CHAPTER II
SURVEY OF RELATED LITERATURE

The aim of the present study was to determine the effect of acute exercise, exercise training, exercise training combined with vitamin C supplementation on physiological changes and rhinitis symptoms in patients with allergic rhinitis. This chapter will explore the literature were listed as followed:-

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1. Allergic rhinitis

1.1 Definition of allergic rhinitis

Allergic rhinitis is defined as an abnormal inflammation of the membrane lining the nose. It is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage (Bousquet et al., 2001). Additionally, airway hypersensitivity may develop. A loss of the sense of smell and an inability to taste may occur. Moreover, some patients experience sleep disturbances, decreased emotional well-being and social functioning, headache, and irritability. On physical examination, nasal obstruction can often be seen with pale to bluish nasal mucosa, enlarged or boggy turbinates, clear nasal secretions, and pharyngeal cobble-stoning (Al Suleimani and Walker, 2007).

Common allergens causing allergic rhinitis include proteins and glycoproteins in airborne dust mite fecal particles, cockroach residues, animal danders, molds, and pollens. On inhalation, allergen particles are deposited in nasal mucus, with subsequent elution of allergenic proteins and diffusion into nasal tissues (Dykewicz and Hamilos, 2010).

1.2 Prevalence and epidemiology of allergic rhinitis

Allergic rhinitis is an extremely common health problem, affecting 20 to 40 million Americans, approximately 26% of the population in the United Kingdom, and approximately 10-25% of the population worldwide (Storms, 2008). The prevalence varies with age: 32% of patients are 17 years or younger, 43% are 18–44 years of age, 17% are 45–64, and only 8% are 65 years or older (Law et al., 2003).

Another important and perhaps under appreciated aspect of allergic rhinitis is its negative impact on quality of life of patients. The total of 80% of patients in the survey studied complained of being frequently (44%) or sometimes (36%) tired because of their nasal allergy problems, and nearly two-thirds reported that they frequently or sometimes felt miserable or irritable during the allergy season. In another survey of 1,322 self-reported allergic rhinitis sufferers, over half indicated that their allergy condition interfered with sleep (68% among those with perennial allergic rhinitis and 51% among those with seasonal allergic rhinitis) (Storms, 2008).

In 1996, the overall direct costs of treating allergic rhinitis exceeded $3 billion with an additional $4 billion for treating comorbidities that are triggered or exacerbated by rhinitis. To this cost must be added indirect costs such as lowered productivity and lost work time. In the United States alone, the number of lost workdays is estimated as 3.5 million a year (Holgate and Broide, 2003; Mahr and Sheth, 2005).

1.3 Classification of allergic rhinitis

Rhinitis may be classified into non-allergic and allergic. Allergic rhinitis is further divided into seasonal and perennial. The allergic inflammatory process may involve different mediators in seasonal and perennial AR. (Figure 2.1) (Kemp, 2009).

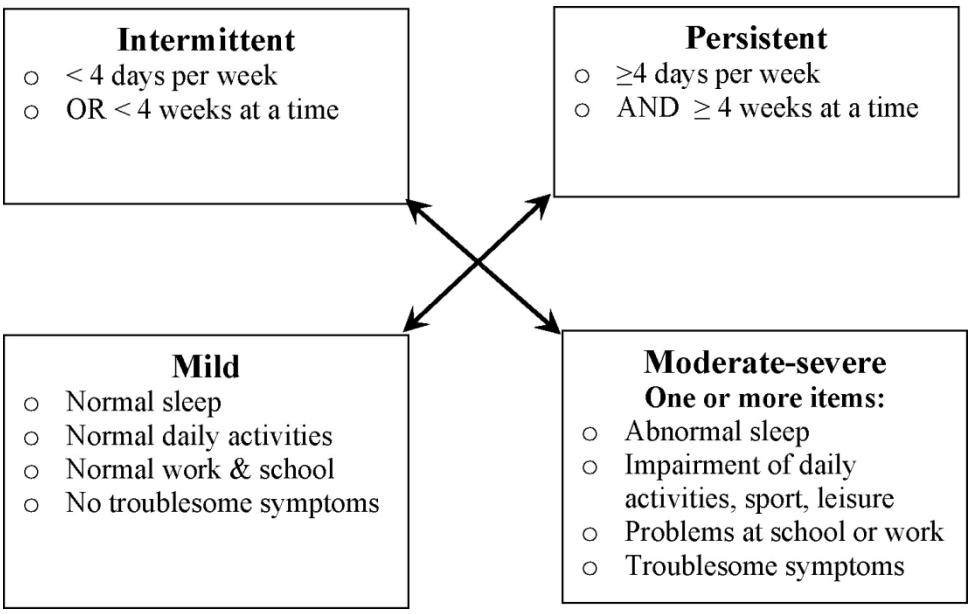

Figure 2.1 Functional classification of allergic rhinitis (Kemp, 2009).

Traditionally, allergic rhinitis has been subdivided into seasonal and perennial, and either mild, moderate, or severe. Mild allergic rhinitis involves no sleep interruption, no impairment of daily activities, and no troubling symptoms. Moderate-to-severe allergic rhinitis involves one or more of those factors. A newer classification system characterizes allergic rhinitis as intermittent, or persistent. In the intermittent form symptoms last less than 4 days per week with a total duration of less than 4 weeks. In the persistent form symptoms occur for more than 4 days per week for longer than 4 weeks (Noble et al., 1995; Bousquet et al., 2001). Seasonal rhinitis is periodic due to the occurrence of seasonal allergens. Pollens that cause seasonal allergic rhinitis in the Northern Hemisphere are from trees in springtime, grass pollens from May to July and weed pollen and mould spores in late summer and autumn. Perennial (year round) disease involves nonseasonal allergens in the air, most commonly from mites (25%; *Dermatophagoides pteronyssinus/farinae*), animal dander antigens (15%; cats, dogs, rodents), fungal spores (10%; *Alternaria*, *Cladosporium*, *Aspergillus*, *Penicillium*), or exposure to workplace antigens (Al Suleimani and Walker, 2007).

Allergic rhinitis is a common occurrence for several reasons. The predisposing factor involves heredity. Primary of specific factor is allergen, the most common include dust, house dust mites, cockroaches and allergens in the atmosphere (grass and fungi). Secondary or precipitating factors which cause the promotion to increase the rhinitis symptoms including infection, direct irritants, physical factors, psycho factors) and anatomical abnormalities (Vichyanond et al., 2000).

1.4 Pathophysiological of allergic rhinitis

Nasal anatomy and physiology

The nasal cavity (Figure 2.2) is divided by the nasal septum, which is composed of bone more proximally and cartilage more distally. The inferior, middle, and superior turbinates in the nasal cavity promote air filtration, humidification, and temperature regulation. The nasal cavity and turbinates are lined with mucosa comprised of pseudostratified columnar ciliated epithelium that overlies a basement membrane and the submucosa (lamina propria). The submucosa consists of serous and

seromucous nasal glands, nerves, extensive vasculature, and cellular elements. Overlying the nasal epithelium is a thin layer of mucus that dynamically moves by means of ciliary action to the posterior nasopharynx. Infections (viral or bacterial) and allergic inflammation impair mucociliary clearance. Because nasal tissues are highly vascular, vascular changes can lead to significant nasal obstruction. Vasoconstriction and consequent decreases in nasal airway resistance result from sympathetic nerve stimulation. Parasympathetic nerve stimulation promotes secretion from nasal airway glands and nasal congestion (Dykewicz and Hamilos, 2010).

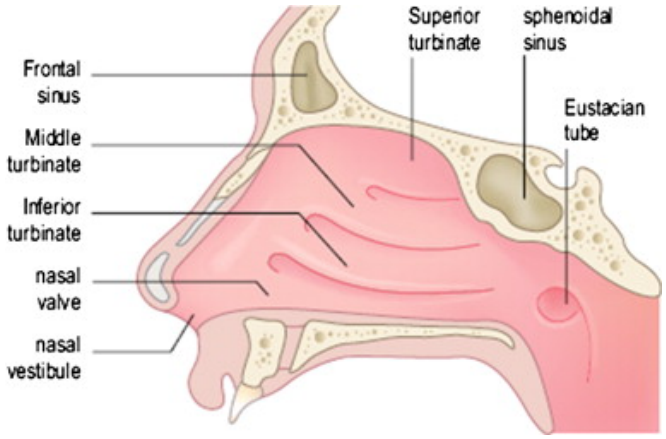

Figure 2.2 Nasal anatomy (Dykewicz and Hamilos, 2010).

There is a rich parasympathetic innervation to nasal glands. Nervous stimulation of glandular cholinoceptors causes marked hypersecretion and is often part of a reflex arc. Blood vessels have both sympathetic and parasympathetic innervation but are controlled mainly by sympathetic fibers. A continuous release of norepinephrine is postulated to keeps the sinusoids partly contracted since the vasoconstrictor effects of stimulation of α-adrenoceptors is more marked than vasodilatation resulting from stimulation of β_2-receptors (Dahl and Mygind, 1998). The release of the classic neurotransmitters, norepinephrine and acetylcholine, has in recent years been found to be accompanied by a number of peptide neurotransmitters. These neurotransmitters are secreted by afferent unmyelinated C fibers (substance P; SP, calcitonin gene-related prptide; CGRP, neurokinin A; NK-A, gastrin-releasing peptide); efferent parasympathetic nerve endings (vasoactive intestinal peptide; VIP, peptide histidine

methionine), and from efferent sympathetic nerve endings (neuropeptide Y; NPY) (Uddman et al., 1987; Lundblad, 1990; Baroody, 1997). Neuropeptides are capable of generating local reflexes that cause an increase in vascular permeability, plasma leakage, vasodilatation, and subsequent tissue oedema (Baraniuk, 1997) (Figure 2.3).

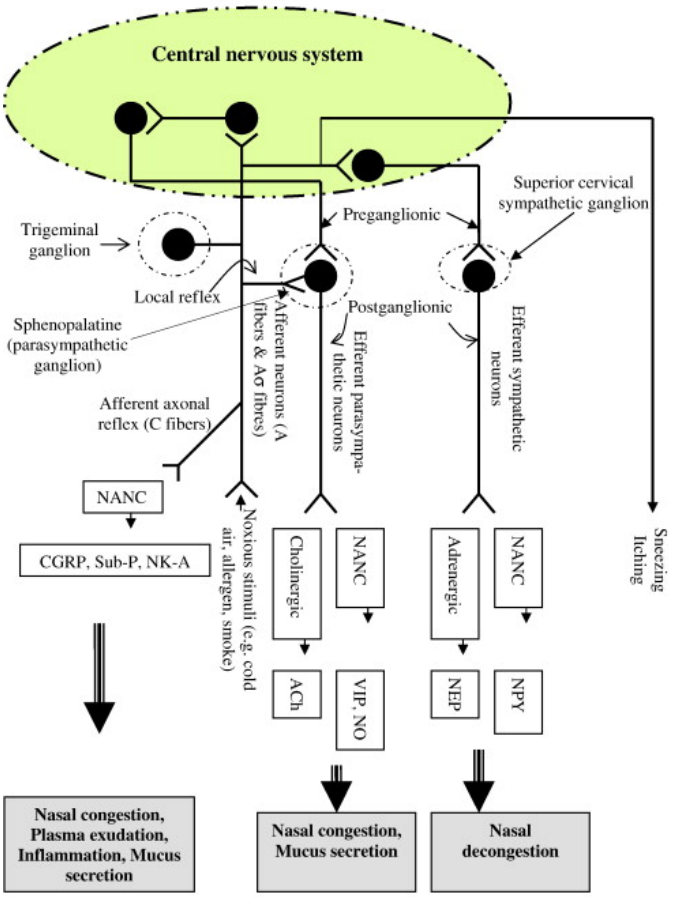

Figure 2.3 Schematic representation of the nasal neuronal control.

(Al Suleimani and Walker, 2007)

Pathophysiology

In the nose allergens are processed by antigen- presenting cells (dendritic cells expressing CD1a and CD11c and macrophages) in the nasal epithelial mucosa, with subsequent presentation of allergenic peptides by MHC class II molecules to T-cell receptors on resting $CD4^+$ T lymphocytes in regional lymph nodes. With costimulatory signals, allergen-stimulated T cells proliferate into Th2-biased cells

that release IL-3, IL-4, IL-5, IL-13, and other cytokines. These cytokines then lead to a cascade of events that promote B-cell isotype switching with subsequent local and systemic production of allergen-specific IgE antibody production by plasma cells, eosinophilic infiltration into the nasal epithelium and mucosa, and mast cell proliferation and infiltration of airway mucosa. (Figure 2.4)

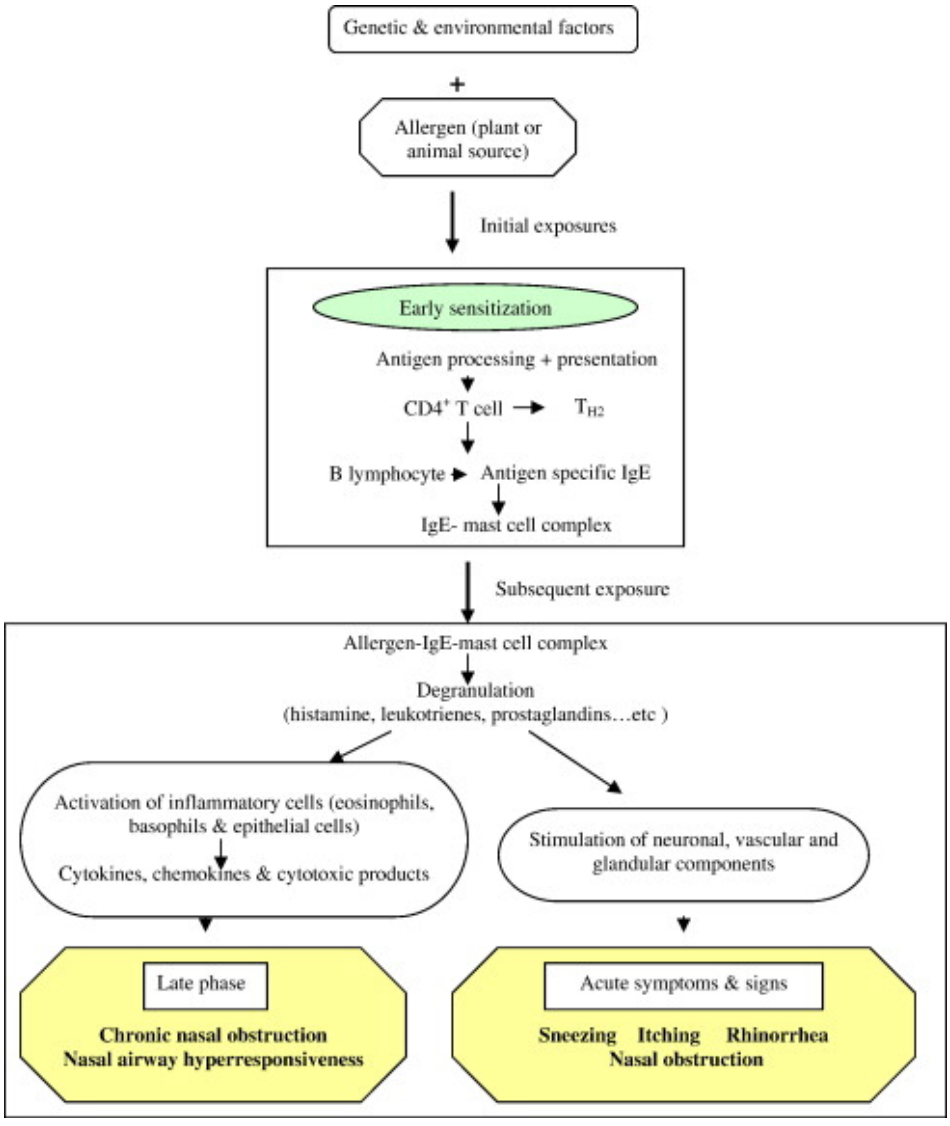

Figure 2.4 Pathophysiology of allergic rhinitis.

(Al Suleimani and Walker, 2007)

Early/immediate allergic response

Within minutes of inhalation of allergen in sensitized subjects, deposited allergens are recognized by IgE antibody bound to mast cells and basophils, causing degranulation and release of preformed mediators, such as histamine and tryptase, and the rapid *de novo* generation of mediators, including cysteinyl leukotrienes (leukotrienes C_4, D_4, and E_4) and prostaglandin D_2. Mediators cause plasma leakage from blood vessels and dilation of arteriovenous arteriole venule anastomoses, with consequent edema, pooling of blood in the cavernous sinusoids (the principal cause of the congestion of allergic rhinitis), and occlusion of the nasal passages. Mediators also stimulate active secretion of mucus from glandular and goblet cells. Histamine elicits itching, rhinorrhea, and sneezing, whereas other mediators, such as leukotrienes and prostaglandin D_2, likely have more important roles in the development of nasal congestion. Stimulation of sensory nerves results in the perception of nasal congestion and itching and can provoke systemic reflexes, such as sneezing paroxysms (Heppt et al., 2004; Wallace et al., 2008).

Late-phase response

Mediators and cytokines released during the early phase set off a cascade of events over the ensuing 4 to 8 hours that lead to an inflammatory response called the late response. Although clinical symptoms during the late phase might be clinically similar to those of the immediate reaction, nasal congestion is more prominent. The cysteinyl leukotrienes also play an active role in recruitment of inflammatory cells. Mediators and cytokines released during the early response act on postcapillary endothelial cells to promote expression of adhesion molecules, such as intercellular adhesion molecule 1, E-selectin, and vascular cell adhesion molecule 1, that promote adherence of circulating leukocytes, such as eosinophils, to endothelial cells. Factors with chemoattractant properties, such as IL-5 for eosinophils, promote the infiltration of the superficial lamina propria of the mucosa with many eosinophils, some neutrophils and basophils, and eventually $CD4^+$ (Th2) lymphocytes and macrophages (Wallace et al., 2008). These cells become activated and release more mediators, which in turn activate many of the proinflammatory reactions seen in the immediate response.

Priming effect

The amount of allergen necessary to elicit an immediate response becomes less when allergen challenges are given repeatedly, a phenomenon called the priming effect (Heppt et al., 2004; Wallace et al., 2008). During ongoing, prolonged allergen exposure and repeated late-phase/inflammatory responses, the nasal mucosa becomes progressively more inflamed and responsive to allergen. Clinically, the priming effect can explain why patients might have increasing symptoms despite decreasing aeroallergen levels as a season progresses and also provides the rationale for initiating effective anti-inflammatory rhinitis therapies before a pollen season or before other chronic or repetitive aeroallergen exposures. In addition, the priming effect from allergen is also associated with mucosal hyperresponsiveness to nonantigenic triggers, such as strong odors and cigarette smoke (Dykewicz and Hamilos, 2010).

1.5 Sign and Symptoms of allergic rhinitis

Classically the sensitized human nasal response to challenge with a relevant antigen can be itemized as consisting of the following symptoms and sign profile (Al Suleimani and Walker, 2007):

(i) sneezing, generally occurs as multiple events and for extended periods;

(ii) itching, in and around the nose and nasal mucosa;

(iii) rhinorrhea, a copious water secretion from the nose;

(iv) nasal congestion with airflow through one of both nasal passages being impaired, even to the point of complete blockade.

The acute signs of allergic rhinitis include the following:

(i) engorged nasal mucosa, with obvious congestion and obstruction;

(ii) infiltration of immune cells into the nasal mucosa as shown by taking swabs of the nasal passages or by nasal lavage.

Allergic rhinitis associated nasal congestion results from dilation of venous capacitance vessels in the nasal submucosa and increase vascular permeability, mucosa oedema with influx of inflammatory cells, and excess secretions (Rappai et al., 2003). The allergic response is composed of two phases: the early phase and late phase. During the early-phase nasal allergic response, antigen deposition on

the mucosa surface results in binding of IgE antibodies to respiratory mucosa mast cells and peripheral blood basophils. Consequent mast cell degranulation and release of chemical mediators (e.g., histamine, leukotrienes, and proinflammatory cytokines) is the process primarily responsible for sneezing, itching, and rhinorrhea (Baranluk, 1997; Gelfand, 2004; Hansen et al., 2004). Nasal congestion – the predominant late phase symptom – results from the infiltration of inflammatory ccells (eosinophils and T ells) into tissue, and consequent prolonged release of mediators (histamine, leukotrienes, and prostaglandins) (Storms, 2004).

Nasal congestion increase in the supine position, thus worsening its effects during sleep (Rundcrantz, 1969). In addition, nasal congestion, rhinorrhea, and sneezing exhibit circadian rhythms, with the greatest intensity in early morning, thus exacerbating their negative effects on sleep (Reinberg et al., 1988; Smolensky et al., 1995). Allergic rhinitis-related inflammatory mediators also exhibit a circadian pattern, with levels peaking in early morning (Aoyagi et al., 1999). Moreover, sympathetic tone decrease at night, resulting in a relative parasympathetic excess, which is associated with nasal congestion and reduced bronchial dilation (Ferguson, 2004).

1.6 Treatment of allergic rhinitis

1. Allergen avoidance

Rhinitis symptoms due to inhaled allergens may resolve in the absence of allergen (Kemp, 2009). Avoidance of inciting factors, such as allergens (house dust mites, molds, pets, pollens, and cockroaches), irritants, and medications, can effectively reduce symptoms of rhinitis. In particular, patients allergic to house dust mites should use allergen-impermeable encasings on the bed and all pillows. Pollen exposure can be reduced by keeping windows closed, using an air conditioner, and limiting the amount of time spent outdoors (Dykewicz and Hamilos, 2010).

2. Medications

Selection of medications should be individualized based on multiple considerations, including patient preference (e.g., intranasal vs oral), individual response (which can differ from average responses in the general population), and cost (Wallace et al., 2008). Some medications are more effective for treating certain types of rhinitis (e.g., allergic vs nonallergic), more severe symptoms, or particular rhinitis

symptoms that are more bothersome to a patient (eg, nasal congestion) (Bousquet et al., 2008; Wallace et al., 2008). Medications also differ in onset of action, with those having more rapid symptom relief better suited to treating episodic rhinitis (defined by the Joint Task Force as allergic nasal symptoms elicited by sporadic exposures to inhalant aeroallergens that are not usually encountered in the patient's indoor or outdoor environment) (Wallace et al., 2008) or intermittent symptoms (defined by Allergic Rhinitis and Its Impact on Asthma guidelines as present <4 days per week or <4 weeks duration) (Bousquet et al., 2008).

3. Allergen immunotherapy/allergy vaccination

Subcutaneous allergen immunotherapy can be highly effective in controlling symptoms of allergic rhinitis and favorably modifies the long-term course of the disease (American Academy of Allergy, 2007). Sublingual immunotherapy with single allergens, although part of clinical practice for the treatment of rhinitis in Europe, is undergoing clinical trials in the United States and is not approved by the US Food and Drug Administration (FDA) at the time of this manuscript's submission. Patients with allergic rhinitis should be considered candidates for immunotherapy on the basis of the severity of their symptoms, failure or unacceptability of other treatment modalities, presence of comorbid conditions, and possibly as a means of preventing worsening of the condition or the development of comorbid conditions (eg, asthma and sinusitis) (American Academy of Allergy, 2007; Wallace et al., 2008). Approximately 80% of patients will experience symptomatic improvement after 1 to 2 years of subcutaneous immunotherapy, and guidelines recommend that treatment be continued for a total of 4 to 5 years (American Academy of Allergy, 2007). In many patients the beneficial effects persist for years after injections are stopped. Allergen immunotherapy for allergic rhinitis can reduce the development of asthma in children and possibly in adults (American Academy of Allergy, 2007; Wallace et al., 2008).

2. Cytokines

Cytokines, a class of molecular-weight molecules produced by many different cells in a highly regulated fashion, change the behavior and function of many different

cells. Cytokines are regulatory and effector molecules that act at picomolar to nanomolar concentrations on cytokine receptors expressed by target cells. Cytokines are involved in signal transduction; they activate genes for growth, differentiation, and cell activity. They play a cardinal role in mediating the host's defense against internal and external antigentic insults (Elgert, 2009).

In 1979, an international workshop was convened to address the need to develop a consensus regarding the definition of these macrophage- and T cell-derived factors. Since they mediated signals between leukocytes, the term interleukin (IL) was coined. The macrophage-derived LAF and T cell-derived growth factor were given the names interleukin-1 (IL-1) and interleukin-2 (IL-2), respectively. Currently, numbers have been assigned to 29 interleukins, and the number will undoubtedly increase as research efforts continue to identify new members of this cytokine family (Coico et al., 2003).

2.1 Characteristic of cytokine and their receptor (Elgert, 2009)

2.1.1 Cytokines are usually low molecular weight (usually < 30 kD) glycoproteins that are biochemically distinct. They are divided into four groups: the the hematopoietin family, the interferon family, the chemokine family, and the tumor necrosis family.

2.1.2 Cytokines are obtained from lymphoid and nonlymphoid tissues and cell.

2.1.3 Cytokines are pleiotropic (they can have multiple overlapping biological activities in disparate organ systems or cell); they are often redundant (different cytokines exhibit the same function). For example, IL-2, IL-4, and IL-5 can induce proliferation of B cells (Figure 2.5)

2.1.4 Cytokines are involved in inflammation and immunity; they regulate the amplitude and duration of the response. Some cytokines acts as regulators of cell division.

2.1.5 Cytokines are produced by lymphoid cells in response to:

a. Nonspecific mitogenic stimulants and

b. Specific antigenic stimulant (if previously sensitized).

2.1.6 Cytokines are compartmentalized. They are usually produced locally and transiently, acting in an autocrine (binding to the same cell that secreted the cytokine) or paracrine (binding to a nearby cell), rather than endocrine (binding to a distant cell), manner (Figure 2.5). The cytokines produced during an immune response interact in a cascade fashion.

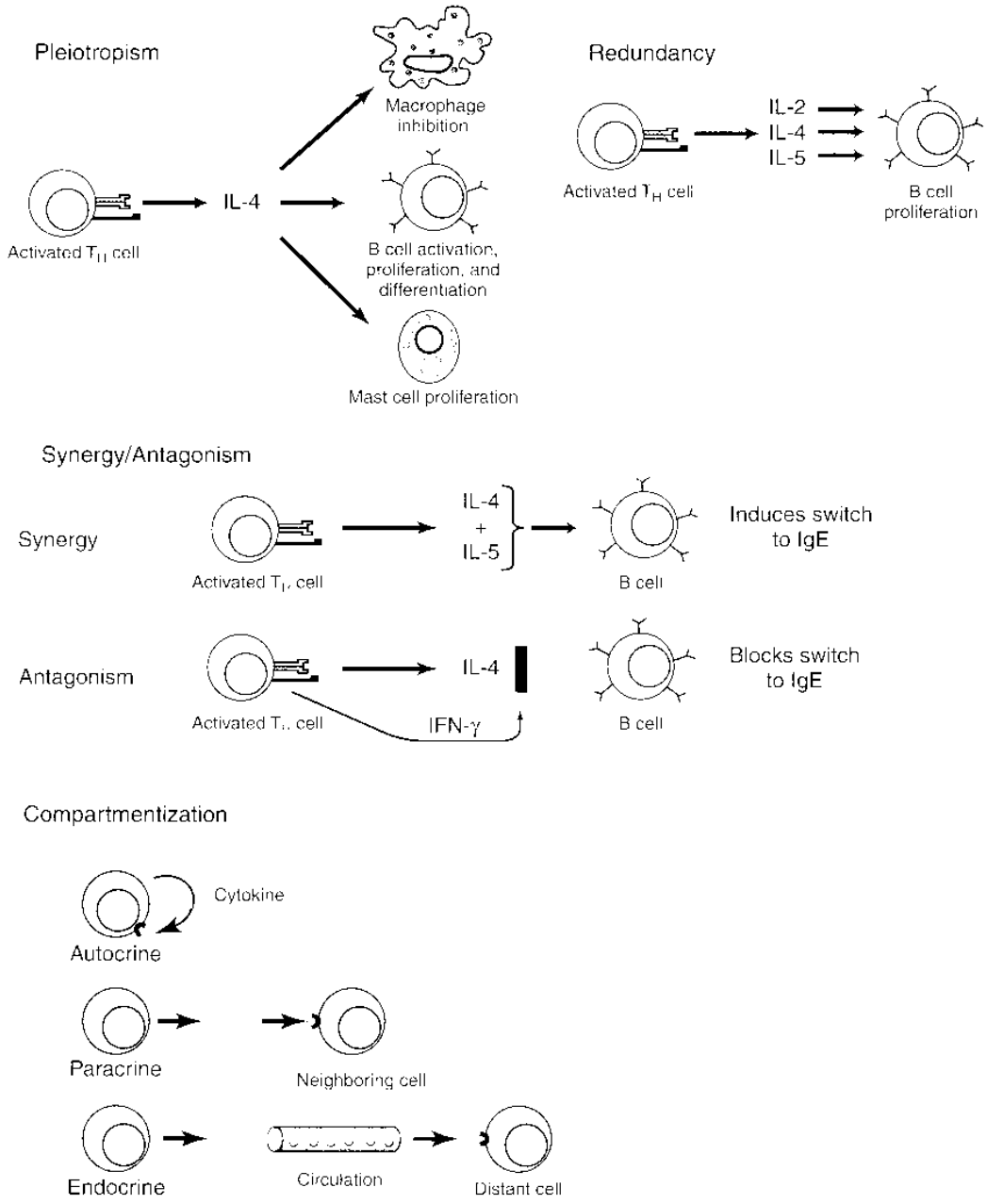

Figure 2.5 Characteristic of cytokine (Elgert, 2009)

2.1.7 Cytokines are synthesized briefly, are secreted in nanomolar amounts, and are self-limiting; thus, they have high specific activity (great biological potency at low concentrations).

2.1.8 Cytokines are nonspecific and antigen-independent in mode of activity. They react directly with many different types of target cells (pleiotropism) through high-affinity cell surface receptors specific for each cytokine or cytokine group. Many of these receptors have two polypeptide chains: a cytokine-specific α chain and a signal-transducing β chain. Some cytokines share chains (such as, the common γ chain), and some have three chains. Cytokine binding leads to a change in the pattern of cellular RNA and protein synthesis and to altered cell behavior. The target cells are as follow;

a. Inflammatory cells: leukocytes (neutrophils, macrophages) and lymphocyes,

b. Noninflammatory cells: endothelial cells, osteoclasts, and fibroblasts.

2.1.9 All cytokine receptors have the typical receptor structure: an extracellular domain, a single membrane-spanning domain, and a cytoplasmic domain. The conserved amino acid sequence motifs found in the extracellular domains are used to defined the cytokine-receptor families: Ig superfamily receptor, class I cytokine receptors, class II cytokine receptors, TNF receptor, and chemokine receptor.

2.1.10 Cytokine interacts in a network by:

a. Inducing each other (cascade-like activity).

b. Transmodulating cytokine cell surface receptors.

c. Interacting synergistically on cell functions.

2.2 Cytokine abbreviations, sources, and functions (Elgert, 2009)

Cytokine abbreviations, sources, and functions were shown in Table 2.1 as following.

Table 2.1 Cytokine abbreviations, sources, and functions

Abbreviations	Sources	Functions
Interleukins		
IL-1α, IL-1β	Monocytes, macrophages, endothelial cells, epithelial cells, and others	Mediates host inflammatory response: vasculature inflammation, fever, stimulates acute phase protein production, promotes T_H2 cell proliferation
IL-2	T_H0, T_H1	Stimulates T-cell growth or activation-induced cell death, costimulates B-cell proliferation, NK cell activation
IL-3	$T_H$cells, NK cell, mast cell	Stimulates hematopoietic cell growth (one of the CSFs); stimulates mast cell growth
IL-4	T_H2 cells, mast cell	Promotes T_H2 cell growth; costimulates B-cell proliferation; enhances IgG_1 and IgE production; stimulates class II MHC molecule expression on B cells; inhibits T_H1 cells
IL-5	T_H2 cells	Stimulates B-cell growth and antibody production; enhances IgA production by stimulated B cells; enhance eosinophil activation and differentiation
IL-6	T cells, macrophages, endothelial cells,	Stimulates hematopoietic progenitors; induces production of acute phase proteins; stimulates T cell activation and IL-2 production; promotes

	and others	B-cell proliferation and antibody secretion
IL-7	Bone marrow cells, thymic stromal cells	Stimulates pre-B cells and pre-T cells (one of the CSFs)
IL-9	IL-2 activated $T_H$cells	Stimulates T cell proliferation; mast cell activation
Abbreviations	Sources	Functions
IL-10	T_H2 cells, macrophages	Inhibits cytokine synthesis by T_H1 cells and activated macrophages; enhances B cell, thymocyte, and mast cell proliferation; in association with TGF-β, it stimulates IgA synthesis
IL-11	Bone marrow stromal cells, fibroblasts	Stimulate megakaryocyte growth; growth factor of macrophage progenitors
IL-12	Macrophages, dendritic cells	Induces IFN-γ production from T and NK cells; enhance of NK cell cytotoxic activity; stimulates differentiation of $CD4^+$ T cell to T_H1 cells
IL-13	Activated T cells, NK cells, and mast cells	Blocks inflammatory monokine production; shares activity with IL-4; growth factor for B cells
IL-14	T cells	B-cell growth factor; inhibits antibody synthesis
IL-15	Mainly dendritic cells and monocytic cell lineage, T cells, epithelial cells, and others	Shares IL-2 bioactivities: T cell and NK cell growth factor; augments NK cell activation
IL-16	T cells	Chemotactic for $CD4^+$ T cells, $CD4^+$ macrophages, eosinophils; completes

		with HIV binding to CD4 molecule
IL-17	Mainly $CD4^+$ T cells (T_H17)	A family of six cytokines; proinflammatory activity; induces severe autoimmunity
IL-18	Monocytic cell lineage, dendritic cells, and others	Promotes T_H1 cells differentiation; induces T cell IFN-γ production; enhances NK cell activity
Abbreviations	Sources	Functions
IL-19	LPS-stimulated monocytes and B cells	Member of IL-10 family of cytokines that induces proinflammatory cytokines; alter T_H1/ T_H2 balance by inhibiting IFN-γ and enhancing IL-4 and IL-13 production
IL-20	Monocytes and keratinocytes	IL-10 family member with similar activity as IL-19
IL-21	Activated T cells	Enhance NK cell and T_c cell cytotoxicity and IFN-γ production
IL-22	Mainly $CD4^+$ T cells	IL-10 family member that inhibits epidermal differentiation and has activity similar to IL-19 and -20
IL-23	Activated dendritic cells	IL-12 family member that stimulates $CD4^+$ T cells to produce IL-17
IL-24	B cells, fibroblasts, melanocytes, NK cells, and T cell subsets	IL-10 family member that induces IFN-γ and TNF-α and low levels of IL-1β, IL-12, and GM-CSF
IL-25	Bone marrow stromal cells, T cell subsets	IL-17 family member that induces production IL-4, IL-5, IL-13, and eotaxin; involved airway disease of the lung
IL-26	T and NK cell subset	IL-10 family member with functions similar to IL-20

IL-27	Dendritic cells, macrophages, endothelial cells, and plasma cells	IL-12 family member that has pro- and anti-inflammatory activities
Abbreviations	**Sources**	**Functions**
IL-28 A/B	Monocyte-derived dendritic cells	An IFN-like molecule that is coexpressed with IFN-β; exhibits antiviral activity and induces class I and II MHC molecule expression
IL-29	Monocyte-derived dendritic cells	Activities similar to IL-28 A/B
IL-30	Antigen-presenting cells	A subunit of IL-27 with functions similar to IL-27
IL-31	Primarity activated T_H2 cells, which can be induced by activated monocytes	Possible recruitment of monocytes, neutrophils, and T cells to areas of skin inflammation
IL-32	Activated NK cells and peripheral blood mononuclear cells	IL-1 family member that is a proinflammatory cytokine; induces TNF-α
IL-33	Smooth muscle cells, epithelial cells; levels by TNF-α and IL-1β induced dendritic cells and macrophages	IL-1 like cytokine that induces T_H2 cell-associated cytokines
IL-35	$CD4^+$ $CD25^+$	IL-12 family cytokine is required to mediate

	FOXP3$^+$ T_{reg} cells	their suppressive activity
Interferons		
IFN-α	Lymphocytes, dendritic cells, and macrophages	Induces antiviral resistance; inhibits cellular proliferation; controls class I MHC molecule expression
Abbreviations	**Sources**	**Functions**
IFN-β	Fibroblasts, dendritic cells	Same activity as IFN-α
IFN-γ	CD4$^+$ and CD8$^+$ T cells, NK cell	Activates B cells, T cells, macrophages, and NK cells; induces class II MHC molecule expression on APCs; T_H1 cell signature cytokine; inhibits all activities of IL-4 on B cell; weakly inhibits viral replication
Tumor necrosis factor		
TNF-α	Monocytes, macrophages, and others such as, activated T cells, fibroblasts, NK cell, and neutrophils	Vascular inflammatory; regulates growth of many different cell types; causes apoptosis of target cells; induces acute phase proteins; promotes angiogenesis and cachexia; activates neutrophils and endothelial cell
TNF-β	Activated T_H1 cell, B cells, astrocytes, fibroblasts, and endothelial and epithelial cells	Causes apoptosis of target cells; promotes fibroblast growth; inhibits osteoclasts and keratinocyte growth; induces terminal differentiation of monocytes; activates neutrophils, enhances adhesion
Colony-stimulating factors		
CSF	Colony-stimulating factors	Stimulate the growth of colonies of granulocyte and macrophages from bone marrow progenitor

		cells; some activate mature macrophages
Other		
TGF-β	Many different cell types	Inhibits and stimulates extracellur matrix formation; also inhibits B-, T-, and NK-cell activity; switches antibody production to IgA

2.3 T-helper lymphocyte and allergy

Th1 and Th2 subsets develop from the same precursor cells, which are $CD4^+$ T lymphocytes, and the pattern of differentiation is determined by environmental stimuli present early during immune responses (Figure 2.6) (Ngoc et al., 2005). Further consideration of these environmental exposures is beyond the scope of this review. Th2 differentiation occurs in response to environmental allergens and helminths via activated antigen-presenting cells under the influence of IL-4. Activated Th2 lymphocytes produce IL- 4, IL-13, and IL-5, which are responsible for IgE production by B cells, eosinophil activation and recruitment, and mucus production (Romagnani, 1994; Akdis et al., 2004). In contrast, Th1 cells differentiate from naı¨ve $CD4^+$ cells in response to microbial activation of antigen-presenting cells under the influence of IL-12. Differentiated Th1 cells secrete interferon-g, which is important in intracellular destruction of phagocytosed microbes. Furthermore, interferon- g produced by Th1 cells and IL-4 produced by Th2 counter-regulate each other (De Vries et al., 1999).

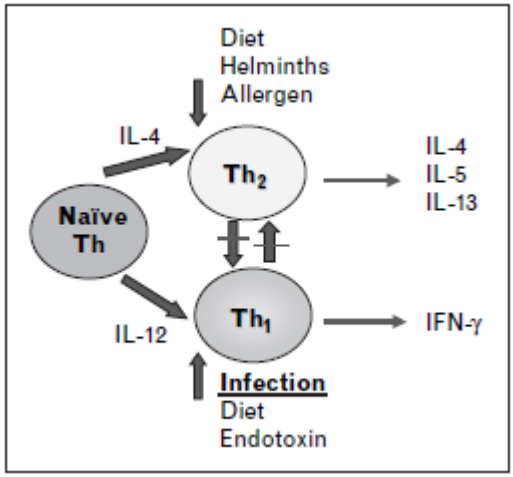

Figure 2.6 T-helper lymphocyte differentiations to Th1 or Th2

(Ngoc et al., 2005)

Despite variation in sample sizes, laboratory techniques, and age or risk factors of the cohort examined, results from cross-sectional and longitudinal studies have consistently demonstrated a strong association between an upregulated Th2 immune response and atopic diseases. Studies have shown that cord-blood IL-13 in response to dust mite (Der p 1) and phytohemagglutinin were associated with atopic dermatitis at age 3 years (Lange et al., 2003). In a group of 175 children with a high genetic risk for atopy based on family history, staphylococcal enterotoxin Binduced IL-13 responses in cord blood were shown to be the strongest independent predictor of allergy development as defined by positive skin-prick test at age 2 years (Rowe et al., 2004). However, the heightened Th2 immune response to allergens or mitogens associated with allergy or atopic diseases is more consistently observed in peripheral blood obtained from children early in postnatal life rather than at birth. For example, a study in which investigators measured unstimulated cord-blood cytokine levels reported an association between lower concentrations of IL-4 and interferon-g at birth and wheeze at 6 years (Macaubas et al., 2003). In another study, it was demonstrated that children who had a positive skin-prick test at age 6 years had lower Th2 (IL-13 and IL-6) cytokine responses at birth. However, a positive skin-prick test to house dust mite at 6 years was associated with higher IL-13 response to house dust mite at 1 year; clinical atopic disease at 6 years was associated with higher IL-5 mRNA responses to house dust mite at 1 year (Prescott et al., 2003). Similarly, Neville and his group demonstrated that, although there were no associations between neonatal phytohemagglutininstimulated Th2 cytokines and atopic markers of allergy (i.e. absolute eosinophil count and total IgE) at age 1 year, there were associations between increased levels of IL-5 and IL-13 (Th2 polarization) and atopic markers of allergy at age 1 year (Neaville et al., 2003). These two studies demonstrated that Th2 cytokines, although low at birth, increase significantly from birth to age 1 year (Neaville et al., 2003) and from birth to age 2 years (Prescott et al., 2003). One study showed an association of increased IL-4 at 18 months and atopic disease at age 6 years (Borres and Bjorksten, 2004). In cross-sectional analysis of an older group of children ages 2–3 years, it was

shown that allergenstimulated IL-13 was associated with allergic sensitization and clinical allergy or wheeze (Contreras et al., 2003). Th2 cytokine responses have been demonstrated in peripheral blood of atopic or asthmatic patients as well as at target sites of inflammation such as asthmatic airways (Boniface et al., 2003; Cho et al., 2004)

2.4 Cytokines and allergic rhinitis

Allergic rhinitis is characterized by the development of nasal mucosal inflammation in response to natural allergen exposure. Inflammatory allergic disorders are characterized by the production of numerous cytokines and chemokines by activated cells present in target tissues, including T cells, mast cells, macrophages and eosinophils. Moreover, allergic inflammation is associated with a shift in the balance between cytokines produced by Th1 and Th2 cells toward a Th2 predominance (Romagnani, 1997). The allergen induces Th2 lymphocyte proliferation with the release of characteristic combination of cytokines such as IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and granulocyte–macrophage colony-stimulating factor (GM-CSF). Th1 cells produce a different cytokine profile characterized by IFN-ϒ secretion (Scavuzzo et al., 2003).

IL-4 cytokine appears to be an essential requirement for IgE production and IL-4 production is critical for the development of Th2 cells. Inside, IFN-ϒ inhibits IgE production and plays a negative regulatory role in the Th2 cell development (Del Prete et al., 1988). However, the mechanisms underlying the preferential activation of Th2 cells by environmental allergens in atopic individuals still remain unclear. A number of recent studies on nasal mucus samples suggest that the level of IL-4 increases in allergic rhinitis (Scavuzzo et al., 2003; Sausenthaler et al., 2009).

IL-2 has been shown to play a major role in the immune system, e.g. it regulates the growth and function of cells that are involved in both cell-mediated and humoral immune responses. IL-2 is produced by T cells in the course of T cell activation and because IL-2 promotes and regulates the growth and function of immune cells (Smith, 1984; Balkwill, 1991).

IL-13 is an important cytokine that regulates inflammatory and TH2 immune responses. IL-13 shares many activities with IL-4, in large part because both

use a common receptor subunit (IL-4Rα-chain) as part of their receptor (Miyahara et al., 2006). As a result, IL-13 like IL-4, acts on B cells and stimulates both proliferation and IgE synthesis in these cells (Defrance et al., 1994; McKenzie et al., 1998). However, IL-13 but not IL-4 appears to be an effector cytokine that directly contributes to bronchial hyperreactivity and mucus overproduction in mouse models of asthma (Zhu et al., 1999). IL-13 has been shown to be produced by T cells, B cells, mast cells, basophils, eosinophils, and natural killer cells (Schmid-Grendelmeier et al., 2002). In allergic rhinitis, the IL-13 gene is expressed in the nasal mucosa of patients with perennial allergic rhinitis (AR) or after allergen provocation. Miyahara et al. (2006) reported that wild-type (WT) mice that were sensitized and challenged (intranasally) exhibited increased levels of IL-13 in nasal tissue homogenates compared with challenged-only mice.

TNF-α is considered to be a pro-inflammatory cytokine that has a crucial role in the initiation and continuation of inflammation and immunity, including allergic inflammation (Iwasaki, 2003). TNF-α is a candidate cytokine relevant to the pathogenesis of these events through its capacity to upregulate the expression of endothelial cell adhesion molecules, mediate granulocyte chemoattraction, and activate eosinophils, mast cells and T cells in allergic rhinitis (Bradding et al., 1995).

3. Oxidant and Antioxidant

3.1 Free radicals and oxidative stress

Oxidative damage is caused by free radicals – chemicals or compounds which, by virtue of having unpaired electrons, are unstable, highly reactive and seek to stabilize themselves by “stealing” electrons from other chemicals or compounds (including proteins, carbohydrates, lipids and DNA), thereby oxidising the latter (Figure 2.7). In the process they create more free radicals, sparking off a chain of destruction. The results of free radical damage or oxidation include cell injury, making the cells more vulnerable to infection and degenerative disease, and DNA damage, interfering with normal cell division and resulting in mutations. Thus oxidative damage accompanies most, if not all, diseases and has been implicated in the pathogenesis of cancer,

diabetes, heart disease, arthritis, neurodegenerative disorders, atherosclerosis, osteoporosis, pancreatitis and, specific to women's health, pre-eclampsia. While free radicals are produced during normal respiration and metabolism, their production can also be triggered by exposure to air pollutants, sun exposure, radiation from X-rays, drugs, viruses, bacteria, parasites, dietary fats, stress and injury (Talaulikar and Manyonda, 2011).

A free radical is a chemical species that has an odd number of electrons. In the context of oxidative stress the radicals are small molecules/ions that are reactive with small activation energies and short lifetimes. The small size makes it possible for many of them to penetrate cell membranes. The free radicals can be considered as a subset of reactive oxygen or nitrogen species. A major part of reactive oxygen species originates as by-products of the aerobic metabolism in the mitochondria. The superoxide anion, O_2^- is produced in the inner membrane of the mitochondria as part of the mechanism, which reduces O_2 to water (Jensen, 2003).

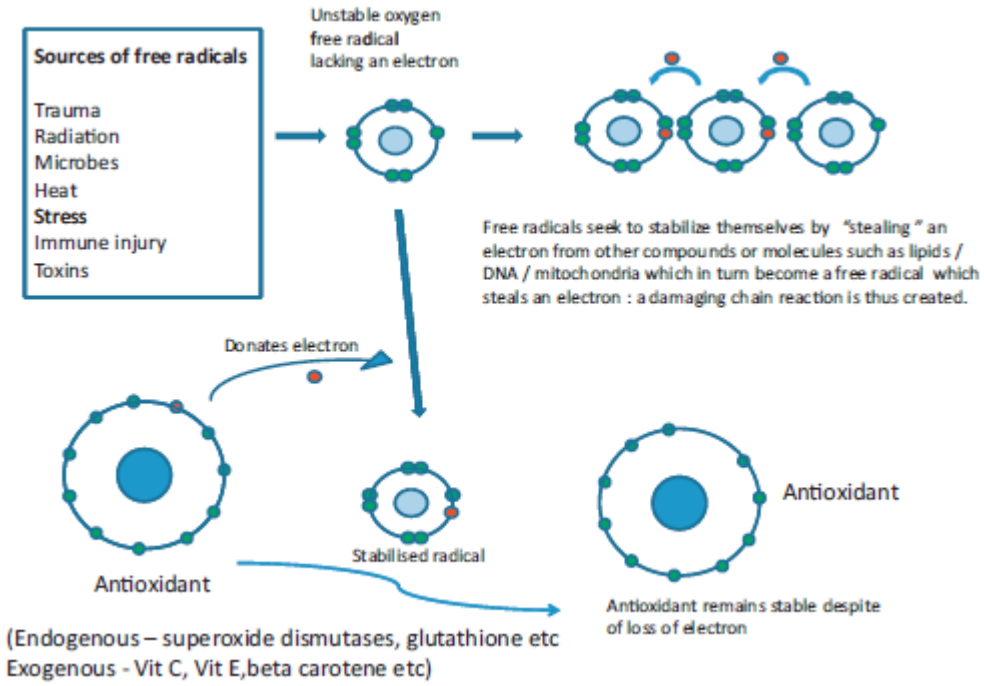

Figure 2.7 Interaction of oxygen free radicals and antioxidants.

(Talaulikar and Manyonda, 2011)

Malondialdehyde

Aldehydes, especially MDA, have been frequently used as markers of oxidative stress in response to exercise. Figure 2.8 presents the chain of chemical reactions leading to MDA, which can be measured by HPLC, spectrophotometry or spectrofluorescence (Halliwell and Chirico, 1993). The most common method used to assess changes in MDA with exercise is the thiobarbituric acid (TBARS) assay.

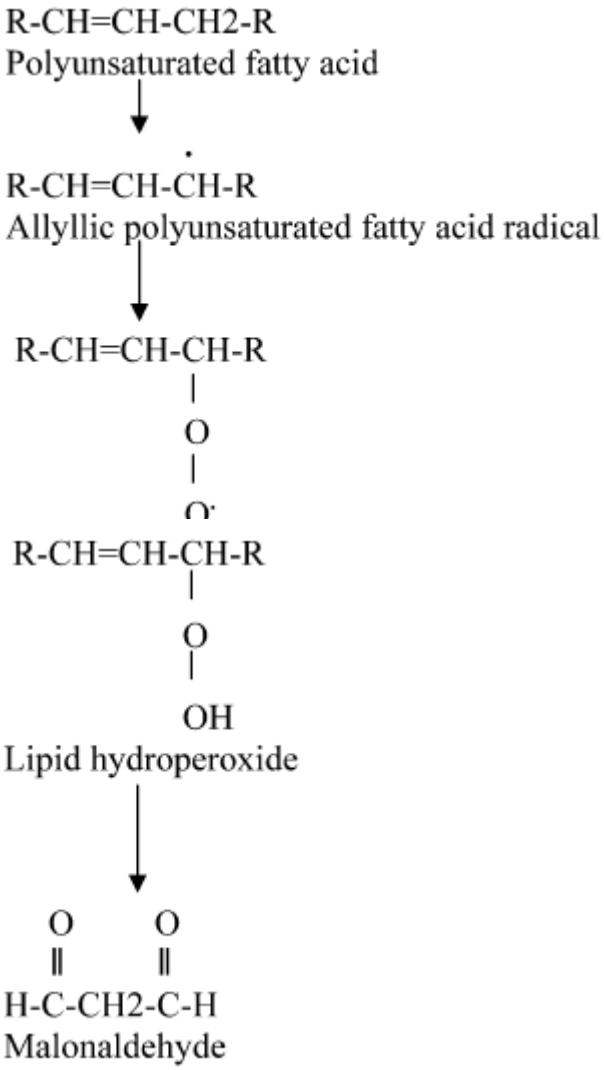

Figure 2.8 Steps of lipid peroxidation (Alessio, 2000).

This method works well when used on defined membrane systems such as microsomes in vitro (Halliwell and Chirico, 1993), but the method has been criticized for use in human studies of oxidative stress because TBARS lacks specificity. The assay also reacts with saturated and unsaturated nonfunctional aldehydes, carbohydrates and prostaglandins (Alessio, 2000).

Resting plasma MDA was found to be higher in sprint trained athletes and marathon runners compared with control subjects (Marzatico et al., 1997). Santos-Silva et al. (2001) also found elevated resting MDA levels in trained adolescent swimmers compared with control subjects. In contrast, Niess et al. (1996) reported higher plasma MDA in untrained subjects compared with trained subjects, and Miyazaki et al. (2001) observed no change in erythrocyte MDA after a 12-week training program.

3.2 Antioxidant

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules by being oxidized itself. As stated above, oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants neutralize free radicals by donating one of their own electrons, ending the electron-"stealing" reaction. The antioxidants do not become free radicals when they donate an electron because they are stable in either form. They act as scavengers, helping to prevent cell and tissue damage. Antioxidants are often reducing agents such as thiols, ascorbic acid or polyphenols. Although oxidation reactions are crucial for life, they can also be damaging; hence plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C and vitamin E, as well as enzymes such as catalase, superoxide dismutase and various peroxidases. Low levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress and may damage or kill cells. Therefore the potential for antioxidants in preventing disease has attracted much attention (Talaulikar and Manyonda, 2011).

It has been known for a long time that diets rich in fruits and vegetables appear to protect against the types of diseases associated with free radical damage, including certain types of cancer, heart disease, dementia, diabetes and stroke. The attractive supposition has been that fruits and vegetables are a rich source of antioxidants that can neutralize free radicals. Green plants are especially vulnerable to

oxidative stress since they produce pure oxygen during photosynthesis, and therefore need to manufacture a range of potent antioxidants to protect themselves. Thus the concept that fruits and vegetables contain antioxidants that could also be given as supplements or in fortified foods gained ground and spawned what is now a multi-billion dollar 'nutraceutical' industry that vigorously promotes the sale and consumptions of capsule-packaged "pure antioxidants" in pursuit of the prevention/amelioration of diseases associated with oxidative stress. The popular range of antioxidants includes vitamin E, vitamin C, carotenoids (including beta carotene and lycopene) and polyphenols (including flavonoids), although the full list of compounds with antioxidant properties is extensive. Vitamin E is the most abundant fat-soluble antioxidant in the body and one of the most efficient chain-breaking antioxidants available, and therefore a primary defender against oxidation. Vitamin C is the most abundant water-soluble antioxidant in the body and acts primarily in cellular fluid, being especially effective in combating free-radical formation caused by pollution and cigarette smoke. In the western world and especially in America it is estimated that up to 50% of the adult population take antioxidant pills on a daily basis to promote health and stave off disease. The question is whether these supplements are effective (Talaulikar and Manyonda, 2011).

3.3 Free radical, antioxidant and exercise

Several studies reported that single bouts of exercise increase blood levels of MDA (Koska et al., 2000; Miyazaki et al., 2001). Marzatico et al. (1997) found plasma MDA increased over 48h post-sprint type exercise in sprinters and immediately post-endurance exercise in marathon runners. Kanter et al. (1988) reported increases in plasma MDA (~70%) following an extreme endurance event (50 m run) in elite athletes. Further, these measures correlated with plasma increases in CK and LDH, markers of muscle damage. Similarly, Child et al. (2000) found an increase in MDA of about 40% immediately after a half marathon.

Not all studies reported increases in MDA in response to exercise (Viinikka et al., 1984). Niess et al. (1996) measured plasma levels of MDA in trained and untrained individuals at rest, before and after an exhaustive bout of exercise. They found no significant increases in MDA in either group following a treadmill test to exhaustion,

either at 15 min post-exercise or 24 h post-exercise. Moderately trained subjects who ran for 2.5 h on a treadmill showed no change in plasma MDA (Duthie et al., 1990; Dufaux et al., 1997). Similarly, there were no documented changes at rest, before or after 4 weeks of high intensity rowing training in plasma MDA levels (Dernbach et al., 1993) in athletes, and Alessio et al. (2000) found no change in plasma MDA after repeated isometric contractions.

Strenuous endurance training was shown to reduce indices of oxidative stress following exhausting exercise (Miyazaki et al., 2001). Untrained male subjects performed an acute period of exercise on a cycle ergometer before and after a 12-week strenuous endurance training program. There was a smaller increase in erythrocyte MDA in response to the exercise bout post-training compared to pre-training. Moreover, decreased levels of MDA in response to exercise have also been reported in highly trained skiers and runners immediately following exercise to exhaustion (Hubner-Wozniak et al., 1994; Rokitzki et al., 1994).

Eccentric exercise, which is known to cause muscle inflammation, has been hypothesized to contribute to increased levels of lipid peroxidation presumably due to macrophage reactions in tissue. Maughan et al. (1989) found increases in MDA 6 h post downhill-running (biased toward eccentric contractions), with these levels returning to baseline levels at 72 h post exercise. Those subjects with the greatest increase in markers of muscle damage, (i.e. CK, lactate dehydrogenase (LDH)) experienced the greatest increases in serum MDA concentrations. However, muscle biopsies taken after a single bout of maximal eccentric exercise failed to show any change in MDA levels (Saxton et al., 1994). Furthermore, Child et al. (1999) reported no change in both plasma and muscle MDA levels following a single bout of eccentric exercise, despite the increase in inflammatory cell invasion into the tissue.

Endurance exercise training protects rats from exercise induced oxidative stress, raising levels of antioxidants and antioxidant enzymes in both skeletal and cardiac muscle (Powers et al., 1999; Leeuwenburgh and Heinecke, 2001). Leeuwenburgh and Heinecke (2001) found that a 10-week exercise program increased glutathione peroxidase and superoxide dismutase activities in the deep portion of vastus lateralis muscle. In another study, they detected a 33% increase in the glutathione

content of this muscle in endurance-trained rats. The rats also had 62% more glutathione peroxidase activity and 27% more superoxide dismutase activity than untrained sibling controls (Leeuwenburgh and Heinecke, 2001).

Moreover, Powers et al. (1999) found that increases in muscle antioxidant enzymes induced by exercise training were muscle-specific. They also showed that high-intensity and moderate-intensity exercise up regulated superoxide dismutase activity in the ventricular myocardium. In addition, we recently demonstrated that old rats that voluntarily ran on a wheel all their lives had higher levels of several skeletal muscle antioxidant enzymes than their sedentary counterparts. The exercising animals also had lower levels of markers of oxidative stress in muscle and urine (Leeuwenburgh and Heinecke, 2001). They continued to be active into old age, though they decreased their running time. This study also detected lower levels of dityrosine in skeletal and heart muscle of the exercising animals. This difference may reflect a decrease in the overall rate of oxidant generation or an increase in antioxidant defenses.

There is support the hypothesis that acute exercise increases oxidant levels and oxidative stress in untrained animals but long-term exercise may counter this effect by increasing the activity of antioxidant enzymes and reducing oxidant production. These defenses may be critical for preventing chronic oxidative damage to muscle during exercise and even at rest (Leeuwenburgh and Heinecke, 2001).

3.4 Oxidative stress and allergic rhinitis

Oxidative stress plays an important role in allergic disorders and increased levels of oxidants are considered as markers of the inflammatory process. Overproduction of oxygen free radicals, while the natural scavenging mechanisms are weakened, is a process that is implicated in cell damage and multiorgan failure (Bowler et al., 2002). The role of oxidative stress in allergic rhinitis is not well studied but is likely to be similar to that of asthma. Ozone exposure exacerbates antigen-induced rhinitis, sneezing, nasal secretions, hyperresponsiveness, and eosinophil infiltration in guinea pigs (Iijima et al, 2001). In allergic rhinitis house dust mite exposure induces nasal eosinophils to produce hydrogen peroxide (Ogasawara et al., 1991).

4. Vitamin C

Vitamin C (ascorbic acid) is a required nutrient for a variety of biological functions. Humans and other primates have lost the ability to synthesize ascorbic acid due to a defect in L-gulono-1, 4-lactone oxidase, an enzyme that catalyzes the conversion of L-gulonolactone into ascorbic acid. Humans, primates, and a few other animals (e.g., guinea pigs) depend on the diet as a source of vitamin C to prevent the vitamin C deficiency disease, scurvy, and to maintain general health. The health-promoting effects of vitamin C can be attributed to its biological functions as a cofactor for a number of enzymes, most notably hydroxylases involved in collagen synthesis, and as a water-soluble antioxidant. Vitamin C can also function as a source of the signaling molecule, hydrogen peroxide, and as a Michael donor to form covalent adducts with endogenous electrophiles in plants. These functions and the underlying mechanisms will be illustrated here with examples from the recent literature. This review focuses on chronic diseases and is not intended to provide an exhaustive account of the biological and clinical effects. Other authors have recently discussed the effects of vitamin C on cancer chemoprevention (Gann, 2009; Gaziano et al., 2009) and in the treatment of cancer (Padayatty et al., 2010), sepsis (Wilson, 2009) and neurodegenerative diseases (Bowman et al., 2009).

Vitamin C is an electron donor and therefore a reducing agent. All known physiological and biochemical actions of vitamin C are due to its action as an electron donor. Ascorbic acid donates two electrons from a double bond between the second and third carbons of the 6-carbon molecule. Vitamin C is called an antioxidant because, by donating its electrons, it prevents other compounds from being oxidized. However, by the very nature of this reaction, vitamin C itself is oxidized in the process (Padayatty et al., 2003).

It is noteworthy that when vitamin C donates electrons, they are lost sequentially. The species formed after the loss of one electron is a free radical, semidehydroascorbic acid or ascorbyl radical. As compared to other free radicals (a species with an unpaired electron), ascorbyl radical is relatively stable with a half-life of

10^{-5} seconds and is fairly unreactive. This property explains why ascorbate may be a preferred antioxidant. In simple terms, a reactive and possibly harmful free radical can interact with ascorbate. The reactive free radical is reduced, and the ascorbyl radical formed in its place is less reactive. Reduction of a reactive free radical with formation of a less reactive compound is sometimes called free radical scavenging or quenching. Ascorbate is therefore a good free radical scavenger due to its chemical properties (Bielski et al., 1975; Buettner and Moseley, 1993).

4.1 Nutrient sources and actions

Vitamin C is an essential water-soluble vitamin that serves as an antioxidant and is responsible for protein metabolism including the biosynthesis of collagen, neurotransmitters and L-carnitine. Vitamin C also plays an important role in immune function and in the absorption of iron from plant-based foods. The antioxidant effects of vitamin C supplementation have been studied primarily for the prevention or delay of certain cancers, cardiovascular disease and disorders involving oxidative stress (Dennehy and Tsourounis, 2010).

Fruits and vegetables are the richest sources of vitamin C. Tomatoes, tomato juice, potatoes and citrus juices are the most abundant sources of vitamin C in the US diet. Other sources include fortified breakfast cereals, bell peppers, broccoli and strawberries (Dennehy and Tsourounis, 2010).

4.2 Vitamin C as an antioxidant

Role of vitamin C on lipid peroxidation

Lipid peroxidation can be considered as an example of a radical chain reaction (Figure 2.9). Reactive oxygen species (ROS) produced by a variety of sources, such as the electron transport chain, xanthine oxidase, myeloperoxidase. And NADPH oxidase, initiate the radical reaction through abstraction of hydrogen atoms from bisallylic C–H bonds, thereby forming lipid radicals (Halliwell and Gutteridge, 1999). Lipids are often prime targets of oxygen radicals because many of the enzymes producing ROS are embedded in lipid bilayers and because the bisallylic C–H bond in polyunsaturated fatty acids (PUFAs) is relatively weak compared to other C–H bonds. Carbon-centered lipid radicals react with molecular oxygen to form peroxyl radicals that,

if not neutralized by α-tocopherol in membranes, may participate in the radical propagation reaction. Lipid hydroperoxides are chemically unstable and, when not reduced by glutathione-dependent reductases to hydroxy-fatty acids, constitute a source of a variety of LPO products, including 2-alkenals, epoxides, and malondialdehyde. Vitamin C has the ability to protect against LPO by acting as a scavenger of ROS and by one-electron reduction of lipid hydroperoxyl radicals via the vitamin E redox cycle (Halliwell and Gutteridge, 1999). Furthermore, findings from our laboratory support a role for vitamin C in protection against cellular damage from LPO-derived 2-alkenals. Vitamin C-adequate cultured human THP-1 cells exposed to the LPO product, 4-hydroxy-2(*E*)-nonenal (HNE) showed a significant reduction in protein carbonylation compared to THP-1 cells that were not preincubated with vitamin C (Miranda et al., 2009; Chavez et al., 2010). The protective effects of ascorbate were associated with an increase in the formation of GSH-HNE conjugate and its phase I metabolites, measured by LC-MS/MS, and with increased transport of GSH conjugates from the cells into the medium (Miranda et al., 2009).

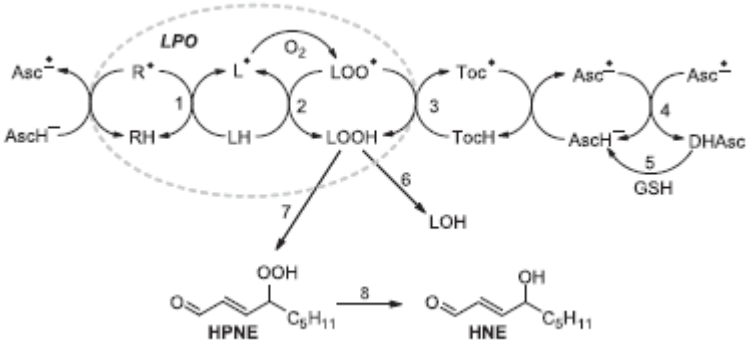

Figure 2.9 Antioxidant effects of vitamins C and E on lipid peroxidation.
(Halliwell and Gutteridge, 1999)

4.3 Clinical efficacy of vitamin C (Dennehy and Tsourounis, 2010)

Bone health

Epidemiologic studies have demonstrated a positive association between BMD and intake of vitamin C. Low vitamin C intakes have been associated with a decline in BMD specifically at the femoral neck and total hip. One study found that

among postmenopausal women who had a history of smoking and estrogen use, vitamin C was associated with a decreased prevalence of self-reported fractures. Among postmenopausal women who were taking estrogen, calcium and vitamin C (mean dose 745 mg daily), higher BMD levels were observed at the femoral neck, total hip, distal radius and lumbar spine as compared to those not taking vitamin C.

Cardiovascular health

Observational studies evaluating vitamin C for primary prevention of coronary heart disease have found conflicting results in women. Across multiple large clinical trials, vitamin C supplementation alone or in combination with vitamin E, and beta-carotene appears to be ineffective at secondary prevention of CHD in pre- and postmenopausal women.

Breast cancer

There is limited evidence to support the use of vitamin C in the primary prevention of total cancer incidence, including breast cancer, among menopausal women. One of the largest studies in women found that vitamin C (500 mg daily) had no effect on the incidence of cancer after 9.4 years of follow-up. Vitamin C (500 mg daily), when combined with vitamin E (400 mg daily) and tamoxifen therapy in postmenopausal women with breast cancer have been shown to reduce tamoxifen-induced increases in triglycerides (41 mg/dL) and VLDL (12 mg/dL) after 3 months of therapy. Since tamoxifen may increase the synthesis of VLDL and reduce the activity of lipoprotein lipase which hydrolyses triglycerides, vitamin C and vitamin E may help mitigate these effects.

Cognition

Vitamin C has not been specifically studied for its effects on cognition in postmenopausal women, however it has been studied in older women (>65 years of age) when combined with vitamin E and beta-carotene. At 3.5 years, vitamin C (500 mg daily) was not associated with cognitive change over time but was more protective against cognitive change among older women with new cardiovascular events as compared to placebo. Another study in older men and women also found that vitamin C and E when combined with NSAIDs resulted in less cognitive decline than in those not taking these vitamins.

4.4 Vitamin C and allergic rhinitis

Vitamin C is also associated with immune cells and immune responses. Millimolar vitamin C, which is far above the plasma concentration, is accumulated in immune cells including neutrophils, B cells, T cells, monocytes, and macrophages and acts as an anti-oxidant to protect these cells from reactive oxygen radicals produced during immune responses such as inflammation and oxidative bursts (Jeong et al., 2010). Podoshin et al. (1991) reported that vitamin C was found to decrease symptoms of perennial allergic rhinitis patient, parallely there was a decrease of the pH of nasal secretion to normal limits. In addition, recent study reported that vitamin C play a role in the development of allergic sensitization and allergic diseases and it was negatively associated with an increased risk of current AR symptoms (Sausenthaler et al., 2009). Thornhill and Kelly, (2000) found that treated with vitamin C have decreased nasal secretions, blockage, and edema. Improvement was seen in only 24 percent of placebo treated patients. The pH of the secretions in the allergic rhinitis sufferers appeared to be more alkaline, over 7.0, with normal nasal secretions tending be in the range of 5.5-7.0. The pH of nasal secretion was found to be within normal ranges after administration of vitamin C; patients with nasal pH's closer to 8.0 seemed to respond more favorably to the vitamin C therapy (Podoshin et al., 1991). Vitamin C is nontoxic and virtually free of side effects, diarrhea and abdominal distention being the most common. For allergic rhinitis, a dosage of at least 2 grams per day should be administered (Bucca et al., 1990).

5. Exercise

Exercise places an increased demand on the cardiovascular system. Oxygen demand by the muscles increases sharply. Metabolic processes speed up and more waste is created. More nutrients are used and body temperature rises. To perform as efficiently as possible the cardiovascular system must regulate these changes and meet the bodys increasing demands (Wilmore and Costill, 2005).

5.1 Acute exercise and chronic exercise

Acute exercise

Acute exercise refers to a bout of exercise done at a specific time for a specific amount of time. Acute anxiety is anxiety that exists in a person in response to a specific event (Landers, 1997).

Immediate Response of the Cardiovascular System to Exercise

After the initial anticipatory response, heart rate increases in direct proportion to exercise intensity until a maximum heart rate is reached. Stroke volume may increase only up to 40-60% of maximal capacity after which it plateaus. Beyond this relative exercise intensity, stroke volume remains unchanged right up until the point of exhaustion (Crawford et al., 1985; Higginbotham et al., 1986). But this is not conclusive and other studies suggest stroke volume continues to rise until the pint of exhaustion (Scruggs et al., 1991). Cardiac output increases proportionally with exercise intensity - which is predictable from understanding the response of heart rate and stroke volume to activity. At rest the cardiac output is about 5L/min. During intense exercise this can increase to 20-40L/min (McArdle et al., 2000). During vigorous exercise this increases to 80-85% of cardiac output. Blood is shunted away from major organs such as the kidneys, liver, stomach and intestines. It is then redirected to the skin to promote heat loss. Systolic pressure, the pressure during contraction of the heart (known as systole) can increase to over 200 mmHg and levels as high as 250mmHg have been reported in highly trained, healthy athletes. Diastolic pressure on the other hand remains relatively unchanged regardless of exercise intensity (Wilmore and Costill, 2005).

Chronic exercise

Chronic refers to something that persists for a relatively long period of time. Chronic depression, for example, would be depression that lasts a long time. A chronic exerciser is someone who does exercise on a regular basis (Landers, 1997). Exercise training specificity refers to adaptations in metabolic and physiologic functions that depend upon the type and mode of overload imposed. A specific anaerobic exercise stress (e.g., strength-power training) induces specific strength-power

adaptations; specific endurance exercise stress elicits specific aerobic system adaptations with only a limited interchange of benefits between strength power training and aerobic training. Nonetheless, the specificity principle extends beyond this broad demarcation. Aerobic training, for example, does not represent a singular entity requiring only cardiovascular overload. Aerobic training that relies on the specific muscles in the desired performance most effectively improves aerobic fitness for swimming, bicycling, running, or upper-body exercise. Some evidence even suggests a temporal specificity in training response such that indicators of training improvement peak when measured at the time of day when training regularly occurred. The most effective evaluation of sport-specific performance occurs when laboratory measurement most closely simulates the actual sport activity and/or uses the muscle mass and movement patterns required by the sport. Simply stated, specific exercise elicits specific adaptations to create specific training effects (McArdle et al., 2000).

Adaptations in the Cardiovascular System to exercise training

The hearts mass and volume increase and cardiac muscle undergoes hypertrophy. It is the left ventricle that adapts to the greatest extent. As well as the chamber size increasing as a result of endurance training more recent studies show that the myocardial wall thickness also increases (Fagard, 1996). Resting heart rate can decrease significantly following training in a previously sedentary individual (Wilmore and Costill, 2005). Stroke volume increases at rest, during submaximal exercise and maximal exercise following training. Stroke volume at rest averages 50-70 ml/beat in untrained individuals, 70-90ml/beat in trained individuals and 90-110ml/beat in world-class endurance athletes (McArdle et al., 2000). In untrained individuals, maximal cardiac output may be 14-20L/min compared to 25-35L/min in trained subjects. In large, elite athletes, maximal cardiac output can be as high as 40L.min (Wilmore and Costill, 2005). Blood pressure can decrease (both systolic and diastolic pressure) at rest and during submaximal exercise by as much as 10mmHg in people with hypertension. However, at a maximal exercise intensity systolic blood pressure is decreased compared to pre-training. Endurance training increase blood volume (Wilmore and Costill, 2005).

5.2 Components of the training session

Exercise is integrated into a comprehensive physical conditioning program, which generally is complemented by an overall health improvement plan. The format for exercise session should include a warm-up period (approximately 5 to 10 minutes), a stimulus or conditioning phase (cardiorespiratory; CR, flexibility, resistance training) (20 to 60 minutes), an a cool-down period (5 to 10 minutes) (Figure 2.10) (ACSM, 2006)

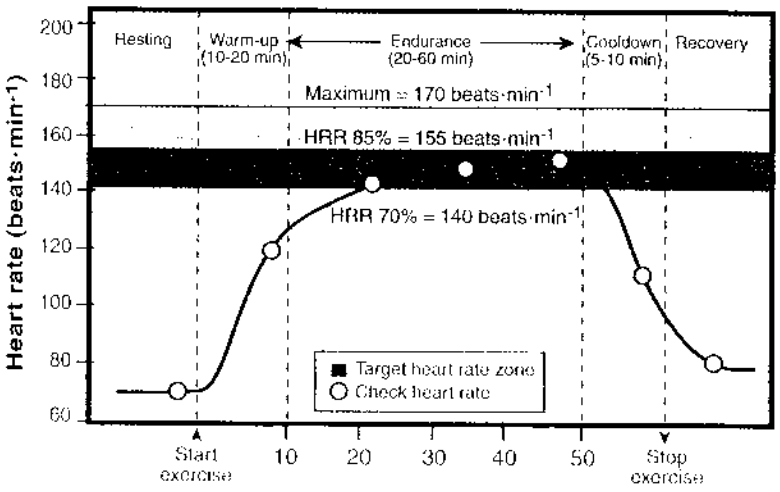

Figure 2.10 Format of a typical aerobic exercise session. (ACSM, 2006)

Warm-up

Warm-up facilitates the transition from rest to exercise, stretches postural muscles, augments blood flow, elevates body temperature, dissociates more oxygen, and increases the metabolic rate from the resting level (1 MET) to the aerobic requirements for endurance training (Bishop, 2003). A warm-up may reduce the susceptibility to musculoskeletal injury by increasing connective tissue extensibility, improving joint range of motion, and enhancing muscular performance (Pollock, 1998). The exercise session should begin with 5 to 10 minutes of low-intensity large muscle activity (10%-30% VO_2R) and progress to an intensity at the lower limit prescribed for endurance training (ACSM, 2006).

Stimulus or conditioning phase

The stimulus (conditioning) phase includes CR (endurance), resistance, and flexibility programming. Depending on the individual's goal or outcomes; one, two, or all program areas can be included. A comprehensive program should include all three conditioning components. Figure 2.10 depicts a typical exercise training session with the CR phase exemplified. Later sections of this chapter focus on exercise programming by CR conditioning, resistance training, and flexibility training (ACSM, 2006).

Cool-down

The cool-down period provides a gradual recovery from the endurance/games phase and includes exercise of diminishing intensities; for example, approximately 5 minutes of slower walking or jogging, cycling and approximately 5 minutes of stretching exercises, and in some cases, alternate activities. The cool-down is critical to attenuate the exercise-induced circulatory responses and return heart rate and blood pressure to near resting values (ACSM, 2006).

5.3 The exercise FITT principles (Dick, 2007)

The FITT principle as a set of rules that must be adhered to in order to benefit from any form of fitness training program. These rules relate to the Frequency, Intensity, Type and Time (FITT) of exercise. These four principles of fitness training are applicable to individuals exercising at low to moderate training levels and may be used to establish guidelines for both cardiorespiratory and resistance training.

Frequency

Following any form of fitness training, the body goes through a process of rebuild and repair to replenish its energy reserves consumed by the exercise. The frequency of exercise is a fine balance between providing just enough stress for the body to adapt to and allowing enough time for healing and adaptation to occur.

Cardiorespiratory Training

The guidelines for cardiorespiratory training (also called aerobic conditioning) is a minimum of three sessions per week and ideally five or six sessions per week. Experts suggest that little or no benefit is attained over and above this

amount. Of course athletes often fall outside the suggested guidelines but even elite performers must give themselves time to rest.

Resistance Training

The frequency of resistance training is dependent upon the particular individual and format of the program. For example, a program that works every body part every session should be completed 3-4 days a week with a day's rest between sessions. On the other hand, a program that focuses on just one or two body parts per session, in theory it could be completed as frequently as six days per week. Many bodybuilders follow such a routine.

Intensity

The second rule in the FITT principle relates to intensity. It defines the amount of effort that should be invested in a training program or any one session. Like the first FITT principle - frequency - there must be a balance between finding enough intensity to overload the body (so it can adapt) but not so much that it causes overtraining. Heart rate can be used to measure the intensity of cardiorespiratory training. Workload is used to define the intensity of resistance training.

Cardiorespiratory Training

Heart rate is the primary measure of intensity in aerobic endurance training. Ideally before you start an aerobic training program a target heart rate zone should first be determined. The target heart rate zone is a function of both your fitness level and age.

Heart rate and maximum heart rate

Heart rate is measured as beats per minute (bpm). Heart rate can be monitored and measured by taking your pulse at the wrist, arm or neck. An approximation of maximum heart rate (MHR) can also be calculated as follows: MHR = 220 - age.

Target Heart Rate

For beginners a target heart rate zone of 50-70 percent of their maximum of heart rate is a good place to start. So if, for example, you are 40 years old that gives you a predicted maximum heart rate of 180 (220 - 40). Multiply 180 by 50% and 70% and your reach a target zone of 90 bpm – 126 bpm. For fitter, more advanced

individuals, a target heart rate zone of 70-85 percent of their maximum of heart rate may be more appropriate. Staying with the example above, that 40 year old now has a heart rate zone of 126 bpm – 153 bpm. There are limitations with heart rate and the heart rate reserve method, while no means flawless, may be a more accurate way to determine exercise intensity.

Resistance Training

For resistance training, workload is the primary measure of intensity. Workload can have three components:

1. The amount of weight lifted during an exercise

2. The number of repetitions completed for a particular exercise

3. The length of time to complete all exercises in a set or total training session

TYPE

The third component in the FITT principle dictates what type or kind of exercise which choose to achieve the appropriate training response.

Cardio Respiratory Training

Using the FITT principle, the best type of exercise to tax or improve the cardiovascular system should be continuous in nature and make use of large muscle groups. Examples include running, walking, swimming, dancing, cycling, aerobics classes, circuit training, cycling etc.

Resistance Training

This is fairly obvious too. The best form of exercise to stress the neuromuscular system is resistance training. But resistance training does not necessarily mean lifting weights. Resistance bands could be used as an alternative or perhaps a circuit training session that only incorporates bodyweight exercises.

TIME

The final component in the FITT principle of training is time

Cardio Respiratory Training

Individuals with lower fitness levels should aim to maintain their heart rate within the target heart rate zone for a minimum of 20-30 minutes. This can increase to as much as 45-60 minutes as fitness levels increase. Beyond the 45-60 minute mark there

are diminished returns. For all that extra effort, the associated benefits are minimal. This also applies to many athletes. Beyond a certain point they run the risk of overtraining and injury. There are exceptions however - typically the ultra-long distance endurance athletes. In terms of the duration of the program as a whole, research suggests a minimum of 6 weeks is required to see noticeable improvement and as much as a year or more before a peak in fitness is reached.

Resistance Training

The common consensus for the duration of resistance training session is no longer than 45-60 minutes. Again, intensity has a say and particularly grueling strength sessions may last as little as 20 - 30 minutes.

5.4 exercise and allergic rhinitis

Exercise is a well-known trigger in allergic disorders such as asthma, (McFadden Jr and Gilbert, 1994; Milgrom, 2004), urticaria, angioedema, (Lewis et al., 1981) and anaphylaxis (Castells et al., 2003) in susceptible patients. However, the effect of exercise on allergic and nonallergic rhinitis is not well recognized or characterized. Outdoor exercise was first observed by Blackley (Blackley, 1873) in the late 1800s to worsen sneezing symptoms in patients with hay fever. This was presumably due to increased pollen exposure; thus, he recommended against exercise in these patients. In contrast, it was later observed that nasal congestion actually improved with exercise, and exercise was then recommended as a form of therapy for patients with hay fever (Hollopeter, 1916). In 1968, Richerson and Seebohm (1968) performed the first scientific studies demonstrating a decrease in nasal airway resistance in individuals with hay fever. Several studies have since confirmed that the nose becomes more patent during exercise in allergic and nonallergic individuals (Syabbalo et al., 1985; Serra-Batlles et al., 1994). The impact of exercise on rhinitis and the effect of rhinitis on exercise received considerable attention before the 1984 Olympics, where evidence indicated that chronic rhinitis occurs and deserves specific management in the athlete (Katz, 1984). The matic episodes caused by bruising and reflex stimulation, but other exposures such as cold air, changes in temperature and weather, outdoor pollution, and indoor exposures (formaldehyde, glues, paints, cleaners, and vinyl) were all suggested as possible triggers of exercise-induced chronic rhinitis (Katz, 1984). In the early 1990s, exercise in cold

temperatures, such as in skiing, was demonstrated to trigger a distinct clinical syndrome termed cold-induced rhinorrhea or skier's nose (Silvers, 1991). Although the primary nasal symptom was rhinorrhea, nasal congestion and sneezing were also involved (Silvers, 1991). More recently, it has been demonstrated that endurance athletes in top elite sports reported physician-diagnosed allergic rhinitis more often than other athletes or control subjects. Furthermore, only half of those athletes who reported allergic rhinitis were taking antiallergic medication (Alaranta et al., 2005).

Recently, some of studies have been studied about acute exercise or single bout exercise that induced the symptoms of allergies, such as exercise induced bronchoconstriction; EIB (Zietkowski et al., 2008, Manjra et al., 2009, Randolph, 2010) and exercise induced rhinitis; EIR (Silvers and. Poole, 2006, Schwartz et al., 2008). These researches were used high intensity exercise (Strenuous exercise) induced acute symptoms of allergic rhinitis. Exercise-induced rhinitis is characterized by itching, sneezing, rhinorrhea and/or postnasal drainage, nasal congestion and occasional anosmia provoked by exercise (Bonini, 2006). Valero A. et al. (2005) conducted a study of patients with allergic rhinitis and asthma with an acute exercise by cycling ergometer for 6 minutes at the intensity 80 - 90% of maximum heart rate. They found that exercise increased in nasal volume occurs, while in the latter there is a drop in forced expiratory volume in 1 second (FEV1). In 2006, Silvers and Poole, (2006) studied on physical activity, indoor versus outdoor exercise in athletes with allergic rhinitis. The survey found that 40% of the patients indicated that their indoor EIR adversely affected athletic performance, and this finding occurred more frequently in patients with nasal allergy vs unaffected individuals. Outdoor EIR occurred in 56.1% of the total population, and patients with nasal allergy reported significantly more rhinitis with outdoor exercise compared with unaffected individuals. In 2010, Aldred et al. (2010) studied of exercise increased the symptoms of allergic rhinitis in athletes swim evaluated by lung function, dyspnea and airway inflammation. The resulted showed that exercise is a decrease in peak nasal inspiratory flow and increased rhinitis symptoms. In 2005, Silvers and Poole survey individuals with and without nasal allergy who exercise regularly to determine the prevalence and nature of nasal symptoms induced by indoor

exercise. They found that exercise-induced rhinitis, predominantly rhinorrhea, commonly occurs in athletes regardless of underlying nasal allergy. A history specific to indoor and outdoor exercise triggers needs to be part of the complete rhinitis history so that specific treatment can be directed. The nose protects the lower airway by filtering, humidifying and warming inspired air, so nasal congestion places the lower airway at an increased risk (Passali et al., 2004). Autonomic reflexes affect nasal congestion by regulating glandular secretions and mucosal blood vessel dilation and permeability. Dynamic exercise stimulates a-adrenoceptors that vasoconstrict and reduce nasal resistance (Fonseca et al., 2006). Isometric exercise increases nasal resistance in rhinitis patients, but minimally affects nasal resistance in healthy subjects. Autonomic nerves also mediate the contraction and relaxation of bronchial smooth muscle. Cholinergic-parasympathetic nerves stimulate bronchoconstriction, whereas b2-adrenergic sympathetic and/or noncholinergic parasympathetic nerves bronchodilate (Canning, 2006). Intensive training may promote vagal hegemony (Triposkiadis et al., 2002) with resting bradycardia, but increased bronchomotor tone and susceptibility to bronchospasm (Filipe et al., 2003). In addition, aerobic training decrease chronic allergic inflammation in the airways (Vieira et al., 2008). Moderate physical activity seems to reduce the amount of inflammation mediators could be a possible explanation for physical activity being linked to frequencies of hay fever (Kohlhammer et al., 2006). However, the effects of aerobic exercise training are few and it is not clear in the patients with allergic rhinitis. Therefore, we are interested to study the effects of exercise training compared with exercise training combined vitamin C supplementation on cytokines and symptoms in allergic rhinitis patients.