain metabolic activity. We did not observe any association between insulin sensitivity and cerebrospinal AD biomarkers, nor between peripheral inflammation and AD biomarkers.

3. Weight loss results in insulin sensitivity and inflammation improvement and has a beneficial effect on cognition

One year after surgery we observed a marked bodyweight reduction (pre-surgery BMI: 43.4±4.5 vs. post-surgery BMI: 24.9±4.5, p<0.001) and significant amelioration of insulin resistance and peripheral inflammation. We also observed an improvement in cognitive performance (memory, attention, and executive function)

Data on biochemical and neuroimaging biomarkers is not completed; however, we observed significant changes in brain structure and metabolism in exploratory analyses.

3. Importance and future implications

This project may have clinical implications and open new lines of investigation:

- Our data shows that obesity negatively impacts several cognitive domains. We also observed that this impairment is partially reversible through weight loss. This is an important clinical message that should be shared with the patients. Indeed, many persons with obesity express difficulties in maintaining attention, and memory complaints. The beneficial effects of weight loss in cognitive performance might be motivational and relieving.

- Multimodal analysis of different clinical, biochemical, and neuroimaging biomarkers in our study points to insulin resistance and inflammation as essential mediators of the negative impact of obesity and type 2 diabetes in the central nervous system. Of note, the relationship between insulin resistance and brain metabolic abnormalities has seldom been reported. Likewise, this is the first study reporting an association between obese-related low-grade chronic inflammation, cognitive performance, and neurodegenerative and brain metabolism abnormalities. These findings may be the basis to test the effects of pharmacological agents primarily addressed to these targets in the treatment or prevention of obese-related or non-obese-related neurodegenerative processes.

- Our data reveals a complex relationship between metabolic diseases and neurodegenerative processes, which deserves further study. Studies assessing more deeply the impact of obesity and type 2 diabetes on the brain throughout the lifespan may be helpful to gain mechanistic insight. Studies using more accurate neuroimaging techniques to assess and track brain neuroinflammation might help to disentangle the participation and dynamics between peripheral and central nervous system inflammatory response.

4. Published Research

Data generated during this project is not yet published. At this time, we are preparing the corresponding manuscripts.
However, during the project course, we have analyzed data from other study cohorts to refine our hypothesis. These analyses could not be performed without *La Marató* support.

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