The Association Between Trace Elements And Depression Among Elderly Patients With Chronic Liver Disease

Thesis

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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LIST OF ABBREVIATIONS

31P MRS	:	Phosphorus magnetic resonance spectroscopy
5- HT	:	Serotonin
Ab	:	Antibody
ADH	:	Antidiuretic hormone
ADP	:	Adenosine diphosphate
AIDS	:	Acquired immunodeficiency syndrome
AIH	:	Autoimmune hepatitis
AIH-1	:	Autoimmune hepatitis type 1
AIH-2	:	Autoimmune hepatitis type 2
ALD	:	Alcoholic liver disease
ALP	:	Alkaline phosphatase
ALT	:	Alanine transaminase
ANA	:	Anti-nuclear antibodies
Anti- SMA	:	Anti-smooth muscle antibodies
Antigen	:	Ag
Anti-LC1	:	Anti-liver cytosol type 1
Anti-LKM1	:	Anti-liver kidney microsomal type 1
AST	:	Aspartate transaminase
ASU	:	Ain Shams University
ATP	:	Adenosine triphosphate
BA	:	Bronchial asthma
BB	:	Beta blocker
BCP	:	Bromcresol purple
Ca	:	Calcium
CBC	:	Complete blood count
CCI	:	Charlson Comorbidity Index
Cd	:	Cadmium
CLD	:	Chronic liver disease
CNS	:	Central nervous system
CO	:	Cobalt
COPD	:	Chronic obstructive pulmonary disease
CSF	:	Cerebrospinal fluid
CT	:	Computed tomography
Cu	:	Copper
DA	:	Dopamine
DBH	:	Dopamine β-hydroxylase
DM	:	Diabetes mellitus
DNA	:	Deoxyribonucleic acid

DPD	:	Dichlorophenyldiazonium tetrafluroborate
DSM-V	:	Diagnostic and Statistical Manual of Mental Disorders 5th edition
Fe	:	Iron
GABA	:	Gamma amino butyric acid
GFR	:	Glomerular filtration rate
GGT	:	Gamma-glutamyl transferase
GPx	:	Glutathione peroxidase
HBV	:	Hepatitis B virus
HCC	:	Hepatocellular carcinoma
HCV	:	Hepatitis C virus
HF	:	Heart failure
HTN	:	Hypertension
IDA	:	Iron deficiency anemia
IFCC	:	International Federation of Clinical Chemistry
IFN-α	:	Interferon-alpha
IgG	:	Immunoglobulin G
IL	:	Interleukin
INR	:	International normalized ratio
IQR	:	Inter Quartile Range
ISE	:	Ion selective electrode
ISHD	:	Ischemic heart disease
K	:	Potassium
LDH	:	Lactate dehydrogenase
LLD	:	Late life depression
LT	:	Liver transplantation
MAO	:	Monoamine oxidase
MDD	:	Major depressive disorder
MDH	:	Malate dehydrogenase
Mg	:	Magnesium
Mn	:	Manganese
MNA	:	Mini Nutritional Assessment
MRA	:	Magnetic resonance angiography
MRI	:	Magnetic resonance imaging
Na	:	Sodium
NADH	:	Nicotinamide adenine dinucleotide
NAFLD	:	Non-alcoholic liver disease
NASH	:	Non-alcoholic steatohepatitis
NE	:	Norepinephrine
NMDA	:	N-methyl-D-aspartate

NSDUH	:	National Surveys on Drug Use and Health
O-CPC	:	O-Cresolphthalein
OH vitamin D3	:	Hydroxy vitamin D3
P	:	Phosphorus
PBC	:	Primary biliary cirrhosis or primary biliary cholangitis
PHQ-2	:	Patient Health Questionnaire-2
PSC	:	Primary sclerosing cholangitis
PT	:	Prothrombin time test
QOL	:	Quality of life
ROS	:	Radioactive oxygen species
Rpm	:	Revolutions per minute
Se	:	Selenium
SOD	:	Superoxide dismutase
SPSS	:	Statistical package for social science
TEs	:	Trace elements
TH	:	Thyroid hormone
TIBC	:	Total iron-binding capacity
US	:	Ultrasonography
WD	:	Wilson's disease
WHO	:	World Health Organization
Zn	:	Zinc

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Abstract

Introduction: Chronic liver disease (CLD) is a considerable burden on the public health, economic and social viewpoints in the society. The prevalence of depression was 10% in community, and 40% in hospitals and long-term care facilities. Trace elements (TEs) and macro-minerals may be varied with different types of CLD. Also, it is linked with the etiology and pathophysiology of depression. Moreover, CLD is associated with mood disorders like depression.

Aim: To detect the association between TEs, macro-minerals and depression among elderly patients with CLD admitted to ASU hospitals and in outpatient clinics.

Subject and Methods: Cross-Sectional diagnostic and etiological study was conducted among 147 patients with CLD. We used the Patient Health Questionnaire (PHQ-2) and if positive PHQ-9 scoring system to diagnose depression. Routine laboratory tests, electrolytes and TEs (zinc (Zn) and copper (Cu)) were analysed.

Results: The overall prevalence of depression was 53.7%. The results showed that disease severity using Child-Pugh Classification, viral liver disease, ISHD, anti-ischemic medications, diuretics, number of drugs, low serum sodium (Na) level, low serum calcium (Ca) level, malnutrition by using mini nutritional assessment (MNA), and increase the number of diseases by using Charlson Comorbidity Index (CCI) were significant for depression (P value: ≤ 0.005).

Conclusions: The current study highlighted that in addition to known risk factors causing depression in CLD, using diuretics and malnutrition are predictors for depression among CLD patients through their effect on serum TEs and macro-minerals, so by treating malnutrition and adjusting the dose and duration of using diuretics may decrease the risk of depression. However, further studies are needed to confirm such association.

Keywords: Chronic liver disease- Trace elements- macro-minerals-depression.

INTRODUCTION

Chronic liver disease (CLD) is a considerable burden on the public health, economic and social viewpoints in the society, it represents a great problem for a majority of the world as it increases the morbidity and mortality, it represents one of the three main causes of death in Africa and Asia, and the tenth cause of death in the United States *(Riley and Bhatti, 2001)*.

The etiology of CLD is divided into alcoholic liver disease (ALD) and non-alcoholic liver disease (NAFLD), the group of patients with non-alcoholic etiology included viral hepatitis B and C, autoimmune liver disease (primary biliary cirrhosis or primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH)), Wilson's disease (WD), non-alcoholic steatohepatitis (NASH) in which fat deposition in the hepatocyte is complicated by liver inflammation and fibrosis *(Lee et al., 2013).*

Depression in older population is prevalent in the community, and is more prevalent among hospitalized older patients, the prevalence of depression was about 10% in community, and about 40% in hospitals and long-term care facilities *(Bryant et al., 2011)*. The World Health Organization (WHO) predicted that by 2020 depression will represent the third leading cause of disability worldwide *(Feng et al., 2013).*

The risk factors for depression include female gender, older age, psychological stressors, low education level, polypharmacy, physical co-morbidities like stroke, hearing impairment, visual impairment, cardiac disease, and chronic lung disease, functional impairment, and reduced cognition *(Feng et al., 2013)*.

Depression has a negative impact on the quality of life (QOL), and poorer outcome of treatment of physical disorders in addition, depression is associated with increased mortality due to either suicide or chronic illness *(Chang-Quan et al., 2009)*.

The human body is composed of elements that is divided into abundant elements and trace elements (TEs), abundant elements consist of the major and semi-major elements, major elements are important constituents of tissues like oxygen, carbon, hydrogen, nitrogen while semi-major elements are usually involved in regulating nerve and muscle function and maintaining acid-base and water balance like sodium (Na), potassium (K), calcium (Ca), magnesium (Mg) and phosphorus (P) *(O'Dell et al., 1997)*.

While TEs include iron (Fe), copper (Cu), and zinc (Zn), manganese (Mn), selenium (Se), cobalt (Co) and cadmium (Cd). They are required in the body for many metabolic pathways in the liver, such as enzymatic functions, protein synthesis, oxidative reactions and anti-oxidant defense *(O'Dell et al., 1997)*.

TEs may be varied with different types of CLD due to their metabolism occur in the liver *(Qasim et al., 2010).* Zn has an important role in the function of over 300 enzymes affecting several organ functions affecting the growth and the immune system development, also, it is important in the function of the liver *(Rink & Gabriel, 2000).*

The liver is the main iron storage organ and it plays an essential role in iron metabolism, the iron transport protein, transferrin, and the major iron storage protein, ferritin, are synthesized in the liver *(Sebastiani et al., 2006)*. The increase in serum ferritin and transferrin saturation cause increased progression of chronic hepatitis C. Cu level increases as the disease progresses from chronic hepatitis to liver cirrhosis *(Ioannou et al., 2003*).

Also, TEs levels are linked with the etiology and pathophysiology of many mental disorders, including depression *(Błażewicz et al., 2017)*. Ca is important for activation of different enzymes and plays a vital role in neuromuscular excitability, low Ca levels can lead to mood disorders and depression. Also, Mg is an important factor in the treatment of depression *(Jung et al., 2009)*.

Mn presents in several proteins and enzymes which are associated with some neurodegenerative disorders. Se is required for the functioning of antioxidant defenses in the brain and nervous system *(Grünecker et al., 2013)*. Cu level is increased in WD which leads to liver damage,

psychiatric symptoms like depression, anxiety and psychosis *(Kodama et al., 2012)*. Zn deficiency is associated with neuropsychiatric manifestations that is presented with altered behavior and cognition, depression and decreased ability to learn *(Howland and Wang, 2008)*.

CLD are frequently associated with psychiatric comorbidities, mainly mood disorders like depression and anxiety, sleep and cognitive impairment *(Häuser et al., 2004).* These symptoms are important as they have an adverse effect upon the course of illness in as amplification of physical symptoms, functional impairment, decrease compliance to treatment, and decreased QOL *(Navinés et al., 2012)*. Patients with CLD had a significantly higher incidence of depression compared to that of healthy population *(Gutteling et al., 2007)*.

Pathogenesis of depression in patients with CLD is insufficiently clarified, these disorders occur due to accumulation of toxins in blood due to the inadequate clearance in a cirrhotic liver *(Hilsabeck et al., 2002)*.

Since the relationship between depression in CLD and TEs, macro-minerals disturbance has not been understood clearly. Therefore, the purpose of the present study is to assess depression in CLD and its association with TEs and macro-minerals disturbance in older patients admitted to Ain Shams University (ASU) hospitals and in outpatient clinics.