Original Article

Apolipoprotein (a) as Predictive Factor in Fibromyalgia Syndrome

Lubna M. H. Farid* BSc, MSc
Kismat M. Turki** BSc, PhD
Mohammad H. Al-Osami*** MBChB, MD

Summary:

Background: Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain with associated symptoms including stiffness, fatigue, sleep disturbance and functional impairment. FMS is depicted by chronic pain for at least three months and tender points identified by the American Collage of Rheumatology (ACR). Although several hypotheses have been developed; the cause of FMS is currently unknown.
This study aims to evaluate the contribution of serum apolipoprotein (a) [Apo (a)], leptin, and serum lipid profile to the pathophysiology of FMS.

Subjects & Methods: The study has included 160 patients with FMS with age range (18-72) years and 60 control individuals who were age and sex matching with FMS patients: 29 patients with chronic musculoskeletal complaints but without FMS and 31 healthy controls. Elisa technique was used for the determination of Apo (a) and leptin. Colorimetric method was used to determine serum lipid profile. BMI was measured in all subjects. Results were evaluated using descriptive and inferential statistics; data were expressed as (mean ± SEM). P value of <0.05 was accepted as significant.

Results: Serum Apo (a) in FMS patients was significantly higher than healthy control group ($P < 0.05$). There were no significant differences among the three subject groups in serum lipid profile and leptin levels.

Conclusion: Apo (a) may play an important role in FMS pathogenesis. Lipid profile and leptin have no role in FMS patients as a cause or result of this syndrome.

Key words: Fibromyalgia, Apo (a), leptin, lipid profile.

Fac Med Baghdad
2010; Vol. 52, No. 2
Received July 2009
Accepted Aug. 2009

Introduction:

Fibromyalgia syndrome (FMS) is the most common rheumatic cause of diffuse pain and multiple regional musculoskeletal pain and disability. It commonly associated with medically unexplained symptoms in other systems (1). FMS is characterized by strong female predominance with peak incidence at ages (20-60) years old, it has been observed in up to 15% of rheumatology patients and 5% of patients from a general medical practice (2, 3). FMS is characterized by chronic widespread pain for at least three months and tender points identified by the American Collage of Rheumatology with associated symptoms including stiffness, fatigue, sleep disturbance, emotional distress and functional impairment with evidence of pain amplification (4-6). Although several hypotheses have been developed; the cause of FMS is currently unknown (7). Apolipoprotein (a) [Apo (a)] is a glycoprotein rich in neuraminic acid that stains strongly with periodic acid-Schiff and exhibits a high apparent molecular weight upon sodium dodecyl sulfate-gel electrophoresis (SDS-PAGE), it is linked by disulphide bridges to Apo B-100 in the Lp (a) particle (8-10).
It belongs to a family of proteins involved in fibrinolysis (11). The physiological function of Apo (a) is still unknown, a function within the coagulation system seems plausible, given the aspect of the high homology between Apo(a) and plasminogen (PLG) (10). The relationship between FMS features and obesity has been demonstrated by epidemic data and experimental pain findings (12, 13). Obesity is associated with increased body fat content that leads to increased serum leptin levels. Leptin is an adipocyte hormone encoded by the obese (ob) gene. It circulates as a 16-kD protein and is transported across the blood-brain barrier (BBB) by a saturable system to exert its central effects. It has a role in the control of energy homeostasis, in which it acts as a negative feedback adiposity signal by interacting with receptors in specific hypothalamic nuclei (14, 15).

*Medical City- the Public Administration
** Department of Physiological Chemistry, College of Medicine, Baghdad University
*** Baghdad Teaching Hospital-Rheumatology & Rehabilitation Consultation Unit

Subjects & Methods:

This study was performed during the period from April 2008 to February 2009. The subjects were selected from the people attending the out patient clinic in Medical City - Baghdad Teaching Hospital - Rheumatology & Rehabilitation

Consultation Unit, where the anthropometric tests (to evaluate body mass index 'BMI') were performed. The other tests were done in Medical City - Teaching Laboratories and the College of Medicine - Department of Physiological Chemistry. The study has included 122 patients with FMS (101females+21males); with age range (18-72) years (FMS (+) patients group); fulfilled ACR 1990 criteria for the diagnosis of FMS and 60 control individuals (48females+12males), who were age and sex matching with FMS (+) patients: 29 patients (25females+4males) with chronic musculoskeletal complaints but without FMS (RA + OA + SLE) (FMS (-) patients control group) and 31 healthy volunteers (23females+4males) without musculoskeletal complaints (healthy control (HC) group). Medical and social history was taken from each subject according to special protocol taking in consideration certain epidemic and clinical related variables. Criteria of exclusion have included: Diabetes mellitus (DM), Sleep apnea, Hypercortisolism, Thyroid problems, and other rheumatic disorders. Disposable plastic syringes of (23 G) needles were used to aspirate five milliliters of venous blood from Chi-Square (?2), Student test (t-test), ANOVA & LSD test (F-test), and Person correlation ® were used to accept or reject the statistical hypotheses. All the statistical analyses were done by using Pentium-4 computer through the SPSS program (version-10) and Excel application. P value of <0.05 was accepted as significant. each patient and control after (12-16) hours fasting from 08.00 a.m. to 12.00 a.m. Serum Apo (a) was determined by DRG Apo (a) ELISA Kit based on the sandwich principle. Kit used was from DRG International, Inc., USA. Serum leptin was determined by DRG Leptin ELISA Kit based on the sandwich principle. Kit used was from DRG International, Inc., USA. Serum total cholesterol (TC) and serum triglycerides (TG) were determined by enzymatic colorimetric test with lipid clearing factor. Kit used was from HUMAN-(CHOLESTEROL liquicolor, CHOD-PAP-Method)-Germany and HUMAN-(TRIGLYERIDES liquicolor mono, CPO-PAP-Method)-Germany respectively. Serum HDL-C was determined by enzymatic colorimetric test after precipitation. Kit used was from HUMAN-(HDL cholesterol)-Germany. BMI assessment was applied on all subjects. Results were evaluated using descriptive and inferential statistics; data were expressed as (mean ± SEM).

Results:

Table-1 has revealed the demographic, clinical and non-clinical features of the study. Table-2 has shown the (mean ± SEM) for age, duration, and BMI of the three groups in the study. There was no significant difference in all these data among the three groups: FMS (+), FMS (-), and HC ($P > 0.05$). Table-3 has revealed the (mean ± SEM) values of lipid profile of the three groups in the study. All of them were within normal values. There was no significant difference in lipid profile among the three groups: FMS (+), FMS (-), and HC ($P > 0.05$) in all parameters except for HDL-C. In spite of the presence of this significant difference the three values were within normal. Data from table-4 has shown that the (mean ± SEM) values for Apo (a) and leptin where Apo (a) levels have reached a peak in FMS (-) group. There were significant differences in Apo (a) levels among the three groups: FMS (+), FMS (-), and HC. Although serum leptin in FMS (+) group is around the upper limit of the normal value, there was no significant difference in leptin among the three groups: FMS (+), FMS (-), and HC ($P > 0.05$)>

Table-1: Demographic, clinical and non-clinical features of the Study.

Parameters	FMS(+)(n=122)n (%)	FMS(–)(n=29) n (%)	HC(n = 31) n (%)	Total (n=182) n (%)	P-value	Sig.
Age (y) <20 20-40 41-60 61-80	 5 (4.1%) 52 (42.6%) 61 (50%) 4 (3.3%)	 – 9 (31%) 16 (55.2%) 4 (13.8%)	 – 12 (38.7%) 18 (58.1%) 1 (3.2%)	 5 (2.7%) 73(40.1%) 95 (52.2) 9 (4.9%)	0.169	NS
Gender Female Male	 101 (82.8%) 21 (17.2%)	 25 (86.2%) 4 (13.8%)	 23 (74.2%) 8 (25.8%)	 149 (81.9%) 33 (18.1%)	0.434	NS
Marital state Married Unmarried Widowed Divorced	 80 (65.6%) 17 (13.9%) 23 (18.9%) 2 (1.6%)	 19 (65.5%) 4 (13.8%) 6 (20.7%) –	 21 (67.7%) 6 (19.4%) 4 (12.9%) –	 120 (65.9%) 27 (14.8%) 33 (18.1%) 2 (1.1%)	0.908	NS
Occupation Employed Housewife Student Others	 27 (22.1%) 75 (61.5%) 4 (3.3%) 16 (13.1%)	 11 (37.9%) 15 (51.7%) – 3 (10.3%)	 9 (29%) 15 (48.4%) 1 (3.2%) 6 (19.4%)	 47 (25.8%) 105 (57.7%) 5 (2.7%) 25 (13.7%)	0.506	NS
BMI (kg/m^2) Lean Normal weight Overweight Obese	 2 (1.6%) 35 (28.7%) 41 (33.6%) 44 (36.1%)	 – 8 (27.6%) 11 (37.9%) 10 (34.5%)	 1 (3.2%) 8 (25.8%) 10 (32.2%) 12 (38.7%)	 3 (1.6%) 47 (25.8%) 58 (31.9) 74 (40.7%)	0.102	NS
Smoking	34 (27.9)	5 (17.2%)	3 (9.7%)	42 (23.1%)	0.072	NS

Table-2: Statistical Data for Age, Duration, and BMI.

Parameters	FMS (+) (n = 22) Mean ± SEM	FMS (-) (n = [illegible]) Mean ± SEM	HC (n = [illegible]) Mean ± SEM	P-value	Sig.
Age (y)	39.95 ± 1.10	40.93 ± 2.40	42.81 ± 2.16	0.42	NS
Duration (y)	4.30 ± 0.37	4.03 ± 1.47	—	[illegible]	NS
BMI (kg/m²)	28.53 ± 0.56	29.11 ± 1.05	27.64 ± 0.89	0.21	NS

Table-3: Statistical Data for Lipid Profile

Parameters (mg/dl)	FMS (+) (n = 22) Mean ± SEM	FMS (-) (n = [illegible]) Mean ± SEM	HC (n = [illegible]) Mean ± SEM	P value	Sig.
TC	176.28 ± 2.99	180.48 ± 5.24	176.71 ± 5.97	0.819	NS
TG	139.53 ± 8.76	126.33 ± 8.06	120.61 ± 12.[illegible]	0.062	NS
HDL-C	55.48 ± 1.06	62.7[illegible] ± 2.46	55.29 ± 1.08	[illegible]	HS
LDL-C	104.23 ± 2.17	90.82 ± 6.97	93.6[illegible] ± 5.37	[illegible]	NS
VLDL-C	27.71 ± [illegible]	28.24 ± 1.61	26.1[illegible] ± 2.36	[illegible]	NS

Table-4: Statistical Data for Apo (a) and Leptin

Parameters	FMS (+) (n = 22) Mean ± SEM	FMS (-) (n = [illegible]) Mean ± SEM	HC (n = [illegible]) Mean ± SEM	P value	Sig.
Apo (a) (U/l)	304.21 ± 65.04	631.7[illegible] ± 164.27	237.60 ± 67.64	0.029	S
(n = 45)		(n = 28)	(n = 17)		
Leptin (ng/ml)	103.83 ± 8.91	129.1[illegible] ± 21.[illegible]	93.88 ± 13.67	0.208	NS

Discussion:

To our knowledge, this is the first study examining the relationship between FMS and Apo (a). Apo (a) may play an important role in the pathogenesis of FMS and confirm the occurrence of the inflammatory process in FMS. Apo (a) may be evenly implicated in the inflammatory process (16), since extravascular coagulation and diminished fibrinolysis are processes that contribute to the etiology of both inflammation and atherosclerosis (16). The exact mechanism whereby Apo (a) is atherogenic remains to be elucidated. Apo (a) has a high affinity for lysine-binding sites on fibrin and may therefore compete with plasminogen at sites of fibrin deposition and thus interfere with the fibrinolytic system (17-19). Apo (a) co-localizes with lipid deposition in the artery walls. This leads to a massive lipid deposition in the artery walls. Results may aid the possibility that Apo (a) has emerged as natural anti-inflammatory molecule to blunt the deleterious effects associated with excessive neutrophil accumulation at sites of inflammation. Apo (a) can inhibit leukocyte recruitment by a mechanism independent of Plasminogen (20), thus, it could play a beneficial role by suppressing inflammation. In addition, a mechanism for this novel function of Apo (a) was also identified: its selective regulation of cytokine production. This represents an important contribution to the understanding of the regulation of neutrophil recruitment during the inflammatory response (20).

Conclusion:

FMS patients are more predisposed to have atherogenic diseases and stroke. Apo (a) test can aid in the confirmation of FMS diagnosis. Normal Apo (a) levels don't rule out FMS occurrence. Lipid profile and leptin have no role in FMS patients as a cause or result of this syndrome.

References:

1. Doherty M, Lanyon P, Ralston S. Musculoskeletal disorders. In: Boon N, Colledge N, Walker B, Hunter J, eds. Davidson principle and practice of medicine. 20th ed. Churchill Livingstone. 2006; 1065-1144.
2. Al-Rawi Z, Ghazmazi M, Gambi S, et al. Validated translation of Arabic questionnaire to screen fibromyalgia patients. Ann Rheum Dis. 21st EULAR Congress 2006 65, 560.
3. Mannoni A, Zoppi M, Tabo C, et al. Prevalence of fibromyalgia in Italy: updated results. Ann Rheum Dis; 21st EULAR Congress 2006; 65: 557.
4. Baker K, Barkhuizen A. Pharmacologic treatment of fibromyalgia. Current Pain and Headache Reports 2005; 9: 301-306.
5. Yunus M, Masi A, Calabro J, et al. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 1981; 11: 151-171.
6. Theadom A, Cropley M, Humphrey K. Exploring the role of sleep and coping in quality of life in fibromyalgia. J Psychosom Res 2007; 62: 145-151.
7. Goenen R, Jacobs J. Fibromyalgia: diagnosis, pathogenesis, and treatment. Curr Opin Anesthesiol 2001; 14: 533-9.
8. Ehnholm C, Garoff H, Renkonen O, et al. Protein and carbohydrate composition of Lp(a) lipoprotein from human plasma. Biochemistry. 1972; 11: 3229-3232.
9. Utermann G, Weber W. Protein composition of Lp (a) lipoprotein from human plasma. FEBS Lett 1983; 154: 357-

361.
10. Wiegandt H, Lipp K, Wendt G. Identifizierung eines lipoproteins mit Antigenwirksamkeit im Lp-System. Hoppe-Seyler's Z Physiol Chem 1968; 349:489-494.
11. Rifai N, Bachorik P, Albers J. Lipids, Lipoproteins, and Apolipoproteins. In: Burtis C, Ashwood E. Tietz textbook of clinical chemistry. 3rd ed. Vol.2 Sec.V. USA, W.B. Saunders Company, 1999; ch.25: p.809-856.
12. Pae C, Luyten P, Marks D, et al. "The relationship between fibromyalgia and major depressive disorder: a comprehensive review." Curr Med Res Opin 2008; 24: 8: 2359-71.
13. Laylander J. "A Nutrient/Toxin Interaction Theory of the Etiology and Pathogenesis of Chronic Pain-Fatigue Syndromes: Part I". J Chronic Fatigue Synd 1999; 5: 1: 67-91.
14. Widjaja A, Stratton I, Horn R, et al. UKPDS 20: plasma leptin, obesity, and plasma insulin in type 2 diabetic subjects. J Clin Endocrinol Metab 1997; 82:2:654-7.
15. Banks W, Kastin A, Huang W, et al. Leptin enters the brain by a saturable system independent of insulin. Peptides 1996; 17: 305-311.
16. Busso N, Dudler J, Salvi R, et al. Plasma Apolipoprotein(a) Co-Deposits with Fibrin in Inflammatory Arthritic Joints. Am J Pathol 2001; 159:4: 1445-1453.
17. Sangrar W, Koschinsky M. Characterization of the interaction of recombinant apolipoprotein (a) with modified fibrinogen surfaces and fibrin clots. Biochem Cell Biol 2000, 78:519-525.
18. Klose R, Fresser F, K?chl S, et al. Mapping of a minimal apolipoprotein(a) interaction motif conserved in fibrin(ogen) ?- and -chains. J Biol Chem 2000; 275:38206-38212.
19. Soulat T, Loyau S, Baudouin V, et al. Effect of individual plasma lipoprotein (a) variations in vivo on its competition with plasminogen for fibrin and cell binding. An in vitro study using plasma from children with idiopathic nephrotic syndrome. Arterioscler Thromb Vasc Biol 2000; 20:575-584.
20. Hoover-Plow J, Hart E, Gong Y, et al. A Physiological Function for Apolipoprotein (a): A Natural Regulator of the Inflammatory Response. Exper Biol Med 2009; 234:28-34.