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BIOCHEMICAL STUDIES ON THE RELATIONSHIP BETWEEN HYPOTHYROIDISM AND/OR SOME RHEUMATIC DISEASES

By

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دراسات بيوكيميائية على العلاقة بين نقص إفراز الغدة الدرقية وبعض الأمراض الروماتيزمية

فوزية فهيم و أحمس غبرال

تم أختيار سبعة وستون شخصاً وقسموا إلى أربعة مجاميع طبقاً للحالة الاكلينيكية واشتملت المجموعة الأولى على الأصحاء والتي اعتبرت كمجوعة ضابطة واشتملت المجموعة الثانية والثالثة على بعض المرضى الذين يعانون من نقص في إفراز الغدة الدرقية وأمراض روماتيزمية معاً واشتملت المجموعة الرابعة على الأشخاص المصابون بالأمراض الروماتيزمية فقط . وتم تعيين ثمانية عشرة مقياساً والتي أعتبرت ذات أهمية في توضيح مدى العلاقة بين أمراض الغدة الدرقية والأم راض الروماتيزمية . وقد أوضحت هذه الدراسة عدم وجود علاقة بين مرض نقص افراز الغدة الدرقية وبعض الأمراض الروماتيزمية ولكن وجود علاقة غير حقيقية من الممكن أن يكون نتيجة لتعاطي الكورتيكوستيرويدات والعقاقير المضادة للروماتيزم . وتقدم هذه الدراسة ستة عشرة علاقة واضحة جديدة .

Key Words: Hypothyroidism, Rheumatoid arthritis, Systemic lupus erythematosus, Osteo arthritis, Poly arthritis.

ABSTRACT

Sixty seven patients were selected and divided into four groups according to their clinical condition covering normal controls, hypothyroid patients suffering from both hypothyroidism and rheumatic disorders and rheumatic patients. Eighteen parameters which were considered of importance in disclosing the relationship between thyroid disorders and rheumatic diseases were determined. This study elucidated that no relationship exists between hypothyroidism and some rheumatic diseases, but the existence of false relationship may be due to the ingestion of corticosteroids and antirheumatic drugs. Sixteen newly significant correlations are reported.

INTRODUCTION

Thyroid disorders have been shown to occur in association with connective disorders such as rheumatoid arthritis (R. A.) and Sjogren's syndrome (S.S.) [1]. Abnormal thyroid status was found to precipitate or exacerbate musculoskeletal disease; and its activity was greatly improved by correction of the thyroid state [2].

In a study of 12 patients with hypothyroidism to evaluate rheumatic complaints, synovial effusions, most commonly involving the knees, were demonstrated in 8 patients [3]. Rheumatic syndromes associated with hypothyroidism most often consist of stiffness, weakness, fatigue, myalagias and other rather non-specific symptoms. Joint effusions, instability and destructive degenerative arthritis are also associated [4].

It may be thus concluded that some of the rheumatic diseases may be related to hypothyroidism. This retrospective study aimed to investigate this conclusion and identify whether or not hypothyroidism is closely related with rheumatic diseases.

MATERIALS AND METHODS

This study was conducted on sixty seven patients who were attending the out-patient clinic of the Air Force Hospital, Cairo, Egypt, their ages ranged between 34-58 years with a mean of 46 years. Complete history and full

clinical examination sheet for each patient was done; they were divided thereafter into four groups according to their clinical condition.

Gr. I NC: Normal controls (25 subjects), clinically free from any disease.

Gr. II Ho: Hypothyroid patients, included 11 patients, 8 with myxedema, and 3 with Hashimoto's disease.

Gr. III Ho R: Patients with both hypothyroidism and rheumatic diseases (6 patients) as follows:
a-five with R. A. and hypothyroidism.
b-One with Osteo-arthritis (O. A.) and hypothyroidism.

Gr. IV R: Rheumatic disorder patients:
included 25 patients, 9 with R. A.; 7 with O. A., 4 with systematic lupus erythematosus (S. L. E.) and 5 with polyarthritis (P. A.).

This study covered the determination of eighteen parameters in blood and serum which were considered of importance in disclosing the relationship between thyroid diseases and rheumatic diseases. These parameters included estimation of haemoglobin (Hb), and erythrocyte sedimentation rate (E. S. R.) in blood [5]; triiodothyronine (T_3) [6], thyroxine (T_4) [7] and thyroid stimulating hormone (TSH) in serum [8] using radioimmunoassay technique (RIA), serum Ca^{++} [9, 10], and Mg^{++} in serum [11], alkaline phosphatase activity (ALP) in serum [12], serum total proteins [13], serum albumin (Al) [14], serum globulin (Gl) and albumin/globulin (A/G), serum uric acid [15], and serum creatinine [16]. Complement three (C_3) in serum [17] using radial immuno diffusion (RID) technique, rheumatoid factors (RFs) and C-reactive protein (CRP) in serum [18] have also been determined.

Statistical analysis of the collected data was carried out by the aid of a digital computer according to the method described by Hill [19].

RESULTS

Results of Gr. II Ho (Table 1) reveal a significant decrease in total T_4 (TT_4) and total T_3 (TT_3), with increased TSH levels in comparison to normal controls (Gr. 1 NC) indicating primary hypothyroidism; while tests performed for rheumatology on this group of patients including C_3, RFs and CRP show insignificant (NS) variations.

Cr. III Ho (Table 1) represents chronic patients of rheumatic disorders who were under doses of Prednisone therapy together with other anti-rheumatic drugs which decrease the TBG levels, these patients show decreased s-TT_4 and TT_3 while TSH level is highly elevated. Tests for rheumatology are positive, while rest of the parameters show significant variations.

Results of Gr. IV R. (Table 1) include results concerning patients who are clinically rheumatic, out of them 28% are seronegatives showing increased TT_4 and TT_3 with normal TSH levels.

One hundred and seven significant correlations (r) were carried out, of which (16) have not been reported before (Fig. 1 - Fig. 16) including :

-Mg and T_3 in Gr. I NC (r = -0.48).
-ALP activity and T_3 in Gr. IV R. (r = -0.53).
-Ca and total proteins in Gr. III Ho. R. (r = 0.51).
-Mg and total proteins in Gr. III Ho. R. (r = 0.57).
-Al and Ca in Gr. III Ho. R. (r = 0.65).
-Al and P in Gr. III Ho. R. (r = 0.54).
-Al and Mg in Gr. III Ho. R. (r = 0.58).
-A/G and ALP activity in Gr. II Ho. and Gr. III Ho. R. (r = 0.47 and 0.81 m) respectively.
-Uric acid and ALP activity in Gr. III Ho. R. (r = 0.56).
-Creatinine and uric acid in Gr. II Ho., and Gr. IV R. (r = 0.47, 0.54 respectively).
-Creatinine and Al in Gr. III Ho. R. (r = -0.60).
-C_3 and total proteins in Gr.III Ho. R. (r = 0.52).
-C_3 and Al in Gr. III Ho. R. (r = 0.58).
-C_3 and ALP activity in Gr. III Ho. R. (r = 0.61).

DISCUSSION

Our findings for Hb and E. S. R. levels are in accordance with those reported by Kyle, and Hazelman [1]; who reported that some degree of anaemia almost invariably accompanies both thyroid and rheumatic disease of any severity, and that E. S. R. level is raised in over 90% of active cases of hormonal disturbances or rheumatic diseases and tends to parallel the activity of these disorders; as Hb level shows significant decrease in Gr. II Ho., Gr. III Ho. R., and Gr. IV R. which reached 16%, 13% and 8% respectively compared to normal controls ($P < 0.001$, Table 1); E> S. R.) level shows highly significant elevation which amounted to 71% for 1st hour, 69% for 2nd hour; 170% for 1st hour, 107% for 2nd hour; and 116% for 1st hour, 97% for 2nd hour for Gr. I Ho., Gr. II Ho., Gr III Ho. R., and Gr IV R. respectively ($P < 0.005$, 0.001, Table 1).

Regarding hormonal parameters, serum T_3 and T_4 levels decrease a significantly in Gr. II Ho. patients (52% and 60% respectively, $P < 0.001$ for both); while they showed significant elevation in Gr. IV R (20% and 19% respectively $P < 0.001$) compared to normal controls (Table 1).

Serum TSH level is drastically elevated in Gr. II Ho. and Gr. III Ho. R. as it amounted to 527% and 732% respectively ($P < 0.001$), while it showed NS change in Gr. IV R. patients compared to control subjects (Table 1). Our results are in accordance with those reported by Ingbar [20]; who stated that primary hypothyroidism is accompanied in serum. Also, these results are in agreement with the view of Larsen [6]; who reported that the concentration of serum T_4 and T_3 is elevated in patients suffering from rheumatic diseases due to administration of salicylates or corticosteroids as antirheumatic drugs because of the competitive displacement by such drugs to T_4 and T_3 from pre-albumin and thyroxine binding globulin (TBG) in serum, consequently, serum concentration of free T_4 and T_3 is elevated. This causes inhibition of thyrotropine secretion, which results in decrease of thyroid activity, iodine uptake and hormone release.

Table 1 Collective table showing Blood Hb, ESR and serum T_3, T_4, TSH, Ca^{++}, P, Mg^{++}, ALP, T.Pr., Al, Gl, A/G, Uric a., Creat., C_3 concentrations of individuals of all groups :

Group	Hb gm/dl	ESR 1st hr	ESR 2nd hr	T_3 ng/dl	T_4 µg/dl	TSH µIU/ml	Ca^{++} mg/dl	P mg/dl	Mg^{++} mg/dl	ALP IU/L	T.Pr. gm/dl	Al gm/dl	Gl gm/dl	A / G	Uric A.. mg/dl	Creat. mg/dl	C_3 IU/ml
I NORMAL CONTROLS																	
X ± S.D.	14.2 ± 1.0	17.5 ± 4.9	32.9 ± 8.5	104.7 ± 8.2	7.4 ± 0.7	2.2 ± 0.3	10.0 ± 0.2	3.2 ± 0.3	2.1 ± 0.1	177.1 ± 12.1	7.3 ± 0.3	4.0 ± 0.2	3.3 ± 0.1	1.2 ± 0.2	4.7 ± 0.7	1.0 ± 0.2	118.2 ± 11.4
Range	12.5 - 15.5	12.0 - 24.0	24.0 - 45.0	92.0 - 120.0	12.0 - 24.0	1.8 - 3.0	9.7 - 10.5	2.3 - 3.9	1.9 - 2.2	150.3 - 205.0	6.8 - 7.9	3.7 - 4.5	2.8 - 4.1	0.9 - 1.6	3.5 - 6.1	0.7 - 1.3	95.0 - 136.0
II HYPOTHYROID PATIENTS																	
X ± S.D.	12.0 ± 1.1	30.0 ± 7.1	55.5 ± 14.6	50.1 ± 3.5	3.0 ± 1.2	13.8 ± 7.0	7.9 ± 1.7	2.1 ± 0.4	1.7 ± 0.6	124.4 ± 27.9	4.8 ± 1.3	3.0 ± 0.4	1.8 ± 0.9	1.2 ± 0.2	5.7± 1.6	0.9 ± 0.2	122.3 ± 31.1
Range	10.5 - 13.5	15.0 - 40.0	25.0 - 75.0	43.0 - 54.0	1.0 - 4.3	2.5 - 20.5	5.0 - 10.2	0.9 - 2.6	1.1 - 2.8	98.0 - 199.0	3.0 - 6.4	2.0 - 3.4	0.1 - 3.2	0.9 - 1.5	4.0 - 8.7	0.6 - 1.2	85.5 - 178.0
% change	-15.5	71.4	68.7	-52.1	-59.5	527.3	-21.0	-34.4	-19.0	-29.8	-34.2	-25.0	-45.5	0.0	21.3	-10.0	3.5
P value <	0.001	0.05	0.05	0.05	0.05	0.001	0.001	0.001	0.005	0.001	0.001	0.001	0.001	*N.S.	0.05	*N.S.	*N.S.
II RHEUMATICS WITH HYPOTHYROIDISM																	
X ± S.D.	12.4 ± 1.4	47.2 ± 43.1	68.2 ± 46.7	71.8 ± 47.0	3.7 ± 1.8	18.3 ± 16.8	8.5 ± 1.2	2.3 ± 1.1	2.0 ± 0.6	153.0 ± 37.5	7.8 ± 1.9	4.4 ± 1.1	3.4 ± 0.8	1.3 ± 0.3	4.7 ± 1.7	1.1 ± 0.2	179.3 ± 41.5
Range	11.0 - 14.0	7.0 - 120.0	20.0 - 140.0	42.0 - 162.0	1.4 - 6.8	5.0 - 50.0	8.4 - 10.4	1.9 - 4.4	1.3 - 2.7	110.0 - 199.0	5.0 - 9.1	2.8 - 5.4	1.8 - 4.2	0.9 - 1.8	2.1 - 6.7	0.7 - 1.3	126.0 - 229.0
% change	-12.7	169.7	107.3	-31.4	-50.0	731.8	-15.0	-28.0	-4.8	-13.6	6.8	10.0	3.0	8.3	0.0	10.0	51.7
P value <	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	*N.S.	0.001	0.05	0.001	0.005	*N.S.	*N.S.	*N.S.	0.001
V RHEUMATIC PATIENTS																	
X ± S.D.	13.1 ± 1.4	37.8 ± 18.2	64.7 ± 21.9	126.0 ± 29.0	8.8 ± 1.8	2.2 ± 1.2	9.2 ± 1.3	2.6 ± 0.7	2.4 ± 1.1	149.4 ± 35.4	9.1 ± 1.0	5.1 ± 0.3	4.0 ± 0.7	1.4 ± 0.4	5.0 ± 1.7	1.1 ± 0.4	157.3 ± 42.7
Range	10.0 - 16.0	8.0 - 78.0	21.0 - 102.0	55.0 - 160.0	4.9 - 12.0	0.5 - 4.1	7.7 - 13.5	1.0 - 7.3	0.8 - 4.4	80.0 - 235.0	7.0 - 12.0	4.7 - 5.7	2.0 - 7.1	0.7 - 2.5	0.8 - 8.7	0.6 - 2.3	71.7 - 278.0
% change	-7.7	116.0	96.7	20.3	18.9	0.0	-8.0	-18.8	14.3	-15.6	24.7	27.5	21.2	16.7	6.4	10.0	33.1
P value <	0.001	0.001	0.001	*N.S.	*N.S.	*N.S.	0.005	0.005	*N.S.	0.001	0.001	0.001	0.001	*N.S.	*N.S.	*N.S.	0.001

Non Significant

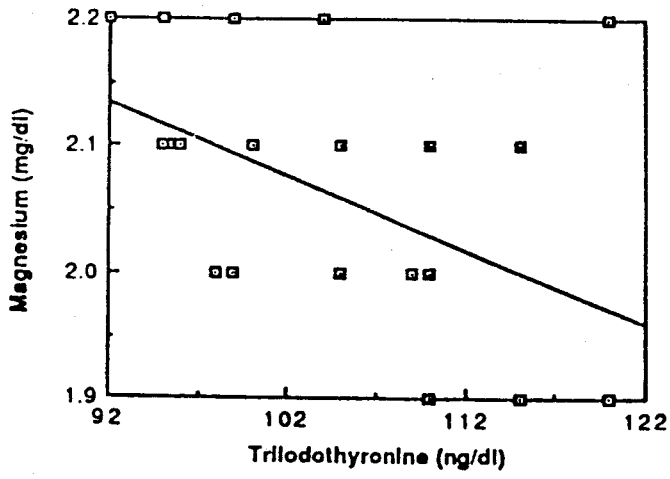

Fig. 1. Regression line between Magnesium and Triiodothyronine in Gr. I NC (r = - 0.48).

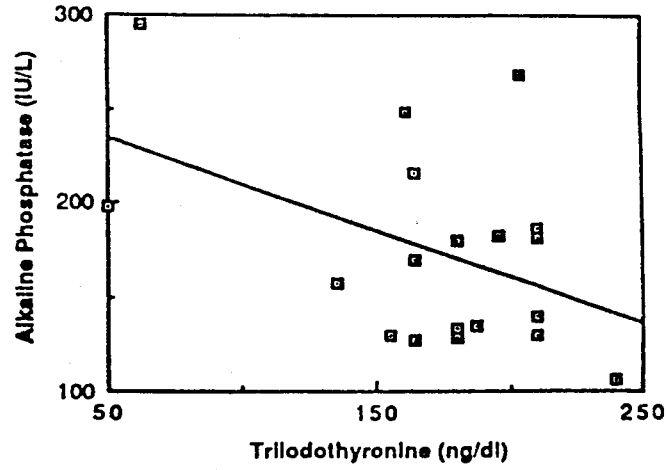

Fig. 2. Regression line between Alkaline Phosphatase and Triiodothyronine in Gr. IV R. (r = - 0.53).

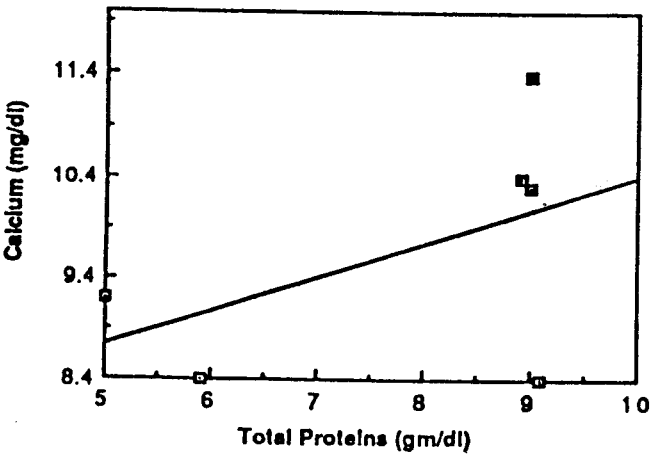

Fig. 3. Regression line between Calcium and Total Proteins in Gr. IV Ho. R. (r = - 0.51).

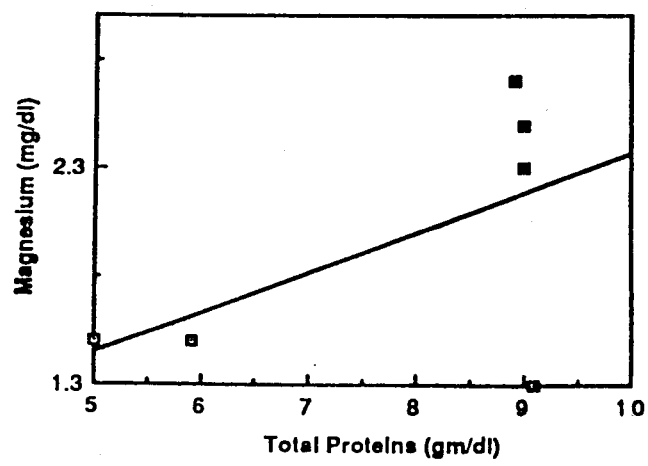

Fig. 4. Regression line between Magnesium and Total Proteins in Gr. IV Ho. R. (r = 0.57).

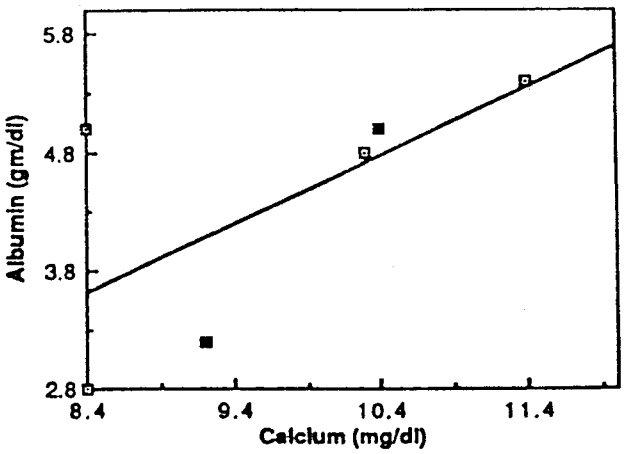

Fig. 5. Regression line between Albumin and Calcium in Gr. IV Ho. R. (r = 0.65).

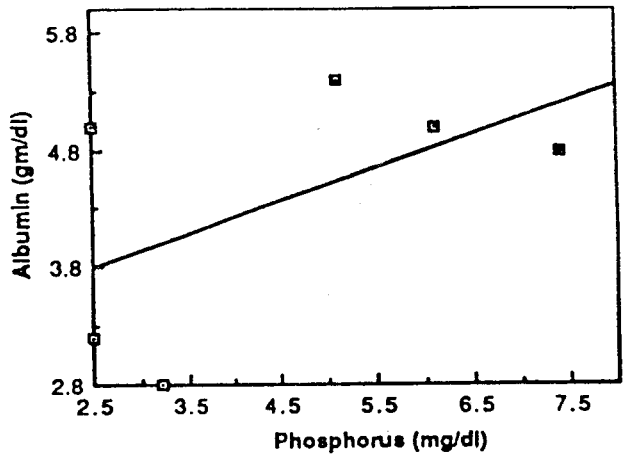

Fig. 6. Regression line between Albumin and Phosphorus in Gr. IV Ho. R. (r = 0.54).

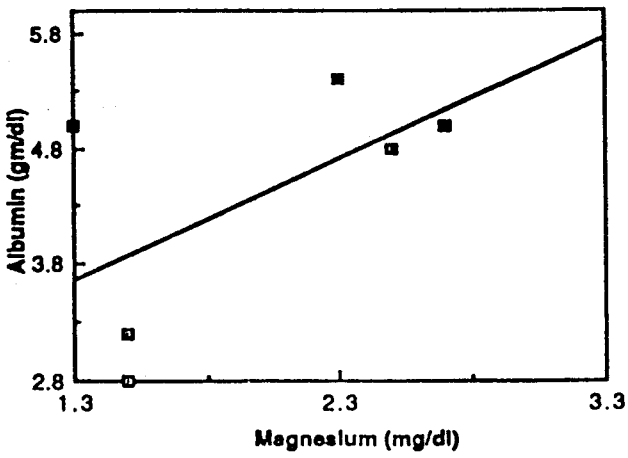

Fig. 7. Regression line between Albumin and Magnesium in Gr. IV Ho. R. (r = -0.58).

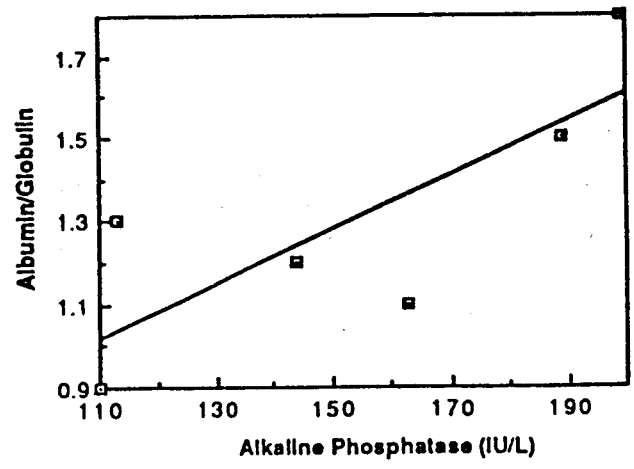

Fig. 8. Regression line between Albumin / Globulin and Alkaline Phosphatase in Gr. II Ho. R. (r = 0.47).

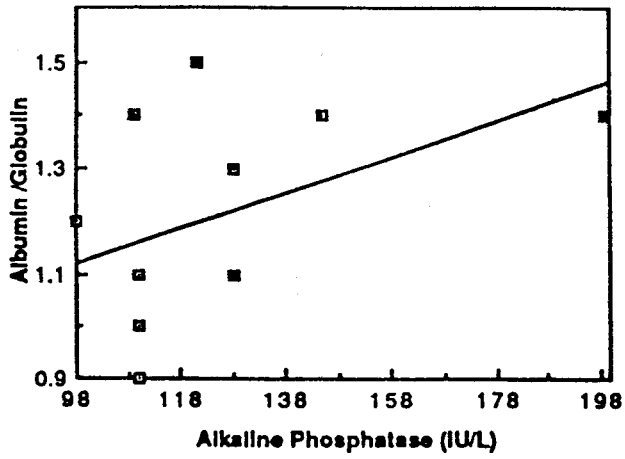

Fig. 9. Regression line between Albumin / Globulin and Alkaline Phosphatase in Gr. IV Ho. R. (r = 0.81).

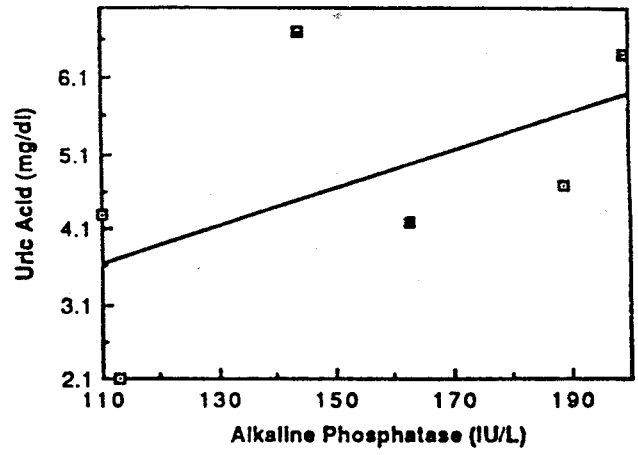

Fig. 10. Regression line between Uric Acid and Alkaline Phosphatase in Gr. IV Ho. R. (r = 0.56).

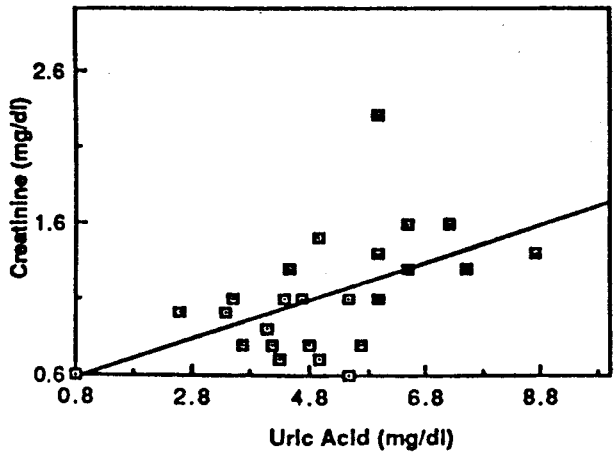

Fig. 11. Regression line between Creatinine and Uric Acid in Gr. II Ho. (r = 0.47).

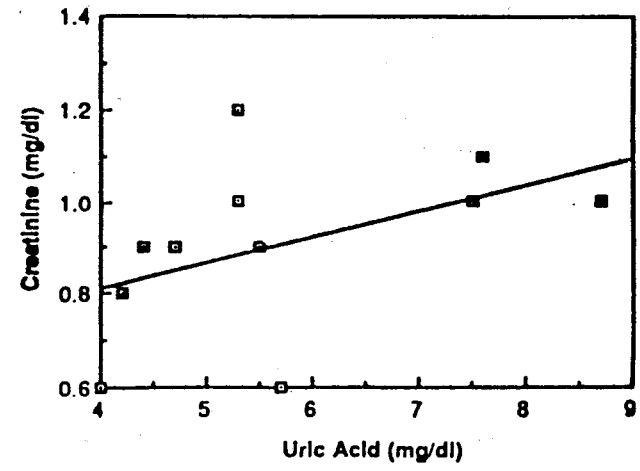

Fig. 12. Regression line between Creatinine and Uric Acid in Gr. IV R. (r = 0.54).

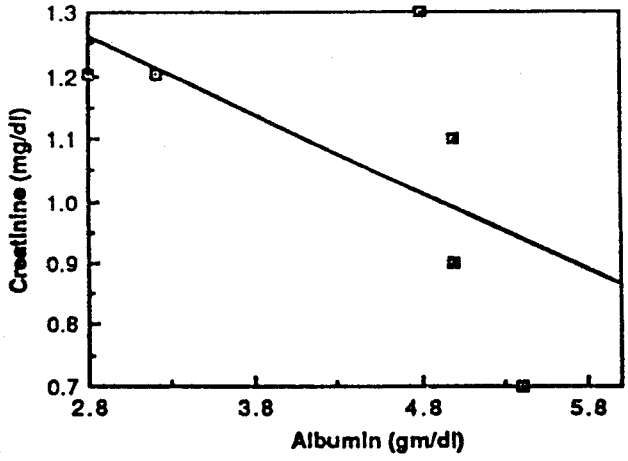

Fig. 13. Regression line between Creatinine and Albumin in Gr. IV Ho R. (r = 0.60).

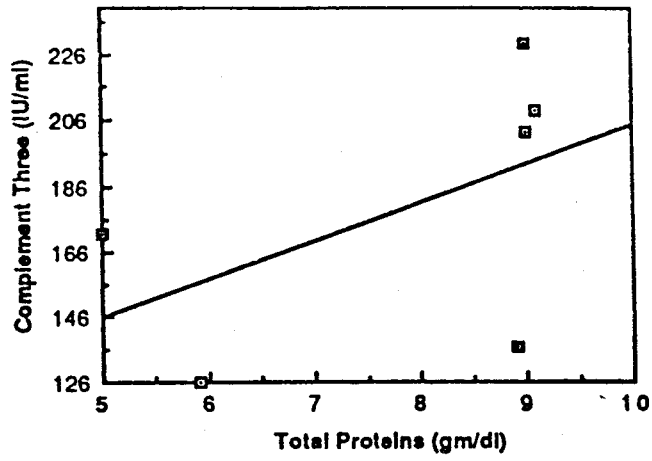

Fig. 14. Regression line between Complement Three and Total Proteins in Gr. IV Ho R. (r = 0.52).

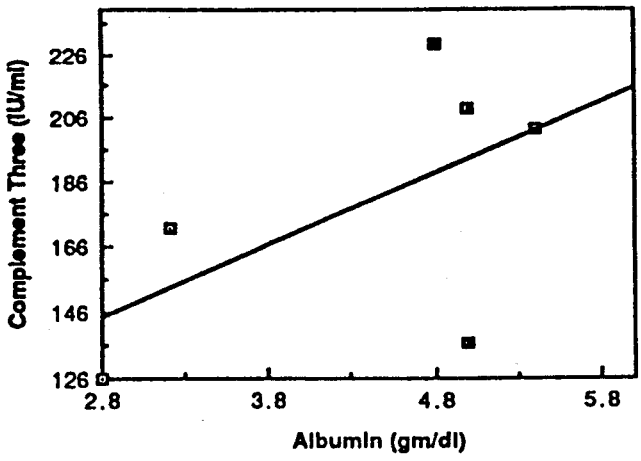

Fig. 15. Regression line between Complement Three and Albumin in Gr. IV Ho R. (r = 0.58).

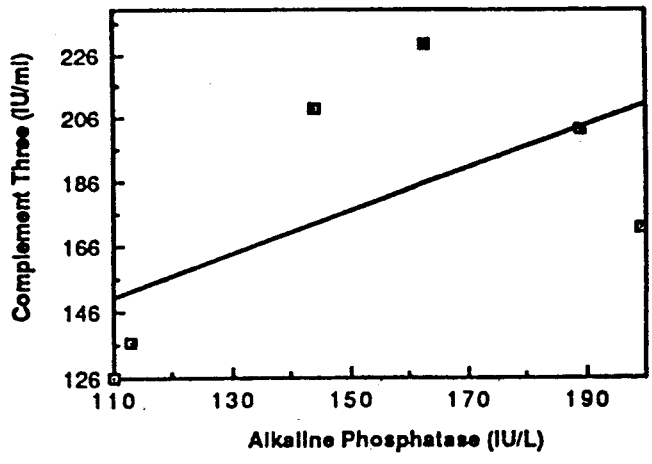

Fig. 16. Regression line between Complement Three and Alkaline Phosphatase in Gr. IV Ho R. (r = 0.61).

Significant decrease is reported in Ca and P level in Gr. II Ho. (21% and 34% respectively, $P < 0.001$); Gr. III Ho. R. (15% and 28% respectively, $P < 0.001$); and Gr. IV R.53 (8% and 18% respectively, $P < 0.005$) Table 1). These results are in agreement with the vies of Castro, *et al.;* [21], who reported a decrease of 18% and 30% in Ca and P levels respectively in hypothyroid patients; and with the view of Golding [22]; who reported that serum Ca and P levels are decrease in rheumatic patients.

Significant decrease (19%, $P < 0.005$) is reported in serum Mg content in Gr. II Ho., whole NS changes are reported in Gr. III Ho. R. and Gr. IV R. for the same element (Table 1). These results are in accordance with those of Dimich, *et al.* [23], who reported an association between hypothyroidism and hypomagnesaemia; and with the view of McCarty [17], who reported that serum Mg level may be slightly elevated or remains within normal range in rheumatic patients. Significant negative decrease is reported in ALP activity in Gr. II Ho., Gr. III Ho. R., and Gr. IV R which reached 30%, 14% and 16% respectively ($P < 0.001$) compared to normal controls (Table 1). These results are also in agreement with those reported by Kaplan [24]; and Golding [22], who stated that ALP is slightly decreased in hypothyroid and rheumatic patients.

Total proteins al and Gl levels show significant decrease (34%, 25% and 45% respectively, $P < 0.001$) in Gr.. II Ho., significant elevation (7%, 10% and 3%, $P < 0.05$, 0.001 and 0.05 respectively) in Gr. III Ho. R. and significant elevation (25%, 28% and 21% respectively, $P < 0.001$) in Gr. IV R. compared to normal controls. As for A/G it shows NS changes in different groups compared to normal controls (Table 1). These results are explained by Ingbar [20]; who stated that hypothyroidism causes a relative increase in proteins' degradation than it synthesis leading to decrease in their levels in serum; and the view of Andres, *et al.* [25]; who reported an increase in a2-globulin and fibrinogen serum levels in rheumatic diseases and stated that a rise of γ-globulin level in inflammatory disease is an evidence of response to antigenic stimulations. Uric acid level shows significant elevation (21%, $P < 0.05$) in Gr. II Ho., NS change in Gr. IV R. compared to normal controls (Table 1). These results are coinciding with those reported by McCarty [17], who stated that the increase incidence of clinical myxedema in patients with gout is slight, but statistically significant. Our results are also in accordance with those reported by Golding [22]; who suggested that serum uric acid is usually within normal range in rheumatic patients, but occasionally may be slightly raised in some patients due to high doses of Aspirin.

Regarding serum creatinine, NS changes are reported in Gr. II Ho., Gr. III Ho. R. and Gr. IV R. compared to normal controls (Table 1). These results are in agreement with those reported by Smith [16]; and Golding [22]; who suggested that s-creatinine level was within normal range in a group of myxoedemeous patients another of rheumatic patients.

In connection to serum C_3 NS elevation is reported in Gr. II Ho., while significant elevation is found in Gr. III Ho. R. (52%) and Gr. IV R. (33%) compared to normal controls ($P < 0.001$, Table 1). Our results are in accordance with the view of Ruddy [26]; who reported an association between the elevation of serum C_3 level and rheumatic diseases except SLE.

The percentage of presence of both RFs and CRP in Gr. I NC and Gr. II Ho. is found to be 0%; whole it is 83% and 66% for Gr. III Ho. R. and 72% and 52% for Gr. IV R. respectively. (Tables 2,3). These results are in agreement with the view of Carson [27]; who reported that RFs are present in serum of variable portion of rheumatic patients with acute and chronic inflammation; and in agreement with those of Nussinow and Arnold [28]; who stated that CRP is present in blood of all rheumatic patients with clinical evidence of disease activity.

Table 2
Showing RFs in different groups.

	Gr. I NC	Gr. II Ho.	Gr. III Ho. R.	Gr. IV R.
%Of presence	-	-	83%	72%

Table 3
Showing CRP in different groups.

	Gr. I NC	Gr. II Ho.	Gr. III Ho. R.	Gr. IV R.
%Of presence	-	-	66%	52%

From the forgoing data, we suggest that there is no association between hypothyroidism and rheumatic diseases, but the existence of a false relationship may be due to the ingestion of corticosteroids and antirheumatic drugs which develop a temporary relation.

It is recommended for researchers in the field of thyroid disorders and rheumatic diseases to adopt serum parameters covering both disorders as a routine. This relationship can be further studied by the human lymphocyte antigen system (HLA system), which plays a role in disease susceptibility; estimation of antibodies in serum synovial fluid; and thyroid scanning, where the study of these factors may help in clearing more details of this relationship.

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