# Erdheim-Chester Disease: Low Low-Density Lipoprotein Levels Due to Rapid Catabolism

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**We have identified a 44-year-old patient with symmetrically excessive xanthomatosis, called Erdheim-Chester disease (ECD), and simultaneously decreased levels of low-density lipoprotein (LDL) cholesterol. Clinically, this patient presents lipoidgranulomatosis of numerous long and flat bones with involvement of the liver, spleen, pericardium, pleura, thyroid, skin, conjunctiva, and gingiva. However, the patient does not have any signs of atherosclerosis. So far, the underlying defect has not been elucidated. We performed a LDL–apolipoprotein B (apoB) kinetic study in the ECD patient and a normal control to determine the etiology of the low LDL level in ECD. LDL was isolated from both subjects, radioiodinated with either $^{131}I$ or $^{125}I$, and injected simultaneously into the ECD patient and the normal control. Normal and ECD LDL was catabolized at the same rate after injection into the control subject (fractional catabolic rate [FCR], 0.43/d and 0.46/d, respectively). Therefore, LDL isolated from an ECD subject is metabolically normal. In contrast, autologous LDL injected into the ECD subject showed a markedly increased catabolism (FCR, 0.69/d) compared with that in the control subject (FCR, 0.43/d). This is the first report about increased catabolism of LDL cholesterol in a patient.**



XANTHOMATA are commonly seen in patients with excessive hypercholesterolemia. They represent lipid deposition, which consists primarily of cholesterol esters.[1] These deposits may accumulate in the tendons, in the cutis, next to eyelids (xanthelasma), and in the cornea, besides causing atherosclerotic plaques.[2,3] Previously, we demonstrated a direct association of a cholesterol-year score with extravascular lipid deposition in tissues of patients with homozygous familial hypercholesterolemia.[4] The cholesterol-year score was calculated based on the age and the yearly mean serum cholesterol concentration. The general implications of this finding are currently investigated based on the Framingham data. Extremely rare findings of lipid deposition can also occur in other tissues of the human body.[5-10] Macrophages presumably play the key role in the genesis of both atherosclerotic plaques and xanthomata.[11] However, the detailed mechanism has not yet been revealed. Various lipid disorders have been identified to cause lipid deposition, mainly familial hypercholesterolemia and familial dysbetalipoproteinemia.[3,12] Hypolipidemia (apolipoprotein A-I [apoA-I] deficiency) can also cause similar clinical manifestations.[13] All of these diseases are due to a single gene defect.

Erdheim-Chester disease (ECD) was first described by the pathologists Erdheim and Chester in 1930.[14] The original description is an excessive infiltration of xanthomata within the cutis and systemically. Since then, there may exist more than 40 reported cases of this disease, although not all seem to fulfill the current criteria for ECD.[15] The clinical diagnosis can be made by the typical constellation of nonexistent severe hyperlipidemia with cutaneous and invasive xanthomata, especially within the long bones. The clinical variability ranges from cutaneous xanthomata to severe lipid deposition infiltrating organs and causing variable clinical symptoms.[16-20] Therefore, the diagnosis of xanthoma disseminatum and ECD may be the extreme expression of the same underlying defect. Histiocytosis-like diseases may be excluded by characteristic immunohistochemistry findings.[21,22] ECD seems to be sporadic, and there is no evidence of a genetic trait thus far. The lipoprotein profile is not commonly reported in the published cases of ECD, presumably since there is no remarkable hyperlipidemia seen in these patients.[15] We now report a case with the typical pattern of ECD. This patient has been reported in part by groups he was referred to.[23-25] We evaluated the in vivo catabolism of LDL to determine the metabolic etiology of low LDL levels observed in this patient.

## SUBJECTS AND METHODS

### *Case Report*

We report on a white male who was first clinically seen at the age of 21 years due to recurrent episodes of edema and bone tenderness above both tibias and the left elbow in 1972 (weight, 72.5 kg; height, 187 cm). At the same time, he noticed nodules on his thorax, upper extremities, and scalp, which he related to acne. A bone biopsy revealed granulomatous tissue of unknown etiology. X-rays showed a sclerotic appearance to the long bones, especially involving both tibias. Distinct hypertrophic osteoarthropathy was detectable. His medical history was unremarkable. He worked in a textile mill and was exposed to steam and various chemicals. He smoked for 4 years, ending at the age of 18 years. He denied use of intravenous drugs. The family history was unremarkable with respect to his disease. His mother died at the age of 53 years of breast cancer. His father died of alcoholic cirrhosis at the age of 59 years. Both parents are Irish descendants. He has four brothers, all of whom are doing well. In 1973, values for serum albumin (albumin, 2.6 g/L; total protein, 5.4 g/L) and low-density lipoprotein (LDL) cholesterol (33 mg/dL) were reported for the first time, and both were depressed. Spinal fluid analysis and bone marrow biopsy were both normal. There was no evidence of infectious disease. At this time, another bone biopsy showed granulomatous lesions with small bodies. Since 1976, the patient has developed dental caries and periodontal disease associated with probable multifocal eosinophilic granuloma. He also developed progressively protuberant polypoid clusters of skin lesions over the neck and back. Since skin and organ infiltration was progressive, the patient was treated for 4 weeks with vinblastine sulfate, methotrexate, and steroids. The treatment was discontinued, since no improvement was detectable. Osteosclerosis was diagnosed with intermittent areas of radiolucent central defects that were elongated, indicating chronic slowly progressing lesions, and thickening of the

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cortex of the radius and ulna bilaterally and the tibia and fibula bilaterally in 1978. At this time, a life-threatening complication occurred due to a superior vena caval obstruction resulting in pericardial and bilateral pleural effusion with central cyanosis. Pericardiocentesis with a pericardial window was performed, and a 22-mm Gortex graft was anastomosed to the innominate vein and to the right atrial appendage. Pericardial histology showed a mild mesothelial reaction and perivascular chronic inflammatory infiltrate. The diagnosis of ECD was made retrospectively. The three tibial bone biopsies between 1972 and 1978 showed lipoid granulomatous processes consistent with foamy histiocytes. Multiple neck biopsies showed dermal infiltrates with foamy histiocytes. A liver and spleen scan (Tc-99m sulfur colloid) showed remarkable hepatosplenomegaly without any localized defects.[24] The bone scan confirmed a hypertrophic osteoarthropathy, which was initially followed by an osteosclerosis primarily involving the tubular bones, with increased radionuclide activity of these areas and the proximal interphalangeal articulations of the hands.[24] Marked osteopenia of the maxilla and mandible with floating teeth were diagnosed.[23,25] Over the following years, the disease did not progress. The major clinical finding was both a constrictive and restrictive cardiomyopathy and paroxysmal atrial flutter, which were treated with digoxin and quinidine. Figures 1 and 2 illustrate the nodular xanthomatous masses of the neck and back at the age of 27. He also developed yellowish infiltrating lesions of the conjunctivae and enlargement of the false vocal cords with a yellowish appearance. A second operation for pericardial stripping for treatment of restrictive congestive heart failure was performed later. Today, he is the father of a healthy boy. He is able to do gardening and delivers newspapers. We have not observed any progress for several years now. The low albumin level did normalize over the years (albumin, 4.2 g/L), but LDL cholesterol (29 to 66 mg/dL) remained remarkably low. Plasma exchange, various diets, and treatment with probucol did not influence the spontaneous course of this disease.

### *Metabolic Study*

The reported ECD patient and a normolipemic control subject participated in a metabolic study after provision of informed consent. They were hospitalized for the study in the Clinical Center of the National Institutes of Health. Both subjects had no hepatic, hematologic, or renal abnormalities, and were not on any medication. The study protocol was approved by the Human Use Research Committee of the National Heart, Lung, and Blood Institute.

### *Isolation of LDL*

LDL was isolated between density 1.019 and 1.063 g/mL, purified by recentrifugation for 22 hours at density 1.070, dialyzed, and concentrated against 50 mmol/L sodium phosphate/100 mmol/L saline (pH 7.4) subsequently.

### *Iodination of LDL*

The prepared samples were sterilized by filtration through a 0.2-μm filter, and radioiodinated by a modification of the iodine monochloride method.[26,27] One milliliter of the prepared LDL solution was added to a 1-mL solution of 1 mol/L glycine (pH 10). Five millicuries of $^{125}I$ and $^{131}I$, respectively, was added to each solution, followed by a slow addition of iodine monochloride. The quantity of ICI added was calculated to yield 1 mol iodine monochloride. The efficiency of the iodination was 25% to 40% for LDL. Each sample was dialyzed against 50 mmol/L sodium phosphate/100 mmol/L saline (pH 7.4), sterilized by filtration through a 0.22-μm filter, and tested for pyrogens before injection into the study subjects. Between 97.0% and 99.5% of the total radioactive iodine was bound to protein after trichloric acid precipitation. Distribution of radioiodine between the proteins of injected LDL was determined by preparative polyacrylamide gel electrophoresis

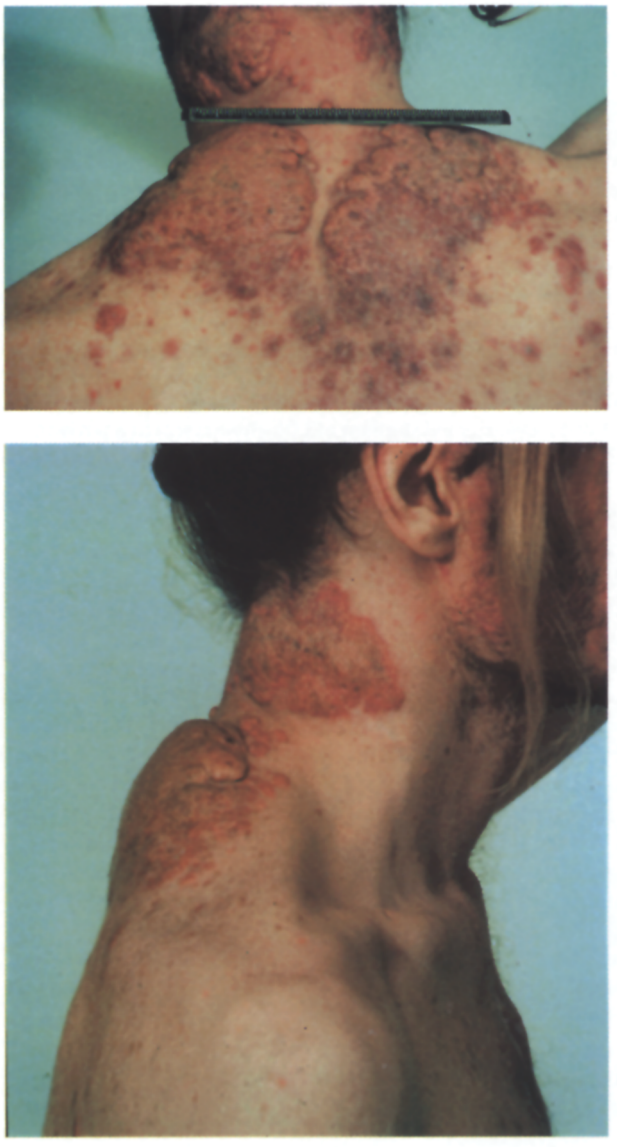

**Fig 1. Nodular xanthomatous masses of the reported cse.**

using 15% acrylamide gels; 84.6% and 89.9%, respectively, of total radioactivity was found on apoB.

### *Study Protocol*

The study subjects were placed on a weight-maintaining diet. Caloric intake was 42% carbohydrate, 42% fat, and 16% protein, with 200 mg cholesterol/1,000 kcal and a polyunsaturated to saturated fat ratio of 1:3, resulting in a limited variation in plasma cholesterol, triglyceride, and apolipoprotein concentrations. Two days before injection, the subjects were started on potassium iodide (1,200 mg/d). Subjects were injected intravenously with up to 25 μCi $^{131}I$ and 15 μCi $^{125}I$. Blood samples were obtained at 10 minutes, 1, 3, 6, 12, 24, and 36 hours, and days 2, 3, 5, 7, 9, 11, and 14, collected into tubes containing EDTA at a final concentration of 0.01%, stored at 4°C, and centrifuged (2,000 rpm for 30 minutes) at 4°C. Aprotinin and sodium azide were added to each plasma sample at a final concentration of 0.05% and 200 Kallikrein inhibitor U/mL. Plasma lipoproteins were isolated by ultracentrifugation, radioactivity in plasma and lipoprotein subfractions was quantified

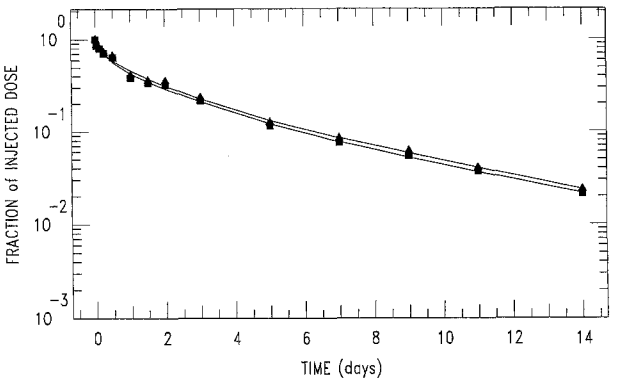


**Fig 2. Metabolism of normal and ECD LDL-apoB in a normal subject. Plasma decay curves as a fraction of the injected dose after simultaneous injection of $^{125}$I-labeled LDL from a normal control (◆) and $^{131}$I-labeled LDL from the propositus (■) into a normal subject are illustrated. The ordinate represents the fraction of injected dose on a logarithmic scale. The abscissa is the time in days on a linear scale.**

in a Packard auto gamma spectrometer (Packard Instrument, Meriden, CT), and the apoB concentration was determined.

### *Analytical Methods*

Plasma cholesterol and triglycerides were quantified on an enzymic analyzer (Gilford System 3500; Gilford Instruments, Oberlin, OH). High-density lipoprotein (HDL) cholesterol was determined in plasma after dextran sulfate precipitation.[28] The remaining lipid and lipoprotein analyses were performed using the methods of the Lipid Research Clinics.[29] ApoB concentrations were determined by radial immunodiffusion.[30,31]

The residence time (1/fractional catabolic rate [FCR]) was calculated from the area under the multiexponential plasma decay curve by a multiexponential computer curve-fitting technique, using the SAAM Manual.[32] The production rate (PR) was determined by dividing the pool size by the residence time. The pool size equals the apolipoprotein concentration multiplied by the plasma volume per kilogram body weight. Plasma volume is determined by dividing the total quantity injected by the radioactivity per unit volume determined in the sample obtained 10 minutes after injection.

## RESULTS

We report on a patient with ECD representing a diffuse lipogranulomatous infiltrating disease. Although lipid deposition within the skin and tendons, known as xanthoma, is usually associated with atherosclerotic plaques, these patients do not present with any severe vascular disease. In addition, there is no excessive hyperlipidemia in these patients, which is usually the cause of lipid deposition. The underlying defect has not yet been elucidated. This case shows severe lipid deposition involving long and flat bones, liver, spleen, pericardium, pleura, skin, conjunctiva, and gingiva. Interestingly, surgical resection of the lipid deposits never led to extensive scars or new initiation sites for lipid deposition. Biochemical analysis in the reported subject showed a temporarily low albumin and a constantly low LDL cholesterol serum concentration. A detailed lipid analysis in patients with ECD has not been reported. Therefore, we speculated that the low LDL in our subject may be a unique symptom in patients with this disease, which may provide more insight into the pathogenesis of ECD. Table 1 illustrates the lipoprotein profile of the patient at the time of the metabolic study. At the same time, the patient had a normal serum albumin concentration of 3.9 g/L. He has been evaluated regularly at our clinic since 1980. Over this period, LDL cholesterol ranged between 29 and 66 mg/dL, with a mean of 47 mg/dL. These values clearly show a remarkable low LDL serum concentration. Corresponding to the low LDL, the patient had a low apoB serum concentration of 51 mg/dL (normal range, 110 ± 35), whereas apoA-I, A-II, A-IV, C-II, and E were within the normal range. Serum concentrations of lipoprotein(a) and β-sitosterol were also normal. The apoE phenotype was 2/3.

We investigated the in vivo metabolism of LDL-apoB in the ECD patient and a normal control to determine the metabolic etiology of low LDL in ECD. To determine if LDL isolated from the ECD subject is metabolized normally, both normal LDL and ECD LDL were injected into a normal subject (Fig 2). The plasma decay curves are superimposable, demonstrating a normal catabolic rate of LDL isolated from ECD. Therefore, the LDL particle isolated from the ECD subject is metabolically normal. This finding is confirmed by the kinetics of normal LDL and ECD LDL injected into the ECD subject. To compare the metabolism of LDL in the patient versus the normal subject, autologous LDL was injected into the patient and the control subject, respectively, and the rate of catabolism was determined (Fig 3). The ECD subject has an increased FCR of the LDL particle compared with the normal subject. LDL-apoB kinetic parameters are summarized in Table 2. As already mentioned, the apoB plasma concentration is markedly decreased in the ECD patient. The FCR for LDL is significantly increased in the ECD patient (FCR, 0.69/d) compared with the control subject (FCR, 0.43/d). The calculated PR is slightly increased in ECD (PR, 16.34 mg/kg/d) compared with our normal range in 15 studied normal controls (13.1 ± 2.8 mg/kg/d). Therefore, decreased LDL and apoB plasma concentrations in the ECD subject are solely due to an increase of the rate of catabolism.

## DISCUSSION

Xanthomas are usually a characteristic finding in patients with severe hyperlipidemia.[3,33] Hyperlipidemic patients often present with circumscript xanthomas, usually located on typical

**Table 1. Characterization of the Study Subjects**

| Subject | Sex | Age (yr) | BMI (kg/m$^2$) | TC (mg/dL) | TG (mg/dL) | Cholesterol (mg/dL) | | | Triglyceride (mg/dL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | VLDL | LDL | HDL | VLDL | LDL | HDL |
| ECD | M | 32 | 20.6 | 110 | 70 | 9 | 43 | 58 | 35 | 16 | 19 |
| Control | F | 24 | 22.8 | 192 | 68 | 12 | 123 | 57 | 25 | 25 | 18 |
| Normal range | | 20-40 | | 185 ± 39 | 114 ± 56 | 17 ± 10 | 118 ± 36 | 50 ± 14 | 62 ± 33 | 43 ± 19 | 33 ± 23 |

Abbreviations: TC, total cholesterol; TG, triglycerides; BMI, body mass index; VLDL, very-low-density lipoprotein.

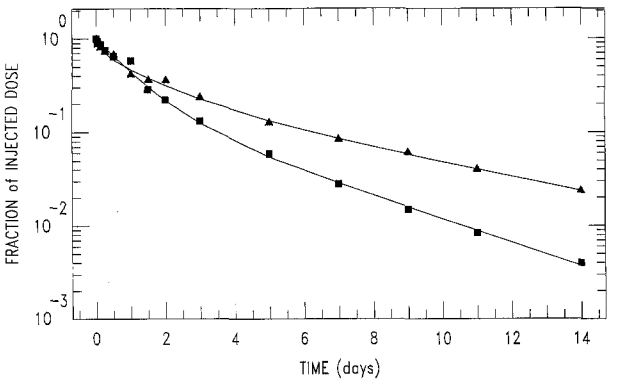


**Fig 3. Metabolism of autologous LDL-apoB in a normal control and ECD subject. Comparison of plasma decay curves as a fraction of the injected dose after injection of autologous $^{131}$I-LDL into the ECD subject (■) and normal $^{125}$I-LDL into a normal subject (▲).**

sites within the skin and tendons.[3,33] In addition, these patients have a premature onset of severe atherosclerosis. We previously reported that the extent of lipid deposition correlates with the extent of atherosclerosis in patients with familial hypercholesterolemia.[4] In contrast, patients with ECD are characterized by extensive cutaneous xanthomas and lipid infiltration of the organs, especially long tubular bones.[15] The site and extent of lipid deposition is unusual compared with that in patients with familial hypercholesterolemia. Interestingly, the reported cases of ECD do not present with premature onset of severe atherosclerosis, although atherosclerosis has been reported in some cases.[15] Therefore, the extent of xanthomas seems not to be associated with the extent of atherosclerotic lesions in ECD. The histology of lipid deposits in ECD showed primarily foamy histiocytes, which are also characteristically seen in atherosclerotic lesions caused, eg, by dyslipidemia.[24,34-36] Biochemically, the xanthomatous tissue in ECD is primarily composed of cholesterol esters, which again are also known for atherosclerotic plaques.[21]

There are also rare cases of patients with apoA-I deficiency presenting with lipid deposition.[13] Therefore, in addition to hyperlipidema, hypolipidemia can lead to formation of xanthomas. Interestingly, several case reports on ECD were presented without any lipid data, some reported normal lipids, and some reported mild hyperlipidemia.[15] Our case report describes a

**Table 2. Kinetic Parameters of LDL-ApoB in the ECD Patient and a Control Subject**

| Subject | ApoB (mg/dL) | PV (mL) | RT (d) | FCR (1/d) | PR (mg/kg/d) |
|---|---|---|---|---|---|
| ECD | 51 | 3,354 | 1.45 | 0.69 | 16.34 |
| Control | 104 | 1,897 | 2.31 | 0.43 | 15.82 |
| Normal range | 110 ± 35 | | 2.09 ± 0.31 | 0.49 ± 0.07 | 13.1 ± 2.8 |

Abbreviations: PV, plasma volume; RT, residence time.

patient with a very low LDL and total cholesterol. Since LDL levels have not been reported in patients with ECD thus far, we can only speculate on the significance of this finding in ECD. However, there are case reports with low values for total cholesterol, suggesting that low LDL levels may be a common feature in these patients.[37,38]

We determined the metabolic etiology of the low LDL in our subject with in vivo radiotracer studies. LDL isolated from the patient and the control subject was radiolabeled and injected simultaneously into the normolipemic control. Both LDL particles had an identical rate of catabolism. This demonstrates that LDL isolated from the ECD subject is metabolically normal. Therefore, the lipid deposits in our patient cannot be explained by altered LDL. In contrast, comparison of autologous injected LDL in the patient and the normal control, respectively, showed a remarkable increase of the FCR (60%) in the ECD subject. Previously published LDL in vivo turnover studies have shown normal or delayed catabolism, but this is the first report demonstrating increased catabolism of LDL. Since LDL is known to be involved in the delivery of cholesterol to peripheral cells, this finding may explain the lipid deposition in ECD. However, the underlying defect still needs to be elucidated in this reported case. Recently, Bergman et al[39] described increased LDL degradation and cholesterol synthesis in monocyte-derived macrophages of three patients with normolipemic xanthomatosis.[39] These in vitro findings are consistent with our data. In summary, the increased catabolic rate of LDL in our patient may reflect a pathophysiological role in the genesis of excessive lipid deposition in ECD. More detailed lipid evaluations and further LDL in vivo kinetics are required in patients with ECD to confirm our data. In addition, further studies are required to characterize the defect at the cellular level in affected patients.

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