Endocrine biomarkers for physical and cognitive frailty in older adults

C. Lema-Arranz[1,2*], A. Hemadeh[1,2], N. Cibeira[3], R. López-López[3], J.L. Rodríguez-Villamil[3], J.C. Millán-Calenti[3], A. López-Cortón[1], N. Fernández-Bertólez[2,4], V. Valdiglesias[2,4], L. Lorenzo-López[3], & B. Laffon[1,2]

[1] Universidade da Coruña, Grupo DICOMOSA, CICA - Centro Interdisciplinar de Química e Bioloxía, Departamento de Psicología, A Coruña, Spain
[2] Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, A Coruña, Spain
[3] Universidade da Coruña, Gerontology and Geriatrics Research Group, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, A Coruña, Spain
[4] Universidade da Coruña, Grupo NanoToxGen, CICA - Centro Interdisciplinar de Química e Bioloxía, Departamento de Biología, A Coruña, Spain
** carlota.lema.arranz@udc.es*

Frailty has emerged as a clinical marker of biological ageing, characterised by diminished physiological reserves and heightened vulnerability to stressors. Cognitive frailty is defined by the co-occurrence of physical frailty and mild cognitive impairment, and is associated with accelerated cognitive decline, functional loss, and higher risk of institutionalisation and death. The endocrine system plays a fundamental role in the maintenance of homeostasis. Beyond genetic determinants of frailty, the endocrine system becomes progressively dysregulated with advancing age and the onset of frailty. A range of hormones have been proposed as potential biomarkers of both physical and cognitive frailty; however, evidence regarding their associations remains inconsistent. This cross-sectional study examined the relationship between endocrine biomarkers and physical and cognitive frailty in a cohort of older adults (N=155; aged ≥65 years) classified according to their physical frailty status using two approaches: the frailty index and the frailty phenotype. Cognitive impairment was identified with the Montreal Cognitive Assessment questionnaire. Serum concentrations of endocrine biomarkers [insulin-like growth factor 1 (IGF-1), cortisol, brain-derived neurotrophic factor (BNDF), α-klotho, and 25-hydroxyvitamin D (25(OH)D)] were determined. Our results showed IGF-1 concentrations declining progressively with increasing frailty severity across all classifications, exhibiting a male-specific association. Adjustment for cognitive performance indicated that physical frailty exerted a greater influence on IGF-1 than cognitive status, highlighting its potential as a biomarker of physical frailty. Lower cortisol levels were detected in individuals with MCI, particularly among those without depression or with less than two chronic conditions. No significant associations were observed for serum BDNF, α-klotho, or 25(OH)D in relation to either physical or cognitive frailty. These findings underscore the potential of IGF-1 as a biomarker of frailty and cortisol as a biomarker of MCI, while highlighting the need for further studies to confirm these associations and elucidate the underlying mechanisms in larger and more diverse cohorts.

Funding: This work was supported by the Spanish Ministry of Science and Innovation: MCIN/AEI [Grant PID2020-113788RB-I00] and Xunta de Galicia (ED431B 2025/26, and ED481A-2025/085 to C. Lema-Arranz).