

ENDOCRINE FRAILITY IN THE ELDERLY

EDITED BY: Antonio Aversa, Sandro La Vignera and Fabio Monzani
PUBLISHED IN: Frontiers in Endocrinology



ENDOCRINE FRAILITY IN THE ELDERLY

Topic Editors:

Antonio Aversa, Professor of Endocrinology, Endocrinology Unit, Department of Experimental and Clinical Medicine, University of Catanzaro Magna Graecia, Italy

Sandro La Vignera, Professor of Endocrinology, Department of Clinical and Experimental Medicine, School "Faculty of Medicine", University of Catania, and Expert Member of the Continuing Education Commission for the Sicilian Health Department, Italy

Fabio Monzani, Professor of Geriatrics, Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy

The senile age is characterized by numerous modifications on the endocrinological level that concern all the main axes. In particular clinical conditions such as: hypogonadism, reduced levels of IGF-1, hypovitaminosis D, osteoporosis, hypothyroidism, sarcopenia, represent frequent problems that require the evaluation of various specialists. Hormonal treatments, mostly substitutive, require the knowledge of precise management rules as well as the knowledge of concrete clinical objectives. In particular, the correct management of sexual activity involves a functional commitment that requires a correct stratification of cardiovascular risk, in particular in consideration of the systemic effects of vasoactive drugs used in the treatment of erectile dysfunction.

The main objective of this Research Topic was to provide a translational vision of geriatric endocrinology that allows the different specialists who interface in the management of patients in the geriatric phase to share a common point of view regarding the endocrinological aspects.

The authors that contributed to this Research Topic illustrated the epidemiological, pathophysiological and clinical aspects of the main hormonal changes that occur in senile age, in such a way that the reader has the possibility to deepen the mechanisms of the various conditions but at the same time has the possibility to obtain information for daily clinical practice regarding the management of these conditions. All topics has been addressed in the form of an article-review. In selected papers, original aspects deriving from clinical and/ or experimental studies underway during the preparation of this collection of articles has been illustrated.

This Research Topic entitled "Endocrine Frailty in the Elderly" analyzed, among others, the following aspects related to geriatric endocrinology:

- Changes of the thyroid function;
- Changes of the adrenal function;
- Changes of the somatotrophic axis;
- Changes in metabolic and pancreatic function;
- Changes in bone function;
- Changes in sexual function; and
- Changes in the characteristics of neuroimaging of senescence.



Prof. Antonio Aversa

Chief of the Postgraduate School of Endocrinology and Metabolic Disease at the University of Catanzaro Magna Graecia, Italy
aversa@unicz.it

Antonio Aversa is Professor in Endocrinology at the University of Catanzaro Magna Graecia since 2015, where he is director of the School of Specialization in Endocrinology and Metabolic Diseases. He is Secretary General of the Italian Society of Andrology and Sexual Medicine (SIAMS) and coordinator of Geriatric Endocrinology Club (EndoGer) of the Italian Society of Endocrinology (SIE). He published more than 150 original papers in peer-reviewed journals and is the Co-Editor of the 'Geriatric Endocrinology Manual'.



Prof. Sandro La Vignera

Professor of Endocrinology, Department of Clinical and Experimental Medicine, School "Faculty of Medicine", University of Catania, and Expert Member of the Continuing Education Commission for the Sicilian Health Department, Italy
sandrolavignera@unict.it

Specialist in Endocrinology. PhD in Andrological Sciences. Professor of Endocrinology at the "Faculty of Medicine" of the University of Catania. Directive Committee Member of the Master in Biology and Biotechnology of Reproduction of the University of Catania. Academician of European Academy of Andrology. Directive Committee Member of the Italian Society of Andrology and Sexual Medicine. Directive Regional Committee Member of the Italian Society of Endocrinology. Editorial Board Member of Scientific Reports-Nature. Guest Editor for Frontiers in Endocrinology and Journal of Clinical Medicine. Best Researcher Award Italian Society of Endocrinology (2017).



Prof. Fabio Monzani

Professor of Geriatrics
Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy
fabio.monzani@med.unipi.it

Fabio Monzani is chief of the postgraduate School of Geriatrics and Gerontology and director of the Geriatrics Unit at the University Hospital of Pisa, Italy. President of the regional section of the Italian Society of Geriatrics and Gerontology (SIGG), Coordinator of the SIGG groups for the study of Geriatric Endocrinology and Geriatric Oncology. Coordinator of several national and international research projects supported by MIUR (Ministero Istruzione, Università, Ricerca) and by the European Community Research Agency. Member of the Scientific Committee of the SIGG annual national meeting.

Table of Contents

- 04 Osteoporosis and Sarcopenia Increase Frailty Syndrome in the Elderly**
Emanuela A. Greco, Peter Pietschmann and Silvia Migliaccio
- 05 Hypothyroidism as a Predictor of Surgical Outcomes in the Elderly**
Marco Vacante, Antonio Biondi, Francesco Basile, Roberto Ciuni, Salvatore Luca, Salomone Di Saverio, Carola Buscemi, Enzo Saretto Dante Vicari and Antonio Maria Borzi
- 06 Androgen Deficiency and Phosphodiesterase Type 5 Expression Changes in Aging Male: Therapeutic Implications**
Antonio Aversa, Ylenia Duca, Rosita Angela Condorelli, Aldo Eugenio Calogero and Sandro La Vignera
- 07 Neuroimaging and Neurolaw: Drawing the Future of Aging**
Vincenzo Tigano, Giuseppe Lucio Cascini, Cristina Sanchez-Castañeda, Patrice Péran and Umberto Sabatini
- 08 The Differential Effect of Excess Aldosterone on Skeletal Muscle Mass by Sex**
Mi Kyung Kwak, Seung-Eun Lee, Yoon Young Cho, Sunghwan Suh, Beom-Jun Kim, Kee-Ho Song, Jung-Min Koh, Jae Hyeon Kim and Seung Hun Lee
- 09 Overt and Subclinical Hypothyroidism in the Elderly: When to Treat?**
Valeria Calsolaro, Filippo Niccolai, Giuseppe Pasqualetti, Alessia Maria Calabrese, Antonio Polini, Chukwuma Okoye, Silvia Magno, Nadia Caraccio and Fabio Monzani
- 10 Diabetes and Aging: From Treatment Goals to Pharmacologic Therapy**
Miriam Longo, Giuseppe Bellastella, Maria Ida Maiorino, Juris J. Meier, Katherine Esposito and Dario Giugliano
- 11 Impact of Paternal Age on Seminal Parameters and Reproductive Outcome of Intracytoplasmic Sperm Injection in Infertile Italian Women**
Mariagrazia Gallo, Emanuele Licata, Caterina Meneghini, Alessandro Dal Lago, Cristina Fabiani, Marcello Amodei, Domenico Antonaci, Donatella Miriello, Roberta Corno, Carmelina Liberanome, Francescantonio Bisogni, Gemma Paciotti, Carlo Meneghini and Rocco Rago
- 12 Adrenal Aging and its Implications on Stress Responsiveness in Humans**
Andreas Yiallouris, Constantinos Tsioutis, Eirini Agapidaki, Maria Zafeiri, Aris P. Agouridis, Dimitrios Ntourakis and Elizabeth O. Johnson
- 13 ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective**
Giovanni Vitale, Giuseppe Pellegrino, Maria Vollery and Leo J. Hofland

Osteoporosis and Sarcopenia Increase Frailty Syndrome in the Elderly

Emanuela A. Greco¹, Peter Pietschmann² and Silvia Migliaccio^{3*}

¹Section of Medical Pathophysiology, Endocrinology and Food Science, Department of Experimental Medicine, University of Rome Sapienza, Rome, Italy

²Department of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology, and Immunology, Medical University of Vienna, Vienna, Austria

³Unit of Endocrinology, Section of Health Sciences, Department of Movement, Human and Health Sciences, University of Rome Foro Italico, Rome, Italy

Musculoskeletal aging is a major public health interesting and strain due to the significant demographic modifications in the population, and it is linked to high risk of falls, loss of autonomy in elderly individuals and institutionalization with small health outcomes. Thus, this pathological status is related to high morbidity and health care rates. Bone mass and muscle mass and strength increase during late adolescence and early adulthood but start to reduce noticeably from the fifth decade of life and are closely linked. Bone and muscle tissues were increasingly recognized, as endocrine target organs and endocrine organs themselves, interacting through paracrine and endocrine signals. During growth, bone mineral content closely correlates with muscle mass, and several evidences suggest that osteoporosis and sarcopenia present common pathophysiological factors and show the correlation between low bone mineral density and sarcopenia in both men and women. Then, sarcopenia and osteoporosis, typical features of aging, are often associated with each other and with the frailty syndrome. In particular, sarcopenia and osteoporosis are major contributors to disability and frailty and the common denominators are age-related chronic inflammation, changes in body composition and hormonal imbalance. Frailty syndrome is characterized by a reduced response to stress, triggering the decline of the physiological functioning of the various systems. Frailty syndrome, typical of the older people, is frequently associated with a reduction in the quality of life and mobility. Falls often are the basis of reduced mobility and ability to perform the common functions of daily life and the increase in the number of institutionalizations. Moreover, the reduction of muscle mass, associated with altered muscle composition, fat and fibrous infiltration and alterations in innervations, and the increase in fat mass, have a synergistic effect on the increase in cardiovascular risk. The aim of this review is to analyze the pathophysiological mechanisms underlying the frailty syndrome and its association with sarcopenia and osteoporosis, and investigate possible intervention measures.

Hypothyroidism as a Predictor of Surgical Outcomes in the Elderly

Marco Vacante¹, Antonio Biondi¹, Francesco Basile¹, Roberto Ciuni¹, Salvatore Luca¹, Salomone Di Saverio², Carola Buscemi³, Enzo Saretto Dante Vicari³ and Antonio Maria Borzi^{3*}

¹Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy

²Cambridge Colorectal Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

³Department of Clinical and Experimental Medicine, Specialization School in Geriatrics, University of Catania, Catania, Italy

There is a high prevalence of hypothyroidism in the elderly population, mainly among women. The most important cause is autoimmune thyroiditis, but also iodine deficiency, radioiodine ablation, and surgery may be responsible for hypothyroidism in elderly hospitalized patients. Thyroid-related symptoms are sometimes comparable to physiological manifestations of the aging process, and hypothyroidism may be related with many symptoms which can be present in critical patients, such as cognitive impairment, cardiovascular, gastrointestinal, and hematological alterations, and eventually myxedema coma which is a severe and life-threatening condition in older adults. Adequate thyroid hormone levels are required to achieve optimal outcomes from any kind of surgical intervention. However, only few randomized clinical trials investigated the association between non-thyroidal illness (or low-T3 syndrome), and adverse surgical outcomes, so far. The goal of this review is to discuss the role of thyroid function as a predictor of surgical outcomes in the elderly.

Androgen Deficiency and Phosphodiesterase Type 5 Expression Changes in Aging Male: Therapeutic Implications

Antonio Aversa¹, Ylenia Duca², Rosita Angela Condorelli², Aldo Eugenio Calogero² and Sandro La Vignera^{2*}

¹Department of Experimental and Clinical Medicine, University "Magna Graecia" of Catanzaro, Catanzaro, Italy

²Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

The age-related decline of serum T occurs in ~20–30% of adult men and it is today defined as late-onset hypogonadism (LOH). In the elderly, such decline becomes more prevalent (up to 60%) and shows-up with erectile dysfunction (ED) and hypoactive sexual desire. A large body of experimental evidences have shown that the combination of T replacement therapy (TRT) and phosphodiesterase type 5 inhibitors (PDE5i) is, usually, effective in restoring erectile function in patients with LOH and ED who have not responded to monotherapy for sexual disturbances. In fact, PDE5i potentiate the action of nitric oxide (NO) produced by endothelial cells, resulting in a vasodilator effect, while T facilitates PDE5i effects by increasing the expression of PDE5 in corpora cavernosa. Meta-analytic data have recognized to PDE5i a protective role on the cardiovascular health in patients with decreased left ventricular ejection fraction. In addition, several studies have shown pleiotropic beneficial effects of these drugs throughout the body (i.e., on bones, urogenital tract and cerebral, metabolic, and cardiovascular levels). TRT itself is able to decrease endothelial dysfunction, oxidative stress and inflammation, thus lowering the cardiovascular risk. Furthermore, untreated hypogonadism could be the cause of PDE5i ineffectiveness especially in the elderly. For these reasons, aging men complaining ED who have LOH should undergo TRT before or at the moment when PDE5i treatment is started.

Neuroimaging and Neurolaw: Drawing the Future of Aging

Vincenzo Tigano¹, Giuseppe Lucio Cascini², Cristina Sanchez-Castañeda³, Patrice Pérán⁴ and Umberto Sabatini

¹Department of Juridical, Historical, Economic and Social Sciences, University of Magna Graecia, Catanzaro, Italy

²Department of Experimental and Clinical Medicine, University of Magna Graecia, Catanzaro, Italy

³Department of Clinical Psychology and Psychobiology, University of Barcelona, Barcelona, Spain

⁴ToNIC, Toulouse Neuroimaging Center, Université de Toulouse, Inserm, UPS, Toulouse, France

⁵Department of Medical and Surgical Sciences, University of Magna Graecia, Catanzaro, Italy

Human brain-aging is a complex, multidimensional phenomenon. Knowledge of the numerous aspects that revolve around it is therefore essential if not only the medical issues, but also the social, psychological, and legal issues related to this phenomenon are to be managed correctly. In the coming decades, it will be necessary to find solutions to the management of the progressive aging of the population so as to increase the number of individuals that achieve successful aging. The aim of this article is to provide a current overview of the physiopathology of brain aging and of the role and perspectives of neuroimaging in this context. The progressive development of neuroimaging has opened new perspectives in clinical and basic research and it has modified the concept of brain aging. Neuroimaging will play an increasingly important role in the definition of the individual's brain aging in every phase of the physiological and pathological process. However, when the process involved in age-related brain cognitive diseases is being investigated, factors that might affect this process on a clinical and behavioral level (genetic susceptibility, risks factors, endocrine changes) cannot be ignored but must, on the contrary, be integrated into a neuroimaging evaluation to ensure a correct and global management, and they are therefore discussed in this article. Neuroimaging appears important to the correct management of age-related brain cognitive diseases not only within a medical perspective, but also legal, according to a wider approach based on development of relationship between neuroscience and law. The term neurolaw, the neologism born from the relationship between these two disciplines, is an emerging field of study, that deals with various issues in the impact of neurosciences on individual rights. Neuroimaging, enhancing the detection of physiological and pathological brain aging, could give an important contribution to the field of neurolaw in elderly where the full control of cognitive and volitional functions is necessary to maintain a whole series of rights linked to legal capacity. For this reason, in order to provide the clinician and researcher with a broad view of the brain-aging process, the role of neurolaw will be introduced into the brain-aging context.

The Differential Effect of Excess Aldosterone on Skeletal Muscle Mass by Sex

Mi Kyung Kwak^{1,2}, Seung-Eun Lee³, Yoon Young Cho⁴, Sunghwan Suh⁵,
Beom-Jun Kim¹, Kee-Ho Song⁶, Jung-Min Koh¹, Jae Hyeon Kim^{3*} and
Seung Hun Lee^{1*}

¹Division of Endocrinology and Metabolism, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

²Division of Endocrinology and Metabolism, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong-Si, South Korea

³Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

⁴Division of Endocrinology and Metabolism, Department of Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea

⁵Division of Endocrinology and Metabolism, Department of Internal Medicine, Dong-A University Medical Center, Dong-A University College of Medicine, Busan, South Korea

⁶Division of Endocrinology and Metabolism, Konkuk University School of Medicine, Konkuk University Medical Center, Seoul, South Korea

The effects of excess aldosterone on skeletal muscle in individuals with primary aldosteronism (PA) are unknown. To examine the effects of aldosterone on skeletal muscle mass in patients with PA, by sex, 309 consecutive patients were enrolled. Skeletal muscle and fat mass of 62 patients with PA were compared with those of 247 controls with non-functioning adrenal incidentaloma (NFAI). Body composition parameters were measured using bioelectrical impedance analysis, and plasma aldosterone concentration (PAC) was measured using radioimmunoassay. The PAC in all women, but not in men, showed an inverse association with both appendicular skeletal muscle mass (ASM) ($\beta = -0.197$, $P = 0.016$) and height-adjusted ASM (HA-ASM) ($\beta = -0.207$, $P = 0.009$). HA-ASM in women (but not in men) with PA was 5.0% lower than that in women with NFAI ($P = 0.036$). Furthermore, women with PA had a lower HA-ASM than 1:1 age- and sex-matched controls with NFAI by 5.7% ($P = 0.049$) and tended to have a lower HA-ASM than 1:3 age-, sex-, and menopausal status-matched controls without adrenal incidentaloma (AI) by 7.3% ($P = 0.053$). The odds ratio (OR), per quartile increase in PAC, of low HA-ASM in women was 1.18 [95% confidence interval (CI), 1.01–1.39; $P = 0.035$]. The odds of HA-ASM in subjects with PA were 10.63-fold (95% CI: 0.83–135.50) higher, with marginal significance ($P = 0.069$) than in those with NFAI. Skeletal muscle mass in women with PA was lower than that in women with NFAI; suggesting that excess aldosterone has adverse effects on skeletal muscle metabolism.

Overt and Subclinical Hypothyroidism in the Elderly: When to Treat?

Valeria Calsolaro^{1,2*}, Filippo Niccolai¹, Giuseppe Pasqualetti¹, Alessia Maria Calabrese¹, Antonio Polini¹, Chukwuma Okoye¹, Silvia Magno³, Nadia Caraccio¹ and Fabio Monzani¹

¹Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

²Neurology Imaging Unit, Imperial College, London, United Kingdom

³Obesity Center at the Endocrinology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Hypothyroidism is characterized by increased thyrotropin (TSH) levels and reduced free thyroid hormone fractions while, subclinical hypothyroidism (sHT) by elevated serum TSH in the face of normal thyroid hormones. The high frequency of hypothyroidism among the general population in Western Countries made levothyroxine (LT₄) one of the 10 most prescribed drugs. However, circulating TSH has been demonstrated to increase with aging, regardless the existence of an actual thyroid disease. Thus, when confronting an increase in circulating TSH levels in the elderly, especially in the oldest old, it is important to carry an appropriate diagnostic path, comprehensive of clinical picture as well as laboratory and imaging techniques. In the current review, we summarize the recommendations for a correct diagnostic workup and therapeutic approach to older people with elevated TSH value, with special attention to the presence of frailty, comorbidities, and poly-therapy. The treatment of choice for hypothyroid patients is hormone replacement with LT₄ but, it is important to consider multiple factors before commencing the therapy, from the age dependent TSH increase to the presence of an actual thyroid disease and comorbidities. When treatment is necessary, a tailored therapy should be chosen, considering poly-pharmacy and frailty. A careful follow-up and treatment re-assessment should be always considered to avoid the risk of over-treatment. It is important to stress the need of educating the patient for a correct administration of LT₄, particularly when poly-therapy is in place, and the importance of a tailored therapeutic approach and follow-up, to avoid overtreatment.

Diabetes and Aging: From Treatment Goals to Pharmacologic Therapy

Miriam Longo¹, Giuseppe Bellastella^{1*}, Maria Ida Maiorino¹, Juris J. Meier², Katherine Esposito³ and Dario Giugliano¹

¹*Unit of Endocrinology and Metabolic Diseases, Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy*

²*Diabetes Division, St Josef Hospital, Ruhr-University Bochum, Bochum, Germany*

³*Diabetes Unit, Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy*

Diabetes is becoming one of the most widespread health burning problems in the elderly. Worldwide prevalence of diabetes among subjects over 65 years was 123 million in 2017, a number that is expected to double in 2045. Old patients with diabetes have a higher risk of common geriatric syndromes, including frailty, cognitive impairment and dementia, urinary incontinence, traumatic falls and fractures, disability, side effects of polypharmacy, which have an important impact on quality of life and may interfere with anti-diabetic treatment. Because of all these factors, clinical management of type 2 diabetes in elderly patients currently represents a real challenge for the physician. Actually, the optimal glycemic target to achieve for elderly diabetic patients is still a matter of debate. The American Diabetes Association suggests a HbA1c goal <7.5% for older adults with intact cognitive and functional status, whereas, the American Association of Clinical Endocrinologists (AAACE) recommends HbA1c levels of 6.5% or lower as long as it can be achieved safely, with a less stringent target (>6.5%) for patients with concurrent serious illness and at high risk of hypoglycemia. By contrast, the American College of Physicians (ACP) suggests more conservative goals (HbA1c levels between 7 and 8%) for most older patients, and a less intense pharmacotherapy, when HbA1C levels are ≤6.5%. Management of glycemic goals and antihyperglycemic treatment has to be individualized in accordance to medical history and comorbidities, giving preference to drugs that are associated with low risk of hypoglycemia. Antihyperglycemic agents considered safe and effective for type 2 diabetic older patients include: metformin (the first-line agent), pioglitazone, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists. Insulin secretagogue agents have to be used with caution because of their significant hypoglycemic risk; if used, short-acting sulfonylureas, as gliclazide, or glinides as repaglinide, should be preferred. When using complex insulin regimen in old people with diabetes, attention should be paid for the risk of hypoglycemia. In this paper we aim to review and discuss the best glycemic targets as well as the best treatment choices for older people with type 2 diabetes based on current international guidelines.

Impact of Paternal Age on Seminal Parameters and Reproductive Outcome of Intracytoplasmic Sperm Injection in Infertile Italian Women

Mariagrazia Gallo^{1*}, Emanuele Licata¹, Caterina Meneghini¹, Alessandro Dal Lago¹, Cristina Fabiani¹, Marcello Amodei¹, Domenico Antonaci¹, Donatella Miriello¹, Roberta Corno¹, Carmelina Liberanome¹, Francescantonio Bisogni¹, Gemma Paciotti¹, Carlo Meneghini² and Rocco Rago^{1*}

¹Physiopathology of Reproduction and Andrology Unit, Sandro Pertini Hospital, Rome, Italy

²Science Department, Roma Tre University, Rome, Italy

Background: We conducted a retrospective study on a cohort of couples attending the Department of Andrology and Reproductive Physiopathology at Sandro Pertini Hospital in Rome for Intracytoplasmic Sperm Injection (ICSI)-assisted reproduction programs. Some of the couples included in the study underwent more than one ICSI cycle. Between January 2015 and April 2017.

Objective: To evaluate whether the advancing of the paternal age may have effect on the seminal parameters, thus negatively affecting the embryo formation, development and quality, as well as the pregnancy rate.

Materials and Methods: Five hundred and forty three ICSI cycles were performed on 439 couples undergoing Assisted Reproductive Technologies (ART). Patients were subdivided into three male and three female age groups having similar size:

Men: ≤ 38 years (MI), 39–43 years (MII), ≥ 44 years (MIII).

Women: ≤ 35 years (FI), 36–40 years (FII), ≥ 41 years (FIII).

Discussion and Conclusion: Male age groups did not reveal any statistical significant differences in any age-related semen parameters. We also confirmed a statistical significant increase in the pregnancy rate of couples with older partner age difference and younger female. We found that the advanced male age increases the probability of obtaining one or no type A embryo ($N_{A \leq 1}$), which was almost doubled in the MIII group in comparison with M_I, suggesting a negative effect of male age on the efficacy of the reproductive outcome in terms of a reduced number of type A embryos. Such an effect does not seem related to semen parameters and may deserve further investigations.

Adrenal Aging and Its Implications on Stress Responsiveness in Humans

Andreas Yiallouris^{1,2}, Constantinos Tsioutis^{1,3}, Eirini Agapidaki¹, Maria Zafeiri^{3,4}, Aris P. Agouridis¹, Dimitrios Ntourakis¹ and Elizabeth O. Johnson^{1,2*}

¹*School of Medicine, European University Cyprus, Nicosia, Cyprus*

²*Laboratory of Education & Research Neuroscience, Department of Anatomy, School of Medicine, National and Kapodistrian University Athens, Athens, Greece*

³*Society of Junior Doctors, Athens, Greece*

⁴*Diabetes and Obesity Center, Konstantopouleio Hospital, Athens, Greece*

Normal aging results in subtle changes both in ACTH and cortisol secretion. Most notable is the general increase in mean daily serum cortisol levels in the elderly, without a noteworthy alteration in the normal circadian rhythm pattern. Glucocorticoid excess seen in the elderly population can have serious consequences in both the structural and functional integrity of various key areas in the brain, including the hippocampus, amygdala, prefrontal cortex, with consequent impairment in normal memory, cognitive function, and sleep cycles. The chronically elevated glucocorticoid levels also impinge on the normal stress response in the elderly, leading to an impaired ability to recover from stressful stimuli. In addition to the effects on the brain, glucocorticoid excess is associated with other age-related changes, including loss of muscle mass, hypertension, osteopenia, visceral obesity, and diabetes, among others. In contrast to the increase in glucocorticoid levels, other adrenocortical hormones, particularly serum aldosterone and DHEA (the precursor to androgens and estrogens) show significant decreases in the elderly. The underlying mechanisms for their decrease remain unclear. While the adrenomedullary hormone, norepinephrine, shows an increase in plasma levels, associated with a decrease in clearance, no notable changes observed in plasma epinephrine levels in the elderly. The multiplicity and complexity of the adrenal hormone changes observed throughout the normal aging process, suggests that age-related alterations in cellular growth, differentiation, and senescence specific to the adrenal gland must also be considered.

ROLE of IGF-1 System in the Modulation of Longevity: Controversies and New Insights From a Centenarians' Perspective

Giovanni Vitale^{1,2*}, Giuseppe Pellegrino³, Maria Vollery⁴ and Leo J. Hofland⁵

¹Laboratorio Sperimentale di Ricerche di Neuroendocrinologia Geriatrica ed Oncologica, Istituto Auxologico Italiano IRCCS, Milan, Italy

²Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

³Faculty of Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy

⁴ASP Redaelli Golgi, Milan, Italy

⁵Division Endocrinology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands

Human aging is currently defined as a physiological decline of biological functions in the body with a continual adaptation to internal and external damaging. The endocrine system plays a major role in orchestrating cellular interactions, metabolism, growth, and aging. Several *in vivo* studies from worms to mice showed that downregulated activity of the GH/IGF-1/insulin pathway could be beneficial for the extension of human life span, whereas results are contradictory in humans. In the present review, we discuss the potential role of the IGF-1 system in modulation of longevity, hypothesizing that the endocrine and metabolic adaptation observed in centenarians and in mammals during caloric restriction may be a physiological strategy for extending lifespan through a slower cell growing/metabolism, a better physiologic reserve capacity, a shift of cellular metabolism from cell proliferation to repair activities and a decrease in accumulation of senescent cells. Therefore, understanding of the link between IGF-1/insulin system and longevity may have future clinical applications in promoting healthy aging and in Rehabilitation Medicine.

Advantages of publishing in Frontiers



OPEN ACCESS

Articles are free to read for greatest visibility and readership



FAST PUBLICATION

Around 90 days from submission to decision



HIGH QUALITY PEER-REVIEW

Rigorous, collaborative, and constructive peer-review



TRANSPARENT PEER-REVIEW

Editors and reviewers acknowledged by name on published articles

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org

Contact us: info@frontiersin.org | +41 21 510 17 00



REPRODUCIBILITY OF RESEARCH

Support open data and methods to enhance research reproducibility



DIGITAL PUBLISHING

Articles designed for optimal readership across devices



FOLLOW US

[@frontiersin](https://twitter.com/frontiersin)



IMPACT METRICS

Advanced article metrics track visibility across digital media



EXTENSIVE PROMOTION

Marketing and promotion of impactful research



LOOP RESEARCH NETWORK

Our network increases your article's readership