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THE INTRICATE PATHWAYS IN AGEING

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Summary

Background. Researchers tried to find out how age-related pathologies can be prevented by keeping the biomarkers levels under control since their changes might induce abnormalities. The purpose was to analyze aspects that might accelerate, and fight off the action of endogenous and exogenous factors on the metabolism of aging.

Material and methods. This study is based on the critical analysis of 35 literature sources out of 74 selected from PubMed, NCBI, Google Scholar data that highlight the most essential concepts.

Results. Biological age represents the modified aspects of metabolism and physiological processes. The antioxidant system and reactive oxygen species play a key role in slowing down, and accelerating the aging metabolism; genetic markers detect the aging factors; genome mutations are responsible for premature aging.

Conclusions. Hence, it's important to make a balance between a healthy lifestyle, a proper skincare routine, and maintaining cognitive functions, in order to hope for a "successful aging" by preventing diseases and increasing life expectancy.

Keywords: biomarker, inflammation, longevity, senility

Introduction

The human body is a creation of nature that undergoes continuous and progressive changes, which ultimately result in a significant process that gradually occurs within the cells of the human body, namely the aging process. This research is based on the analysis and description of the metabolism of aging, aspects that promote and induce the acceleration of this process, and factors involved in coping and confronting aging. There is an increasing number of studies aimed at discovering all the aspects necessary to achieve and promote the concept of "successful aging", starting from nutrition and physical activity to proper functioning of cellular components and specifically of mitochondria that is the source of energy and an integrated element in metabolism.

Along with aging, there is an increased risk of developing age-related diseases. In this context, the researchers defined "epigenetic clock", to determine clinical biomarkers in order to predict the disease rate as they age, as well as monitor these changes. Among the biomarkers associated with the aging process and related pathologies are the ones of the cardiovascular system, of metabolic and inflammatory processes, of the central nervous system, markers of the antioxidant system and oxidative stress, and genetic markers [1, 2]. Thus, scientists can identify the cause of the signs of aging and of metabolism degradation, functions of cellular organs, and prevent the occurrence of age-related pathologies by future monitoring via modern technologies. Moreover, the "epigenetic clock" shows the methylation level of some sites, which later indicates the biological age of an individual. Some researchers believe that the mortality rate or the manifestation of age-related diseases might be predicted by comparing the epigenetic age with the chronological age of the person under study [3].

Indeed, recent studies have shown that the epigenome has a direct or indirect impact on the aging phase, being affected by a multitude of endogenous and exogenous factors, which, unless monitored, accelerate this process. Degradation of the human genome has been found to directly affect the structure of the epigenome, however, some theories show that some epigenetic changes could be reversible and allow a return to their initial phase, such as fertilization and production of pluripotent stem cells [3, 4].

Therefore, successful aging has become a current health issue and researchers urge people to follow certain rules to take advantage of "successful aging", such as minimizing the risks to developing various diseases, maintaining cognitive and physical functions, positive emotions, and thoughts, problem-solving, avoiding stressful factors, and self-caring both externally and internally [5].

The present research aims to analyze the aspects of active aging, the metabolism of aging, and the exogenous and endogenous factors, which determine these processes.

Materials and methods

The study was conducted by analyzing critically and constructively the scientific publications, articles, clinical trials, (non)randomized and cohort studies, in order to understand the basic activity of metabolism in the process of aging. The study was based on publications dating from the beginning of the 21st century to its second decade, numbering 35 out of a total of 74 articles selected for examination and research.

The detailed analysis allowed excluding less relevant data and highlighting the main issues on the physiological processes underlying senility. Databases such as PubMed, NCBI, CrossRef, Google Scholar are the information pillars of this research, which, along with a comprehensive study, enabled to highlight the essential concepts and ideas on the metabolism and the causative factors of aging and age-related diseases.

Results

Metabolic Biomarkers of Ageing

According to the recent studies, researchers have found that biomarkers have a specific role in unraveling age-related metabolic changes.

Firstly, the cardiovascular biomarkers correlate mostly with aging. It has been proved that blood pressure rate increases due to the biological age, notably the systolic blood pressure that is above 140 mmHg. Enhanced levels of homocysteine are also a major causative factor of cardiovascular diseases that contribute to the onset of atherosclerosis [2].

Secondly, several metabolic processes are influenced by the expression rate of certain biomarkers, including high levels of LDL (low-density lipoprotein) that increases with age and leads to coronary atherosclerosis. On the other hand, VLDL (very low density lipoprotein) and high triglycerides level might induce the onset of coronary heart disease and myocardial infarction. Unfortunately, the level of HDL (high-density lipoprotein) decreases with aging, resulting in the manifestation of cardiovascular diseases with widespread specificity. Metabolic syndrome, prediabetes, and diabetes are diagnosed by determining glycemia, a biomarker that commonly shows elevated blood glucose levels [2].

Leptin is one of the hormones secreted by the adipose tissues and is directly proportional to the amount of fat in the body of an individual. However, it was found that over time the percentage of circulating leptin in plasma is higher in women compared to men. Its secretion is also inhibited by other hormones, such as testosterone, whereas insulin, glucocorticoids and estradiol stimulate the leptin secretion. Moreover, studies have shown that leptin levels decrease along with aging, more obviously in women than in men, however hormone-independent variations may occur [6].

The inflammatory process is a triggering factor of aging, whereas the C-reactive protein is the biomarker which increases in chronic diseases. However, this index may also boost in people taking oral contraceptives or those who want to combat the signs of aging by resorting to hormone replacement therapy. An significant element is growth factor similar to insulin (IGF-1), as its levels are associated with increased risk of cancer, while diminished levels might result in coronary heart disease and even death [2], though, some studies in laboratory mice showed that a low level of IGF-1 was linked with delayed aging [7]. High cortisol amount, over the limits of diurnal variation, can contribute to developing cardiovascular diseases, whereas low concentrations of dehydroepiandrosterone favors the onset of senility signs, thus, a hormone replacement therapy is performed due to its anti-aging effects [2].

Interleukin-6 (IL-6) is a significant index of the inflammatory process, while its amplificated levels might induce the development of acute diseases and lesions. It commonly increases with age, causing osteoporosis and contributing to the exacerbation of Alzheimer's disease. Other biomarkers characteristic of the inflammatory process include the enhanced rate of fibrinogen, albumin, tumor necrosis factor-alpha (TNF-α), which leads to an inflammatory response, affect the immune defense system, boost the chances of becoming overweight, as well as to develop diabetes, depression, and rheumatoid arthritis [2].

The specific markers of central nervous system activity include amyloid-beta 42 present in neuropathological processes; total (t)-tau and phosphorylated (p)-tau together with F2-isoprostanes increase the risk of Alzheimer's disease [2].

A reduction in the oxidative stress and antioxidant defense system will lead to higher levels of reactive oxygen species (ROS), thus developing sarcopenia, Parkinson's and Alzheimer's disease, and even the senile onset. Antioxidants fight against free radicals, thus mitigating their harmful effect on the human body, some examples being ascorbic acid, tocopherol, beta-carotene, omega-3, -6, flavonoids, coenzyme Q, glutathione; lutein, and zeaxanthin, that block the action of free radicals and prevent the stationary macular degeneration [2].

Finally, yet importantly, genetic markers are essential in detecting the aging triggers. The main indicators include apolipoprotein E, causing cardiovascular diseases; the specific angiotensin-converting enzyme (ACE), present in cardiovascular and kidney disorders, which has a major impact on longevity; and mitochondrial DNA (deoxyribonucleic acid) mutations that produce a series of mutations that affect longevity, these defects being regarded as changes in the C150T gene within mitochondrial DNA. Additionally, the telomere length has been found to decrease with aging [2]; yet, in nonagenarians, (super-)centenarians it remains unchanged. Other studies suggest that these individuals have a chromosomal stability and good antioxidant function, being similar to research studies on young people [8]. A new molecular marker associated with cell senescence, termed as $p16^{INK4a}$ has been discovered, which is essential for maintenance of homeostasis – the balance between the aging process and suppression of tumor processes [8].

Aging caused by the inflammatory response

Once the pathogens or various allergens enter the body, the protection mechanisms are activated by the immune system during the acute inflammatory phase by mobilizing defensive cells, limiting the spread of pathogens, and in the end destroying them. Commonly, an appropriate defense reaction leads to tissue repair and regression of the inflammatory process. However, uncontrolled acute inflammation may become chronic when it becomes uncontrolled. Chronic inflammation is also characteristic in the elderly, the immune system undergoes some changes that involve the inappropriate activity of cytokines and chemokines, such as those mentioned above, viz. increased levels of IL-6 and TNF-α [9].

ROS activity, resulting from the action of neutrophils, influences the expression of NF-kBs (nuclear factor kappa-light-chain-enhancer of activated B cells), which are essential for balancing the immune responses against inflammation. In turn, NF-kBs can trigger pro-inflammatory genes or inflammation, which activate cytokines and chemokines causing cell senescence [9], secretome formation [10] and subsequently the formation of the inflammasome [11, 12]. The activity rate of autophagy decreases in the elderly, which causes the accumulation of senescent cells. Thus, recent studies have concluded that chronic inflammation is one of the triggering causes of cardiovascular diseases such as atherosclerosis, age-related neurodegenerative diseases, dementia, and autoimmune diseases, and even cancer, which involves NF-kB, a basic inflammatory mediator that initiates and contributes to tumor progression [9].

Conversely, some studies suggest that genetic variations of interleukin-1 (IL-1) may reduce life expectancy in older men and predispose them to the risk of age-related diseases. IL-6 also called "gerontologist's cytokine", has anti-inflammatory activity, however, in old age, its levels increase and induce the risk of cardiovascular diseases, like sarcopenia and atony [13].

Finally, the present research has identified that it is possible to successfully age and increase life expectancy if inflammatory processes are suppressed, such as the long-term uncontrolled inflammation that predisposes the body to accelerated aging and mortality rates. Moreover, it has also been found that the paternal age at conception might predict the length of telomeres in the descendants [14].

Nicotinamide adenine dinucleotide (NAD^+)

Nicotinamide adenine dinucleotide is a coenzyme involved in oxidative phosphorylation and ATP (adenosine triphosphate) production, despite having a DNA repair capacity, its damage caused by excessive expression of free radicals, involves NAD^+ depletion, resulting in accelerated aging [15].

This vitamin deficiency leads to the development of pellagra and the onset of 3D: diarrhea, dermatitis, and dementia. Studies have identified that small amounts of vitamin B_3 are also characteristic of aging, thus, it is believed that the use of nicotinamide may contribute to delaying this process and fighting ROS [15].

Sirtuins also work together with NAD^+, which in the form of histones promotes longevity, especially SIR2 (silent information regulator 2) for yeast and mammalian-specific SIRT1, due to their ability to repair DNA and maintain genome stability [16, 17].

There are various pathways of NAD^+ synthesis, primarily taken from various dietary sources, such as de novo synthesis of tryptophan via kynurenine pathway; from nicotinic acid by Preiss-Handler pathway; and from nicotinamide, nicotinamide ribose through the Salvage pathway. Some researchers stated that NAD^+ precursor supplementation in lab mice showed a delayed aging process [18, 19]. At the same time, studies have found that the Salvage pathway is defective during the senility period, mostly involving the skeletal muscles, white adipose tissues, and other organs [19].

Studies have been carried out in humans, which have revealed that supplementation with NAD^+ precursors by restoring its balance, might contribute to an aging delay. However, its overdose might trigger harmful effects and excessive secretion of pro-inflammatory cytokines [18], as well as predispose the body to development of autoimmune diseases and tumors. NAD^+ is correspondingly involved in neuroprotection, whereas a defective metabolism can lead to the onset of neurodegenerative diseases [19].

Metabolism of premature aging

Some genetically determined pathologies can induce intrinsic premature aging, including Werner syndrome, Cockayne syndrome, and Hutchinson-Gilford syndrome [20].

Hutchinson-Gilford syndrome is characterized by changes at the molecular level such as shortening of telomeres, unstable genome, and development of premature senescence. These unfavorable conditions lead to an accelerated aging, manifesting itself in the second year of life, which determines a short life expectancy, around 13 or no more than 20 [21, 22]. This pathology is determined by genetic mutations, namely the *de novo* missense mutation in the LMNA gene responsible for the coding of type A nuclear laminae [23, 24].

People with this pathology may develop alopecia, skin, bone, cardiovascular abnormalities, growth retardation, age-specific spots, as well as dry and thin or flaky skin. After the facts mentioned above, according to the levels of biomarkers, we comprehend that the level of leptin is below the permissible limits, this being caused by the lack of adipose tissue and by the amount of estradiol that is particularly low, resulting further in insufficient sexual development. Thus, a number of studies have focused on finding therapeutic measures that would prevent accelerated aging by using farnesyltransferase inhibitors and reducing progerin synthesis, such as everolimus that increases progerin clearance, as well as other studies conducted on mice to prove that high-fat diets and ketogenic diets are effective methods to increase longevity [25].

On the one hand, Hutchinson-Gilford syndrome is characteristic for children, however, on the other hand, there is also a progeria characteristic for adults that is specific to the 3rd and 4th decade of life, called Werner syndrome [26], being caused by mutations in the WRN gene that is responsible for DNA repair and which stabilizes the telomere metabolism [23, 27]. People with this abnormality indicate growth retardation at puberty and later on, as well as alopecia, atrophy, hypogonadism, arteriosclerosis, abnormal skin changes up to 25 years old, hyperpigmentation or hypopigmentation, hyperkeratosis [26]. Some studies also highlight that these people are likely to develop various forms of cancer, especially of thyroid and skin cancer [27]. Therapy consists of maintaining normal glucose levels, monitoring cataracts, arteriosclerosis, use of anticancer drugs and radiation therapy as needed, and diet management [26].

Finally, the present research encompasses only several aspects of the metabolism of aging, the basic indicators

being the biomarkers characteristic of the senility evolution. Researchers are looking for new clinical trials that would allow great findings of slowing down or ceasing the aging process, especially in people with progeria. Scientists continue to prove new technologies and ways to manage these processes by promoting the idea of "successful aging", as well as alternatives to achieve this phenomenon.

Discussions

The concept of "successful aging" has become increasingly popular, science and medicine are fighting side by side to discover new forms of preserving all aspects of youth and eternal beauty. Psychosocial adaptation is a key factor in the aging process, since a favorable environment might determine a good quality of life [28]. Optimism and positivism along with accumulated successes allow the person to be aware of the facts achieved over the years, these features becoming appropriate for monitoring cognitive functions [29].

In addition to these, regular individual physical activity according to the needs of the body is mandatory, as it allows avoiding and slowing down the occurrence of various diseases, contributing to an enhancement in the longevity rate. Even if physical activity has an impact of less than 2% on successful aging, it helps to combat and prevent the incidence of a multitude of pathologies, especially of high blood pressure, occurring in more than half of the elderly population [30].

Over the years, major changes arise not only inside the body, within the cellular metabolism, but also outside, resulting in dehydrated thin skin, followed by the appearance of wrinkles and fine lines, as well as loss of its elasticity and luster, becoming more sensitive to traumas and lesions and associated further with a more prolonged regeneration.

Therefore, when it comes to skin aging, two key aspects are being involved, viz. intrinsic and extrinsic aging. Intrinsic aging is caused by a deficient cellular metabolism, primarily of basal cells, fibroblasts, and melanocytes responsible for pigment spots that occur in the skin epidermis, keratinocytes, and collagen fragmentation process initiated after the age of 20-25 years [31].

Explicit examples of intrinsic aging are Werner's syndrome, Hutchinson-Gilford, Cockayne and Down syndrome. This process is determined by mutagenic changes in DNA; unbalanced levels of hormones, such as deficiency of dehydroepiandrosterone, estrogen, testosterone, growth hormone, oxytocin and melatonin, excess of cortisol; excess and lack of ROS and deficiency of the antioxidant system. Exogenous factors are responsible for activating and advancing the extrinsic aging process, including smoking, pollution, lack of sleep, poor fluid intake, and ultraviolet (UV) radiation. Thus, exogenous factors act together with the endogenous ones, amplifying oxidative stress and ROS synthesis. Subsequently, they damage the DNA and protein structure, resulting in an accelerated aging process [32].

To combat ROS, pharmaceutical medicine has created a wide range of products based on active substances with antioxidant properties, including glutathione, ascorbic acid, ferulic acid, niacinamide, resveratrol, tocopherol, coenzyme Q. Resveratrol is widely used due to anti-aging and anti-inflammatory effects. It possesses anti-microbial activity with a strong antioxidant and anti-tumor action, having a cardioprotective, neuroprotective and even anti-diabetic effects [33].

As people age, the facial muscles, and not only, undergo certain changes caused by their deterioration and accumulation of lipofuscin, resulting in skin pigmentation or so-called "age spots" [34]. Their treatment is quite rigorous and complex, thus, a sun protection factor of minimum of 30+ is recommended to use to prevent these conditions. However, if they occur, alpha-hydroxy acids, such as citric, glycolic, lactic, malic, tartaric acid should be introduced into daily skincare routine, as well as beta-hydroxy acids such as salicylic acid to fight hyperpigmentation and post-acne spots, topical retinoids, azelaic acid, adapalene, benzoyl peroxide, and alpha arbutin. The amount of collagen in the skin can be improved by topical use of vitamin C and the consumption of dietary supplements with marine collagen that will help to prevent and reduce wrinkled appearance. People can also opt for topical creams with retinol, peeling effects and honokiol that underwent several clinical trials, showing amazing results [35]. Finally, yet importantly, the key to skin moisturizing is the daily fluid consumption and the use of creams and serums, containing active substances such as hyaluronic acid, which maintain hydration and fight off wrinkles and signs of aging. Besides this, caffeine helps moisturize the area around the eyes, reduces bags under the eyes, and the pigmented appearance of the eye contour.

Therefore, we can conclude that besides a healthy lifestyle, a balanced diet and a daily skincare routine are necessary to follow, being customized depending on age and pathologies, however, hydration and sun protection are essential in the skincare routine regardless the age.

Conclusions

People are the ones who have an endless craving for everything that would bring them pleasure, initially searching for the fountain of youth, then experimenting to obtain the elixir of youth, and finally discovering ways to become immortal. This review article involves several aspects of aging metabolism and ways in which the Earth's population would age actively, productively, and successfully.

Medicine has no limits, researchers are constantly discovering new ways to prolong life expectancy since centenarians, and super-centenarians have become successful models of aging. Even if not all clinical trials approve this idea in terms of "success", they become the central source of new studies, based on changes in the genome, cellular metabolism, structure and composition of cell membrane proteins, the presence of biomarkers, ROS and the ability of the antioxidant defensive system.

Finally, there is a multitude of aging metabolism components, as well as both direct and indirect ways of influencing mental, cognitive and physical functions of the body in preventing diseases and disabilities and promoting a healthy lifestyle with a potential increase in life expectancy.

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