Vitamin D Deficiency: Correlation to Interleukin-17 in Chronic Hepatitis C Virus Egyptian Patients

Thesis

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List of Abbreviations

Abbr.	Full-term
ADCC	**:** Antibody-dependent cell-mediated cytotoxicity
ALT	**:** Alanine aminotransferase
AP-1	**:** Activator protein 1
APC	**:** Antigen-presenting cell
C/EBP	: CCAAT-enhancer binding protein
C-BAD	: C/EBPβ activation domain
CCL20	**:** C-C Motif Chemokine Ligand 20
CCR6	**:** Chemokine receptor 6
CIA	**:** Chemiluminescence Immunoassay
CLDN1	**:** Claudin-1
CTLA 8	**:** Cytotoxic T-lymphocyte antigen-8
CVD	**:** Cardiovascular diseases
CXCL	**:** Chemokine (C-X-C motif) ligand
CYP24A1	**:** Catabolic enzyme 24-hydroxylase
DBP	**:** Vitamin D-binding protein
DC-SIGN	**:** Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin
DOPPS	**:** Dialysis Outcomes and Practice Patterns Study
EAE	**:** Experimental autoimmune encephalomyelitis
EIA	**:** Enzyme-linked immunosorbent assay
ERKs	**:** Extracellular signal–regulated kinases
FGF23	**:** Fibroblast growth factor 23
FN1	: Fibronectin

FOXP3 : Forkhead box P3

G-CSF : Granulocyte - Colony Stimulating Factor

GRO : Chemokines growth-regulated oncogene

HBD2 : Human β-defensin 2

HCC : Hepatocellular carcinoma

HCV E2 : Hepatitis C Virus E2 Envelope Glycoprotein Core Structure

HLA : Human leukocyte antigen

HSC : Hepatic stellate cells

IFNγ : Interferon gamma

IL : Interleukin

JNKs : c-Jun N-terminal kinases

MAPK : Mitogen-activator protein kinase

MCP-1 : Monocyte chemoattractant protein-1

MIP-3 : Macrophage inflammatory protein 3

ML-1 : Mistletoe lectin-1

MPGN : Membranoproliferative glomerulonephritis

NASH : Non-alcoholic steatohepatitis

NF- κB : Nuclear Factor κ B

NK : Natural killer

P38 : Mitogen-activated protein kinases

PAMPs : Pathogen-associated molecular patterns (PAMPs)

PBC : Primary biliary cirrhosis

PCR : Polymerase chain reaction

RIBA : Recombinant immunoblot assay

ROR : Related orphan receptor

RPM : rotation per minute

SA-HRP **:** Streptavidin-horseradish peroxidase
SD **:** Standard deviation
SEF : Similar expression to FGF receptor
SOCS3 **:** Suppressor of cytokine signaling 3
SRB1 **:** Scavenger receptor class B-1
STAT3 **:** Signal transducer and activator of transcription 3
TGF-β **:** Transforming growth factor beta
Th1 **:** T helper
TILL : TIR-like loop
TLR **:** Toll like receptor
TMB **:** Tetramethylbenzidine
TNF **:** Tumor necrosis factor
TRAF **:** TNF receptor associated factor
Treg **:** Regulatory T cells
UTR **:** Untranslated regions
VDR **:** Vitamin D Receptor
1,25(OH)2D3 **:** 1,25-dihydroxyvitamin D3

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Abstract

Background: HCV is a hepatotropic non-cytopathic virus able to persist in a great percentage of infected hosts due to its ability to escape from the immune control. Liver damage and disease progression during HCV infection are driven by both viral and host factors. **Aim of the Work:** to assess vitamin D level and intrleukin-17 level in chronic hepatitis C patients and to determine whether there is a correlation between the two. **Subjects and Methods:** The present study was conducted in Clinical Pathology Department, Ain Shams University Hospitals. It included 50 adult individuals divided in to two groups. First group: Thirty Egyptian chronic hepatitis C virus (HCV)-infected patients (HCV RNA positive > 6months). Second group: Twenty healthy volunteers who are age and sex-matched. **Results:** The current study showed that there was no correlation between vitamin D and IL-17 among both groups. **Conclusion:** It has been observed that chronic HCV patients have high level of IL-17 and low level of vitamin D. We could assume that vitamin D deficiency can be one of the causes of elevation of the IL-17 resulting in more inflammatory consequences in the liver. **Recommendations:** Further investigations are recommended to clarify the rule of IL-17 in the pathogenesis of chronic hepatitis C disease.

Key words: HCV, Interleukin-17, immune control, vitamin D.

Introduction

An estimated 2%–3% of the world's population is living with hepatitis C virus (HCV) infection, and each year, >350.000 die of HCV-related conditions, including cirrhosis and liver cancer. The epidemiology and burden of HCV infection varies throughout the world, with country-specific prevalence ranging from <1% to >10%. In contrast to the United States and other developed countries, HCV transmission in developing countries frequently results from exposure to infected blood in healthcare and community settings. Hepatitis C prevention, care, and treatment programs must recognize country-specific epidemiology, which varies by setting and level of economic development ***(Averhoff et al., 2012)***.

HCV is a hepatotropic non-cytopathic virus able to persist in a great percentage of infected hosts due to its ability to escape from the immune control. Liver damage and disease progression during HCV infection are driven by both viral and host factors. Specifically, adaptive immune response carries out an essential task in controlling non-cytopathic viruses because of its ability to recognize infected cells and to destroy them by cytopathic mechanisms and to eliminate the virus by non-cytolytic machinery. HCV is able to impair this response by several means such as developing escape mutations in neutralizing antibodies and in T cell receptor viral epitope recognition sites and inducing HCV-specific cytotoxic T cell anergy and deletion. To impair HCV-specific T cell reactivity, HCV affects effector T cell

regulation by modulating T helper and Treg response and by impairing the balance between positive and negative co-stimulatory molecules and between pro- and anti-apoptotic proteins ***(Larrubia et al., 2014).***

Human IL-17 (IL-17) - producing CD4 Tcells, Th 17, comprise a proinflammatory T-cell subset. Previous studies have identified Th 17 as a known arm of the CD4+ T-cell effector response. It has been demonstrated that several key cytokines, including IL-1, IL-6, tumor necrosis factor alpha, and IL-23 create a cytokine milieu that regulates the differentiation and expansion of human TH17 cell ***(Zhang et al., 2005).***

IL-17A can mobilize, recruit, and activate neutrophils, leading to massive tissue inflammation, and promote the progression of autoimmune disease. Furthermore, serumIL-17 levels are increased and serve as a marker of the severity of acute hepatic injury ***(Yasumi et al., 2007).***

Vitamin D is a fat-soluble vitamin which is essential for maintenance of bone mineralization through the regulation of calcium and phosphorus homeostasis. Vitamin D also exhibits many non-skeletal effects, particularly on the immune, endocrine, and cardiovascular systems.Acting through the VDR, 1,25-dihydroxyvitamin D is a potent immune system modulator. The VDR is expressed by most cells of the immune system, including regulatory T cells and antigen-presenting

cells, such as dendritic cells and macrophages. Under specific circumstances, monocytes, macrophages, and T cells can express the 25-hydroxyvitamin D3-1α-hydroxylase enzyme and produce 1,25-dihydroxyvitamin D, which acts locally to regulate the immune response. There is considerable scientific evidence that 1,25-dihydroxyvitamin D has a variety of effects on immune system function, which may enhance innate immunity and inhibit the development of autoimmunity. Conversely, vitamin D deficiency may compromise the integrity of the immune system and lead to inappropriate immune responses ***(Smolders et al., 2011).***

Vitamin D undergoes hepatic 25-hydroxylation, rendering the liver critical to the metabolic activation of this vitamin. Vitamin D deficiency is highly prevalent in CLD patients, and vitamin D levels are inversely related to the severity of CLD. Declining levels of carrier proteins such as albumin and vitamin D-binding protein might also be critical in CLD ***(Stokes et al., 2013).***

The active form of vitamin D, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], has a direct repressive effect on the expression of IL-17A in T cells. The mechanism of $1,25(OH)_2D_3$ repression of IL-17A expression was found to be transcriptional repression, mediated by the vitamin D receptor (VDR) ***(Joshi et al., 2011).***

Aim of the Work

To assess vitamin D level and intrleukin-17 level in chronic hepatitis C patients and to determine whether there is a correlation between the two.