REVIEW ARTICLE

Medicina Sportiva, Vol. 8 (1): 5–16, 2004

ANTI-AGING INTERVENTIONS: THE EFFECTS OF DIETARY RESTRICTION AND EXERCISE

Barbara Kłapcińska

Department of Physiological and Medical Sciences, Biochemistry Unit, Academy of Physical Education, Katowice, Poland

Abstract

Restriction of food intake and regular physical activity retard age-associated decline in functional and cognitive capacities and prevent age-related diseases in rodents, non-human primates and humans. This review focuses on the possible biological mechanisms underlying the anti-aging action of these interventions. The following mechanisms are considered: (1) attenuation of oxidative stress; (2) up-regulation of antioxidant defenses; (3) modulation of glycemia and insulinemia; (4) enhancement and protection of brain function.

Key words: aging, dietary restriction, exercise

Introduction

According to demographic surveys the worldwide proportion of humans over 65 years of age will more than double, from 6.9 % in 2000 to 16.4 % in 2050 (1). During this period, the population of octo- and nonagenarians will grow from 1.9 to 4.2%, and that of centenarians is predicted to become 16 times larger in 2050 than in 1998 (2.2 million compared to 135 000) (1). The advanced age is known to be associated with chronic health problems and various kinds of disabilities (arthritis, rheumatism, spine problems, cardiovascular disease, cognitive impairment, neurodegenerative disorders) (2) Therefore, there is a growing public interest in the development of strategies that would be efficient in delaying aging, while preserving a good overall physical and mental health. Among the anti-aging interventions, tested in numerous studies with animals (mainly rodents or non-human primates) and humans, calorie (dietary) restriction and regular physical activity appeared to be the most efficient (3).

Dietary restriction attenuates oxidative stress

One of the most important findings of the free radical research was that decreasing the daily dietary intake (without essential nutrient, vitamin and mineral deficiency) increases average life span (4). Dietary restriction (DR) has been recognized as the most effective way of slowing the aging process in laboratory animals (5). Over the years, several theories have been presented to explain the anti-aging effects of caloric restriction. Postulated mechanisms include depressed metabolic rate, reduced oxidative stress, increased DNA repair capacity and altered expression of genes involved in energy metabolism or encoding

for mediators of stress responses (6). One favored hypothesis suggests that DR acts by decreasing oxidative stress (4). It has been postulated that limited food intake, or dietary restriction (DR), is associated with proportionate decreases in oxygen utilization (5, 7). Taking into account that over 90% of oxygen is consumed by mitochondria, this means that food restriction results in less superoxide anion formation and less ATP production. Less superoxide radicals decreases oxidative stress and thus aging rate (thereby increasing life span), whereas less ATP production (less energy input) results in adaptation of metabolic rate in the effort to sustain body maintenance and function. Numerous studies on animal models have evidenced that dietary manipulation can modify many aspects of free radical metabolism such as free radical generation, lipid and protein peroxidation, DNA damage and repair, and antioxidant defenses, thereby reducing levels of oxidative stress in various tissues (8). This hypothesis is supported by results of numerous studies which evidenced that, as compared to ad-libitum (AL)-fed rodents, the rate of oxidant generation in mitochondria from DR animals was significantly lower. Moreover, the age-related accumulation of oxidatively damaged proteins, lipids and DNA was clearly less (9).

Dietary restriction appeared to be effective in stimulating enzymatic processes of elimination of reactive aldehydic products, such as 4-hydroxynonenal (HNE), generated from lipid peroxidation in mitochondria (10). It was found that both main pathways of the elimination of HNE in rat liver mitochondria, i.e. *via* HNE oxidation by aldehyde dehydrogenase and conjugation of HNE with glutathione by glutathione-S-transferase (GST), were well preserved in DR animals throughout their lifespan. The findings of the same investigation also concludes that the activities of both these enzymes were reduced with age in ad-libitum (AL)- fed controls. Another finding was that the fluidity of the mitochondrial membrane from DR rats deteriorated less than in their AL-fed counterparts. The increase in membrane rigidity is a phenomenon observed during senescence. There is substantial evidence that this was due to alterations of membrane lipid structure owing to lipid peroxidation (11). Results obtained in an earlier study suggest that DR may lead to the modification of fatty acid composition localized in the phospholipid layer of the mitochondrial and microsomal membranes by increasing linoleic acid and decreasing docosapentanoic acid contents in both membranes (12). Interestingly, the improvement in membrane fluidity was also observed in animals subjected to chronic exercise training. The most effective anti-aging action was observed when caloric restriction was combined with exercise training (13). Moreover, in the exercised and dietary-restricted animals the antioxidant defense was enhanced, as it was reflected by the highest activities of catalase and glutathione peroxidase, and higher levels of cytosolic ascorbate and glutathione (GSH).

It should be stressed that DR was found to maintain high levels of physical activity over the life span. Such a conclusion was drawn from the experiment with rodents in which rats having free access to running wheels and receiving daily 40% less calories lived longer and were capable of sustaining high running activity even after all AL-fed sedentary or exercised animals had succumbed (14). These findings have been supported by results obtained by Radak et al. (15) who reported that even the late onset of DR can reverse age-related alterations of protein metabolism. It appeared that DR had beneficial effects on the locomotive functions in rodents, mainly due to the increased proteasome activi-

ty. This was reflected by a marked reduction of the age-associated accumulation of potentially detrimental oxidatively modified proteins in the tendon.

The theory suggesting enhancement of protein turnover and renewal during aging following lifelong or late onset of DR, which may contribute to the extension of life span in dietary restricted animals, was also supported by Goto el al. (16) and Spindler (17). In the latter investigation DR was also found to enhance the enzymatic capacity for gluconeogenesis (17) initiated from carbon required for glucose synthesis which is provided from peripheral protein turnover.

Limiting protein intake in rodents has been shown to have the same effect as caloric restriction, i.e. the extension of life span. The accumulation of oxidatively modified proteins, which is known to increase during aging, was found to be substantially decreased in animals fed diets restricted in either protein or calories (18). This was reflected by significantly lower level of protein carbonyls in animals fed a low-protein diet as compared to rats consuming normal food containing 20% casein. Moreover, in rats exposed to γ-irradiation a greater increase in protein carbonyls was observed in animals fed high-protein as compared to low-protein diets. Increasing the dietary content of easily peroxidized amino acids might also contribute to free radical damage, thus leading to a decline in life expectancy. In agreement, when 1% of either histidine or lysine is added to a semisynthetic diet containing 20% of casein as the sole source of protein, average life expectancy was decreased. Conversely, replacing casein by a soybean protein containing a lesser amount of easily oxidized amino acids increased life expectancy by about 13% (19).

Another important observation was that calorie or protein restriction may reduce the occurrence of cancer in rodent models (20, 21, 22), which might reflect the fact of fewer DNA mutations induced by oxidants in DR animals. DR has also been shown to strengthen DNA repair (23), although few studies have focused specifically on repair of oxidative lesions (24). Most interesting are the results of a recent study which evidenced that calorie restriction, even if started late in life, suppressed tumorigenesis in p53-deficient mice prone to spontaneous neoplasms (sarcoma and lymphoma) (25).

Dietary restriction improves insulin sensitivity

The widely documented physiological effect of DR is an increase in insulin sensitivity as reflected by reduced blood glucose and insulin levels (26). It has recently been postulated that increased insulin levels (hyperinsulinemia), being secondary to insulin resistance, could accelerate aging through its effects on antioxidant enzymes and free radical generation processes (27). An underlying molecular mechanism could be that significantly lower plasma levels of insulin and triiodothyronine following calorie-restricted feeding alter (at the level of transcriptional control exerted by these hormones) activity of desaturase enzymes that are important in the control of membrane lipid unsaturation. Lower double bond content would result in higher resistance of mitochondrial membranes to peroxidative damage (5).

One of the consequences of DR is a reduction in body fat stores. The fat cells play an important role in metabolic regulation of glucose metabolism, as they release free fatty acids (FFAs) that reduce both glucose uptake in muscle and insulin secretion from the pancreas (28). They are also involved in production of “adipokines” (leptin, adiponectin and tumor necrosis factor TNFα) implicated in the regulation of ener-

gy expenditure, food intake and insulin sensitivity (28). Numerous studies have evidenced that body weight loss may increase insulin sensitivity and glucose disposal (29). A long-term maintenance of stable normal adult body weight prevented the development of impaired glucose tolerance, hyperglycemia and type-2 diabetes mellitus (NIDDM) in older-aged rhezus monkeys (30). These results support previous findings from studies with rodents which evidenced the anti-aging action of DR (28).

Especially interesting are the results of a study on the effect of DR on pinealectomy-induced insulin resistance in rats (31). It was shown that lack of melatonin after pinealectomy increased insulin resistance and decreased expression of GLUT4 gene. Calorie restriction led to the improvement in insulin sensitivity, mainly due to enhanced GLUT4 gene expression and insulin-induced GLUT4 translocation, towards the plasma membrane in white adipose tissue.

Dietary restriction enhances brain function

One of the most interesting recent findings on caloric restriction is that not only it can increase maximum life span in many species, but it has also been shown to retard brain aging (32). There is sufficient evidence that the life-extending effect of DR in rodents is associated with up-regulation of brain-derived neurotrophic factor (BDNF) in the brain, which may increase the resistance of neurons to aging (33). Moreover, BDNF signaling in the brain can increase sensitivity to insulin in peripheral tissues (34) suggesting its role in the regulation of glucose metabolism and body weight (35). It was documented that BDNF acts directly on the brain to regulate glucose metabolism, which results in enhancement of insulin action in peripheral tissues (36). These findings imply that BDNF is a major regulator of energy metabolism. It was also demonstrated that administration of BDNF increases insulin content as compared to the pretreatment levels and restores granulated β-cells in diabetic (*db/db*) mice pancreatic islets. This anti-diabetic effect, observed also after intracerebroventricular BDNF administration, was not due to alterations in appetite.

Of great importance is the investigation displaying profound effects of DR on brain vulnerability to injury and disease (37). This was evidenced by a substantial reduction of seizure-induced damage to hippocampal neurons in rats maintained on calorie restricted diet. Moreover, DR appeared to exert protective effects on neurons against degeneration in animal models of Alzheimer's, Parkinson's and Huntington's diseases (38) and stroke.

Dietary restriction - human studies

A vast majority of research on the effects of DR on ageing was performed with the use of animal models, mainly rodents, and more recently in non-human primates (39, 40). As these studies are still in progress, final conclusions on whether chronic DR may increase maximal life span cannot be drawn. However, the median lifespan of restricted rhezus monkeys has been demonstrated to exceed that of their AL-fed controls (41). Factors implicated in extension of life span are similar to those found in rodents, i.e. reduced body fat, lower fasting glucose, insulin, serum triglycerides and cholesterol. The application of DR to human population would certainly pose many ethical and physical concerns which may discourage researchers and participants from making decision of using it with the aim of retarding aging.

Of great importance addressing the ethical and physical concerns of this area are results of the "Biosphere 2" experiment aimed at the evaluation of changes in physiological, hematological, hormonal and

biochemical parameters in humans subjected to severe, selective calorie restriction for two years (42, 43, 44). Biosphere 2 was a closed ecological "miniworld" enclosure near Tuscon in Arizona containing 7 biomes (rain forest, Savannah, ocean, desert, agricultural station and habitat for humans and domestic animals), which were intended to provide sufficient food supply for humans sealed inside. Eight healthy subjects (4 men and 4 women) lived therein for 2 years while being totally isolated from the external world, as all organic material, all water and nearly all air had to be recycled, and all food was grown inside. Their diet (1750-2100 kcal/d, approximately 11-12 % energy from protein, 9-11% from fat and ~77-80% from complex carbohydrates) was rich in vitamins, minerals and trace elements. All the physiological and hematological parameters studied after 2 years of calorie restricted diet were very close to those found in similar experiments with rodents or monkeys (43). Despite a marked weight loss, especially during the first 6 months, all biospherans remained in excellent physical and mental health throughout the entire 2-year period.

Whether the prolonged period of energy restriction would extend longevity in humans remains yet a point to be elucidated. It may seem justified to quote Harman, that "Caloric restriction can almost certainly increase the maximum life span of humans. However, the increase associated with a tolerable level of restriction would undoubtedly be small. The goal for humans is to significantly increase healthy life span while living a normal life. Efforts to achieve this goal should also include some acceptable degree of caloric restriction" (7).

Insulin resistance during aging – the effect of exercise

Exercise is considered a very important component of healthy living in advanced old age. Aging is known to be associated with an increase in body weight and fat mass, both in the abdominal as in visceral regions (45). It has been documented that exercise training is beneficial in protecting individuals from a number of chronic age-related diseases, including non insulin-dependent diabetes mellitus (NIDDM). Regular aerobic exercise has been found to increase lean body mass (LBM) (46), enhance insulin sensitivity, and improve glucose metabolism (29, 47, 48) in elderly subjects. With this been known, lifestyle interventions such as dietary modification and physical activity may present the best options sufficient to preserve better health status during aging by delaying the onset of insulin resistance. This was confirmed by results of a study in which the euglycemic clamp technique was applied to measure the glucose infusion rate (GIR) per LBM, which provides a quantitative estimate of insulin action, in sedentary young and old subjects as well as in young and aged athletes (49). A significant decrease in GIR/LBM was reported in older controls as compared with younger trained individuals and young controls. The lowest GIR/LBM, indicative of a severe impairment of glucose tolerance, was found in the bedridden subjects. These results suggest that insulin sensitivity decreases with the aging process and may be further affected by physical inactivity, whereas physical training may improve insulin responsiveness in aged individuals up to the levels similar to those of young athletes. It is also evident that physical activity in young people may improve insulin sensitivity (49). Similar results have been recently presented by Ryan et al. (29) who also found that regular physical activity had beneficial effect on β-cells sensitivity to glucose and the peripheral tissue sensitivity to insulin throughout the large age span (18 to 69 yr) in female subjects. The exact mechanism

implicated in this improvement is still not fully understood. However, human studies have evidenced an increase in GLUT 4 protein expression in muscle cells and GLUT 4 protein translocation towards the plasma membrane. Despite only a limited number of studies performed in humans, it seems probable that exercise training can modulate insulin sensitivity in skeletal muscle by enhancing the dynamic processes of protein phosphorylation and activation of the insulin/phosphoinositol 3-kinase (PI3K) signaling pathway (50).

Insulin resistance and the resulting hyperglycemia is a known cause of increased generation of free radicals (51). It appears that many reactions associated with hyperglycemia, such as glucose autooxidation, protein glycation and formation of advanced glycation end products (AGEs), may acutely and chronically increase the production of reactive oxygen species (ROS), resulting in an oxidant/antioxidant imbalance. It has recently been found that enhanced mitochondrial formation of ROS in pancreatic β-cells exposed to elevated glucose levels resulted in suppression of the first phase of the glucose-induced insulin secretion (52). Excessive glucose was also found to alter signal transduction pathways through the activation of protein kinase C (PKC) and increased diacylglycerol levels (DAG), which is implicated in the diabetic vascular and neurological complications (53). Of further importance is the suggestion that all three pathways of hyperglycemic damage (mitochondrial superoxide overproduction, AGEs formation, PKC activation) may be blocked by inhibitors of mitochondrial electron transfer chain (ETC), the uncouplers of oxidative phosphorylation or Mn-SOD (54), which may imply that enhanced superoxide production by the ETC presents a causal link between elevated glucose and all pathways responsible for hyperglycemia-induced damage.

In all tissues with diabetic complications where glucose uptake is independent of insulin (retina, lens, kidney, peripheral nerves), exposure to elevated glucose levels causes an increase in intracellular sorbitol and fructose levels due to increased activity of aldose reductase (AR) and sorbitol dehydrogenase (SDH), which not only increases cellular levels of sorbitol and fructose but also decreases the ratio of NADPH to $NADP^+$ and increases in cytosolic $NADH/NAD^+$ ratio. The depletion in NADPH cell stores by AR may inhibit other NADPH-requiring enzymes, e.g. glutathione reductase, which may result in a drop of reduced glutathione (GSH) levels, thus increasing the susceptibility of endothelial cells to damage by H_2O_2 (55). Moreover, it was evidenced that acute elevations in glucose levels may depress natural antioxidant defences, e.g. incubation of purified bovine Cu-ZnSOD with different glucose concentrations (10-100 mmol/l) reduced the enzyme activity by approximately 60%- this may lead to reduced protection against the damaging effects of superoxide radicals (56).

Increased oxidative stress in aged NIDDM patients was evidenced by measuring their plasma total antioxidant potential that was significantly lower, and lipohydroperoxide content of low-density lipoproteins that was higher in diabetics as compared to the age-matched healthy controls (57). It can, therefore, be presumed that the loss of antioxidant capacity may substantially contribute to accelerated aging processes as it is observed in diabetic patients.

Interestingly, an analysis of age-related trends in insulin resistance in a large sample of healthy elderly subjects, whose age ranged from 28 to more than 100 years, revealed that over the age of 50 up to 80-85 there was an increase in insulin resistance (IR). Interestingly, beyond 85-90 years

of age, there was a marked improvement in insulin sensitivity. An additional significant conclusion that can be drawn from this study is that very old individuals are free from diabetic complications and that the selection for longevity starts at approximately 85 years of age (58).

Exercise up-regulates antioxidant defenses

Regular physical activity is recommended for its associated beneficial effects on health in both young and old individuals. This recommendation is of particular importance in elderly individuals, whose sedentary lifestyle and frequently observed obesity make them vulnerable to chronic diseases including cardiovascular disease, hypertension, NIDDM, as well as to functional and cognitive decline. It should be stressed, however, that unaccustomed and strenuous exercise may be associated with muscle damage and inflammation which gives rise to excess free-radical formation, thus deepening the imbalance between free radical production and the body's antioxidant defense systems. The extent of this imbalance determines the degree of oxidative stress normally associated with enhanced exercise-induced utilization of oxygen. On the other hand, regular aerobic exercise may up-regulate antioxidant defense systems in skeletal muscles, blood, and, to a lesser extent, in cardiac and liver tissues. Cellular response to oxidative stress and the proliferative capacity of many different cell types have been recently found to decline with aging (59). Therefore, a consideration must be given to issues aimed at the activation of the host defense mechanisms in response to oxidative stress. It appears that the best mechanism for activating such responses is the stress itself (3). This implies that a sublethal or conditioning stress can lead to enhanced survival and reduced tissue damage following a subsequent, more severe stress. This concept, called "hormesis" refers to the often observed phenomenon of a beneficial biological action from a factor or agent that is generally viewed as detrimental (60). In humans, a conditioning stress such as regular exercise is believed to elicit many anti-aging benefits (3). Obviously, subjection of the athlete to repeated bouts of exercise repeatedly results in acute stress. It is therefore possible that some of benefits of regular exercise are derived through such a stress-tolerance mechanism (3). However, animal studies revealed that aged skeletal muscle has a limited capacity to further increase its antioxidant potential (61).

In one of the most recent studies with the participation of healthy elderly humans, no effect was found of a 12-weeks' training on oxidative stress, measured as the ratio of free radical reaction products of antipyrine (para-, meta-, and ortho-hydroxyantipyrine) to plasma antipyrine after 45 min cycling at 50% W_{max} (62). These authors conclude that despite the evident improvement in functional capacity of the elderly following training, the participants did not cope better with the exercise-induced oxidative stress that did the controls, although their antioxidant defense mechanisms were not compromised.

Exercise enhances and protects brain function

Exercise is an universal activity capable of inducing change throughout the body. Recently, several exciting findings have extended this concept to include the brain as an organ that directly benefits from exercise (63). Changes in gene expression in the hippocampus, a brain region critical for learning and memory, suggest that physical activity initiates modifications in molecular mechanisms supporting the health and enhancing the plasticity of the brain. These findings are derived mainly from

recent experiments performed by Cotman's group from the Institute for Brain Aging and Dementia of the University of California (Irvine), which are also supported by results reported by other authors (64).

An animal model of a voluntary wheel running was chosen as it closely mimics what humans have when exercising because animals choose the time, speed, and distance of running throughout the experiment. The brain region showing the earliest and most sustained neurotrophic up-regulation was the hippocampus. The hippocampus is also known as a target for early neurodeterioration in neurodegenerative diseases like Alzheimer's disease (AD). After 2-7 nights of voluntary running, a 20% increase in BDNF mRNA as well as significant rise in BDNF protein, as compared to sedentary animals, were found in rat hippocampus (63). However, the increase in BDNF mRNA level was observed only when running distance exceeded a threshold level of approximately 500 m per day. It should be stressed that some rats could voluntarily run a distance of 20 km in one night. Similar results were obtained by Gomez-Pinilla et al. (64).

Maintenance of cerebral BDNF is important for effective neural function and longevity (63). BDNF is a member of neurotrophic family that supports the proper functioning of glutamatergic neurons connecting cognitive, sensory and motor brain regions. It exerts its neuroprotective role by promoting survival of hippocampal, striatal, and septal neurons in culture and *in vivo* as well as by protecting the brain against insults such as ischemia. Hippocampal BDNF mRNA expression was strongly influenced by physical activity, as significant increases in BDNF transcripts levels were already found after 6 h of voluntary running (65). Interestingly, when rats capable of running spontaneously up to 20 km/night were abruptly deprived of habitual running, a marked decrease lasting up to 10 days was observed in expression of mRNA encoding for BDNF and for its high affinity receptor TrkB in certain hippocampal areas (66). These observations verify that both spontaneous running and its sudden termination give rise to area-specific and trophic factor-specific changes in hippocampus.

More recently, a similar study has pointed to the possibility of application of exercise in an early rehabilitation after brain injury (67). The underlying rationale is that motor enrichment may prime the brain to respond more adaptively to brain injury by up-regulating trophic factors such as BDNF, glial cell line-derived neurotrophic factor (GDNF) and fibroblast growth factor (FGF)-2. A sedentary lifestyle before brain injury may result in a decrease of levels of trophic factors below the baseline, leaving the brain more vulnerable to degeneration. It also seems possible that in the chronic stages after brain injury that the application of exercise would reactivate mechanisms of brain plasticity, thus making rehabilitation more effective.

The finding that exercise may cause an up-regulation of BDNF has potential significance in preventing or treating clinical depression (68), as depression is commonly observed in the elderly population. Antidepressant drugs are known to increase BDNF mRNA levels in animals, and BDNF itself is recognized for its antidepressant action (68). Interestingly, a decrease in BDNF after an abrupt deprivation of animals of their free access to running wheel correlates with depression often reported by athletes whose training has been suddenly interrupted following an injury. A decline in BDNF mRNA levels in the hippocampus was also found after exposure of animals to severe stress. It was found that the combined action of an antidepressant such as tranylcypromine, combi-

ned with exercise, led to significantly greater increases in hippocampal BDNF mRNA levels than did either treatment alone (63). The impact of exercise on reducing brain stress responses presents an exciting area for future studies.

Suggestions derived from the growing body of evidence of the exercise-induced up-regulation of BDNF imply that physical activity in humans may efficiently increase the brain's resistance to damage and age-related neurodegenerative diseases. Extensive research on humans provides convincing arguments that physical activity, particularly if maintained through later life, could be beneficial for preserving good overall health and cognitive function (69).

The aforementioned argument that exercise can mediate brain function is supported by research from trials with people aged 60-75 years in which two groups of elderly subjects underwent either aerobic (walking) or anaerobic exercise (stretching) (70). The aerobic group showed marked improvements in neuropsychological measures and the enhanced physical fitness, while the effect was lacking in anaerobic exercisers. In another study, a comparison of clinical evaluations of cognitive function, spaced by 5 years, of 4,615 adults aged 65 years and older, revealed that high levels of physical activity corresponded with decreased incidence of cognitive impairments. These results were particularly significant in women (71). A similar study examining questionnaire data from 193 participants with Alzheimer's disease (AD) and 358 healthy controls revealed that the individuals with no cognitive impairments were more active (in terms of activity, diversity and percentage intensity) during their midlife than the group with AD (72). However, the relationship between oxidative stress and physical activity in advanced age is still poorly understood, there is also a substantial lack of data regarding the effects of acute exercise and training in elderly subjects. There is no doubt that involvement in regular exercise can result in a significant improvement of the quality of life in elderly populations. Moreover, it appeared to be a useful tool in preventing falls and fall-related fractures, which are the major source of death and injury in older people (73). It should be stressed, however, that the quality and quantity of exercise necessary to elicit substantial health benefits differ from those needed to result in significant gains in fitness (74). Finally, the fact should be emphasized that aging is certainly a highly complex process, and factors that are crucial for the aging of one individual may be different from those most important to another (75). Therefore, individual counseling strategies, including prescription of the adequate daily exercise regimen for older adults, have to be adopted with the aim of attaining the optimum response, such as overall physical and mental health. Physical activity programs addressed to the older adult community should preferably be integrated into daily lives rather than be implemented at the independent individual basis. The effectiveness of such an approach has been confirmed by results of a recent study (76) that provided evidence supporting the hypothesis that the group-mediated counseling program led to much higher adherence of older adults to moderate physical activity, which was in contrast to the low frequency of participation in a traditional exercise program.

Conclusion

Regular physical activity and restriction of dietary food intake without essential nutrient, vitamin and mineral deficiency presents important components of the modifiable lifestyle habits. Physical activity and DR have a potent impact on slowing aging processes through the improvement

of general health and functional capacities, up-regulation of antioxidant defenses as well as the reduction of age-related risks of cognitive impairment in elderly persons.

Acknowledgement

This work was supported by grant PBZ-KBN/22/P05/99 from the State Committee for Scientific Research (Warsaw, Poland).

References

1. Oettel M, Hübler D, Patchev V. Selected aspects of endocrine pharmacology of the aging male. *Exp Gerontol* 2003; 38: 189-98.
2. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative disease of aging. *Proc Natl Acad Sci USA* 1993; 90: 7915-22.
3. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature* 2000; 408: 239-47.
4. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. *Science* 1996; 273: 59-63.
5. Merry BJ. Molecular mechanisms linking calorie restriction and longevity. *Int J Biochem Cell Biol* 2002; 34: 1340-54.
6. Lee CK, Klopp RG, Weindruch R, Prolla TA. Gene expression profile of aging and its retardation by caloric restriction. *Science* 1999; 285: 1390-3.
7. Harman D. Aging: Overview. *Ann NY Acad Sci* 2001; 928: 1-21.
8. Yu BP. Aging and oxidative stress: modulation by dietary restriction. *Free Radic Biol Med* 1996; 21: 651-68.
9. Masoro EJ. Caloric restriction and aging: an update. *Exp Gerontol* 2000; 35: 299-305.
10. Chen JJ, Yu BP. Detoxification of reactive aldehydes in mitochondria: effects of age and dietary restriction. *Aging (Milano)* 1996; 8: 334-40.
11. Choe M, Jackson C, Yu BP. Lipid peroxidation contributes to age-related membrane rigidity. *Free Radic Biol Med* 1997; 18: 977-84.
12. Laganiere S, Yu BP. Anti-lipoperoxidation action of food restriction. *Biochem Biophys Res Commun* 1987; 145: 1185-91.
13. Kim JD, McCarter RJ, Yu BP. Influence of age, exercise, and dietary restriction on oxidative stress in rats. *Aging (Milano)* 1996; 8: 123-9.
14. McCarter RJ, Shimokawa I, Ikeno Y et al. Physical activity as a factor in the action of dietary restriction on aging: effects in Fischer 344 rats. *Aging (Milano)* 1997; 9: 73-9.
15. Radak Z, Takahashi R, Kumiyama A et al. Effect of aging and late onset dietary restriction on antioxidant enzymes and proteasome activities, and protein carbonylation of rat skeletal muscle and tendon. *Exp Gerontol* 2002; 37: 1423-30.
16. Goto S, Takahashi R, Artaki S, Nakamoto H. Dietary restriction initiated in late adulthood can reverse age-related alterations of protein and protein metabolism. *Ann NY Acad Sci* 2002; 959: 50-6.
17. Spindler SR. Calorie restriction enhances the expression of key metabolic enzymes associated with protein renewal during aging. *Ann NY Acad Sci* 2001; 928: 296-304.
18. Youngman LD, Park JY, Ames BN. Protein oxidation associated with aging is reduced by dietary restriction of proteins or calories. *Proc Natl Acad Sci USA* 1992; 89: 9112-6.
19. Berlett BS, Stadtman ER. Protein oxidation in aging, disease, and oxidative stress. *J Biol Chem* 1997; 272: 20313-6.
20. Lok E, Scott FW, Mongeau R et al. Calorie restriction and cellular proliferation in various tissues of the female Swiss Webster mouse. *Cancer Lett* 1990; 51: 67-73.
21. Thompson HJ, Zhu Z, Jiang W. Dietary energy restriction in breast cancer prevention. *J Mammary Gland Biol Neoplasia* 2003; 8: 133-42.
22. Lu S, Chen GL, Ren C et al. Methionine restriction selectively targets thymidylate synthase in prostate cancer cells. *Biochem Pharmacol* 2003; 66: 791-800.
23. Haley-Zitlin V, Richardson A. Effect of dietary restriction on DNA repair and DNA damage. *Mutat Res* 1993; 295: 237-45.
24. Beckman KB, Ames BN. The free radical theory of aging matures. *Physiol Rev* 1998; 78: 547-81.
25. Berrigan D, Perkins SN, Haines DC, Hursting SD. Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice. *Carcinogenesis* 2002; 23: 817-22.
26. Picarel-Blanchot F, Alvarez C, Bailbe D et al. Changes in insulin action and insulin secretion in the rat after restriction early in life: influence of food restriction versus low-protein food-restriction. *Metabolism* 1995; 44: 1519-29.
27. Fancchini FS, Hua NW, Reaven GM, Stoohs RA. Hyperinsulinemia: the missing link among oxidative stress and age-related diseases. *Free Radic Biol Med* 2000; 29: 1302-6.
28. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. *Nature* 2001; 414: 799-806.
29. Ryan AS, Muller DC, Elahi D. Sequential hyperglycemic-euglycemic clamp to assess beta-cell and peripheral tissue: studies in female athletes. *J Appl Physiol* 2001; 91: 872-81.

30. Hansen BC, Bodkin NL. Primary prevention of diabetes mellitus by prevention of obesity in monkeys. *Diabetes* 1993; 42: 1809-4.
31. Zanquetta MM, Seraphim PM, Sumida DH et al. Calorie restriction reduces pinealectomy-induced insulin resistance by improving GLUT4 gene expression and its translocation to the plasma membrane. *J Pineal Res* 2003; 35: 141-8.
32. Weindruch R. Caloric restriction: life span extension and retardation of brain aging. *Clin Neurosci Res* 2003; 2: 2279-84.
33. Mattson MP. Brain evolution and lifespan regulation: conservation of signal transduction pathways that regulate energy metabolism. *Mech Ageing Dev* 2002; 123: 947-53.
34. Mattson MP, Duan W, Maswood N. How does brain control lifespan? *Ageing Res Rev* 2002; 1: 155-65.
35. Duan W, Guo Z, Jiang H et al. Reversal of behavioral abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. *Endocrinol* 2003; 144: 1446-53.
36. Nakagawa T, Tauchida A, Itakura Y et al. Brain –derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. *Diabetes* 2000; 49: 436-44.
37. Duan W, Lee J, Guo Z, Mattson MP. Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. *J Mol Neurosci* 2001; 16: 1-12.
38. Duan W, Guo Z, Jiang H et al. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. *Proc Natl Acad Sci USA* 2003; 100: 2911-6.
39. Roth GS, Ingram DK, Lane MA. Calorie restriction in primates: will it work and how will we know? *J Am Geriatr Soc* 1999; 47: 896-903.
40. Hansen BC, Bodkin NL, Ortmeyer HK. Calorie restriction in nonhuman primates: mechanisms of reduced morbidity and mortality. *Toxicol Sci* 1999; 52: S56-S60.
41. Lane MA, Black A, Handy A et al. Caloric restriction in primates. *Ann NY Acad Sci* 2001; 928: 287-95.
42. Walford RL, Mock D, MacCallum T, Laseter JL. Physiologic changes in humans subjected to severe, selective calorie restriction for two years in biosphere 2: health, aging, and toxicological perspectives. *Toxicol Sci* 1999; 52: 61-5.
43. Walford RL, Mock D, Verdery R, MacCallum T. Calorie restriction in biosphere 2: alterations in physiologic, hematologic, hormonal, and biochemical parameters in humans restricted for a 2-year period. *J Gerontol A Biol Sci Med Sci* 2002; 57: B211-B24.
44. Weyer C, Walford RL, Harper IT et al. Energy metabolism after 2 y of energy restriction: the biosphere 2 experiment. *Am J Clin Nutr* 2000; 72: 946-53.
45. Schwartz RS, Shuman WP, Bradbury VL et al. Body fat distribution in healthy young and older men. *J Gerontol* 1990; 45: M181-M5.
46. Schwartz RS, Shuman WP, Larson V et al. The effect of intensive exercise training on body fat distribution in young and older men. *Metabolism* 1991; 40: 545-51.
47. Ryan AS. Insulin resistance with aging. Effects of diet and exercise. *Sports Med* 2000; 30: 327-46.
48. Andersson B, Xu X, Rebuffe-Scrive M et al. The effects of exercise training on body composition and metabolism in men and women. *Int J Obes* 1991; 15: 75-81.
49. Sato Y, Oshida Y, Ohsawa I et al. The role of glucose transport in the regulation of glucose utilization by muscle. In: Maughan RJ, Shirreffs SM, eds. *Biochemistry of Exercise IX.* Human Kinetics Publishing Inc., 1996: 37-50.
50. Kirwan JP, Jing M. Modulation of insulin signaling in human skeletal muscle in response to exercise. *Exerc Sport Sci Rev* 2002; 30: 85-90.
51. Ceriello A. Oxidative stress and glycemic regulation. *Metabolism* 2000; 49: 27-9.
52. Sakai K, Matsumoto K, Nishikawa T et al. Mitochondrial reactive oxygen species reduces insulin secretion by pancreatic beta-cells. *Biochem Biophys Res Commun* 2003; 300: 216-22.
53. Koya D, King GL. Protein kinase C activation and the development of diabetic complications. *Diabetes* 1998; 47: 859-66.
54. Nishikawa T, Edelstein D, Du XL et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000; 404: 787-90.
55. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care* 1996; 19: 257-67.
56. Oda A, Bannai C, Yamaoka T et al. Inactivation of Cu, Zn-superoxide dismutase by in vitro glycosylation and in erythrocytes of diabetic subjects. *Horm Metab Res* 1994; 26: 1-4.
57. Aguirre F, Martin I, Grisnpon D et al. Oxidative damage, plasma antioxidant capacity, and glucemic control in elderly NIDDM patients. *Free Radic Biol Med* 1998; 24: 580-5.
58. Barbieri M, Rizzo MR, Manzella D et al. Glucose regulation and oxidative stress in healthy centenarians. *Exp Gerontol* 2003; 38: 137-43.
59. Holbrook NJ, Ikeyama S. Age-related decline in cellular response to oxidative stress: links to growth factor signaling pathways with common defects. *Biochem Pharmacol* 2002; 64: 999-1005.

60. Masoro EJ. Hormesis and the antiaging action of dietary restriction. *Exp Gerontol* 1998; 33: 61-6.
61. Leewenburgh C, Fiebig R, Handwaney R, Ji LL. Aging and exercise training in skeletal muscle: responses of glutathione and antioxidant enzyme systems. *Am J Physiol* 1994; 267: R439-R45.
62. Meijer EP, Coolen SAJ, Bast A, Westerterp KR. Exercise training and oxidative stress in the elderly as measured by antipyrine hydroxylation products. *Free Rad Res* 2001; 35: 435-43.
63. Cotman CW, Engesser-Cesar Ch. Exercise enhances and protects brain function. *Exerc Sport Sci Rev* 2002; 30: 75-59.
64. Gomez-Pinilla F, Ying Z, Roy RR et al. Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *J Neurophysiol* 2002; 88: 2187-95.
65. Oliff HS, Berchtold NC, Iackson P, Cotman CW. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. *Brain Res Mol Brain Res* 1998; 61: 147-53.
66. Widenfalk J, Olson L, Thoren P. Deprived of habitual running, rats downregulate BDNF and TrkB messages in the brain. *Neurosci Res* 1999; 34: 125-32.
67. Kleim JA, Jones TA, Schallert T. Major enrichment and the induction of plasticity before or after brain injury. *Neurochem Res* 2003; 28: 1757-69.
68. Siuciak JA, Lewis DR, Woegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol Biochem Behav* 1997; 36: 131-7.
69. Cotman CW, Berchtold NC Exercise; a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 2002; 25: 295-301.
70. KramerAF, Hahn S, Cohen NJ et al. Ageing, fitness and neurocognitive function. *Nature* 1999; 400: 418-9.
71. Laurin D, Verreault R, Lindsay J et al. Physical activity and risk of cognitive impaiment and dementia in elderly persons. *Arch Neurol* 2001; 58: 498-504.
72. Friedland RP, Fritsch T, Smyth K et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc Natl Acad Sci USA* 2001; 98: 3440-5.
73. Carter ND, Kannus P, Khan KM. Exercise in the prevention of falls in older people. A systematic literature review examining the rationale and the evidence. *Sports Med* 2001; 31: 427-38.
74. Mazzeo RS, Tanaka H. Exercise prescription for the elderly. *Sports Med* 2001; 31: 809-18.
75. Stadtman ER. Importance of individuality in oxidative stress and aging. *Free Radic Biol Med* 2002; 33: 597-604.
76. Rejeski WC, Focht BC. Aging and physical disability: On integrating group and individual counseling with the promotion of physical activity. *Exerc Sport Sci Rev* 2002; 30: 166-70.

Received: November 26, 2004
Accepted: February 09, 2004

Address for correspondence:
Barbara Kłapcińska
Department of Physiological and Medical Sciences, Biochemistry Unit
Academy of Physical Education
Ul.Mikołowska 72A
40-065 Katowice, Poland
e-mail: barbara@awf.katowice.pl