HCV infection and clearance in relation to atherosclerosis and metabolic syndrome in an Egyptian village

Thesis submitted for partial fulfillment of M.D. in Public Health

By

Aya Mostafa Kamal ElDin

Assistant Lecturer, Department of Community Medicine,
Environmental and Occupational Medicine
Faculty of Medicine, Ain Shams University

Supervised by

Prof. Dr. Sawsan Mohamed El-Ghazali

Professor of Public Health and Behavioral Medicine
Head of the Department of Community, Environmental and Occupational Medicine
Director of Behavioral Medicine Unit
Faculty of Medicine, Ain Shams University

Prof. Dr. Mubarak Mohamed Hussein

Professor of Tropical Medicine
Department of Tropical Medicine
Faculty of Medicine, Ain Shams University

Prof. Dr. Mostafa El-Hosseiny Mostafa

Professor of Community Medicine, Environmental and Occupational Medicine
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University

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الطبيبة/ آية مصطفى كمال الدين
المدرس المساعد بقسم طب المجتمع والبيئة و طب الصناعات
كلية الطب - جامعة عين شمس

تحت إشراف

الأستاذ الدكتور/ سوسن محمد الغزالى
أستاذ الصحة العامة و الطب السلوكى و مدير وحدة الطب السلوكى
رئيس قسم طب المجتمع والبيئة و طب الصناعات
كلية الطب - جامعة عين شمس

الأستاذ الدكتور/ مبارك محمد حسين
أستاذ بقسم طب الأمراض المتوطنة
كلية الطب - جامعة عين شمس

الأستاذ الدكتور/ مصطفى الحسينى مصطفى
أستاذ بقسم طب المجتمع والبيئة و طب الصناعات
كلية الطب - جامعة عين شمس

كلية الطب
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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
CAD	Coronary Artery Disease
CDC	Centers for Disease Control and Prevention
CHC	Chronic Hepatitis C infection
CI	Confidence Intervals
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
ECG	Electrocardiography
EGIR	European Group for the Study of Insulin Resistance
EIA	Enzyme-linked Immunosorbent Assay
GGT	Gamma Glutamyl transpeptidase
HAV	Hepatitis A Virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCADS	Hepatitis C associated Syndrome
HCC	Hepatocellular Carcinoma
HCV	Heptitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunedeficiency Virus
HOMA	Homeostasis Assessment Model
HTN	Hypertension
ICD	International Classification of Diseases
ID	Identification number
IDF	International Diabetes Federation
IFN	Interferon
IL	Interleukin
IMT	Intima-Media Thickness
IR	Incidence Rate
IR	Insulin Resistance
ISI	Insulin Sensitivity Index
IQR	Interquartile Range

IV	Intravenous
IVGTT	Intravenous glucose tolerance test
LDL	Low Density Lipoprotein
MHz	Megahertz
mmhg	millimeter mercury
mmol/l	millimol per liter
MOHP	Ministry of Health and Population
µg/min	microgram per minute
µm	Micrometer
N	Number
NAFLD	Non Alcoholic Fatty Liver Disease
NASH	Non Alcoholic Steatohepatitis
NCEP-ATPIII	National Cholesterol Education Program-Adult Treatment Panel III
NHTMRI	National Hepatology and Tropical Medicine Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NS	Non Structural region of the genome
OR	Odds Ratio
PAN	Polyarteritis Nodosa
PWV	Pulse-Wave Velocity
PY	Person Years of observation
QUICKI	Quantitative insulin-sensitivity check index
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
RR	Relative Risk
RT-PCR	Real Time Polymerase Chain Reaction
SBP	Systolic Blood Pressure
SD	Standard Deviation
Si	Insulin Sensitivity
SOCS	Suppressor of Cytokine Signaling Proteins
SPSS	Statistical Program for Social Sciences
SVR	Sustained Virological Response
T2D	Type II Diabetes
TG	Triglycerides
TGF-β	Tumour Growth Factor beta
TNF	Tumour Necrosis Factor
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

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Hepatitis C virus infection and clearance in relation to atherosclerosis and metabolic syndrome in an Egyptian village

INTRODUCTION:

The developing countries face the twin burden of escalating non-communicable disease and declining, but still prevalent, infectious disease. Egypt has the highest hepatitis C virus (HCV) prevalence in the world (overall prevalence of HCV antibody is 12% in the general population, reaching 40% in persons over age 40 in rural areas) [1], and a population which is prone to diabetes and cardio-vascular disease (CVD).

A causal link between infection and CVD has been proposed but its mechanism is still unclear [2]. Pathogens could plausibly promote the development of atherosclerosis in a number of ways, including pro-inflammatory and pro-thrombotic effects, and disturbances of lipid metabolism [3,4]. Whether hepatitis C increases CVD risk is uncertain. HCV infection is associated with increased common carotid IMT and carotid-artery plaques in some [5,6], but not all studies [7,8].

Discrepancies between studies are likely to be due to inadequacies in study design; for example, the numbers of individuals infected with hepatitis C have often been small [9], some combined hepatitis C and hepatitis B [10], while in others comparator groups could be hospital based [6] which may bias the relationship between atherosclerosis and HCV.

Also, HCV infection in population based studies is associated with a 3.5 fold increased prevalence, and an 11 fold increased incidence of diabetes [9,10]. HCV positive individuals appear more insulin resistant than non infected controls [11]. The mechanism of this association is unclear. Diabetes could be the consequence of inflammatory or autoimmune responses to hepatitis. The enhanced risk of atherosclerosis in diabetes, in part at least, is attributed to the classical dyslipidaemic pattern of insulin resistance. This consists of elevations in circulating triglyceride, and a reduction in HDL cholesterol levels [12]. But an anomaly presents itself in HCV. Lipid and lipoprotein abnormalities in HCV are characterised by **hypo**cholesterolaemia and **hypo-**betalipoproteinaemia, i.e. reduced levels of apolipoprotein B

(apoB)-containing lipoproteins, such as LDL and VLDL cholesterol [13]. Superficially, in terms of atherosclerotic risk, this circulating lipoprotein pattern would be viewed as favourable, and runs directly counter to observations in the classical manifestations of the metabolic syndrome [14].

The proposed study will inform understanding of the links between infectious and CVD, the mechanisms and impact of the discordant effects of hepatitis C on glucose tolerance and lipid metabolism, and how this relates to atherosclerotic risk. This study will further our knowledge of the metabolic syndrome, as people with chronic hepatitis C infection appear to show a breakdown in the natural association between diabetes and dyslipidaemia providing valuable insights into the mechanisms of insulin resistance and its sequelae, and indicators for prevention, for all populations. Finally, clearance of infection appears to reverse some of the metabolic changes described above. It is unclear what the impact of such reversal will be on atherosclerotic risk, but is an important public health question.

OBJECTIVES:

1. To determine the association of HCV infection and atherosclerosis

2. To identify the relationship between HCV infection and metabolic syndrome

SUBJECTS AND METHODS:

Study design

Analytical multiple community based cross-sectional studies within the ongoing Zawyat Razin village cohort study.

Study subjects

Participants will be recruited from cohort adults aged over 35 from three main groups: chronically infected with HCV (positive anti-HCV antibodies and positive RNA); cleared HCV infection (positive anti-HCV antibodies and negative RNA), and never infected (negative anti-HCV antibodies). Hepatitis B antigen positive individuals will be excluded.

Ethical consideration

The study protocol is approved by the MOHP Institutional Review Board and a local ethics committee set up for hepatitis studies in Egypt. Participants will be provided by documented informed consent

Study sample

Sampling will be stratified by gender and 5 year age group