Phospholipid Autoantibodies And Gastrin Secretion As Markers For Diabetic Neuropathy

Thesis Submitted for partial fulfillment of M.D. Degree in Internal Medicine 66015

By

Phoebe Roshdy Yossif, M.B., B.cH., MSc.

Prof. Dr. Hussein El-Damasy

Professor of Internal Medicine and Endocrinology

Prof. Dr. Mohamed Osama Abdel Ghani

Professor of Neurology and Psychiatry

Dr. Mohamad Hesham El Gayar

Assistant Professor of Internal Medicine and Endocrinology

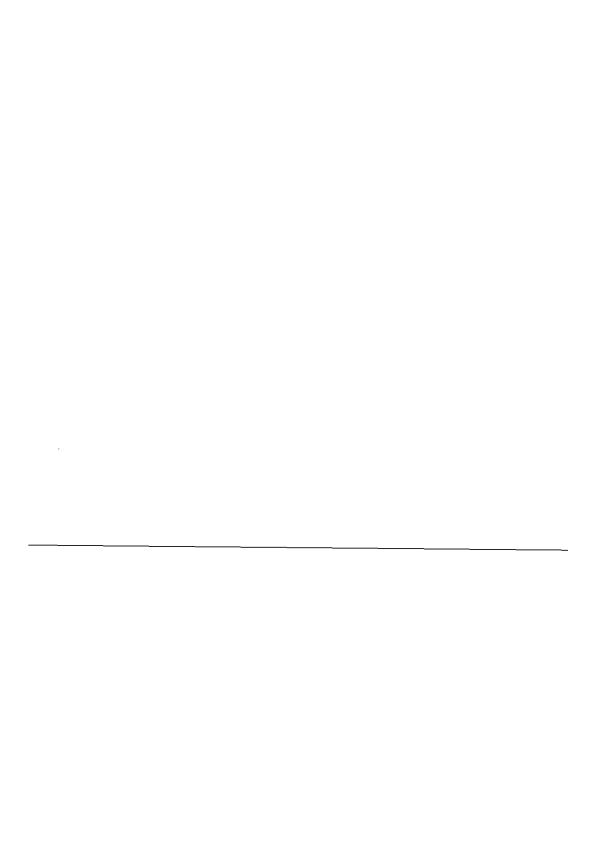
Dr. Raef Malak Botros

Lecturer of Internal Medicine

Dr. Nehad Shokry Shoe

Lecturer of Internal Medicine

Faculty of Medic Ain Shams Univers (1999)







Acknowledgment



Thanks to GOV for giving me the power and strength to earry out this work.

I wish to express my sincere gratitude and thanks to the eminent Prof. Dr. Hussin Cl-Damasy, professor of Internal Medicine and Endocrinology, Ain Shams University for giving me the privilege of working under his supervision. His constant, encouragement, close supervision and constructive guidance were the paramount axes in the selection, initiation and progress of this work.

My debt gratitude goes for Prof. Dr. Mohamed Osama Abd El-Ghani. Professor of Neuropsychiatry, Ain Shams University for his remarkable effort and valuable advice that have been of utmost help.

I would like to express my hearty thanks to Prof. Dr. Hisham Cl-Gyar, Assistant Professor of Internal Medicine and Endocrinology, Ain Shams University for his constant support, considerable help and continuous guidance which were the major factors behind the completion of this work.

I would like to express my deep gratitude to Dr. Raef Malak, becturer of Internal Medicine, Ain Shams University who was the first one to trigger the idea of this work and who helped me so much by his

continuous guidance and meticulous revision of this work.

My deepest gratitude and cardinal thanks extends to Dr. Nehad Shokry, tecturer of Internal Medicine, Ain Shams University for her faithful supervision, great co-operation and valuable encouragement that have been of great help.

I would like to thank Dr. Ayman Nasef, Lecturer of Neuropsychiatry, Ain Shams University who facilitated many obstacles and greatly helped me to carry out this work.

I would like to thank Dr. Lalia Aziz Sobeih, fellow of Chemistry, Ain Shams University Hospital and Dr. Samia El-Tohamy Ismael, Chemist in Endocrinology Department for their great cooperation and considerable help.

I Thank the patients for their co-operation and patience and to whom I dedicate this work.

Phoebe Yossif (1999)

List of Abbreviation

ACA	Anticardiolipin antibody.
AN	Autonomic neuropathy.
APA	Antiphospholipid antibody.
CCK	Cholecystokinin.
CD5	Cluster of differentiation 5
CF ADM	Complement fixing adrenal medullary antibody.
CF SG	Complement fixing sympathetic ganglia antibody.
CL	Cardiolipin.
CVS	Coefficient of variance.
DL	Distal latency.
DM	Diabetes mellitus.
DPN	Diabetic peripheral neuropathy.
GAD	Glutamic acid decarboxylase.
GRP	Gastrin releasing peptide.
HbA ₁ C	Haemoglobin A ₁ C (Glycated haemoglobin)
HCO ₃	Bicarbonate.
HLA	Human leucocytic antigen.
HP	Helicobacter pylori.
ICA	Islet cell antibody.
IDDM	Insulin dependent diabetes mellitus.
IGF	Insulin like growth factor.
LA	Lupus anticoagulant.
NCV	Nerve conduction velocity.
NGF	Nerve growth factor
NIDDM	Non-insulin dependent diabetes mellitus.
PC	Phosphatidyl choline.
PE	Phosphatidyl ethanolamine.
PI	Phosphatidyl inositide.
PLAs	Phospholipid antibodies.
PLs	Phospholipids

PP	Pancreatic polypeptide.	
PS	Phosphatidyl serine.	
RIA	Rdioimmunoassay.	
SLE	Systemic lupus erythematosus.	
SMS	Stiff man syndrome.	
TDT	Thermal discriminatoin threshold.	
VDRL	Venereal disease research laboratory.	
VIP	Vasoactive intestinal peptide.	
VPT	Vibration perception threshold.	



Table of Contents



Abstract	
Introduction and Aim of	_
Work	1
Review of Literature	
Diabetic Neuropathy	3
Classification of diabetic neuropathy	4
Prevalence of diabetic neuropathy	5
Natural history of diabetic neuropathy	5
• • •	7
Pathogenesis of Diabetic Neuropathy	
A- Autoimmune mechanisms of diabetic neuropathy	8
B- Microvascular and compression mechanisms in	19
the etiology of diabetic neuropathy	
C- Role of growth factors in pathogenesis of	28
diabetic neuropathy	
D- Laminin role in pathogenesis of diabetic	33
neuropathy	
Pathology of Diabetic Neuropathy	34
Anterior horn cell and sensory and autonomic	34
ganglia changes	
Nerve fiber changes	35
Changes in supportive tissues	38
Clinical Aspects of Diabetic Neuropathy	41
Diabetic peripheral neuropathy	41
Clinical features of diabetic peripheral neuropathy	41
Measurements of peripheral nerve function	45
Diabetic autonomic neuropathy	50
Common manifestations of autonomic neuropathy	50
Tests of autonomic functions	58
Staging of autonomic dysfunction	60

Genetics and autonomic neuropathy	63
Staging of diabetic neuropathy	64
Relationship between neuropathy, retinopathy and neuropathy	64
Management of Diabetic Peripheral	65
Neuropathy	
A- Specific measures	65
B- Symptomatic therapy	73
C- Miscellaneous agents	78
Management of Diabetic Autonomic	80
Neuropathy	
	85
Prognosis of Diabetic Neuropathy	88
Antiphospholipid Antibodies	
Antiphospholipid antibodies classification	89
Laboratory detection of ACA and other APA Antiphospholipid antibodies specificity and	98 102
pathophysiology	102
Possible mechanisms of action of APAs	103
Antiphospholipid antibodies and some clinical syndromes	108
Gastrin	116
Cubicate and Mathada	4.5.
Subjects and Methods	136
Results	142
Discussion	177
Summary and Conclusion	192
Appendix 1	_
Appendix 2	
Appendix 3	
Appendix 4	
Appendix 5	
References	196
Arabic Summary	



List of Tables



	And the state of t	
All the said of	Classification of diabetic neuropathy	4
ż	Established and investigated drugs for the treatment of diabetic neuropathy	77
3	Antiphospholipid antibodies; classification	89
4	Potential causes of bleeding in patients with LA	96
<u>\$</u>	Summary of the proposed metabolic disturbances by APAs	103
6	Stimulatory tests for gastrin, reference range and individual variation	127
7	Occurrence of autonomic neuropathy in type I and type II diabetics	147
8	Occurrence of amyotrophy in type I and type II diabetics	149
9	Correlation between neuropathy and impaired thermal sensitivity	151
10	Comparison between group I and group II regarding level of IgG ACA and IgM ACA	152
11	Comparison between diabetic patients with neuropathy (group I) and control group regarding level of IgG and IgM ACA	154
12	Comparison between diabetic patients without neuropathy (group II) and control group regarding level of IgG and IgM ACA	156
13	Comparison between type I and type II diabetics with neuropathy regarding s. IgG ACA	158
14	Comparison between male and female diabetics with neuropathy regarding MNSI and MMDNS	160
15	Comparison between oral hypoglycemic drugs treated patients and insulin treated patients with neuropathy regarding MNSI and MMDNS	162

List of tables (continued)

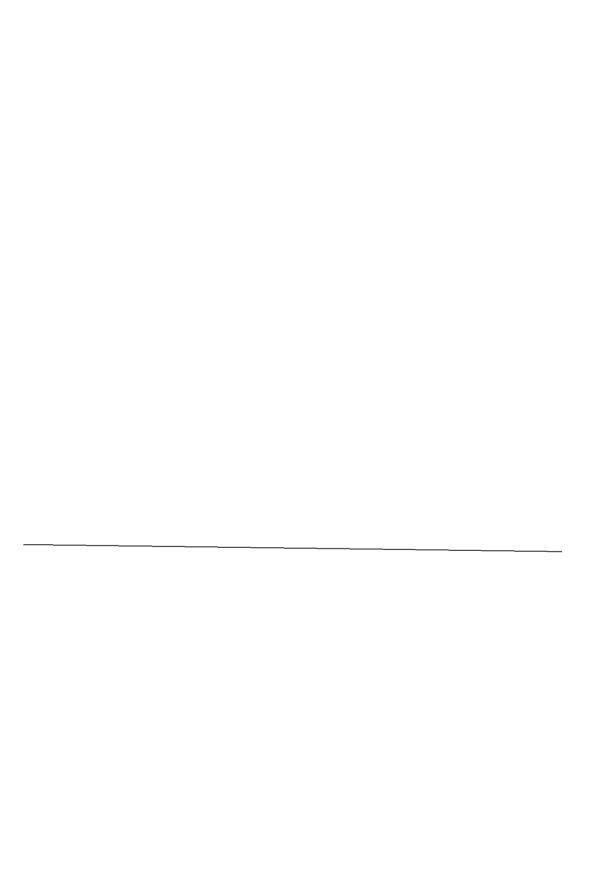
16	Comparison between mean fasting and postprandial blood glucose in group I and group II	164
17	Comparison between all diabetic patients in the study and the healthy control regarding fasting and postprandial serum gastrin	165
18	Comparison between diabetic patients with autonomic neuropathy and healthy controls regarding fasting and postprandial serum gastrin	166
19	Comparison between diabetic patients without autonomic neuropathy and control group regarding fasting and postprandial serum gastrin	168
20	Comparison between diabetics with peripheral neuropathy only and healthy controls regarding fasting and postprandial serum gastrin	169
21	Comparison between diabetics with and without neuropathy regarding fasting and postprandial serum gastrin	170
22	Comparison between diabetics with and without autonomic neuropathy regarding fasting and postprandial serum gastrin	171
23	Comparison between diabetics with neuropathy and healthy controls regarding fasting and postprandial serum gastrin	173
24	Comparison between diabetic patients without peripheral or autonomic neuropathy and healthy	174
	controls regarding fasting and postprandial serum gastrin	



List of Figures



	Service of the servic	
	Diagramatic summary of pathogenesis of diabetic neuropathy	7
2	Diagram showing interrelationships between metabolic and vascular factors in the development of diabetic neuropathy	26
3	Occurrence of Autonomic neuropathy in Type I and Type II Diabetics.	148
4	Occurrence of amyotrophy in type I and type II diabetics	150
5	Serum IgG ACA and IgM ACA in diabetics with neuropathy (group I) and diabetics without neuropathy (group II)	153
6	Serum IgG ACA and IgM ACA in diabetic patients with neuropathy (group I) and control group	155
7	Scrum IgG ACA and IgM ACA in diabetics diabetics without neuropathy (group II) and control group	157
8	Serum IgG ACA in Diabetic patients with neuropathy either type I or Type II.	159
9	MNSI and MMDNS in diabetics with neuropathy either male or female.	161
10	MNSI and MMDNS in diabetics with neuropathy under treatment with oral hypoglycemic drugs and insulin therapy	163
11	Fasting and postprandial serum gastrin level in diabetics with autonomic neuropathy and healthy control	167
12	Fasting and postprandial serum gastrin level in diabetics with autonomic neuropathy and diabetics without autonomic neuropathy	172



Abstract:

There is growing evidence suggesting the role of autoimmunity as one possible etiology of diabetic neuropathy. On the other hand, gastrin changes in diabetic autonomic neuropathy may be an important easily measured indicator.

Subjects and Methods: Sera from 26 diabetic patients with neuropathy (group I) (diagnosed according to MNSI and MMDNS), 25 diabetics without neuropathy (group II) and 10 healthy controls were examined for IgG ACA, IgM ACA using ELISA technique, along with measuring fasting and postprandial serum gastrin using RIA.

Results: ACA IgG was found to be significantly higher in diabetics with neuropathy than diabetics without (P<0.05) and highly significant higher in the later group than healthy control (P<0.01), and both fasting and postprandial serum gastrin were significantly higher in diabetics with autonomic neuropathy than diabetics without (P<0.05 and <0.01 respectively).

Conclusion: It is concluded that autoimmunity may play an important role in pathogenesis of diabetic neuropathy and that diabetics with autonomic dysfunction suffer from hypergastrinemia both basal and postprandial in absence of other causes of high gastrin secretion.

