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Original Article

Biochemistry Section

Evaluation of Serum Magnesium, Lipid Profile and Various Biochemical Parameters as Risk Factors of Cardiovascular Diseases in Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is chronic inflammatory disease, associated with increased risk of cardiovascular diseases (CVD) than the general population. Chronic inflammatory conditions are likely to alter magnesium level and various biochemical parameters.

Objectives: To study the probable changes in serum magnesium, lipid profile and various biochemical parameters and to assess risk factors of CVD in newly diagnosed RA patients compared to controls.

Materials and Methods: We studied 50 newly diagnosed RA adult patients and 50 healthy individuals as controls. Serum magnesium, calcium, lipid profile, uric acid and other biochemical parameters were measured in study subjects. Results were expressed as Mean ± SD and compared between RA subjects and controls by Independent sample t-test and Pearson correlation.

Results: We found decreased serum magnesium and calcium in RA subjects compared to the controls ($p < 0.001$). RA subjects had atherogenic lipid profile characterized by elevated total cholesterol ($p = 0.054$), LDL cholesterol ($p = 0.008$) and decreased HDL cholesterol ($p < 0.001$). Serum uric acid was higher in RA cases compared to controls ($p = 0.025$). Serum magnesium was negatively correlated with total cholesterol, LDL cholesterol and positively correlated with HDL cholesterol in RA cases.

Conclusion: Decreased magnesium level, dyslipidemia and increased uric acid observed in our study together may be more potent risk factors for CVD in newly diagnosed RA subjects. We recommend that serum magnesium should be investigated as a part of cardiovascular risk management in RA. We suggest that decreased serum magnesium and increased serum uric acid may be considered as nontraditional risk factors of CVD in RA. Further prospective studies are needed to confirm the impact of inflammation on various biochemical parameters and cardiovascular outcomes in patients with RA.

Keywords: Cardiovascular risk factors, Dyslipidemia, Inflammatory, Uric acid

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology affecting various joints of the body leading to swelling, pain, stiffness and finally functional inability. It is affecting 0.8% of the total population of world with an annual incidence of 0.5 - 1% in both developed and developing countries [1,2]. It is the most common inflammatory disease affecting approximately 0.75% of Indian adult population [3].

Microbiological and pathological investigations are predominantly used in the diagnosis and prognosis of RA, whereas the utility of biochemical parameters is limited. Recently various biochemical parameters in RA are being explored by many studies [1,4-7]. There is paucity of information regarding the pattern of biochemical parameters like, magnesium, total proteins, albumin, globulin, glucose, urea, creatinine, bilirubin and various enzymes like transaminases in RA. Inflammation, irrespective of etiology is capable of inducing marked systemic alterations in trace metal distribution and metabolism [8].

Magnesium (Mg) is an essential nutrient and fourth most abundant mineral found in the body [9] Mg levels are changed in chronic inflammations and decreased level of Mg has been suggested to be reasonable marker of RA [4]. Magnesium is routinely measured in the blood and has many functions in the cardiovascular (CV) system, like as an activator of sodium potassium ATPase, antiarrhythmic and associated with risk of CD [9-12].

The role of calcium in RA is not clear but interrelationship between calcium, vitamin D, parathyroid hormone suggests the possible role of calcium in RA and there is alteration in bone minerals like calcium, phosphorus [12]. Altered lipid levels have been reported in various inflammatory diseases including RA [13]. There is increased risk of atherosclerosis and cardiovascular diseases (CVD) in RA subjects than the general population [14] and additional factors are responsible for CVD in RA [15,16]. Based on present knowledge our study was primarily aimed to study the probable changes in serum magnesium, lipid profile and other biochemical parameters in newly diagnosed RA patients compared to healthy controls. We hypothesized that RA patients would have decreased serum magnesium and alteration in other biochemical parameters compared to healthy controls. Secondary objectives were 1) to explore relationship between serum magnesium, lipid profile and other biochemical parameters in RA and 2) to assess risk factors of CVD in newly diagnosed RA patients.

MATERIALS AND METHODS

The present cross-sectional, case control study was carried out in the Biochemistry department, Surat Municipal Institute of Medical Education & Research (SMIMER), Surat, Gujrat, India, during January 2012 to June 2012. The patients attending medicine OPD were selected for the study. We studied 50 newly diagnosed RA patients and 50 age and sex matched healthy individuals as control. Controls were other healthy individuals having similar

socioeconomic, cultural and geographical background, selected after specific questionnaire- like age, occupation, monthly income and locality. Study was approved by institutional ethical committee and informed and written consent was taken from all participants.

Inclusion Criteria: Newly diagnosed cases of RA as per revised criteria of American Rheumatology Association (ARA) [17] having diseases duration less than one month and without history of anti-rheumatic treatment. We studied both males and females of age group 20-60 y. In all patients Rheumatoid Factor (RF), (Aspen Laboratories Pvt. Ltd; India) was positive.

Exclusion Criteria: Known cases of RA who were taking anti-rheumatic treatment (including anti-inflammatory and /or glucocorticoids), patients suffering from diabetes mellitus, endocrine disorders, tuberculosis, cardiovascular, liver, kidney disease, obese (BMI > 30), patients taking lipid lowering drugs or any other therapy including vitamins and minerals and trauma cases were excluded from the study.

Laboratory analysis: Blood sample was collected after overnight fast and laboratory analysis was done in the Clinical Biochemistry laboratory on the same day by using commercially available kits on fully automated clinical chemistry analyser Erba-XL 300 (Transasia Bio-Medicals Ltd. Mumbai, India). Serum magnesium measured by Calmagite method (Crest Biosystems, Goa, India), calcium by modified Arsenazo method (Pathozyme Diagnostics, India), phosphorus by UV molybdate, end point assay (Span Diagnostics Ltd. India). Total cholesterol, triglycerides and HDL cholesterol measured by enzymatic method (Aspen Laboratories Pvt. Ltd; India) [18]. LDL cholesterol and VLDL cholesterol were calculated by the Friedewald's formula [18]. Alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase measured by the modified International Federation of Clinical Chemistry (IFCC) method (Span Diagnostics Ltd. India). Other biochemical parameters were estimated by using commercial reagent kits (Pathozyme Diagnostics, India), bilirubin by modified Gendrassik and Groff method, uric acid by the uricase/PAP (peroxidase coupled with 4-aminophenazone) enzymatic method, creatinine by modified Jaffe's fixed time kinetic method, total protein by Biuret reaction and albumin by Bromocresol Green method. Urea was estimated by enzymatic (urease/glutamate dehydrogenase, kinetic) method, glucose by glucose oxidase-peroxidase (GOD-POD) enzymatic method. Sodium (Na+), potassium (K+) and chlorides (Cl-) collectively called as electrolytes were measured by ion selective electrode method using Combisys-II, Eischweiler BGA plus E instrument (Eischweiler automatic analysing systems, Eschweiler GmbH & Co. Germany).

STATISTICAL ANALYSIS

Data analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago). The data was carefully evaluated to obtain the mean values and SD and compared as student's unpaired 't'-test between subjects and control. A p-value < 0.05 was considered as statistically significant. Person correlation coefficient (r) was calculated to explain relation of serum magnesium with other biochemical parameters in RA subjects.

RESULTS

The present study was conducted in 100 subjects (39 males and 61 females) of which 50 RA and 50 control subjects [Table/Fig-1]. We found lower magnesium concentrations in RA subjects (1.73 ± 0.46 mg/dl) compared to the controls (2.12 ± 0.25 mg/dl), t (98) = 5.12, and data was statistically significant [Table/Fig-2,3]. Serum calcium level was lower in RA (7.75 ± 0.63 mg/dl) compared to controls (9.99 ± 0.66 mg/dl), t (98) =17.17. Alkaline phosphates level was increased in RA subjects (348.54 ± 99.51 IU/L) compared to controls (150.02 ± 52.26 IU/L), t (98) = -12.48. In RA subjects there was higher total cholesterol and LDL cholesterol (p = 0.054) and (p = 0.008) respectively RA patients had statistically significantly lower HDL cholesterol levels compared to control group. There were significant increase in the levels of phosphorus, total proteins and albumin in RA subjects compared to controls [Table/Fig-2]. The study found that RA patients had higher uric acid and alanine transaminase (ALT) compared to controls. Serum creatinine and urea was decreased in RA cases compared to controls. There was no significant difference in the levels of triglyceride, VLDL cholesterol, total bilirubin, direct bilirubin, indirect bilirubin, urea, glucose, aspartate transaminase (AST) and electrolytes (Na+, K+ and Cl-) between RA cases and control group [Table/Fig-2,3].

	Rheumatoid arthritis (n =50)		Control subjects (n =50)		Total (n =100)
Age	< 35 y	> 35 y	<35 y	>35 y	
Males	4	15	4	16	39
Females	6	25	11	19,	61
Total	10	40	15	35	100

[Table/Fig-1]: Demographic characteristics of RA patients and control group

Magnesium was negatively correlated with alkaline phosphatase (-0.89), total cholesterol (-0.371), LDL cholesterol (-0.342) and direct bilirubin (-0.368) in RA patients. Magnesium had a fair degree of positive correlation with urea (0.293) in RA [Table/Fig-4].

Biochemical parameters	Rheumatoid arthritis(n =50)	Control subjects (n =50)	p-value
	Mean ± SD	Mean ± SD	
Magnesium (mg/dl)	1.73 ± 0.46	2.12 ± 0.25	<0.001*
Calcium (mg/dl)	7.75 ± 0.63	9.99 ± 0.66	<0.001*
Phosphorus (mg/dl)	4.58 ± 1.13	3.66 ±1.10	<0.001*
Alkaline phosphatase (IU/L)	348.54 ± 99.51	150.02 ± 52.26	<0.001*
Aspartate transaminase (AST) (IU/L)	29.14 ± 12.49	29.94 ± 30.41	0.864
Alanine transaminase (ALT) (IU/L)	29.24 ± 10.20	25.14 ± 9.41	0.039*
Total cholesterol (mg/dl)	212.58 ± 41.38	195.60 ± 45.66	0.054
Triglyceride (mg/dl)	146.84 ± 40.99	137.24 ± 40.13	0.24
HDL cholesterol (mg/dl)	31.22 ± 7.33	41.56 ± 9.00	<0.001*
LDL cholesterol (mg/dl)	150.66 ± 42.34	126.08 ± 49.28	0.008*
VLDL cholesterol (mg/dl)	29.38 ± 8.27	27.42 ± 7.93	0.23
Glucose (mg/dl)	110.02 ± 29.67	109.30 ± 20.93	0.889
Total bilirubin (mg/dl)	0.92 ± 0.36	0.87 ± 0.08	0.387
Direct bilirubin (mg/dl)	0.3820 ± 0.25	0.33 ± 0.06	0.167
Indirect bilirubin (mg/dl)	0.53 ± 0.10	0.65 ± 0.77	0.305
Total protein (gm/dl)	7.80 ± 1.10	7.14 ± 0.67	0.001*
Albumin (gm/dl)	4.68 ± 0.70	4.07 ± 0.48	<0.001*
Globulin (gm/dl)	3.64 ± 3.74	3.06 ± 0.53	0.279
Urea (mg/dl)	27.51 ± 29.01	30.52 ± 6.45	0.0587
Creatinine (mg/dl)	0.91 ± 0.21	1.10 ± 0.32	<0.001*
Uric acid (mg/dl)	4.46 ± 1.74	3.73 ± 1.45	0.025*
Sodium (mmol/L)	142.26 ± 6.54	142.980 ± 5.11	0.541
Potassium (mmol/L)	4.44 ± 1.02	4.64 ± 0.713	0.26
Chloride (mmol/L)	101.12 ± 5.85	102.60 ± 4.95	0.176

[Table/Fig-2]: Serum magnesium and other biochemical parameters in newly diagnosed RA patients and control subjects
* p < 0.05 statistically significant

DISCUSSION

Rheumatoid arthritis (RA) is a multifactorial disease which affects the immune system and ultimately various tissues in the body [1]. RA is

Biochemical parameters	Levene's test for equality of variances	t-test for Equality of Means						
	F	p-value	t	df	p-value	Mean Difference	95% CI for mean difference	
							Lower	Upper
Magnesium	18.93	<0.001	5.12	98	<0.001	0.384	0.235	0.532
Calcium	0.875	0.352*	17.172	98	<0.001	2.234	1.976	2.492
Phosphorus	0.394	0.532*	-4.104	98	<0.001	-0.9180	-1.3619	-0.4741
Alkaline phosphatase	11.951	0.001	-12.48	98	<0.001	-198.52	-230.19	-166.84
Aspartate transaminase(AST)	0.479	0.491*	0.172	98	0.864	0.8	-8.429	10.029
Alanine transaminase (ALT)	0.031	0.861*	-2.088	98	0.039	-4.1	-7.997	-0.203
Total Cholesterol	1.893	0.172*	-1.948	98	0.054	-16.98	-34.27	0.316
Triglyceride	0.294	0.589*	-1.183	98	0.24	-9.6	-25.69	6.499
HDL cholesterol	5.441	0.022	6.286	94.14	<0.001	10.32	7.06	13.58
LDL cholesterol	3.232	0.075*	-2.702	98	0.008	-24.74	-42.91	-6.567
VLDL cholesterol	0.581	0.448*	-1.209	98	0.23	-1.96	-5.177	1.257
Glucose	7.998	0.006	-0.140	88.091	0.889	-0.720	-10.928	9.488
Total bilirubin	2.817	0.096*	-0.868	98	0.387	-0.046	-0.151	0.0591
Direct bilirubin	1.387	0.242*	-1.392	98	0.167	-0.052	-0.1261	0.0221
Indirect bilirubin	1.728	0.192*	1.030	98	0.305	0.1140	-0.105	0.3336
Total protein	9.416	0.003	-3.592	81.30	0.001	-0.660	-1.026	-0.294
Albumin	4.681	0.033	-5.055	86.16	<0.001	-0.612	-0.8527	-0.3713
Globulin	2.143	0.146*	-1.088	98	0.279	-0.582	-1.6432	0.4792
Urea	4.692	0.033	1.925	88.759	0.057	3.02	-0.098	6.138
Creatinine	15.986	<0.001	3.5	84.65	<0.001	0.1914	0.0826	0.3001
Uric acid	0.454	0.502*	-2.272	98	0.025	-0.73	-1.367	-0.092
Sodium	0.188	0.665*	0.613	98	0.541	0.72	-1.611	3.051
Potassium	0.033	0.856*	1.134	98	0.26	0.2	-0.15	0.55
Chloride	0.086	0.769*	1.364	98	0.176	1.480	-0.674	3.634

[Table/Fig-3]: Independent sample t-test for biochemical parameters between RA cases and controls (n=100)
*Equality of variances assumed as Levene's test p-value is > 0.05

characterized by local and systemic inflammation and wide range of biochemical markers contribute directly or indirectly to pathogenesis of RA [5]. Age is also one of the factors in the development of RA. In our study out of 50 RA subjects 40 subjects were above 35 y and only 10 subjects were below 35 y. In the present study we found that for every male, 1.7 females were affected with RA. In our study 62 % of subjects affected with RA were females. Our study supports the findings of Bhowmick et al., [19].

Chronic inflammatory conditions are likely to alter magnesium level and possible mechanism of decrease magnesium in RA is due to chronic inflammation and autoimmune injury [4,20,21]. We have used photometric method of measurement of magnesium, which is most frequently used method in clinical laboratories, although, atomic absorption spectrophotometer (AAS) is used as reference method for measurement of magnesium [22]. In the present study, we found decreased level of serum magnesium in RA subjects as compared to controls. The results of our study are correlating with the study by Manole et al., [4] and Amin et al., [20]. Cortes et al., [21] suggested that the RA, an autoimmune disease is associated with serum magnesium disturbances. We are in concordance with Cortes et al., [21].

It has been known that RA is associated with serum mineral disturbances and oxidative stress [20]. Decreased levels of serum magnesium and calcium may be due to many reasons. Water softeners and purifiers used for purification of water may decreases calcium and magnesium in drinking water [23]. We observed decreased level of serum calcium and increased level of serum phosphorus in RA subjects as compared to controls. Similar results observed by other studies [12,20,24] support our study.

Makhdoom et al., found that increase in level of alkaline phosphatase in RA patients as compared to normal range [12]. We observed increased level of alkaline phosphatase in RA subjects compared to controls. Our results corroborate the findings of Makhdoom, et al., [12].

We found increased level of total protein and albumin in RA compared to control subjects. The increase in proteins may be due to inflammation which induces marked systemic alterations in trace metal distribution which is linked with the production of an acute phase plasma protein as response to host defense [8]. We observed increased level of serum uric acid in RA patients, similar like Magnus et al., [7] and Ponoulas et al., [25] study. However, there was no statistical difference in the concentration of glucose, bilirubin, aspartate transaminase (AST), sodium, potassium and chloride between RA subjects and controls.

The lipid pattern observed in newly diagnosed RA in our study is atherogenic lipid profile or dyslipidemia. Similar atherogenic lipid profile was observed by Mullick et al., [26] in early cases of RA. We found different lipid profile pattern in newly diagnosed RA cases unlike other studies [27,28]. Serum magnesium observed in our study is negatively correlated with total cholesterol, triglycerides, LDL cholesterol and positively correlated with HDL cholesterol; our findings are supported by Mahalle et al., [11]. It is evident from our observation that decreased serum magnesium concentration is associated with atherogenic lipid profile and increases the risk of CVD, supported by other studies [9-11, 29]. Therefore magnesium preservation is very important in general especially in the subjects affected with disorder like RA. Although there was non-significant increase in total and direct bilirubin in newly diagnosed RA patients

Biochemical parameters	Pearson's correlation coefficient (r-value)
Calcium (mg/dl)	0.069
Phosphorus (mg/dl)	-0.028
Alkaline phosphatase (IU/L)	-0.89
Aspartate transaminase (AST) (IU/L)	-0.1
Alanine transaminase (ALT) (IU/L)	0.019
Total cholesterol (mg/dl)	-0.371
Triglyceride (mg/dl)	-0.27
HDL cholesterol (mg/dl)	0.037
LDL cholesterol (mg/dl)	-0.342
VLDL cholesterol (mg/dl)	-0.266
Glucose (mg/dl)	0.059
Total bilirubin (mg/dl)	-0.342
Direct bilirubin (mg/dl)	-0.368
Indirect bilirubin (mg/dl)	-0.197
Total protein (gm/dl)	0.206
Albumin (gm/dl)	0.205
Globulin (gm/dl)	0.195
Urea (mg/dl)	0.293
Creatinine (mg/dl)	0.144
Uric acid (mg/dl)	0.17
Sodium (mmol/L)	-0.025
Potassium (mmol/L)	0.138
Chloride (mmol/L)	-0.035

[Table/Fig-4]: Pearson correlation of magnesium with other biochemical parameters in RA subjects (n=50)
Interpretation of correlation coefficient (r):
1. r between 0 and 0.25 indicate little or no linear relationship
2. r between 0.25 and 0.5 indicate fair degree of linear relationship
3. r between 0.5 and 0.75 indicate moderate to good linear relationship
4. r above 0.75 indicates a very good linear relationship
5. r = 0, then no relationship
Note: if r is positive, it indicates positive correlation, if r is negative, negative correlation

unlike Fischman et al., [6], there was a negative correlation between serum magnesium and bilirubin (total and direct) in our study. The increase in bilirubin level may be its possible anti-inflammatory role in RA [6]. Panoulas et al., [25] suggested that increased serum uric acid may be independently associated with CVD in RA subjects. Patients with RA have increased risk of CVD which may be due to abnormal lipid profile and systemic inflammatory response [13,14]. The change observed in the results of our study is possibly due to chronic inflammation and immune response that occurs in RA. Thus, in addition to dyslipidemia, hypomagnesemia and increased uric acid together are more potent risk factors of CVD events in RA patients. The increased incidence of CVD in RA subjects is independent of traditional CVD risk factors and additional mechanisms and factors are responsible for CVD in RA [14-16,30]. Based on findings of our study, we suggest that decreased serum magnesium and increased serum uric acid may be considered as additional nontraditional risk factors of CVD in RA.

LIMITATIONS

Limitations of our study are small sample size, non measurement of extended lipid profile and other markers of inflammations. Specific information on dietary intake of magnesium was not obtained.

CONCLUSION

Our study concludes that newly diagnosed RA patients had significantly lower serum magnesium, calcium levels and increased levels of alkaline phosphatase, phosphorus, total proteins, albumin and uric acid compared to controls. We observed atherogenic lipid profile characterized by increased total cholesterol, LDL cholesterol and a reduction in the HDL cholesterol in newly diagnosed RA. Low level of magnesium, dyslipidemia and increased uric acid observed in our study together may be more potent risk factors for CVD in newly diagnosed RA subjects. We recommend that serum magnesium should be investigated as a part of cardiovascular risk management in RA. We suggest that magnesium supplementation, may prove to be beneficial to reduce the risk of CVD in RA patients. Further prospective, long-term studies are needed to determine the role of inflammation and its impact on various biochemical markers and cardiovascular outcomes in patients with RA.

List of abbreviations:

HDL= high density lipoprotein

LDL= low density lipoprotein

VLDL= very low density lipoprotein.

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