

Poor Appetite & Aging: The Role of Physical Activity under a Geroscience Perspective

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Poor appetite is a very prevalent condition in old adulthood, reaching about 30% of older people; higher prevalence can be found in specific geriatric populations, such as hospitalized individuals and nursing home residents. Poor appetite is associated with several adverse health events, such as frailty and sarcopenia, mood issues, and even mortality, including in the absence of overt clinical signs of malnutrition (eg, weight loss) (1). For a long time considered as a natural consequence of the aging process, loss of appetite received only marginal attention from the scientific community and it is currently under-evaluated, under-diagnosed and under-treated in clinical practice. The multidimensional etiology of this condition renders it difficult to have a symptomatic drug to treat it. As a consequence, no medication has an indication for treating poor/loss of appetite to date. Furthermore, preventive strategies to avoid the onset of appetite loss have been particularly neglected in the scientific literature.

Recent advances in the field of aging research pave the way for a new approach to improve the understanding on poor appetite in older people. Of particular interest is the birth of Geroscience (2), which main hypothesis relies on two fundamental pillars: 1. There is an interplay between the biology of aging and the biology of chronic conditions, including diseases (eg, cardiometabolic, cancers), geriatric syndromes (eg, frailty, poor appetite/anorexia of aging), and functions (eg, mobility, cognition); 2. By intervening and slowing down the rates of biological aging it is possible to prevent/delay the onset and decrease the severity of a plethora of age-related chronic conditions.

Therefore, under a Geroscience perspective, poor appetite and the anorexia of aging may in theory be prevented/treated by targeting biological aging. In this context, and in the absence of an effective pharmacological approach to treat appetite loss in older adults, physical activity and exercise have a potential role to play since they are one of the most powerful interventions leading to a successful biological aging. Indeed, several studies demonstrated the benefits of physical activity/exercise on the basic cellular and molecular mechanisms of aging, the so-called “hallmarks of aging” (3, 4). This perspective makes from physical activity/exercise crucial strategies to regulate appetite in older people since it adds an aging biology mechanism of action to the direct benefits of body movement on the appetite circuitry (not necessarily dependent on the aging process, such as the control of ghrelin levels). Indeed, most literature on the

role of physical activity/exercise as an appetite regulator comes from investigations on young adults, a population either not concerned yet by cellular and molecular changes that drives organism’s aging or for which these biological changes are still decades away from leading to overt clinical consequences. Some of the multiple ways physical activity/exercise may benefit appetite regulation and avoid appetite loss/anorexia of aging are provided in the Table below.

Table 1. Benefits of physical activity/exercise on determinants of poor appetite /anorexia of aging in older adults

Determinants of appetite loss in older people	How physical activity/exercise may tackle the determinant
Swallowing problems	Swallowing problems and frailty/sarcopenia are related conditions (5, 6). Exercise is a major intervention (7, 8) for frailty/sarcopenia, and might indirectly benefit swallowing.
Altered gastrointestinal motility	Limited evidence in human suggests aerobic exercise improved gastrointestinal motility in young adult women (9), and psychiatric inpatients (10).
Reduction in muscle mass & basal metabolic rate	Exercise (11), specially resistance exercise, is one of the main interventions to keep muscle mass during aging and, then, to maintain basal metabolic rate.
Comorbidities/conditions Neurological diseases Gastrointestinal diseases Depression Fatigue Sarcopenia Inflammatory conditions Disability	Physical activity & exercise are associated with a reduced risk to develop (12) several chronic conditions, but also to treat(13) them, including neurological diseases, depression, sarcopenia, and disability (14). Moreover, exercise has anti-inflammatory properties (15).
Loneliness/social isolation	Physical activity and exercise are powerful interventions that facilitate socialization (16)

Therefore, from a Geroscience perspective, physical activity/exercise would prevent or reduce the severity (perhaps also the duration) of appetite loss in older adults by slowing down cellular and molecular cascades that drive aging. The interactions of body movement with appetite regulation molecules involved in the aging process constitutes a promising

research field. In this context, the potential associations of physical activity/exercise with growth differentiating factor 15 (GDF15) seems particularly important. Indeed, differently from other appetite regulators for which the associations with aging is either inexistent or still unclear (17, 18), such as ghrelin (the so-called “hunger hormone”), PYY, cholecistine, and GLP-1, GDF15 is considered a marker of biological aging (19) since it is associated with several hallmarks of aging, including mitochondrial function, the SASP phenotype of senescent cells, and inflammation. Furthermore, GDF15 has been shown to be associated with the evolution of cognitive function and mobility (20). GDF15 is a protein involved in stress-signaling that binds to the GFRAL receptor in the brain, with anorexigenic effects (21, 22). GDF15 may be considered as an exerkin, since it is secreted by the muscle during exercise (23). Moreover, acute exercise (24, 25) leads to increased GDF-15 levels in blood, and long-term physical activity (26) is associated with low GDF-15 levels. The potential joint role of exercise and GDF15 or the mediating effect of GDF15 in the exercise-appetite regulation axis is not yet elucidated (27). Another potential molecule that can mediate the associations between physical activity/exercise and appetite regulation through aging-related biological mechanisms is leptin. Indeed, leptin is a satiety peptide that seems to play a role in aging-related conditions (28) and that is responsive to exercise (exercise reduces leptin levels (29)).

Investigations on the potential mediating role of GDF15 and leptin regarding physical activity/exercise effects in appetite regulation in different older adult populations is required. In particular, looking at such associations in different phenotypes of poor appetite (eg, with/without: weight loss; frailty; depression), different durations of appetite loss (eg, persistent versus transient), as well as how appetite- and aging-associated markers relate to each other would shed light on this research field. Mechanistic studies in animals should also be stimulated.

Conflict of interest: I declare to have received Consultancy fees from Pfizer.

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