

Physiological Basis of Human Longevity: the Concept of a Cascade of Human Aging Mechanism

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ABSTRACT

The research is devoted to the fundamental issue of medicine and biology - the study of factors limiting the life span of a person. As a model, the system of adaptation of the human body to the forces of natural gravity is chosen, the disadaptation to which manifests itself in falls and everyday injuries. The object of the study was the selection of severe fractures of bone tissue due to fall, taken in the age aspect. Statistical and meta-analytical research methods were used. It is shown that the age-related increase in mortality due to household falls, coming to severe bone fractures, is non-linear and increases in geometric progression. As a result of the coincidence of the age characteristics of bone fragility and age-related kidney function, an assumption is made about the role of involution of the renal tissue in the development of osteoporosis in the elderly and the need for a new approach to the prevention of osteoporosis and domestic injuries.

Key words: gravity, vestibular function, fall, osteoporosis, hip fracture, aging, cascade mechanism.

Introduction

This work continues the study of patterns forming a space-time continuum based on human health reliability theory postulates complex systems^{1,2}. In this study, the most common system of aging patterns were recorded, accompanying the process with different kinetics:

- linear nature of the accompanying morphological changes
- non-linear nature characterizing fading functionality of organs and systems with age¹. A space-time continuum in the present context is represented as biosocial continuous chain of events accompanying and forming individual structure and the speed of the life cycle in time and space according to various scenarios.

The analysis of numerous data on the age characteristics of the human body³⁻⁷ reflects a variety of approaches to the study of the causes and patterns of age-related processes. Comparative approach, based on the analysis of quantitative data on the state of organs and systems of the human body in different periods of his life, revealed a number of interesting facts. The abundance of factual material collected by the researchers create self-age process

management capabilities. This, apparently, explains the explosive interest of people to the “anti-aging” problem. Very popular in the world have a different formula to determine the “passport” and “biological” age, which caused some researchers ironic attitude to the “rejuvenating websites”⁸. The main emphasis in the study of ‘biological’ age of the author’s case in the comparison of the data of numerous physiological and biochemical research laboratory customers were to become in healthy people. This so-called age norms of health indicators. According to most of them international consensus has been reached. Similar studies are “cross” type of statistical research. How to react to a particular body for future trials of life, such studies can not answer to give. To do this, you need to deploy on time, “longitudinal studies” research. According to most of them international consensus has been reached. Similar studies are “cross” type of statistical research. How to react to a particular body for future trials of life, such studies can not answer to give. To do this, you need to deploy on time, “longitudinal studies” research. According to most of them international consensus has been reached. Similar studies are “cross” type of statistical research. How to react to a particular body for future trials of life, such studies can

not answer to give. To do this, you need to deploy on time, “longitudinal studies” research.

Thus, evaluation of the age of the kinetics of the changes in health becomes an important theoretical and practical significance, which is responsible for the relevance of the chosen direction in this paper.

The Aim of the present study was to clarify the STC health laws based on the kinetic approach to the evaluation of certain key clinical and metabolic processes in the space-time continuum system, ensuring human activity throughout life and dwindling when aging.

The object of the study is the relationship of metabolic processes and clinical outcomes maladjustment to the forces of gravity in the STC system, as well as their analysis in terms of the kinetic features. We used meta-analytic, deductive and conceptual methods.

Methods

Under the kinetics of a process implies the character of changes of elements in any system. Formal kinetics, particularly considering methods for finding the dependence of the chemical reaction rate on the concentration of the reactants⁹. To distinguish linear and linear processes described respective laws¹⁰. The importance of understanding the differences line by nonlinear laws is that reflecting the processes taking place in a particular system, they also reflect the specifics of the regulatory mechanisms inherent in this system. Thus, with the kinetics described by a linear law, the incoming external disturbing signal is generated proportional response. When the kinetics, reflecting the non-linear law, the answer may not reflect the scale of the input signal.

An important distinction of these processes is their degree of control on the part of the system. For a system with a linear process of changing the size of deflection - it merely changes the scope, but not the means of action. At occurrence of nonlinear processes “in the system may vary considerably and will form action until fundamental processes picture quality changes”¹⁰.

One of the forms of the nonlinear nature of the process is a cascade. Cascade mechanism is characterized by a sequence of well-determined events where the primary event causes the next. This subsequent event, in turn, is the cause of a new event, considered as a consequence of the subsequent. Cascading mechanisms are well represented in biology¹¹, at the level of the metabolism of living organisms. In these cases, a protein at a specific stage of existing as a substrate under the influence of impact (enzymatic, electrical, biochemical) becomes an active enzyme which acts on another protein as a substrate, turning it in an active enzyme. Such a sequence may involve several steps or stages.

A striking example of the cascade in biology is a cascade of enzymatic reactions that accompany the process of blood coagulation, activation of immune responses in allergy, explosive nature of lipid peroxidation upon depletion of antioxidant defense and other processes.

Thus, along with the evolution Process specific for homeostatic functions well traceable throughout the human spatio-temporal continuum, there are risks out of control of a number of reactions followed an exponential character homeostasis disorders. Lack of knowledge about these risks creates uncertainty - “a state of complete or partial lack of information necessary for an understanding of the events, their consequences and their probabilities”^{12,13}.

All the above features of the course of metabolic processes in biological systems can be illustrated by the example of age-related disorders of the human body is constantly adapting to a force acting in the world as gravity.

As part of classical mechanics describes the gravitational attraction the law of universal gravitation Newton, which states that the force of gravitational attraction \mathbf{F} between the two material points weight $\{\displaystyle \mathbf{m}_1\}$ \mathbf{m}_1 and \mathbf{m}_2 , separated by distance \mathbf{r} is proportional to both masses and inversely proportional to the square of the distance - that is:

$$\mathbf{F} = G (\mathbf{m}_1 * \mathbf{m}_2) / r^2,$$

where $\{\displaystyle G\}$ G - gravitational constant, Equal to approximately $6.67 \times 10^{-11} \text{ m}^3 / (\text{kg s}^2)^{14}$.

The gravitational effect on the level of organs and tissue does not stop throughout the existence of the body. Arterial and venous circulation, movement of food through the digestive tract, urinary excretion, the formation of edema, stagnation in the lungs, the work of the vestibular apparatus, the formation of blood clots in the vessels of the lower limbs, blood rheology and erythrocyte sedimentation rate - this is not a complete list of the participation of gravitational forces in biological and pathological processes.

The influence of gravitational waves and propagates in a microcosm. At this level, because of the principle of equivalence of mass and energy, the atomic structure of matter acquire their specific gravitational charge. Under certain environmental conditions the gravitational interaction of microparticles becomes electromagnetic force reaching gigantic values with equal gravitational electric charge¹⁵.

Disadaptation of the human body to the gravitational forces of the Earth appears in the body balance disorders and falls. There is a wide class of disorders of vestibular function in humans (N81), including at ICD-X following disorders: N81.0 (Meniere’s disease). R81.1. (Benign paroxysmal vertigo), N81.2 (Vestibular neuronitis), N81.3 (Other peripheral vertigo: Lermuaye syndrome, otic, otogenic, peripheral vertigo) N81.4 (Central origin vertigo), and others.

And if functional disorders of the vestibular function of the brain, such as dizziness, is quite difficult to quantify due to lack of medical facilities in the mandatory statistics such states, the age estimates of the number of falls involving injuries, can be carried on the balance sheet statistics trauma centers and services.

Ranked Among the different types of bone fractures associated with age-related changes in bone metabolism, hip fractures is most dangerous.

The analysis of numerous research data shows wide geographical variation frequency hip fractures worldwide. The higher frequency hip fractures submitted in industrialized countries than in developing countries. The highest rates of disease are seen in Northern Europe and the United States and the lowest in Latin America and Africa. Asian countries such as Kuwait, Iran, China and Hong Kong, show the average hip fracture. There is also a gradient from north to south, observed in the European studies, and confirmed by the United States¹⁶.

Asian auditor's report, published in Beijing in 2009¹⁷. It reflected the growing nature of the problems associated with the proliferation hip fractures and Asia.

Swedish scientists estimated the total number of hip fractures in men and women (Code ICD-X S72.0) in 1990 worldwide was 338 000 and 917 000 people respectively, a total of 1.26 million. They suggested that in case of preservation of the age and sex incidence of the number of hip fractures will increase approximately double to 2.6 million by 2025 and four - to 4.5 million by 2050¹⁸. According to the amendment to increase the average length of people in the future¹⁹ to increase the frequency hip fractures up to 6.26 million. 2050.

In the US, more than 1.6 million people annually admitted to the hospital due to severe bone fractures. Including: 700 000 vertebral fractures; up to 400,000 hip fractures; 250,000 wrist fractures, and more than 300 000

different combination of fractures. health care costs for treatment of fractures up to 38 million dollars a day (according to the hospitals and nursing homes). 80% fractures reported in women (ratio of male: female = 1: 4)²⁰.

Hip fracture risk in women is equal to its combined risk of developing breast cancer, uterus and ovaries. 17% of men who have reached 90 years, suffering a fracture of the proximal femur. Approximately 25% of the injuries are fatal within a year after a hip fracture. Almost 70% of those experiencing acute postoperative stage are forwarded to a nursing home, as in need of constant care, and only 25% of victims of hip fractures restore the previous level of independence. The rest of the survivors are in different classes of disability requiring supportive care at home or in nursing homes.

According to russian authors²¹⁻²³ in the country every 5 minutes there is a hip fracture caused by osteoporosis. In this case, up to 90% of hip fractures occur in those over 65 years. In some regions of the Russian Federation, the mortality within 6 months after hip fracture reaches 55%.

WHO forecasts are disappointing: in 2050 it is expected that the number of victims of a hip fracture women will increase by 240%, men - 310%. Only 10% of patients after a hip fracture return to previous activity²³.

In the above Louise Margolis statistical data from the US²⁰ draws attention to the remark about the exponential growth of hip fracture risk with age. A number of authors noted a linear decrease in calcium content and bone density with age.

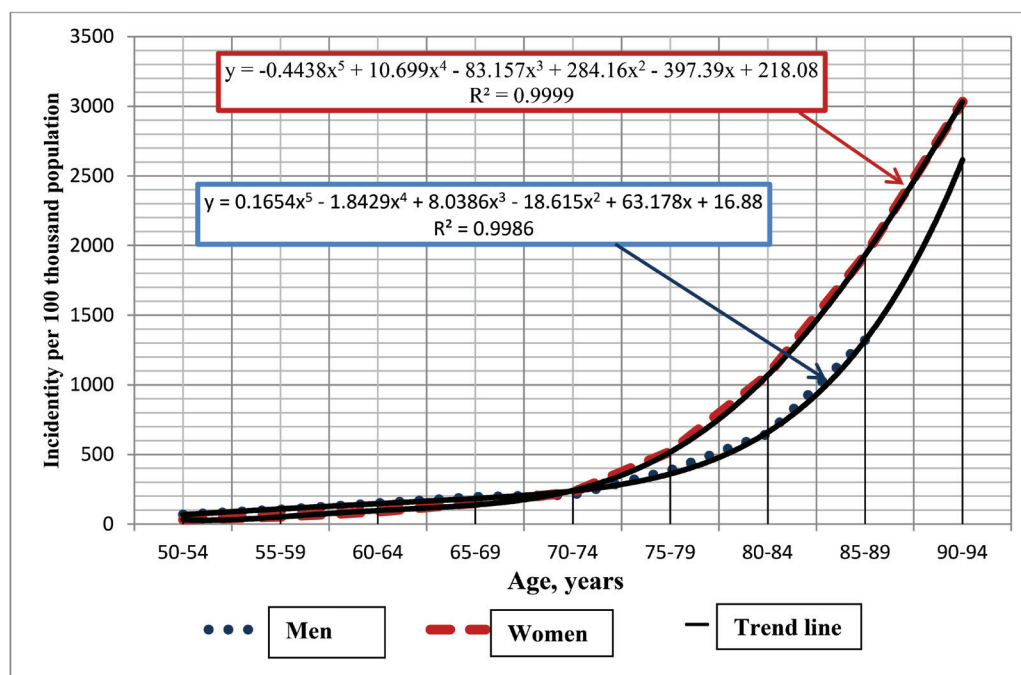


Fig. 1. The exponential increase in injuries associated with hip fracture in men under 89 years and women up to 94 years in Russia. After this age marked decrease in the occurrence of fractures, due to the sharp restriction of physical activity at this age.

So after the onset of menopause (pre-, peri - and post-menopausal women), aged 50-51 years, women lose up to 2-3% of their bone mass in the first 5 years of endocrine adjustment. Then calcium loss rate is reduced, so that the bone density in women is reduced by about 30% between the ages of 50 to 80 years, during which time they lose up to 20% of their bone mass after menopause^{20,24,25}.

The term “exponential growth” entered our lexicon to refer to fast and, as a rule, unrestrained increase. It stands for “growing rate of increase values of a measurable phenomenon”²⁶. For any exponentially growing events assertion - “the more important quantity takes, the faster it grows”²⁷.

A similar pattern was found in a large study on the prevalence hip fractures and held in the Russian Federation in 1992-1997. Study of 16 russian cities were involved²⁸. Under observation were 1,749,274 people over the age of 50 years. Reconstruction of the table data of this work, graphic material shows pronounced exponential nature of the growth of age disadaptation man to the forces of gravity (Fig. 1).

This statistical study reflects a phenomenon which should not be linear, but exponential. The most distinct Similar processes are described mathematical approximation related to the polynomial approximation²⁹. Thus, the trends of graphic images in Fig. 1 more fully described / approximated by the following mathematical expressions calculated Microsoft Excel 2007 program:

$$y_{\text{wom}} = -0,4438x^5 + 10,699x^4 - 83,157x^3 + 284,16x^2 - 397,39x + 218,08$$

$$y_{\text{men}} = 0,1654x^5 - 1,8429x^4 + 8,0386x^3 - 18,615x^2 + 63,178x + 16,88$$

The obtained mathematical expressions passport age of the person (x) Serves as an argument to form a polynomial power function (y) - annual amount of fresh Hip fracture cases per 100 thousand population.

The exponential growth of accidents with Hip fracture accompanied by a similar increase in mortality of people from this injury. Fig. 2 shows a graphic reconstruction of tabular data research³⁰ on the level of mortality of people of different ages from Hip fracture. According to the authors of this work, the mortality rate in the total group of men and women during the first year after a hip fracture in men amounted to - 26.8% in women - 19.7%. The overall mortality rate for persons over 65 years was 21.2%. Calculations show that the mortality rate value increases in a quadratic and cubic extent depending on the chronological age of women (see Fig. 2).

Thus, for example, women’s health, it can be noted that the loss of 20% of calcium by bone tissue in post-menopausal period²⁰ accompanied by a 20-fold increase in mortality in the first year after hip fracture³⁰. Such exponential growth in the United States from Hip fracture age mortality observed in the study³¹: mortality from hip fractures in men and women aged 65-74 years less than 75-84 years 1.5 times and less than 2.5 times, than in people over 85 years.

Discussion of the Results

The above facts do not explain the exponential growth Hip fracture and mortality from it only one mechanism of osteoporosis, develop gradually, with the linear nature of the composition and changes in bone structure. This contradiction can be explained by taking into account the impact of comorbid diseases, existing and emerging, regardless of the underlying disease³², and the accompanying process of osteoporosis in men and women. In this case, according to the principles of the theory of stability of complex systems, all accompanying diseases as indicators of failure or disorders accompanying processes are mutually potentiate each other, sharply or exponentially increasing the risk of occurrence Hip fracture and poor outcome.

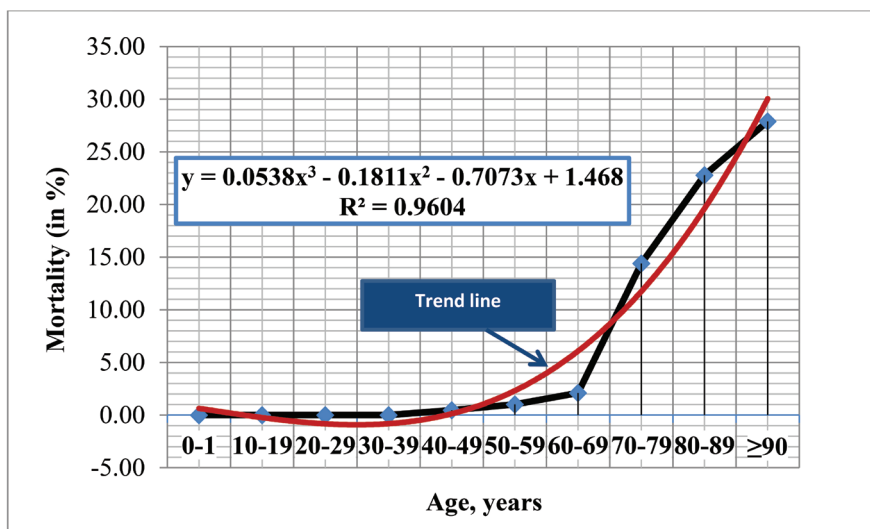


Fig. 2. Age dynamics of mortality Hip fracture.

The guide Mayo Clinic (USA) on risk factors in Hip fracture³³. The following presents Hip fracture comorbid diseases:

- Acute myocardial infarction or of myocardial history;
- Cancer or metastatic carcinoma;
- Cerebrovascular disorders;
- Chronic lung disease;
- Chronic renal insufficiency;
- Congestive heart failure;
- Dementia;
- Diabetes with or without complications;
- Liver moderate or severe;
- Paralysis;
- Peripheral vascular disease;
- Rheumatological disease;
- Peptic ulcer disease;
- Cirrhosis of the liver.

In the OM Lesniak (2017) proposed a classification related osteoporosis factors³⁴. The author highlights:

- modifiable factors: alcohol abuse, smoking, excessive physical exercise;
- malnutrition factors: malnutrition and low body mass index (BMI), malabsorption, vitamin D.
- diseases and their treatment: chronic kidney disease, chronic obstructive pulmonary disease, late onset of puberty, an excess of glucocorticoids (endogenous or exogenous), HIV infection and treatment with protease inhibitors, hypercalciuria, hypogonadism (including androgen-deprivation therapy), inflammatory joint diseases, mastocytosis, multiple myeloma, osteogenesis imperfecta, primary hyperparathyroidism, hyperthyroidism.

It becomes obvious that the age-violation of human adaptation to the forces of gravity ends with the inevitable

fall, followed by an adverse outcome when damaged bones of the skull, spine or hip. By itself, the specific cause of the fall may be random, but the drop is not very random. It is prepared by numerous elements clinical disorders in human osteoporotic patient: chronic kidney disease deficiency of vitamin D, alcohol abuse and multiple accompanying chronic conditions (“Comorbidity cascade”).

“Surprisingly, - informs “Live Science” site^{35,36}: - but according to the American Association of Neurological Surgeons (the AANS) is the most common way to die after 65 years - the fall (emphasis added). For example, according to the US Commission on the Consumer Product Safety (CPSC), in 2006 more than one million people a year applied to the emergency room in US hospitals about head injuries related to accidents that have occurred in the conditions of life. Among the most common indirect causes of elderly falls called: floors or floor coverings (260,983 cases); ladders or steps (114,752); beds (101,548); tables (70,452); chairs (50 482); baths or showers (34.446); a door (32 009); carpets (14 867); shelves, balconies, open floor (13, 994); toilets (11,246); Bunk bed (10 778); countertop (10 683); door thresholds or CT box (10 014) and other elements of premises³⁵.The AANS has an extensive list of tips to prevent head injuries³⁶.

As can be seen from the list, sooner or later, the elderly comes psychophysical disadaptation to the outside world, including family life. And if a child, imperfect vestibular system leads to frequent falls baby makes the first steps, and each episode of the fall served as adjusted subsequent movements in old age any fall, jump, slipping often lead to dramatic consequences caused disadaptation to gravity - fall and increased fragility of osteoporotic bone with subsequent life-threatening numerous clinical complications (based on the cascade).

Comorbid diseases of aging (sclerotic lesions of cerebral blood vessels, endocrine disorders, cardiovascular diseases, etc.) violate the central nervous system and mental

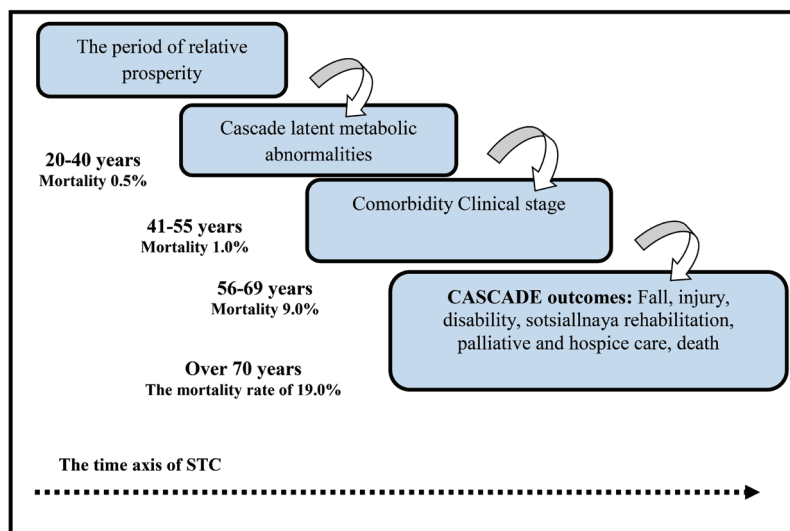


Fig. 3. Cascade mechanism of maladjustment to the effects of gravity.

activity: reduced cognitive human performance falls vision, lost his care and caution, slows the rate of reaction to sudden event. Comorbid disease form comorbid cascade that promotes disruption of function and subsequent vestibular fact - fall elderly person. But the real cause of domestic bone fractures is osteoporosis.

In turn, extensive comorbid cascade of clinical manifestations preceded by a cascade of metabolic disorders, often goes unnoticed, "linear" and not cause concern among healthcare professionals.

Projection of these faults on PVC allows conceptually determine the kinetics of age following adaptive violations against the gravitational force (Fig. 3).

Thus, bone fractures have occurred through no fault of external causes, due to the internal metabolic processes that destroy, after a person's age, skeletal resistance to gravity loads. In this case, hidden from prying eyes, causing no complaints change dramatically over a few years, significantly change the quality of life and increases their risk of adverse outcomes in violation of the functions of the vestibular apparatus.

Offered in Fig. 3 cascade model naturally raises the question of timely preventive measures against osteoporosis. Of all the "bouquet" comorbid diseases contact cascade reasonably allocated destruction of kidney tissue, the most important with regard to the regulation of bone metabolism, as in the previous work¹, we have shown the difference between the morphologic and functional speed of aging. In this case, impairment of renal function remarkably accurately resemble an exponential increase in injuries associated with hip fracture (Fig. 1).

It is known that the kidney regulates a number of important processes of vital bone: calcium homeostasis, and phosphorus metabolism of vitamin D. When they tackle formed secondary osteoporosis clinic³⁷. The kidneys are the target organ and base degradation of parathyroid hormone (PTH) is synthesized alpha hydroxylase, which is formed with a biologically active form of vitamin D - 1,25 (OH) 2D3. It is shown that already at an early stage glomerulonephritis, conditions are created for disorders of calcium metabolism, exacerbated in chronic renal failure. Reduced ionized calcium is proportional reduction of glomerular

filtration. The negative effect on calcium homeostasis provides and hyperphosphatemia. In chronic renal failure (CRF) in the occurrence of hypocalcaemia participates calcium and protein-bound fraction. In the pathogenesis of reducing total and ionized calcium in renal disease play an important role not only disruption of synthesis 1,25(OH)2D3 but deficiency 25(OH)D3 due proteinuria³⁷.

Kidney transplantation also revealed no significant advantages in respect of bone metabolism, since the use of immunosuppressive drugs gives rise to a secondary cortico-induced osteoporosis³⁷.

Conclusion

Human aging process is accompanied by a progressive decrease of adaptation to external influences, in particular to the forces of gravity.

Process disadaptation to gravity is shown by both the nervous and mental activity (disorders of the vestibular apparatus and the fall), and on the part of the skeletal system (increased bone fragility due to osteoporosis).

Disadaptation process is exponential.

This nature of age-related changes of human kidney suggests the existence of close functional link between adequate working kidney nephrons and bone metabolism.

Changes disadaptation to gravitational effects are cascading nucleating in a period of relative prosperity through latent metabolic abnormalities that give rise to a new stage of co-morbid diseases, which in turn give rise to a cascade of clinical outcome - many complications after bone fractures resulting from falls.

Focused monitoring of renal function is able to provide substantial assistance in the organization of preventive measures against latently emerging osteoporosis.

Threaded type of change in the space-time continuum of health logically assumes a non-linear nature of the corrective action to maintain homeostasis. A particular case of such a "cascade therapy" may be used in the practice of several chronic diseases, pulse therapy, "involves the introduction of ultra-high doses of drugs in a very short time in lesions of connective tissue" and other diseases^{38,39}.

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FIZIOLOŠKA OSNOVA LJUDSKE DUGOVJEČNOSTI: KONCEPT KASKADE LJUDSKOG STARENJA

SAŽETAK

Istraživanje je posvećeno temeljnom pitanju medicine i biologije - proučavanje čimbenika koji ograničavaju životni vijek osobe. Kao model, odabran je sustav prilagodbe ljudskog tijela snagama prirodne gravitacije, disonaptacija koja se manifestira u padovima i svakodnevnim ozljedama. Cilj studije bio je odabir teških lomova koštano tkiva uslijed pada, uzet u dobnom aspektu. Upotrijebljene su statističke i meta-analiitičke metode istraživanja. Pokazano je da porast mortaliteta zbog kućanstava pada, dolazi do teških fraktura kostiju, je nelinearan i povećava se geometrijski. Kao rezultat koincidencije dobnih karakteristika krhke kostiju i dobnih funkcija bubrega, pretpostavka je o ulozi involucije bubrenog tkiva u razvoju osteoporoze u starijih osoba i potrebi za novim pristupom prevenciju osteoporoze i ozljeda u obitelji.