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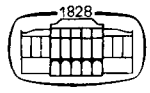
Hormones, Lipoproteins and Atherosclerosis

Editor

M. Palkovič

Bratislava, Czechoslovakia



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PREFACE

The research of lipoproteins and their relationship to atherosclerosis has advanced rapidly over the last two decades. A host of new information has accumulated on the structure, composition and metabolism of lipoproteins as well as on their pathophysiological significance. Although atherosclerosis is a multifactorial disease, hyperlipoproteinemia or an altered spectrum of lipoproteins have been demonstrated to be the major risk factors of this disease, and there is strong evidence indicating that hormones, in turn, play a decisive role in the control of lipoprotein metabolism as well as in the development of atherosclerosis.

The international symposium on "Hormones, Lipoproteins and Atherosclerosis" held in Bratislava, Czechoslovakia, organized as a satellite symposium of the 28th Congress of Physiological Sciences in Budapest, was devoted to the problems of hormonal effects on lipoprotein metabolism and atherosclerosis, and was also concerned with problems of composition, structure, synthesis, and degradation of liporoteins, as well as with genetical and clinical aspects.

The participants of the Symposium have contributed to this volume not only by presenting new data but also new ideas and stimulating new trends in the research and therapy of metabolic derangements of lipoproteins and the resulting pathological conditions. I am most appreciative, and I am confident that they will induce increased interest in the promising research of the mutual relationships of hormones, lipoproteins and atherosclerosis.

I wish to acknowledge my indebtedness to Prof. P. Alaupovic, Oklahoma City, Okla. USA, Chairman of the Symposium, for his invaluable help in the organization and the very course of the Symposium and for his greatly appreciated advice on the preparation of this volume. I extend my thanks and appreciation also to the Centre of Physiological Sciences and the Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, for the overall assistance given. Thanks, too, are due to the editorial staff of Akadémiai Kiadó, and to my collaborators involved in the task of preparing this volume, and it is particularly to Dr. Nina Škottová, Ph. D., General Secretary of the Symposium, that I express my unstinting thanks. I gladly thank also Dr. Magda Kouřilová for her language assistance.

M. Palkovič

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BIOCHEMICAL AND CLINICAL SIGNIFICANCE OF APOLIPOPROTEINS AND LIPOPROTEIN FAMILIES

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SUMMARY

Recent advances in lipoprotein research have already produced a profound impact on the existing views about the definition and classification of plasma lipoproteins. The discovery of several apolipoproteins, the identification of discrete lipoprotein particles and the marked protein heterogeneity of density classes have become incompatible with the view that operationally-defined lipoproteins represent the fundamental chemical and metabolic entities of this system. To provide a new conceptual framework for the structural and functional complexity of lipoproteins, we have introduced the concept of lipoprotein families or particles as the fundamental components of the system. The individual, polydisperse families are characterized and identified solely on the basis of their apolipoprotein composition. The biochemical significance of this concept resides in its recognition of apolipoproteins as the most probable determinants of the structural integrity and functional specificity of lipoproteins. Due to their distinct chemical and immunologic properties, apolipoproteins also represent the most suitable markers for studying the metabolic interactions and fate of lipoprotein particles. The already available results on the quantification of apolipoproteins suggest that apolipoprotein profiles may be better markers than lipids for identifying the genetic and biochemical basis of dyslipoproteinemias. Clinically, the apolipoprotein profiles and lipoprotein families may provide new means for the differential diagnosis of dyslipoproteinemic states, for predicting the severity of atherosclerotic process and monitoring the progress of therapeutic interventions.

As a unique class of conjugated proteins, soluble plasma lipoproteins share some but differ in other physical properties from those of simple proteins. As charged macromolecules, they behave in electric fields as simple proteins. However, due to their lipid constituents, they have relatively low hydrated densities and behave in gravitational fields more as lipids than simple proteins. For this reason, the electrophoretic mobility and hydrated density have been used as the most important operational criteria for characterizing and classifying plasma lipoproteins. Although historically, the "electrophoretic" classification preceeded the "ultracentrifugal" classification, the latter has gained a greater popularity both from practical and conceptual points of view. Gofman and his coworkers (1954) observed that the lipoproteins displayed a pattern of minimal and maximal concentrations along a density gradient from 0.92 g/ml to 1.21 g/ml and classified lipoproteins according to their density ranges into four major density classes designated as chylomicrons ($d < 0.94$ g/ml), very low density lipoproteins (VLDL, $d = 0.94$-1.006 g/ml), low density lipoproteins (LDL, $d = 1.006$-1.063 g/ml) and high density lipoproteins (HDL, $d = 1.063$-1.21 g/ml). Distribution studies (Ewing et al., 1965; Nichols, 1967) showed that each of these major density classes is a polydisperse system of lipoprotein particles heterogeneous with respect to hydrated density and size. Studies on the chemical composition of density classes singled out lipids as the major contributors to this compositional heterogeneity of lipoprotein particles (Nichols, 1967). Despite the recognized variety of lipoproteins differing in size, hydrated density and lipid composition, early studies on the protein moieties indicated

the existence of only two apolipoproteins, one of which was the main protein of HDL and the other of VLDL and LDL (Avigan et al., 1956). By the mid-sixties, the plasma lipoproteins could be defined as macromolecular complexes of lipids and at least two specific proteins referred to as α- and β-protein: the lipids and proteins linked through non-convalent interactions. The lipoproteins were viewed as a system of discontinuous macromolecular distributions heterogeneous with respect to size and hydrated density and the polydisperse lipoprotein density classes were accepted as the fundamental physicochemical and metabolic entities of the system (Oncley, 1964; Scanu, 1965; Fredrickson et al., 1967; Nichols, 1969). Initially, the main reasons for a wide acceptance of this conceptual view were the availability of a relatively simple ultracentrifugal methodology for preparative isolation of lipoprotein density classes and the emphasis on plasma lipids as the potential injurious agents in the genesis and development of atherosclerotic lesions (DeLalla and Gofman, 1954; Gofman et al., 1954). This view was strengthened later by a number of clinical and metabolic studies which related certain derangements of lipid transport to a particular density class or electrophoretic band (Fredrickson et al., 1967).

Although results of terminal amino acid analyses indicated that LDL and HDL are characterized by distinct protein moieties, similar studies in chylomicrons and VLDL suggested that these two density classes may contain apolipoproteins different from those characteristic of LDL and HDL. To explore this possibility, Gustafson et al. (1964) submitted chylomicrons and VLDL to a partial delipidization and isolated three distinct phospholipid-protein residues. Two of these residues

were shown to contain the protein moieties characteristic of LDL and HDL, respectively. However, the third phospholipid-protein residue contained a protein characterized by serine and threonine as the n-terminal amino acids, high phospholipid binding capacity and specific peptide patterns and immunologic characteristics. Following Oncley's suggestion that the major protein moiety of HDL be called ApoA and that of LDL ApoB, the third recognized apolipoprotein isolated from chylomicrons and VLDL was called ApoC. More recently, four additional apolipoproteins were discovered as normal constituents of plasma lipoproteins. One of these referred to initially as the "thin-line" polypeptide, was designated ApoD (McConathy and Alaupovic, 1973). Another one, isolated from VLDL (Shore and Shore, 1973; Shelburne and Quarford, 1974) and called initially the "arginine-rich" polypeptide, was designated ApoE. A minor acidic polypeptide isolated from HDL was named ApoF (Olofsson et al., 1978). The most recent addition to the growing number of apolipoproteins is a minor polypeptide isolated from HDL and VLDL and called ApoG (Ayrault-Jarrier et al., 1978). Shore and Shore (1968) showed that ApoA consists of two non-identical polypeptides called A-I and A-II, and Brown et al., (1969) demonstrated that ApoC is composed of three non-identical polypeptides referred to as C-I, C-II and C-III. Studies on the quantitative determination of apolipoproteins have shown that ApoA and ApoB are the major and ApoC, ApoD, ApoE, ApoF and ApoG the minor apolipoproteins (Alaupovic et al., 1978). It has not yet been established whether apolipoproteins B, D, E, F and G consist of a single polypeptide chain or several non-identical polypeptides. There are several reports in the literature describing the occurrence of additional apolipoproteins. However, insufficient

information exists about their chemical and immunologic characteristics, preventing their recognition as integral components of the plasma lipoprotein system.

Immunologic characterization of plasma lipoproteins revealed a wide distribution of apolipoproteins throughout the entire density spectrum (Alaupovic et al., 1972; Alaupovic, 1980). The major apolipoproteins of VLDL are ApoB, ApoC and ApoE which account in normolipidemic subjects for approximately 40-50%, 25-40% and 10-15%, respectively: ApoA and ApoD are only present in trace amounts. The major apolipoprotein constituent of LDL is ApoB; of HDL it is ApoA. However, both classes contain measurable amounts of ApoC and ApoE. Approximately 65% of ApoD is present in HDL and 35% in VHDL. ApoF and ApoG are found mainly, if not exclusively, in HDL and VHDL. HDL may contain up to 10-15% of the total plasma ApoB. This apolipoprotein heterogeneity of density classes is also found in various dyslipoproteinemic states which differ from normolipidemia and from one another with respect to both the relative and absolute concentrations of apolipoproteins (Alaupovic, 1980).

One of the most important questions raised by the newly disclosed apolipoprotein heterogeneity of major density classes related to the mode of apolipoprotein localization on individual lipoprotein particles within a defined density class. Are all apolipoproteins present on the same lipoprotein particle or does each apolipoprotein reside on a separate lipoprotein particle? Could lipoproteins be identified and characterized by their apolipoproteins? To establish the localization of apolipoproteins in individual lipoprotein particles, we have examined the whole plasma and major lipoprotein density classes by double diffusion

analyses and immunoelectrophoresis using various combinations of monospecific antisera to all well characterized apolipoproteins (Alaupovic et al., 1972; Suenram et al., 1979; Alaupovic, 1980). The immunodiffusion and immunoelectrophoretic patterns were interpreted according to Ouchterlony's principles (1968). A non-identity reaction obtained by antisera to two different apolipoproteins indicated that these two proteins resided on separate lipoprotein particles; on the other hand, an identity reaction was interpreted as an indication that these apolipoproteins were present on the same particle. Partial identity between two apolipoproteins indicated the presence of at least two separate lipoprotein particles: one of which contained both and the other a single apolipoprotein. Results of such studies from this and other laboratories (Kostner and Alaupovic, 1972; Pearlstein and Aladjem, 1972; Lee and Alaupovic, 1974; Fellin et al., 1974; Patsch et al., 1975; Alaupovic, 1980a) have shown clearly that each density class, but especially LDL and HDL, consist of several qualitatively distinct lipoprotein particles rather than single homogeneous complexes. The finding that apolipoproteins in each major density class occur in non-equimolar ratios provided further evidence that not all individual lipoprotein particles of the same density class could have the same apolipoprotein composition. Immunologic examination of LDL and HDL indicated that most of the discrete lipoprotein particles of these two density classes are characterized by the presence of a single apolipoprotein. On the other hand, chylomicrons and VLDL seem to contain triglyceride-rich lipoprotein particles characterized by the presence of two or more apolipoproteins. As shown schematically in Figure 1, each major density class consists of a mixture

of discrete lipoprotein particles which have similar hydrated densities but different apolipoprotein composition. These experimental facts illustrate clearly that operational concepts based on hydrated densities cannot describe in chemical terms the complex metabolic relationship between specific lipoproteins. Thus, the lipoprotein heterogeneity of density classes is incompatible with the view that operationally defined lipoproteins represent the fundamental physicochemical and metabolic entities of the system.

To account for the lipoprotein heterogeneity of operationally defined lipoprotein classes, we have proposed that the plasma lipoprotein system consists of distinct lipoprotein families as the simplest physicochemical entities of this macromolecular system (Alaupovic, 1972). A lipoprotein family is defined as a polydisperse system of lipoprotein particles characterized by the exclusive presence of a single apolipoprotein. An apolipoprotein is defined as a lipid-binding protein capable of forming a lipoprotein family. Apolipoproteins may consist of a single polypeptide chain or may be composed of several non-identical polypeptides. To express the relationship between apolipoproteins, constitutive polypeptides and corresponding lipoprotein families, we have devised a system of nomenclature referred to as the ABC-nomenclature (Alaupovic, 1980a).

As shown in Table I, the apolipoproteins are designated by capital letters, the non-identical polypeptides by Roman numerals and the polymorphic forms of apolipoproteins or polypeptides by Arabic numerals. The lipoprotein families are named according to their corresponding apolipoproteins. The ApoA-containing lipoprotein family is called

lipoprotein A (LP-A), the ApoB-containing lipoprotein family lipoprotein B (LP-B), etc. A lipoprotein particle which contains, for example, ApoB, ApoC and ApoE is called LP-B:C:E.

Figure 1 illustrates schematically the relation of the classification system based on the lipoprotein-family concept to that derived from the ultracentrifugal lipoprotein pattern. Single circles identify the simplest forms of lipoprotein families, i.e., those characterized by the presence of a single apolipoprotein. The succession of single circles of each lipoprotein family indicates its polydisperse character and its distribution along the density gradient. The large circles with several apolipoproteins depict the triglyceride-rich lipoprotein particles of lower hydrated densities which incorporate several individual lipoprotein families within their triglyceride core (association complexes of lipoprotein families). These complexes of unknown molecular structure, but defined apolipoprotein composition, are also heterogeneous with respect to hydrated density and size; they correspond to chylomicrons and VLDL. A typical association complex (LP-B:C:E), formed most probably in the systemic circulation through the interaction of a nascent triglyceride-rich LP-B with triglyceride-poor LP-C and LP-E, dissociates during lipolysis into separate lipoprotein families LP-B, LP-C and LP-E (Eisenberg and Olivecrona, 1979; Deckelbaum et al., 1979). In general, lipoproteins above a density range of 1.019-1.030 g/ml exist as discrete, separate particles, whereas at densities below that range, lipoproteins occur in the form of triglyceride-rich association complexes. Osborne and Brewer (1977) have suggested that the discrete, simple forms of lipoprotein families be referred to as "primary" lipoproteins and the

associated forms of lipoprotein-families as "secondary" lipoproteins. These authors have also suggested that the complex equilibrium between the "primary" and "secondary" lipoproteins is governed by the laws of mass action.

The first procedures for the isolation of LP-A, LP-B and LP-X from LDL of patients with obstructive jaundice (Seidel et al., 1969) and LP-A, LP-B and LP-C from HDL of normolipidemic subjects (Kostner and Alaupovic, 1972) were based on a combination of methods including immunosorbers, heparin precipitation, Cohn fractionation and hydroxylapatite column chromatography. However, these initially developed procedures were inadequate for fractionating a complex mixture of lipoproteins consisting of both discrete and associated forms of lipoprotein families. The newly developed fractionation procedures are based on the affinity chromatography of lipoproteins on concanavalin A (McConathy and Alaupovic, 1974; Fainaru et al., 1977) and immunosorbers with antibodies to individual apolipoproteins as ligands (McConathy and Alaupovic, 1976). Further development and application of those procedures to the isolation of chemically well defined lipoprotein families or particles, remains one of the most important and urgent methodological tasks in the lipoprotein field.

The biochemical significance of the lipoprotein family concept resides in its recognition of apolipoproteins as the most probable determinants of the structural integrity and functional specificity of lipoproteins. This concept identifies the simplest, antigenically well-defined lipoprotein particles (discrete lipoprotein families or "primary" lipoproteins) as the fundamental physicochemical entities of the

plasma lipoprotein system. It recognized their polydisperse character and their ability to associate or incorporate into triglyceride-rich complexes (association complexes or "secondary" lipoproteins). The lipoprotein family concept provides a chemical rather than operational classification system of lipoproteins flexible enough to accomodate the existing experimental facts and probably new facts, especially those pertaining to the discovery of new apolipoproteins. Due to their unique chemical and immunologic properties, apolipoproteins represent the most suitable markers for studying the metabolic interactions of lipoprotein particles and relatively simple means for monitoring normal and deranged lipid transport processes.

If the proper functioning of the lipid transport system depends on the availability of apolipoproteins and certain optimal concentrations of circulating lipoprotein families, any impairments of this metabolic process should result in changed concentrations of lipoprotein families commensurate with the type and extent of the underlying metabolic defect. For this reason, specific metabolic derangements of lipid transport ought to be recognized by characteristic apolipoprotein patterns or, more precisely, by qualitative and quantitative changes in the concentrations of free and associated forms of lipoprotein families. At the present, the only practical means for measuring the levels of lipoprotein families is by quantifying the corresponding apolipoproteins. Due to the great complexity of plasma lipoproteins, reliable and accurate procedures for the quantitative determination of apolipoproteins have to be based on highly specific and sensitive immunologic methodology. Several modifications of radioimmunoassay, radial immunodiffusion and electroimmuno-

assay have been described for quantification of almost all well characterized apolipoproteins with the exception of C-I, ApoF and ApoG. During the last several years, we have developed electroimmunoassays for nine apolipoproteins and applied them to determination of apolipoprotein profiles in various types of dyslipoproteinemia (Alaupovic et al., 1978).

Hypolipoproteinemias such as Tangier disease, abetalipoproteinemia, hypobetalipoproteinemia and deficiency of lecithin:cholesterol acyltransferase (LCAT) are all characterized by distinct apolipoprotein profiles. Patients with Tangier disease have negligible concentration of A-I and a very low concentration of A-II; the reduction of A-II level is not proportional to that of A-I. The levels of all other apolipoproteins are slightly reduced in comparison with normal levels. Abetalipoproteinemia is characterized by the absence of ApoB and reduced levels of ApoA, ApoC and ApoD; the levels of ApoE are normal. The molar ratio of C-I/C-III is reversed from that found in normals. Although the patients with hypobetalipoproteinemia have very low levels of ApoB, the concentrations of other apolipoproteins are not affected as in patients with abetalipoproteinemia. However, the molar ratio of C-I/C-III is higher than in normals. The apolipoprotein pattern in patients with LCAT deficiency is characterized by reduced levels of A-I, A-II, ApoB, ApoC and ApoE, but a normal level of ApoD.

Results of the quantitative determination of plasma apolipoproteins in patients with primary hyperlipoproteinemias have indicated the occurrence of four characteristic apolipoprotein profiles (Alaupovic et al., 1978; Alaupovic, 1980a). The first of these profiles is characterized by decreased levels of A-I, A-II and ApoB. This profile is characteristic

of patients with hyperchylomicronemia and applies equally to patients with familial lipoprotein lipase deficiency and those with familial C-II deficiency. Homozygotes for C-II deficiency are also characterized by the absence of C-II. The second profile is typified by proportional increases of all three ApoC polypeptides and ApoE. This profile is characteristic of patients with familial dysbetalipoproteinemia (phenotype III) and patients with phenotype V. The characteristic feature of the third apolipoprotein profile is the elevation of ApoB levels found in patients with familial hypercholesterolemia (phenotypes IIa and IIb). The fourth apolipoprotein profile is characterized by a disproportionate increase in the level of C-III polypeptide; this is reflected in reduced ratios of C-I/C-III and C-II/C-III. This pattern is typical of patients with familial hypertriglyceridemia and, frequently, of patients with phenotype IV. There may be a fifth apolipoprotein profile seen in patients with familial combined hyperlipidemia characterized by increased levels of ApoB and ApoE, but additional information is needed for such a conclusion. Preliminary results on the distribution of apolipoproteins suggest, but do not prove, that increased level of ApoB in hypercholesterolemic patients is due to increased concentrations of LP-B, whereas the increased level of C-III in patients with familial hypertriglyceridemia may be due to the presence of triglyceride-rich lipoprotein particles (LP-C-III) containing C-III as their protein moiety. It is not yet known whether LP-C-III is a normally occurring lipoprotein particle or a particle formed as a result of overproduction of triglycerides. The proportional increase of ApoC, ApoE, and ApoB levels seem to reflect increased concentrations of triglyceride-rich LP-B:C:E association complexes, whereas reduced levels of A-I, A-II and B indicate, most probably,

impaired degradation of chylomicrons (triglyceride-rich LP-A:B:C:E association complexes). Whereas these two latter apolipoprotein profiles may typify catabolic defects such as deficiency(ies) of lipolytic activities or unsuitable substrates or both, the former apolipoprotein profiles may be characteristic markers of anabolic defects or, in case of ApoB, of the receptor deficiency.

There is already some evidence that various types of secondary hyperlipoproteinemias display either one of the four common apolipoprotein profiles or some of the combinations thereof. For example, those insulin-requiring diabetics with high levels of plasma lipid have slightly lower levels of A-I and A-II, but significantly increased levels of ApoB, ApoC and ApoE than normal subjects. In contrast, patients with adult-onset diabetes have normal levels of ApoA and ApoE, but significantly increased concentrations of ApoB and C-III. Similarly, patients with chronic renal failure have an elevated concentration of C-III as the most characteristic feature of their apolipoprotein pattern. Preliminary results show that some of the liver diseases are also characterized by distinct apolipoprotein profiles. Patients with acute infectious hepatitis have significantly reduced levels of ApoA and ApoC, but highly elevated levels of ApoB. Biliary cirrhosis is characterized by elevated levels of C-III and ApoE, whereas patients with liver cirrhosis have reduced levels of A-I and A-II, but normal levels of C-III and ApoE.

The results presented suggest that determination of apolipoprotein profiles offers a new approach to the study of normal and deranged lipid transport. The apolipoprotein profiles may be utilized for diagnostic purposes or as a very sensitive means for monitoring the progress of

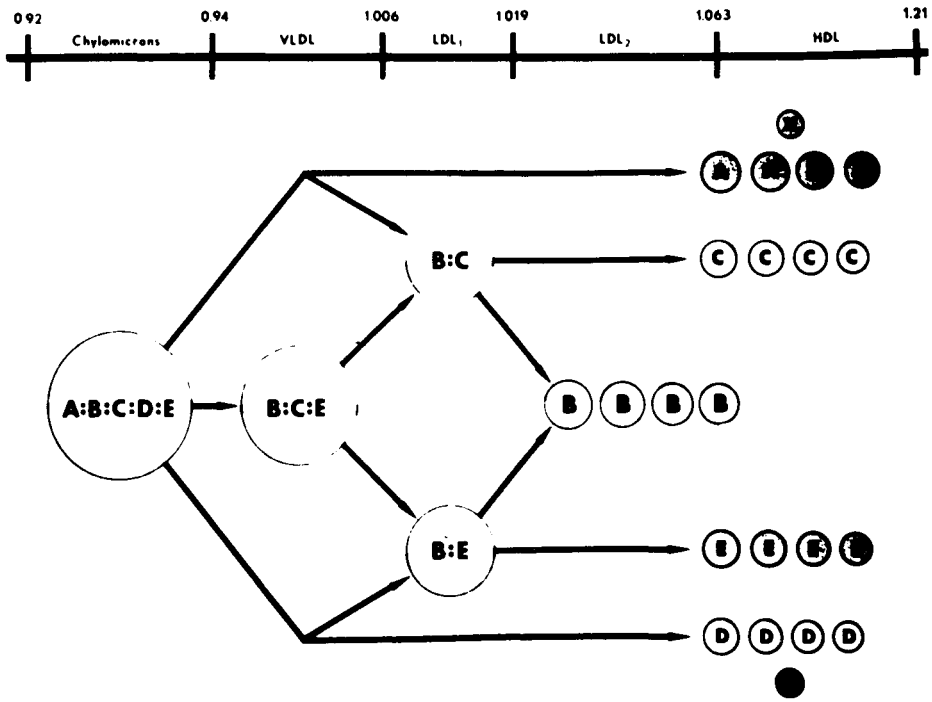

Fig. 1. A schematic view of the distribution of lipoprotein families /discrete forms and association complexes/ along the density gradient from 0.92 to 1.21 g/ml.

Table I

Nomenclature of apolipoproteins and lipoprotein families

Apolipoproteins	Constitutive Polypeptides	Polymorphic Forms	Lipoprotein Families
ApoA	A-I	A-I-1	LP-A
		A-I-2 (etc)	LP-A-I
	A-II		LP-A-II
ApoB	N K	N K	LP-B
ApoC			LP-C
	C-I		LP-C-I
	C-II		LP-C-II
	C-III	C-III-0	LP-C-III
		C-III-1	
		C-III-2	
ApoD	N K	N K	LP-D
ApoE	N K	E-1	LP-E
		E-2	
		E-3 (etc)	
ApoF	N K	N K	LP-F
ApoG	N K	N K	LP-G

N K = not known

therapeutic measures designed to normalize the underlying metabolic defects of lipid transport or both. However, additional studies are needed to evaluate the real potential of this approach.

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