CHAPTER I

INTRODUCTION

I. STATEMENT AND SIGNIFICANCE

At the present day, the aging populations are increased more than the former time and they will be more increase in the future. In 2001, the population of aging in Thailand was 9.29 % and was projected to increase to 10% in 2005 and to 12% in 2030 (1). Similarly the aging population in Chiang Mai province has increased from 8.43% in 1991, to 12.9% in 2000 which may reach 13.8% in 2005 (2).

Many theories of aging have been proposed. In 1956, Denham Harman who proposed the free radical theory of aging which suggested that normal aging process results from progressive defect in protection against free radicals reaction (3,4). Free radical is any molecules or atoms with unpaired electron causing the species to be highly reactive (3,5,6). Free radicals are constantly formed in a human body mostly in the mitochondria where oxygen was reduced to yield energy and water (4). The electron becomes unpaired leading to production of highly reactive species (ROS) such as superoxide radical ($O^{\bullet}_2$), peroxy radicals ($LOO^{\bullet}$), hydroxyl radical ($OH^{\bullet}$), etc. (7). There are many mechanisms by which free radicals cause aging i.e. DNA cross-linking, membrane lipid peroxidation and oxidation of proteins and carbohydrate (3,7). The activities of free radicals in many age-related diseases have long been of interest. The deleterious health outcomes are associated with the accumulation of large amounts of lipid peroxidation. For example, The oxidative damage causing tissue injury in chronic inflammatory or some kind of cancers and the oxidation of low-density lipoprotein cause atherosclerosis (7). However,

living organisms have developed complex antioxidant systems to control the production of the free radical and to reduce the damage. These systems are superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). Diet is another source of antioxidant, such as tocopherol, ascorbate, carotenoid, vitamin A and some metals, e.g. selenium (Se) for the function of antioxidant enzyme (5,9). Vitamin E has a peroxyl and hydroxyl radicals scavenger. It is the most widely distributed antioxidant in the body, which is highly effective in protecting against membrane lipid peroxidation (4,6,8-10).

Recently, dietary supplementation of antioxidants has received more attention and the topic of free radicals and antioxidants including relationship between exercise and antioxidant in aging is a research focus.

The increase of oxygen consumption in physical exercise can increase the flow of electron through the mitochondrial electron transport system, which also increases the free radicals production (8,10,11). Kantet, M.M., et al. (12) reported that exercise in various groups of trained and untrained human subjects can increase lipid peroxidation. However, not all studies have demonstrated the evidence of oxidative stress after exercise. Many studies have reported a significant increase in the activity of antioxidant enzyme in animal (13-15). In human, Kretzschma, M.M., et al.(16) reported that basal plasma glutathione level was higher in trained than in untrained subjects. Brites, F.D., et al.(17) found that regular exercise in human can improve plasma antioxidant status in comparison to sedentary control.

Many studies in human showed that the ingestion of vitamin E (200-800 IU per day) could reduce lipid peroxidation level after exercise (18-21). In contrast, Meydani, S.N., et al.(22) reported that vitamin E supplementation had no significant effects on plasma concentration of glutathaione peroxidase, superoxide dismutase or other antioxidant vitamins and minerals. Cannon, I.G., et al. (23) also

found that vitamin E supplementation increased plasma creatine kinase (CK) and superoxide in human after exercise.

The information about the effects of exercise and vitamin E supplementation on lipid peroxidation in elderly man is limited and still controversial. Moreover, there is no study in Thai elderly men that compare the effect of regular exercise and exercise plus vitamin E supplementation. Thus, this study was performed to investigate the effects of a) exercise training and b) exercise training plus vitamin E supplementation on total serum antioxidant capacity, lipid peroxidation and lipid profile levels in elderly men.

The objectives of this study are as follow.

1. To study the effects of exercise training on total antioxidant capacity, lipid peroxidation and lipid profile in Thai elderly men.
2. To study the effects of exercise training with vitamin E supplement on total antioxidant capacity, lipid peroxidation and lipid profile in Thai elderly men.
3. To compare the effects of exercise training and exercise training with vitamin E supplement on total antioxidant capacity, lipid peroxidation and lipid profile in Thai elderly men.

II. LITERATURE REVIEW

1. Aging Physiology

Aging is a process associated with changes in physical characteristics and with the decline of many physiologic functions. Many of changes that accompany aging accordingly with physical inactivity due to bed rest or insufficient exercise, for example; changes in cardiovascular function, bone mass, body composition, body fat distribution and insulin sensitivity.

1.1 Aging – associated changes in endurance exercise capacity

The best physiologic measure of an individual's endurance work capacity is the amount of oxygen consumed at maximal exercise (maximal aerobic power or VO_2max) (24). Maximal oxygen uptake (VO_2max) declines steadily after age 20 to the level of 35 to 40% at age 65 (25). Reduction in VO_2max with aging is the result from the loss of muscle mass (26), the decreases in fat-free mass (27) and the alteration of cardiovascular and pulmonary function (28-29). Most cross-sectional studied have indicated that the heart rate decreases with age in both men and women. In aging, there is an increase in elastic and collagenous tissue in all path of the conduction system of the heart. Beginning at age 60 there is a decrease in the number of pacemaker cells in the sino-atrial node (SA node) (30). In addition, the reduction of maximum heart rate (HRmax) is a consequence of lowered stroke volume (31).

1.2 Aging – associated changes in muscle strength

Maximum muscle strength of men and women is generally achieved between the ages of 20 and 30 year (25). Other data from individuals beyond age 65 suggested that the loss of strength is further accelerated with aging (32). The muscle strength decreases with age because of a reduction in muscle mass. The smaller muscle mass in elderly reflects a loss of number of muscle fibers or total muscle protein induced by inactivity (24,25). Moreover, there is general agreement that the metabolic potential of muscle does not change with age. Larsson, L., et al. (33) found that the type II fiber atrophy might be responsible for the decline in strength performance during aging.

1.3 Aging – associated changes in body composition

The most common approach has been to consider the body as having two compartments, the fat and fat-free body masses (FFM) or lean body mass (LBM). The FFM includes all minerals, protein and water plus all other body constituents. After age 60, FFM is reduced despited increasing body fat, mostly due to a reduction in total muscle mass (34,35). Snead, D.B., et al. (36) using body density from underwater weighing to estimate changes in FFM showed that a decline from 2.0 to 4.1 kg per decade on a relative basis. These losses vary from a 4% to 6% loss of FFM per decade between age 45 and 78 years. The loss of fat free mass or skeletal muscle mass with advancing age may be the result of several factors including a decreased rate of protein synthesis, increased protein degradation, reduced intake of protein and/or energy, and/or a reduced in voluntary contractile activity (37,38).

1.4 Aging – associated changes in endocrine system

Endocrine functions, particularly in pituitary, pancreas, adrenal and thyroid glands are changed with age. The pituitary gland reduces the release of thyroid-stimulating hormone (thyrotropin), causing thyroid hypofunction. Thyroid dysfunction affects metabolic function, including decreased glucose metabolism and protein synthesis (25). In elderly, mean pulse amplitude, duration and fraction of secreted growth hormone (GH) gradually decrease. A circulating insulin like-growth factor (IGF-1) level stimulates tissue growth and interactions between the hypothalamus and anterior pituitary gland are decreased. A growing body of evidence indicates that muscle size and strength, body composition and bone mass alteration are directly relate to hormonal changes with aging (34).

1.5 Aging – associated changes in nervous system

The central nervous system function of aging is reduced. The nerve conduction velocity and the number of spinal cortex axon declined 10% and 37% , respectively. Such changes partially explain age-related decrements in neuromuscular performance (34). Partitioning reaction time into central progressing time and muscle contraction time indicates that aging exerts the greatest effect on stimulus detection and information processing to produce a response. For example, the knee jerk reflex does not require central nervous system processing, instead, it becomes less affected by aging than voluntary responses and movement patterns (25).

The summary alterations of physiologic parameters in aging are shown in table 1.

Table 1 Alteration of physiologic parameters in aging (39).

Physiologic parameters	
Decreased	Increased
Maximum oxygen consumption	Systolic blood pressure
Resting and maximum cardiac out put	Peripheral resistance
Stroke volume	Serum total cholesterol
Sense of balance	Urinary nitrogen and creatinine
Lean body mass	
Glucose tolerance test	
Sympathetic activity and neurotransmission	
Immune response	

2. Theory of aging

Aging is the condition of becoming old, some of changes in organism, membrane, cytoplasm and/or nucleus with the passage of time leading to functional impairment (39). There are changes within tissue associated with or responsible for increasing susceptibility to disease, DNA disturbances, and progressive break down in protein synthesis, crossing of macromolecules, autoimmune disorder and damage because of genetic and environmental factors involve free radical reaction (40). The nature of aging process has been subjected to many theories. The theories are proposed to explain aging and can be divided into two main groups: i) genetic theories and ii) damage-accumulation theories. The genetic theories proposed that aging is a process of development and differentiation, and is a sequence of events encoded into the genome. The damage-accumulation theories of aging have been proposed some progressive accumulation of damage because repair and

maintenance are less than those required for indefinite survival. One of the most interesting theory in damage-accumulation theories is the free radical theory. The free radical theory proposed that normal aging results from random deleterious effects of free radicals produced during normal aerobic metabolism (4). Free radicals cause the aging process in many ways e.g., induction of DNA cross-links lead to somatic mutation, the production of defective gene products and the generation of malignant changes (3). Increasing of lipid peroxide level and antioxidant defenses do not completely protect against ROS-mediated damage in aging process (3,6,41).

3. Aging and free radical

3.1 Free radical

The electronic structures are paired with an antiparallel spin, thermodynamically more stable, if electron are unpaired in this situation force electron transfers from other molecules or atoms to be restricted antiparallel spin and it causes situation in which one- electron transfer can produce an unpaired electron (6). A free radical is a molecule or molecular fragment containing an unpaired electron in its outer orbit and is generally very reactive (42,43). The conventional radical dot (•) designates the presence of one or more of the unpaired electron (6). Free radicals can be formed in three ways: (i) by the hemolytic fission, each atom receives one-electron from each of the pair shared when covalent bond breaks, (ii) by the loss of single electron from a non-radical, (iii) by the gain of a single electron by a non- radical (43). When a radical gives one electron to, or takes one electron from, that non- radical becomes a radical, they usually proceed as a chain reaction (44). In general, human cells are aerobic and consume molecular oxygen in energy producing process. It has been estimated that between 2 to 5% of

the total electron fluxes during normal metabolism "leaks off" to generate free radicals (9,45,46). Actually oxygen (O_2) is a diradical and contains two unpaired electrons with no reactivity. However, even during electron transport chain process, single electron leak from reaction paths in the mitochondria and the first one-electron incorporate with oxygen generates the superoxide anion radical ($O_2^{\bullet}$), which is produced as superoxide. . The addition of a second electron and two protons generate the active species hydrogen peroxide (H_2O_2) that is not a radical but can harm tissues as it accumulates. A third electron addition produces the highly reactive hydroxyl radical ($OH^{\bullet}$) and release hydroxide ion. A fourth electron addition harmlessly generates a water molecule (6,15,42,47). The reactions are as follows.

$$O_2 + e^- \longrightarrow O^{\bullet}_2$$

$$O_2 + H_2O \longrightarrow HO^{\bullet}_2 + OH^-$$

$$HO_2 + e^- + H \longrightarrow H_2O_2$$

$$H_2O_2 + e^- \longrightarrow OH^{\bullet} + OH^-$$

In the series of single-electron transfers molecular oxygen is first reduced to the superoxide radical ($O_2^{\bullet}$) and from superoxide, with the addition of two electron, to hydrogen peroxide (H_2O_2). Hydrogen peroxide is itself then univalently reduced, with the addition of another proton, to water and hydroxyl radical ($OH^{\bullet}$). A final univalent reduction and the addition of another proton convert the hydroxyl radical to water (43).

In addition, the toxicity of $O^{\bullet}_2$ and H_2O_2 in living organisms is due to their conversion into $OH^{\bullet}$ and into reactive radical the metal ion complexes (48). These processes are often refered to as either the iron catalyzes Harber-Weiss reaction as follows (6).

$$H_2O_2 + O^{\bullet}_2 \xrightarrow{Fe/Cu} O_2 + OH^{\bullet} + OH$$

or superoxide-driven Fenton reaction as follow

$$Fe^{2+} + H_2O_2 \longrightarrow \text{intermediate} + Fe^{3+} + OH^{\bullet} + OH^{-}$$

Another term often used in the free radical is oxidative stress (7). Oxidative stress is an imbalance between antioxidant and reactive oxygen species (ROS) generation, when the rate at which the ROS are generated exceeds the capacity of the cell for their removal (3,7). Oxidative stress cause biologically important molecules damage including membrane ion transport and/or other specific proteins, carbohydrate, DNA-strand breakage, rises in intracellular free Ca^{2+} and peroxidation of lipid (15,44).

3.2 Lipid peroxidation

Lipid peroxidation is a complex process whereby polyunsaturated fatty acids (PUFAs) in the phospholipids of cellular membranes undergo reaction with oxygen to yield lipid peroxides (LOOH) (43,45). The process of lipid peroxidation can be divided into three steps as follows.

3.2.1 Initiation step

The first step is the initiation process usually proceeds with the formation of conjugated diene bonds generate by abstraction of hydrogen atom. A free radical ($R^{\bullet}$) removes a H atom from a lipid molecule (LH), thus generating a lipid radical ($L^{\bullet}$)(6). The initiation step is shown below:

$$LH + R^{\bullet} \longrightarrow L^{\bullet} + RH$$

3.2.2 Propagation step

Propagation of lipid peroxidation relies on the interaction of molecular oxygen with carbon-centered free radicals ($L^{\bullet}$) and forms another radical, which the lipid peroxy radical ($LOO^{\bullet}$). $LOO^{\bullet}$ in turn removes another H atom from lipid molecule, producing a lipid hydroperoxide (LOOH) as well as another $L^{\bullet}$. As in the reaction below:

$$L^{\bullet} + O_2 \longrightarrow LOO^{\bullet}$$

$$LOO^{\bullet} + LH \longrightarrow LOOH + L^{\bullet}$$

3.2.3 Termination step

The chain reaction can be terminated by antioxidants (AH). The antioxidant will react with the free radicals and interrupt the reaction process, thereby terminate the reaction.

$$LOO^{\bullet} + AH \longrightarrow LOOH + A^{\bullet}$$

$$LOO^{\bullet} + L^{\bullet} \longrightarrow LOOL$$

Oxidation of PUFAs causes the formation of hydroperoxides with conjugated dienes. These hydroperoxides can undergo formation of hydrocarbon gasses (e.g., pentane) and aldehydic compound, in particular the volatile low molecular weight aldehyde, malondialdehyde (MDA) (48). Peroxidation of lipid molecules invariably changes lipid molecular structures (49), decrease membrane fluidity, destabilizes membrane receptors, and increases membrane permeability with loss of cytosolic portions. The most harmful effect is that the reactive radical (Figure 1) can also catalyze amino acid oxidation, protein- protein cross linking, protein strand scission, and can attack polyunsaturated fatty acid in cell membrane (48-50). Lipid peroxides (LPO) can initiate lipid peroxidation at another sites giving hydrogen peroxide, which can hemolyse red blood cell. Aldehydes react with DNA and produce mutagenesis and carcinogenesis (41).

3.3 Aging and the action of lipid peroxidation

The activities of free radicals in many age-related diseases have long been of interest. The increase in levels of plasma lipids with aging is also evident with respect to triglyceride. The increase of triglyceride is significant at 40 years of age or higher. Atherosclerosis is the disease which most related to old age (39). The increased low-density lipoprotein (LDL) and cholesterol levels cause endothelial damage and increase fatty deposits on the cell lining of arterial wall, forming the fatty streak by macrophages to remove noxious molecule such as oxidized LDL. The fatty streak is the precursor lesion that subsequently leads to development of the intermediate and the final complication lesion of altheroscelrosis (6,51,52) (Figure 2).

3.4 Aging and antioxidant

Antioxidant is any substance, which low concentrations compared with those of an oxidisable substrate that significantly delays or prevents oxidation of that substrate (3,6). They are called by generic names as antioxidants, free radical scavengers, chain terminators or reductants (53). The antioxidant defense systems have been termed "primary" and "secondary". Primary defenses interact with free radicals generated directly from oxygen (namely $O_2^{\bullet}$), with compound including vitamin E, A and C, glutathione and uric acid, scavenging enzyme such as superoxide dismutase (SOD), catalase (CAT), peroxidase (POD).

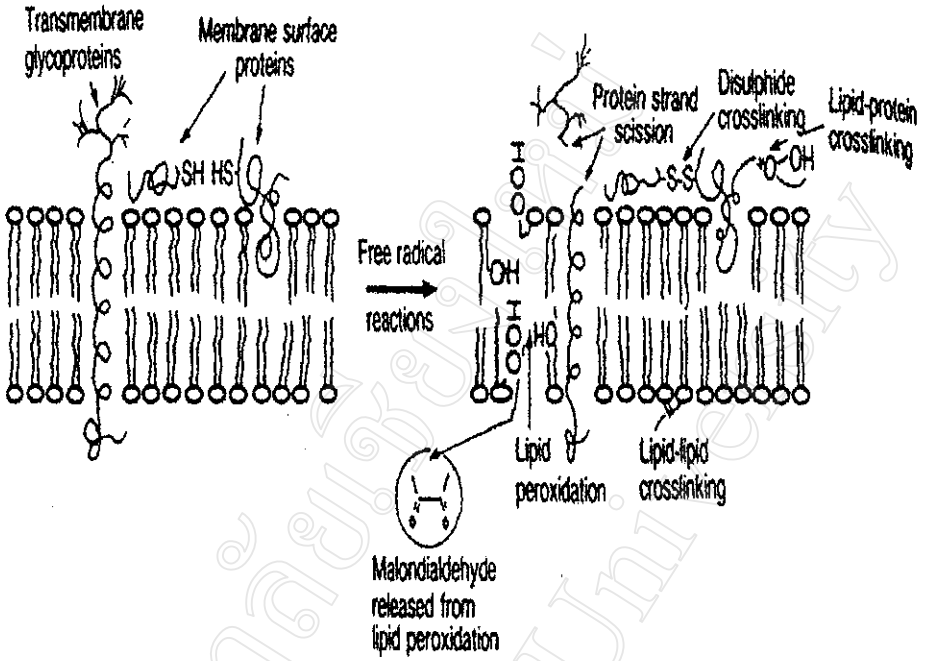


Figure 1 Free radical and damage of the membrane.

Free radicals initiates lipid peroxidation to short chain fatty acyl derivatives and the by-product malondialdehyde. Variety of cross-link reactions can be mediated malondialdehyde reactions. Free radicals can catalyze amino acid oxidation, protein-protein cross linking and protein strand scission (5).

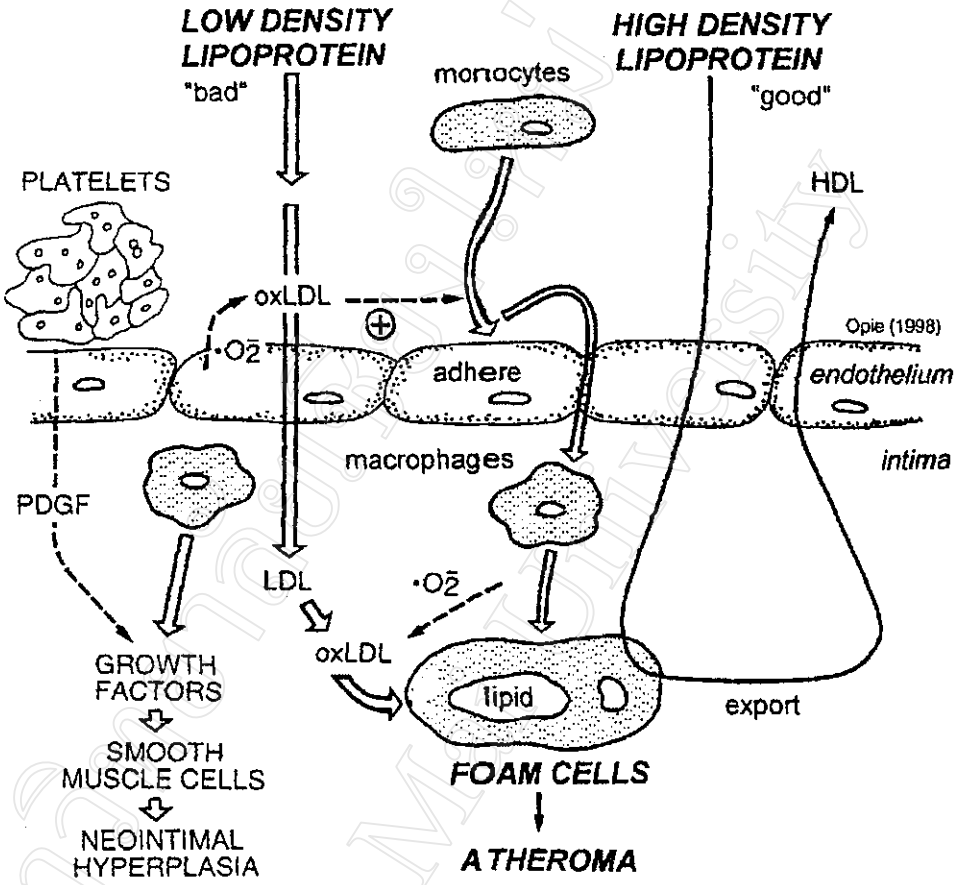


Figure 2 Role of lipoproteins in atherosclerosis.

When low-density lipoproteins become oxidized (oxLDL), they are trapped in the intima of the arterial wall forming foam cells (Opic, L.H., 1999) (51).

HDL: high density lipoprotein, LDL: low density lipoprotein, oxLDL: low density lipoprotein oxidize, $O^{\bullet}_{2}$: superoxide radical

Secondary defenses scavenge radicals arising from dismutation of $O_2^{\bullet}$ such as lipolytic enzyme, phospholipases, proteolytic enzyme, protease, peptidase, DNA repair enzyme, and endonuclease (6,54). Mechanisms of antioxidant action that may protect against oxygen toxicity include: i) preventing reactive oxygen species (ROS) formation, ii) binding metal ions needed for catalysis of ROS generation, iii) repairing of damage caused by ROS and triggering the expression of genes that encode antioxidant proteins. iv) providing a favorable environment for effective functioning of other antioxidant (53,55). Aging has been proposed to be a result of continuous reactions of the cell components with free radicals throughout life span. Aging causes a reduction of protein turnover and cell generative capacity, which in turn decreases cellular antioxidant enzyme (56).

3.4.1 Superoxide dismutase (SOD)

SOD is the enzyme involves in cellular defense against oxidative processes. It catalyzes the dismutation of the superoxide radical anion and diminishes toxic effects due to this radical or to other free radical derived from secondary reaction. There are two types of SOD isozyme in eukaryote. CuZn-SOD and Mn-SOD are found in the cytosolic compartment and mitochondria, respectively (57). Thus, the principle function of SOD is to catalyze the conversion of superoxide ($O^{\bullet}_2$) to hydrogen peroxide (H_2O_2) as shown in the reaction below (55).

$$2O^{\bullet}_2 + 2H^{+} \xrightarrow{\text{SOD}} H_2O_2 + O_2$$

3.4.2 Catalase (CAT)

Most aerobic cells contain catalase activity. In animals catalase presence in all major body organs, being especially concentrated in liver and

erythrocytes (48). The primary function of CAT is to decompose H_2O_2 to H_2O. It shares this function with glutathione peroxidase (GPX), although the substrate specificity and affinity as well as the cellular location of the two antioxidant enzymes are different (57).

$$2H_2O_2 \xrightarrow{CAT} H_2O_2 + O_2$$

3.4.3 Glutathione peroxidase (GPX)

GPX is found in animal's liver and lung and human's erythrocytes. It has high activity in liver, moderate activity in heart, lung and brain, and low activity in muscle (48). GPX consists of four apparently identical subunits, each of which contains one atom of selenium (Se). Se-deficient animals have markedly decreased GPX activity (58).

GPX catalyses the oxidation of GSH to GSSG at the expense of hydrogen peroxides as follows (48).

$$H_2O_2 + 2GSH \xrightarrow{GPX} GSSG + 2H_2O$$

or

$$2GSH + ROOH \xrightarrow{GPX} GSSG + H_2O + ROH$$

3.4.4 Vitamin E (Tocopherol)

Vitamin E is a lipophilic free radical scavenger that is the most widely distributed antioxidant in the nature. There are eight different forms which can be subdivided into two classes: tocopherols ($\alpha, \beta, \gamma, \delta$) and tocotrienols ($\alpha, \beta, \gamma,$

δ). Tocopherols differ from tocotrienols in which tocopherols have a saturated phytyl side chains, whereas tocotrienols have unsaturated side chains (Figure 3) (4,9,42). To function effectively, vitamin E must be absorbed, transported, delivered to cell and integrated into lipid droplets and into cellular membranes and organelles or tissues. The absorption of vitamin E from the intestinal lumen is dependent upon processes necessary for digestion of dietary fats and uptake into enterocytes (59). It enters the circulation from the intestine in chylomicron via the lymphatic pathway. During chylomicron catabolism by lipoprotein lipase, vitamin E can be transferred to other lipoproteins and to the tissue. Vitamin E reaches the liver by uptake of chylomicrons remnants and transported in plasma in VLDL, the metabolism of which affects transfer to LDL and HDL (Figure 4) (60) scavengers, chain terminators or reductants (53). The antioxidant defense systems have been termed "primary" and "secondary". Primary defenses interact with free radicals generated directly from oxygen (namely $O_2^{\bullet}$), with compound including vitamin E, A and C, glutathione and uric acid, scavenging enzyme such as superoxide dismutase (SOD), catalase (CAT), peroxidase (POD). The most effective biological form is d-α-tocopherol. While, other tocopherols are less effective than α-tocopherol as antioxidant in human but have more important roles in plant (4). Vitamin E is an efficient terminator of free radical propagation reactions in membrane lipid. It has little tendency to extract a hydrogen atom from another compound and the reaction propagated. However, vitamin E interacts efficiently and directly with lipid peroxy radicals to lose hydrogen atom and become the fully oxidized tocopheryl quinone (4,49,60).

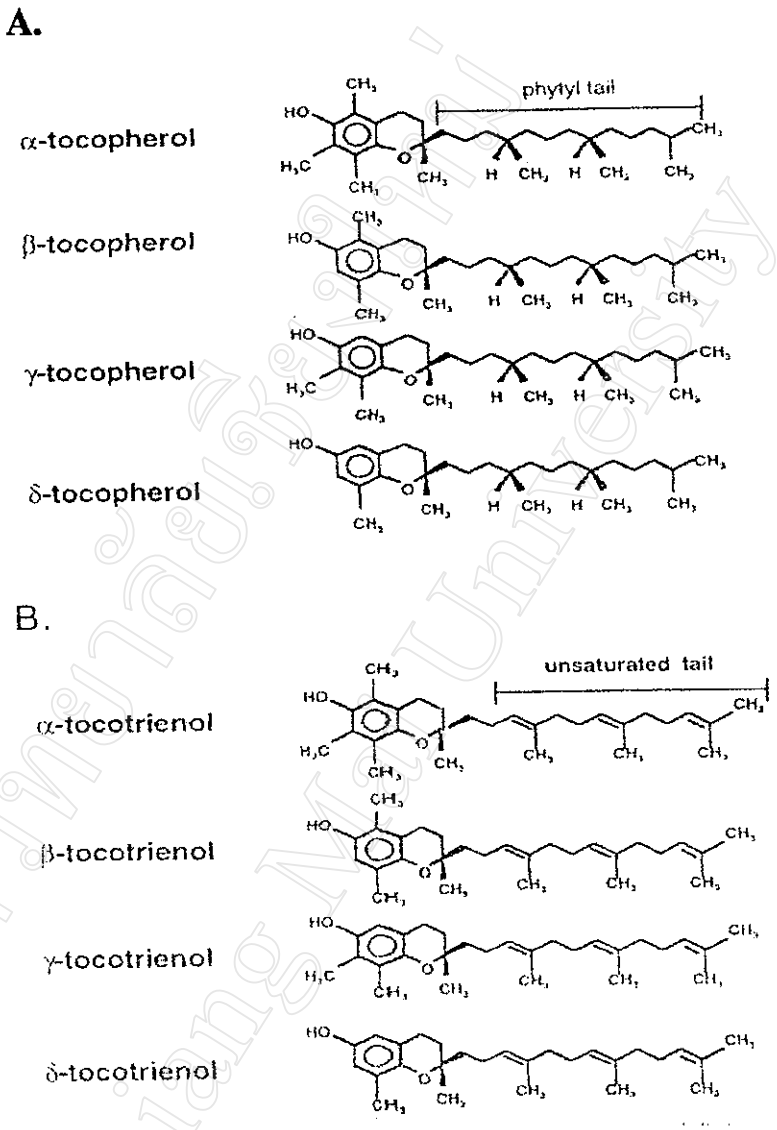
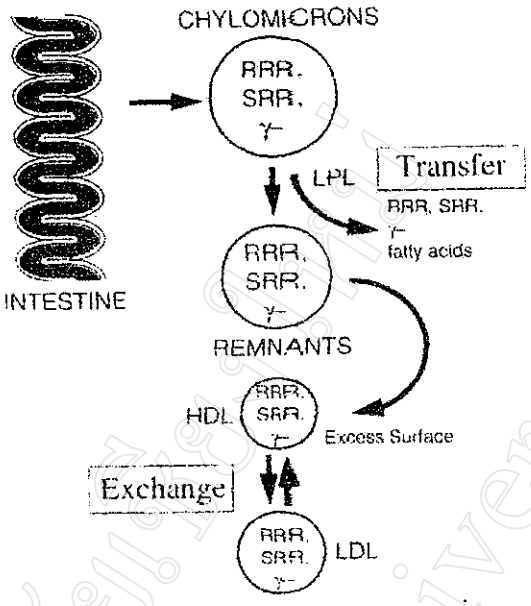


Figure 3 Structure of vitamin E homologues (9).

(A) Four naturally occurring tocopherols and (B) four naturally occurring tocotrienols.

A.



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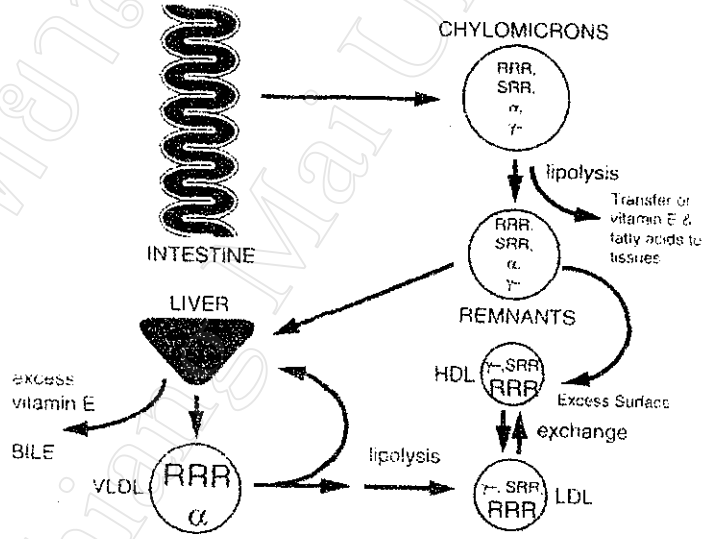

Figure 4 Pathways for the absorption and preferential delivery of vitamin E to peripheral tissues (4).

A: pathways for the preferential delivery of vitamin E to peripheral tissue. B: pathways for absorption of vitamin E and its delivery to tissues during chylomicron catabolism.

HDL: high density lipoprotein, LDL: low density lipoprotein, VLDL: very low density lipoprotein, RRR, SRR, α-, γ-: forms of vitamin E, LPL: lipoprotein lipase.

The recommended dietary allowances (RDA) for the elderly of vitamin E intake are 8.0 mg and 10.0 mg of women and men, respectively. In general healthy older people, eating a balanced diet does not need a multivitamin and mineral supplement (61). Many studies reported the change in vitamin E status with age and variable results have been recorded, showing positive result, negative result and no correlation between plasma vitamin E levels and age. However, healthy aging appears to have little effect on the plasma vitamin E concentration (3). Some reports showed that vitamin E supplementation reduced the rate of lipid peroxidation. Dillaed, C.J., et al. (19) examined the protective effect of vitamin E on exercise–induced oxidative damage as measured by increased amount of exhaled pentane. Vitamin E supplementation can reduce this oxidative damage. Meydani, M., et al. (21) found that vitamin E supplementation (800 IU α-tocopherol per day) for 48 day can lower an exercise–induced increase in oxidative injury, as measured by decreased excretion of urinary thiobarbituric acid adducts in young and older men and in women.

4. Body lipid profile

Lipids are compounds that are insoluble in water. They are readily soluble in nonpolar solvents such as ether, chloroform or benzene. The hydrophobic nature of lipid is due to the predominance of hydrocarbon chains (- CH_2 – CH_2 – CH_2 -) in their structures. There are many different ways to classify lipids, for example five classes are recognized (62).

1. Fatty acid and their immediate derivatives, e.g., prostaglandins and leukotrienes.
2. Glycerol ester, e.g., acylglycerol and phosphoglyceride.
3. Sphingolipids, e.g., sphingomyelin and glycosphingolipids.

4. Cholesterol and derivatives, e.g., cholesterol ester, bile acid, steroid hormone, vitamin D.
5. Isoprene derivatives, e.g., dolichols, vitamin A, vitamin E and vitamin K.

Lipids of major physiologic significance are fatty acids and their esters, together with cholesterol and other steroids (63).

After meal, lipoproteins mediate the transport of lipid from the intestine as chylomicrons and from the liver as very low-density lipoprotein (VLDL), to most tissue for oxidation and to adipose tissue for storage. Four major groups of lipoproteins have been identified that are important physiologically and clinically diagnosis. These are i) chylomicron, derived from intestinal absorption of triacylglycerol ii) very low-density lipoproteins (VLDL), derived from the liver for the export of triacylglycerol iii) low-density lipoproteins (LDL), representing a final stage in the catabolism of VLDL; and iv) high-density lipoproteins (HDL), involved in VLDL and chylomicron metabolism and also in reverse cholesterol transportation (64).

Chylomicron and VLDL are first metabolized by hydrolysis with lipoprotein lipase in extra hepatic tissues. Most of the triacylglycerol is removed leaving, and a lipoprotein remnant in the circulation. These remnants are taken up into the liver by receptor-mediated endocytosis, but some of the remnants (IDL) in further hydrolyzed to form LDL which is finally taken up by the liver and other tissue by the LDL receptor (64).

Cholesterol as an amphipatic lipid, is present in tissue and in plasma lipoproteins in the form of free cholesterol, combined with long-chain fatty acid, or cholesterol ester. Lipoprotein transports free cholesterol in the circulation, where it readily equilibrates with cholesterol in other lipoproteins and membrane. LDL is the mediator of cholesterol and cholesterol ester uptake into many tissues. Free

cholesterol is removed from tissue by HDL and transported to the liver for conversion to bile acid in the process known as reverse cholesterol transportation (65). Cholesterol is the parent molecule from which all other steroids in the body are synthesized. These cholesterol derivatives include major hormones such as the adrenocortical and sex hormones, vitamin D and bile acid (62) (Figure 5).

4.1 Lipid profile in aging

Lipids have important beneficial biologic functions that include the use of triglyceride for energy production or as stored fat in adipose tissue and the use of cholesterol as a component, in conjunction with phospholipids, of cellular membranes or in the synthesis of steroid hormones. Age-related increase in plasma cholesterol is less marked between 20 and 40 years in women than in men. The increase in the levels of plasma lipids with aging is also evident with respect to triglyceride. Most lipids significantly increase at 40 years in men (39). Primary effects of aging upon the regulation of lipoprotein metabolism have been difficult to identify other than those related to alteration in adiposity and sex hormone physiology described earlier. Certain studies have suggested that aging associates decrease in LDL receptor activity.

4.2 Exercise and lipid profile

High-intensity exercise training is associated with less atherogenic lipoprotein profiles. Thompson, P.D., et al. (66) studied in middle-age men and found that high-intensity exercise training, can reduce plasma triglyceride, increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI level when compared to sedentary controls. However, similar improvements have been detected in some moderate-intensity exercise studied.

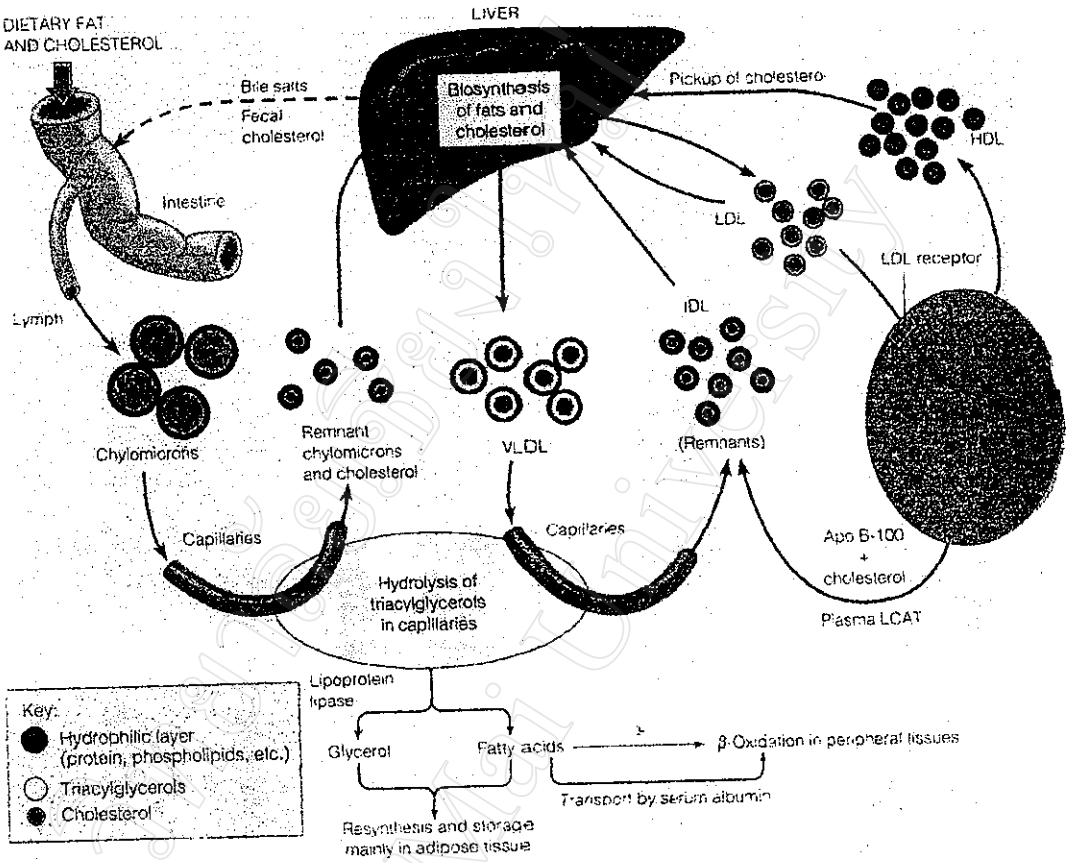

Figure 5 Summary of overall aspects of lipoprotein metabolism and transport.

HDL: high density lipoprotein, LDL: low density lipoprotein, VLDL: very low density lipoprotein

Brownell, K., et al. (67) studied in moderate-intensity training and showed that HDL-C increase 5.1%, LDL decreases 6% and the HDL/LDL ratio increases 12.4%. Similarly, the studying of Hunttunen, J.K., et al. (68) reported that the ratio HDL-C/apolipoprotein AI increased, but the level of LDL-C and apolipoprotein AII decreased in 4-month trained group.

There are very few data on the effects of physical activity on lipoprotein profile in older individuals. A study of trained older men, have demonstrated that total and LDL-C levels are more related to body fat than to physical training (24).

5. Effect of exercise and exercise training on lipid peroxidation and antioxidant

5.1 Effect of exercise

Exercise is an important change in lifestyles, which benefit in good health, better quality of life and longevity (69). Regular physical activity and exercise training can slow down the age-related functional dysability and average lifespan may be increased by 2-7 years (70). Regular physical activity can impact health and longevity. Cardiovascular health is improved and cancer risk also decreased (69). Exercise is naturally leading to bodily changes. Response to exercise as functional changes are sudden, temporary and disappeared shortly after the exercise period is finished, for example, the increase in heart rate, the increase in breathing, the rise in blood pressure.

However, there are some evidences that acute exercise may be harmful. The increased oxygen consumption during exercise accompanied with the elevation of reactive oxygen species (ROS), which is considered to be an oxidative stress (8,11,12). Exercise increases metabolism and metabolic leaks and thought to be an important source of oxygen-derived free radicals. The rate of oxygen uptake by

the body during exercise may increase about 10-15-folds (55). Free radicals are generated by various ways, including i) increasing the leak of electron transport in mitochondria ii) increase in epinephrine and other catecholamines iii) inflammatory response (70,71). Figure 6 summarizes the potential damages caused by ROS, which is generated from strenuous exercise.

5.2 Effect of exercise training on lipid peroxidation and antioxidant

Physical activity and exercise have generally been used interchangeably to represent any bodily movement produced by the contraction of skeletal muscle. Exercise training is used when activity is performed for the sole purpose of enhancing physical fitness (72). The objective of training is to facilitate biologic adaptations that improve performance in specific task (25). One example of an adaptation to training is the increase in strength and size of muscle fibers. Another example of an adaptation is the increased VO_2max. About 50% of the increase in VO_2max is due to an increase in maximal cardiac out put. The other 50% due to an increase in oxygen extraction at the muscle (25,73-74). However, five major factors can influence the effectiveness of training, i.e., intensity, frequency, duration, mode and progression (25,74).

5.2.1 Intensity of exercise training

Intensity refers to the percentage of one's maximum capacity that is being used in exercise training. It is the most critical factor for successful aerobic training (25,73,74). Intensity can be expressed in either absolute (e.g., watts) or relative terms (percentage of functional capacity). Relative intensity is usually expressed as a percentage of individuals functional capacity, e.g., maximum oxygen consumption (VO_2max), maximum heart rate (HRmax),

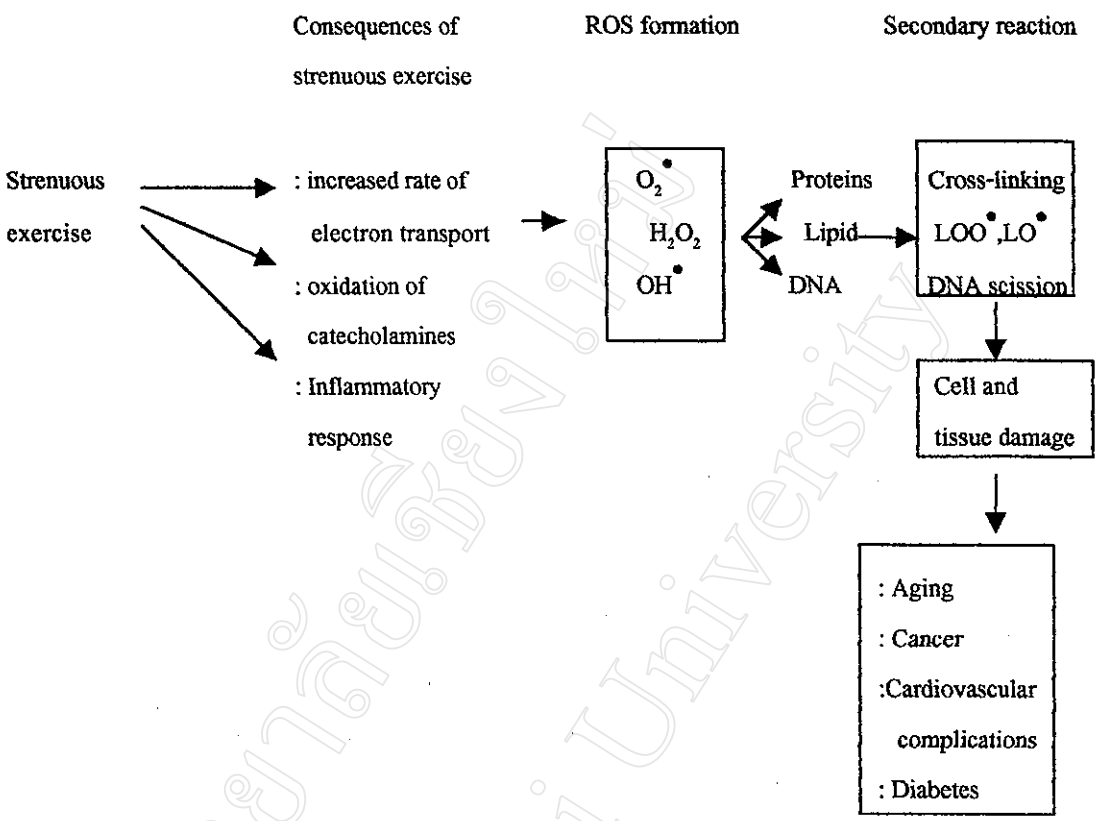

Figure 6 Relationship between exercise and diseases.

During strenuous exercise, the production of oxygen radicals is no longer counteracted by antiradicals defenses. Damage of cell structures therefore occurs, giving rise to an accelerated aging process and to pathological complication.

ROS: reactive oxygen species, $O^{\bullet}_2$: superoxide radicals, H_2O_2: hydrogen peroxide, $OH^{\bullet}$: hydroxyl radical, $LO^{\bullet}$: peroxyl radical.

or rating of perceived exertion (RPE). Exercise intensity representing the minimal or threshold stimulus for cardiovascular improvement between of 40 to 85% of HRmax. Typically, the conditioning intensity for healthy adult is between 60 and 70% of HRmax (75).

5.2.2 Frequency of exercise training

Frequency refers to the number of exercise bouts per week that an individual undergoes (74). Exercise at least 3 days a week for at least 6 weeks generally can initiate adaptive changes in the aerobic system. In general, training two-days a week does not change in aerobic capacity or body composition. However, training for 4 or 5 days a week generated either no greater or only slightly greater improvement compared with thrice weekly exercise (25,74).

5.2.3 Duration of exercise training

Duration is the amount of time for an exercise (74). The optimum duration of an exercise session depends on the intensity. In general, performing less exhaustive, moderate exercise for 20 to 30 minutes in each session is a realistic exercise recommendation for the average person (3,25).

However, longer duration at lower intensity can also be an effective training. For example, walking for 40 minute per session, 4 days a week for a total of 160 minutes per week is as effective in increasing the aerobic power as jogging for 30 minutes, 3 days a week for the total of 90 minutes per week (74).

5.2.4 Mode of exercise training

Mode of training refers to the type of exercise training being utilized. There are numerous types of aerobic exercise, i.e., strength training,

flexibility exercises, and endurance training exercise (74). Type of exercise depends in part on the duration, intensity and frequency of exercise (25).

5.2.5 Progression of exercise training

Progression refers to a gradual increase in intensity and duration of exercise training over time (74). The most significant conditioning effect may be observed during the first 6 to 8 weeks of the exercise program (75).

Although physical exercise is known to have many beneficial effects, it is also shown evidence that free radicals production can increase during exercise. Recently, it has been accepted that regularly performed exercise or exercise training has positive effect on oxidative stress. Venditti, P., et al.(33) reported that glutathione peroxidase was increased after swimming in trained rats, compared with the untrained. Kanter, M.M. (11) studied the untrained and 21 weeks swimming trained mice and found a greater increase of blood and liver CAT, SOD and GPX in the trained mice, compared to the untrained. Alessio, H.M., et al. (50) studied the in untrained and the treadmill-trained rats and suggested that training could result in a reduction in MDA during moderate exercise by the activation of the scavenging enzyme (CAT). However, Laughliin,R.S., et al.(114) reported that exercise training can induce increase in GPX but decreased in CAT and without change in SOD level. It is possible that those steps are also followed during exercise; adrenosine is related and activate adrenosine receptor, thereby activating antioxidant enzyme (Figure 9).(140)

In elderly men, effects of exercise training on lipid peroxidation are more limited and findings are also contradictory. Brite, F.D., et al. (17) have reported that soccer players under regular training show an improve plasma antioxidant

status in comparison to sedentary. Tessier, F., et al. (76) found that 10-week endurance training program can progress the antioxidant potential of GPX.

6. Aging and exercise training

Many physiological changes occurring with aging that can alter the exercise prescription include reduction in maximal aerobic power, cardiovascular reserve, peripheral vascular elasticity, muscular strength and musculoskeletal flexibility. Thus, the individualization of exercise prescription is essential and the medical screening is a must for the elder (52,74,75). The most important exercise for older person are non-weight-bearing activities, such as swimming, bicycling and floor exercise. Slow warm-up period is desirable in order to increase circulation and designed to gradually increase the metabolic rate from the resting level to required level for conditioning. Training heart rate can be as low as 40 to 60 % of HRmax and progress to 70 to 75% of HRmax (74). Guidelines for aerobic exercise prescription for healthy aging recommend an intensity of 60 to 75% of maximum heart rate, three days per week for at least 6 weeks (77).

6.1 Effect of exercise training on maximum oxygen consumption

Exercise training in aging enhances the heart capacity to pump blood and increase aerobic capacity to the same relative degree as in younger adults (78). Blumenthal, J.A., et al. (79) found that aging subjects generally exhibited a 10 to 15% improvement in peak oxygen consumption after 4 months of aerobic exercise training, and 1 to 6% improvement in aerobic power with additional aerobic exercise training. Similarly, Hagberg, J.M., et al. (80) studied 26 weeks exercise

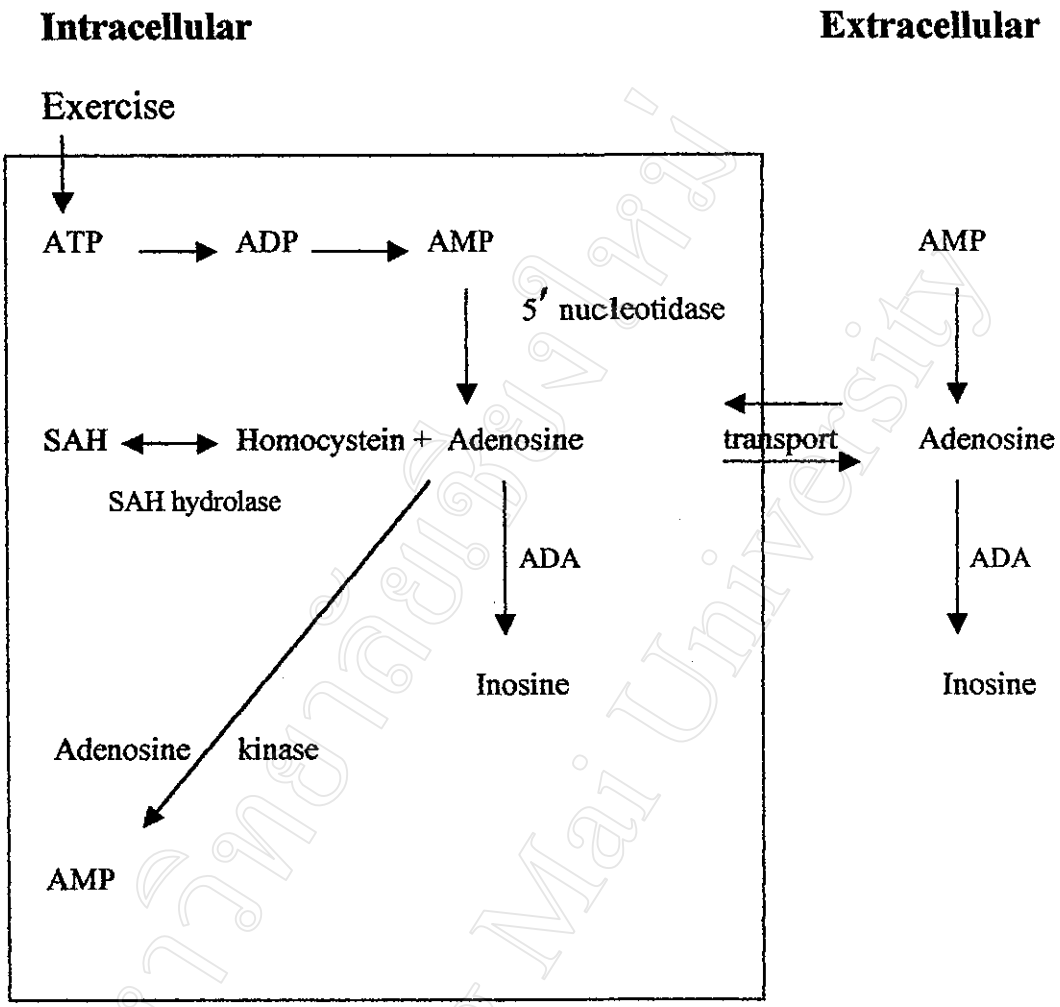

Figure 7 Exercise and generation of adenosine.

ATP: adenosine triphosphate, ADP: adenosine diphosphate, AMP, adenosine monophosphate, SAH: S-adenocysteine, ADA: adenosine deaminase

trained 70-to-79-year old men and found that VO_2max increased a 16% in the first 13 weeks of training and increased by a total of 22% after 26 weeks of training. Sidney, K.H., et al. (82) reported that exercise training progressively reduced skinfold thickness, by an average of 1.6 mm at 7^{th} weeks, by 2.4 mm at 14^{th} weeks and by 3.3 mm at 1 year after training. However, the decrement in overall adiposity showed a preferential decrease in the central distribution of fat. Kohrt, W.M., (83) indicated that exercise training favorably modify the abdominal fat distribution profile that was typical of older men and women.

6.2 Effect of exercise training on muscle strength

There are fewer studies of the effect of strengthening exercise than those of aerobic exercise in older men. Some of studies in healthy aging have utilized more vigorous strength training, where resistance is set as high as 80% of the one-repetition maximum or 1-RM (the maximal weight that the subject can lift once) (84,85). A study of strength trained men and women, 65-75 years old, showed a significant increases in strength/muscle volume (MQ) and 1-RM were found in both group (86). However, the aerobic conditioning program (e.g. endurance exercise training) a markedly affect the VO_2max but do not affect muscle strength (80).

At the present, the regular exercise alone positive effects on reducing oxidative stress in animals and human. Its effect involves on increase in antioxidant capacity. More over, vitamin E is shown to be highly effective in protecting against membrane lipid peroxidation. However, the effects of exercise training and vitamin E supplement in elderly men are still controversial.