



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكرو فيلم

# بسم الله الرحمن الرحيم



**HANAA ALY**



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم



# شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



**HANAA ALY**



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 تغييرات



### يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



**HANAA ALY**

**Study Association of Serum Immunoglobulins and  
Non-alcoholic Fatty Liver Disease in Egyptian  
Patients**

**Thesis**

Submitted for partial fulfillment of the Master Degree in  
Gastroenterology & Hepatology

By

**Abdul-Aziz Mahmoud Mahmoud Elmaradny**  
M.B., B.Ch, Faculty of Medicine, Ain Shams University

Under Supervision Of

**Prof. Dr. Emad Ahmed Awad**

*Prof. of Internal Medicine, Hepatology & Gastroenterology  
Faculty of Medicine – Ain Shams University*

**Prof. Dr. Shereen Abou Bakr Saleh**

*Prof. of Internal Medicine, Hepatology & Gastroenterology  
Faculty of Medicine – Ain Shams University*

**Dr. Ahmed Mohamed ElGhandour**

*Assistant Prof. of Internal Medicine, Hepatology &  
Gastroenterology  
Faculty of Medicine – Ain Shams University*

**Faculty of Medicine  
Ain Shams University  
2021**

# دراسة رابطة الغلوبولين المناعي في الدم وأمراض الكبد الدهنية غير الكحولية في المرضى المصريين

رسالة

توطئة للحصول على درجة الماجستير في  
أمراض الجهاز الهضمي والكبد

مقدمة من

الطبيب/ عبدالعزيز محمود محمود المرادني  
بكالوريوس الطب، كلية الطب، جامعة عين شمس

تحت إشراف

**أ.د. عماد أحمد عوض**

أستاذ الباطنة العامة والجهاز الهضمي والكبد  
كلية الطب - جامعة عين شمس

**أ.د. شيرين أبو بكر صالح**

أستاذ الباطنة العامة والجهاز الهضمي والكبد  
كلية الطب - جامعة عين شمس

**د. أحمد محمد الغندور**

أستاذ مساعد الباطنة العامة والجهاز الهضمي والكبد  
كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠٢١



## Acknowledgement

First of all, all gratitude is due to **Allah** almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

Really I can hardly find the words to express my gratitude to **Prof. Dr. Emad Ahmed Awad**, Prof. of Internal Medicine, Hepatology & Gastroenterology, Faculty of Medicine – Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.

I would like also to express my sincere appreciation and gratitude to **Prof. Dr. Shereen Abou Bakr Saleh**, Prof. of Internal Medicine, Hepatology & Gastroenterology, Faculty of Medicine – Ain Shams University, for her continuous directions and support throughout the whole work.

I cannot forget the great help of **Dr. Ahmed Mohamed El Ghandour**, Assistant Professor of Internal Medicine, Hepatology & Gastroenterology, Faculty of Medicine – Ain Shams University for his invaluable efforts, tireless guidance and for his patience and support to get this work into light.

Last but not least, I dedicate this work to **my family**, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.



*Abdul-Aziz Mahmoud Mahmoud Elmaradny*



# List of Contents

	Page
Acknowledgment .....	--
List of Abbreviations .....	i
List of Figures .....	iii
List of Tables .....	v
Protocol .....	vi
Introduction .....	1
Aim of The Work .....	4
Review of Literature .....	5
• NAFLD .....	5
• Immunoglobulins .....	35
• Mechanisms linking Immunoglobulins to NAFLD .....	61
• Treatment of NAFLD .....	82
Patients and Methods .....	86
Results .....	90
Discussion .....	132
Summary .....	141
Conclusion .....	144
Recommendations .....	145
References .....	146
Arabic Summary .....	--

## **List of Abbreviations**

AIHA	: Autoimmune haemolytic anaemia
ALD	: Alcoholic liver disease
ANA	: Anti nuclear antibody
APRI	: Aspartate transaminase-to-Platelet Ratio Index
ARBs	: Angiotensin receptor blockers
AST	: Aspartate Transaminase
BMI	: Body mass index
CAP	: Controlled attenuation parameter
CCR	: Chemokine receptor
CDR	: Cirrhosis dysbiosis ratio
CIA	: Anti-collagen induced
CRN	: Clinical Research Network
DAGs	: Diacyl glycerols
DNA	: Deoxyribonucleic acid
DSB	: DNA double-strand break
FAS	: Fatty acid synthesis
FcR $\gamma$	: Fc receptor gamma chain
Fv	: Variable fragment
FXR	: Farnesoid X receptor
GGT	: Gammaglutanyl transpeptidase
HCC	: Hepatocellular carcinoma
IC	: Immune complexes
ICAM3	: Intercellular adhesion molecule 3
IFN	: Interferon
IgA	: Globulin A
IgG	: Immunoglobulin G
IgM	: Immunoglobulin M
Igs	: Immunoglobulins
IgSF	: Immunoglobulin super-family



IL-1 $\beta$	: Interleukin-1 $\beta$
IL-6	: Interleukin-6
INR	: International Normalized Ratio
ITAM	: Immunoreceptor tyrosine-based activation motif
LS	: Liver stiffness
MDB	: Mallory-Denk bodies
MDBs	: Mallory-Denk bodies
MetS	: Metabolic syndrome
NADPH	: Nicotinamide Adenine Dinucleotide Phosphate
NAFLD	: Non-alcoholic Fatty Liver Disease
NASH	: Nonalcoholic steatohepatitis
NCAN	: Neurocan
NHEJ	: Nonhomologous end-joining
NLRP3	: NLR family pyrin domain containing 3
OCA	: Obeticholic acid
OSA	: Obstructive sleep apnea
PCOS	: Polycystic ovarian syndrome
PDFF	: Proton density fat fraction
PI3K	: Phosphoinositide 3-kinase
PNPLA3	: Palatin-like phospho lipase domain-containing
PPAR	: Proliferator-activated receptor
RSS	: Recombination signal sequence
SHM	: Somatic hypermutation
Syk	: Spleen tyrosine kinase
T2DM	: Type 2 diabetes mellitus
TdT	: Terminal deoxynucleotidyl transferase
TE	: Transient elastography
Th17	: T helper 17
TM6SF2	: Transmembrane 6 superfamily member 2
TNF	: Tumour necrosis factor
TNF- $\alpha$	: Tumor necrosis factor – alpha
US	: Ultrasonography

## List of Figures

<b>Fig.</b>	<b>Title</b>	<b>Page</b>
1	Prevalence of NAFLD in different regions.	6
2	The progressive stages of NAFLD.	7
3	Established and suspected risk factors for nonalcoholic fatty liver disease.	8
4	Pathogenesis of NAFLD.	15
5	Nonalcoholic fatty liver disease (NAFLD) as a systemic disorder.	18
6	Steatosis in NAFLD. Macro-vesicular steatosis, predominantly distributed in zone 3.	20
7	Lobular inflammation in nonalcoholic steatohepatitis. Necroinflammatory foci (arrows) are scattered in the hepatic lobule (hematoxylin and eosin staining).	21
8	NAFLD. Ballooned hepatocytes (black arrows). Mallory-Denk bodies (white arrow).	22
9	Two-dimensional model of an IgG molecule.	37
10	Rearrangement events in the human $\kappa$ locus	40
11	Representation of the chromosomal organization of the Ig H, $\kappa$ , and $\lambda$ gene clusters	44
12	Structural and glycosylation properties of immunoglobulins.	49
13	Interaction partners of the immunoglobulin G (IgG) Fc-fragment.	72
14	Management and therapeutic strategies for non-alcoholic fatty liver disease (NAFLD).	82
15	Age among the studied groups.	91
16	Sex among the studied groups.	91
17	BMI among the studied groups.	92

<b>Fig.</b>	<b>Title</b>	<b>Page</b>
18	Waist circumference among the studied groups	92
19	DM among the studied groups.	92
20	Hemoglobin among the studied groups.	93
21	TLC among the studied groups.	94
22	Platelets among the studied groups.	94
23	FBG among the studied groups.	95
24	Creatinine among the studied groups.	96
25	Urea among the studied groups.	96
26	Cholesterol among the studied groups.	97
27	Triglycerides among the studied groups.	98
28	LDL among the studied groups.	98
29	HDL among the studied groups.	98
30	ALT among the studied groups.	100
31	AST among the studied groups.	100
32	GGT among the studied groups.	100
33	Total bilirubin among the studied groups.	101
34	Direct bilirubin among the studied groups.	101
35	Albumin among the studied groups.	101
36	INR among the studied groups.	102
37	IgA among the studied groups.	103
38	IgM among the studied groups.	104
39	IgG among the studied groups.	104
40	APRI score among the studied groups.	106
41	NAF score among the studied groups.	106
42	FLI score among the studied groups.	107
43	Liver fibrosis among the studied groups.	107
44	ROC curve for immunoglobulins in differentiating NASH from NAFLD.	114

<b>Fig.</b>	<b>Title</b>	<b>Page</b>
45	Diagnostic characteristics of immunoglobulins cutoff points in differentiating NASH from NAFLD.	116
46	Comparison according to steatosis grades regarding IgM imunoglobulins among NASH group.	117
47	Comparison according to steatosis grades regarding IgG imunoglobulins among NASH group.	118
48	Comparison according to steatosis grades regarding IgA imunoglobulins among NASH group.	118
49	ROC curve for immunoglobulins in differentiating S-3 from S-1/2 among NASH group.	119
50	Diagnostic characteristics of immunoglobulins cutoff points in differentiating S-3 from S-1/2 among NASH group.	121
51	Comparison according to fibrosis grades regarding IgM imunoglobulins among NASH group.	122
52	Comparison according to fibrosis grades regarding IgG imunoglobulins among NASH group.	123
53	Comparison according to fibrosis grades regarding IgA imunoglobulins among NASH group.	123
54	ROC curve for immunoglobulins in differentiating F-1 from F-0 among NASH group.	124

<b>Fig.</b>	<b>Title</b>	<b>Page</b>
55	Diagnostic characteristics of immunoglobulins cutoff points in differentiating F-1 from F-0 among NASH group.	126
56	Comparison according to steatosis grades regarding IgM immunoglobulins among NAFLD group.	127
57	Comparison according to steatosis grades regarding IgG immunoglobulins among NAFLD group.	128
58	Comparison according to steatosis grades regarding IgA immunoglobulins among NAFLD group.	128
59	ROC curve for immunoglobulins in differentiating F-1 from F-0 among NAFLD group.	129
60	Diagnostic characteristics of immunoglobulins cutoff points in differentiating F-1 from F-0 among NAFLD group.	131

## List of Tables

Table	Title	Page
1	The SAF Diagnostic Algorithm for Defining NASH.	33
2	Properties of Immunoglobulin Isotypes/Subclasses.	50
3	Changes in intestinal IgA associated with ALD and NAFLD/NASH in human.	77
4	Demographic characteristics among the studied groups.	90
5	CBC among the studied groups.	93
6	FBG (mg/dL) among the studied groups.	95
7	Kidney functions among the studied groups.	96
8	Lipid profile among the studied groups.	97
9	Liver functions among the studied groups.	99
10	Immunoglobulins among the studied groups.	103
11	Liver scores among the studied groups.	105
12	Correlations of IgA among the studied groups.	108
13	Correlations of IgM among the studied groups.	110
14	Correlations of IgG among the studied groups.	112
15	Diagnostic performance of immunoglobulins in differentiating NASH from NAFLD.	113
16	Diagnostic characteristics of immunoglobulins cutoff points in differentiating NASH from NAFLD.	115
17	Comparison according to steatosis grades regarding immunoglobulins among NASH group.	117

<b>Table</b>	<b>Title</b>	<b>Page</b>
18	Diagnostic performance of immunoglobulins in differentiating S-3 from S-1/2 among NASH group.	119
19	Diagnostic characteristics of immunoglobulins cutoff points in differentiating S-3 from S-1/2 among NASH group.	120
20	Comparison according to fibrosis grades regarding immunoglobulins among NAFLD and NASH groups.	122
21	Diagnostic performance of immunoglobulins in differentiating F-1 from F-0 among NAFLD and NASH groups.	124
22	Diagnostic characteristics of immunoglobulins cutoff points in differentiating F-1 from F-0 among NASH group.	125
23	Comparison according to steatosis grades regarding immunoglobulins among NAFLD groups.	127
24	Diagnostic performance of immuno-globulins in differentiating F-1 from F-0 among NAFLD.	129
25	Diagnostic characteristics of immunoglobulins cutoff points in differentiating F-1 from F-0 among NAFLD group.	130