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Lipoprotein Peroxidation in Adult Psoriatic Patients

A. M. OFFIDANI[1], G. FERRETTI[2], M. TAUS[2], O. SIMONETTI[1], N. DOUSSET[3], P. VALDIGUIE[3], G. CURATOLA[2] and G. BOSSI[1]

[1]Institute of Dermatology, and [2]The Institute of Biochemistry, University of Ancona, Italy, and the [3]Institute of Biochemistry, CHU Rangueil, Toulouse, France

Psoriasis, a chronic inflammatory skin disease characterized by an aberration of lipid metabolism, has been associated with an increased risk for atherosclerosis. Since oxidatively modified lipoproteins are involved in the pathogenesis of atherosclerosis, we investigated the lipid composition and in vitro induced peroxidation of very low density lipoproteins (VLDL) and low density lipoproteins (LDL) from psoriatic patients. 11 male adult psoriatics and 16 male age-matched healthy subjects were studied. Lipid peroxidation of VLDL and LDL was performed by incubation with $CuSO_4$ for 24 h at 37°C. The compositional analysis showed a significant increase in tryglycerides and phospholipids, both in VLDL ($p < 0.05$) and in LDL ($p < 0.001$) from psoriatic patients, compared with controls. Moreover a significant increase in total cholesterol (TC) ($p < 0.01$) and apoprotein (P) ($p < 0.05$) was found in LDL from psoriatics. The levels of thiobarbituric acid reactive substances (TBARS), as a measurement of lipid peroxidation, were significantly higher in Ox-VLDL and in Ox-LDL from psoriatics ($p < 0.01$) than the corresponding values in controls. Moreover, basal values of TBARS were significantly higher in VLDL and LDL from psoriatic patients than those from controls. In conclusion, the lipoprotein compositional changes associated with the modifications of TBARS before and after Cu^{2+} treatment of lipoproteins may suggest an increased risk for atherosclerosis in adult psoriatic patients. ***Key words: psoriasis; low density lipoprotein; very low density lipoprotein; lipid peroxidation; atherosclerosis.***

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Annamaria Offidani, Ospedale Umberto I°, P.zza Cappelli 1, 60100 Ancona, Italy

The etiology of psoriasis, a chronic inflammatory skin disease characterized by an accelerated turnover of epidermal cells and an incomplete differentiation in lesional epidermis, is still unknown but genetic, metabolic and immunologic mechanisms have been suggested (1). At membrane level, modifications of phospholipid (PL) fatty acid composition with a significant increase in arachidonic acid (AA) in the plasma membrane of skin cells and erythrocytes of adult psoriatic patients (2) suggest an aberration in the lipid metabolism as a generalized phenomenon in psoriasis. The lipid compositional changes, as demonstrated in our previous studies, are associated with modifications of membrane fluidity in erythrocytes of adult and pediatric subjects (3, 4).

Changes in plasma lipid and lipoprotein composition in middle-aged male psoriatic patients (2) that include a tendency toward an increase in cholesterol and triacylglycerol, associated with very low density lipoproteins (VLDL) and a decrease in high density lipoprotein-cholesterol (HDL-C), also suggest that psoriasis may be linked to disorders of lipid metabolism (5). The modifications in plasma lipoprotein composition, more pronounced in patients with the severe form of the disease (5), may be related to the increased risk for atherosclerosis observed in adult psoriatic patients (6). In fact, many epidemiological studies have clearly demonstrated that the risk for coronary heart disease is positively correlated with low density lipoproteins (LDL) and plasma total cholesterol (TC) and negatively correlated with high density lipoproteins (7–8). Moreover, recent studies have demonstrated that also oxidatively modified lipoproteins play a key role in the pathogenesis of atherosclerosis (9–10).

To further investigate plasma lipoprotein alterations in psoriasis, we studied the chemical composition and the susceptibility to in vitro oxidation, triggered by copper ions, of VLDL and LDL isolated from adult psoriatic patients, compared with healthy adult subjects.

METHODS

Patients

We studied 11 male adult patients, affected by psoriasis. In all the patients the disease was moderate, stable, and of plaque type. Mean age was 58 ± 16 years. None of the patients had received any systemic or topical medication for at least 2 weeks preceding the study. The duration of the disease ranged from 5 to 30 years. None of the patients had a history of cardiovascular disease or familial hyperlipidemia, nor had a known diabetes mellitus and all had normal laboratory tests for liver and renal function.

The control group consisted of 16 healthy adult male subjects, of mean age similar to the psoriatic patients.

Isolation of VLDL and LDL and in vitro peroxidation

Human plasma VLDL and LDL were prepared by sequential ultracentrifugation (L70 Beckman Ultracentrifuge), according to Havel et al. (11) and they were dialysed against 150 mM NaCl before peroxidation treatment. The peroxidation of VLDL and LDL was performed as described previously (12).

500 µl of VLDL, with a protein concentration of 0.03 g/l, was incubated with 10 µM CuSO4 for 24 h at 37°C. LDL were incubated with copper ions (5 µM) for 24 h at 37°C.

The determination of peroxidation products was performed by evaluating thiobarbituric acid reactive substances (TBARS) as described by Yagy (13).

Chemical composition of lipoproteins

The levels of cholesterol (C), triacylglycerol (TG) and phospholipids (PL) in total plasma level and lipoprotein fractions were determined by enzymatic methods (14–16).

Protein concentration was determined as described by Lowry et al. using bovine serum albumin as standard (17).

Statistics

All the results are expressed as means ± SEM. Statistical differences between data from psoriatic patients and controls were determined according to Student's *t*-test.

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Table I. *Composition of VLDL and LDL from psoriatic patients and controls*

	VLDL	LDL
Cholesterol (mmol/l)		
controls (16)	0.6±0.5	4.1 ±2.54
patients (11)	1.5±1.2	9.67±3.41***
Phospholipids (mmol/l)		
controls (16)	0.4±0.3	1.3 ±0.83
patients (11)	1.1±0.7*	3.71±1.31***
Triacylglycerol (mmol/l)		
controls (16)	1.1±0.7	0.61±0.43
patients (11)	2.6±1.5*	1.30±0.69*
Proteins (g/l)		
controls (16)	0.2±0.2	1.54±1.01
patients (11)	0.3±0.3	2.97±0.97*

The values are expressed as means ± SEM; ***$p<0.01$, *$p<0.05$.

RESULTS

Lipoprotein composition

The contents in TG and PL were significantly increased in VLDL of psoriatic patients, compared with controls ($p<0.05$), while protein and cholesterol levels were not modified (Table I). Compositional changes have also been observed in LDL from psoriatic subjects, with a significant increase in TC and PL ($p<0.01$), TG ($p<0.05$) and P content ($p<0.05$) (Table I).

Lipoprotein peroxidation

The susceptibility of plasma VLDL and LDL derived from psoriatic subjects to in vitro oxidation with copper ions was compared with that of lipoproteins obtained from male adult controls. The levels of TBARS in VLDL and LDL from psoriatic patients were significantly higher compared with the corresponding values in lipoproteins from controls before chemical treatment (Table II).

In VLDL and LDL of controls, a significant increase in TBARS after incubation of lipoproteins with copper ions, demonstrates the efficacy of the peroxidation treatment (Fig. 1). A significant increase in TBARS in Ox-VLDL and Ox-LDL from psoriatic patients has also been shown, with respect to untreated VLDL and LDL (Fig. 1).

DISCUSSION

Psoriasis in middle-aged patients has been associated with alterations of plasma lipid levels (5). However, a detailed biochemical compositional study of plasma lipoproteins has not previously been carried out in psoriatic patients. In particular, the levels of PL and apoprotein that, at the lipoprotein surface, constitute the interphase between water and non-polar lipid core and which help to stabilize the characteristic structure of lipoprotein particles, has not been investigated previously. This interphase is directly involved in exchange processes between lipoproteins and cells (18).

The significant increase in TG content observed in the present study in VLDL and in LDL from psoriatics is in agreement with previous findings in adult and pediatric patients (5, 19). Moreover, a significant increase in PL has been observed in VLDL and in LDL from psoriatic subjects.

Table II. *Oxidative state of native VLDL and LDL in controls and patients*

Lipoprotein oxidation (nmol MDA/mg protein.

	VLDL	LDL
Controls	2.99±0.92	15.84±1.43*
Patients	9.87±3.00	35.22±4.74**

*$p<0.001$ and **$p<0.01$ vs controls.
Values are expressed as means ± SEM.

The regulation of lipid composition in lipoproteins involves complex mechanisms; crucial components are lipoprotein receptors in the liver and extrahepatic tissues that mediate the uptake and degradation of cholesterol-carrying lipoproteins (20). Changes in the transport of LDL receptors to the cell surface have been shown in psoriatic vis-à-vis normal skin (21). Moreover, a lowered LDL-receptor activity has been observed in cultured dermal fibroblasts isolated from the skin of psoriatic patients (22). The LDL receptor abnormalities, if confirmed in other psoriatic cells, could be involved in the changes in low density lipoprotein composition.

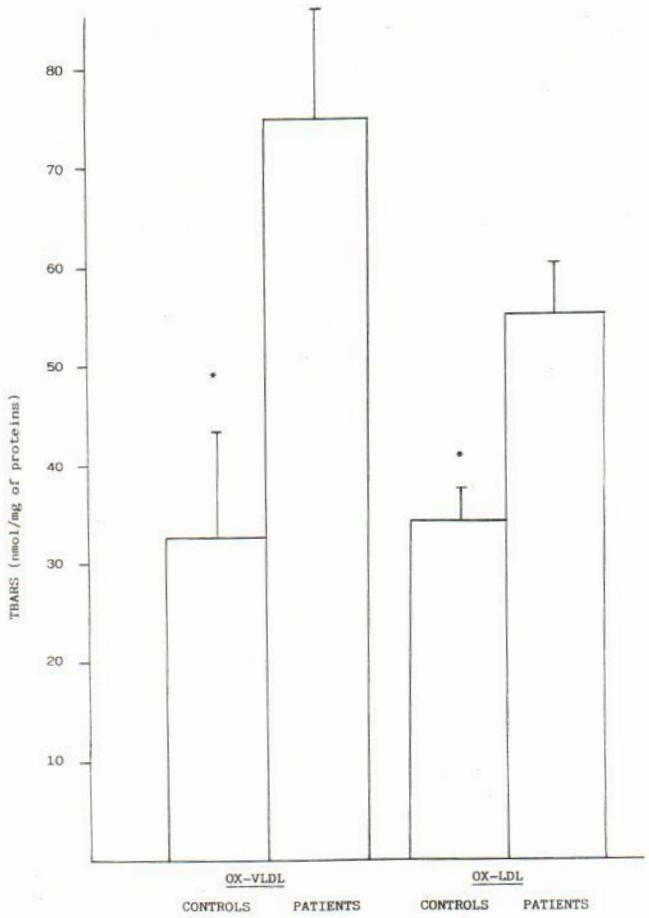

Fig. 1. TBARS content (nmol/mg of protein) in VLDL and LDL from controls and psoriatic subjects after incubation with copper ions ($p<0.01$).*

In lipoproteins from psoriatic patients the lipid compositional changes are associated with modifications of lipid peroxidation as demonstrated by the levels of TBARS, before and after Cu^{2+} treatment, that are significantly higher in VLDL and LDL of psoriatic subjects than in lipoproteins from controls. Lipoprotein oxidation is dependent on the availability of the lipid substrates; therefore the higher basal level mediated oxidation observed in VLDL and LDL can probably be ascribed to the increase in PL and TC in lipoproteins of patients compared with controls. In fact, Cu-triggered oxidation involves mainly PL and TC that are localized at the lipoprotein surface. In psoriasis, modifications in susceptibility to lipid peroxidation have also been demonstrated at membrane level, with an increased production of MDA following stimulation with thrombin in platelets of psoriatic adult patients (23). These alterations have been correlated to the changes in PL fatty acid composition, with an increase in AA that exposes the membrane to lipid peroxidation by free radicals (23).

In conclusion, our results demonstrate lipid compositional changes and a higher susceptibility to in vitro oxidation in VLDL and LDL of psoriatic patients vis-à-vis controls.

Some hypotheses can be advanced about the mechanism (s) that result in the compositional changes in lipoproteins in psoriasis.

As far as concerns the higher susceptibility to in vitro peroxidation of VLDL and LDL of psoriatics, since oxidatively modified lipoproteins play a key role in the pathogenesis of atherosclerosis, our results support an increased risk for atherosclerosis as previously suggested in adult psoriatic patients (6). This hypothesis is also supported by the significant increase in TG in lipoprotein of psoriatics. The role of triglycerides and of TG-rich-lipoproteins in atherogenesis and thrombogenesis has recently been affirmed (24–25).

The usefulness of fish oil supplementation, rich in polyunsaturated fatty acids (PUFA), in the treatment of psoriasis has been proposed previously (26). However, it must be emphasized that a large increase in PUFA in plasma lipoproteins increases the risk of lipid peroxidation (27). The higher susceptibility to in vitro oxidation demonstrated in the present study in lipoproteins of psoriatics and the modest clinical improvement in adult patients after fish oil treatment (28), do not justify a diet rich in PUFA in the treatment of psoriasis.

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REFERENCES

1. Baker H. Psoriasis. In: Rook A Wilkinson DS, Ebling FJG, Champion RH, Burton JL, eds. Textbook of Dermatology, 4th edn, vol. II. Oxford: Blackwell Scientific Pubblication, 1986: 1469–1478.
2. Hammerström S, Hamberg M, Samuelsson B, Duell EA, Stawski M, Voorhees JJ. Increased concentration of non-esterified arachidonic acid, 12 L-hydroxy 5, 8, 10, 14 eicosatetranoic acid, prostaglandin F2 in epidermis of psoriasis: evidence for perturbed regulation of arachidonic acid levels in psoriasis. Proc Natl Acad Sci USA 1975; 72: 5130–5134.
3. Ferretti G, Offidani AM, Simonetti O, Valentino M, Curatola G, Bossi G. Changes in membrane properties of erythrocytes and polymorphonuclear cells in psoriasis. Biochem Med Metab Biol 1989; 41: 132–138.
4. Ferretti G, Simonetti O, Offidani AM, Messini L, Cinti B, Marchiseppe I, Bossi G, Curatola G. Changes of plasma lipids and erythrocyte membrane fluidity in psoriatic children. Pediatr Res 1993; 33: 506–509.
5. Valquist C, Michaelsson G, Vessby B. Serum lipoprotein in middle-aged men with psoriasis. Acta Derm Venereol 1987; 67: 12–15.
6. McDonald CJ, Calabresi P. Psoriasis and occlusive vascular disease. Br J Dermatol 1978; 99: 469–475.
7. Illingworth DR, Connors WE. Hyperlipidemia and coronary heart disease. In: Connors WE, Bristow JD, eds. Coronary heart disease: prevention, complication and treatment. Philadelphia: Lippincott, 1985; 21–42.
8. Grundy SM. Cholesterol and coronary heart disease. A new era. JAMA 1986; 256: 2849–2858.
9. Witzum JL, Steiberg D. Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest. 1991; 88: 1785–1792.
10. Steinberg D, Witzum JL. Lipoproteins and atherogenesis. JAMA 1990; 264: 3047–3052.
11. Havel R, Eder HA, Braigon JH. The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. J Clin Invest 1955. 39. 1345.
12. Lavy A, Brook GJ, Dankner G, Amotz AB, Aviram M. Enhanced in vitro oxidation of plasma lipoproteins derived from hypercholesterolemic patients. Metabolism 1991; 40: 794–799.
13. Yagi K. A biochemical approach to atherogenesis. Trends Biochem Sci 1986; 11: 18–21.
14. Warnick GR. Enzymatic methods for quantification of lipoprotein lipids. In: Segrest JP, Albers JJ, eds. Methods in enzymology. New York: Academic Press, 1986; 129: 101–123.
15. Allain CC, Poon LS, Chan CGS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1979; 20: 470–474.
16. Bucolo G, David H. Quantitative determination of triglycerides by the use of enzymes. Clin Chem 1973; 20: 470–475.
17. Lowry OH, Rosebrough NJ, Farr AL, Randall R. Protein measurements with folin phenol reagent. J Biol Chem 1951; 193: 265–275.
18. Lund-Katz S, Phillips MC.Packing of cholesterol molecules in human low-density lipoprotein. Biochemistry 1986; 25: 1562–1568.
19. Ferretti G, Alleva R, Taus M, Simonetti 0, Cinti B, Offidani AM, Bossi G, Curatola G. Abnormalities of plasma lipoprotein composition and fluidity in psoriasis. Acta Derm Venereol (Stockh) [in press].
20. Brown MS, Kovanen PT, Goldstein JL. Regulation of plasma cholesterol by lipoprotein receptors. Science 1981; 212: 628–635.
21. Tada J, Mommas-Kienhuis AM, Vermeer BJ. The application of postembedding immunoelectronmicroscopy to visualize the LDL receptor on normal and diseased skin. Int J Dermatol 1988; 91: 399.
22. Leren T, Maartman-Moe K, Thune P, Berg K. Low density lipoprotein receptors in cultured skin fibroblasts from psoriatic patients. Clin Genetics 1984; 25: 230–241.
23. Corrocher R, Ferrari S, De Gironcoli M, Bassi A, Olivieri 0, Guarini P, Stanzial A, Barba AL, Gregolini G. Effect of fish oil supplementation on erythrocyte lipid pattern, malondialdehyde production and giutathione-peroxidase activity in psoriasis. Clin Chim Acta 1989; 179: 121–132.
24. Schwandt P. Triglyceride-rich lipoproteins and atherosclerosis. Drugs 1990; 40 (Suppl 1): 38–41.
25. Austin MA. Plasma triglycerides and coronary heart disease. Arteriosclerosis Thromb 1991; 11: 2–14.
26. Ziboh VA, Cohen KA, Ellis CN, Miller C, et al. Effects of dietary supplementation of fish oil on neutrophil and epidermal fatty acids. 1986; 122: 1277–1282.
27. Parthasarathy S, Koo JC, Miller E, Barnett J, Witztom JL, Steinberg D. Low-density lipoprotein rich in oleic acid is protective against oxidative modification: implications for dietary prevention of atherosclerosis. Proc Natl Acad Sci USA 1990; 87: 3894–3898.
28. Maurice PDL, Allen BR, Barkley ASJ, Cockbill SR, Stammers J, Bather PC. The effect of dietary supplementation with fish oil in patients with psoriasis. Br J Dermatol 1987; 117: 599–606.