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AGEISM

Problems and Prospects

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Dietary Restriction – A Way to Elixir of Youth

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Aging or getting old is a universal feature of most organisms and has been a global concern of every society. The maximum lifespan of an organism is a constitutional feature of speciation to polygenic controls and to environmental influences. There is a progressive functional decline of physiological functions associated with decreased fecundity and increased vulnerability to diseases. In the current times, the fountain of youth seems no longer a legendary fairy tale. There are now scientific evidences to suggest that the age-related impairments can be reversed by dietary and other interventions. Among various intervention strategies, dietary restriction (DR), a reduction in calorie intake without malnutrition, has been shown to be the most powerful modulator of the aging process in diverse groups of organisms. It is an efficacious means of increasing longevity and reducing age-related pathology. A manner in which dietary restriction help extend human lifespan and reduce age-related diseases has been of immense interest to the scientific community. These studies strongly support the role of DR in increasing

longevity, enhancing functional capacity and reducing diseases of old age in wide group of experimental animals. Studies in humans and other experimental animals indicate that good nutrition and regular physical exercise not only contribute significantly to health and well-being, but also prolong mean and maximum lifespan. Indeed, these interventions are now accepted as a natural way to tackle a number of diseases of old age. One of the major goals of gerontologists is to prolong health-span part of the lifespan and have healthy old age without disability. In my opinion, if one can follow a strict regimen of 15-25 per cent of reduction in what she/he normally takes, it could provide a better health and longer lifespan. Some of the biochemical changes that happen during such intervention in experimental animals are presented herein.

Various theories have been put forward to explain the phenomenon of aging, however, none has yet accounted for all phenotypes, though many have attempted to explain at least some of the major and most frequent aging phenomena.[1,2] These theories have been grouped as molecular, cellular and systemic theories. *Molecular theories* envisage that the genes (specific DNA sequences) govern the lifespan of any species in a close knit with the environmental factors. It may result from changes in DNA template activity, which regulates the formation of the final cellular products. The molecular theories include codon restriction, somatic mutation, error theory, and gene regulation theory. They also include antagonistic pleiotropy, dysdifferentiation and soma disposal hypothesis. *Cellular theories,* on the other hand, relate to changes that occur in structural and functional elements of cells with the passage of time. These theories include wear and tear, age pigments, free radicals, cross-linking and membrane alterations. *System level theories* include the endocrine and neuroendocrine and immunological systems. These theories relate overall performance of an

organism to the efficacy of a variety of control mechanisms that regulate the interaction between different organs and tissues. Adaptation to external and/or internal stress depends on the control mechanisms orchestrated by the joint interplay of the nervous and endocrine systems. Complete surveillance to foreign invaders is looked after by the concerted efforts of the immune system. The failure of which leads to a reduced adaptability of an organism to the pathogenic challenges in old age. Healthy aging and maximum longevity may thus depend on the genetic make-up of an organism under a strict control by the nature and nurture. The impact of dietary restriction has been associated with most of the mechanistic approaches of various theories proposed for causation of aging.

A manner in which dietary restriction help extend human lifespan and reduce age-related diseases has been of immense interest to the scientific community. After an early work of McCay and his collaborators,[3] many more experimental studies have been undertaken using a wide range of strategies.[4-6] These studies strongly support DR in increasing longevity, enhancing functional capacity and reducing age-associated diseases in experimental animals. Studies in humans indicate that good nutrition and regular physical exercise not only contribute significantly to health and well-being, but also prolong mean and maximum lifespan. Indeed, these interventions are now accepted as a natural ways to tackle a number of diseases of old age. One of the major goals of gerontologists is to prolong health-span part of the lifespan and have healthy old age without disability.

Biochemical Changes During DR

DR influences animal's reproduction to endocrine and neuroendocrine responses, immunological systems, metabolic responses, gene expression profiles, and also pathophysiological conditions. It has been postulated that DR by reducing the secretion of pituitary hormones, such as

growth hormone (GH), lowers the oxidative damage of tissues, thereby reduce the age-related pathologies and extend lifespan.[7] Moderate caloric restriction in rodents delays puberty without loss of fertility and enhances longevity[8]. This has been correlated with retarded maturation of the hypothalamo-pituitary-gonadal (HPG) axis. The anti-aging property of DR seems to have evolutionary significance and might have evolved in nature in response to food scarcity[9]. During such periods, inbuilt resources would be diverted from reproduction to maintenance of the adult body and thereby increase survival until the next period of food availability. Another neuroendocrine axis that appears to be influenced by DR is the hypothalamus-pituitary-adrenal (HPA) axis. During periods of restriction, the axis is stimulated possibly due to a feeling of stress by underfeeding leading to an increased level of circulating glucocorticoids. Although transient increase in glucocorticoids improves performance at spatial memory tasks and helps synaptic efficacy, long-term elevations of glucocorticoids are associated with decreased cognitive performance, attenuated synaptic efficacy and neuronal atrophy. Elevation of glucocorticoids during aging is also associated with mild cognitive impairment and hippocampal atrophy. DR paradoxically increases plasma glucocorticoids and also prolongs lifespan. It has been suggested that the beneficial effects of DR outweigh the deleterious effects of glucocorticoids. It is proposed that the lifespan extension in rodents by DR could be an example of hormesis (having a beneficial effect in response to a low-intensity stressor) and that sustained moderate hyperadrenocorticism helps life prolongation. Hormesis thus refers to a phenomenon of beneficial biological action from a factor that is generally viewed as detrimental in nature. The anti-aging action of DR could be viewed as a nutritional stress, which might stimulate metabolic responses for better survivability. During mild stress, the organism regulates its metabolism to allocate more energy for its maintenance and

survival and could be in a better condition after the stress, if it is not too harsh. Recently, this laboratory has reported an increased level of hepatic glucocorticoid receptors during three months of alternate days feeding in mice.[10] The increase in the level of hepatic glucocorticoid receptors could be a contributory factor in controlling the glucocorticoid-mediated metabolic responses during long-term DR in mice. Such rodents are found to be more resistant to a variety of other stresses such as trauma, heat shock and drug toxicity. Recently, it has been reported that an age-dependent decrease in liver and kidney glucocorticoid receptor function is reversed by DR in older mice.[11,12]

Several molecular, cellular, structural and functional changes occur in the brain during old age. Nerve cells might adapt to these changes or succumb to neurodegenerative events that result in diseases like Alzheimer's and Parkinson's. Multiple mechanisms operate to maintain the integrity of nerve circuits. These include production of neurotrophic factors and cytokines, expression of various cell survival-promoting proteins, preservation of genomic integrity and mobilization of neural stem cells to replenish damaged neural and glial cells.[13] Such neuro-protective and restorative mechanisms are compromised during aging process giving rise to neuropathological complications in elderly individuals. DR has been shown to reduce the pace of age-dependent decrease in genome integrity.[14] The adaptive responses in brain aging could be determined by the combined action of genetic and environmental factors. Neuroprotective functions thus are achieved by dietary calorie restriction, and by behavioral (physical and intellectual activity) modifications.

Numerous reports exist on the effects of DR in reducing mitochondrial damage, free radical accumulation, and lipid peroxidation. Such reduction could be possible partly by a decrease in the energy expenditure due to lower metabolic load in restricted animals and/or by an increased activity of

those enzymes that are responsible for scavenging the reactive oxygen species. In fact, oxidative damage has been linked to many major degenerative diseases, including atherosclerosis, diabetes, Parkinson's disease, Alzheimer's disease, and cancer[15,16]. It is corroborated with the genetic studies on *C. elegans*, wherein reactive oxygen species (ROS) are closely attributed in lifespan determination.[17] Accumulation of oxidatively damaged proteins is evident during aging in many organisms. DR has been shown to reduce the age-related increase in the half-life of proteins, suggesting that the dwelling time of the proteins is reduced in DR animals. Thus, DR can increase turnover of proteins and thereby attenuate potentially harmful consequences of altered proteins.[18]

Reduced immunological surveillance is a major predicament for increased morbidity and mortality in old age. Hence, the restoration of immunologic function may provide a beneficial effect in reducing pathology and maintaining healthy status in old age. Among various interventions, DR has been shown to be a powerful modulator of aging process. Several mechanisms have been proposed to explain its robust beneficial effects on various physiological processes, including the immune system. Overall immunological status of rodents fed with a caloric restricted diet is superior to the status of *ad libitum* (AL) fed animals.[19] The incidence of autoimmune diseases, which increase during aging of normal fed animals, is significantly decreased in response to DR. The molecular mechanism(s) of such protective action remain(s) to be elucidated.

Orchestrated expressions of many genes provide a powerful molecular description of the normal aging process. Nearly 23% of the genome in fruit flies shows altered transcription with age. DR leads to a slower progression of normal age-related changes in transcript levels, particularly of genes involved in cell growth, metabolism, and reproduction.[20] A detailed analysis of expression patterns of genes in skeletal muscle of mice during aging revealed a greater expression of genes involved in oxidative stress, DNA-

damage, neural atrophy and a decrease expression of genes leading to slower rate of glycolysis and mitochondrial dysfunction in aged animals. Most of these deficits in the expression of genes were either fully or partly reversed by DR in age-matched mice. Worth mentioning are the genes involved in protein metabolism (synthesis and turnover), carbohydrate metabolism (gluconeogenesis and pentose phosphate pathways) and fatty acid synthesis whose compromised expressions otherwise during aging were increased by DR in mice. Taken together, these observations suggest that DR may retard aging process by causing a metabolic shift toward enhanced protein turnover and lowered macromolecular damages caused by various toxic agents.[21] The health- and lifespan-extending properties of DR reveal that aging is accompanied by the altered gene expression associated with increased inflammation, cellular stress, and fibrosis and reduced capacity for apoptosis (programmed cell death), xenobiotic metabolism, normal cell cycling, and DNA replication.[22] It has been observed that both the long- and short- term DR reverses many of these changes. Hence, it seems plausible to obtain the benefits of DR in aging animals that have such functional impairments.

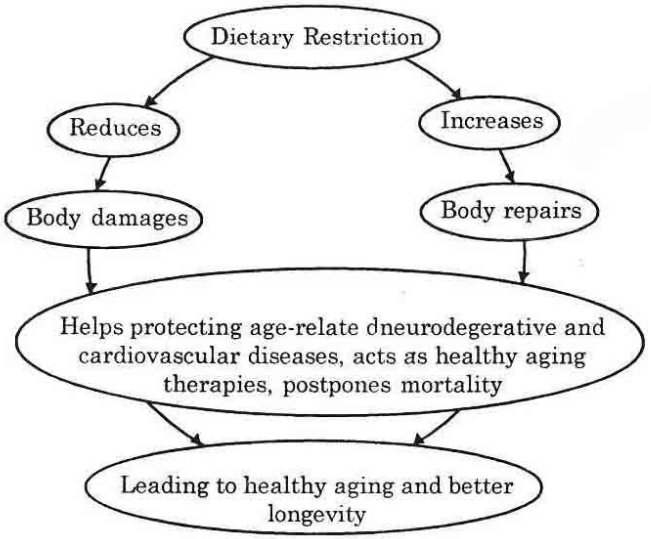
Human Studies Using DR

Quite some studies have been done on human subjects involving one or other regimen of DR. Islamic individuals who fast during the daylight and consume meal after sunset, their plasma high-density lipoprotein (HDL), also called good cholesterol, levels increase[23] by 30%. HDL removes cholesterol from the blood and carries it to the liver. It is inversely related to the atherosclerosis and other cardiovascular diseases. A similar increase in HDL level was also observed in DR monkeys. After 12 weeks of DR to non-diabetic healthy male individuals, the level of HDL-cholesterol is increased with concomitant decrease in hepatic lipase activity. The decrease in hepatic lipase could be a genuine link for increased HDL-cholesterol level in DR individuals.[20] A study of naturally occurring South Indian population of three age groups

(young, 8-14 years; adult, 20-35 years; old, above 55 years), who were having normal and undernourished diets on the basis of body mass index (BMI) and history of their dietary intake, reveal that the DNA repair capacity was found to be higher in the lymphocytes of age-matched undernourished individuals.[24] A slower reduction in DNA repair capacity was also observed as a function of age in undernourished individuals as compared to normal fed ones. These studies provide a crucial link between DNA repair mechanisms and nutritional status in humans. It has been seen that 16 weeks of energy restriction (by 33%) results in significant reduction in body mass, lean body mass and fat mass in sedentary overweight men.[25] It is known that the people of Okinawa, one of the prefectures of Japan, have highest longevity in the world. Okinawa has the highest prevalence of centenarians in the world at 33.6 per 100,000 populations, in contrast to an average of 10 per 100,000 in most developed countries. They have high number of those who live longer than 105 years, called supercentenarians. Major contributory factors to such a higher longevity are mild climate, unique eating habits, and an active lifestyle. Among these, eating habits could be a most crucial factor influencing Okinawan longevity. Japanese living on the island of Okinawa, eat 20% less food than those in Tokyo.[26,27] Majority of Okinawans believe that proper eating is the most efficacious medicine for better health. It is being perceived that the longevity can be attributed one-third to our genes and two-third to lifestyle, of which nutrition is an important component.[27] Healthful aging may thus depend on the genetic makeup within strict control of nature and nurture. The average life expectancy of Okinawans living in Brazil is 17 years shorter than Okinawans who live in Okinawa.[27] Thus, it is quite reasonable to practice the dietary interventions to achieve better health and lifespan in humans as well.

There is a serious possibility that only few people would reduce their food intake enough to lengthen their lives, gerontologists are now looking for alternatives that could

mimic the beneficial effects of DR in people who may not like to go for actual restrictions. These alternative interventions are termed as DR mimetics. DR mimetics targets improvement of mitochondrial function, use of antioxidants, administration of compounds (2-deoxyglucose) known to lower blood glucose levels and increase insulin sensitivity, regular physical exercise and maintenance of body weight over the lifespan.[28,29] In search of a DR mimetic, Howitz *et al.*[30] have found resveratrol, a plant polyphenol present in red wine, extending the lifespan of budding yeast *S. cerevisiae*, which is analogous to lifespan extension by caloric restriction in the same organism. Once, the effects of such DR mimetic agents are fully established in higher organisms, including humans, they may serve a better substitute for those having lesser compliance of DR on a long-term basis. The DR mimetic drugs, preferably from plant sources, could be a suitable alternative to achieve beneficial effects of actual DR[22] (eating food without having it). Many uses of such herbal products have been listed in Ayurveda, an ancient Indian system of medicine since 600 BC. A gum resin, called gugglu in Sanskrit, from Commiphora mukul used for the treatment of obesity and lipid disorders has its mention in the Sushruta Samitha written around 2500 years ago. The extract of resin, known guggulipid, has been successfully shown to exhibit lipid-lowering activity in normal and hyperlipidimic animals.[31] It is known to elevate HDL (good cholesterol) levels with concomitant lowering of low density lipoproteins (LDL) in rabbits on high fatty-diet and also shown to have lipid-lowering effects in humans.[32,33] Out of many such plant products being investigated, extract of aloe vera, a tropical plant, is now a familiar ingredient in variety of health formulations and cosmetics. A life-long dietary use of aloe vera extract has been found to suppress free radical induced oxidative damage and hepatic cholesterol rise in aging rats.[34] Uses of such natural herbal products may alternatively exert many of the similar beneficial effects of DR, without cutting the food intake.



Multiple effects of dietary restriction leading to healthy aging and better longevity - a way to elixir of youth

Concluding Remarks

Though a battery of data available on the merits of DR, there are some points which are yet to be considered before it could be floated as a health care resort for humans. Among these, the most vital ones are the duration and periods of onset of such restrictions and/or the uses of mimetic pharmaceutical and nutraceutical agents. DR and its mimetics, once fully evaluated, could provide an attractive way to elixir of youth and to achieve healthy longevity in various organisms, including humans.[35]

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