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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 I: TUBERCULOSIS

1.1 Introduction

It is over ten years now since the World Health Organization declared tuberculosis as a global health emergency and yet tuberculosis remains a major public health threat globally (Dye et al 1999, Churchyard and Grant 2000). Approximately two billion people are infected with *Mycobacterium tuberculosis* globally resulting in estimated annual deaths of 1.87 million (range 1.4 – 2.8 million) (Dye et al 1999, Corbett et al 2003). At the end of the twentieth century, the World Health Organization estimated there to be 8.3 million new cases of tuberculosis in the year 2000 (range 6.3 – 11.1 million). The incidence of tuberculosis has increased world – wide because of the Human Immunodeficiency Virus (HIV) pandemic. Human Immunodeficiency Virus infection is an important risk factor for development of active tuberculosis and in developing countries where this co-infection is common, the number of tuberculosis cases has dramatically increased (Fatkeheuer et al 1999, Prasad et al 2000, Corbett et al 2003). In South Africa alone, there were 2 million co-infected adults and the distribution of tuberculosis has ethnic and geographical inclinations with blacks and mixed race groups having very high incidences (Over 500 / 100,000) compared with other ethnic groups (Corbett et al 2003).

1.2 HIV and tuberculosis

The HIV pandemic afflicting developing as well as developed countries is one of the reasons for the enormous increases in tuberculosis infections world- wide (Prasad et al 2000). Developing countries top the list for these increases of tuberculosis infections (Dye et al 1999). World- wide between 7 – 12% of all new tuberculosis cases in adults (aged 15 – 49 years) were attributable to HIV infection with much higher proportions in the African region (31 %). HIV – tuberculosis co-infection prevalence rates equaled or exceeded 50 % in some African countries (Corbett et al 2003).

Tuberculosis is a leading cause of death in people who are HIV positive and accounts for about 11 % of Acquired Immunodeficiency Syndrome (AIDS) deaths world- wide (World Health Organization 2002 August). There are many associations between HIV and tuberculosis. Human Immunodeficiency Virus infection increases the risk of reactivating latent *Mycobacterium tuberculosis* infections and increases the risk of rapid tuberculosis progression soon after infection or re-infection with *Mycobacterium tuberculosis*. Susceptibility to tuberculosis in these patients is related to a progressive decline and dysfunction of CD 4 + cells, abnormal macrophage function with resultant reduced TH_1 cell responses and increase in TH_2 responses (Barnes and Havlir 1999). The increased susceptibility to tuberculosis can occur in early stages of HIV infection but becomes more pronounced as the degree of

immunosupression increases (Barnes and Havlir 1999). Other effects of HIV on tuberculosis include increased severity of tuberculosis, increased infections at sites other than the lungs and primary progression of tuberculosis. This is due to impaired T – cell cytotoxicity against *Mycobacterium tuberculosis* - infected antigen presenting cells. There is also increased incidence of drug resistance, increased atypical presentation of tuberculosis and increased occurrence of infections with mycobacteria other than tuberculosis (Barnes and Havlir 1999). Further, there is increased occurrence of opportunistic infections, shortened survival, increased frequency of adverse reactions to anti-tuberculosis and other drugs compared to other patients who are not HIV positive. The occurrence of tuberculosis in HIV patients, on the other hand, is associated with immune activation and increased viral replication. There is also accelerated clinical progression of HIV disease with consequent increases in opportunistic infections and death (Churchyard and Grant 2000).

1.3 Nutrition and tuberculosis

Increases in tuberculosis world- wide can not be attributed solely to the HIV pandemic. Other factors that have contributed to the increase include socio-economic dynamics (Hudelson 1996). Malnutrition, one of the offshoots of these dynamics, has a direct bearing on the pathogenesis and the final outcome of tuberculosis infection (Getz et al 1951, Mayer 1971,

Ikeogu et al 1997, Le Roux et al 1999, Hemila et al 1999, Byrd et al 2002). Improving patients' nutritional status impacts favourably on the outcome of tuberculosis infection, since nutrition is an important prognostic factor. This is supported by a Finnish study, in which increased fruit intake was associated with a decrease in tuberculosis infection risk (Schwenk and Macallan and 2000). The poor nutritional status may be due to starvation (inability to grow or purchase food), anorexia, impaired absorption of nutrients or increased catabolism. In patients who are malnourished with tuberculosis, the reasons for increased mortality may include the following; malnutrition facilitates the spread and multiplication of tubercle bacilli by preferentially suppressing cell- mediated immunity (Good 1981, Strachnan et al 1995), there may be impaired complement activity and secondary antibody response to antigens (Peronne 1999), there is increased inflammatory mediators (increased production and secretion of cytokines eg IL- 1, IL- 6 and tumor necrosis factor alpha), there are dramatic shifts in plasma concentrations of certain essential micronutrients e.g vitamin C and other anti- oxidants (Karyadi et al 2000, Niyongambo et al 2002), there is decreased production of serum albumin and haemoglobin, and there may be decreased plasma drug concentration time curves as a result of increased renal clearance of unbound drug and under dosage (Byrd et al 2002).

1.4 Tuberculosis and vitamin C

1.4.1 Introduction

Vitamin C is a water soluble vitamin, which is a constituent of various foods such as citrus fruits and vegetables. Vitamin C is concentrated in many tissues but the highest concentrations in man are in the adrenal cortex. Normal plasma vitamin C levels are 10 – 20 mg/ml, while the white cell vitamin C levels are 20 – 40 mg/10^8 leucocytes.

1.4.2 Functions of vitamin C

Vitamin C has many functions in the body: it is a co-factor for enzymes involved in a number of functions because of being an electron donor. It is involved in tissue repair and collagen formation, biosynthesis of catecholamines, tyrosine metabolism and amidation of peptide hormones (Padayatty and Levine 2000). It is a powerful water- soluble antioxidant, protects low-density lipoproteins from oxidation, reduces harmful oxidants and promotes iron absorption. At physiological concentrations vitamin C does not produce reactive intermediates. Vitamin C protects 11 β hydroxylase from superoxides and hence has a role in steroidogenesis and it further regenerates vitamin C from α tocopheroxyl radicals (Awotedu et al 1984, Hornsby et al 1985, Redman et al 1995, Stocker et al 1997, Hemila et al 1999,

Padayatty and Levine 2000, Goralczyk et al). Previous studies have demonstrated low plasma levels of micro- nutrients (vitamin C, vitamin E and β- carotene) in patients with pulmonary tuberculosis (Gezt et al 1951, Awotedu et al 1984, Plit et al 1998, Madebo et al 2003, Bakaev et al 2004). The decrease is attributed to a number of possible factors including accelerated turnover, shifts in plasma concentrations, increased collagen formation and tissue repair and decreased intake (Plit et al 1998). The decreased vitamin C levels may impair chemotaxis, phagocytosis of neutrophils and macrophages in tuberculosis patients (Redman et al 1995, Stocker et al 1997, Hemila et al 1999).

1.5 Adrenal function in tuberculosis

1.5.1 Introduction

The adrenal cortex synthesizes from cholesterol a variety of steroids, namely, glucocorticoids, mineralocorticoids and adrenal androgens. Separate zones of the adrenal cortex synthesise different hormones, with the outer (glomerulosa) zone for aldosterone biosynthesis and the inner (fasiculata -reticularis) zone for cortisol and androgen biosynthesis. The secretion of cortisol has a pronounced circadian cycle, which can be overridden by stress. More than 90 % of cortisol is protein bound and plasma levels are determined by rate of secretion, rate of inactivation and the rate of

excretion of free cortisol. The liver is a major organ for steroid inactivation, while in the kidney 11 β hydroxysteroid dehydrogenase converts cortisol to cortisone (inactive). The major functions of glucocorticoids include: carbohydrate, protein, lipid and nucleic acid metabolism; anti- inflammatory functions; maintaining vascular responsiveness to circulating vasoconstrictors; decreasing capillary permeability during acute inflammation; depletion of circulating eosinophils and T cells by redistribution from circulation into other compartments; inhibition of production and action of mediators of inflammation such as lymphokines and prostaglandins; inhibition of production and action of interferon by T-lymphocytes; inhibition of production of IL-I, IL-6 by macrophages; decreased production of bradykinin, platelet activating factor and serotinin; decreased antibody production.

1.5.2 Tuberculosis and the adrenal gland

Controversy still remains pertaining to adrenal function in tuberculosis infection. Adrenal function impairment may arise from infection, functional adrenal failure, or the effects of tuberculosis treatment. Haematogenous dissemination of tubercle bacilli occurs after primary infection and the rich vascularity and high local levels of corticosterone (which suppresses cell- mediated immune responses), make the adrenal gland an ideal nidus for the bacilli

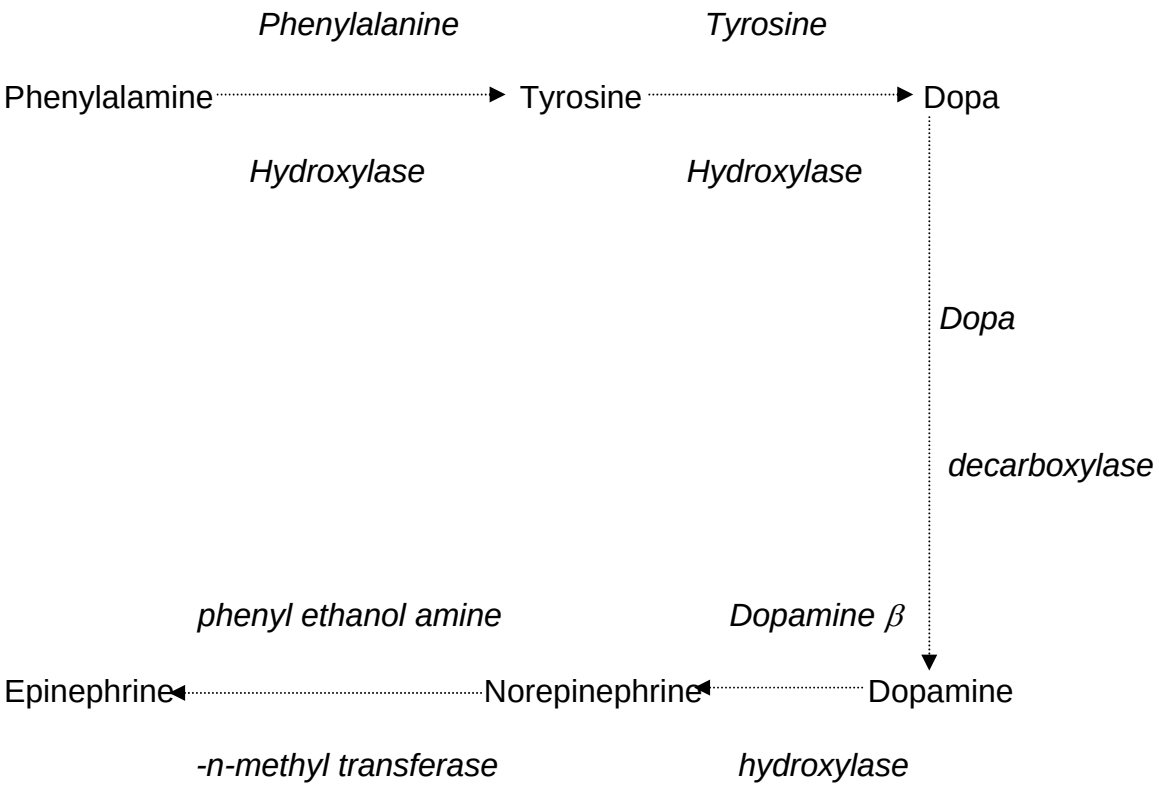
(Ellis and Tayoub et al 1986, Prasad et al 2000). The involvement of the adrenals with tuberculosis is usually silent, but progressive, and overt clinical features of adrenal insufficiency appear only when more than 80 – 90 % of the adrenal glands are destroyed (Sarma et al 1990). The tuberculosis infection down-regulates the hypothalamo -pituitary axis leading to lower overall basal cortisol levels (Hernandez-Pando et al 1998, Prasad et al 2000). Further, there are changes in the circadian rhythm release of cortisol with persistent elevations of cortisol that should be present only in the mornings. The disturbed cortisol related diurnal rhythm interferes with the balance of TH_1 to TH_2 cytokine output, which may lead to dysregulation of the cell function (Rook et al 1996). Drugs used in the treatment of tuberculosis, especially rifampicin, may impact on adrenal function in a number of ways, which includes induction of hepatic microsomal enzymes (Keven et al 1998). Normally 75 % of circulating cortisol is bound to corticosteroid binding globulin, 10 % is free and the remainder is bound to albumin. Hepatic enzyme induction causes increased levels of corticosteroid binding globulin, which therefore decreases cortisol levels. Other drug effects include increased endogenous and exogenous steroid metabolism, increased activity of 16 α hydroxylase with increased reduction of DHEA to its metabolites (Rook et al 1996). Normally DHEA causes expression of TH_1 cytokines (1L-2, Interferon γ), (Hernandez-

Pando 1998). The low DHEA / cortisol ratio (Venter et al 2006) causes a decrease in production of IL-2, increased activation of TH_2 cytokine release and a fall in the CD4 / CD8 ratio (Rook et al 1996).

1.6 Catecholamines and tuberculosis

1.6.1 Introduction

The catecholamines include norepinephirine, epinephrine and dopamine, which are released from the adrenal medulla and sympathetic neurones (epinephrine from the adrenal medulla and norepinephrine from the sympathetic neurones). Catecholamine synthesis starts from phenylalanine as shown below:



Catecholamines are considered stress hormones. Stress induces tyrosine hydroxylase, dopamine β hydroxylase and phenyl ethanol amine-n-methyl transferase (Hafeiz et al 1992). The increased catecholamine levels have a beneficial physiological effect in either "fight" or "flight" responses. Other functions include; immune modulation by modulating IL-2 and INF γ levels (Ramer-Quinn et al 1997, Alaniz et al 1999), thermo- regulation and energy balance (Thomas and Palmiter 1997), induction of production of glucocorticosteroids and maintenance of cardiovascular tone and behaviour.

1.6.2 Catecholamines and tuberculosis

As previously noted, adrenal function impairment in tuberculosis may arise from infection or functional adrenal failure (Hernandez-Pando et al 1998, Prasad et al 2000). Tuberculosis is a stressful event, which induces some of enzymes in catecholamine synthesis such as tyrosine hydroxylase, dopamine β hydroxylase, phenyl ethanol amine-n methyl transferase (Hafeiz et al 1992), with a resultant increase in catecholamine levels. On the other hand, tuberculosis has been associated with low plasma vitamin C levels through a number of mechanisms as previously mentioned (Getz et al 1951, Awotedu et al 1984, Plit et al 1998). Vitamin C is a co-factor in the synthesis of norepinephrine from dopamine. The

decreased levels of plasma vitamin C could be associated with low levels of norepinephrine but increased levels of dopamine. The enhanced dopamine levels inhibit prolactin production, which interferes with T cell function (Alaniz et al 1999).