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Study of vitamin C levels in relationship to stress hormone response and acute phase reaction in patients with newly diagnosed pulmonary tuberculosis

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CHAPTER 2: ACUTE PHASE RESPONSES

2.1 Introduction

Acute phase responses refer to diverse systemic effects that accompany inflammation. These responses include changes in plasma concentration of many proteins synthesized in the liver, and a wide range of physiologic, biochemical, behavioral and nutritional changes. These systematic changes accompany both acute and chronic inflammation (Gabay and Kushner 1999). Concentrations of many acute proteins increase during inflammatory response and these include components of the complement cascade, coagulation, the fibrinolytic system, biochemical transport proteins and various others (Lawn et al 2001).

2.2 Regulation of acute phase responses

Cytokines are the chief stimulants of the production of acute phase proteins and are produced by a variety of cells including monocytes and macrophages. Some of these cytokines include IL-1, IL-6, INFγ, transforming growth factor β and IL – 8. The cytokine effect may be inhibited or enhanced by other cytokines, cytokine receptor antagonists and circulating receptors. Glucocorticoids generally enhance the stimulating effects of cytokines on the production of acute phase proteins whereas insulin decreases this effect on some acute phase proteins (Gabay and Kushner 1999, Lawn et al 2001).

2.3 C – Reactive protein

This protein is produced by the hepatocytes and has many patho-physiological roles in inflammatory process. It is a component of innate immune system. Among its actions are recognition of phospho- choline and binding of both foreign antigens and phospholipid components of damaged host cells; activation of complement (which enhances clearance of the bound foreign antigen and damaged cells); and induction of pro-inflammatory cytokines, which enhance further clearance of foreign antigens and damaged cells (Gabay and Kushner 1999). The net effect of all these is anti- inflammatory by preventing adherence by neutrophils to endothelial cells by decreasing surface expression of L-selectin, inhibiting generation of super- oxide by neutrophils, and by stimulating synthesis of IL-1 receptor antagonists by mononuclear cells. Plasma levels of CRP are increased in different inflammatory conditions and correlate with the severity of the illness. The concentrations of this acute phase reactant decrease with chemotherapy (Baynes et al 1986). CRP levels are further decreased in healthy subjects supplemented with vitamin C (Sanchez-Moreno et al 2003), while the white cell vitamin C levels are decreased in acute phase response (Louw et al 1992).

2.4 Ferritin

2.4.1 Introduction

Ferritin, a 450 KDa protein, plays a critical role in the intercellular metabolism of iron. Following delivery to the anterocytes by transferrin transporters (apical/basolateral), iron is coupled to mitochondria for haem biosynthesis, non-haem iron containing enzymes and proteins, and ferritin for storage in the cells. The functions of ferritin include: storage of iron with protein and iron haemostasis, decreasing toxic properties of iron and defense against pathogens (Toth and Bridges 1987, Caso et al 1997).

2.4.2 Ferritin and tuberculosis

Disturbances in iron metabolism are well documented in infection, malignancy and tissue injury. The abnormalities relatively common in tuberculosis infection include low levels of total iron binding capacity of transferrin, low serum iron concentration, reduced transferrin saturation, increased iron stores and raised serum ferritin. Monocytes and macrophages of the reticulo- endothelial system produce ferritin through IL-1 mediation (Al-Omar and Oluboyede, Baynes et al 1986, Morris et al 1989, Plit et al 1998). HIV dysregulates ferritin synthesis and secretion in the reticulo-endothelial system by increasing IL-1 (Caso et al 1997).

Mycobacteria need iron to multiply in the host and cause disease, but free iron is limited to mycobacteria through a number of mechanisms. In the extra cellular site, iron is limited by the host's high affinity binding proteins (transferrin and lactoferrin). In the intra- cellular environment, iron is limited by down- regulation of the transferrin receptor, iron uptake, ferritin and localization of iron in the reticulo- endothelial system (Baynes et al 1986, Gobin et al 1996). These are the body's defenses in preventing bacterial pathogens obtaining iron for multiplication and hence causing disease.

2.4.3 Ferritin and vitamin C

There has been a demonstration of interplay between metabolism of iron and vitamin C. Vitamin C mobilizes iron from the crystal core of ferritin by reducing ferric iron to the ferrous state (Bridges 1987). Vitamin C further increases ferritin mRNA translation by a cotinase mode thereby increasing ferritin (Toth and Bridges 1995), and vitamin C increases absorption of iron. On the other hand iron promotes oxidation of vitamin C to dehydroascorbic acid, which is subsequently degraded to break- down products (Bridges 1987). This may explain the occurrence of vitamin C deficiency in iron-loaded individuals.

2.5 Smoking and vitamin C

Active and passive smoking is recognized as a risk factor for cardiovascular disease, cancer and pulmonary disease (Dietrich et al 2003, Preston et al 2003). A number of mechanisms are involved and these include free radicals generated in cigarette smoke, which cause oxidant damage to macro- molecules e.g. lipids, proteins and DNA. Reactive oxidants created from smoke induce activation of the inflammatory immune response which may cause morphological and functional changes in alveolar macrophages, CD4 lymphopenia, defects in monocyte response, increased airway resistance and pulmonary epithelial permeability, decreases in anti- proteases, decreased responsiveness to antigens and increases in elastases (Maurya et al 2002). Plasma vitamin C levels are decreased in smokers, the reason for which could be related to either increased metabolic turnover of vitamin C in smokers, which is approximately double those in non-smokers, or decreased consumption of vitamin C rich food e.g. fruits and vegetables, by smokers (Preston et al 2003, Dietrich et al 2003).

2.5.1 Smoking and tuberculosis

Cigarette smoking affects many organ systems but the lungs bear most insults. Functional abnormalities caused by smoking on the lungs include decreased clearance of inhaled substances, changes in pathogen

adherence, abnormal vascular and epithelial permeability, changes in CD4+ cells, alveolar macrophage structural and functional impairment, altered neutrophil chemotaxis from vascular spaces into the lung, increased inflammatory cytokines, IL-1 and IL-8, decreased natural killer cells and increased oxidant stress with tissue damage in the lung. These factors in combination may contribute to the increased susceptibility to tuberculosis infections (Alcaide et al 1996, Yach 2000, Maurya et al 2002, Kollapan and Gopi 2002, Den Boon et al 2005).