

Frailty as a dysruption of steroid “syncrinology” in elderly man

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Abstract. In the background of the endocrinological hypothesis of aging, frailty in man can be seen as a dysruption of syncrinology, a term with which we could define the harmonized activity of steroid hormones (DHEAS, cortisol, testosterone). Such endocrine age-related modifications might promote the activation of sarcopenia, which exerts a core position in the progression of frailty in the elderly. Consequently, the use of replacement treatment in order to delay the beginning of such steroid derangement might be a suitable strategy to improve the quality of life of man, whose life length has been significantly extended. (www.actabiomedica.it)

Key words: Frailty, sarcopenia, elderly, DHEAS, testosterone

Introduction

There is an hypothesis for the knowledge of the pathway of aging phenomena founded on the age-related modifications of hormonal milieu. In order to shed light on the mechanism through which the interrelations between hormone changes and aging develop, we analyzed the rich data base from a population-based sample, in Chianti (Tuscany, Italy), a study of factors affecting mobility in late life, conducted on about 1500 persons living in the Chianti geographical area (1). In the male subjects of the population, attention has been focused on sarcopenia, a parameter showing a typical age-related trend and characterized by a progressive decrease of muscle mass and strength. Calf muscle cross-sectional area evaluated by quantitative computerized tomography was used as a proxy measure of muscle mass while muscle strength was assessed by hand held dynamometer on 8 muscle groups of the lower extremities. Univariate regression analysis showed a significant negative association between age on the one hand and muscle mass ($R=0.23$) and muscle strength ($R=0.42$) on the

other (2). Among the number of parameters available in the data base we focused our attention on sarcopenia because in the progression of frailty of older subjects it exerts a core position being liable for decrease of physical activity and walking speed, for poor endurance and exhaustion. On the other hand, if we make a survey of the most significant components able to activate the promotion and the progression of sarcopenia, we have to take into account chronic undernutrition, in turn promoted by decrease in total energy expenditure and decrease in resting metabolic rate, along with chronic diseases and chronic inflammation. Finally the neuroendocrine dysregulation concerning specifically the ratio between anabolic and catabolic steroid secretion must be considered as well (3, 4) (fig 1).

In the population studied the pattern of steroid secretion from corticoadrenal gland shows a progressive significant reduction of DHEAS levels ($R=0.13$), being cortisol nearly unchanged, and consequently with a significant age related increase of cortisol/DHEAS ratio ($R=0.074$) (5); as for gonadal steroid secretion, we found a significant decrease for total te-

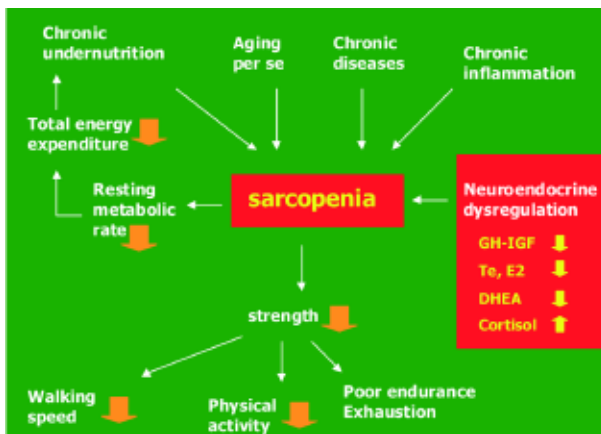


Figure 1. The role of neuroendocrine dysregulation in the hypothetical cycle of frailty

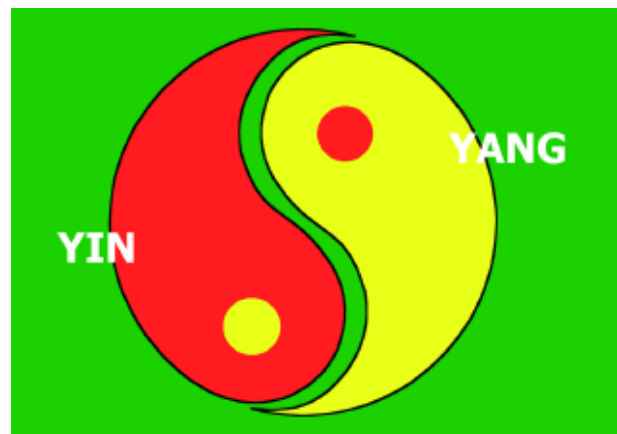


Figure 2. The Celestial Wheel of the two modalities, Yin and Yang

stosterone (R=0.09), free fraction (R=0.18) and bioavailable fraction (R=0.40) of testosterone (6).

Afterwards, we tried to verify the presence of a relationship between muscle parameters on the one hand and steroid hormone pattern on the other, adjusting the analysis for potential confounders like age, physical activity and caloric intake. From separate analysis on DHEAS and testosterone pattern, some significant relationships came out even if with some limitations; in fact, for DHEAS the relationship is limited to the range of age from 60 to 80 years (2), while for testosterone the relationship is evident only for low steroid serum concentration (< 60th percentile) (6). Such considerations underline the weakness of this statistical analysis.

In a further step of the statistical study, at first we weighed the level of frailty according to Fried's criteria, that builds a score which takes into account pre-vaillingly the efficacy of muscle performances like exhaustion, physical activity, walking speed, grip strength and weight loss (3). Subsequently, an other score was defined describing the balance of steroid hormone (DHEAS, testosterone, cortisol) secretion, giving in each subject one point for each hormone located in the worst age and sex specific percentile. Finally, when the frailty score has been correlated with that of steroid hormones, Odd's ratio for risk of frailty has been demonstrated significant only when the three hormones were simultaneously considered (Odd's ratio =10.0 with 95% CI =1.6-6.4); the significance disappears when each steroid was considered indivi-

dually (paper submitted). That is to say that the biological effect of steroids on muscles must be considered globally, assuming that homeostasis comes out from the well balanced involvement of the different hormonal components able of opposite anabolic and catabolic spurs, and that the disruption of such balance for the absolute or relative prevailing of catabolic component makes easier the development of sarcopenia.

This is not a new hypothesis but a modern revision of an hypothesis present even in the ancient Chinese medicine according to which everything in nature, both inanimate and living component, results from antagonistic movement of two forces Yin and Yang. Yin does not exist without Yang, nor does Yang exist

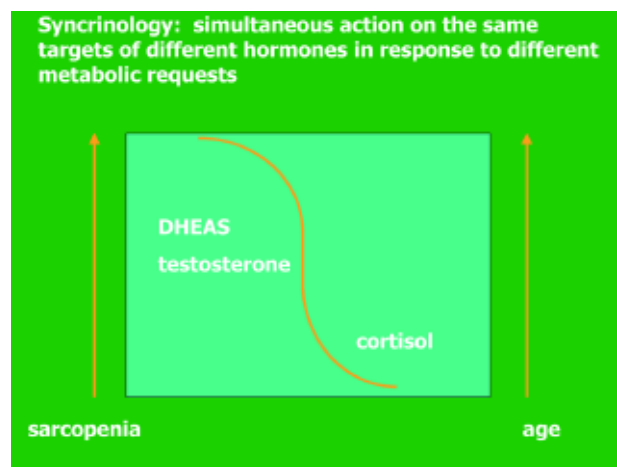


Figure 3. Ratio between anabolic and catabolic hormonal spurs in the different period of life

without Yin, thus forming the concept of the unity of the two opposites. As an example hot, dynamic, external, upward, ascending, progressive, brilliant, vigorous, hyperactive belong to Yang while cold, static, internal, downward, descending, retrogressive, dull, weak, hypoactive belong to Yin. These two forces are interdependent; the relationship between them is constantly changing and under certain conditions each of them may transform into the other and vice versa.

The concept is graphically defined with the Celestial Wheel where the two opposing forces are represented like two big commas, the head of one of which (yellow in the figure) corresponds to the tail of the other (red); the two big points (red and yellow) mean that each modality contains the germ of its opposite (Fig. 2).

Such philosophy transferred to medicine suggests that the normal life activities of the body result from harmonious relationships of the two opposites, Yin and Yang. If the pattern of mutual restraint fails, the balance of Yin and Yang is lost and the body is transformed from its healthy state into a morbid condition (7).

Such interpretation perfectly fits the clinical situation previously described, where sarcopenia is seen as a clinical epiphenomenon of a dysruption of the equilibrium between anabolic and catabolic spurs. This ratio is decidedly in favour of the anabolic component in the first period of life, when protein synthesis meets growth requirements; in the last decades of life the ratio is reversed, still in a teleological position, in a body born not to be immortal but which is going to start its descent (Fig. 3).

The use of replacement treatments in order to delay the beginning of such steroid derangement might be a suitable strategy to improve the quality of life of man whose life length now has been significantly extended (8).

By a semantic point of view, when you want to define the mechanisms of action of hormones, terms have been proposed like endocrinology, paracrinology, autocrinology and intracrinology, each of them with a

specific meaning. I would like to add to them the term of *syncrinology*, just to signify that homeostasis is strongly conditioned by harmonized action of a number of hormones capable to exert simultaneously their biological effect on the same target, being the ratio between the hormonal components variable according to the different metabolic requests of the moment. Sarcopenia, the core of elderly frailty, can be seen as the direct consequence of the dysruption of such steroid syncrinology.

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