

*Review article***The role of Anti-Aging Medicine promoting “Dynamic Engagement of All Citizens.”**

Yoshikazu Yonei

Anti-Aging Medical Research Center and Glycative Stress Research Center, Graduate School of Life and Medical Sciences,
Doshisha University, Kyoto, Japan

Abstract

This section describes the role of Anti-Aging Medicine in health promotion which is essential and important for promoting “Dynamic Engagement of All Citizens,” a statement by Japanese Government in 2016. For the evaluation of aging, we examine the functional age of skeletal muscle, blood vessels, nervous system, hormonal system and bone, and the risk factors for aging. When we find the weak point in aging, to which we give priority, treat preferentially and restore body balance. We have formulated the hypothesis that it is possible to shorten the difference between average life expectancy and average healthy life expectancy by measuring the functional age of the body system, detecting weak points of aging, and attempting anti-aging and rejuvenation in all the people.

For the purpose of the Government statement, it is necessary to improve the health of the elderly and utilize their labor power. Younger people's separation from their labor for the purpose of caring for their older family members should also be prevented. Metabolic syndrome, locomotive syndrome (disturbance of motor function) and cognitive impairment, which are ever-increasing recently, should also be prevented at an early stage. In other words, the goal is to create a system in which the elderly require no care. The reduction of public medical costs can also be expected through the health promotion of the elderly. Furthermore, the new concept of Anti-Aging Medicine can contribute to produce new business for realizing the society with dynamic engagement.

KEY WORDS: dynamic engagement, health promotion, glycative stress, cognitive impairment, locomotive syndrome

Introduction

The average Japanese life expectancy is very long; 80 years for males and 86 years for females in 2016. However, in terms of a healthy life expectancy, it is seven years shorter for males and eleven years for females. During these years, they are forced to live unhealthy lives. In some cases, they need to receive care. To accommodate this, their family members often withdraw from their jobs. For the realization of “Dynamic Engagement of All Citizens,” such situations should be eliminated as much as possible. That is where Anti-Aging Medicine comes in, one of which slogans is “striving for the elderly requiring no care.” In this paper, the roles played by Anti-Aging Medicine for the realization of Dynamic Engagement of All Citizens are described focusing on metabolic syndromes (MetS), locomotive syndromes (LocS) and cognitive impairments (CognI).

Pathological aging

The physical body is composed of various organs and systems. The process of aging depends on the individual

and the risk factors contributing to aging also vary by individual. The onset of pathological retrograde alterations begins somewhere on the body from the 30s (the weak points of aging), leading to disease and further adversely affecting other healthy parts. This is pathological aging. It is the best way to healthy longevity so that one can age evenly in a good balance as a whole¹⁾. If anti-aging is expressed as “anti-pathological aging,” it is easy to understand (*Fig. 1*). Aging has two meanings of “getting old” and “growth and maturation.” The latter is often forgotten. Those who did not grow and mature in the proper way are placed in disadvantage once they begin getting old. Anti-aging is required for children, young people, ova and generative functions²⁾.

The degree of physical aging is assessed in terms of functional age and risk factors in anti-aging medical checkups (*Fig. 2*)^{3,4)}. Functional age is divided into the muscular, vascular, neural, hormonal and bone ages. They are prioritized by order of the highest functional age and corrective instructions are implemented. Anti-Aging Medicine's goal is “the prevention of aging of functional age

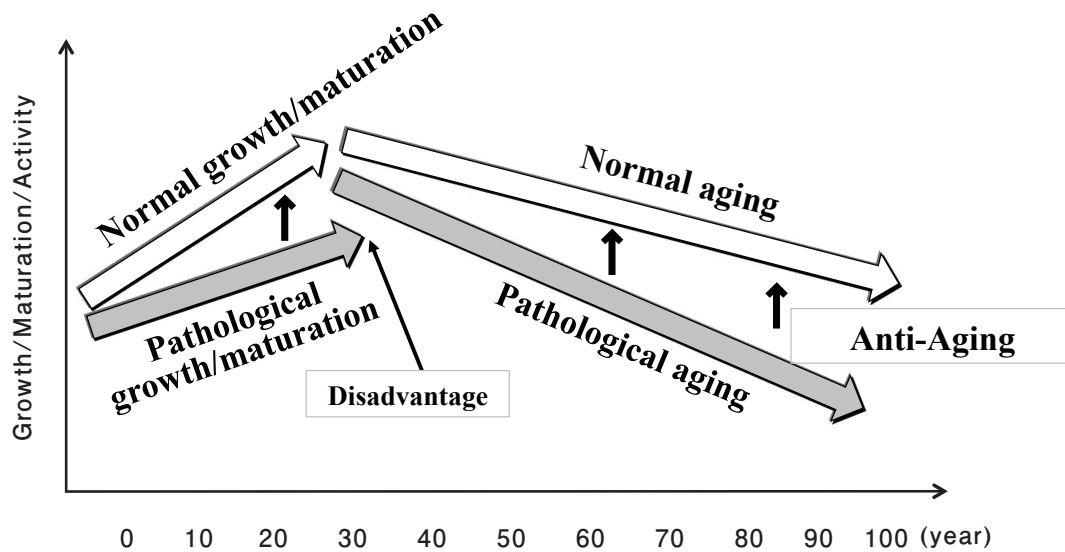


Fig. 1. “Anti-aging” is “anti-pathological aging.”

Aging has two meanings; “growth and maturation” and “getting old.” Recently, children’s lifestyle diseases are increasing. Thus, anti-aging for children is necessary.

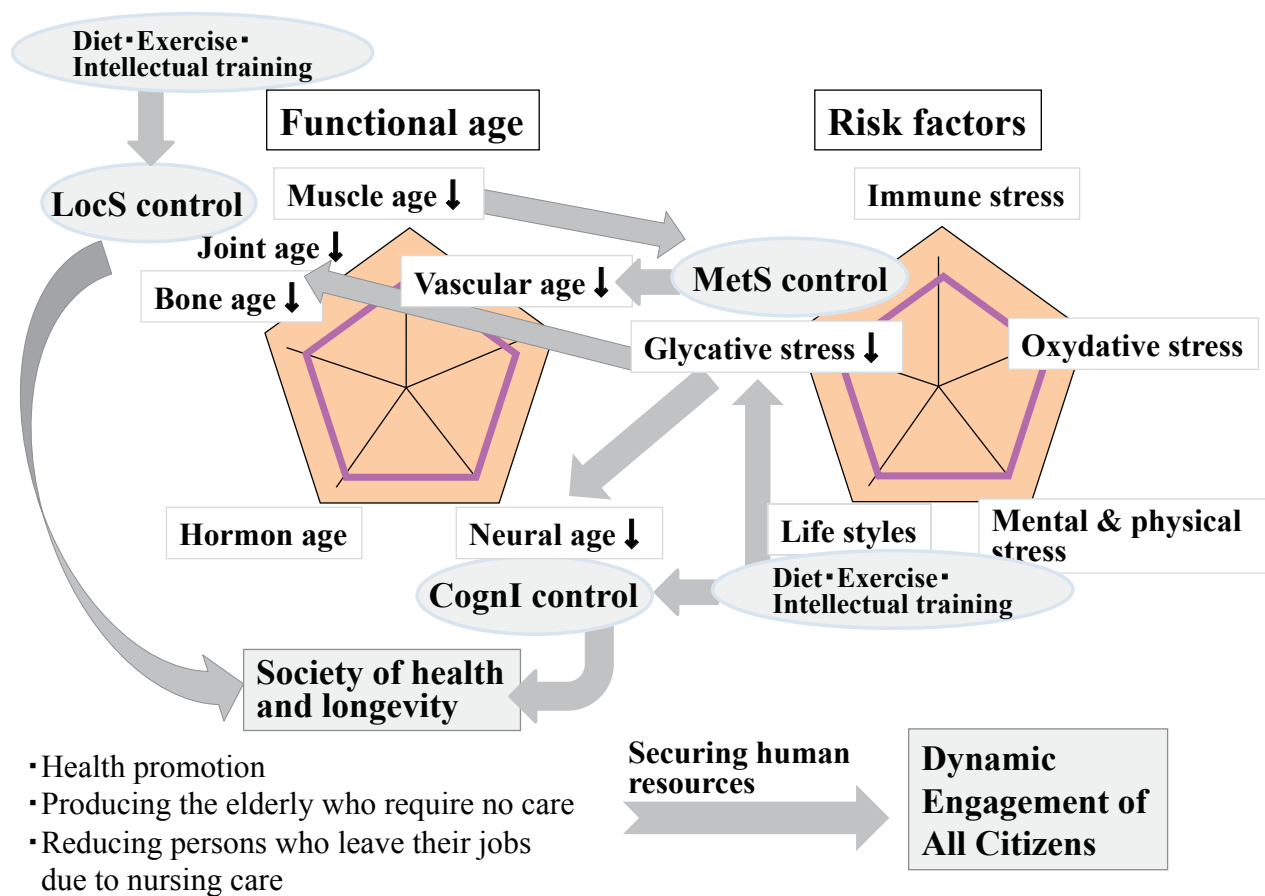


Fig. 2. The degree of aging is assessed as functional age and aging risk factors.

Metabolic syndrome (MetS), locomotive syndrome (LocS), cognitive impairment (CognI) are increasing recently. In order to create the society with healthy longevity, it is important to understand the positioning of these states and work out the countermeasures against them, considering holistic balance.

and rejuvenation.”

I have my hypothesis that it is possible to reduce the difference between the average Japanese life expectancy and healthy life expectancy by measuring the whole of Japanese functional age, finding the weak points of aging, preventing physical aging and planning to rejuvenate the body. I would like to have many institutions involved in the medical examinations of companies, communities and schools to introduce anti-aging medical checkups, so that we can verify my hypothesis by accumulating and analyzing and practically using their big data.

What Anti-Aging Medicine is trying to accomplish is the promotion of health, improvement of life quality and healthy longevity. In the current Japanese society, a decreasing birthrate and an aging population are of importance. The Japanese medical economy is a large financial burden of the government due to the steep rises in public medical expenses and nursing care as well as public welfare expenses. The government declared a policy for the “Dynamic Engagement of All Citizens.” Anti-Aging Medicine can cooperate with this policy by integrating all sciences, determining the mechanism of aging, evaluating physical age, considering how to achieve healthy longevity and implementing a health enhancement program.

In order to ensure the working force required by the policy of “Dynamic Engagement of All Citizens,” it is required to promote the health of the elderly and utilize them as part of the labor force. It is also important to prevent the withdrawal from work in order to care for parents. The ever-increasing metabolic syndromes (MetS), locomotive syndromes (LocS) and cognitive impairments (CognI) that are increasing lately should be intercepted and prevented at an early stage. It is the creation of the elderly who require no care. Medical costs can be lowered by the enhancement of their health.

Countermeasure against metabolic syndrome (MetS)

For the purposes of preventing physical functional aging and promoting rejuvenation, risk-factor management is important. The risk facts are divided into the categories of oxidative stress, glycative stress, mental and physical stress, immune stress and lifestyle habits. Human beings have been fighting with oxidative stress for several million years. Because of this, the human body is equipped with higher-level anti-oxidative systems. The first is the enzyme system removing free radicals such as superoxide dismutase (SOD), catalase and peroxidase. The second system positively using endogenous free radical-eliminating substances such as coenzyme Q10 (CoQ10), alpha lipoic acid and melatonin⁵⁾, and exogenous free radical eliminating substances such as vitamins and phytochemicals. The third is the enzyme system repairing the damage caused by oxidation⁶⁾.

Meanwhile, it has only been several decades since glycative stress became threatening and humans are too vulnerable to it. According to the investigation on the health history of centenarians, those who had a history of diabetes count for only 6 %⁷⁾, which is very low considering that the rate of diabetes of those in their 70s is 20 %. This means that glycative stress is a big barrier to achieving healthy longevity. The disorders caused by strong glycative stress, such as metabolic syndrome, obesity, diabetes and dyslipidemia, are ever-increasing. This is an age when we have to fight with glycative stress.

Glycative stress and its effects are shown in [Fig. 3](#)^{8,9)}.

Reducing sugars including glucose and fructose, lipids and alcohol generate aldehyde in the course of being metabolized inside the body. Aldehyde reacts with proteins in the body and generate advanced glycation end products (AGEs) through various processes. In MetS patients, visceral fat increases, the secretion of adiponectin decreases, insulin resistance increases and postprandial hyperglycemia occurs. The longer the time period of postprandial hyperglycemia higher than 160 mg/dL is, the more the aldehyde derived from glucose increases, the more glycation reaction proceeds and AGEs are accumulated. In most cases, MetS patients develop dyslipidemia, and as a result, aldehyde derived from triglyceride increases and glycation reaction proceeds. If glycated low-density lipoprotein (LDL) increases, caused by the glycation of LDL-cholesterol, it promotes the formation of atheroma on blood vessel walls and arteriosclerosis proceeds. Although high-density lipoprotein (HDL) cholesterol is considered to be good, glycated HDL is bad¹⁰⁾. AGEs are not only accumulated, but they also bind to the specific receptors on the surface of inflammatory cells, RAGE (Receptor for AGEs), as a ligand, and causes inflammatory cytokine formation¹¹⁾.

The improvement of life style through dietary education, intellectual education and physical education is indispensable as countermeasures against metabolic syndromes. At the same time, when considering physical balance holistically, it is recommended to apply anti-aging technique for muscular age, including muscle resistance training for those whose muscle mass is low and strength is weak, as well as anti-aging techniques for hormonal age, including dehydroepiandrosterone (DHEA) replenishment for those whose secretions of DHEA is low^{12,13)}. For those whose mental and physical stress is strong, countermeasures against mental and physical stress by decreasing the secretion of cortisol should be given priority.

Locomotive syndrome (LocS) and glycative stress

The actual condition of LocS is formed by the aging of locomotive organs such as bones, muscles and joints amplified by the decrease of neural function. In particular, the deterioration of motor nerves negatively affects the impairment of locomotive organs and it brings serious problems, including the decrease in the activities of daily living (ADL) and falling accidents. The final form of a LocS is a bedridden state, in other words, the state of nursing care level 5. In order to prevent a bedridden state, it is very important to prevent the deterioration of motor nerves through early diagnosis in order to support the creation of the elderly who need no care.

Bone protein type-I collagen counts for 1/2 of the volume of bone and 1/3 of bone weight. Bones are built by bone collagen being strongly bound to each other by physiological cross-links. However, if glycative stress is strong, these physiological cross-links are lost, and are replaced with pathological cross-links caused by glycation. This leads to the bones becoming fragile and the risk of fracture increases¹⁴⁾.

Because MetS patients are accompanied by visceral obesity, they often greatly gain body weight. Since obesity puts an excess weight burden on the hip and knee joints, it causes osteoarthritis. LocS patients are often associated with obesity and osteoarthritis.

Cartilage-derived proteins such as type-II collagen¹⁵⁾, proteoglycan¹⁶⁾, elastin¹⁷⁾ and others are modified by glycative stress and form glycat ed protein of deteriorated quality.

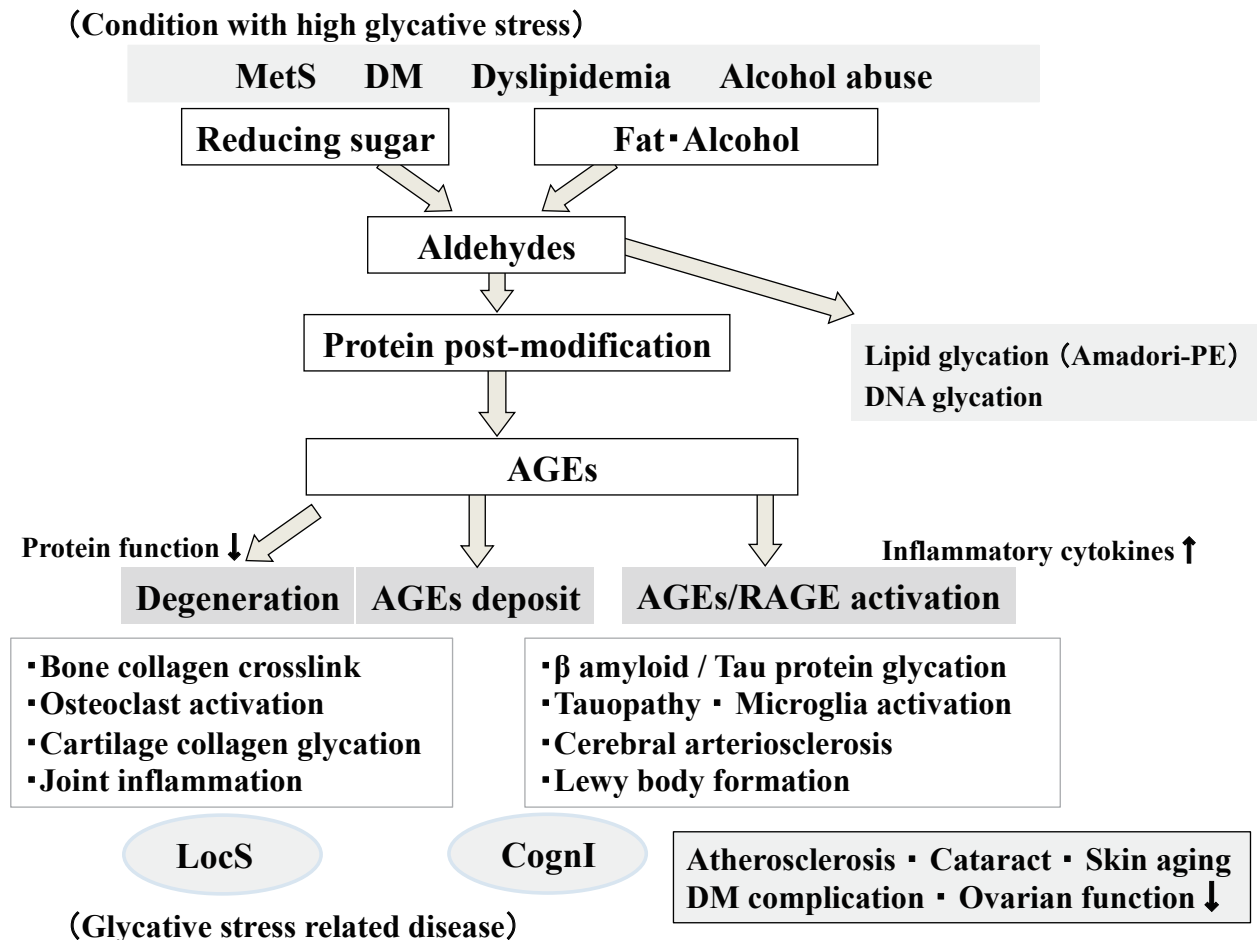


Fig. 3. Glycative stress is the risk factor of locomotive syndrome and cognitive impairment.

Metabolic syndrome (MetS) is a state where glycativ stress is strong. The glycation of proteins derived from bones and joints (formation of AGEs) and the inflammation caused by signal activation of the AGEs/RAGE pathway are involved in locomotive syndrome (LocS). Alzheimer's disease, vascular dementia and Lewy body disease are generally mixed in cognitive impairment (CognI). CognI is formed with the glycation of protein in brain such as β -amyloid, tau protein and Lewy bodies, activation of microglia through the AGEs/RAGE signal pathway and cerebral arteriosclerosis.

These AGEs bind with RAGE on the surface of macrophage system cells in the articular cavity and cause inflammation. Our laboratory is engaged in the development of anti-glycation functional foods that prevent the glycation of protein derived from joints and promote the resolution and evacuation of AGEs, as a constituent member of the consortium of "Creation of Agri-innovation" (2014-2019) of "Next-Generation Agriculture, Forestry And Fisheries Creative Technology," a part of "Cross-Ministerial Strategic Innovation Promotion Program (SIP)," of which the Ministry of Agriculture, Forestry and Fisheries is in charge.

Skeletal muscle mass decreases with age¹⁸⁾. For LocS patients whose muscle age is remarkably advanced and also have a strong element of sarcopenia, muscle strengthening should be focused on. Skeletal muscles have a joint protection effect and prevent osteoarthritis. If skeletal muscles are well maintained, falling injuries can be avoided more easily. As for the methods of muscle resistance training, there are squat, dumbbell, abdominal muscle and back muscle exercises. New methods including Kaatsu training^{19,20)}, power rehabilitation for the elderly^{21,22)} and electrical muscle

stimulation (EMS)^{23,24)} have been devised, opening a new market leading to economic revitalization.

For the MetS patients who have a lower skeletal muscle mass and whose muscles are aging, priority should be given to the increasing of muscle mass and the redress of muscle aging. Approximately 80% of glucose is consumed by skeletal muscles. The decrease of skeletal muscle mass leads to the decrease of the basal metabolism and excess calories are accumulated as visceral fat. If those patients place too high of a priority on dietary restriction, then skeletal muscle mass increasingly decreases resulting in bodily damage. A sense of holistic balance is required for proper guidance.

Cognitive impairment (CognI) and glycativ stress

Executive brain functions include attentive ability, frontal lobe function, visuo-perceptual function, cognitive ability, memory and whole mental functions. Executive brain function cannot be assessed by only one test. The Wisconsin card sorting test^{25,26)} recommended by the Japan Brain Dock Society and can be an opportunity for the early detection of

cognitive impairment in young people as a screening test.

Cerebral arteriosclerosis and the accumulations of β -amyloid and tau proteins in brain are considered to be the cause of CognI²⁷⁾. A countermeasure against MetS (= countermeasure against glycativ stress) is useful for the prevention of cerebral arteriosclerosis. As the mechanism that increases the risk of CognI among diabetes patients, it is presumed that the toxicity and recalcitrant nature of β -amyloid²⁷⁾ and tau proteins^{28,29)} are strengthened by being glycated, and the inflammation is caused through neurofibrillary tangle and AGEs/RAGE system. Glycative stress is also involved in the formation of Lewy bodies³⁰⁾.

As the functional elements for the countermeasure against CognI among the deliverables of SIP consortium, the research of rosmarinic acid including lemon balm, morin of flavonoid derived from seaweed, terpenes derived from yuzu (*Citrus junos*) and extracted materials from rice bran are progressing. These elements have anti-glycation effects including the inhibition of the formation, resolution and evacuation of AGEs. The verification experiments of the inhibition of glycation by β -amyloid, the permeability of blood brain barrier (BBB) and the evaluations of their effectiveness in humans are expected. These research projects lead to the activations of agriculture, forestry and fisheries (primary industries), the creation of the sixth industry and the activation of local economies.

The treatment of serious completed CognI is difficult, making the improvement of life styles including dietary habits, physical exercise and intellectual education beginning in middle age or even younger ages is very important. If neural function is not used, it deteriorates, so it is important to use it through physical activities. “Cognisize” (cognizance + exercise) and “Cogniwalk” (special walking to keep cognitive function) are recommended. Cerebral arteriosclerosis and the accumulation AGEs in the brain can be prevented by dietary education as a countermeasure against glycativ stress. Intellectual education is a countermeasure against mental and physical stress and for improving the quality of sleep. Cortisol, a stress hormone, causes the elevation of blood glucose levels and the increase of insulin resistance, and also contributes to glycativ stress³¹⁾. Melatonin secreted during sleep has an effect to accelerate the resolution of AGEs in addition to anti-oxidant activity³¹⁾. We would like the bedding industry to join in our project in countering glycativ stress.

What differences are among independent elderly people, those requiring support and those requiring care?: Use of the elderly and factors preventing it.

“The 2025 issue” in an aging society was a warning to various medical communities regarding the lack of medical and care facilities caused by the increase of the elderly with locomotive, cognitive and other impairments. Even at present, the number of individuals waiting for admission to special nursing homes is more than 500,000 and nursing care staff are also in short supply. The number of workers who are forced to leave their job to care for their parent is increasing. In order to understand the differences among the elderly who are living independently³²⁻³⁴⁾, those who require support and commute to day care center (care prevention program executors)³⁵⁾ and those who require care and are admitted to geriatric health services facility³⁶⁾, the results of anti-aging medical checkup were compared³⁷⁾. As a result, the more the neural age advances, the higher the level of

nursing care is needed (Fig. 4). It shows that the decrease of neural function is a large factor in the deterioration of ADL, preventing the elderly from living independently and being a working force. It is important to detect CognI at an early stage and retard its progression.

Conclusion:

What can contribute to Dynamic Engagement of All Citizens?

Fig.5 shows “the new three arrows” for Dynamic Engagement of All Citizens and what Anti-Aging Medicine can do for it.

The first target is a strong economy. The Japanese Society of Anti-Aging Medicine improves the health of citizens, the source of economic dynamism, and cooperates in the creation of new health and medical industries. From the viewpoint of industrial health, this society aims to improve productivity, lower the absence rate, increase the labor participation rate and reduce the expenditure of Health Insurance Society. Local activation is indispensable for nurturing smart agriculture and the sixth industries.

The awareness of glycativ stress is currently not very high. The economic scales of diagnostic equipment, functional food, cosmetics and medical drugs relating to glycativ stress are still too small. However, when viewed from the opposite side, the industries relating to glycativ stress have a lot of room to develop. We share the knowledge concerning glycativ stress and establish a foundation for future activities, through the establishment of the Society for Glycativ Stress Research and the publication of “Glycativ Stress Research,” an academic journal. SIP consortium is conducting the research and development of anti-glycativ stress effects (inhibition of formation, resolution and evacuation of AGEs and signal control of the AGEs/RAGE pathway) as new functionalities and contributing to the creation of new industries.

Our second target is child care support. Women are highly suited to the medical professions and it is encouraged they take up a medical career for the betterment of society. We would like to positively support the activities of female doctors and medical staff to be a good role models to others. Responding to social situations such as late marriage and late childbearing, we consider various measures such as the rejuvenation of the ovum and the health maintenance of reproductive functions. In Doshisha University, we are in charge of the courses on “Public Health” and “Introduction to Anti-Aging Medicine” for undergraduate students as well as the “Advanced Course of Anti-Aging Medicine” for graduate students where we, among other things, provide guidance about maintaining ovarian and testicular function in good health, and during the course, provide anti-aging guidance for children and young people.

Our third target is social security. Government spending for nursing service and others is tremendous. The purposes of Anti-Aging Medicine are the extension of healthy longevity and middle and old aged health promotion aiming at the elderly who need no care, in order to slash public medical expenses.

From the above, we believe that Anti-Aging Medicine can greatly contribute to the realization of the Dynamic Engagement of All Citizens.

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Conflict of interest statement

There are no items deemed to be conflicts of interest in this research.

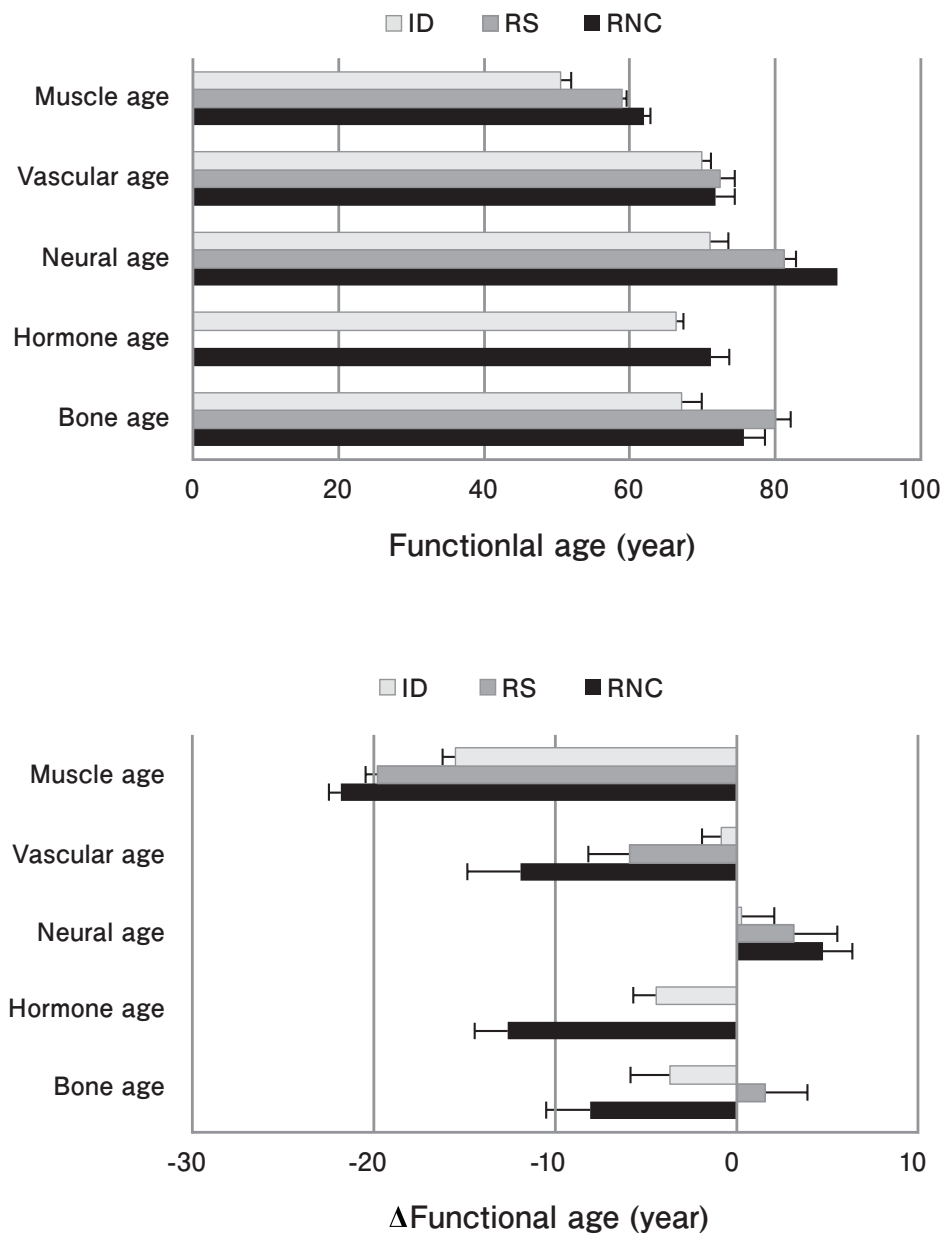


Fig. 4. Comparison of functional age (a) and Δ functional age (b) of the groups of the elderly with different nursing care level.

The results are shown as average value \pm standard error. Independent living (ID) group was $n = 44$, 70.8 ± 1.2 years, required support (RS) group was $n = 32$, 78.4 ± 1.6 years, required nursing care (RNC) group was $n = 19$, 83.7 ± 1.6 years and Δ functional age was defined as “functional age – actual age.” The Δ Neural age of RNC was highest, that of RS was next and that of ID was lowest ($p < 0.05$). In other words, the higher the nursing care level is, the more distinct the neural aging is. The hormone age of RS has not been investigated. The data was quoted from Reference 37.

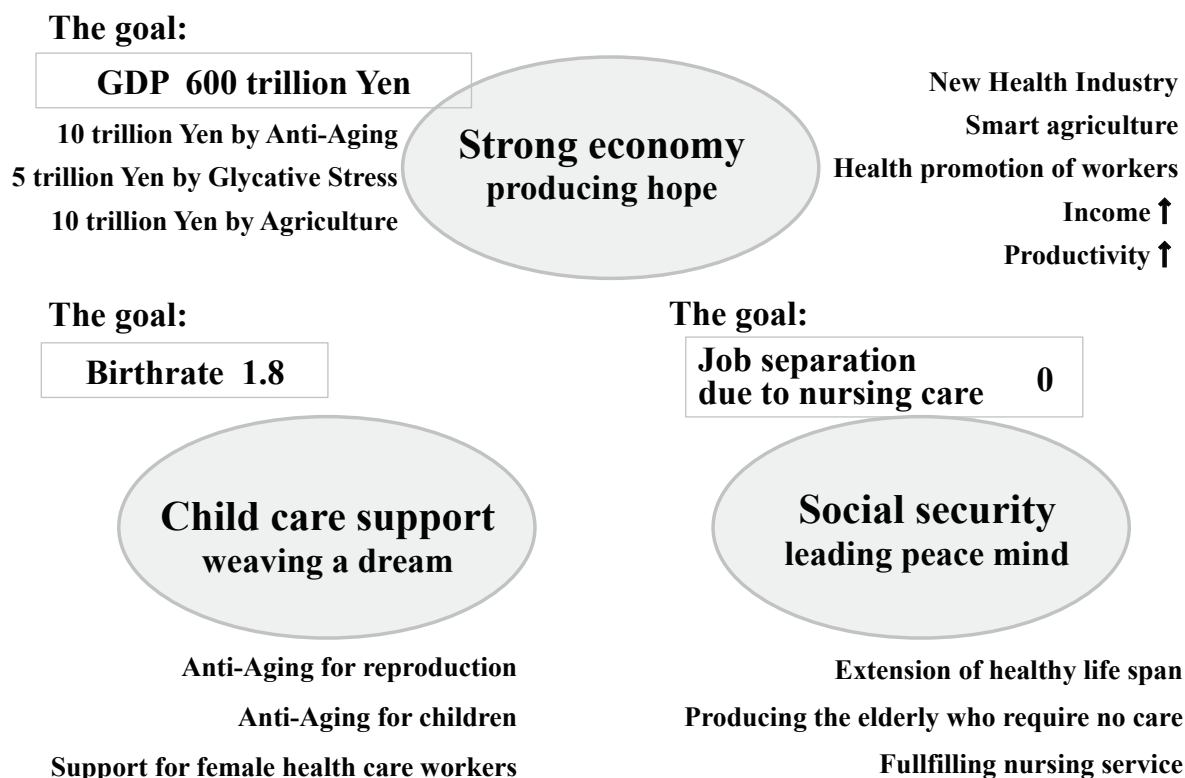


Fig. 5. “New three arrows” for Dynamic Engagement of All Citizens and Anti-Aging Medicine.

The improvement of the health of all citizen leads to the utilization of the elderly, a decrease of those who leave their job to care for their parents, engagement of women, increase in birth rates and productivity improvement. New health and medicine industries are created working towards the revitalization of local communities and a strong economy.

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