



Retarding Aging - Healthy Aging

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ABSTRACT

The inevitability of aging and fear of dying has haunted human race and it has been a human dream to retard aging and defy death. With aging, several changes occur in our endocrine glands and now it is known that some of the clinical features of aging are related to the effects of declining hormone levels.

We should use aging synonymously with senescence. Memory loss is an agonizing consequence of senescence and is possibly related to loss of cholinergic cells. The age related muscle wasting (sarcopenia) is due to several factors including decrease in production of growth hormone and circulating insulin-like growth hormone (IGF-1).

For preventing overall general age retardation, four methods have been under investigation; (1) Calorie restriction, (2) Genetic manipulations, (3) Prevention of oxidative damage, and (4) Treating ailments of the aged that might affect age-retardation. This is done by (a) HRT treatment, (b) Telomere manipulation as a means of combating some afflictions of the aged and (c) Regular exercise, balanced nutrition and social support which have salutary effect in prevention of ailments in the elderly and thus prolonging lifespan.

Healthy aging is a multifactorial phenomenon and is influenced by genetic predisposition, biological and psychological development factors.

The factors which promote healthy aging are (1) adequate healthy food, (2) physical exercise, (3) anti-stress exercises including yoga, meditation, (4) potable water, (5) shelter, (6) sanitation, (7) healthy environments, (8) education, (9) employment, (10) counselling on purposeful living and (11) human dignity.

The bottom line is that we cannot achieve healthy aging with high tech medicine alone. Taking care of ourselves personally and our environment are the keys to healthy aging.

INTRODUCTION

We may try to improve or enhance our performance but we all know that our body is bound to degrade over a period of time. As the body ages, we loose flexibility and reaction time, speed, strength, mental agility, memory and recall, immune response and overall functioning. The inevitability of aging and fear of dying has haunted human race and it has been a human dream to retard aging and defy death.¹

ENDOCRINOLOGY OF AGING

The endocrine system regulates body composition, fat deposition, metabolism, muscle mass and muscle strength, and body weight.² With aging several changes occur in our endocrine glands and now we know that some of the clinical features of aging are related to the effects of declining hormone levels. With aging, there is decrease in gonadal production of testosterone in men (andropause), oestrogen in women (menopause), decrease in the activity of growth hormone (GH/insulin-like growth factor (IGF) axis) (somatopause) and adrenal production of

dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS-S) (adrenopause). Hence, there have been several reports of hormone replacement therapy (HRT) to delay or prevent some of the consequences of aging. However, HRT is not without side-effects.

We should use "aging" synonymously with "senescence" rather than merely to describe the actual age of the person.² The desire for ageless bodies covers the pursuit not only of longer lives, but also of lives that remain active longer. It involves not only to add years to life but also to add life to years. For life extension, one may consider three broad approaches.

1. Efforts to cut down infant mortality and other causes of death due to infections in young people so that people live to old age. Developed countries have achieved this goal.
2. Efforts to further prolong the lives of elderly persons by reducing the incidence and severity of diseases during middle age.

3. Attempt to be made to overall retard the effects of senescence more generally by affecting the general processes of aging thus increasing the overall life span. Amongst these 3 approaches, it is the third one direct and general age retardation which is being pursued by several workers.¹

TARGET SPECIFIC DEFICIENCIES OF OLD AGE

Improvement of memory

Memory loss is an agonizing consequence of senescence. Research on cause of memory loss in Alzheimer's has given a clue to the cause of memory loss in aging. In Alzheimer's, the cholinergic cells are among the first to die, hence it was postulated that cholinergic mechanism may be involved in memory formation.³ This has led to the development of acetylcholinesterase inhibitors as class of drugs which block the enzyme that destroys acetylcholine (a neurotransmitter which is crucial to forming memories). These drugs have a true but limited effect on improving memory in some patients of Alzheimers. However in aging, in absence of pathology, whether these results can be extrapolated. Nonetheless there is some evidence to show that donepezil (one of the major acetylcholinesterase inhibitors) when compared to placebo has shown improvement in the performance of middle-aged pilots.⁴

Improvement of muscle mass and muscle strength

Diminution of muscle strength and muscle mass is one of the most obvious and significant sign of body senescence. With aging, most of the persons become sedentary and the production of growth hormone and circulating insulin-like growth hormone (IGF-1) also decreases. As IGF-1 is less, the muscles become smaller, weaker and less easily repaired when injured. Also the aged muscles respond poorly to action of IGF-1 and muscle IGF-1 (mIGF-1), with the result that even impact of vigorous exercise on muscle size and strength diminishes with age.⁵ This age-related muscle diminution is called sarcopenia. There are several factors which predispose to the development of sarcopenia. Elderly persons either reduce the output of and/or become more resistant to anabolic stimuli to muscle, such as CNS input, growth hormone, oestrogen, testosterone, insulin action, dietary protein and physical activity. The loss of alpha-motor neuron input to muscle that occurs with aging,⁵ is an important factor since nerve cell to muscle cell connections are critical in maintaining muscle mass and strength. For prevention of sarcopenia and for muscle enhancement, use of human growth hormone, introduction of IGF-1 genes have given encouraging results. They seem to reduce age-related loss of strength and of muscle mass.

GENERAL (BODYWIDE) AGE-RETARDATION

Caloric Restriction

It has been observed since seven decades of experimental work that reduction in food intake (caloric intake) of animals with supplementation of vitamins and minerals, results in prolongation of lifespan. It has been found both in invertebrates and vertebrates (including mammals) that giving 60% of the normal food intake (40% reduction) has significant impact not only on lifespan but also on the rate of decline of all functions (neurological, muscle, immune). In mice and rats, lifespan is extended by more

than 30% and in some studies by more than 50%.⁶ Recently 16% increase in lifespan of dogs has been reported by caloric restriction.⁶ Also similar observations have been reported in monkeys.⁷ The biological basis of anti-aging effects of caloric restriction have not been well understood.

Genetic manipulation

Over last few decades, researchers have identified single gene alterations that in a number of species e.g. nematodes, fruit-flies, mice, leads to increase in lifespan. In worms, flies and mice, an alteration in a receptor for an insulin-like growth factor (present also in humans) has resulted in significant increase in lifespan. From these experiments, one can say that the rate of aging may be influenced by highly conserved general mechanism across many species and that single gene alterations that extend life may ultimately be discovered in humans. However single gene mutations combined with caloric restriction have been shown to result in a nearly 75% increase in lifespan (upto nearly three and half years) in mice. The 75% extension is so far the greatest increases lifespan achieved in mammals.⁸

Prevention of Oxidative Damage

It has been documented that oxygen free radicals cause gradual deterioration of many of the body's cells and tissues. To counteract that our body produces or receives through diet, a number of anti-oxidants such as superoxide dismutase (SOD), catalase (CAT), vitamin C, vitamin E, alpha-lipoic acid and coenzyme Q10. Oxidative stress which our body ultimately receives depends upon the balance of oxygen free radicals (oxidants) and anti-oxidant levels. Synthetic anti-oxidants have been proved experimentally to prolong lifespan of mice and fruit-flies. Our laboratory experiments (Sainani et al)⁹ using macrophage cell culture and oxidants (e.g. hydrogen peroxide, cigarette smoke) and anti-oxidants (e.g. SOD, glutathione peroxidase (Gpx), vitamins E, C, β carotene) have also clearly shown that anti-oxidants can prevent the oxidative damage to macrophages.

Although not a uniformly consistent observation, a number of epidemiological studies have found a link between antioxidants intake and low incidence of dementia, Alzheimer's disease and cognitive decline in elderly people. Naturally occurring compounds (e.g. vitamin C, ubiquinone, lipoic acid, beta-carotene, melatonin, curcumin, creatine) with antioxidant capacity are available. Combination of anti-oxidants might be of even greater potential benefit. Dietary anti-oxidants are important in modulating oxidative stress of aging and age-associated diseases. There are studies to show that polyphenols or vitamin E may assist in preventing cardiovascular disease, in part by decreasing expression by endothelial cells of pro-inflammatory cytokines, adhesion molecules and monocyte adhesion.

More recently Grundman et al¹⁰ have found that some of these antioxidants may prevent tumour growth by inhibiting angiogenesis via suppression of interleukin B and modulation of the cell junction molecule, VE-cadherin. These findings further support the beneficial effects of fruits and vegetables which contain several forms of phytochemicals with anti-oxidant activity to reduce the risk of CV disease and cancer, the leading causes of morbidity and mortality among the elderly.

Gemma et al¹¹ in their experimental study using aged rats have shown that diets enriched in foods with high anti-oxidant activity reverse age-induced decreases in cerebellar beta-adrenergic function. These diets reduce pro-inflammatory cytokine levels.

Kumar et al¹² carried out an experimental work on rats and concluded that the aqueous extract of *Celastrus paniculatus* seed has cognitive enhancing properties and an antioxidant effect might be involved.

Morris et al¹³ have carried our longitudinal population based study and have concluded that vitamin E intake, from foods or supplements is associated with less cognitive decline with age.

Methods of treating ailments of the aged that might affect age-retardation

Hormone treatment

Over the past 15 years, research is going on to explore the possibility of slowing or even reversing the aging affects by hormone replacement therapy (HRT). The hormones used are human growth hormone, dehydroepiandrosterone (DHEA), oestrogen, progesterone, testosterone, and melatonin. An important study showed that human growth hormone over six months period caused loss of fat, increased muscle mass, improved skin elasticity and low cholesterol levels.¹⁴ As regards increase in lifespan, doubts have been raised. It seems HRT may play an important role in unlocking the secrets of aging process.

Telomere Research

Since over 2 decades, it has been established that telomeres (which form the tips of chromosomes) can shorten overtime as cells divide, and eventually this shortening cause cells to stop dividing and to die. However, certain cells such as germ cells, some stem cells, cancer cells, hair follicles do not undergo process of degeneration with the help of an enzyme called telomerase which slows the erosion and shortening of telomeres. Also there are reports that suggest telomere length correlates with cell aging, so that preventing the shortening of telomers can slow the aging of cells. Recently a study has shown a statistically significant link between shorter average telomere length and increased rates of mortality in the elderly.¹⁵ There seems to be a great promise of telomere manipulation as a means of combating some afflictions of the aged.

Importance of physical activity, nutrition and social support for optimal aging

Over the last several decades, many researchers and clinicians have considered the question of what factors determine how well one ages and what elements are necessary for optimal aging. The discovery that diet and healthy lifestyle are as important as genetic inheritance, which can determine how well one ages and can have a positive impact on quality of life, no matter how late in life these are initiated.

Although genetics is known to influence longevity and optimal aging, research suggests that good lifestyle choice (i.e. maintaining optimal weight, remaining physically, cognitively and socially active and following healthy dietary pattern) also play essential role.

Physical activity

Adequate physical activity even if initiated in later years, contributes to high physical and cognitive functioning and overall health.¹⁶⁻¹⁸ Particularly physical activity contributes to muscle function and tone, flexibility, cardiovascular health, positive mood and cognition. It has been found to prevent falls and improve brain function even after brain injury. It also improves strength and flexibility of muscle and prevent muscle loss. It has also been shown that moderate intensity physical activity is associated with longevity and well-being.^{16,18,19} Conversely physical inactivity has been associated with muscle wasting, reduced muscle strength and increased mortality. Also sedentary lifestyle leads to increasing disability and dependence on others for assistance for activities of daily living. Physical activity may be the primary factor for promoting optimal aging.

Nutrition

There is evidence that healthy nutrition is a powerful lifestyle factor which may delay or prevent

chronic diseases in later life and will add years of health, productivity and high functioning. However, faulty nutrition or inadequate nutrition results in decline of organ function which affects digestion, metabolism and absorption of nutrients.²⁰ Proper nutrition with an emphasis on consuming fruits and vegetables has long term health benefits and improves physical, cognitive and social functioning. There are reports that many elderly persons are deficient in vitamins and minerals including vitamins B₆, B₁₂, D, folic acid, anti-oxidant vitamins A,C,E and beta-carotene as well as minerals, selenium, calcium and iron which are essential for overall health.^{17,21-24} Malnutrition can cause long term cognitive impairment.¹⁷ Elders with various vitamin deficiencies, especially of B₁₂, may be at risk for cognitive disorders including dementia while other nutrients such as antioxidants and vitamin C may be protective against cognitive decline.^{17,25} Many important causes of deaths in US including CAD, stroke and cancer are influenced by diet. Beta-carotene has been associated with reduced risk for cancer and cataracts, and vitamin C, Beta-carotene and folic acid may prevent heart disease. There is strong evidence that folic acid deficiency can increase risk for CAD and stroke. Optimal calcium intake reduces risk of osteoporosis. Also high protein diet such as soyabean and physical activity may protect against osteoporosis. Dietary fiber is healthy to consume as it is associated with lowering of blood fat and sugar levels which helps in preventing DM and CAD and in promoting colon health.^{22,25,26}

Social support

Social support is essential in promotion and maintenance of overall long term health by contributing to physical and cognitive functioning and supporting engagement with life. Epidemiological data confirms that social support (i.e. strong social networks and high social contact) is related to longevity and mortality.²⁷

HEALTHY AGING

According to Young et al²⁸ healthy aging is a multifactorial phenomenon, biological and psychological development factors. The population of older women is diverse in health, function, social context and age. Hence, health promotion strategies

should be customised accordingly to optimise the health of the varied subgroups of older women according to their personal preferences and health trajectory.

Empirical evidence indicates that musculoskeletal and cardiovascular functioning and symptoms of chronic disease in old age are strongly related to lifestyle choices involving physical activity and nutritional intake. Therefore several organisations have developed physical activity and nutritional intake recommendations aimed at maintaining or increasing the functional ability of old persons. These physical activity recommendations include engaging in cardiorespiratory, flexibility, strength and balance training for 3-5 days per week. Broad nutritional recommendations for elderly include low fat, plenty of vegetables, fruits, whole grains, 8 glasses of water per day + vitamin + mineral supplement.²⁹

Living to a late age without suffering any major health problems is a genetically influenced trait. Ninety five pairs of male fraternal twins concordant for healthy aging (attaining the age 70 years free of cardiovascular disease (CAD, DM and stroke) and prostate cancer, were studied genetically.³⁰ A region on chromosome 4 at marker D4S156-4 produced logarithm of odds (LOD) score of 1.67, this was the same marker previously linked to extreme longevity segregating as an autosomal dominant trait in centenarian families. This study confirms that a locus on the long arm of chromosome 4 is associated with better physical aging and/or longevity. Healthy aging begins with the foetus.³⁰

Until now prospective studies of aging have begun with 50 to 60 years olds, not adolescents. In the study by Valiant and Western,³¹ cohort of adolescent boys (332 intercity youths) were followed for 60 years or until death. Complete physical checking was done every 5 years and psychosocial data every 2 years. The multivariate analysis suggested that positive aging at 70 could be predicted by variables assessed prior to age 50. More hopeful still, if the six variables under some personal control were controlled, depression was the only uncontrollable variable that affected the quality of subjective and objective aging. In this cohort, psychological rather than sociological predictors appeared more important.

Five thousand eight hundred eighty eight participants (age 65 years and older) in the cardiovascular health³² study were examined at baseline and over a maximum 7 years follow up.³² At baseline they were free from chronic diseases such as CVD, COPD, or self reported cancer. During follow up, numerous lifestyle factors such as abstinence from smoking, wine consumption, lower waist circumference, higher educational status were correlated with healthy aging. These data suggest that a number of modifiable behavioural factors (physical activity, smoking, and obesity) and cardiovascular risk factors (DM, HDL-cholesterol and HT) influence the maintenance of good health in elderly.

Elderly are at risk of nutritionally, inadequate diets especially proteins, vitamin D, B₁, B₁₂, B₆, fluid. The dietary and health promoting interventions should focus on maximizing function and quality of life.³³

There is increasing evidence that remaining physically, cognitively or socially active confers health benefits by delaying or preventing the onset of disease and disability in the elderly. The desire to be innovative has been considered an important development

objective in later years to give meaning to one's life, and may provide the necessary impetus for older women to initiate and maintain health-promoting activities.³⁴

The first of the Baby Boomer Generation will officially enter the beginning of old age in 2011 by turning sixty five. Recent findings³⁵ indicate that if members of this cohort group engage in certain healthy behaviour and thought patterns in their middle years, they will experience a vital, satisfying life in their 70s and beyond. The authors³⁵ recommend anti-aging measures to be practised during middle age, which are likely to prevent disease-related disability, cognitive impairment and late life depression. These include regular exercise, engaging in cognitively stimulating activities, maintaining an optimistic mental outlook and finding meaning in life. The good news for the Baby Boomers that their behaviour at age 50 will impact how they will feel at age eighty.

The purpose of the study by Reed et al³⁶ was to predict staying healthy in contrast to developing clinical illness and/or physical and mental impairments. More than 8000 Japanese were followed up for 28 years with repeat examinations and record for deaths and incident clinical illness. The most consistent predictors of healthy aging were low blood pressure, low glucose levels, no smoking and normal weight. One can conclude that beyond the biological effects of aging, much of the illness and disability in the elderly is related to risk factors present at mid life.

A scientifically based complimentary medicine program³⁷ to promote healthy aging includes (1) diet, (2) nutrient supplements to meet specific needs, (3) exercise, (4) stress management, (5) promotion of structural integrity, (6) environmental adjustment, (7) counselling on purposeful living and (8) normal intercellular communication. This focuses on the following modifiable factors of unhealthy aging: altered mitochondrial function and oxidative stress, increased protein glycation, chronic inflammation, defects in methylation, reduced detoxification ability and altered immunity.³⁷

Diczfalusy³⁸ analyzed nine pillars of human dignity (sufficient food, potable water, shelter, sanitation, health services, healthy environment, education, employment and personal security). The author along with members of international federation of gynaecology and obstetrics has participated and contributed to the global intellectual process by which gender equity and reproductive health assumed a central role in world affairs. A rapidly aging world population constitutes another major challenge. The author feels confident that the International Federation of Gynaecology and Obstetrics has and will continue to have a vital role in achieving nine pillars of human dignity.

The life-expectancy of women currently exceeds that of men by 7 years, yet women spend approximately twice as many years disabled prior to death as their male counterparts. The diseases that they suffer are heart diseases, cancer, stroke, fracture, osteoarthritis, pneumonia, cataracts and these mostly contribute to their disability. They should reduce weight, should take plenty of vegetables, fruits, calcium, vitamin D supplements. Regular screening for breast and colo-rectal cancer should be done. They should be encouraged to do exercise (walking). All these measures will improve the course of many chronic diseases.³⁹

With aging, there is loss of muscle mass (sarcopenia) which leads to decrease in BMR, muscle strength and activity levels. In

sedentary persons, declining energy needs are not matched by an appropriate decline in energy intake with the result that body fat increases. Increased body fat and abdominal obesity results in insulin resistance and development of NIDDM among the elderly. Hence regular exercise is strongly recommended, which will increase nutrition needs and functional capacity in the elderly and may postpone/prevent development of NIDDM.⁴⁰

To investigate survival factors in healthy aging among rural Japanese elderly residents,⁴¹ a nested case control study was conducted by Takezaki et al.⁴¹ It was concluded that psychological factors and recent health examinations were positively associated to survival in healthy aging. Smoking and chronic disease contributed negatively to survival.

Recent advances have made it possible to cure acute disorders and to manage chronic ones. This has opened the prospect of increased longevity and a productive and healthy old age. The high tech treatment has made it possible to maintain high levels of function and quality of life. However in some respects we have learnt about the limitations of a particular therapy, for example, we now know the multiple risks posed by hormone replacement therapy⁴² and by artificially inducing lean body mass in the elderly. Instead models of health care recommend to the critical role of our own behaviour. Research in preventive medicine shows that physical and mental exercise and social engagement seem to be the most important contributors to healthy aging. Simple cognitive exercise can effectively improve memory.⁴³ One may surmise we are the one most responsible for our own health.

Behavioral approaches to treatment are being successfully applied to previously untreatable conditions such as urinary incontinence.⁴⁴ Physicians who have been relying first on drugs to manage their patients should concentrate on training their patients to manage their own health. Healthy aging requires not only a personal commitment but a commitment to the environment and to public health. The most vital thing is that we should have an environment free of toxic health hazards as well as a social environment more conducive to better nutrition, exercise, better education, less income disparity and reduced stress.

The bottom line is that we cannot achieve healthy aging with high tech medicine alone. Taking care of ourselves personally and our environment publicly are the keys to healthy aging. With such commitment, we cannot only postpone death but achieve dignity with age.

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