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Minireview

Apolipoproteins and their role in different clinical conditions: An overview

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Apolipoproteins or apoproteins are a group of proteins associated with lipoproteins in different proportions and play significant roles in several diseases. Different types of apolipoproteins, including apolipoproteins A, B, C, D, E, H and J and their subclasses have been reported, in addition to a few more apolipoproteins reported recently. These proteins have varied, but definite roles in normal physiology in our body. Moreover, their blood levels have strong association with clinical conditions during different diseases and are used as diagnostic and prognostic markers and to compute index of risk for some serious disease entities. Present article gives an overview of the structural features, physiological significance and diagnostic and clinical implications of apolipoproteins.

Keywords: Apoproteins, lecithin-cholesterol acyl transferase, lipoprotein(a), lipoprotein lipase, clinical implications.
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Apolipoproteins or apoproteins are the polypeptides found in various types of lipoproteins. Earlier, the existence of three major groups of apolipoproteins — Apo A, Apo B and Apo C were reported[1], but lately, more apolipoproteins, such as D, E, H and J have been characterized. The classification of apolipoproteins based on their various characteristics, physiological function and chromosomal locations is summarized in Table 1. The genes of apolipoproteins are located on chromosomes 1, 2, 3, 6, 11 and 19 (Table 1). All these apolipoproteins are associated with lipoproteins and involved in the transport of chylomicrons, triglyceride, cholesterol, fatty acids, etc. They also act as cofactors or activators of enzymes like lecithin-cholesterol acyl transferase (LCAT) and lipoprotein lipase (LPL). They are differently implicated in various diseases and play significant role in diagnosis and prognosis of several disease conditions. Present review briefly summarizes some of the characteristics and implications of apolipoproteins in different clinical entities.

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Abbreviations: LCAT, lecithin-cholesterol acyl transferase; HDL, high density lipoprotein; LPL, lipoprotein lipase; LDL, low density lipoprotein; VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; Lp(a), lipoprotein(a); CSF, cerebro spinal fluid; CAD, coronary artery disease; AFP, alfa feto protein; HCC, hepato cellular carcinoma; AD, Alzheimer's disease; APP, amyloid precursor protein; SLE, systemic lupus erythematosusRA, rhematoid arthritis; PSEIr 1 & 2, presenilins 1 & 2.

Structural characteristics of apolipoproteins

Apolipoprotein AI, AII and AIV (Apo AI, AII, AIV)

Apo A-I is a single polypeptide containing 243 amino acids, derived from a precursor, pre-apo A. It is synthesized in liver and then secreted into the plasma and lymph. Its gene is located on chromosome 11, in proximity to genes coding for Apo C-III and Apo A-IV. It has a lipid-binding domain and LCAT[2] and is also the major lipoprotein of cerebrospinal fluid (CSF)[3]. Plasma Apo A-II is a 154 amino acids polypeptide containing two identical polypeptide chains linked by a disulphide bond at position 6. Its gene is located on chromosome 1. It is synthesized in liver as pre-apo A-II, which is converted to Apo A-II after removal of an 18 amino acids sequence intracellularly and is secreted into plasma. On subsequent removal of another 5 amino acids sequence, it is matured to Apo A-II. It appears to activate hepatic triglyceride lipase[2]. Mature Apo A-IV is a 377 amino acids peptide and contains about 6% carbohydrate. It is present in plasma in various isoforms[2]. Its gene is located on chromosome 11. It is synthesized in the intestine and appears to activate LCAT[4]. Patients with cirrhosis were found to have low levels of Apo A-IV.

Table 1—Classification and properties of major human plasma apolipoproteins

Apolipoprotein	Chromosomal location	Functional activity	Lipoprotein carrier(s)	References
Apo A-I	11	Cofactor LCAT	Chylomicron, HDL	2
Apo A-II	1	Not known	HDL	2
Apo A-IV	11	Activation of LCAT	Chylomicron, HDL	4
	2	Secretion of triglyceride from liver binding protein to LDL receptor	VLDL, IDL, LDL	4
Apo B-48	2	Secretion of triglyceride from intestine	Chylomicron	6
Apo B-100	2	Cholesterol transport from liver	LDL	6
Apo C-I	19	Activation of LCAT (?)	Chylomiron, VLDL, HDL	6
Apo C-II	19	Cofactor of LPL	Chylomiron, VLDL, HDL	8
Apo C-III	11	Inhibition of apo CII, activation of LPL	Chylomiron, VLDL, HDL	3
Apo D	3	Unknown	HDL	2
Apo E	19	Facilitation of uptake of chylomicron remnant and LDL	Chylomiron, VLDL, HDL	7
Apo (a)	6	Unknown	Lp (a)	18

Apolipoprotein B (Apo B-100 and Apo B-48)

Plasma Apo B-100 and Apo B-48 are found in plasma lipoproteins[5] and share a number of features. Apo B-100 is produced in liver and is present along with the other apoproteins in VLDL, IDL and LDL_2 variant, while Apo-B-48 is produced in the intestine and found in chylomicrons and their remnants. There is only one gene for Apo B, which is found on chromosome 2. It produces only Apo B-100 having a polypeptide chain of 4536 amino acids. In intestine, it codes for much smaller Apo B-48, with 2152 amino acids[6]. The mechanism of production of two different polypeptides from a single gene is not yet clearly understood[6].

Apolipoprotein C-I, C-II and C-III (Apo C-I, C-II, C-III)

Apo C-I is a small polypeptide of 57 amino acids. It is an activator of LCAT[7]. Its gene is located on chromosome 19, in proximity to Apo E gene[8]. Mature Apo C-II is a single chain polypeptide with 73 amino acids. Its gene is located on chromosome 19 and shows close genetic linkage with that of Apo E. It activates the lipoprotein lipase[2] and is reported to act as a possible receptor for hepatitis C virus[9]. Mature Apo C-III contains 79 amino acid residues and is coded by the gene on chromosome 11. The oligosaccharide chain contains one galactose, one gactosamine and 0-2 residues of sialic acids[7]. It inhibits the action of Apo C-II and activates lipoprotein lipase[8,10].

Apolipoprotein D (Apo D)

A glycosylated polypeptide chain of 169 amino acids, Apo D has a molecular weight of about 33,000. Its gene is located on chromosomes 3[2]. It has no structural similarity to other apoproteins[11,12] and is present in the blood, intestine, liver and brain[13]. In plasma, it is found mainly in HDL, in association with LCAT and Apo A-I[7,8]. Three isoforms of Apo D have been reported by isoelectric focusing. It is a member of lipocalins superfamily of proteins that are involved in transport of small hydrophobic ligands[12]. However, its exact function is not yet known[11]. The candidate ligands for Apo-D are pregnenolone, cholesterol, progesterone and arachidonic acid. It has been viewed as a marker for diagnosis of female breast cancer[14], male breast cancer, gynecomastia[15], prostate cancer[16], malignant melanoma, schizophrenia and also Alzheimer's disease[17].

Apolipoprotein E (Apo E)

The gene for Apo E is found on chromosome 19. It codes for a single polypeptide chain of 299 amino acids, which is subsequently glycosylated. There are three common alleles of Apo E—E2, E3 and E4, of which E3 is the most common. Apo E4 differs from E3 and E2 by a single amino acid at positions 112, 158 respectively. There are mainly six genotypes—E2/E2, E3/E3, E4/E4, E2/E3, E2/E4 and E3/E4. Each allele possesses a different ability to bind to the LDL receptor[18]. Its absence has been correlated with significant elevation of chylomicrons and VLDL remnants in blood. It plays an important role in transportation of lipid to central nervous system. Its role has also been implicated as an antioxidant and modulator of neurotropic factor[18].

Apolipoprotein H (Apo H)

A beta-2 glycoprotein, Apo H is synthesized by the liver and is believed to bind to hepatitis-B surface

antigen (HBsAg) in the pre S1 region and helps in its carriage and entry to hepatocytes. It is also reported to help in clearing the viral particle[19].

Apolipoprotein J (Apo J)

It is a 70 kDa glycoprotein, circulating as disulphide linked heterodimer component of lipid poor HDL and VLDL. Its function is not yet clear, but it is thought to be involved in lipid transport, regulation of complement function, sperm maturation and membrane recycling[20].

Apo(a)

A unique protein component of lipoprotein(a), [Lp(a)], Apo(a) exhibits a significant homology with plasminogen. It is made of a serine protease-like domain and has high degree of variation in polypeptide chain[21]. The variation at the Apo(a) locus is now co-related with the susceptibility to coronary heart disease. Lp(a) concentrations have relation with genesis, progression and complications of both atherosclerosis and thrombosis[22].

Physiological changes in apolipoprotein levels

At birth, the levels of apo A, B and Lp(a) are low in cord blood[18], possibly due to the relative immaturity of the liver. In first 3-4 months of life, these levels rise sharply and remain unchanged till puberty. After puberty, Apo A-I levels show a declining trend in male population. The level of Apo B-100 increases in men till around 50 years of age. Men and post-menopausal women share a similar lipid and apo-A and B profiles. The Lp(a) value shows a gradual rise and reaches adult level in the 3rd year of life[18].

Apolipoproteins and medical conditions

Inherited disorders

These include the defects in synthesis of Apo A-I, catabolism of Apo A-I (Tangier's disease), familial defective Apo B-100 disorder, deficiency of Apo C-II, familial combined hyperlipidemia and familial hypoalphalipoproteinemia. Defect in synthesis of Apo A-I leads to a significant decrease in HDL and Apo A-I levels in serum[23]. Mutation that causes rearrangement at Apo A-I gene inactivates Apo A-I and Apo C-III. Deletion of the entire locus or an insertion in the Apo A-I gene leads to the decreased synthesis and low concentration of Apo A-I[24].

Defect in catabolism of Apo A-I (Tangier's disease) is characterized by reduced plasma HDL level, abnormal HDL composition and accumulation of cholesteryl ester in many tissues throughout the body. Kinetic studies have shown that an increase in the catabolism of HDL, rather than its reduced biosynthesis, leads to the reduced HDL concentration[25]. In homozygous state, the plasma HDL and Apo A concentrations are reduced to zero level, while in heterozygous state, the concentration of HDL, Apo A-I and Apo A-II is reduced to nearly half the normal values[18].

Familial defective Apo B-100 disorder is the result of mutation in Apo B-100 gene (single substitution at 3500 residue). The positive charge on the surface of B-100 fraction of Apo B decreases, resulting in decreased affinity of LDL to LDL receptor[18]. Familial combined hyperlipidemia appears to result from the overproduction of VLDL and Apo B-100. In this condition, lipid to protein ratio is found to be low and VLDL and LDL particles to be small and less dense[18].

Apo C-II is an activator of lipoprotein lipase and if it is deficient or defective, activity of the enzyme is reduced. The fall of Apo C-II level up to 10% of the normal level may maintain normal body metabolism, however, at this level, there is an impaired catabolism of chylomicrons, causing increase in plasma level of triglycerides and cholesterol. This is accompanied by a decrease in the levels of plasma Apo C-III, E, A-I, A-II and Apo B-100 as well as HDL and LDL[18].

Familial hypoalphalipoproteinemia is characterized by a decrease in HDL level, while the plasma level of LDL and total lipids remain in the normal range. The molecular basis of the disease is not known. The changes in lipid profile are thought to be a consequence of decreased biosynthesis or defective catabolism of either Apo A-I or HDL[26].

Acquired disorders

Cardiovascular diseases

Coronary artery disease (CAD) is one of the most common diseases associated with dyslipidemia and dyslipoprotenemia. Elevated Lp(a) levels are an independent risk factor for premature CAD[27]. The mechanism for atherogenic action of Lp(a) is still unknown[28], however, it interferes with fibrinolysis[29,30] and promotes smooth muscle proliferation and binding of proteoglycan to arterial wall[31]. Lp(a) level and Apo(a) isoforms are the important markers for CAD.

In order to assess the predictive power of apolipoproteins as a marker of CAD in relation to various other risk factors like age, hypertension,

diabetes, family history, smoking and plasma levels of total cholesterol, triglyceride, low and high density lipoproteins, etc., the Apo A-I and Apo B concentrations were measured in Indian patients undergoing elective diagnostic coronary arteriography. The ratio of Apo A-I to Apo B and the measurement of Apo A-I and B were observed to provide a better marker for predicting the possibility of CAD, compared to traditional lipid profile level[32]. It was also found that overall the levels of these apolipoproteins seemed to be lower in Indian population, compared to the Western countries[33].

Cancer

The serum levels of Apo A and alpha-fetoprotein (AFP) reflect the changes in liver during liver diseases, including hepatocellular carcinoma (HCC)[34]. Apo E, particularly its phenotype epsilon 4 allele was suggested to provide protection from development of adenoma and carcinoma of proximal colon[35]. It was found to be a potent inhibitor of proliferation, tumor cell growth and metastasis[36]. Apo(a) was also associated with the suppression of colorectal cancer[37].

The expression of Apo D is reported in female and male breast cancer patients and in gynaecomastia[38]. A significant positive relationship was also found between its tumoral expression in primary tumors and metastatic lymph nodes in different types of carcinoma. In metastatic lymph nodes of breast carcinoma, Apo D expression shows a different pattern of immunostaining and is of less clinical significance than in primary tumors. In male breast cancer, a positive association of Apo D content with prognosis of diseases has been found and the Apo D expression is considered as a significant independent indicator of relapse-free survival[15]. Apo D has been used as a marker for female[14] and male[15] breast cancers, gynecomastia[15] and prostate cancer[16].

Significantly low levels of Apo A-I and A-II and the HDL fraction were reported in patients with hepatic metastasis of colorectal cancer, primary liver cancer and cirrhosis. The decrease in Apo A-II levels was more prominent in cirrhosis. Apo B level was found to be increased in hepatic metastasis. Thus, the determination of apolipoproteins and lipids of HDL fraction offers a new approach to the study of liver diseases[39]. Lp(a) is synthesized by the liver cells, and patients with liver cirrhosis show its low serum levels associated with the degree of liver failure[40]. On the contrary, increased Lp(a) serum levels were reported in cancer patients. In HCC patients, the cells *in vivo* seem to produce increased amount of serum Lp(a) levels, despite the reduced or impaired liver protein synthesis typical of liver cirrhosis[41].

Central nervous system (CNS)

Apolipoproteins and their receptors which mainly control lipid metabolism, have a significant role in the risk of cardiovascular disease, as well as in the development and degeneration of the CNS[42]. The variations in the genes coding for the apolipoproteins and their receptors lead to several metabolic disturbances in the body and an apparent change in patients' response towards dietary ingredients and therapeutic drugs. The role of Apo E in neurodevelopment, influence of Apo A-IV on triglyceride metabolism and relation of Apo A-I and HDL metabolism with ABC family of transporters have been recently reviewed[43].

Alzheimer's disease (AD) is the most common type of dementia in the elderly population. Three genes — the amyloid precursor protein (APP) gene, and presenilins 1 (PSEN1) and 2 (PSEN2) genes have been identified responsible for the rare early-onset familial form of the disease. The mutations in these genes account for less than 5% of the total number of AD cases. The remaining cases are sporadic late-onset cases, with a complex etiology due to interactions between environmental conditions and genetic features of the individual. Apo E gene was found to be associated with sporadic late-onset AD cases[17,44,45].

In post-traumatic brain injury, Apo E concentration in cerebro-spinal fluid (CSF) decreases due to its retention within the parenchyma of CNS, where it may have a protective role[46,47]. A decrease in Apo E levels is reported in CSF after subarachnoid haemorrhage also[47,48]. Recently, a simple method has been developed to detect Apo E level and its polymorphism in CSF[49].

Endocrinological disorder

Alteration of lipid profile is well known in endocrinal disorders like diabetes mellitus, thyroid dysfunction, sex hormone imbalance and acromegaly. The plasma Lp(a) levels increase in hypothyroid patients due to impaired catabolism of Lp(a) and Apo B[50,51]. Furthermore, serum Apo A-I containing lipoproteins are not under direct control of thyroid hormones[51]. There is moderate effect of thyroid hormone level on metabolism of Lp(a)[52]. Congenital hypothyroid infants have shown high levels of Apo A-I, C-III and E and low levels of Apo B[52,53]. Patients

with Turner syndrome have high levels of Apo A-I and Lp(a), though lipid parameters remain normal. Lp(a) and Apo A-I levels decrease with sex hormone replacement therapy[54].

Renal disease

Alteration of lipoprotein metabolism in renal disease results in elevated levels of Apo B containing LP. The nephrotic syndrome and heavy proteinuria are associated with increased formation of cholesterol-rich Apo B-containing LP in LDL and VLDL. However, the characteristic feature in renal failure is the accumulation of intact or partially metabolized triglyceride-rich LP in IDL and VLDL. The potentially atherogenic Apo B-containing LPs have been linked to the pathogenic processes that result in progressive glomerular and interstitial lesions and ultimate loss of renal function[55-57].

Patients with chronic renal disease suffer from a secondary form of complex dyslipidemia. The most important abnormalities are an increase in serum triglyceride levels, small LDL particles and a decrease in HDL cholesterol level. The highly atherogenic LDL subclass, namely LDL-6 or small dense LDL accumulates preferentially in hypertriglyceridemic diabetic patients with nephropathy or on hemodialysis. All these LDL subclasses contain Apo B. A study conducted in patients with chronic renal failure and end stage renal disease showed that Lp(a) levels were high in heamodialysis and peritoneal dialysis patients[58].

Pancreatic diseases

Plasma Apo B-48 levels are reported to be significantly lower in patients with chronic pancreatitis caused by malabsorption. Therefore, Apo-B-48 can be used as a diagnostic marker for chronic pancreatitis[59]. In acute pancreatitis, serum amyloid protein (an apoprotein), that acts as an acute phase reactant was found to be a good alternative to c-reactive protein[60] in diagnosing the disease.

Skin diseases

In patients with cutaneous amyloidosis, Apo A-I and E were found to have an association with components deposited in secondary cutaneous amyloidosis. However, Apo A-I was not associated with amyloid deposits in primary cutaneous amyloidosis[61].

Hematology disorders

Lp(a) is similar to low-density lipoprotein, but is unique in having an additional apolipoprotein apo(a) covalently linked to it. Physiologically, Lp(a) participates in haemocoagulation and wound healing[62]. Epidemiologically, there is evidence that it is a risk factor for atherosclerosis, particularly in populations with high serum LDL levels, as it has thrombogenic tendency. Lp(a) level was found to be significantly increased in the renal diseases and atherosclerosis[62,63].

Aging

Apoproteins like Apo A, Apo A-IV, Apo B and Apo C-III are reported to be associated with aging[64], though the mechanism of the same is not fully understood.

Transplantation

In patients undergoing liver transplantation for end-stage liver disease, Apo(a) levels in serum were reported to reach normal value within 2 weeks of transplantation, suggesting that the low levels of Apo(a) observed in severe liver diseases become normal after liver transplant[65] .

Liver diseases

Different types of apolipoproteins like Apo A-I and B-100 and their ratios may be used as markers for degree of alcoholic intoxication and the risk of cardiovascular complications[66]. In a prospective study in alcoholic patients, Apo A-I was related to the degree of liver damage, though the exact mechanism of its involvement in liver damage is not clear. In cholestatic liver disease, plasma Apo A-I and E reflect the degree of cholestasis[67,68] by their proportionally higher values.

Autoimmune diseases

Systemic lupus erythematosus (SLE) is a classic autoimmune disease characterized by the production of auto-reactive T cells and autoantibodies that may affect multiple organs. A close association has been found between cholesterol-rich lipoproteins (such as LDL-cholesterol) and cardiovascular disease in SLE patients. Since serum Lp(a) levels are significantly higher in SLE[69] patients, they have a risk of developing cardiovascular disease and atherosclerosis. Dyslipoproteinemia is a common feature in adult SLE pre-menopausal patients, which is characterized by an increase in total cholesterol, triglycerides and Apo B, and also an abnormal distribution of HDL subclasses. Corticosteroid therapy and proteinuria are the best predictors of dyslipoproteinemia in these patients[70].

Cardiovascular diseases and atherosclerotic manifestations have been reported to be the most

common cause of death in rheumatoid arthritis (RA). The reduced Apo A and HDL-cholesterol levels represent an important factor in the etiology of such manifestations[71].

Amyloidosis

The Apo A-II/A-I ratio is found to be a useful biochemical marker of amyloidosis in patients with rheumatoid arthritis. The ratio is significantly lower in amyloidosis secondary to underlying disorders[72].

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