Role of Apolipoprotein A-V in Pediatric Sepsis: Review Article

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Abstract

Sepsis induces the release of lipid mediators, which control both lipid metabolism and inflammation. However, the role of serum apolipoprotein A-V (ApoA5) in sepsis is poorly understood in pediatric patients. So, we aimed in this review to investigate the role of apolipoprotein A-V (ApoA5) in sepsis.

KeyWords: Apolipoprotein A-V, Sepsis, Pediatrics.

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Introduction:

ApolipoproteinAPOA-V gene (APOA5) is a member of the APOA4 / APOC3 / APOA1 apolipoprotein cluster and is located on a short arm of chromosome 11 (11q23) (**1**).

Triacylglycerols, or plasma triglycerides, have been the subject of intense challenge for a long time as a risk factor for all-cause mortality as well as cardiovascular disease, cancer, renal illness, and other morbidities. It's intriguing that international recommendations typically do not factor plasma triglyceride values into risk calculators, despite these new discoveries (**2**).

Chylomicrones, the biggest lipoprotein particles that carry dietary triglycerides from the gut, and very low-density lipoproteins (VLDL), which carry triglycerides made in the liver, are the principal carriers of plasma TGs in blood. The primary enzyme involved in triglyceride degradation is lipoprotein lipase, which catalyses the lipolysis of triglycerides in chylomicrones and extremely low-density particles (**3**).

APOA5 has been referred to as "a potent TG reducer" and as having a "low concentration, high impact" since its discovery. The liver seems to be the primary organ where APOA5 is expressed. The protein's circulating mature form is extremely helical and hydrophobic; in rats, it is mostly linked with HDL and to a lesser extent VLDL. APOA5 is connected to HDL, VLDL, and chylomicrons in human plasma but not LDL. Since then, immunoblotting of the chylous component of intestinal lymph has proven that APOA5 is linked to chylomicrons in that fluid. Its plasma concentration in humans is incredibly low when compared to other apolipoproteins, ranging from 20 to 500 ng/ml, which is around 1000 times lower than APOB and 10,000 times lower than APOA1 on a molar basis. According to this, there is one APOA5 molecule for every 24 VLDL particles (**4**).

Apolipoprotein A5 discovery

The apolipoprotein A5 gene (APOA5, gene ID 116519, OMIM accession number - 606368) was first identified by **Pennacchio et al. (4)** by comparative sequencing of around 200 kbp of human and mouse DNA as the final member of the gene cluster encoding the apolipoproteins APOA1/ APOC3/ APOA4/ APOA5, which is located on human chromosome 11 at location 11q23. The importance of this gene in determining plasma

triglyceride levels was demonstrated by the development of two mouse models (APOA5 transgenic and APOA5 knock-out). Plasma triglyceride levels were greater in the knock-out mice and lower in the transgenic mice, although plasma cholesterol levels were the same in both animal models**(4).**

With the exception of apolipoprotein B, which has 29 exons, the apolipoprotein A5 gene is small, measures about 3 kbp in length, is made up of 4 exons (the start codon is located in the second exon), and 3 introns. Its codes for a 366 amino acid protein, including the 23 amino acid signal peptide and the 343 amino acids mature APOA5 protein **(3).**

It's interesting to note that a Dutch study by **van der Vliet et al. (6)** who concurrently identified the same gene as apolipoprotein, which is connected to the early stages of liver regeneration, but neglected to acknowledge its critical function in regulating plasma triglyceride levels. **Ngaosuwan et al. (7)** revealed that the function of apolipoprotein A5 as an acute phase protein is absolutely unrecognized and has not been well researched **(3).**

Gene structure and expression regulation

On chromosome 11q23, the human APOA1/C3/A4/A5 gene clusters are found, with the APOC3 gene being around 35 kbp upstream of the APOA5 gene locus. They have conserved sequences throughout evolution. A set of proximal promotors with four elements (283/+ 24) and distal enhancer with six elements (800/500) are present in the human APOC3 gene regulatory regions. The APOC3 enhancer functioned as a shared regulatory region to control the expression of the APOA1, APOC3, and APOA4 genes in the hepatic and intestinal tissues, according to earlier animal and cell culture research. However, a 26 kb DNA XhoI-fragment containing only the APOA5 gene and lacking the APOC3 enhancer was successful in achieving sufficient liver-specific APOA5 gene expression in vivo. Further evidence that the APOC3 enhancer didn't affect APOA5 expression in transgenic mice was provided by Gao et al. Two components of the APOA5 promotor region have been discovered to be essential for controlling the production of the protein in human hepatic cell lines (**8**).

Specific transcription factor binding to gene regulatory elements triggers the start of gene expression, and molecules that interfere with this process can control the corresponding gene expression. In fact, a number of molecules have been linked to the same direction regulation of APOA5 expression, including upregulation with hepatocyte nuclear factor 4 (HNF4-), glucose, and insulin, and downregulation with AMP-activated protein kinase, as well as insulin and tumour necrosis factor (TNF-). The fact that all of these chemicals, with the exception of TNF-, are significant elements directly engaged in glucose metabolism raises the possibility that APOA5 dysregulation has a role in diabetic dyslipidemia. The promotion of APOA5 by the farnesoid X-activated receptor (FXR) and peroxisome proliferator-activated receptor (PPAR) was another instance of opposite direction regulation. As a result, boosting the level of apoA5 in the blood may help fibrates, one form of PPAR-agonist, reduce plasma TG levels(**8**).

Apolipoprotein A1/C3/A4/A5 Gene Cluster Polymorphisms and Associated Risks

The altered fasting and postprandial TG levels are associated with some mutations in the APOA5 gene, such as T-1131C and Ser19Trp. The APOA5 gene also contributes to three major haplotypes based on five polymorphisms: 1131T>C, c.3A>G, c.56C>G, IVS3+476G>A, and c.1259T>C, respectively (**9**).

The APOA1/C3/A4/A5 gene cluster has been implicated with a variety of diseases, including those with elevated TG and TC levels. the effects of the haplotypes in the APOA1/C3/A4/A5 gene cluster contribute to the known recurrences of the familial combined hyperlipidemia (FCH) families in a systematic manner (**9**).

Plasma and serum levels of TG molecules and their consistent associations with

CVD, growth hormone deficiency (GHD), and CHD risks are increasing in APOC3 and APOA5 rs2854116 and rs662799 polymorphisms in the European population, but contrast shows lower risks for the Triethnic groups (Non-Hispanics, African-Americans, and Hispanics) in C allele with the higher HDL levels (**9**).

APOA5 gene polymorphisms on obesity and the metabolic syndrome

APOA5 single nucleotide polymorphisms (SNPs) and obesity

One of the most effective controllers of plasma TG concentrations, APOA5, has been associated with obesity. However, its mechanisms of action are not well understood. There is evidence linking the existence of APOA5 gene SNPs to an increased risk of obesity. SNPs contributed to the onset of obesity and changes in the blood levels of lipids and proteins (**10**).

Table (1): The single polymorphisms of APOA5 gene and the association with obesity and metabolic syndromes

Gene	SNP/position	Association with diseases
APOA5	-1131 T > C	CAD
		Elevated plasma TG
		Elevated LDL-TG
		Decreased HDL-C
		Elevated VLDL-C
		Decreased LDL particle size
		Elevated TG after fasting
		Elevated postprandial TG
		Elevated postprandial VLDL
		Higher dense postprandial LDL
		Elevated postprandial CRP
		Elevated total cholesterol
		Elevated BMI
		Elevated fat intake
		Lower obesity risk
	c.1259 T > C	Elevated plasma TG
		Protective against obesity (alone)
	c.56C > G	Higher BMI, waist and hip circumference
		Extreme obesity (carried with LPL m107)
		Decreased HDL
	c.3A > G	Elevated metabolic syndrome risk
	c.553G > T	Elevated metabolic syndrome risk
	c.724C > G	Elevated plasma TG
	IVS3 + 476G > A	Elevated plasma TG

CAD coronary artery disease, *TG* triglyceride, *LDL* low density lipoprotein, *VLDL* very low-density lipoprotein, *LDL-C* low density lipoprotein cholesterol, *CRP* C-reactive protein, *LPL* lipoprotein lipase, *SNP* single nucleotide polymorphism, *BMI* body mass index (**10**).

APOA5 SNPs and metabolic syndrome

APOA5 SNPs could potentially affect the metabolic syndrome since obesity has been shown to promote its development. Indeed, higher TG levels and lower HDL levels, two elements of metabolic syndromes, were reported to be associated with APOA5 SNPs (**10**).

Apolipoprotein A5 in coronary artery disease

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APOA5 polymorphisms that result in lower apoA5 levels were linked to a higher risk of coronary artery disease (CAD). A significant meta-analysis has demonstrated the link between the -1131 T > C promoter polymorphism of the APOA5 gene with risk of CAD. Per C vs. T allele, there was a 1.18 risk ratio for CAD. Furthermore, a number of independent studies have consistently shown a significant association between APOA5 variants and the risk of myocardial infarction (MI). Strong correlation between early-onset acute MI and the APOA5 -1131 T > C gene variant was discovered by **De Caterina et al. (11),** (**8**).

Further research by **Jorgensen et al. (12)** revealed that variations in the APOA5 gene (c.-1131 T. C, S19 W, and c.*31C. T) are 87% more likely to increase the risk of MI. Exons of APOA5 were sequenced in 6721 patients with MI and 6711 controls by **Do et al. (13)** With an allele frequency of less than 1%, 46 distinct non-synonymous single nucleotide variations, splice-site variants, or indel frameshifts were found. Additionally, APOA5 gene carriers (1.4% of cases versus 0.6% of controls) had a 2.2-fold higher risk of MI than non-carriers (**8**).

Furthermore, it has been proposed that variations in plasma RC levels serve as a partial mediator of the effects of apoA5 on CAD risk. RC is genetically elevated as a result of APOA5 gene variations (c.-1131 T. C, S19 W, and c.*31C. T) and is linked to an increased risk of MI. However, RC increases of up to 56% were associated with APOA5 gene variants (c.-1131 T. C, S19 W, and c.*31C. T), which also had a 1.87 odds ratio for MI (**8**).

The word "RC" is used to describe the total cholesterol content of triglyceride rich protein (TRL), which includes intermediate-density lipoproteins (IDL) and VLDL in the fasting state as well as VLDL, IDL, and chylomicron remnants in the non-fasting state. There is mounting evidence that RC is a separate causative risk factor for ischemic heart disease. Furthermore, in patients with ischemic heart disease, elevated RC levels were linked to an increase in all-cause mortality **(14).**

Association of Serum Apolipoprotein A5 Concentration with Nonalcoholic Fatty Liver Disease

In the absence of alcohol or any other clear causes of liver damage, nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic illness characterised by an abnormal buildup of hepatic fat and steatosis. It has been established that obesity, insulin resistance, and dyslipidemia are all intimately associated to NAFLD. While this is going on, it is known as a liver manifestation of the metabolic syndrome and is frequently linked to a higher risk of type 2 diabetes and cardiovascular disease. Nearly 25% of people worldwide have NAFLD, which poses a serious threat to the world's economy and healthcare system **(15,16,17, 18).**

Study performed in China revealed that in general series and NAFLD patients, the genotypes of rs10750097(G/G), rs1263173(A/A), rs17120035(T/T), and rs662799(G/G) significantly influenced clinic features, suggesting that these polymorphisms may be linked to NAFLD **(19).**

However, **Liuet al.** revealed that despite there is no discernible difference between ApoA5 levels, NAFLD, and metabolic syndrome, there is an inverted "U-shaped" correlation between ApoA5 levels and the prevalence of hypertriglyceridemia (**20**).

According to **Li et al**., sortilin reduces the hepatic apoA5 production that is caused by olanzapine-induced NAFLD. This knowledge provides a new spotlight on NAFLD prevention methods for schizophrenia patients who take olanzapine (**21**).

Apolipoprotein A5 and pediatric sepsis

In a pediatric intensive care unit (PICU), sepsis—a systemic, harmful host response to infection that causes organ failure and septic shock—is frequent and linked to high rates of morbidity and death. According to a recent analysis, poor nations had higher pooled case fatality rates (31.7%) than industrialized countries (19.3%). Pediatric doctors find it difficult to accurately predict the course and

prognosis of sepsis following admission to the PICU, despite significant medical advancements (**22**).

Non-cardiovascular dysfunction was one of the definitions of sepsis in the first worldwide guidelines for the Pediatric Surviving Sepsis Campaign (SSC) published in 2020 (**23**). The presence of a suspected infection and unusual physical examination results, such as poor perfusion, hypotension, tachycardia, temperature anomalies, and altered mental status, are among the clinical signs of pediatric sepsis (**24**).

Severe metabolic changes and a large release of catecholamines, stress hormones, and inflammatory mediators accompany the systemic inflammatory response seen in sepsis. Inadequate metabolic control in the liver increases mortality from bacterial infection (**25**), and coordinated metabolic and epigenetic disturbances control the sepsis-induced switch from hyper- to hypo inflammation in innate immune cells **(26).** Currently, metabolic interventions or resuscitation may show to be a novel cornerstone for enhancing sepsis outcomes. There is little information to say if indicators for metabolic stress can predict how sepsis will develop or turn out (**27**).

In rats and humans, the apoA5 gene appears to regulate triglyceride homeostasis. Patients with familial combination hyperlipidemia have different plasma triglyceride levels depending on nucleotide variants in the ApoA5 gene. High-density lipoprotein cholesterol (HDL-C) levels are lowered and plasma triglyceride levels are elevated as a result of the acute-phase reactions in sepsis. According to a recent study in adult sepsis patients, low ApoA5 levels are linked to a greater death rate, but the correlation vanished when HDL-C levels were taken into account. (**9**).

In pediatric patients with sepsis, the blood ApoA5 level is related to signs of disease severity including shock, acute kidney damage, acute liver injury, gastrointestinal dysfunction, or multiple organ dysfunction syndrome. Additionally, the prognostic value of ApoA5 in children with sepsis, and additional research is required to confirm this finding in a large prospective study with a well-designed study (**28**).

Despite the fact that a number of studies have found a direct link between ApoA5 gene polymorphisms and vascular disorders such hypertension, coronary artery disease, and stroke, the underlying mechanism has not been fully explored (**29**). Recent research suggested that ApoA5 may protect against acute inflammation and lipopolysaccharide (LPS)-induced fulminant liver failure as well as serve as a diagnostic and prognostic indicator in children with sepsis. These investigations showed that ApoA5 could affect vascular disorders in other ways than TG modulation (**30, 31**).

Acute-phase proteins such APOA5, copeptin, and pancreatic stone protein (PSP) can be used to diagnose pediatric sepsis in critically ill pediatric patients and identify its severity. Serum levels of PSP and copeptin were positively correlated with mortality and had the ability to distinguish between non-survivors and survivors. Although APOA5 serum concentrations had a negative correlation with mortality, they were not as effective as the other biomarkers in identifying survivors from non-survivors. (**32**).

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