Acta Biomed 2010; 81; Suppl 1: 9-14 



# Aging as an allostasis condition of hormones secretion: summing up the endocrine data from the inChianti study

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**Abstract.** Aging phenomena can be seen as a breakdown of the intercellular organisation mechanisms like those represented by endocrine secretions. Such hypothesis is decidedly supported by the analysis of endocrine data coming out from the epidemiological inChianti study. Among the age related endocrine changes a leading role is played by the decline of hormones capable of anabolic effect like Testosterone, IGF-1, DHEAS on the one hand and on the other hand by the even slight increase of the hormones capable of catabolic activity like Cortisol and thyroid hormones. The derangement of this endocrine equilibrium that can be defined with the term of "allostasis", when chronically protracted, might be seen as responsible for many aging phenomena. Consequently specific hormone supplementations might be suggested as a proper strategy to counteract the functional declines occurring in the last decades of life. Nevertheless clinical intervention trials are mandatory in order to validate the hypothesis and to properly verify the risk/benefit ratio. (www.actabiomedica.it)

**Key words:** Aging, endocrine changes, anabolic decline, allostasis

## Introduction

Animals and humans, differently from unicellular organisms, possess two levels of organisation. One level is intracellular under the genomic control of each cell. A second level is represented by intercellular connections which can be obtained through cell to cell communication mechanisms at tissue level and through the activation of integrative systemic connections like endocrine and immune systems with the mediation of extra-cellular milieu (1).

In the past aging phenomena have been prevailingly seen as a breakdown of the intracellular organisation mechanisms. Inside the cell the genome contains the program of the progression of aging as it has been demonstrated by the elegant in vitro experiments on human fibroblasts (2). Environmental agents can directly interact with the cellular genetic apparatus during the whole life span, being nutrition disorders, stress, temperature abnormalities, ionising radiations, toxins, oxidative agents the most frequent involved components (3).

More recently attention has been also focused on the age related impairment of the integrative mechanism of endocrine and immune systems, two components involved in a bi-directional tight interconnection (4). In the present report the role of the neuroendocrine systems, namely of those involved in the control of anabolic/catabolic ratio metabolism, will be extensively analysed; such hormonal modifications represent a crucial pathogenetical component of many aging phenomena constructing the corpus of a specific branch of medicine known with the definition of "geriatric endocrinology". The beginning of this medical approach can be identified in the ancient experiences of Brown-Sequard, the French pathologist who in 1889 described the putative "pouissance dynamogenique" of an extract of animal testes in humans (5).

More recently during the second part of 19th century Butturini and Patrono from the Universities of Parma and Rome analysed this topic from a more scientific point of view. Patrono in 1958, firstly in the medical literature, in a book entitled "Ormonoterapia e vecchiaia" (6) extensively described the different characteristics of the "aging-disease" and of the "diseases of aging", focusing the pathogenetical role of endocrine changes and the hypothetical positive effect of hormone replacement tretments. Finally in the last decades of 19th century our group has been involved in a strong promotional cultural activity organising seven national and international meetings on the specific topic of geriatric endocrinology. Recently our group has been involved in the analysis of endocrine pattern in the epidemiological study inChianti; the age related changes of hormone concentration have been extensively correlated with several clinical functional parameters with the specific aim to focus the role of endocrine pattern in the pathogenesis of aging phenomena.

**Age related endocrine changes in the inChianti study population and their putative clinical implications**

The inChianti study is an epidemiologic al study of risk factors for mobility disability in the old age. The analysed population is a representative sample (1453 subjects) of the population living in Greve in Chianti and Bagno a Ripoli, two small towns located in the country side of Florence (Italy) (7).

The most significant changes of endocrine pattern over the life span in our studies concern in the male subjects the decline of serum Testosterone (total and bioavailable) and in both sexes the decline of serum DHEAS and of IGF-1, the substantially unmodified serum concentration of Cortisol and the variable behaviour of Thyroid functio n parameters (fT4, fT3 and TSH) frequently consistent with the condition of subclinical hyper- or hypo-thyroidism. The deterioration of motor organisation, the primary target of the inChianti study, which is at the basis of frailty condition in the old age, is founded on the involvement of several physiological subsystems tightly related to mobility and motor performances: muscles (mass and strength), bone and joints, CNS (cognition and affectiveness), peripheral nerves, metabolic efficiency, aerobic capacity; therefore answering the question if hormone changes are capable to affect the progression of frailty condition in aging people is like to say if such hormone changes appear to be someway related to the deterioration of any of these subsystems.

a) As for Testosterone decline a significant association was documented for muscle strength evaluated with hand grip parameter. Subdividing male subjects in three groups according to total Testosterone serum concentration (normal > 3.5, borderline 3.4 – 2.3, hypogonadic < 2.3 ng/ml) a significant association with muscle strength decline was observed (p for trend < 0.001) (8). Furthermore a significant correlation of total and bioavailable Testosterone with age adjusted Hemoglobin concentrations was demonstrated both in the whole and in the restricted population (i.e. excluding subjects with documented secondary anemia), suggesting that older men and women with low Testosterone levels have a higher risk of anemia (9). Another metabolic implication of Testosterone was demonstrated with the finding of a significant association between Testosterone concentration and metabolic syndrome in older men of the inChianti population. The concentration of total Testosterone but not of bioavailable Testosterone was found significantly lower ($p<0.03$) in the subjects showing at least 3 criteria typical of metabolic syndrome; in these subjects the concentration of SHBG was found lower as well, suggesting a role of SHBG more than that of a simple binding protein. Multiple linear regression models evaluating the relationship between Metabolic Syndrome and circulating levels of hormones showed a significant negative association for total Testosterone and SHBG serum concentrations (10).

b) On the basis of our findings an implication on physical performances in males can be suggested also for IGF-1. In fact a significant association between knee extension torque and IGF-1 concentration was documented in men ($p < 0.05$) but not in women after adjustment for age and BMI, suggesting a positive effect of IGF-1 on muscle function (11).

c) When we moved to analyse the role of DHEAS we found an independent positive association between DHEAS serum concentration and muscle parameters (muscle mass and lower extremity muscle strength) in men after adjusting for putative confounders like age, serum Testosterone, physical activity, total caloric intake; the association however was significant only in the range of age between 60 and 79 years (12). For DHEAS a significant positive relationship was demonstrated also for cognitive function evaluated with MMSE score in the global population in a cross sectional analysis ($p < 0.005$); subdividing the subjects by gender the association appeared quite evident for males ($p< 0.01$) and borderline for females ($p= 0.06$). The hypothesis of a protection of DHEAS on cognitive decline was endorsed by the longitudinal analysis in the over 3-year follow up: the highest decreased of MMSE score was found in the group of subjects in the lowest quartile of DHEAS (p for trend < 0.05) and the percentage of the participants who lost at least 1 point in MMSE score was highest again in the group of subjects in the lowest quartile of DHEAS (13).

d) In subjects over 65 years the subclinical Thyroid dysfunctions are the most prevalent Thyroid abnormalities, being subclinical hyperthyroidism much more prevalent than subclinical hypothyroidism. In proper adjusted analysis participants with subclinical hyperthyroidism were significantly more likely to have cognitive impairment (hazard rate = 2.26 p= 0.003) (14) and poor physical performance defined by SPPB lower than 10 (hazard rate = 2.97 p = 0.048) (15).

e) Finally Cortisol serum concentrations underwent a slight change over the life span in both sexes being Cortisol/DHEAS molar ratio significantly increased with the progression of age (R = 0.074). Unfortunately in the inChianti study Cortisol levels were assayed only in a morning serum sample, while in the literature the integrated values of Cortisol over the 24 hours frequently show a progressive increase with age, and therefore we did not draw correlation studies between Cortisol and any kind of clinical outcomes. Anyway a number of observations is available from literature proving significant associations of sarcopenia, osteopenia, impairment of cognitive performances and of immunocompetence with Cortisol increase (16).

**Personal comments and conclusions**

As it has been previously shown the relationships between hormonal changes and functional parameters are significantly achieved in some specific areas. Nevertheless for other several outcomes statistical evidence was not completely found even if the presence of a trend was frequently documented. At the basis of the failure of such evidence a number of specific complexities can be suggested.

a) First of all we have to consider that the determination of hormone serum concentration is not an exhaustive sign of its biological effect. After the secretion from endocrine glands into the blood stream each hormone undergoes a number of metabolic steps capable to significantly modify its biological peripheral action: the link to the binding proteins, the peripheral metabolism like the bioconversion to different hormones, the impact with the peripheral receptors and finally the post-receptor events. Hormone assay satisfies only the first part of this complicated way, being most of it almost completely disregarded (17).

b) The second consideration comes from the assumption that each biological hormone effect is obtained through the simultaneous involvement of several hormonal components acting in the same direction. Going back to the hormones previously described, all of them are able to control protein synthesis in the whole body through anabolic (Testosterone, DHEAS, IGF-1) or catabolic (Cortisol, Thyroid hormones) mechanisms. Consequently a slight decline or increase of a single anabolic or catabolic component respectively might not be significantly correlated with a clinical outcome but the sum of two or three slight unsignificat hormone changes can promote a significant biological effect. Such role of multiple hormone dysregulation has been demonstrated for the survival outcome in the longitudinal study (Kaplan-Mayer analysis) at 6 year follow up in the inChianti male population; only men with 3 anabolic hormones in the

lowest quartile have a significant increase in mortality (test for trend p< 0.001). Having multiple hormonal deficiencies rather than a deficiency in a single anabolic hormone is a robust biomarker of health status in older persons (18).

c) Finally we must underline that each biological hormone effect must be seen as a sum of simultaneous converging activities on the same target of agonistic and antagonistic components: a particular condition that we defined with the term of "syncrinology" (17). On the basis of these premises the unsignificant decline of an anabolic hormone can become clinically effective if it is associated with a concomitant, even unsignificant per se, increase of the catabolic antagonist; the molar ratio between anabolic and catabolic hormones assay might be a more proper parameter to be used.

As a consequence of these preliminary remarks, a characteristic age related endocrine pattern comes out, represented by the derangement of the ratio between anabolic and catabolic spurs, being progressively declined the former and increased the latter. Such endocrine pattern might be one of the most important pathogenetic component at the basis of the condition of frailty of aging people. The decline of protein synthesis and in the meantime the progression of catabolic activity involve a number of tissues and organs of the whole body and their related functions (muscle, bone, cardiovascular system, central and peripheral nervous system, erythropoiesis, immunocompetence in primis); consequently a lot of aging phenomena can be seen as an expression of such endocrine disorder. This consideration comes out from the analysis of the secretions of a single endocrine gland, like corticoadrenal gland, in which the progressive decline of DHEAS secretion on the one hand is accompanied on the other hand by the increase of Cortisol. This assumption is even more corroborated when we enlarge the analysis to the whole group of the other hormones capable of anabolic ( Testosterone and IGF-1) and catabolic (Thyroid hormones) effects.

Borrowing the term proposed by Sterlyng and Eyer (19) we can define this condition with the word of "allostasis": while homeostasis from Greek means "remaining stable by staying the same", "allostasis" was similarly coined from Greek to mean "remaining stable by being variable". Such hormone movements may be manifested during the normal course of daily activities as a result of stressful events and appear to be an adaptive mechanism in the short run; yet they can become damaging allostatic mediators when they are chronically protracted.

Such allostatic state in the last decades of life, in a body not born to be immortal, can be seen as a kind of natural way promoting the inevitable decline of the whole body. In the same way another example of allostatic state can be considered that of the first decades of life in which, in response to the need of growth and developing energies, the anabolic/catabolic balance on the contrary appears to be dysrupted for a decidedly prevalence of anabolic component. Consequently a good strategy to antagonise aging phenomena might be that to delay, with proper supplemental hormone treatments, the appearance of the unavoidable anabolic decline (Fig.1).

At present we can assume that observational studies available in the literature are quite sufficient to endorse the activation of proper randomized controlled clinical intervention trials absolutely useful for a scientific validation of the hypothesis. Unfortunately not so many trials are still available in order to say a definite word concerning the relationship between hormone change and any clinical outcome. This step of clinical research is mandatory just to verify the effective biological consequence of any hormone secretion decline.

In line with the concept previously defined of "syncrinology", anabolic hormone replacement treatment, through its specific biologic effect, might be an easy consistent strategy to be performed; more difficult is that to try the inhibition of antagonist hormones. For some hormones like DHEA, replacement treatment is capable of both these effects; in fact DHEA is able on the one hand to realise its anabolic specific effect and on the other hand in the mean time, through the inhibition of ACTH secretion and through the competition with peripheral Cortisol receptors, to counteract the catabolic effect of Cortisol.

Nevertheless when the hypothesis will be validated with clinical trials other unanswered questions will remain: which is the risk/benefit ratio for each hor-

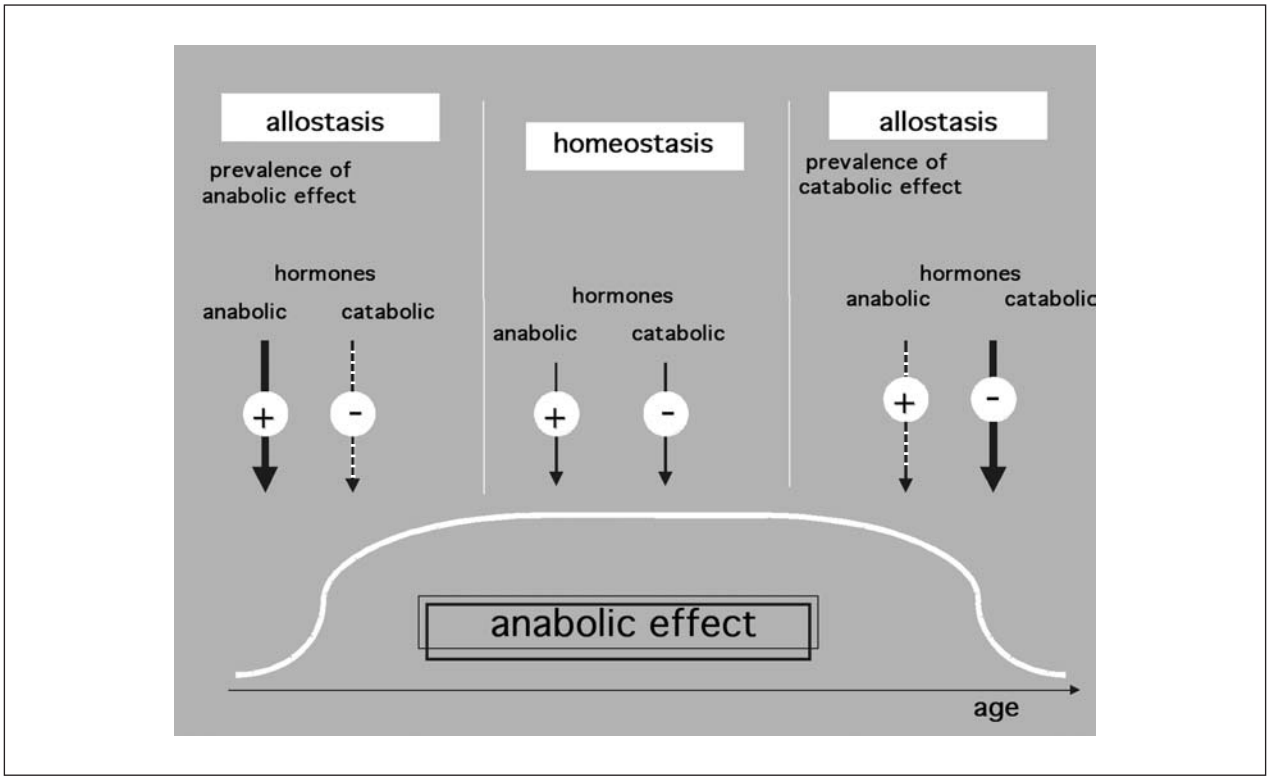


**Figure 1**. The age related anabolic decline as an expression of allostatic chronic condition of hormone secretion.

mone supplementation? How long should be the treatment protracted? Which is the most proper pharmaceutical preparation? Therefore a long and complicated way is still in front of us.

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Accepted: December 18th, 2009
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