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Alterations in Serum Lipids in Lepromatous Leprosy Patients with and without ENL Reactions and their Relationship to Acute Phase Proteins[1]

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Leprosy is a chronic infectious disease which is characterized by a wide spectrum of clinical forms depending upon the host's immune response ([26]). Patients with lepromatous (LL/BL) disease have impaired cell-mediated immunity (CMI) and are usually unresponsive to challenge with *Mycobacterium leprae* antigens. This is in contrast to tuberculoid (TT/BT) leprosy patients who have pronounced CMI ([26]). Additionally, leprosy patients can develop acute reactional complications which are characterized as reversal reactions (RR) or erythema nodusum leprosum (ENL). ENL develops more frequently toward the lepromatous pole and is characterized by symptoms resembling serum sickness ([41]) and is accompanied by both local and systemic inflammation.

The host response to infection and inflammation is accompanied by changes in the hepatic synthesis of a number of acute phase proteins that play a crucial role in maintaining homeostasis during the course of infection and inflammation ([17, 28]). C-reactive protein (CRP) and serum amyloid A (SAA) are two such proteins whose levels are often elevated 10- to 100-fold in humans during acute inflammatory episodes and are generally lower in chronic inflammatory conditions ([37]). Hussain, *et al.* ([14]) have recently shown that the levels of CRP and SAA are markedly elevated in ENL patients as compared to non-reactional lepromatous patients and endemic controls, indicating that the synthesis of acute phase proteins is stimulated during ENL reactions.

The host response to bacterial, viral or parasitic infections is also accompanied by several alterations in lipid metabolism, such as increased serum triglyceride (TG) levels, enhanced hepatic lipid synthesis, and a decrease in lipoprotein lipase activity ([2, 6, 18, 34]). Decreased serum cholesterol levels also have been reported during infection in humans ([2, 35]). It has been proposed that, in addition to changes in acute phase protein synthesis, changes in lipid and lipoprotein metabolism are also a part of the acute phase response ([12]). The stimulation of acute phase protein synthesis and the changes in lipid metabolism during infection are now thought to be mediated by cytokines which modulate the immune and inflammatory responses. It has been shown that tumor necrosis factor (TNF), interleukin-1 (IL-1) and IL-6 induce the synthesis of acute phase proteins *in vivo* and *in vitro* ([25, 32]). Similarly TNF, IL-1 and IL-6 increase hepatic lipid synthesis and decrease lipoprotein lipase activity resulting in an increase in serum TG levels ([11, 21, 22]). TNF also has been shown to decrease HDL-cholesterol levels in rodents and primates ([22]). Serum TNF levels are markedly elevated during ENL, and TNF also has been implicated in the pathogenesis of ENL ([24, 27, 36]).

SAA is secreted mainly by hepatocytes and is associated with HDL-cholesterol in the circulation ([20]). Although the primary function of SAA has not been characterized, it has been proposed that SAA represents a signal to redirect HDL to sites of inflammation where cholesterol is taken up by

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TABLE 1. *Characteristics of leprosy patients presenting with ENL reaction.*

No.	Age (yrs)	Sex	Diagnosis[a]	BI[b]	No. previous episodes	Time since reaction (days)	Prereaction treatment[c]
1.	26	M	LL	5	5	NA	Untreated
2.	26	M	LL	4	0	14	DDS/B663
3.	30	M	LL	5	3	5	Untreated
4.	23	M	LL	3	0	7	MDT
5.	47	M	LL	5	2	4	MDT
6.	50	M	LL	3	0	NA	B663/DDS
7.	43	M	LL	0	0	NA	MDT
8.	30	F	LL	4	2	3	DDS/B663
9.	30	M	LL	5	4	12	MDT
10.	28	M	LL	3.5	0	3	MDT
11.	26	F	LL	4.5	1	5	DDS
12.	24	M	LL	3.5	0	3	MDT
13.	17	F	LL	4	0	10	DDS/B663
14.	27	F	LL	4	0	5	DDS
15.	64	M	BL	0	0	7	DDS/B663

[a] LL = Lepromatous leprosy; BL = borderline lepromatous leprosy.
[b] BI = Bacterial index at time of diagnosis.
[c] MDT = Multidrug therapy; DDS = dapsone; B663 = clofazamine.

macrophages ([15]). Since SAA and HDL metabolism are closely related and changes in serum lipid concentrations are commonly observed during acute infections, this study was designed to determine whether a chronic infection like leprosy produces any changes in serum lipid concentrations.

MATERIALS AND METHODS

Study subjects. The study group consisted of 15 histologically confirmed leprosy patients with clinical features of ENL, including tender papules, nodules and fever. Other symptoms recorded included arthritis (61%), neuritis (67%) and iritis (18%). The mean age of the ENL patients was 32 years (range 17–64 years) with a male : female ratio of 3:1. The clinical characteristics, bacterial index (BI), previous history of ENL episodes and treatment status of ENL patients before reaction is presented in Table 1. All of the ENL patients included in this study had typical ENL on histology including polymorphonuclear neutrophil infiltrate into the dermis and subcutis of the lepromatous leprosy lesions ([14]). All patients had severe ENL reactions and needed hospitalization, and were treated symptomatically with analgesics and nonsteroidal antiinflammatory drugs. None of the patients with ENL received thalidomide treatment and only two received steroid treatment.

The study group also included 14 untreated leprosy patients who were classified as lepromatous (LL) (N = 9) or borderline lepromatous (BL) (N = 6) according to the standard criterion of Ridley and Jopling ([33]). These patients were considered stable lepromatous patients since there was no known history of any previous reactional episodes. The control group included 18 healthy endemic controls (EC) (mean age 30 years; range 25–60 years) who had no known contact with leprosy patients and were employed at The Aga Khan University Medical College.

Serum lipid concentrations. Five ml of blood was collected in glass tubes without any anticoagulant. In ENL patients blood samples were collected before the initiation of treatment. Blood was kept at room temperature for 1–2 hr and then overnight at 4°C. The blood samples were centrifuged to remove red blood cells and the serum was separated. The serum was further aliquotted in small volumes and stored at −70°C. Serum triglyceride and total cholesterol levels were measured by standard enzymatic assays as described earlier ([23]). Serum HDL-cholesterol was measured enzymatically after precipitation of LDL and VLDL with heparin-manganese chloride ([1]). LDL-cholesterol levels were determined by the method of Friedwald, *et al.* ([8]).

Quantitation of SAA and CRP concentrations. SAA levels were measured by using

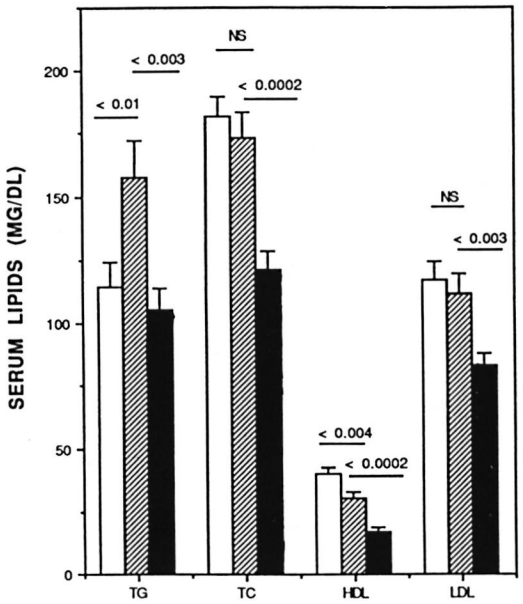

FIG. 1. Serum triglyceride (TG), total cholesterol (TC), HDL and LDL levels in control subjects (N = 18), untreated lepromatous leprosy (LL/BL) (N = 14) and ENL (N = 15) patients. Serum lipid levels were measured using standard enzymatic assays as described under Materials and Methods. □ = Controls; ▨ = LL/BL; ■ = ENL.

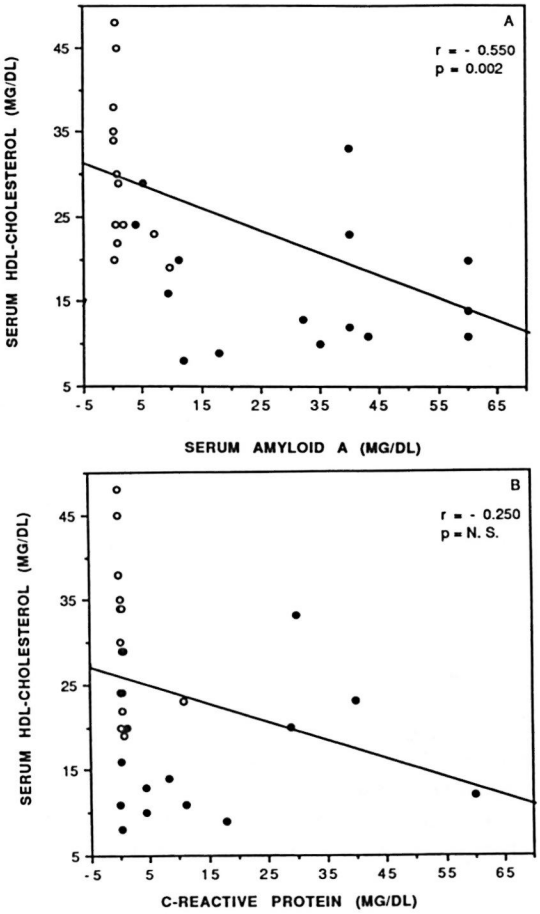

FIG. 2. **A** = Correlation between HDL-cholesterol and serum amyloid A levels and **B** = correlation between HDL-cholesterol and C-reactive protein levels in nonreactional patients. ○ = Lepromatous disease (N = 14); ● = ENL patients with lepromatous disease (N = 15). Serum HDL, SAA and CRP levels were measured as described under Materials and Methods. Linear regression analysis was used to determine their r and p values.

a competitive inhibition ELISA with a goat anti-human SAA and an SAA-alkaline phosphatase conjugate. The ability of samples to inhibit conjugate binding was compared with that of the standards as described in detail earlier ([14, 31]). CRP levels were measured by a similar assay in which plates were coated with affinity purified rabbit antibodies to human CRP as described earlier ([10, 14]).

Statistical analysis. The data are presented as mean ± S.E.M. The level of significance between control and patient populations was determined by Student's unpaired *t* test. p Values of <0.05 were considered statistically significant. Linear regression analysis was used to determine the correlation between acute phase proteins and serum lipid concentrations.

RESULTS

Serum lipid levels in LL/BL and ENL patients. Serum triglyceride, total cholesterol, and HDL- and LDL-cholesterol levels were measured in patients with lepromatous (LL/BL) disease without any clinical sign of reaction and in leprosy patients who had clinical signs of ENL and were also histologically confirmed for ENL. Serum lipid levels in these patients were compared to a group of healthy endemic controls.

The data presented in Figure 1 compare serum lipid levels in the controls, LL/BL and ENL patients. Serum triglycerides were increased by 37% over controls in LL/BL patients (controls 114.7 ± 9.7; LL/BL 157.5 ± 14.5; $p < 0.01$). There was no significant difference in serum total or LDL-cholesterol concentrations between control and LL/BL patients; whereas HDL-cholesterol levels were significantly decreased in LL/BL pa-

TABLE 2. *Correlation between acute phase proteins and serum total, HDL- and LDL-cholesterol concentrations in LL/BL and ENL patients.*[a]

Parameters	r Value	p Value
SAA vs total cholesterol	−0.533	0.002
SAA vs HDL-cholesterol	−0.550	0.002
SAA vs LDL-cholesterol	−0.422	0.02
CRP vs total cholesterol	−0.275	N.S.
CRP vs HDL-cholesterol	−0.250	N.S.
CRP vs LDL-cholesterol	−0.245	N.S.

[a] The correlation between serum acute phase proteins and total, HDL- and LDL-cholesterol concentrations was determined by linear regression analysis. N = 29 (14 LL/BL and 15 ENL) for SAA, CRP, total, HDL- and LDL-cholesterol measurements.

tients (LL/BL 30.4 ± 2.4; controls 40.2 ± 2.1; $p < 0.004$).

We next compared serum lipid concentrations between patients with stable lepromatous disease and ENL reaction (Fig. 1). Serum triglyceride levels were significantly lower in ENL patients (ENL 105.6 ± 8.3; LL/BL 157.5 ± 14.5; $p < 0.003$). Serum total cholesterol levels were decreased by 30% in ENL patients (ENL 121.3 ± 7.0; LL/BL 173.5 ± 10.3; $p < 0.0002$). Similarly, LDL-cholesterol levels were significantly lower in ENL patients compared to LL/BL patients ($p < 0.003$). Serum HDL-cholesterol levels, which are already lower in LL/BL patients compared to controls, further declined by 44% in ENL patients (ENL 16.9 ± 2.0; LL/BL 30.4 ± 2.4; $p < 0.0002$). Thus, as compared to controls, a net decrease of 58% in HDL-cholesterol levels was observed in ENL patients (ENL 16.9 ± 2.0; controls 40.2 ± 2.1; $p < 0.0001$).

Correlation between acute phase proteins and serum lipid concentrations. We have shown previously that both SAA and CRP levels were significantly higher in patients with ENL compared to patients with lepromatous disease and endemic controls ([14]); whereas the differences between LL/BL patients and endemic controls were not statistically significant. Since SAA and CRP have been shown to interact with lipoproteins ([15, 29]), we therefore investigated the relationship between lipoproteins and acute phase proteins. The correlation between HDL-cholesterol and SAA or CRP concentrations in LL/BL and ENL patients is shown in Figure 2. The data presented indicate that there is a significant negative correlation ($r = -0.550$, $p = 0.002$) between HDL-cholesterol and SAA concentrations in both stable lepromatous (LL/BL) patients and ENL patients (Fig. 2A). In the stable LL/BL group, 6 of 14 patients had HDL-cholesterol concentrations of <25 mg/dl; only 2 of 14 had a SAA concentration of >3 mg/dl (the upper limit of normal). On the other hand, 13 of 15 patients in the ENL group had HDL levels of <25 mg/dl which is consistent with the very high SAA concentrations in the ENL group. Furthermore, when we calculated the SAA/HDL ratio for individual patients in stable lepromatous and ENL groups, the mean SAA/HDL ratio was approximately 30-fold higher in patients who developed ENL reaction (LL/BL 0.075 ± 0.04; ENL 2.26 ± 0.42; $p < 0.001$). On the other hand, the correlation between CRP and HDL-cholesterol concentrations in LL/BL and ENL patients was not statistically significant (Fig. 2B).

Table 2 summarizes the correlations of SAA and CRP with total, HDL- and LDL-cholesterol. A significant negative correlation was also observed between SAA and total or LDL-cholesterol concentrations; whereas there is no statistically significant correlation between CRP and total or LDL-cholesterol concentrations. There was no correlation between the age of the patients and serum lipids or acute phase protein concentrations. Similarly, there were no significant differences in the levels of serum lipids or acute phase protein concentrations in ENL patients presenting with or without arthritis or neuritis.

DISCUSSION

Disturbances of lipid and lipoprotein metabolism are commonly observed in a variety of bacterial, viral and parasitic infections in experimental animal models as well as humans ([2, 6, 18, 34]). In this study, we have shown that there are marked changes in serum lipid concentrations in patients with lepromatous disease and ENL reactions. The most significant finding in LL/BL patients was an increase in serum triglyceride and a decrease in HDL-cholesterol levels. These results are comparable to changes in lipid metabolism in other chronic parasitic and viral infections such as visceral leishmani-

asis or acquired immunodeficiency syndrome where patients have been shown to have higher serum triglyceride and lower HDL-cholesterol levels ([4, 13]).

ENL patients had markedly lower total, LDL- and HDL-cholesterol levels as compared to endemic controls. A comparison of lipid levels between LL/BL and ENL patients also reveals that the decreases in serum lipid concentrations were more pronounced in ENL patients. Since ENL is characterized by a severe acute inflammatory reaction and inflammation has been associated with perturbations in lipid metabolism ([5]), it is likely that the changes in serum lipid concentrations during ENL may be a part of the acute inflammatory process of the ENL reaction.

Acute phase response represents the body's reaction toward infection, inflammation or injury, and is generally characterized by stimulation of the acute phase protein synthesis in the liver and systemic changes such as fever ([17, 28]). Recently, it has also been proposed that changes in lipid metabolism during infection or inflammation are also a part of the acute phase response ([12]). SAA is an acute phase protein and is associated with HDL-cholesterol in the circulation ([20]). Although SAA has been characterized as a very sensitive indicator of acute inflammation ([39]), no specific function has been attributed to it. It has been postulated that SAA may act as a signal to redirect the metabolism of HDL toward macrophages ([15]). Recent studies from this laboratory have shown that SAA levels are increased severalfold in ENL patients when compared with endemic controls and LL/BL patients ([14]).

We now demonstrate that there is a significant negative correlation between serum HDL and SAA levels in both nonreactional and reactional LL/BL patients (Fig. 2A). A majority of patients with high SAA levels in both groups had lower HDL-cholesterol levels. It can be speculated that a profound increase in SAA during ENL reaction may contribute to a decrease in HDL levels by redirecting the metabolism of HDL from hepatocytes toward macrophages at the site of inflammation. There is also a significant negative correlation of total and LDL-cholesterol with SAA levels. The redirection of lipid metabolites from hepatocytes to macrophages may be partly to assist the growth and multiplication of *M. leprae* which is surrounded by a glycolipid coat ([30]). This redirection of lipid metabolites also may be responsible for the development of foamy macrophages which are nonfunctional. The lipids in the foamy macrophages can be derived from both the bacilli as well as the host. However, it is not possible to determine the exact source of origin of lipids in macrophages in an *in vivo* study. Kisilevsky, *et al.* ([16]) have shown that SAA-rich HDL has a 3- to 4-fold higher affinity for macrophages compared to a much lower affinity for hepatocytes. A recent study that used recombinant SAA showed that at the sites of inflammation proteolytic enzymes cleaved the SAA-HDL complex and that the free SAA was involved in enhancing the migration of leukocytes ([3]), also a hallmark of ENL histopathology ([14]). The free cholesterol released by such action can then be taken up by the macrophages which ultimately become foam cells ([9, 19]). Foam cells are also a prominent histological feature in skin biopsies from lepromatous leprosy and ENL lesions ([14, 40]).

Since in the circulation SAA is bound to HDL, we calculated SAA/HDL ratios in individual nonreactional and reactional LL/BL patients. The mean SAA/HDL ratio is almost 30-fold higher in ENL patients compared to stable LL/BL patients, suggesting that the ratio of SAA/HDL may provide an even more sensitive marker than SAA alone for the diagnosis of ENL reactions in leprosy patients.

The major function of CRP is believed to be opsonization of microorganisms, foreign particles and immune complexes, and facilitation of their clearance by phagocytic cells ([17, 28, 37]). CRP also is known to interact with lipoproteins. It has been shown that CRP binds to triglyceride-rich and apo-B containing particles ([29]). Our results indicate that unlike SAA and HDL, there is no significant correlation between CRP and total, HDL- or LDL-cholesterol concentrations, suggesting that the effect of SAA on cholesterol metabolism is highly specific.

Although we did not address the issue of the mechanisms and mediators involved in producing the changes in serum lipid levels in patients with lepromatous disease and ENL reactions in this study, based on avail-

able experimental data one can speculate that these changes may be related to cytokines produced during leprosy and ENL reaction ([26]). TNF is markedly elevated during ENL ([24, 27, 36]) and is thought to play a major role in the pathogenesis of ENL ([26]). It also has been shown that TNF is a key mediator of changes in triglyceride and cholesterol metabolism produced during infection ([23]). Moreover, several other cytokines, including IL-1 and IL-6 which are produced concomitantly, also exert significant effects on lipid metabolism ([22]). TNF has been shown to increase serum triglyceride and lower HDL-cholesterol levels in rodents as well as in primates ([11, 21, 22]). In HepG2 cells, TNF induced LDL receptor mRNA and increased the binding of LDL to its receptors ([38]). Both of these mechanisms could increase LDL clearance and contribute to decreased serum LDL and total cholesterol levels. TNF is one of several cytokines which are involved in stimulating the synthesis of a variety of acute phase proteins including SAA ([25]). A close correlation between CRP levels and TNF has recently been shown in ENL patients ([7]). On the other hand it is also likely that other cytokines, such as IL-1, IL-6 or interferon-gamma which are also induced during leprosy and ENL reactions ([24, 26]), may be involved in producing the changes in serum lipid levels and in acute phase proteins in leprosy. Further studies are required to understand the role of cytokines in the metabolic disturbances and their relationship with the acute phase response during leprosy and reactional states.

SUMMARY

The concentrations of serum lipids were measured in patients with lepromatous (LL/BL) leprosy and erythema nodosum leprosum (ENL). The relationships between serum lipid levels and serum amyloid A (SAA) and C-reactive protein (CRP) were also examined in these patients. LL/BL patients had significantly higher serum triglyceride and lower HDL-cholesterol concentrations compared to the endemic controls. ENL patients had significantly lower total, HDL- and LDL-cholesterol levels compared to the endemic controls. The levels of all lipid metabolites also were significantly lower in ENL patients compared to LL/BL patients. The concentrations of SAA and CRP were markedly elevated in ENL patients but were not statistically different in LL/BL patients compared to control subjects. There was a significant negative correlation between SAA and HDL-cholesterol levels in both stable lepromatous and reactional (ENL) patients; there was no statistically significant correlation between CRP and HDL-cholesterol levels. SAA levels also had a significant negative correlation with total and LDL-cholesterol levels. Our results indicate that serum lipids are significantly altered in patients with lepromatous disease and ENL reaction. Our results also suggest that an increase in SAA levels may divert the metabolism of lipoproteins from hepatocytes toward macrophages, resulting in a decrease in serum lipoprotein levels.

RESUMEN

Se midió la concentración de lípidos en el suero de pacientes con lepra lepromatosa (LL/BL) y eritema nodoso leproso (ENL). También se examinaron las relaciones entre los niveles de lípidos en el suero y los niveles de amiloide A (SAA) y de proteína C reactiva (CRP). Comparados con los controles de zona endémica, los pacientes LL/BL tuvieron niveles significativamente más altos de triglicéridos y más bajos de HDL-colesterol. Los pacientes con ENL tuvieron niveles significativamente menores de colesterol total, de HDL-colesterol, y de LDL-colesterol que los controles de zona endémica. Los niveles de todos los metabolitos de lípidos también fueron significativamente menores en los pacientes con ENL que en los pacientes LL/BL sin reacción. Las concentraciones de SAA y de CRP en los pacientes con ENL estuvieron más elevadas que en el grupo control pero no fueron estadísticamente diferentes de las encontradas en los pacientes sin reacción. Tanto en los pacientes lepromatosos estables como en los reaccionales (ENL) hubo una correlación negativa entre los niveles de SSA y de HDL-colesterol pero no hubo ninguna correlación estadísticamente significativa entre los niveles de CRP y HDL-colesterol. Los niveles de SAA también mostraron una correlación negativa con los niveles de colesterol total y de LDL-colesterol. Nuestros resultados indican que los lípidos del suero están significativamente alterados en los pacientes con la enfermedad lepromatosa y reacción ENL. También sugieren que el incremento en los niveles de SAA puede desviar el metabolismo de lipoproteínas de los hepatocitos a los macrófagos dando como resultado una disminución en los niveles de lipoproteínas en el suero.

RÉSUMÉ

La concentration de lipides sériques a été mesurée chez des patients présentant une lèpre lépromateuse (LL/BL) et un érythème noueux lépreux (ENL). Les

relations entre les taux de lipides sériques, l'amyloide A sérique (SAA) et la protéine C-réactive (CRP) ont aussi été examinées chez ces patients. Les patients LL/BL avaient un taux sérique de triglycérides significativement plus élevé et des concentrations en HDL-cholésterol plus basses, que des témoins de régions endémiques. Les patients avec un ENL avaient des taux de cholésterol total, HDL- et LDL-cholestérol plus bas que les témoins des régions endémiques. Les taux de tous les métabolites lipidiques étaient également significativement plus bas chez les patients ENL par rapport aux patients LL/BL. Les concentrations de SAA et de CRP étaient élevées de façon marquée chez les patients ENL, mais n'étaient pas significativement différents chez les patients LL/BL par rapport aux témoins. Il y avait une correlation négative significative entre les taux de SAA et de HDL-cholestérol chez les patients lépromateux stables et les patients en réaction (ENL); il n'y avait pas de correlation statistiquement significative entre les taux de CRP et de HDL-cholestérol. Les taux de SAA avaient aussi une correlation négative significative avec les taux de cholestérol total et LDL. Nos résultats indiquent que les lipides sériques sont significativement modifiés chez les patients avec une maladie lépromateuse et une réaction ENL. Nos résultats suggèrent aussi qu'une augmentation des taux de SAA pourrait détourner le métabolisme des lipoprotéines des hépatocytes vers les macrophages, résultant en une diminution des taux de lipoprotéines sériques.

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