Subclinical vitamin D Deficiency and Acute Lower Respiratory Infection in Children Under 5 Years

Thesis

Submitted for Partial Fulfillment of
Master Degree in Pediatrics

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LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
ADHR	Autosomal dominant hypophophatemic rickets
ALRI	Acute lower respiratory infection
AMPs	Antimicrobial peptides
AMs	Alveolar macrophages
BMD	Bone mineral density
BTS	British thoracic society
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CXR	Chest x ray
ESR	Erythrocyte sedimentation rate
FGF23	Fibroblast growth factor 23
Hib	Homophiles influenzae type b
MED	Minimal erythema dose
MHC	Major histocompatibility complex
MMP-9	Matrix metalloproteinasis-9
NHANES	National Health and Nutrition Examination Surveys
PCR	Polymerase chain reaction
PERCH	Pneumonia Etiology Research for Child Health
PRR's	Pattern recognition receptors
PTH	Parathyroid hormone
RCTs	Randomized controlled trials
RR	Relative risk
RSV	Respiratory syncytial virus
TIO	Tumor-induced osteomalacia
TLR	Toll-like receptor
TSST-1	Toxic shock syndrome toxin-1
TWAR	Taiwan acute respiratory
UV	Ultraviolet
VDI	Vitamin D intoxication
VDR	Vitamin D receptor
VDREs	Vitamin D responsive elements
WHO	World Health Organization
XLH	X-linked hypophosphatemic rickets

Socio-economic status was determined according to **Park and Park (1979)**:

	Mother	Father
Scoring of the education level		
• Illiterate	1	1
• Primary education	2	2
• Preparatory education	4	4
• Secondary education	5	5
• University education	7	7
Scoring of the occupation		
• No occupation or unskilled worker	1	1
• Industrial worker	2	2
• Skilled worker	4	4
• Semiprofessional	5	5
• Professional	7	7

Classification of socioeconomic standard:

- Score less than or equal to 8 Low
- Score between 9-18 Mid
- Score between 19-28 High

INTRODUCTION

Vitamin D is a fat-soluble vitamin, unique in that it is primarily produced in the skin during sun exposure rather than absorbed from the diet ***(Sundaram and Coleman, 2012).***

While the role of vitamin D in bone and mineral metabolism has been well studied, its activities on other physiological and pathophysiological processes have been of increasing interest in recent years. Vitamin D, which is photosynthesized in the skin or is derived from nutrition, is metabolized two times, before it mediates its calcemic effects by binding to the nuclear vitamin D receptor (VDR) ***(Janssens et al., 2009).***

The first hydroxylation of vitamin D takes place in the human liver on C-25 position by mitochondrial 25-hydroxylase enzyme and the 25-hydoxylated molecule is further hydroxylated at position 1α by the mitochondrial cytochrome P450 enzyme 25-hydroxyvitamin-D-1α-hydroxylase in the proximal tubule of the nephron and converted to the bioactive 1α,25-dihydroxy(1,25-(OH)2D3). The 1α-hydroxylation of 25-(OH) D3 is upregulated by parathyroid hormone (PTH), calcitonin, low calcium- and phosphate levels as well as by estrogen, prolactin and growth hormone ***(Kann., 1994)***. Calcitonin, cortisol, high phosphate levels and 25-(OH) D3 suppress the 25-hydroxy-1α-hydroxylase activity ***(Zhong et al., 2009).***

Of the many disorders where vitamin D is believed to play an important role, epidemiological data suggest that several lung diseases, all inflammatory in nature, may be related to activities of vitamin D. Immunomodulatory properties of the steroid hormone are likely to be important in this regard ***(Koul, 2012)***.

AIM OF THE WORK

To determine whether subclinical vitamin D deficiency in Egyptian children under 5 y of age is a risk factor for severe acute lower respiratory infection (ALRI).

Acute Lower Respiratory Tract Infections

Acute respiratory tract infection (ARTI) is a major cause of morbidity and mortality worldwide, particularly in children ***(O'Grady et al., 2010)***. An estimated 1.9 million children die from ARTI every year, with 70% of the mortality occurring in Africa and Southeast Asia ***(Williams et al., 2002)***. Most respiratory tract infections are caused by viruses ***(Khor et al., 2012)***.

A. General anatomy of LRT:

LRT is usually divided into two segments.

I. The Respiratory Airways: This includes the trachea, bronchi, and bronchioles.

II. The Lungs: This includes alveolar ducts, alveolar sacs, and the alveoli ***(Gonlugur et al., 2005)***.

The alveoli are lined with two types of cells, the Type 1 and Type 2 pneumocyte. The Type 1 pneumocyte is a very large thin cell stretched over a very large area. This cell can not replicate and is susceptible to a large number of toxic insults. Type 1 pneumocytes are responsible for gas exchanges occurring in the alveoli ***(Meenakshi et al., 2004)***.

The Type 2 granular pneumocyte is smaller, roughly cuboidal cell that is usually found at the alveolar septal junctions. This cell is responsible for the production and secretion of surfactant ***(Gonlugur et al., 2005)***.

B. Defense mechanisms of airway

Particles from 2 um to 0.2 um (like most bacteria and all viruses) can go all the way down inside the alveoli avoiding the defenses of the upper respiratory tract and the mucociliary elevator ***(Meenakshi et al., 2004)***.

The following defense mechanisms in the alveoli protect the parenchymal cells from invasion by microorganisms.

- Alveolar macrophages (the most important)
- Complement components
- Alveolar lining fluid containing surfactant, phospholipids, neutral lipids, IgG, IgE, IgA, secretory IgA, certain complement components, that maybe important in activation of alveolar macrophages
- B cells, T cells, and Null cells that can elicit a localized immune response to infection
- Lymphoid tissue associated with the lungs ***(Gonlugur et al., 2005)***

C. Defense mechanisms during infection.

During pulmonary infection, neutrophils migrate out of the pulmonary capillaries and into the air spaces. After phagocytosis, neutrophils kill ingested microbes with reactive oxygen species (e.g., hypochlorite), antimicrobial proteins (e.g., bactericidal permeability-inducing protein and lactoferrin), and degradative enzymes (e.g., elastase) (figure, 1) ***(Mizgerd, 2008).***

D. Invaders mechanisms used to avoid the normal defense mechanisms of the lung.

To kill the microorganism in the alveoli it must be phagocytized by the alveolar macrophage. If these microbes can avoid phagocytosis or survive once phagocytized they can survive in the lung. Microorganisms have developed a number of ways to avoid phagocytosis. Once phagocytized certain organisms can survive in the phagocyte ***(Gonlugur et al., 2005)***.

E. Modes of transmission

- Inhalation of small airborne infectious particles.
- Aspiration of resident naso-oropharyngeal flora or large airborne particles after deposition in the naso-oropharynx.
- Hematogenous spread to the lung from another site of infection.
- Direct extension from a contiguous site of infection
- Exogenous penetration and contamination of the lung can occur due to accidental trauma (car accident) or surgery ***(Ferguson, 2007)***.

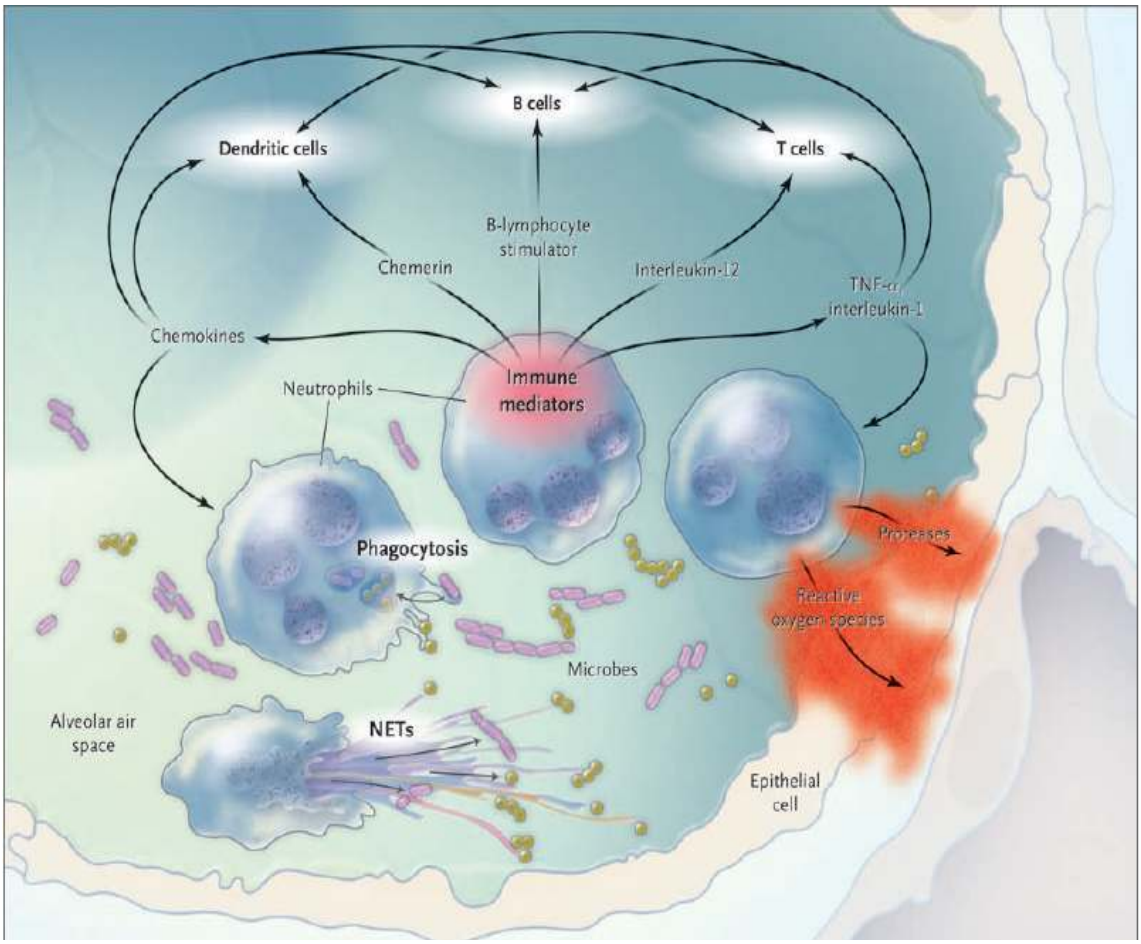

Figure (1): Neutrophils and lung infection. Neutrophils are effector cells of innate immunity, killing microbes using phagocytosis and neutrophil extracellular traps (NETs). Neutrophils also generate a variety of immune mediators to direct immune responses, influencing other cells of innate and adaptive immunity. Finally, neutrophils damage tissues, with products such as proteases and reactive oxygen species injuring cells and digesting matrix. TNF denotes tumor necrosis factor ***(Mizgerd et al., 2008)***

LRTI Classification

Lower respiratory tract infection (LRTI) is infection below the level of the larynx and may be taken to include:

- Bronchitis
- Bronchiolitis
- Pneumonia ***(Zorc and Hall, 2010).***

Acute Bronchitis

Acute bronchitis is a clinical term implying a self-limited inflammation of the large airways of the lung that is characterized by cough without pneumonia. In children, acute bronchitis usually occurs in association with viral respiratory tract infection ***(Horner and Bacharier, 2009).***

Epidemiology

Bronchitis, both acute and chronic, is prevalent throughout the world and is one of the top 5 reasons for childhood physician visits in countries that track such data. The incidence of bronchitis in British and German schoolchildren is reported to be 20.7% and 28% respectively ***(Weigl et al., 2005).***

Pathogenesis

Acute bronchitis leads to the hacking cough and phlegm production that often follows upper respiratory tract infection. This occurs because of the inflammatory response of the mucous membranes within the lungs' bronchial passages. Viruses, acting alone or together, account for most of these infections ***(Brodzinski and Ruddy, 2009).***

Mucociliary clearance is an important primary innate defense mechanism that protects the lungs from the harmful effects of inhaled

pollutants, allergens, and pathogens. Mucociliary dysfunction is a common feature of chronic airway diseases ***(Voynow and Rubin, 2009).***

The role of irritant exposure, particularly cigarette smoke and airborne particulates, in recurrent (wheezy) bronchitis and asthma is becoming clearer. ***Kreindler and colleagues (2005)*** demonstrated that the ion transport phenotype of normal human bronchial epithelial cells exposed to cigarette smoke extract is similar to that of cystic fibrosis epithelia, in which sodium is absorbed out of proportion to chloride secretion in the setting of increased mucus production. These findings suggest that the negative effects of cigarette smoke on mucociliary clearance may be mediated through alterations in ion transport ***(Kreindler et al., 2005).***

Etiology

- Adenovirus
- Influenza
- Parainfluenza
- Respiratory syncytial virus
- Rhinovirus
- Human bocavirus
- Coxsackievirus
- Herpes simplex virus
- S. pneumoniae
- Moraxella catarrhalis
- Homophiles influenzae (nontypeable)
- Chlamydia pneumoniae (Taiwan acute respiratory [TWAR] agent)
- Mycoplasma species
- Allergies
- Chronic aspiration or gastroesophageal reflux
- Fungal infection
- Plastic bronchitis ***(Zaccagni et al., 2008).***

Diagnosis:

Acute bronchitis begins as a respiratory tract infection that manifests as the common cold. Symptoms often include coryza, malaise, chills, slight fever, sore throat, and back and muscle pain. The cough in these children is usually accompanied by a nasal discharge. The discharge is watery at first, then after several days becomes thicker and colored or opaque. It then becomes clear again and has a mucoid watery consistency before it spontaneously resolves within 7-10 days. Purulent nasal discharge is common with viral respiratory pathogens and, by itself, does not imply bacterial infection ***(Freymuth et al., 2004)***.

Initially, the cough is dry and may be harsh or raspy sounding. The cough then loosens and becomes productive. Children younger than 5 years rarely expectorate. In this age group, sputum is usually seen in vomitus (ie, posttussive emesis). Parents frequently note a rattling sound in the chest. Hemoptysis, a burning discomfort in the chest, and dyspnea may be present ***(Brunton et al., 2004).***

Chronic bronchitis cannot be diagnosed radiologically. Although findings such as increased lung markings or tubular opacities, bronchial wall cuffing (thickening) can be seen with bronchitis, they are nonspecific. The main reason for getting a chest X-ray is to exclude other conditions, such as bronchiectasis, which can mimic the disease clinically ***(Kamin et al., 2010)***.