

Role of Glucocorticoids and Stress in Age-Related Mechanisms of Sarcopenia and Osteoporosis

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Abstract

This mini-review describes at first the ontopathogenic model based on the concept of developmental origins of health and disease (DOHaD) and thereafter explains the possible roles of glucocorticoids (GC) and stress in age-related tendencies to sarcopenia, osteoporosis, and obesity. The interactions between GC, stress and pro-inflammatory cytokines in these disorders are also considered. It is concluded that excessive exposure to stress and/or exogenous GC should be adequately prevented or controlled from the very beginning of human life.

Keywords: glucocorticoids, ontopathogenic model, osteoporosis, sarcopenia, stress

Abbreviations: DOHaD: developmental origins of health and disease; GC: glucocorticoids; IL: interleukins; HPA: hypothalamic-pituitary-adrenal; 11 β -HSD: 11beta-hydroxysteroid dehydrogenase

Introduction

At present, the problems of the skeletal–muscular system attract, especially, directed attention in gerontology and geriatrics, as related also to endocrinology. This is associated, first of all, with a clear-cut tendency in advanced age categories to decrease in muscle mass and higher fragility of bone tissues that are designated as sarcopenia and osteoporosis respectively. Unfortunately, such alterations result frequently in partial or complete loss of mobility and therefore, of an independent lifestyle, forcing the elderly to a much greater extent of sedentarism [1], and in some, more serious cases in higher mortality, especially as referred to femoral hip fracture.

Surprisingly enough, the causal factors of such adverse scenarios are based, at least in a certain part of the human population, already in the very early stages of ontogeny, including prenatal ones. The article presented analyzes age-related mechanisms of sarcopenia and osteoporosis on the basis of modeling the ontopathogeny, *i.e.*, etiopathogeny that proceeds along the whole ontogeny (or at least its major part), beginning from pre- and postnatal development till

adult state and continuing in the intermediate age groups and in senescence, focusing the principal attention on the role of glucocorticoids (GC) and stress.

Role of Glucocorticoids and Stress in the Ontopathogenic Model

At present, the concept of developmental origins of health and disease (DOHaD) can be considered sufficiently elaborated [2]. This concept describes the phenomena of biological programming/imprinting and embedding that occur in perinatal and early postnatal development, mainly on the basis of stress and similar adverse processes (malnutrition, infections, etc.) that provoke higher levels of endogenous GC in pregnant women and her fetus, as well as in offspring, first of all newborn. In practice, it has already been proved that intrauterine growth restriction (IUGR) is caused by stress or excess GC and as a consequence, lower birth weight (< 2.5 kg) serves as a predictor of elevated risk of various disorders in subsequent ontogeny, especially in senescence, first of all in those cases when there occurs compensatory catch-up somatic growth in the same persons (with low birth weight) during childhood and adolescence. Why does this happen and how does this reflect changes in the skeletal-muscular system?

It appears that during the aforementioned compensatory growth, there occurs a predominant increase in adipose tissue fraction, along with a decrease in lean mass fraction, including the skeletal-muscular system [3, 4]. As a result of this situation, the bases are founded for subsequent sedentary lifestyles because of relative weakness or insufficient development of skeletal muscles, including those participating in respiration [5]. Unfortunately, this tendency is supported in major part by the modern, digitized civilization that literally “ties” children, adolescents, and adults to computers, tablets, and cellular phones [6], not only for electronic games but also for communication, education, and work activities. What happens then in subsequent ontogeny?

Problems of Skeletal-Muscular System in Aging

To the present moment, it is already quite clear that the decrease in body weight below a certain critical value serves as a very serious indicator of subsequent mortality. In fact, the loss of more than 40% of body mass results frequently in irreversible alterations, up to the fatal outcome [7]. However, the loss of even 5–10% of body mass can provoke serious consequences for the health and well-being of elderly persons [1]. How GC and stress are involved in the mechanisms of such alterations?

It appears that GC have important physiologic functions of providing pools of amino acids and glucose in the blood due to their capacity to diminish protein synthesis and augment proteolysis, *i.e.*, protein destruction in skeletal muscles, and gluconeogenesis, *i.e.*, the biochemical transformation of amino acids to glucose. It is interesting that in the liver, GC have frequently inverse influence, which is necessary for the synthesis of serum albumin and acute phase proteins. It means that GC have two-sided activities: these hormones are essential for maintaining the body functions during stress, but in the cases of their excess, especially in long term, cumulative GC action can provoke adverse consequences, including sarcopenia [8]. It means that chronic stress may be involved in the age-related disruption of skeletal muscle function. How do GC and stress affect bone tissue?

The capacity of prolonged pharmacotherapy with GC increases the risk of bone fractures is already well-known, especially in the elderly [9]. As for endogenous GC, it appears that these hormones are able to provoke a switch of progenitor cells in connective tissue from osteogenic differentiation to adipogenic one, *i.e.*, the formation of adipose tissue [10]. Perhaps, exactly because of this peculiarity do elderly persons demonstrate simultaneously the tendencies to obesity and osteoporosis?

Sarcopenia is associated with the results in the following outcome: alterations of body weight and so-called body mass index (BMI, equal to the ratio of body weight to height or stature squared, in kg/m², widely used for evaluation of excessive body weight as a precursor of obesity) may be minimal, masking therefore both obesity and sarcopenia in aging [1].

However, only GC are not involved in the age-related disruption of the functions of the skeletal-muscular system.

Interactions of Glucocorticoids with Pro-Inflammatory Cytokines and Leptin

As already mentioned by us earlier, the proper name “interleukins” (IL) has deviated the attention of researchers for a long time from the true pleiotropic (or multifaceted) spectrum of these cytokine functions. As a matter of fact, at least IL-1 takes an integral part of the hypothalamic-pituitary-adrenal (HPA) axis, actively interacting with GC [11]. In particular, pro-inflammatory cytokines enhance the activity of the whole HPA axis, first of all during the so-called immunologic stress, for example, during infectious diseases, whereas GC diminishes the production of such cytokines.

However, pro-inflammatory cytokines are able to cause resistance to GC, resulting in the possibility of a parallel increase in the levels of both GC and IL-1 and other cytokines. On the other hand, these cytokines are also involved in the mechanisms of sarcopenia and osteoporosis [12] and moreover, their production is elevated in obesity, thus completing the picture of triple pathology including obesity, sarcopenia, and osteoporosis.

What is the role of leptin in this scheme? Although there exist some data that catabolic GC action may be mediated by leptin [13], nevertheless, its role in age-related alteration of the skeletal-muscular system was not studied yet in sufficient mode. However, it is quite possible that in association with aging, there occurs the development of leptin resistance, similar to that taking place in relation to insulin resistance in diabetes mellitus type 2. Probably, this allows to explain the tendency to excessive weight and obesity in some elderly persons, although the proper adipose tissue produces leptin possessing anorectic action.

It is without any doubt that hormonal regulation is extremely complex and deserves thoughtful mathematical modeling and computerized simulation, however, the main problem today consists of the necessity for the elaboration of theoretical apparatus for manifold interactions, *e.g.*, between GC, pro-inflammatory cytokines, and leptin simultaneously. Nevertheless, not only endogenous, but also exogenous GC can contribute negatively to skeletal-muscular problems.

The Role of Corticosteroid Pharmacotherapy and Perspectives of Its Control

Earlier, we discussed the importance of endogenous and exogenous GC in the phenomena of programming/imprinting and embedding, including those of pharmacotoxicologic nature [14]. This theme is quite complicated for polemic discussion since frequently the physicians don't have any choice, to use or not to use these hormonal agents with anti-inflammatory and immunosuppressive action, because in many cases they are vitally needed, especially for saving the patients, for example, in the epoch of the Covid-19 pandemic [15].

However, our aim in this situation is not to favor the so-called steroid phobia, but to find out the opportunities for effective control of adverse side effects of GC. Therefore, in our previous publications, we have already evaluated the possibilities to counteract GC and stress effects by means of using several anti-stress bioregulators [16–18]. It is interesting that the secretion of many of these agents diminishes in aging [19] and moreover, their partial usage as geroprotectors is actively discussed.

Nevertheless, finally, we would like to attract attention to another possibility, and to do this, we ought to mention that both endogenous and some synthetic GC (such as prednisolone, but not dexamethasone) are subject to pre-receptor metabolism by means of two interrelated enzymes, types 1 and 2 of 11beta-hydroxysteroid dehydrogenase (11β-HSD) that cause GC activation and inactivation respectively [20]. The research performed in the last years has established that inhibitors of 11β-HSD type 1 can be quite useful for counteracting senescent alterations in various tissues. However, it is still preliminary to talk about definitive success, since both GC excess and insufficiency are quite dangerous (the last one is because of the increase in the levels of pro-inflammatory cytokines).

What are the other possibilities besides pharmacotherapy?

The Role of Physical Exercise and a Healthy Lifestyle

As usual, it is important to find out the “golden mean” in every such aspect. Indeed, both sedentarism and excessive physical activity can have adverse consequences, similar to cases of insufficient and excessive nutrition, etc. On the other hand, moderate physical exercise and partial undernutrition, in spite of increasing the levels of endogenous GC, may be quite useful, since they are turning on the hormetic mechanisms. On the contrary, allostasis phenomena can result in allostatic load and overload, provoking pre-disease and clinically manifested disorder respectively [21].

The golden mean in these cases is perhaps the balance between occupancy of corticosteroid receptors of type 1 and 2, or mineralocorticoid and GC receptors in the hippocampus, *i.e.*, the brain region partially responsible for negative feedback in the HPA axis [22]. The serious problem is however the following: excessive action of stress or GC on the hippocampus, beginning from the very early stages of ontogeny, by means of cumulative exposure can provoke neurotoxic degeneration, thus disrupting the whole HPA axis function, especially during the acute and chronic stress, what may result in the formation of vicious circle, with a cascade-like increase in the levels of endogenous GC, provoking age-related disorders: cardiometabolic, neuropsychiatric and probably, also skeletal-muscular.

Conclusion

Therefore, it is extremely important to control stress and action of exogenous GC from the very early stages of ontogeny. Here we should outline the essential role of health professionals and psychologists in organizing and executing educational campaigns, also discussing the dangers of auto medication with GC out of adequate medical control.

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Conflicts of Interest

The author affirms that conflict of interest does not exist.

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