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RESEARCH ARTICLE

CORRELATIVE STUDY BETWEEN LIPID PROFILE AND DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS – A HOSPITAL BASED STUDY.

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Abstract

Objective: To study the serum lipid profile, disease activity and their correlation in patients with Rheumatoid Arthritis.

Materials and methods: The study was carried out on 50 diagnosed patients of RA in the Department of Biochemistry, Assam Medical College and hospital, Dibrugarh. 50 apparently age and sex matched individuals were taken as controls.

Fasting lipid profile (Total cholesterol, HDL-c, LDL-c, Triglyceride) was estimated in semiautoanalyser using standard method. Disease activity was assessed by DAS28 ESR score.

Results: Serum total cholesterol (TC) and HDL-c were significantly lower in cases than controls ($p<0.05$ and $p<0.01$ respectively). Patients with active disease had significantly lower level of TC and HDL -c than those in remission. Triglyceride levels was significantly higher in cases than controls ($p<0.05$).

Conclusion: Study reveals that the lipid profile is altered in Rheumatoid arthritis characterized by low TC, HDL and elevated triglycerides. Further in active cases the mean serum level of total cholesterol and HDL cholesterol were significantly lower than cases in remission. A significant negative correlation was seen between HDLc and DAS28.

Introduction:-

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis affecting around 0.5%-1% of the adult population worldwide[1]. RA is associated with increased cardiovascular morbidity and mortality, that is largely attributed to accelerated atherosclerosis. Both traditional and novel risk factors have been invoked to explain the accelerated atherogenesis in RA. Dyslipidemia is a classical and important modifiable risk factor for atherosclerosis. Asian Indians are a metabolically disadvantaged ethnic group with high prevalence of obesity, diabetes and dyslipidemia[2]. Dyslipidemia is highly prevalent in RA affecting 55-65% of patients and can manifest in patients with both early and advanced disease[3]. Traditionally, the atherogenic lipid profile comprises of increased total cholesterol (TC), low density lipoprotein (LDL), triglycerides (TG), and decreased high density lipoprotein (HDL). In chronic inflammatory diseases such as RA, however, different concentrations of lipids can be found throughout different stages of the disease: increased TC and LDL in the years prior to disease onset, reduced levels

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of TC and HDL-C during early active disease, and different patterns in established RA[4]. The inflammatory process that occurs in RA and the treatment factors may modify the lipid profile in these patients[5.] Despite RA being the commonest inflammatory joint disease seen in India and evidence that cardiovascular disease and atherosclerotic manifestation as a common cause of death in patients with RA, little information is available on lipid levels in Indian patients with RA and in particular from the North Eastern region.

So keeping the above mentioned facts in mind, the present study was undertaken with the following aims and objectives.

1. Estimation of serum lipid in patients with Rheumatoid arthritis.
2. To study the correlation between serum lipid profile and disease activity in patients with Rheumatoid arthritis.

Materials and Methods:-

This case control study was conducted on cases of Rheumatoid arthritis who attended the Rheumatology clinic or were admitted in the Medicine wards of Assam Medical College and Hospital from August 2013 to September 2014.

Study population comprised of 50 cases of Rheumatoid arthritis .50 apparently healthy age and sex matched individuals were taken as controls. Attempt was made to take patients attendant or relative as control.

The study was conducted on cases of Rheumatoid arthritis diagnosed by 2010 Rheumatoid arthritis Classification Criteria: An American College of Rheumatology /European League Against Rheumatism Collaborative Initiative (ACR/EULAR 2010)[6].Only those cases were included from whom informed consent could be taken.

Cases in remission were defined by the criteria laid by ACR/EULAR Provisional Definition of Remission in Rheumatoid arthritis[7].

Exclusion criteria:-

1. Rheumatoid arthritis patients with other concomitant disorders that alter the lipid parameters were excluded from the study (Diabetes mellitus, malabsorption syndrome, thyroid disorders, hypertension, and central obesity)
2. Those on diuretics, OCP, statins and other drugs capable of altering lipid values
3. Pregnant women
4. Refusal of consent

After obtaining informed consent, the individuals were subjected to detailed history and clinical assessment. Approval from Institutional Human Ethics Committee was obtained prior to initiation of study.

Disease activity was assessed by DAS28 ESR score.

Disease Activity in Rheumatoid Arthritis (Disease Activity Score in 28 joints) [1, 8]

$DAS28=0.56\times\sqrt{(TJC28)} +0.28\times\sqrt{(SJC28)} +0.70\times\log(ESR) +0.014\times GH.$

TJC=Tender joint count, SJC=Swollen joint count, ESR=Erythrocyte sedimentation rate,

GH= assessment of global health, done by 100mm Visual analogue scale.

Patients with score less than 2.6 were considered to be in remission while those with score more than or equal to 2.6 were with active disease.

Serum total cholesterol, triglyceride and HDL cholesterol were estimated enzymatically in semiautoanalyser using standard kits. LDL cholesterol was calculated using standard WHO approved formula (Friedewald's formula). ESR was measured by Westergren method. Quantitative estimation of CRP was done by Dimension RxL Max autoanalyser , Siemens.

Statistical analysis:-
The results were expressed in terms of percentage and mean ± SD (standard deviation). Analysis of results was done by unpaired Students t test. Pearsons coefficient of correlation was used to assess the relation between lipid profile and disease activity. Statistical analysis was done using Microsoft Excel 2007 and online software; Graphpad.

Results:-

The study comprised of fifty cases of RA and fifty apparently healthy controls. The cases were mostly clustered in the age group of 31-40 years (32%).The male: female ratio was seen to be 1:5 suggesting a higher preponderance in females. Of the 50 cases of rheumatoid arthritis, 13 cases were in remission and 37 cases had active disease according to the disease activity score (DAS 28 ESR).

The serum total cholesterol (TC) in cases was 150.86± 12.18 mg/dl which was significantly lower ($p<0.05$) than controls (157.27±16.65 mg/dl).

HDL cholesterol in cases was 41.7±7.20 mg/dl which was lower than controls (46.33 ± 7.60 mg/dl); the decrease being highly significant ($p<0.01$).

As for serum triglyceride and VLDL, they were significantly higher ($p<0.05$) in cases than controls. LDL in cases was lower than controls, although not statistically significant.

Table Showing Lipid Profile In Cases And Controls:-

PARAMETER(mg/dl)	CASES (MEAN ± SD)	CONTROLS (MEAN ± SD)	p value
TOTAL CHOLESTEROL	150.86 ± 12.18	157.27 ± 16.65	<0.05*
TRIGLYCERIDE	133.01 ± 27.33	118.76 ± 39.11	<0.05*
HDL	41.7 ± 7.20	46.33 ± 7.60	<0.01**
LDL	82.00 ± 13.36	87.19 ± 15.61	>0.05
VLDL	26.6 ± 5.46	23.74 ± 7.83	<0.05*

* Significant, ** highly significant

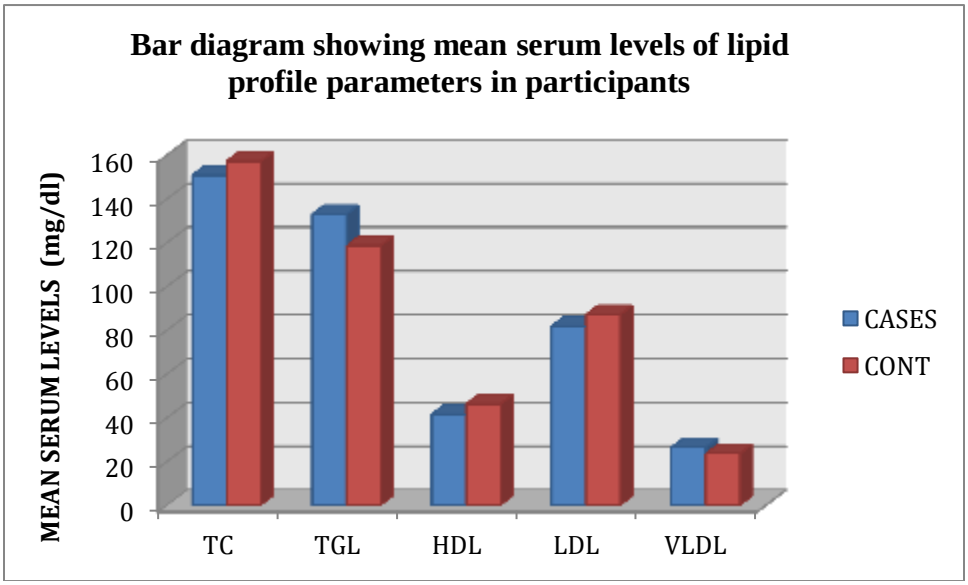


Table Showing CRP Levels In Cases And Controls:-

CRP(mg/dl)	MEAN±SD	p value
CASES	11.19±9.52	<0.001
CONTROLS	1.01±0.95	

The laboratory results of CRP showed that there was higher value of CRP (11.19±9.52 mg/dl) in RA patients than healthy control group (1.01±0.95 mg/dl) with the difference being very highly significant.

Table showing comparison of serum Total Cholesterol, HDL and CRP in between active cases (DAS 28 score > 2.6) and those in remission (DAS 28 score< 2.6). n= No of patients.

PARAMETER	ACTIVE (n=37)	REMISSION (n=13)	p value
TOTAL CHOLESTEROL(mg/dl)	148.70 ± 11.42	157.0 ± 12.61	<0.05*
HDL(mg/dl)	39.92 ± 6.28	46.73 ± 7.48	<0.01**
CRP(mg/dl)	14.72 ± 8.61	1.15 ± 0.25	<0.001***

* Significant, ** highly significant, *** very highly significant

The mean serum level of total cholesterol in active cases is 148.70 ± 11.42 mg/dl and in remission is 157.0± 12.61 mg/dl. T-test revealed significant difference in between the two groups showing that the total cholesterol in active cases is lower in comparison to cases in remission.($p<0.05$)

HDL level in cases in remission is 46.73±7.48 mg/dl and 39.92±6.28 mg/dl in active cases, thus signifying that HDL in active cases is low compared to those in remission. The difference is highly significant. ($p<0.01$)

There was no significant difference in the levels of serum triglyceride, LDLc, and VLDLc in between active cases and those in remission.

There is very highly significant difference ($p<0.001$) in the CRP levels in the two groups.

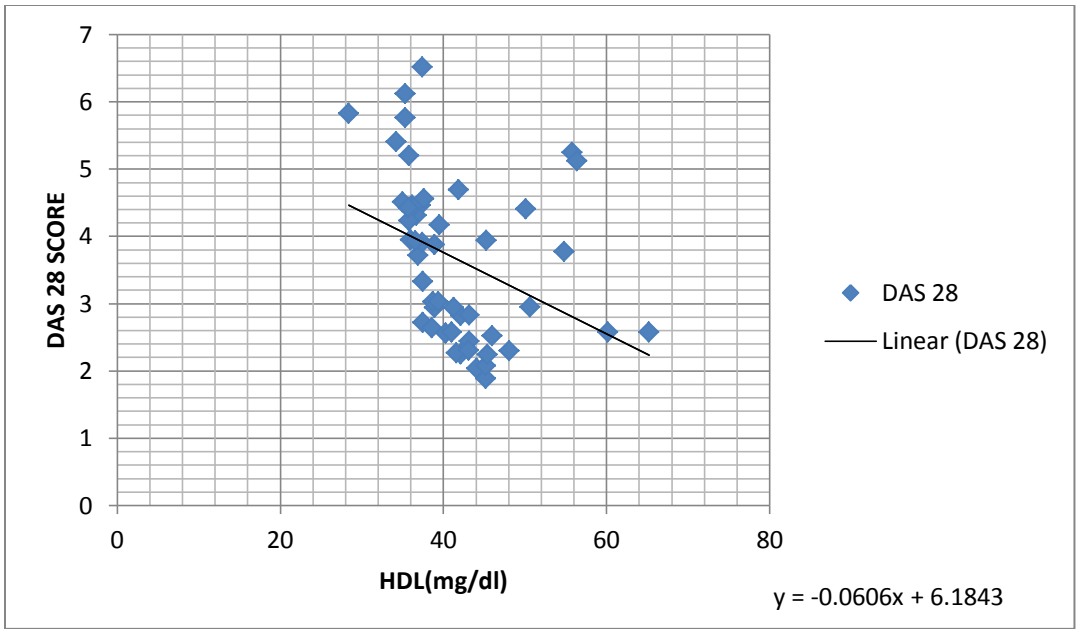
Table showing correlation between DAS 28 and lipid profile in cases.

PARAMETER	DAS 28	
	(r)	p value
TOTAL CHOLESTEROL	-0.17	>0.05
TRIGLYCERIDE	0.04	>0.05
HDL	-0.36	<0.05*
LDL	0.005	>0.05
VLDL	0.04	>0.05

* Significant

A significant negative correlation is seen between HDL and DAS28 in patients with rheumatoid arthritis. For total cholesterol, negative correlation is seen, though not significant

Scatter diagram showing negative correlation between HDL and DAS 28 score:



Regression analysis:-
In the equation y=a+bx

Taking y=DAS28 score and x= Serum HDLc concentration
Regression analysis revealed that a= 6.1843 b = - 0.0606

Now the equation becomes:-

DAS28 score= 6.1843 – 0.0606 X S.HDLc

Thus, the DAS28 score can be calculated from the serum HDLc level.

Discussion:-

Our study was based on the estimation of serum lipid in 50 diagnosed cases of Rheumatoid arthritis and 50 apparently age and sex matched individuals who served as controls. Also the study was undertaken to find out any correlation between serum lipid profile and disease activity in patients with RA.

The male: female ratio was 1:5 thus signifying increased preponderance of RA in females. The findings are consistent with the study by Varunkumar et al (2013)[9] and Dessein et al (2002)[10].

The laboratory results of CRP showed that RA patients had higher CRP levels (11.19±9.52 mg/dl) compared to healthy control group (1.01±0.95 mg/dl) with the difference being very highly significant. Active cases had a significantly higher CRP level than cases in remission ($p<0.001$). Georgiadis et al (2006)[11] in a case control study observed the CRP level of 28.15±20.75 mg/dl which was significantly higher than controls (2.1±1.3 mg/dl). In a study by Borman et al (1999)[12] on dyslipidemia in rheumatoid arthritis, the CRP level was found to be 18.25±14.03 mg/l in patients of rheumatoid arthritis. They also stated that active disease was associated with higher levels of CRP.

The serum total cholesterol (TC) in cases was 150.86± 12.18 mg/dl which was significantly lower ($p<0.05$) than controls (157.27±16.65 mg/dl). Further, in active cases the mean serum level of total cholesterol was significantly lower ($p<0.05$) than cases in remission. Vottery et al (2001)[13] compared the lipid profiles of 25 RA cases with age and sex matched controls. They observed that the total cholesterol was significantly lower in RA patients and in patients with active disease; the decrease in total cholesterol was significant in comparison to controls. Lazarevic et al (1992)[14], Svenson et al(1987)[15] and Kim et al(2004)[16] also reported that the level of serum total cholesterol was

lower in patients with RA than healthy controls. However many workers: Georgiadis et al (2006)[11], Nassir et al (2007)[17] and Kowsalya et al(2011)[18] have observed that RA patients exhibited higher levels of serum total cholesterol in comparison to controls.

Serum triglyceride in our study was found to be 133.01±27.33 mg/dl in patients with RA which was higher when compared to controls (118.76 ± 39.11 mg/dl); the difference being statistically significant ($p<0.05$). Mahdi et al (2012)[19] and Vinapamula et al (2013)[5] also found that RA patients had significantly higher levels of serum triglyceride than controls ($p<0.001$ and $p<0.05$ respectively). Contrary to the above findings, some workers; Lakatos and Harsagyi (1988)[20] and Vottery et al (2001)[13] have found significantly lower level of serum triglyceride when compared to controls. However no significant difference was seen in levels of serum triglyceride in active cases and those in remission.

In the present study HDL cholesterol in cases was 41.7±7.20 mg/dl which was significantly lower ($p<0.01$) than controls (46.33 ± 7.60 mg/dl). Further, in active cases the mean serum level of HDL cholesterol (39.92±6.28 mg/dl) was significantly lower ($p<0.01$) than cases in remission (46.73±7.48 mg/dl). Lazarevic et al (1992)[14] observed that the HDL was significantly decreased in RA patients as compared with healthy blood donors. RA patients with severe activity had significantly decreased HDL levels as compared to patients with minimal activity. Boers et al (2003)[21] reported that the HDL cholesterol level in patients with active disease was significantly lower than patients in remission (0.94±0.31 mmol/l vs 1.18±0.13 mmol/l). However, Vinapamula et al (2013)[5] found no difference in the HDL cholesterol level in between cases and controls.

On assessing the LDL cholesterol level, no significant difference was found in between the cases and controls although cases had a lower level of LDL cholesterol (82.00± 13.36 mg/dl) than controls (87.19± 15.61 mg/dl). Our finding is similar to Vinapamula et al (2013)[5] where they observed that RA patients had low total cholesterol (115.67 ± 34.85 mg/dl) when compared to controls (125.48 ± 30.80 mg/dl) although not significant statistically. Mahdi et al (2012)[19], Kowsalya et al (2011)[18] and Mullick et al (2014)[22] have reported significantly higher level of LDL cholesterol in cases than controls.

In the present study the mean serum level of VLDL cholesterol in cases was 26.6±5.46 mg/dl which was significantly higher ($p<0.05$) than controls (23.74±7.83 mg/dl). Kowsalya et al (2011)[18], Nassir et al (2007)[17] have reported significantly higher level of VLDL cholesterol in RA patients than controls.

On comparing the levels of LDLc and VLDLc in between active cases and those in remission, there was no significant difference.

On studying the correlation between lipid profile (TC, Triglyceride, HDLc, LDLc, VLDLc) and disease activity score (DAS 28-ESR), a significant negative correlation was seen between HDLc and DAS 28($r = -0.36$, $p<0.05$). For total cholesterol, negative correlation($r= -0.17$) was seen though not significant statistically. Mullick et al (2014)[22] found a significant inverse correlation between HDLc and DAS28($r = -0.35$,$p<0.01$).

The overall findings of the present study were found to be at par or close to the findings of most of the earlier workers in this field. Our study reveals that the lipid profile is altered in Rheumatoid arthritis characterised by low total cholesterol (TC), HDL and elevated triglycerides. Futher, active disease was associated with lower levels of TC and HDL. An inverse correlation was seen between HDLc and disease activity (DAS 28); patients with high DAS-28 scores had lower values of HDLc.

The cause of the derangement in the lipid profile cannot be ascertained for sure. Inflammation as supported by high levels of CRP as well as disease activity might be responsible. Ernest Choy et al (2014)[23] have suggested that inflammation in RA could lead to lipid changes probably by suppression of the reticuloendothelial system and reduced low-density lipoprotein (LDL) particle synthesis. It is possible that under high inflammatory burden, excessive APR (acute phase reactants) production may impair trafficking of cholesterol in the liver or impede normal cholesterol production. Additionally, CRP mediates the uptake of LDL and oxidized LDL by macrophages, induces LDL deposition and increases LDL uptake by hepatocytes. The inflammatory burden in RA is associated with qualitative as well as quantitative changes in lipoproteins.

RA is associated with increased levels of IL 6 and TNF α. IL- 6 may lead to decreased levels of total cholesterol as suggested by Hashizume and Mihara(2011)[24]. TNF-α increases hepatic lipogenesis leading to hypertriglyceridemia(Steiner 2009)[25]. The reduced HDL-C in RA patients may be due to increased activity of cholesterol ester transfer protein (CETP) as hypothesised by Georgiadis et al(2006)[11] .

Conclusion:-

Our study reveals altered lipid profile in Rheumatoid Arthritis patients characterized by low total cholesterol, HDLc and elevated triglycerides. Further in active cases the mean serum level of total cholesterol was significantly lower than cases in remission. HDL cholesterol was significantly lower in active cases than those in remission. A significant negative correlation was seen between HDLc and DAS28.

Inflammation in RA is likely to alter the lipid profile in patients. Low HDL cholesterol is a strong predictor of cardiovascular events whereas raised triglycerides is atherogenic (Sattar et al)[26].Cardiovascular morbidity and mortality is enhanced in RA and there is evidence that dyslipidemia is a risk factor.

However further studies with large sample size and longer duration might be of help to explore this area of RA in the light of autoimmunologic response so as to predict the alterations of the parameters assayed as predictive indices.

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