Serum Lipids in Patients with Active Rheumatoid Arthritis And It's Relation to Drug Therapy

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Summary:

Objective *To detect the changes in serum Lipids among Iraqi patients with active Rheumatoid Arthritis (RA) and the effects of drug therapy.*

Patients and methods *Fifty Iraqi patients with untreated active Rheumatoid Arthritis and 50 matched healthy control were studied with concentration on estimation of fasting serum Lipid profile which is repeated after 3month treatment with different disease modifying anti Rheumatic drugs (DMARDs) regimens.*

Results *Fifty Iraqi patients were included in this prospective study 47 females (94%) and 3 males (6%). The mean age of patients was (45±3.20).*

fifty healthy individuals were included in this study as a control group 45 females (90%) and 5 males (10%) the mean age of the control group was (44.9±2.9).

Our results showed a significant reduction of VLDL, LDL, HDL, serum cholesterol and serum triglyceride in-patients with active RA (p=<0.05, 0.001, 0.001, 0.001 and 0.018 respectively).

There was a significant relationship found between ESR and VLDL (P<0.05), serum triglyceride (P<0.04) and serum cholesterol (P<0.01). And there was a significant relationship between serum lipids and articular index VLDL (P<0.05), serum cholesterol (P<0.01) and TG (P=0.01).

After 3-months treatment with Methotrexate or Methotrexate + Chloroquine ± large dose steroid or Chloroquine alone.

There was a significant reduction of inflammatory activity and serum lipids return to levels similar to that of control group.

Conclusions:

The dyslipidemia associated with active RA characterized by low serum lipids and can be normalized by controlling disease activity with antirheumatic drugs including steroids.

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Introdution

Rheumatoid Arthritis (RA) is a chronic inflammatory systemic disease that produces its prominent manifestation in the diarthrodial Joints(1).

Lipids are a heterogenous group of compounds which are relatively insoluble in water but dissolve in non polar organic solvents such as Chloroform, the major lipids found in Blood are Cholesterol. Triglyceride, Phospholipids and non esterified Fatty acids, because the lipids are insoluble in water, they are transported from the circulation only if they become associated with specific proteins to form a lipoprotein[2,3].

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Fasting serum Cholesterol (N: 150-240 mg/dl)
Fasting serum Triglyceride (TG) (N: 60-190 mg/dl)
Fasting high density Lipoprotein (HDL) (N: 35-75 mg/dl)
Fasting low density Lipoprotein (LDL) (N: 108-188 mg/dl)
Fasting serum very low density Lipoprotein (VLDL) (N: less than 40 mg/dl).
Atherogenic index = serum Cholesterol /HDL Cholesterol=(N: less than 3.5)[4,5]

There is growing evidence that inflammation plays a role in the initiation and progression of Atherosclerosis[9] and a similarity between Rheumatoid synovitis and Atherosclerotic plaque has been noted[5].

It is postulated that the systemic inflammation associated with RA acting either in isolation or in senergy with traditional and /or novel risk factors [6].

This study was undertaken to detect the changes in serum Lipoproteins in Iraqi patients with untreated active RA and its relation to disease activity and the effect of drug therapy.

Patients and Methods

This prospective study comprised 50 Iraqi patients Fulfilling the ACR criteria for the diagnosis of RA[7]. data on each classification criteria were collected and complete clinical examination was done for all of them.

All patients have active disease. Who are selected not on non steroidal anti-inflammatory drugs for at least 48 hours and not taken a disease Modifying Anti Rheumatic drugs (DMARDs) for at least 3 months.

Another 50 healthy individuals matched for age and sex were collected serving as a control group.

Blood samples were taken from individuals in both groups after an overnight fasting for 18 hour for estimation of serum cholesterol, LDL, VLDL HDL and TG. And repeated after 3 months treatment with different DMARDs for 38 patients (7 patients not complete the study for unknown reason and 5 patients on irregular treatment), the patients after treatment are divided into 5 groups according to the type of drug therapy.

Group – 1: represents patients who were treated with methotrexate (MTX) only and they are (9) patients.

Group- 2: represents patients who were treated with MTX + chloroquine and they are (11) patients.

Group-3: represents patients who were treated with MTX + intravenous (i.v) Methyl prednisolone(mp) (they receives 500 mg of Methyl prednisolone given for 3 successive days) and they were (6) patients.

Group-4: represents patients who were treated with MTX + chloroquine + intravenous (i.v) Methyl predinosolone (MP) and they were(8) patients.

Group - 5: represents patients who were treated with chloroquine only and they are (4) patients only.

laboratory investigations which includes : Blood urea, serum creatinine, Liver enzyme, Rheumatoid factor (RF), Hemoglobin (Hb) were done in Laboratory Teaching Center, X-ray was done in Radiology Department of Baghdad Teaching Hospital.

Patients and individuals with diabetes, hypertension hypothyroidism, malignancy, chronic renal railure, chronic Liver disease, familial hyper Lipidemia, smokers as well as patients on B – blockers, thiazide diuretics, contraceptive drugs and lipid lowering agents were excluded from the study.

Results

The characteristics of both RA patients and controls are shown in table(1), there were 50(47 females and 3 males) patients with RA who fulfilled the ACR (American College of Rheumatology) criteria for the classification of RA and 50 (45 females and 5 males) individuals in the control group.

The mean age for RA patients and controls were 45± 3.2 (range 28-60 years) and 44.9±2.9 (range 25-60 years) respectively .

The disease duration for patients was 10.4± 8.0 years

The body mass index (Kg/m^2) were 23.5±3.5 and 23.3±3.1 for patients and controls respectively.

Rheumatoid factor (RF) was positive in 37(74%) patients with RA .

ESR(mm/h) was 65.3±4.8 and 15.4±1.8 for patients and controls respectively.

Hemoglobin (Hb) levels were 10.5±0.23 and 12.2±0.16 for patients and controls respectively.

The characteristics of 50 patients with RA and 50 healthy individual are shown in table (1).

Table(1) characteristics of RA patients and controls

Parameter	RA patients N=50 No.(%)	Controls N=50 No.(%)	p. value
1-Age mean (years) Range (years)	45.0±3.2 28-60	44.9±2.9 25-60	Ns
2-Gender female(F) male(M)	47(94) 3(6)	45(90) 5(10)	- -
3-Disease duration (years)	10.±8.0	-	-
4-BMI(Kg/m^2)	23.5±3.5	23.3±3.1	NS
5-RF positvity(%)	31(74%)	-	-
6-ESR (mm/h)	65.3±4.8	15.4±1.8	<0.001*
7-Hb (gm/dl)	10.5±0.232	12.2±0.16	<0.001*

Values are the (mean ±SD).,ESR = Erythrocyte Sedimentation Rate; Hb= hemoglobin ; BMI = body mass index; RF= Rheumatoid factor.

Ns=not significant.

The serum lipid levels in RA patients and controls are seen in table (2).

VLDL levels were reduced by 30% in patients with active RA compared to control group and the differences were statistically significant (P<0.05) .

LDL levels were reduced by 25% in RA patients compared with control group ant the differences were statistically significant (P<0.001).

HDL levels were reduced by 25% in RA patients compared to control group and the differences were statistically significant (P<0.001).

Serum cholesterol levels were reduced by 30% in RA patients compared to control group and the differences were statistically significant (P<0.001).

Serum Triglyceride levels were reduced by 15% in RA patients compared to control group and the differences were statistically significant (P= 0.018).

Table (2) serum Lipoproteins levels (mean ± SD) in patients with RA (n=50) and controls

Lipid profile	Individuals in both groups		P- value
	RA patients (n=50)	Controls (n=50)	
VL DL	12± 1.5	17± 0.8	< 0.05*
LDL	122±3.8	166± 3.1	<0.001*
HDL	44± 1.9	58±1.9	<0.001*
CHOL.	138± 3.2	293±3	<0.001*
TG	121± 4	149±4.4	0.018*

By using a correlation analysis; there was a significant relationship found between ESR and VLDL (p<0.05), and serum TG (P<0.04) and serum cholesterol (P<0.01).

There were a significant relationship between Lipids and articular index, VLDL (P<0.05), serum cholesterol (p=<0.01) and TG (p=0.031) .

Also there was significant relationship between serum Lipids and Hb level VLDL (P=0.049), LDL (p<0.04) . After 3 month treatment with different DMARDS the results were the following;

In group 1 (n =9) who recieved MTX only there were a significant Increase in VLDL (p<0.05), LDL (p = 0.003), HDL (P = 0.01) , serum cholesterol (p = 0.021) and serum Triglyceride (p = 0.023) as shown in table (3A) .

Table (3A)., serum lipoprotein levels (mean ± SD) in (9) patients with RA before and after treatment with MTX only .

Lipid profile	Before treatment	After treatment	p-value
VLDL	11±4	18±6	<0.05*
LDL	140±13	158±11	0.003*
HDL	40±15	58±19	<0.01,*
CHOL	204±18	234±12	0.021*
TG	124±18	160±22	0.023*

Values are (mean ± SD)

In group- 2 (n =11) which represents patients who were treated for 3months with MTX + chloroquine ; there were a significant increase in all serum Lipoprotein ; VLDL (p< 0.05), LDL (0.001), HDL (p = 0.021) serum cholesterol (p = 0 716) and serum TG (p<0.05) . as shown in Table (3B).

Table (3B) . serum Lipoprotein levels (mean ± SD) in (11) patient with RA before and after treatment with MTX+ chloroquine.

Lipid profile	Before treatment	After treatment	p-value
VLDL	13±6	21±7	<0.05*
LDL	121±13	147±17	<0.001*
HDL	39±6	52±5	<0.021,*
CHOL	221±13	230±13	0.716
TG	133±16	148±14	<0.05*

Values are (mean ± SD)

In group- 3 (n=6) which represents patients whom they were treated with MTX + i.v Mp , there were a significant increase in all serum lipoprotein levels VLDL (p=0.031), LDL (p=0.002), HDL (p=0.016) , serum cholesterol (p=0.003) and TG (p=0.040) as shown in table (3c).

Table (3c) : the serum lipoprotein levels in (6) patients with RA before and after 3 month treatment with MTX+i.v MP.

Lipid profile	Before treatment	After treatment	p-value
VLDL	12±9	26±11	0.031*
LDL	138±13	150±16	0.002*
HDL	49±6	53±18	0.016,*
CHOL	44±8	238±13	0.003*
TG	208±16	152±20	0.0461*

Values are (mean ± SD)

In group- 4 (n=8) which represents patients whom they were treated with MTX + chloroquine + i.v MP; there were a significant increase in serum lipoprotein levels VLDL (p<0.05), LDL(p=0.019), HDL (p=0.015) cholesterol (p=0.0886) and TG (p<0.05) as shown in table (3D).

Table (3D); serum lipoprotein levels in (8)patients before and after treatment with MTX + chloroquine + i.v mp.

Lipid profile	Before treatment	After treatment	p-value
VLDL	12±7	28±8	<0.05*
LDL	116±11	150±17	0.019*
HDL	38±5	51±9	0.015,*
CHOL	186±13	222±11	0.0886
TG	128±12	141±14	0.0461*

Values are (mean ± SD)

In group- 5(n=4) which represents patients who treated with chloroquine only; there were a significant changes in VLDL ($p< 0.05$) LDL (0.015), HDL ($p=0.018$), cholesterol ($p=0.062$) and TG ($p<0.05$) as shown in table (3E).

Table (3E); the serum lipoprotein levels in(4)patients with RA before and after treatment with chloroquine.

Lipid profile	Before treatment	After treatment	p-value
VLDL	12±3	28±8	<0.05*
LDL	106±11	150±17	0.015*
HDL	48±5	51±9	0.018*
Chol.	214±13	223±11	0.062
TG	123±12	143±14	<0.05*

Values are(mean ±SD)

There were a significant improvement of disease activity after treatment for 3 months with MTX, chloroquine or combination of both and/or i.v MP as shown in table (4).

Table (4) Clinical and laboratory measures of disease activity (mean±SD) for all RA patients before and after 3 months treatment with different DMARDS.

Parameter	Before treatment (n=50)	After treatment (n=38)	p-value
ESR(mm/h)	65±4.8	35±5.2	<0.001*
Tender joint count	18.5±7.9	4	<0.001*
Swollen joint count	13.2±5.6	3	<0.001*
Duration of morning stiffness (minutes)	90	30	0.003*

Values are (mean ± SD)

Discussion

In this study we showed a considerable changes in serum lipid levels in patients with active RA, these changes are characterized by low serum cholesterol, TG, VLDL, LDL and HDL; which is statistically significant and in accordance with results of other studies [8].

During inflammation there are massive shifts in the synthesis and secretion of proteins in the liver to allow for greatly increased production of acute-phase proteins at the cost of the synthesis of other protein and The liver is also a key organ in lipoprotein metabolism and a reduced production of lipoproteins in the liver in response to inflammatory mediators is possible[9].

The changes in serum lipoproteins in patients with active RA include an increase in sympathetic over activity due to pain (stress-mediated changes) but the pattern of serum lipids changes are different from those observed in our patients and consist of elevated LDL, VLDL, with hypercholes-terolemia and hypertriglyceridemia. [9].

Our study showed a significant decrease in HDL levels, which is unfavorable profile with regard to cardiovascular riske [10]

Accelerated atherosclerosis in RA patients could be attributed to other atherogenic lipoprotein sub-fractions like the small. LDL with high affinity for arterial matrix component[11] or to certain inflammatory mediators or some acute phase proteins (the high sensitivity c-reactive protein and serum amyeloid-A protein)[12].

Our results are not consistent with results of some studies regarding changes in serum cholesterol and LDL[13] (as they reported an elevation in both).

In the beginning of our study we instruct patients to not take NSAIDs 48h before blood sampling the influence of these agents can not be ruled out fully, although studies showed that NSAIDs has no significant effect on serum lipids[10]. On other hand the long term use of NSAIDS may contribute to an underestimation of the true vascular risk through its antiplatelet effect or through its correlation with hypertension [14].

After 3 months of treatment with different DMARDs we reported a significant increase in all serum lipids towards the normal levels.

In patients who received chloroquine alone or in combination with MTX and /or steroids; the changes in serum cholesterol although statistically not significant but data showed that is also increasing towards normal levels; these results are in consistent with results of other studies[15,16,17] while it is different with results of other study [18].

The variation could be attributed to short period of treatment.

The physical activity has to be considered in the interpretation of the drug mediated effect on lipoproteins. studies showed that exercise increase HDL in men and to less extent in women[19], but most of our patients were housewives, and they have more or less a similar degree of physical activity.

The improvement in serum lipids are parallel to improvement in inflammatory activity, this results are similar to other studies [20].

Conclusion

The dyslipidemia associated with active RA characterized by low serum lipids and can be normalized by controlling disease activity with antirheumatic drugs including steroids.

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