



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



MONA MAGHRABY



The relationship between serum homocysteine level and cognitive function in elderly patients with chronic kidney disease

Thesis

*Submitted in Partial Fulfillment for MD degree in
Geriatrics and Gerontology*

By

Yumna Abdellatif Elsafy Elgazzar

(Msc – Geriatrics and Gerontology)

Supervised by

Prof. Dr. Hala Samir Sweed

*Professor of Geriatrics and Gerontology
Faculty of Medicine – Ain Shams University*

Prof. Dr. Tomader Taha Abdel Rahman

*Professor of Geriatrics and Gerontology
Faculty of Medicine – Ain Shams University*

Dr. Heba Youssif Youssif Kamel

*Assistant Professor of Geriatrics and Gerontology
Faculty of Medicine – Ain Shams University*

Dr. Ramy Mohamed Mahmoud

*Lecturer of Clinical Pathology
Faculty of Medicine – Ain Shams University*

*Faculty of Medicine
Ain Shams University
2020*

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

First and for most, thanks to Allah "The Most Merciful"

In all gratitude, I extend my most sincere thanks to Prof. Dr. Hala Samir Sweed, Professor of Geriatrics and Head of Geriatric Medicine Department, Faculty of Medicine, Ain Shams University, for honoring me with her supervision of this thesis. Her help, guidance, and valuable advices were a great encouragement throughout the work,

I wish to express my deep appreciation and sincere gratitude to Prof. Dr. Tomader Taha Abdel Rahman Professor of Geriatric Medicine, Ain Shams University, for her supervision, valuable instructions and guidance.

I am deeply indebted and sincerely thankful to Dr. Heba Youssif Youssif Kamel, Assistant Professor of Geriatric medicine, Ain Shams University, who gave me valuable help and directions throughout the work,

I wish to express my great thanks and gratitude to Dr. Ramy Mohamed Mahmoud, Lecturer of Clinical Pathology, Ain Shams University, for his kind supervision and great help in this work,

Last but not least, I would present all my appreciations to my Family and colleagues without them; this work could not have been completed; to them I dedicate this work,

Yumna Elgazzar

List of Contents

Title	Page No.
List of Tables	i
List of Figures	iv
List of Abbreviations.....	v
Introduction	1
Aim of the Work.....	4
Review of Literature	
Homocysteine Neurotoxicity	5
Homocysteine and Kidney Disease.....	18
Cognitive Impairment in Chronic Kidney Disease.....	28
Subjects and Methods.....	44
Results	52
Discussion	75
Conclusion	88
Study Limitations and Future Recommendations.....	89
Summary	91
References	94
Appendices	126
Arabic Summary	—

List of Tables

Table No.	Title	Page No.
Table (1):	Comparison between cases (CKD) and control as regards socio- demographic variables.....	52
Table (2):	Comparison between cases (CKD) and control as regard associated co-morbidities.	54
Table (3):	Distribution of the stage of CKD among cases.	55
Table (4):	Disease duration (Mean $\pm$ SD) among CKD cases	55
Table (5):	Comparison between cases of CKD and control as regards the mean serum creatinine, eGFR, and the mean serum homocysteine level.	56
Table (6):	Comparison between different stages of CKD cases as regard mean serum creatinine, eGFR and serum homocysteine level	57
Table (7):	Distribution of Clinical Dementia Rating scale scores among CKD cases and control subjects	59
Table (8):	Comparison between CKD cases and controls as regards the results of CDR (Clinical Dementia Rating Scale) intact or impaired cognition.	59
Table (9):	Comparison between Cases of CKD and Controls as regard the CERAD-NB subtests scores.....	60
Table (10):	Comparison between CKD cases of different stages as regard the CERAD-NB subtests scores.....	62

List of Tables Cont...

Table No.	Title	Page No.
Table (11):	Correlation coefficient between the CERAD-NB subtests performance and different parameters (Age, education, s. creatinine, eGFR and s. homocysteine) in mild to moderate CKD cases (stage 3).....	63
Table (12):	Correlation coefficient between the CERAD-NB subtests performance and different parameters (Age, education, s. creatinine, eGFR and s. homocysteine) in advanced CKD cases (stage 4).....	64
Table (13):	Correlation coefficient between the CERAD-NB subtests performance and different parameters (Age, education, s. creatinine, eGFR and s. homocysteine) in ESRD cases (CKD stage 5).....	65
Table (14):	Correlation coefficient between serum homocysteine level and the CERAD-NB subtests performance and in CKD cases	66
Table (15):	Comparison between the mean serum homocysteine level and gender, working status, marital status, education, presence of diabetes, presence of hypertension and presence of heart disease among CKD cases	68
Table (16):	Correlation coefficient between CERAD-NB Total Scores and age, educational level among Cases of CKD.....	69
Table (17):	Correlation coefficient between CERAD-NB total scores and serum homocysteine, eGFR, serum creatinine, Stage of CKD and disease duration among CKD cases	70

List of Tables Cont...

Table No.	Title	Page No.
Table (18):	Backward linear regression model for the CERAD-NB total score-I and significant predictors of the score	72
Table (19):	Backward linear regression model for the CERAD-NB total score-II and significant predictors of the score	74

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Homocysteine metabolic pathway	6
Figure (2):	Comparison between stages of CKD cases as regards the mean eGFR and serum homocysteine level.	58
Figure (3):	Correlation coefficient between serum homocysteine level and CERAD total score I.....	71
Figure (4):	Correlation coefficient between serum homocysteine level and CERAD total score II.	71

List of Abbreviations

Abb.	Full term
%ICV.....	Percentage of intracranial volume
A β	Beta-amyloid plaques
AD.....	Alzheimer's disease
ADL	Activity of Daily Living
BBB.....	Blood brain barrier
CDR	Clinical Dementia Rating
CERAD-NB	Consortium to Establish a Registry for Alzheimer's disease neuropsychological battery
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DM.....	Diabetes Mellitus
DTI.....	Diffusion tensor imaging
eGFR.....	Estimated glomerular filtration rate
ELIZA.....	Enzyme-Linked Immunosorbent Assay
ESRD	End-stage renal disease
FA	Folic Acid
FA	Fractional anisotropy
Hcy.....	Homocysteine
HHcy	Hyperhomocysteinemia
HTN.....	Hypertension
MCI.....	Mild cognitive impairment
MD	Mean diffusivity
MDRD.....	Modification of Diet in Renal Disease
Met.....	Methionine
mGluR1	Metabotropic glutamate receptors subtype1
MMSE	Mini Mental State Examination Scores
MOCA.....	Montreal Cognitive Assessment
MRI.....	Magnetic resonance imaging

List of Abbreviations Cont...

Abb.	Full term
NAC	N-acetylcysteine
NF-KappaB.....	Nuclear factor kappa B
NFTs.....	Neurofibrillary tangled
NMDA	N-methyl-D-aspartate
PTH	Parathyroid hormone
RRT	Renal replacement therapy
SAH.....	S-adenosyl homocysteine
SAM.....	S-adenosyl methionine
tHcy.....	Total plasma homocysteine
VaD.....	Vascular dementia
VAT.....	Vascular access thrombosis
VISP	Vitamin Intervention for Stroke Prevention
VITATOPS	Vitamins To Prevent Stroke
VTE.....	Venous thromboembolism
WMLs	White matter lesions

INTRODUCTION

Patients with chronic kidney disease (CKD) have been found to have cognitive impairment. However, the core features and clinical correlates of the development of cognitive impairment and chronic kidney disease are still unclear. Cognitive impairment was described as an occult burden prevalent in CKD and end-stage renal disease (ESRD) patients. Several studies have suggested its occurrence in earlier stages of kidney disease but unacknowledged as a significant public health burden (*Etgen et al., 2012; Sarnak, 2013; Heaf, 2017*).

The *American Journal of Kidney Diseases* added to the evolving story of cognitive impairment in kidney disease by measuring mild and severe cognitive impairment in hemodialysis and peritoneal dialysis patients, this came to a prevalence of cognitive impairment anywhere from 30 to 70% (*Griva et al., 2010*).

CKD patients are at higher risk of cognitive decline and even dementia. Investigation of the clinical correlates of cognitive impairment in CKD could potentially result in the identification of treatment targets in order to modify the poor cognitive outcome (*Tamura et al., 2016*).

Cognitive impairment in CKD is associated with poorer clinical outcomes, including a higher admission rate, a greater duration of hospitalization, more difficulty adhering to

medications, a poorer quality of life and a higher mortality rate (*Rodriguez-Angarita et al., 2016*).

Patients with CKD have higher levels of serum homocysteine Hcy than subjects without CKD. Homocysteine is primarily transsulfurated in the kidney and deficiency of this renal transsulfuration contributes to elevation of plasma Hcy (*Li et al., 2007; Van Guldener et al., 2005*).

Homocysteine is derived from the demethylation of the essential amino acid methionine. Remethylation occurs by two main pathways: the first uses folate and vitamin B12 as cofactors, while the second, transsulfuration, uses vitamin B6 as a cofactor (*Skovierova et al., 2016*).

Homocysteine may affect cognitive function through impairing methylation of myelin sheath or the excitotoxic effect of homocysteine metabolites on N-methyl-D-aspartate glutamate receptors which markedly enhances the vulnerability of neurons to oxidative stress and injury (*Kamat et al., 2013*) which has emerged as an independent risk factor for several neurodegenerative diseases such as vascular dementia, Alzheimer's disease (AD) and stroke (*Zhuo et al., 2011*).

Serum homocysteine has been associated with atrophic changes in the brain and is considered a marker for low serum vitamin B12 and folate. Studies have reported raised serum homocysteine, low serum vitamin B12 and low serum folate to