OpenAccessPub

Review Article

Journal of Aging Research And Healthcare ISSN: 2474-7785

Freely Available Online

The trajectory of immunoglobulins immune response against the different amounts of xenobiotics matches the trajectory of biological changes associated with ageing: A systematic review.

Yilkal Tariku Belay[1,*]

[1]School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Uganda

Corresponding author: Yilkal Tariku Belay, School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Uganda

Keywords: Ageing, Balb c mice, immunoglobulins immune response, Genetic information

Received: Nov 22, 2022 **Accepted:** Dec 10, 2022 **Published:** Mar 11, 2023

Editor: Ian James Martins , PRINCIPAL RESEARCH FELLOW Edith Cowan University

DOI: 10.14302/issn.2474-7785.jarh-22-4381

Abstract

Background: Ageing is a life process in which progressive molecular, cellular, physiological and anatomical changes manifesting in humans and animals including other organisms lead to the decline of biological functions. Immunoglobulins (Igs) are glycoprotein molecules produced by white blood cells mainly B lymphocytes following signal transduction as a result of their interaction with pathogenic microbes or poisonous substances introduced into the body systems. They elicit responses against the side effects of pathogens and poisons in which their response efficiency usually declines as we are ageing.

Objective: Thus, the similarities between Igs' immune response against the different amounts of xenobiotics and the biological changes associated with ageing have been systematically assessed using the reports of different study results on humans and animals.

Methods: First, a literature search was carried out in google, PubMed and google scholar using planned search terms related to the title of this study. Review and original articles were retrieved, downloaded and saved on a computer. And then the effects of different factors i.e. xenobiotics, age, sex and lifestyle-based practices on the levels of serum Igs (IgG, IgA and IgM) in animals and humans have been studied using a systematic review of different literature sources. Finally, the relationship between the findings of various studies has been assessed and judgment on the possible cause of ageing has been made.

Results: The findings of different research have demonstrated that the signaling efficiency of immunoglobulin M (IgM) has been limited by the amount of test compounds administered to study Balb c mice in the oral route. The response efficiency of IgM immune response against the lower doses of test compounds were high compared to the higher doses of test compounds which was low. The results of different other studies also demonstrated that the decline of serum IgM levels was associated with ageing. The relationship between alcohol consumption and the concentration of serum Igs was also described in the report of different studies. These studies have shown that there was lower level of IgG in the blood serum of alcohol consumers compared to non-consumers. The study has also demonstrated a lower level of serum IgM with higher alcohol consumption and higher serum concentration with moderate beer consumption.

Conclusion: The trajectory of Igs' immune response against different amounts of xenobiotics was highly associated with the trajectory of biological changes during ageing. These research findings might be the possible evidence to conclude that ageing is caused by the foodstuffs and non-foodstuffs we usually consume, the lifestyles we usually experience and the way of life we usually live in the environment which gradually defiling the natural processes of the body.

Introduction

Ageing is a life process in which progressive molecular, cellular, physiological and anatomical changes manifest in humans and animals including other organisms. It causes innumerable biological changes within the different biological systems of the body during its transition period from the infancy to the late adulthood stages. The mechanism of ageing that leads to the decline of biological functions which again leads to an increased risk of physical weakness, diseases and death is not yet well known. Ageing takes place not only in the whole body but also in a single cell and an organ system over the entire lifespan of humans and animals including other living things. It has many facets in which a number of different theories attempted to explain one or more aspects of ageing. There is, however, no single theory explains all aspects of the biological processes

associated with ageing. The genetic theories of ageing, for instance, state that the gene of a cell or an organism contains a program that determines its lifespan without an explanation for the possible mechanism of ageing. Ageing is a complex life process that needs multidisciplinary approach to better understand its biological cause. This systematic review designed to extract scientific data from different studies focused on the effects of non-genetic factors on the expression of genetically determined programs at the molecular and cellular levels of humans and animals which are highly associated with ageing.

Immunoglobulins (Igs) are specialized glycoprotein molecules created from our genes following signal transduction as a result of their interaction with the molecule of poisons and pathogenic microbes [1, 2]. They are found embedded in the cell membrane to recognize pathogens or any other antibiological agents and elicit an immune response against them which usually declines as we are ageing. Membrane-bound immunoglobulins are non-covalently associated with two accessory peptides that form the B cell receptor complex (cell surface receptor for an antigen) which allows cell signalling and cell activation [1, 2]. The receptor on the surface of the B cell is a prototype of the immunoglobulins that the B cell is prepared to produce [1, 2]. The B cell receptor is a heterodimer of immunoglobulin alpha and immunoglobulin beta that enables the cell to transduce the signal and respond to the presence of antigen on the cell surface [1, 2]. The signal generated causes the growth and proliferation of B cells and the production of immunoglobulins inside the plasma cells [2]. This means that as the number of B lymphocytes increases, the levels of immunoglobulins in the blood serum would also increase.

Immunoglobulins also exist freely in the plasma which are part of the adaptive immune system and comprise five classes that include IgG, IgM, IgA, IgE and IgD (7). Immunoglobulin M (IgM) provides a rapid immune response against antigens which is mainly found in blood and lymph fluids [7]. Immunoglobulin G (IgG) and immunoglobulin A (IgA) are long-lasting high-affinity antibodies (4). Immunoglobulin-A (IgA) is found in high concentrations in those mucus membranes lining the respiratory system and gastrointestinal tracts as well as in tears and saliva (3). Immunoglobulin-G (IgG) is the most abundant type of antibody which is found in all fluids of the body and protects from bacterial and viral infections [3]. Immunoglobulin-E (IgE) is found in the lung, skin and mucus membrane mainly associated with allergic reactions. Immunoglobulins trigger a response against the undesirable effects of noxious chemicals introduced into the body to defend the integrity of the biological systems (3). Under normal biological circumstances, the magnitude of Igs immune response is directly proportional to the number of harmful molecules that interacted with its receptor subtypes which believed to be immunoglobulin molecules (1, 2, and 6). However, the results of many studies demonstrated that the levels of serum immunoglobulins have been limited by the amount of xenobiotics injected to study animals [5].

Immunoglobulin measurement is usually carried out for the purposes of diagnosis and monitoring various disease conditions such as primary immunodeficiency and autoimmune diseases [7]. Reference ranges of immunoglobulins are based on the 2.5th and 97.5th percentiles in healthy adults [7]. However, several factors that influence the levels of serum Igs are not generally considered in the interpretation of the measurement [7]. Ageing is one of the factors which is usually associated with lower IgM and IgG in the elderly population compared to the younger population [4, 7]. Sex and ethnicities are other factors which were reported in different studies conducted by Samer R. Khan et al [4, 7]. Other studies conducted by the same investigators have also shown the relationship between the levels of serum immunoglobulins to diet, smoking, hormones, alcohol consumption and other lifestyles and miscellaneous determinants [7]. Although some studies had conflicting findings, this systematic review has selected only the results of research that match the title of this review article. And then the similarities between the immunoglobulins immune response against the different amounts of xenobiotics and the biological changes associated with ageing have been systematically assessed using the reports of different research results on humans and study animals which are presented in detail in the results and discussion sections of this review article.

Methods

This study was conducted in accordance with the Preferred Reporting Items for systemic reviews and Meta-Analyses (PRISMA) guidelines. I have attached the PRISMA checklist together with this manuscript which is being sent to the editor's email address.

Search Plan for Relevant Literatures

Searching for primary literature sources reporting on the relationship between the effects of different factors (i.e. age, sex, ethnicity, endogenous and exogenous compounds) on the levels of serum IgA, IgG and IgM in all human age groups has been carried out in google, PubMed and google scholar with a range of planned search terms related to the topic of this review which is listed as follow:

- Levels of serum immunoglobulins in human
- Determinants of serum immunoglobulin levels
- Reference ranges of serum immunoglobulins in humans
- Immunoglobulin synthesis mechanism
- Genome function
- Major types of genes
- Ageing
- Biological Changes associated with Ageing

Only original and review articles were retrieved. 41 full text articles which were available online were downloaded and saved on a computer for possible inclusion in the study. The title and abstract of 8 other research articles which were not open access were also considered for possible inclusion in the report of this systematic review.

Eligibility Criteria

First, judgment on the quality of primary study results retrieved from different databases has been made based on the methodological quality, content and subject relevance for inclusion. The results of studies that are associated with specific health conditions as determinant factors of the levels of serum immunoglobulins were excluded. Some other studies that had conflicting results with the topic of this review article were also excluded. The results of primary studies relevant to the topic of this systematic review have been identified and appraised for their suitability for inclusion.

Study Selection and Data Extraction

Of the 49 different literature sources retrieved from different databases, a total of 42 review and research articles that have satisfied the eligibility criteria mentioned above have been considered for data extraction. There was, however, a challenge to find a research or review article with a full report on the levels of serum immunoglobulins in all age groups. Therefore, the levels of immunoglobulins in the blood serum of different age groups have been extracted from different studies with similar methodological quality, content and subject relevance and combined in the report of this review article. Only research and review articles that had reported the different factors (age, sex, ethnicity, lifestyle practices, and xenobiotics)

associated with the levels of serum immunoglobulins in human and animal studies have been selected and filed to be included in the report of this systematic review article.

Data Processing

First, the effects of different xenobiotics at different amounts on the levels of serum Igs have been extracted from different animal studies. And then, the effects of age, sex and ethnicity and lifestyle practices on the levels of serum immunoglobulins in different age groups have been extracted from the results of different population-based cohort studies. Judgment on the magnitude of other biological changes such as loss of muscle tissue, loss of bone density and joint flexibility associated with ageing has also been made. Finally, the relationships between the effects of xenobiotics and ageing have been assessed, arranged, processed and analysed using a computer package (Microsoft office word and excel 2013). The subjects that this study dealt with have been identified and organized into meaningful sections and subsections. For completeness, data from different data sources were used for the compilation of this review report.

Data Presentation

Validated data from different literature sources were presented in form of tables, pictures and use of descriptive statements under the themes mentioned in the result and discussion sections of this systematic review.

Results

Of the 49 primary literature sources retrieved and downloaded from the google, PubMed and google scholar websites, only the results of 42 types of researches that have satisfied the data selection criteria described under the methods section have been included in this review article. The data extracted from selected studies are being presented under the themes mentioned below:

Biological Changes Associated With Consumption of Different Grades of Xenobiotics

The results of most studies have demonstrated that the trajectory of the Igs immune response against the different levels of doses of xenobiotics was highly associated with the trajectory of biological changes associated with ageing in humans (Figure 1 & Figure 2) [4, 5, 7, 13-23]. The efficiency of immunoglobulins immune response was inversely related to the amount of harmful molecules of test compounds administered into the body systems [5] which was evaluated against the levels of Igs in the blood serum of Balb c mice treated with different amounts of doses orally. The response efficiency of IgM immune response was high against the lower amounts of test compounds and low against the higher amounts of the same test compounds administered to study animals in the same route (Table 1, Figure 1) [5].

The relationship between alcohol consumption and concentration of serum Igs was also described in the reports of different studies on humans [7-12]. In the report of these studies, there was a lower level of IgG in the blood serum of moderate alcohol consumers compared to non-consumers [8]. The research results for IgM demonstrated that there was lower serum concentrations with higher alcohol consumption [9] and higher with moderate beer consumption [9, 12]. A positive relation was, however, reported between alcohol consumption and the levels of IgA in blood serum [7].

The association of hormones, either endogenous or exogenous (predominantly contraceptives or corticosteroids), with the levels of serum immunoglobulins was assessed by Samer R. Khan et al [7]. The association of contraceptives with serum Igs levels was heterogeneous. Oral corticosteroids were associated with lower IgG levels and a longer duration of treatment led to a slower recovery in the concentration of serum IgG afterward [7]. The report indicated that the prostaglandin EI analogue misoprostol did not change serum immunoglobulins level [7].

The association of a dietary factor with serum levels of immunoglobulins was also assessed by Samer R. Khan et al using 23 study reports. The majority reported on the supplementations of micro/macronutrients or probiotics and few of them on the nutritional status or fasting in relation to the level of serum immunoglobulins [7]. Most dietary components were not associated with serum immunoglobulins level. Consumption of Laycium Barbarum juice, resistant corn starch, or saffron tablets, however, was associated with higher IgG levels. Saffron supplementation and roots of North American ginseng were associated with lower IgM and IgA levels respectively. Three observational studies assessed the correlation between dietary components and serum immunoglobulins level and established a positive correlation between dietary energy and carbohydrates with IgA and a negative correlation between 25-hydroxyvitamin D levels and IgA [7].

The association of smoking with the levels of serum immunoglobulins has been reported in different studies. A study conducted by Yang M et al has reported that there were lower levels of IgM in cigarette smoking individuals compared to non-smokers [9]. Twelve studies assessed by Samer R Khan et al reported that there were lower IgA and IgG levels in the blood serum of cigarette smokers compared to non-smokers or compared to ex-smokers regardless of daily cigarettes smoked and duration of smoking [7]. The study reported that there were also lower IgM levels in the blood serum of smokers compared to non-smokers [7].

Biological Changes Associated with Ageing

Ageing refers to the overall processes of biological changes in the lifespan of animals and humans in which its mechanism is not yet well known. It causes innumerable biological changes within the different biological systems of the body during its transition period from infancy to late adulthood stage (old age) (18). The biological changes during the transition from the infancy to adulthood stage normally exhibit transformational changes during which a person has gradually reached the highest attainable maturation level both physically and mentally. It is naturally characterised by a progressive improvement in the biological functions of the body systems. Ageing causes both positive and negative impacts on the function of the body systems at different stages. For example, the efficiency of the immune system is normally reaching its highest quality during the process of biological changes to the adulthood stage while it is getting to its lowest quality during the process of biological changes to late adulthood stage (old age). For example, in the first year of human life, the level of immunoglobulins is increasing quickly perhaps because of antigenic challenges from the environment (Figure 4). By one year of age, the concentration of IgG, IgM and IgA in blood serum is approximately 60%, 100% and 30% respectively, of the concentrations in adult blood serum (Figure 4) [18, 28]. However, the results of most research demonstrated that there is a decline in the level of serum immunoglobulins mainly IgM with increased age which may contribute to the increased susceptibility of elderly individuals to infectious diseases (figure 2 and Figure 4) [4, 7, 13-17, 31]. For example, most of the research and review articles assessed in this systematic review have shown that the decline of serum IgM levels was associated with ageing [4, 6-31]. The level of serum concentration of IgM in younger age groups was higher than older age groups (Figure 2 and Figure 4). According to the reports of different studies, there was also a trend for lower IgG levels associated with ageing (Figure 4) [4, 7, 13-17, 20, 31]. Furthermore, the biological changes in other biological systems are also associated with ageing. The skeletal system which was structured with less bone density at the infancy stage would become structured with high bone density, the muscular system which was less toned at the infancy stage would become highly firm and strong, and the joints exhibit conscious movement with less duration of motion and flexibility as compared to the late adulthood stages (old age) (Figure 3) (21, 22). It also brings an improvement in cognition and emotion in which a person becomes able to solidify his/her abstract thinking and start to understand cause and effect (23). This means that a person becomes able to think hypothetically and able to make decisions independently, plan for the future, and assume adult responsibilities, follow rules and regulations to maintain the systems and institutions that are already in place (23). However, all these biological advancements acquired during the early adulthood stages would be reversed during the biological changes in old age (24 -28). For example, cognitive, visual and memory impairment among many others are the undesirable biological changes associated with the biological transitions in the late adulthood stage. The muscular system becomes less toned and the duration of joint movement is increasing with less degree of flexibility. The social characteristics of a person become a type of an infancy stage in which it depends on caregivers for its need (23). Thus, the ageing process encompasses the biological changes that are progressively advancing

during the early adulthood stages (approximately < 40 years) followed by biological regressions that are gradually declining during the late adulthood stages (approximately ≥ 40 years) of human life (Figure 3).

Discussion

The Genetic Information Encoded in a Gene Determines the Biological Destiny

In this study, the relationship between the immunoglobulins immune response against graded xenobiotics and the biological changes associated with ageing has been systematically assessed using the reports of different research results on humans and study animals. First, the effects of different xenobiotics at different amounts on the levels of serum immunoglobulins have been studied on Balb c mice which were treated orally [5]. Then, the effects of age, sex and lifestyle-based practices on the levels of serum immunoglobulins (IgG, IgA and IgM) in different age groups of humans have been studied using a systematic review of the results of different population-based studies [4, 6 -31]. Finally, the correlations between the different study findings have been assessed and judgment on the possible cause of ageing has been made.

The results of several studies have demonstrated that the undesirable side effects of test compounds have been manifested within a short period of time when the higher doses were administered to Balb c mice in the oral route. It also remained after a long period of time when the lower doses were administered in the same route [5, 36]. Study animals treated with different amounts of xenobiotics had no equal opportunity to exist in life but equal fate for death at different lifespans depending on the levels of doses administered into the body (Figure 5). Death was extremely likely following the decline of IgM levels in the blood serum of treated Balb c mice [5]. The results of other research assessed in this study have also shown that the levels of serum Igs mainly IgM were inversely related to the amounts of xenobiotics consumed by different study groups [4, 5, 7 & 9]. The levels of serum IgM were quickly depleted when the higher doses of test compounds were administered and were quickly increased when the lower amounts of the same test compounds were administered to Balb c mice (Table 1) [5]. The levels of serum IgM, IgG and IgA were reported in other population-based cohort studies in which the amounts of Igs, mainly IgM in the blood serum of an individual was also inversely related to the amount of alcohol consumption [4, 7 &9]. It should be noted that the synthesis of immunoglobulin molecules is always directed by the genomic DNA through mRNA coding within B lymphocytes which are the major plasma cells responsible for the production of circulating, humoral antibodies which of course are also known as immunoglobulins [2, 37]. First, the harmful molecules of xenobiotics bind with a receptor on the surface of B cells which is believed to be immunoglobulin beta and immunoglobulin alpha types that transduce the biological signal into the nucleus of B cells [2, 37]. Following the transduction of biological signals, the gene provides the B cells with information to make an immunoglobulin molecule [2, 37]. Thus, the signal generated as a result of interaction with the harmful molecules or pathogenic microbes causes the growth and proliferation of B cells and the production of immunoglobulins inside the plasma cells [2]. However, several study findings on humans and animals have indicated that the signaling efficiency of Igs has been limited by the higher levels of doses of administered xenobiotics which resulted in low levels of serum Igs which is known as **desensitization** The response efficiency of a receptor (the relationship between the magnitude of a biological signal elicited and a biological or physiological output) is determined by the efficiency of the feedback response of an effector. The response efficiency of a receptor is being evaluated against the output of a biological system generated as a result of the effector's feedback mechanism such as the levels of serum immunoglobulins after dosing. A receptor could be part of a molecule, a cell or an organ system in the body which is able to respond to external stimulus and transmit biological signal to an effector. It forms the most important interface between an effector and its environment. An effector, on the other hand, is part of the body which could be a molecule, a cell or an organ system that produces a biological or physiological effect in response to a biological signal from a receptor site. There are different types of intermediate messengers that carry a biological signal from the receptor to the effector site to facilitate the manifestation of such a biological or physiological effect. This means that a biological message from a receptor has no biological or physiological effect without an effector's feedback response. An organism could no longer exist as a living creature when the biological equilibrium between the efficiency of the receptors and effectors signaling mechanisms is impaired that subsequently leading to a coma in which an effector could no longer respond to the receptors' message. The existence of life would be ceased soon after the cessation of the effectors' signaling cascades. Hence, death refers to an organism that has lost complete biological interaction with its environment due to impaired signalling mechanism from the effectors' site. Thus, the efficiency of the feedback mechanisms of an effector to the receptors' biological message determines the sustainability of the biological processes of the body systems. However, the sustainability of the different biological and physiological functions has been influenced by the excessive biological signals generated from the receptor types. For example, the signaling efficiency of immunoglobulins has faded away as the amount of doses of xenobiotics administered to study animals has been uniformly increased which resulted in low levels of serum Igs and subsequently caused death (Table 1) [5]. Furthermore, the signaling efficiency of our sensory receptors to tastes would usually fade away as the molecules of a substance interacting with the taste buds increases. The signaling efficiency of our sensory receptors to pain would also usually fade away as the amount of alcohol consumption increases and many more to mention. These biological and physiological phenomena are just because the biological equilibrium between the signaling cascades of a receptor and an effector is no longer exists when the amount of a molecule interacting with a receptor type exceeds the response efficiency of an effector. This implies the fact that an effector has a predetermined biological capacity to sustain the natural processes of a biological system. This could be the possible evidence to say that life, in general, has predetermined response efficiency to xenobiotics which determines the efficiency of biological processes to sustain the different functions of the body systems for a limited period of time. This should be because the genome (effector), should have predetermined genetic information encoded in it which determines the transcription efficiency (capacity to process biological molecules) to regulate the different components of the body systems, in this case, the immune system to produce needed biological responses against the undesirable effect of higher doses. Following the depletion of serum Igs levels, study animals started dying at different lifespans depending on the amount of doses administered (Figure 4) [5, 36]. This could be possible evidence for the limited transcription efficiency of the genome which was associated with depleted levels of serum Igs during the biological processes of Balb c mice treated with different amounts of doses (Table 1). The limited transcription efficiency of the genome might be the reason why we don't continue growing throughout our lifespan. Different biological systems ceased viability at some stage in the ageing process of humans and animals. Plants, animals and humans ceased growth at some stage in their lifespan, a woman or an animal ceased ovulation at some stage in their lifespan. There are innumerable other biological losses in the ageing processes of humans and animals which might be associated with the limited transcription efficiency of the genome that determines the viability of the different body systems to produce needed biological molecules such as proteins, fats and carbohydrates to meet the demand of the body. As we age, the biological demand of our body increases in which the limited transcription efficiency of the genome could no longer satisfy the biological processes which ultimately result in pathological and physiological changes such as loss of muscle tissue, loss of vision and hearing, loss of sensation, osteoporosis, reduced bone density and joint flexibility among others [20, 38-42]. This means that the transcription efficiency of the genome (the effector) to instruct the different body systems to maintain their viability would be exhausted at some stage in the lifespan of humans and animals depending on the intensity of its response to the biological signals (receptors' message). Every one of us could have a minimum or maximum lifespan depending upon our lifestyle-based experiences which could potentially accelerate the ageing processes at different rates.

The viability of our genes determines the efficiency of our biological processes that make the differences who we are, how we respond and survive and what our features look like. For example, different studies by Samer R Khan et al, have described the effects of ethnicity and sex on the levels of different serum immunoglobulins. There were higher levels of serum immunoglobulins in Africans, Asians, Amazonians and Melanesians compared to Caucasians [7]. An Afghan study has also reported immunoglobulins level which was higher in the Hazaras compared to other tribes [5]. The same study reported that there were higher levels of IgA and IgG, but lower levels of IgM in the blood serum of men compared to women [4, 7]. These differences in the amount of serum immunoglobulins are most likely associated with the differences in the genetic information encoded in different genes found in different sex and ethnic groups mentioned above that guide the body systems to produce biological molecules.

Almost every cell in our body contains a complete copy of the genome which contains instructions that guide our cells to make biological molecules such as immunoglobulins, fats and carbohydrates which perform different functions in our biological systems [32, 33]. Each gene carries instructions that determine our features, such as eye and hair colors, and height in which there are different versions of genes for each feature of the body [34]. A study conducted by Woodwark C. et al reported that a vast amount of gene types and genetic variations exist that are perhaps divided into five major types in a comprehensive way.

- Complementary genes
- Supplementary genes
- Duplicate genes
- Polymeric genes
- Sex-linked genes

Due to the increased accuracy of breakpoint mapping of copy number variable region (CNV), it is now possible to classify a gene as Type I, Type III, and Type II" CNV depending upon whether a gene falls entirely within a CNV, overlaps the CNV or actually contains the CNV respectively [34]. Type I genes tend to be involved in immune response or sensory receptors while type III genes are involved in cell to cell signaling and type II genes are a complex mix of all three types [32-35].

The findings of different research cited in this systematic review have clearly shown that the biological changes associated with the consumption of different xenobiotics at different amounts were highly related to the biological changes associated with ageing in humans. These research findings might be the possible evidence to say that ageing is caused by the foodstuffs and non-foodstuffs we usually consume, the lifestyles we usually experience and the way of life we usually live in the environment which is potentially accelerating our biological processes by consuming the available biological resources such as the genetic information and the energy that lead to a gradual loss of the viability of biological systems. For example, if we don't eat, we don't get old but we die. If we eat frequently, we get old. If we get old, we eventually die. Death is unavoidable in one way or another. Metabolism is, therefore, life-sustaining biological mechanism for a limited period of time by which xenobiotics are bio-transformed into different biological molecules such as immunoglobulins, fats and other biomolecules depending on the transcription factors of a gene that are depleting as we are ageing. Our body has limited available resources to process and transform xenobiotics into biologically needed molecules in which misusing them may defile the natural ageing processes. Sleep is an essential biological cycle that switches off the active state of the body and the mind to restore the lost biological resources during active metabolism. Our lifespan would have been completed within a week if we don't have a sleep for a few hours every day.

The dose of xenobiotics beyond the biological efficiency of the body, (the capacity of the body systems to process them into needed biological products or harmless metabolites), could undoubtedly cause unhealthy ageing. In other words, the natural processes of life could not continue as usual with the biological activity that does not limited to its biological need. This means that the dose of a substance doesn't determine biological safety but a biological condition that fulfils the biological need of the body which actually determines a lifespan.

Conclusions

Different studies have clearly shown that the trajectory of the immunoglobulins immune response against the different levels of doses of xenobiotics matches the trajectory of biological changes associated with the ageing processes of humans. The dose of a substance has never determined the biological safety but the biological condition that fulfils the biological need and capacity of the body which was actually determined the lifespan of treated study animals. These research findings might be the possible evidence to conclude that ageing is caused by the foodstuffs and non-foodstuffs we usually consume, the lifestyles we usually experience and the way of life we usually live in the environment which perhaps assaulting our biological processes. The misuse of elements of life may, therefore, lead to unhealthy ageing.

Registration and Protocol

N/A

Funding

N/A

Competing Interest

The author declared that there is no any conflict of interest.

Availability of Data

The datasets generated and analyzed during this systematic review could be accessed from the corresponding author on reasonable request.

Author Contribution

YB contributed in concepts, data curation, data analysis, methodology, validation, statistical analysis, manuscript preparation, manuscript editing and review. The author read and approved the final manuscript.

Acknowledgement

N/A

References

1. Schroeder H. and Cavacini L. Structure and function of the immunoglobulins, J Allergy Clin Immunol 2013: 125 (202): S41-S52, doi: 10.1016/j.jaci.2009.09.046
2. John D Hawkins, (19820;The molecular biology of immunoglobulin synthesis; Biochemical Education. 10 (1), 1-6: doi/10.1016/0307-4412(82)90003-6
3. Hoffman W, Lakkis PG, Chalasani G, Gells B, (2016); Antibodies, and More, Clin J Am Soc Nephrol, 11; 157-54; doi;10.2215/CJN.09430915
4. Samer Raza Khan, Layal Chaker, Mohammad Arfan Ikram, et al, (2021); Determinants and reference ranges serum immunoglobulins in meddle-aged and elderly individuals: A population based study, Journal of clinical immunology, 41; 1902-14; doi;10.1007/s10875-021-01120-5
5. Belay, Y. T. (2019). Study of the principles in the first phase of experimental pharmacology: The basic step with assumption hypothesis, BMC Pharmacol. Toxicol. 20, 2-12, https://doi.org/10.1186/s40360-019-0306-x

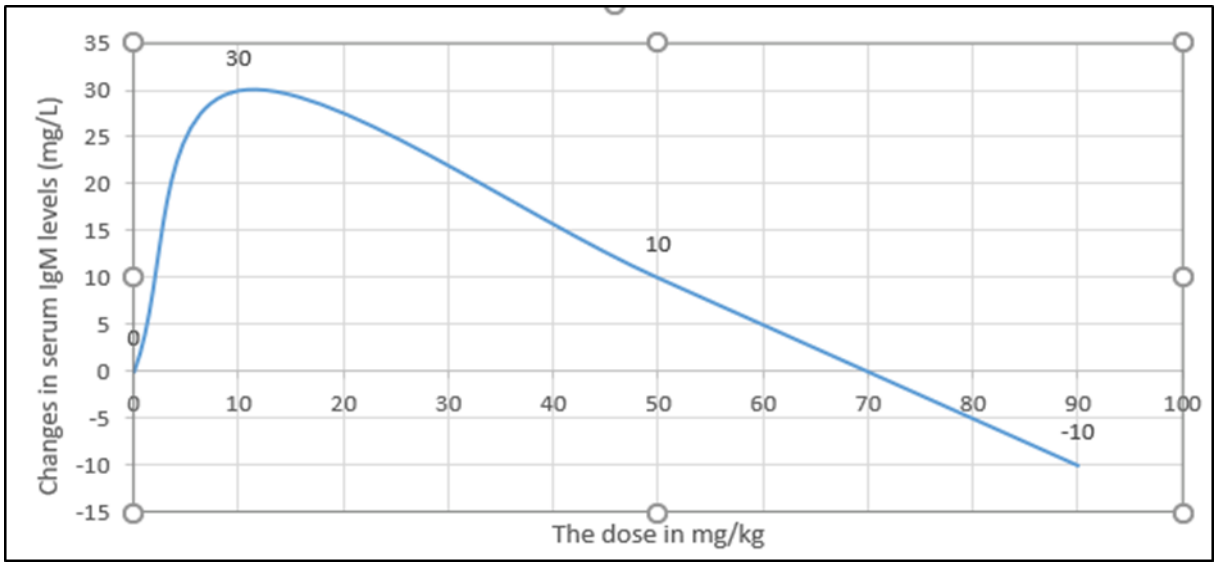

Figure 1. The trajectory of the immunoglobulin M (IgM) immune response against the different leveles of doses administered into study Balb c mice

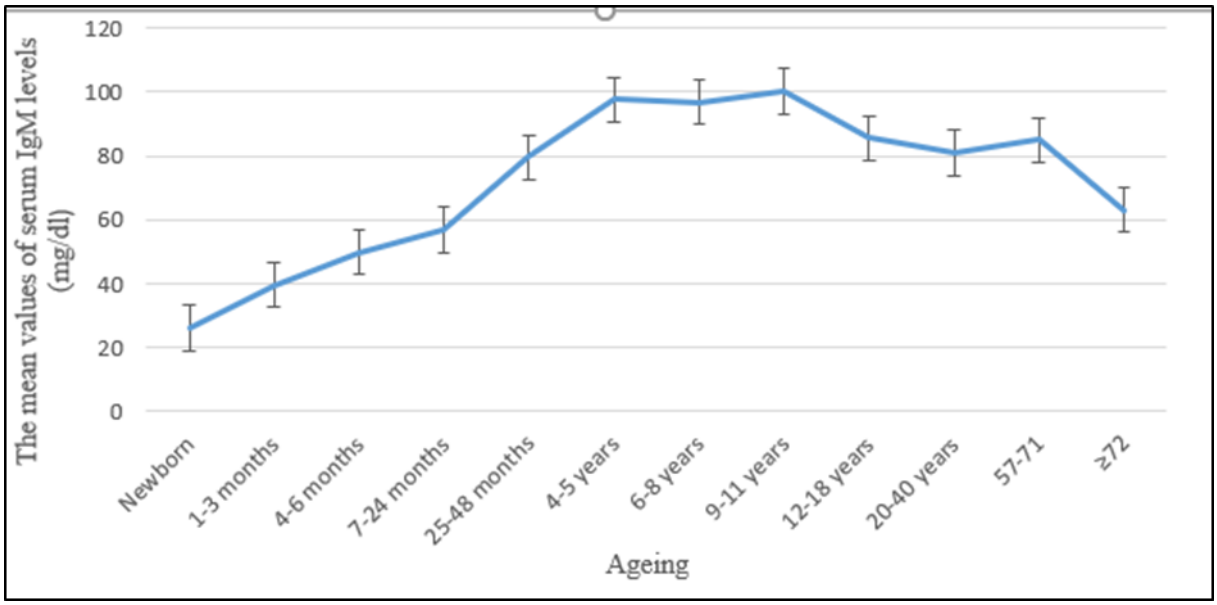

Figure 2. Age associated changes in the levels of serum IgM.

Table 1. The changes in the levels of serum immunoglobulins at four hour after dosing [5]

Test chemical	Tested doses	Quantitative immunoassay before treatment		Quantitative immunoassay at four hour after treatment		*ΔIg* serum levels
		IgG	IgM	IgG	IgM	*Δ Ig*
Dichlorvos	10 mg/kg	<1100 mg/L	70 mg/L	<1100 mg/L	90 mg/L	+20 mg/L
	50 mg/kg	<1100 mg/L	70 mg/L	<1100 mg/L	80 mg/L	+10 mg/L
	90mg/kg	X	X	X	X	X
Chlorpyrifos	10 mg/kg	<1100 mg/L	90 mg/L	<1100 mg/L	120 mg/L	+30 mg/L
	50 mg/kg	<1100 mg/L	50 mg/L	<1100 mg/L	70 mg/L	+20 mg/L
	90mg/kg	<1100 mg/L	90 mg/L	<1100 mg/L	80 mg/L	-10 mg/L
Cypermethrin	10mg/kg	<1100 mg/L	70 mg/L	<1100 mg/L	90 mg/L	+20 mg/L
	50 mg/kg	<1100 mg/L	80 mg/L	<1100 mg/L	70 mg/L	-10 mg/L
	90 mg/kg	<1100 mg/L	80 mg/L	<1100 mg/L	50 mg/L	-30 mg/L

x The mouse died much earlier than the time for blood specimen collection.

6. David D. Chaplin, (2010); Overview of the immune response, J Allergy Clin Immunol, 125; 3-23; doi:10.1016/j.jaci.2009.12980
7. Samer R, Khan, Anna C, Van der Burgh, Rbin P. Peeters, et al, (2021); Determinants of serum immunoglobulin levels: A systematic review and meta-analysis, Front. Immunol, doi;10.3389/fimmu.2021.664526
8. Gonzalez-Quintela A, Alende R, Gude F, et al; (2008), Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities, Clin Exp Immunol; 151, 42-50; doi;10.1111/j.1365-22492007.03545.x
9. Yang M, Wu Y, Lu Y, Liu C, Sun J, et al, (2012); Genome-wide scan identifies variant in TNFSFT3 associated with serum IgM in a healthy Chinese male population, plos one7; e47990; doi;10.1371/journal pone.0047990
10. Beharka A., Paiva S., Leka L., Ribaya –Mercado J. Russel R., and Meydoni S., (2001); Effects of age on the gastrointestinal-associated mucosal immune response of humans, Journal of Gerontology, 56A (5), B218-B223.
11. Kokavec A, Crowe SF, (2006); Effect of moderate white wine consumption on serum IgA and plasma insulin under fasting conditions, Ann Nutr Metab, 50; 407-4012; doi; 10.1159/000094631
12. Romeo J, Wamberg J, Nova E, et al, (2007); Changes in the immune system after moderate beer consumption, Ann Nutr Metab, 51, 359-66; doi;10.1159/000107675
13. Barret D J. Stenmark S, Wara DW, Ammann AJ, (1980); Immunoregulation in aged humans, Clin Imminol Immunolpathol, 17, 203–2011, doi:10.1016/0090-1229(80)90088-4
14. Cassidy JT, Nordby GL, Dodge HJ, (1974); Biologic variation of human serum immunoglobulin concentration; sex-age specific effects, J Chronic Dis, 27; 507-517, doi;10.1016/0021-9681(74)90026-5
15. Behr W, Schlimok G, Firchau V, Paul HA, (1985); Determination of reference intervals for 10 serum proteins measured by rate nephelometry, taking into consideration different sample groups and different distribution functions, J Clin Chem Clin Biochem, 23, 157-66, doi;10.11515/cclm.1985.23.3157
16. Bhat GA, Mubarik M, Bhat MY, (1995); Serum immunoglobulin profile in normal Kashmini adults, J Postgrad Med, 41, 66-69
17. Batory E,Jancso A, Puskas E, Redei A, Lengyel E (1984); Antibody and immunoglobulins level in aged humans, Arch Gerontol Geriatr, 3, 175-88; doi; 10.1016/0167-4943(84)90098
18. John W. Rowe and Robert L. Kahn, (1987); Human ageing: Usual and successful, American Association for the advancement of science (AAAS); Vol. 237, pp. 143-149.
19. Artur M. Galazka; The Immunological Basis for Immunization Series, Normal development of serum immunoglobulins, WHO, 1996
20. De Greef GE, Van Tol MJ, Van Den Berg JW, Van Staalduimen GJ, Janssen CJ, Radl J, et al, (1992); Serum immunoglobulin class and IgG subclass levels and the occurrence of homogeneous immunoglobulins during the course of ageing in humans, Mech Ageing Dev, 66, 29-44; doi;10.1016/0047-6374(92)90071-k
21. Freemont AJ, Hoyland JA (2007); Morphology, mechanisms and pathology of musculoskeletal ageing. J Pathol 211: 2; 252-259, DOI:10.1002/

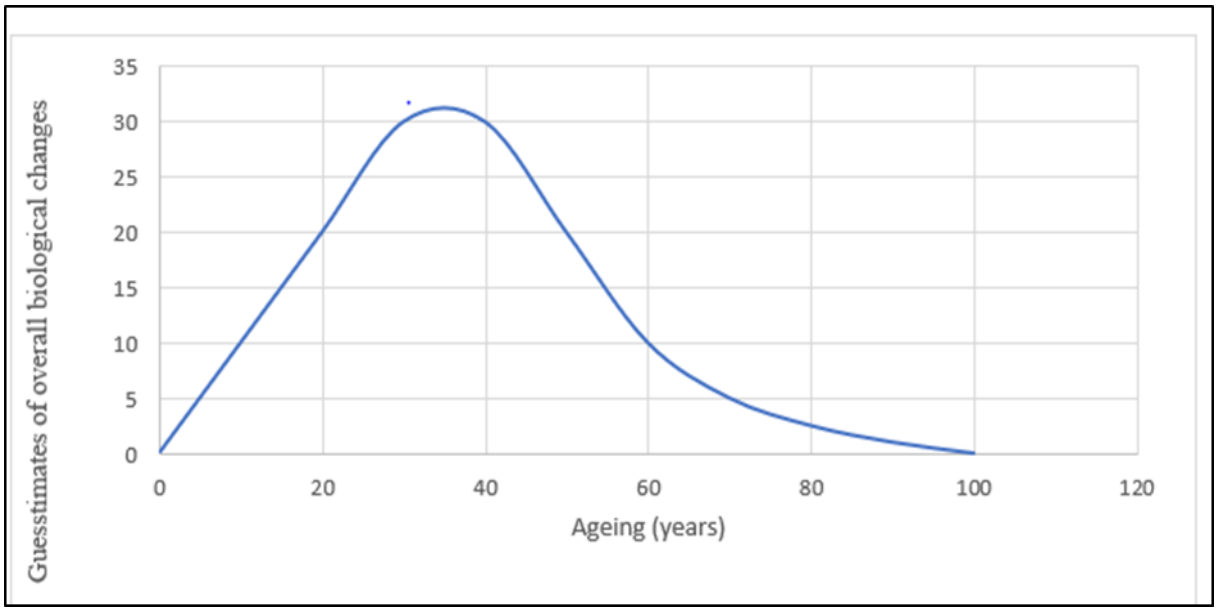

Figure 3. The trajectory of biological changes associated with ageing

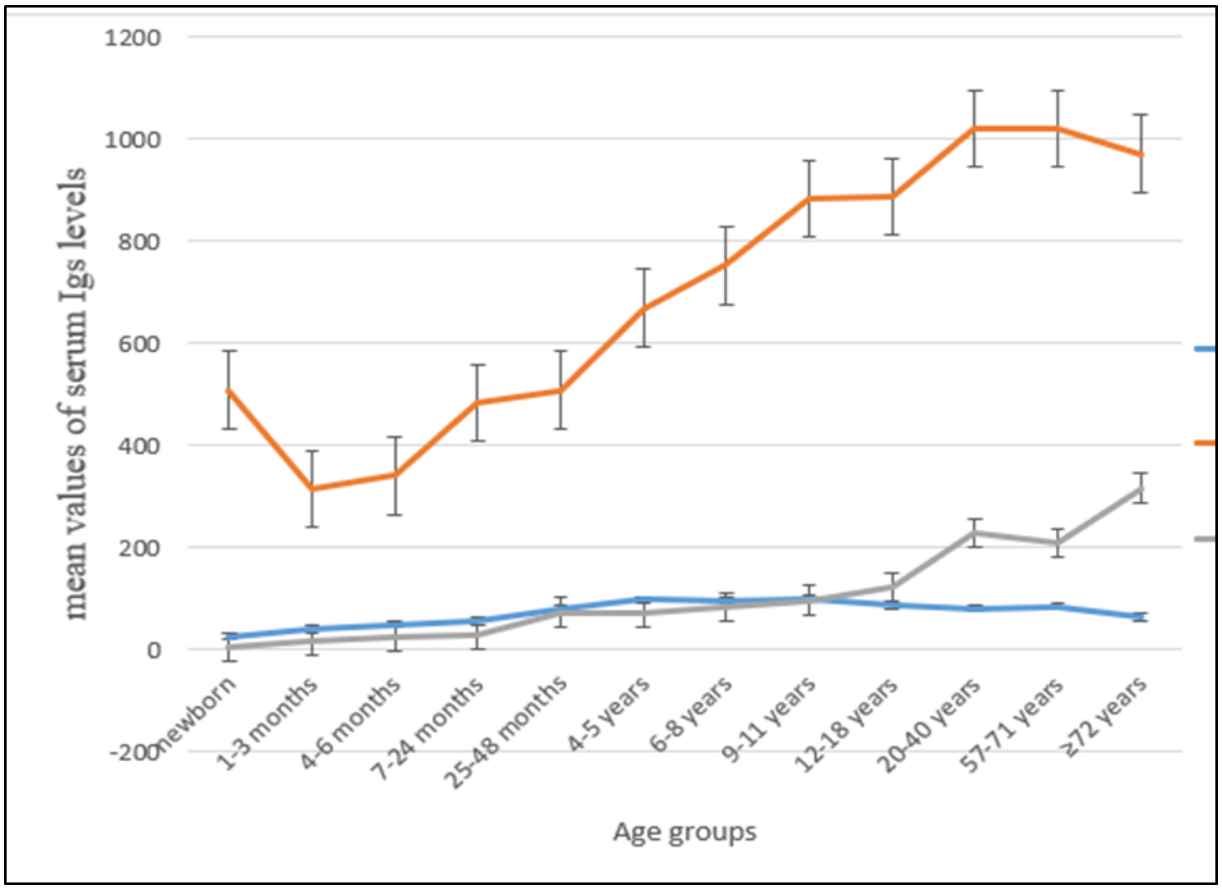

Figure 4. The mean values of serum immunoglobulin levels in different age groups of humans. The data was extracted from different population-based cohort studies [4, 10, and 29].

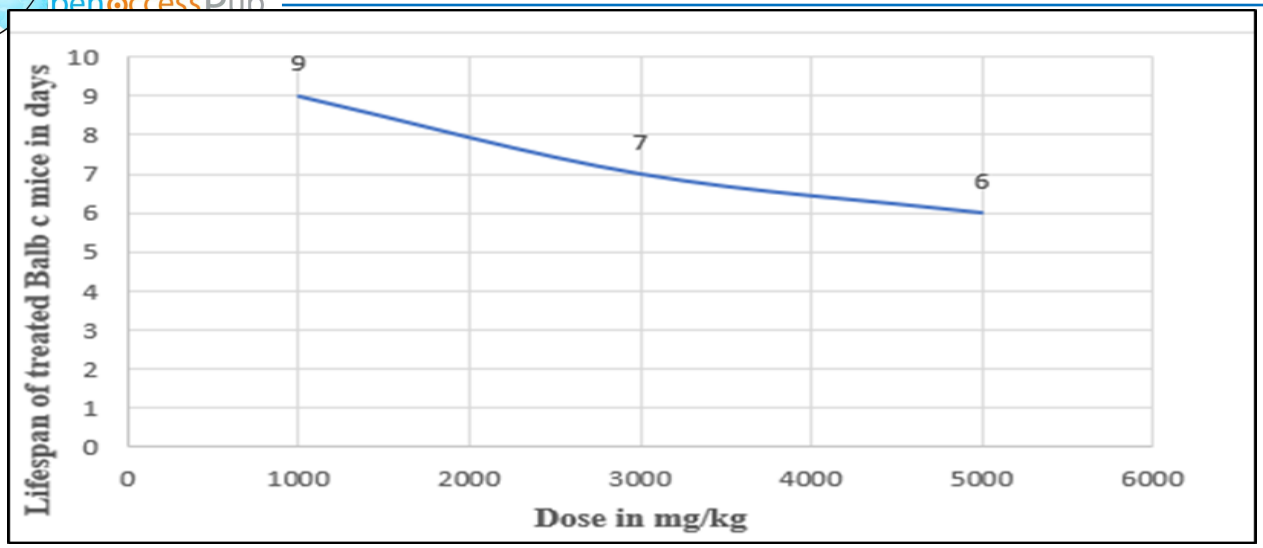

Figure 5. The maximum lifespan of Balb c Mice treated with different amounts of test extracts (1000, 3000 and 5000) mg/kg

path.2097.

22. Paulo F.L. da Silva, Björn Schumacher, (2021), Principles of the Molecular and Cellular Mechanisms of Aging, Journal of Investigative Dermatology, Volume 141(4), Supplement Pages 951-960, ISSN 0022-202X, https://doi.org/10.1016/j.jid.2020.11.018.
23. Kendra Cherry, 2021; Eric Ericson's Stages of Psychosocial Development; Retrieved on 26th March 2022, https://www.verywellmind.com/erik-eriksons-stages-of-psychosocial-development-2795740 .
24. Pereira-Smith OM, Ning Y (1992). "Molecular genetic studies of cellular senescence". Exp Gerontol. 27 (5–6): 519–22, doi: 10.1016/0531-5565(92)90006-L. PMID 1426085
25. Hadjidakis DJ, Androulakis II. Bone Remodeling. Ann N Y Acad Sci. 2006 Dec; 1092:385-96
26. Yamada K, Healey R, Amiel D, et al: (2002); Subchondral bone of the human knee joint in aging and osteoarthritis. Osteoarthritis Cartilage: Elsevier; 10 (5); pp. 360-369, https://doi.org/10.1053/joca.2002.0525
27. Li Y, Wei X, Zhou J, Wei L. (2013); the age-related changes in cartilage and osteoarthritis. Biomed Res Int. 2013; doi: 10.1155/2013/916530
28. Lopez-Otin, C; Blasco, MA; Partridge, L; Serrano, M; Kroemer, G (2013). The hallmarks of aging. Cell. 153 (6): 1194–1217. doi:10.1016/j.cell.2013.05.039. PMC 3836174. PMID 23746838
29. GA Kardar, M Oraei, M Shashavani, Z Namdar, GE Kazemisefate, MT Haghi Ashtiani et al, (2012); Reference intervals for serum immunoglobulins IgG, IgA, IgM and complements C3 and C4 in Iranian healthy children; Iranian J Publ Health; 41(7);59-63
30. Jazeyeri M, Fourfathallah A, Javad M, et al, 2013); The concentration of tatal serum IgG and IgM of healthy individual varies at different age intervals, J Biomag, 3(4), 241-245; doi:10,1016/j.biomag.2013.09.002
31. Oyeyinka G O, Aiydun B A, Erasmus R T, Adewoye H O, et al (1995); Complement and immunoglobulin levels in Ilorin Nigeria and environ, African Journal of medicine and medical sciences, 24 (1), 9-19; PMID: 7495207
32. Tapial J., Kevin C. H. Ha, Sterne-weiler T., Gohr A., Braunschweig U., Hermoso-Pulido A., et al, (2017); An atlas of alternative splicing profiles and functional associations reveals new regulatory programs and genes that simultaneously expressmultiple major isoforms, cold spring harbour laboratory press, 27;1759-1768: doi:10.1101/gr.220962.117.
33. Lakna Panawala, (2017); Difference between gene and genome, The biology blog; https://www.researchgate.net/publication/313839958
34. Woodwark C., Betman A., (2011); The characterisation of three types of genes that overlie copy number variable regions, PLoS ONE 6(5): e14814, doi:10.1371/journal.pone.0014814
35. Patthy, L. Modular, (2003); Assembly of Genes and the Evolution of New Functions. Genetica 118, 217–23, https://doi.org/10.1023/A:1024182432483
36. Belay Y. Study of safety and effectiveness of traditional dosage forms of the seed of Aristolochia elegans mast against malaria and laboratory investigation of pharmaco-toxicological properties and chemical constituents of its crude extracts, Ann Trop Med Public Health, 2011, 4:33-41
37. Zagury D., Jonathan W., Jamieson J., and Palade G. (1970)' Immunoglobulin synthesis and secretion, The journal of cell biology, 46, 52-63
38. Belikov, Aleksey V. (January 2019). Age-related diseases as vicious cycles. Ageing Research Reviews. 49: 11–26. doi:10.1016/j.arr.2018.11.002. PMID 30458244
39. Hadjidakis DJ, Androulakis II. (2006); Bone Remodeling. Ann N Y Acad Sci. Dec;1092:385-96
40. Yamada K, Healey R, Amiel D, et al: (2002); Subchondral bone of the human knee joint in aging and osteoarthritis. Osteoarthritis Cartilage: Elsevier; 10 (5); pp. 360-369, https://doi.org/10.1053/joca.2002.0525
41. Li Y, Wei X, Zhou J, Wei L. (2013); the age-related changes in cartilage and osteoarthritis. Biomed Res Int. 2013; doi: 10.1155/2013/916530
42. Lopez-Otin, C; Blasco, MA; Partridge, L; Serrano, M; Kroemer, G (2013). The hallmarks of aging. Cell. 153 (6): 1194–1217. doi:10.1016/j.cell.2013.05.039. PMC 3836174. PMID 23746838.