SERUM LIPID AND LIPOPROTEIN PROFILES
IN PATIENTS WITH XANTHOMAS
A Correlative Study on Xanthoma and Atherosclerosis (I)

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In an attempt to correlate xanthomas with atherosclerosis, the characteristics of serum lipid and lipoprotein profiles are explored in xanthoma patients. Xanthomas are classified into 5 subtypes: xanthelasma, planar xanthoma, papulo-eruptive xanthoma, tuberous xanthoma and tendon xanthoma.

The clinical characteristics of xanthoma patients are summarized in the following. 1) Xanthelasma in 2 different types: one normolipemic and the other hyperlipidemic; of 30 xanthelasma patients, 5 were normolipemic, one of them had low HDL-cholesterol. 2) Tuberous and tendon xanthomas were all hypercholesterolemic, with serum cholesterol above 300 mg/dl and LDL-cholesterol above 255 mg/dl, while HDL-cholesterol was within normal range. 3) The xanthoma patients were generally not obese. 4) Their laboratory findings often showed such abnormalities as elevated levels in serum fibrinogen, LDH, CPK and uric acid.

The resemblance of the clinical characteristics between xanthomas and atherosclerotic vascular disease, e.g., myocardial infarction, was striking. If the causation of their common tissue alterations by lipid accumulation is pathologically and biochemically defined, the correlation between those 2 kinds of disease can be established.

XANTHOMA is a lesion caused by abnormal deposition of lipids in various parts of the skin and tendons.¹⁻¹² Skin lesions are commonly flat plaques of yellow color, or round tuberous

eruptions of reddish yellow tint in the skin of eyelids, elbows and buttocks. Tendon involvements appear either as hard nodular elevation on the extensors of the hands and the knees, or hard thickening of the Achilles tendons of the feet. These are clinical manifestations of usually asymptomatic disorders of lipid metabolism, and could be a premonitory sign of atherosclerosis which is caused by rarely visible and palpable

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TABLE I DIAGNOSTIC CHARACTERISTICS OF 5 TYPES OF XANTHOMAS

<i>Xanthelasma</i>	<i>Shape and Size</i>	<i>Localization</i>
<i>Xanthelasma</i>	<i>Flat plaques of yellow color in size of 1 × 1 mm to 10 × 10 mm or more</i>	<i>At the inner canthus of the upper eyelids, and later extends to the lower eyelids</i>
<i>Planar Xanthoma</i>	<i>Slight elevations in irregular outline of yellowish brown color</i>	<i>Along the crease or dermal lines of the palm, arms and legs</i>
<i>Papulo-eruptive Xanthoma</i>	<i>Round and low papule of yellow or reddish color in size of less than 10 mm in diameter</i>	<i>On the inside of forearms or the buttock and the backward of the thigh</i>
<i>Tuberous Xanthoma</i>	<i>Round tubercles with smooth surface of reddish yellow color in size of more than 10 mm in diameter</i>	<i>On the extensor side of the elbow, knee and foot joints</i>
<i>Tendon Xanthoma</i>	<i>Hard nodular or cylindrical thickening of irregular surface in size of soybean to quail's egg</i>	<i>On the extensors of the hands, elbows and knees, or in the Achilles tendons</i>

aberration in lipid metabolism and is insidiously and steadily developing in the arteries of the organs seated deep in the body. Therefore, xanthomatosis deserves more attention of clinicians as an important clue to the existence of long-lasting, severe dyslipoproteinemias and atherosclerosis.

In a series of studies, the clinical features of different types of xanthomas were defined and then their relationship to atherosclerosis were examined in the light of their pathogenesis and prognosis. This report describes the first approach to the clinical study of various types of xanthoma with particular reference to their lipid and lipoprotein profiles.

SUBJECTS AND METHODS

By the site, size and shape of the lesion, xanthomas were divided into 5 types¹³: xanthelasma, planar, papulo-eruptive, tuberous, and tendon xanthoma. The diagnostic criteria for each type of xanthoma are summarized in the Table I.

A total of 86 patients, 49 males and 37 females, with an average age of 52 ± 14 (male 51 ± 11 , female 53 ± 14) were diagnosed as xanthomas. Among them, 30 (14 male and 16 female) had xanthelasma, 2 (female only) planar xanthomas, none papulo-eruptive xanthoma, 8 (7 male and 1 female) tuberous xanthomas, and 46 (28 male and 18 female) tendon xanthomas. Tendon was diagnosed as xanthomatous when the Achilles

tendon in a patient of normal body weight was found by an X-ray photography to be thicker than 8.5 mm in the male and 7.8 mm in the female. Likewise diagnosed as xanthomatous when the Achilles tendons measured with a slide caliber at the level of the internal malleolus of the foot were found wider than 2.2 cm in the male and 1.9 cm in the female. This setting of the upper limits at these values was justified by the findings of the preliminary studies made on the healthy adults of percent body weight deviation¹⁴ within 10%, which gave an average thickness of 7.5 ± 1.3 mm for male and 6.8 ± 1.0 mm for female, and an average width of 1.9 ± 0.3 cm in the right leg and 1.8 ± 0.3 cm in the left for male, while 1.7 ± 0.2 cm in the right leg and 1.6 ± 0.3 cm in the left for female.

The time of manifestation and duration of xanthomas had to be estimated by inquiring the patients as to the time when they first noticed the lesion, and also performing physical examinations, measurements of body weight, blood pressure, and the thickness of their Achilles tendons of both feet. Skin lesions were recorded by taking color pictures, and X-ray photography of the Achilles tendons. The overnight fasting blood was drawn from the patients to determine serum total cholesterol,¹⁵ phospholipids,¹⁶ triglycerides,¹⁷ free fatty acids,¹⁸ lipid peroxides,¹⁹ LDL-²⁰ and HDL-cholesterol,²¹ and lipoprotein electrophoresis²². Blood chemistry was performed to test the liver functions, renal functions and thyroid gland functions in addition to periph-

TABLE II LIPID AND LIPOPROTEIN PROFILES OF XANTHOMA PATIENTS

	Xanthelasma			Planar			Tuberous			Tendon		
	Total	male	female	male	female	female	Total	male	female	Total	male	female
Number of Case	30	14	16	2	2	2	8	7	1	46	28	18
Age (year)	57±9	56±8	57±9	44±30	44±30	44±30	53±10	51±10	66	48±13	49±12	48±15
Incid. (%)	35	—	—	—	2	2	9	—	—	54	—	—
B.W. Dev. (%)	+10±12	+12±8	+8±15	+3±4	+3±4	+3±4	+8±7	+7±6	+19	+7±12	+9±11	+3±12
Achilles R (cm)	2.3±0.8	2.4±0.8	2.1±0.5	1.7±0.1	1.7±0.1	1.7±0.1	2.7±0.5	2.7±0.5	—	2.5±0.5	2.6±0.5	2.4±0.5
L (cm)	2.2±0.8	2.5±0.8	2.2±0.5	1.9±0.2	1.9±0.2	1.9±0.2	2.8±0.5	2.8±0.8	—	2.5±0.5	2.6±0.5	2.3±0.4
TC (mg/dl)	299±95	295±96	303±93	500±484	500±484	500±484	389±85	374±80	495	362±79	354±83	374±71
PL (mg/dl)	295±68	293±71	297±65	501±139	501±139	501±139	357±40	358±43	350	342±60	345±67	341±44
TG (mg/dl)	160±75	197±79	126±51	431±296	431±296	431±296	122±44	124±47	108	172±139	196±169	135±60
FFA (mEq/L)	0.70±0.31	0.52±0.13	0.85±0.30	1.47±1.08	1.47±1.08	1.47±1.08	0.59±0.43	0.44±0.17	1.48	0.68±0.35	0.56±0.27	0.84±0.84
LDL-c (mg/dl)	255±93	266±96	248±91	402	402	402	331±94	304±95	409	317±75	303±81	328±62
HDL-c (mg/dl)	50±14	52±13	48±15	66±4	66±4	66±4	52±12	48±12	64	49±14	50±13	48±15
Fibrinogen (mg/dl)	317±76	310±74	327±70	311	311	311	307±81	311±86	286	330±82	319±85	371±45
LDH (W.U.)	326±69	307±74	344±59	436±30	436±30	436±30	300±56	300±56	—	342±58	333±55	363±54
CPK (IU/L)	59±21	61±24	56±14	70	70	70	59±18	59±18	—	73±35	82±36	50±16
UA (mg/dl)	4.6±1.0	4.8±0.9	4.3±0.9	2.9	2.9	2.9	5.3±0.4	5.3±0.4	—	4.8±1.1	5.3±0.8	3.9±0.7

B.W.Dev.: Percent body weight deviation, TC: Total serum cholesterol, PL: Phospholipids, TG: Triglycerides, FFA: Free fatty acids

TABLE III RELATION BETWEEN TYPE OF XANTHOMA AND PHENOTYPE OF SERUM LIPOPROTEINS

<i>Xanthoma</i>	<i>Phenotype of Hyperlipidemias</i>					<i>Total</i>
	<i>N</i>	<i>IIa</i>	<i>IIb</i>	<i>III</i>	<i>IV</i>	
<i>Xanthelasma</i>	5	17	8	—	—	30
<i>Planar</i>	—	1	—	1	—	2
<i>Tuberous</i>	—	8	—	—	—	8
<i>Tendon</i>	—	36	10	—	—	46
	5	62	18	1	—	86

N: normolipidemic

eral blood, and urine²³⁻²⁶ ECG was taken both in resting state and after two-step exercise load.²⁷

RESULTS

Clinical data covering lipid and lipoprotein profiles of xanthoma patients were given in the Table II.

The average age was 57 ± 9 (male 56 ± 8 , female 57 ± 9) for the 30 xanthelasma patients, 44 ± 30 (female only) for the planar xanthomas, 54 ± 12 (male 52 ± 11 , female 66) for the 8 tuberous xanthomas, and 48 ± 13 (male 49 ± 12 , female 48 ± 15) for the 46 tendon xanthomas.

The time of manifestation of xanthomas, useful to estimate the duration of the lesion, was often questioned of the patients but without success. The patients did not always clearly remember the time when they first noticed the presence of xanthoma even of the lesion in the eyelids which must be most easily perceived. Barring too serious error in our guess work, the average age at which the xanthoma became manifest was estimated to be 45 ± 10 years and the average duration being 10 ± 8 years.

The body weight deviation of the xanthoma patients was within the range of $\pm 10\%$ except for some xanthelasma patients, and the absence of marked obesity was characteristic of these patients.

The high blood pressure, according to WHO criteria²⁸ was found 5% in systolic and 3% in diastolic pressure of the tendon xanthoma patients, but they were 30% and 35% respectively in xanthelasma patients whose average age was higher than other xanthoma patients.

Serum lipids were mostly so high as to be ranked as severe in the severity grading²⁹ as they counted over 300 mg/dl with cholesterol and

triglycerides. LDL-cholesterol calculated by Friedewald's formula²⁰ was also high 296 ± 92 mg/dl, while HDL-cholesterol, however, remained within the normal range of 48 ± 13 mg/dl. With xanthelasma, 5 cases out of 30 showed the normal serum lipid levels, one of whom, however, had a low value of 32 mg/dl in HDL-cholesterol. A small portion of the patients with xanthelasma, planar xanthoma, and tendon xanthoma had a high level of not only cholesterol but also of triglycerides. The Table III is summed up the relation of the type of xanthoma to the phenotype of serum lipoproteins. The patients who had high cholesterol level tended to manifest xanthelasma, tuberous and tendon xanthomas, while those in whom hypertriglyceridemia accompanied tended to show xanthelasma and planar xanthomas.

Blood chemistry tests often revealed abnormalities mostly in serum fibrinogen, LDH, CPK and uric acid. Five out of 46 patients with tendon xanthoma gave abnormally high values of serum fibrinogen counting over 400 mg/dl, and 6 out of 30 xanthelasma patients, 2 planar patients and 8 of 46 tendon xanthoma all showed abnormally high LDH values. Abnormalities of CPK were found in one xanthelasma patients and 7 tendon xanthoma. Uric acid was found elevated in 2 xanthelasma and 2 tendon xanthoma cases (see Table II). The results of ECG tests and the incidence of coronary ischemic disease in these patients will be reported elsewhere.

DISCUSSION

We have studied 86 cases of xanthoma patients to determine their occurrence and the lipid profiles of each type of this disease, and then interpreted the significance of the abnormalities

Fig. 1. Clinical characteristics of xanthoma patients. B.W.Dev: body weight deviation, TC: total cholesterol, PL: phospholipids, TG: triglycerides, FFA: free fatty acids, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, UA: uric acid, B.P. Sys.: systolic blood pressure, B.P.Diast.: diastolic blood pressure

revealed by clinical tests.

Classification and Relative Frequency of Xanthoma

We defined and classified xanthomatosis into 5 types by the location, size and appearance as in the Table I. A different classification is possible on the basis either of cutaneous morphology, histological findings, background metabolic disorders, or their combinations. However, from the clinical viewpoint, it is most practical to diagnose and determine the type of lesion on the spot of examinations, since it is not always possible to perform biopsy on all the xanthoma patients, nor determine precisely the mechanism of their background disorders. Consequently our classification mainly by the appearance into 5 types is simple and yet vastly serviceable and applicable to wide use.

The relative frequency of each type of xanthoma in our classification was high 54% in tendon xanthoma, 35% in xanthelasma, 9% in tuberosus xanthoma, and 2% in planar xanthoma. This relative frequency may not apply to all clinics, as what we have encountered was mostly in the subjects with marked hyperlipidemias. However, the high incidence of tendon xanthoma in hyperlipidemic subjects indicated that we ought to pay more attention to the tendon thickening in the patients, which is too often overlooked.

Clinical Features of Xanthoma Patients

Viewed from lipid and lipoprotein metabolism,

the clinical characteristics of xanthoma patients can be summed up as follows (Fig. 1). 1) The xanthoma patients are seldom obese, their body weight deviation being within $\pm 10\%$. 2) Total serum cholesterol is as high as above 300 mg/dl, except for some of the patients with xanthelasma. 3) The cause for the rise in total cholesterol is mainly the elevation in LDL. 4) HDL-cholesterol is within the normal range, except for a sole case in xanthelasma patients. 5) Serum triglycerides are slightly increased in xanthelasma and tendon xanthomas. 6) Some xanthelasma patients are normal in serum lipid and lipoprotein concentrations, and 7) the xanthoma patients sometimes show abnormalities in their blood chemistry other than in serum lipids such as fibrinogen, CPK, LDH and uric acid.

These clinical characteristics suggest that xanthomas arise from the disorders in lipoprotein metabolism, due in particular to elevated LDL concentrations. A long duration of marked rise in LDL causes a load on cholesterol metabolism in peripheral tissues, which leads to the accumulation of esterified cholesterol both in and out of the dermal cells. This is evidenced by the reports^{30,31} where familial hypercholesterolemia counting above 300 mg/dl are shown to have complications of xanthoma at such a high rate as 2.6% in children below 10 years of age, 12.5% in teenagers, 69.2% in twenties, 90.0% in thirties, and 70.3% above forties. These high incidences of xanthoma complication in hypercholesterolemia may be correlated with atherosclerotic vascular changes which will inevitably be induced

by a long continued elevation in serum cholesterol or LDL.

Significance of Abnormalities in Blood Chemistry of Xanthoma Patients

Some patients particularly of xanthelasma have normal values in serum lipids. This seems to suggest the importance of local conditions of the tissue in the pathogenesis of xanthoma. For instance, the development of vascular beds, disturbance in lymphatics, density of innervation, and frequency of mechanical stress may be related to the fact that xanthomas usually evolves in a symmetrical form in certain locations of the skin and tendons.

Xanthoma patients, regardless of their serum lipid concentration, often have an abnormally high level of serum lipid peroxides, fibrinogen, CPK, LDH and uric acid. Their relation to pathogenesis of xanthoma and atherosclerosis, however, is not yet known. Nevertheless, those changes in blood chemistry may be interpreted as a sign of degeneration caused by the accumulation of esterified cholesterol in peripheral tissues including the skin, tendons and arteries, and as an additional clue to elucidating the correlation between xanthoma and atherosclerosis.³²

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REFERENCES

1. THANNHAUSER SJ, MAGENTANTZ H: The different clinical groups of xanthomatous disease: A clinical physiological study of 22 cases. *Ann Intern Med* 11: 1662, 1937
2. THANNHAUSER SJ: Lipoidosis: Disease of the Intracellular Lipid Metabolism. 2nd ed, Grune & Stratton, New York, 1950
3. MCGINLEY J, JONES H, GOFMAN J: Lipoproteins and xanthomatous disease. *J Invest Dermatol* 19: 71, 1952
4. LEVER WF, SMITH PA, HURLEY NA: Idiopathic hyperlipemic and primary hypercholesterolemic xanthomatosis. *J Invest Dermatol* 22: 33, 1954
5. ZOLLNER N, WOLFRAM G: Lipidosis and secondary disorders of lipid metabolism. In *Biochemical Disorders in Human Disease*, 3rd ed, ed by THOMPSON RHS, WOOTTON IDP, JA Churchill, London, 1970, p 609
6. FREDRICKSON DS: Plasma lipid abnormalities and cutaneous xanthomatosis. In *Dermatology in General Medicine*, ed by FRITZPATRICK TB, McGraw-Hill, New York, 1971, p 1173
7. POLANO MK: Xanthomatosis and hyperlipidemia. *Dermatologica* 149: 1, 1974
8. FLEISCHMAJER R, DOWLATIN Y, REEVES JRT: Familial hyperlipidemias: Diagnosis and treatment. *Arch Dermatol* 110: 43, 1974
9. OKUDAIRA Y: Disorders due to accumulation of metabolites. I. Disorders of skin lipid metabolism. In *Nippon Hifukazensho*, Vol 6, Part 3, ed by KITAMURA H, MIURA O, TAKAHASHI S, YOKOYAMA J, Kanehara Shuppan Co, Tokyo, 1959, p 61 (in Japanese)
10. KOJIMA M, TAKAHASHI K: Concept of Xanthomas. *Saishin Igaku* 21: 522, 812, 1966 (in Japanese)
11. INOUE S, KIKUCHI I: Xanthelasma. *Shinryo* 12: 1097, 1970 (in Japanese)
12. HATA Y: Xanthomatosis and disorders in lipoprotein metabolism. In *All about Disorders of Lipid Metabolism*, No.34, ed by TAKAHASHI Y, Nankodo, Tokyo, 1979, p 302 (in Japanese)
13. POLANO MK: Xanthoma types in relation to the types of hyperlipoproteinemia. *Nutr Metab* 15: 107, 1973
14. MINOWA S, TAKAHASHI K, MAYUZUMI N, MIYASHITA H: Studies on the standard body weight of Japanese. *Nihon Iji-Shinpo*. No. 1988, 24, 1962 (in Japanese)
15. RICHIMOND W: Preparation and properties of a cholesterol oxidase from *Nocardia* sp. and its application to enzymatic assay of total cholesterol in serum. *Clin Chem* 19: 1350, 1973
16. TAKAYAMA M, ITOH S, NAGASAKI T, TANIMIZU I: A new enzymatic method for determination of serum choline-containing phospholipids. *Clin Chem Acta* 79: 93, 1977
17. FLETCHER MJ: A colorimetric method for estimating serum triglycerides. *Clin Chem Acta* 22: 393, 1968
18. DUNCOMBE WG: The colorimetric micro-determination of non-esterified fatty acids in plasma. *Clin Chem Acta* 9: 122, 1964
19. YAGI K: A simple fluorometric assay for lipoperoxide in blood plasma. *Biochem Med* 15: 212, 1976
20. FRIEDEWALD WJ, LEVY RI, FREDRICKSON DS: Estimating of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifugation. *Clin Chem* 18: 499, 1972
21. Manual of Laboratory Operations, Lipid Research Clinics Program. Vol 1, Lipid and Lipoprotein Analysis (DHEW Publication No. NIH 75-627), National Heart and Lung Institute NIH, Bethesda, 1974
22. KOHN J: A lipoprotein staining method for zone electrophoresis. *Nature* 189: 312, 1961
23. VERMYELEN C, DE VERKER RA, VERSTRATE M: A rapid enzymatic method for assay of fibrinogen-fibrin polymerization time (EPT-test). *Clin Chim Acta* 8: 418, 1963
24. WONG PCP, SMITH AF: Biochemical difference between the MB and MM isozyme of creatinine kinase. *Clin Chim Acta* 68: 147, 1976
25. WROBLEWSKI F, LADUE JS: Lactic dehydrogenase activity. *Proc Soc Expl Biol Med* 90: 210,

- 1955
26. GODMAN N, SCHMITZ JM: Automated determination of uric acid with use of uricase-peroxidase system. *Clin Chem* 17: 1154, 1971
 27. MASTER AM, GUBENER R, DACK S, JAFFE HL: Differentiation of acute coronary insufficiency with myocardial infarction from coronary occlusion *Arch Intern Med* 67: 647, 1941
 28. Report of a WHO Expert Committee: Arterial Hypertension. *WHO Technical Report Series* 628: 3, 1978
 29. HATA Y, SHIGEMATSU H: Severity grading of hyperlipidemia: A guide for diagnosis and treatment. *Keio Igaku* 56: 473, 1979 (in Japanese)
 30. SCHROTT HG, GOLDSTEIN JL, HAZZARD WR, MCGOODWIN MM, MOTULSKY AG: Familial hypercholesterolemia in a large kindred: Evidence for a monogenic mechanism. *Ann Intern Med* 76: 711, 1972
 31. KWITEROWICH P Jr, FREDRICKSON DS, LEVY RI: Familial hypercholesterolemia (one form of familial type II hyperlipoproteinemia): A study of its biochemical, genetic, and clinical presentation in childhood. *J Clin Invest* 53: 1237, 1974
 32. HATA Y, SHIGEMATSU H: Possibility of xanthoma as a pathological and clinical model for atherosclerosis. *Jpn J Med* 20: 137, 1981