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A Systematic Review of Apolipoprotein A-I Mimetic Peptides for Atherosclerosis Therapy via Activation of the Reverse Cholesterol Transport Pathway

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Review Article

Abstract

BACKGROUND: HDL has been identified as a potential new treatment for atherosclerosis. Targeting lipid metabolism via the Reverse Cholesterol Transport (RCT) pathway can improve HDL metabolism. Apolipoprotein A-I mimetic peptides (ApoA-I MPs) are able to increase HDL metabolism. Thus, this systematic review aimed to examine the potential effect of ApoA-I MPs against atherosclerosis in mice models through the RCT mechanism.

METHODS: This systematic review was conducted using previous in vivo studies published in four scientific databases over the last ten years (PubMed, SCOPUS, ProQuest, and Science Direct) and was based on the Systematic Review Protocol for Animal Intervention Studies (SYRCLE) protocol.

RESULTS: This study's primary outcome was a reduction in atherosclerotic plaque, where 16 articles were qualified for this study. Based on the risk of bias analysis, these articles had a low risk of bias. Most in vivo studies (13 of 16) showed that ApoA-I MPs significantly reduced atherosclerotic plaque formation. Generally, ApoA-I MPs played an important role in regulating HDL metabolism (HDL remodeling process, increased cholesterol efflux, and stimulated RCT pathway) and anti-inflammatory agent. ApoA-I MPs may differ in their ability to reduce atherosclerotic plaque depending on the peptide sequence and administration route.

CONCLUSIONS: ApoA-I MPs can reduce atherosclerotic plaque formation in mice by increasing cholesterol efflux via the RCT pathway. Further investigation is required to support the development of ApoA-I MPs as a new therapy for atherosclerosis in humans.

Keywords: Apolipoprotein A-I mimetic peptides, Atherosclerosis, HDL Metabolism, Reverse Cholesterol Transport

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Introduction

Atherosclerosis is a chronic plaque formation in the inner arterial wall that increases global cardiovascular disease morbidity and mortality rates.[1] This disorder caused 31% of global deaths in 2015.[1] Furthermore, atherosclerosis is negatively correlated with high-density lipoprotein (HDL) cholesterol levels, making HDL metabolism an important potential target for the development of atherosclerosis therapy.[2] RCT is an alternative pathway for boosting HDL metabolism.

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Table 2. Characteristics of eligible studies

No	Authors (Year)	Animal Models	Age	Gender	Diet	Diet Duration	Peptide Type	Dose	Route	Duration	Groups and Samples
1	Navab et al. (2011)	Mice ApoE-/- C57BL/6	8-9 month	female	WD	8 wk	D-4F, Sc-D-4F	900 µg/ day	SQ and PO	8 wk	I: Sc-D-4F SQ; II: D-4F SQ; III: Sc-D-4F PO; IV: D-4F PO (n=12/ group)
2	Ou et al. (2012)	Mice LDLr-/- C57BL/6	8 wk	female	WD	10 wk	D-4F	1 mg/ kg/ day	IP	4,7, 10 wk	I: Standard Feed; II: WD 10 wk; III: WD 10 wk + D-4F 4 wk; IV: WD 10 wk + D-4F 7 wk; V : WD 10 wk + D-4F 10 wk (n=6 / group)
3	Qin et al. (2012)	Mice ApoE-/- C57BL/6	4 wk	female	Standard Feed	6 wk	L-4F and Rev-D-4F	1.6 mg/ day	PO	6 wk	I: Control (n=15); II: L-4F (n=12); III: Rev-D-4F (n=12)
4	Chattopadhyay et al. (2013)	Mice ApoE -/- C57BL/6	4–6 month	female	WD	6-7 wk	L-6F	60 mg/ kg /day	PO	6-7 wk	IA: WD (n=30) ; IIA: WD + 6F (n=30)
		Mice LDLr-/- C57BL/6	10 wk	female	WD	2 wk	EV and Tg6F Tomatoes	40 mg/ kg/ day	PO	2 wk	IB: WD (n=20); IIB: WD + WT Tomatoes (n=8); IIIB: WD + Tg6F (n=8)
		Mice LDLr-/- C57BL/6	4-5 month	female	WD	13 wk	EV and Tg6F Tomatoes	45 mg/ kg/ day	PO	13 wk	IC: WD (n=28); IIC: WD + EV Tomatoes (n=8); IIIC: WD + Tg6F (n=20)
5	Ditiatkovski et al. (2013)	Mice ApoE -/- C57BL/6	10 wk	male	HFD	4 wk	ELK-2A2K2E peptide	30mg/ kg/ wk	IP	16 wk	I: Placebo; II: ELK-2A2K2E (n=8/group)
6	Li et al. (2013)	Mice LDLr-/- C57BL/6	3 month	male	HFD, UFP	10 wk	D-4F	0.2 mg/ ml/ Mice	SQ	10 wk	I: FA; II: FA + D-4F; III: UTP; IV: UTP + D4F (n=9/group)
7	Uehara et al. (2013)	Mice LDLr-/- and C57BL/6	6-7 wk	male	HFD	3x / wk for 16 wk	ScFAMP, LD FAMP5, HD FAMP5	10 and 50 mg/kg	IP	3x /wk for 16 wk	I: ScFAMP (n=7); II: LD FAMP5 (n=5); III: HD FAMP5 (n=7)
8	Ying et al. (2013)	Mice ApoE -/- C57BL/6 and WT	8 wk	male	HFD	16 wk	L-4F	1 mg/ kg/ day	IP	16 wk	I: Control; II: HFD; III: Simva; IV: L-4F; V: Simva + L-4F (n=6/group)
9	Averill et al. (2014)	Mice LDLr-/- C57BL/6	10 wk	male	HFH SC	12 wk	L-4F	100 µg / day	SQ	12 wk	I: Control; II: L-4F (n=5)
10	Zhao et al. (2014)	Mice LDLr-/- C57BL/6	10 wk	female	HFD	10 wk	DMPC *nanoparticle*	7.5, 40, 75 mg/ kg	IP and PO	10 wk	IP I: Control (n=10); IP II: DMPC ULV (n=10); IP III: monomer / DMPC (n=12); IP IV: trimer / DMPC (n=15); PO I: kontrol (n=18); PO II: DMPC MLV (n=8); PO III: monomer / DMPC (n=10); PO IV: trimer / DMPC 75 mg/kg (n=10); PO V: trimer / DMPC 7,5 mg/kg (n=8)
11	Schwendeman et al. (2015)	Mice LDLr-/- C57BL/6	8 wk	male	HCD	14 wk	5A-POPC and 5A-SM rHDL	50 mg/ kg	IP	3x/ wk for 6 wk	I: Baseline; II: PBS; III: 5A-POPC; IV: 5A-SM rHDL (n=7-8/group)
12	Ditiatkovski et al. (2017)	Mice ApoE -/- C57BL/6	6-7 wk	male	HFD	12 wk	5A, ELK-2A2K2E, 5A-C1, ELK-2A2K2E+5A-C1, ELKA-CH2, ELK-2A, 5A-CH1	30 mg/ kg	IP	4 wk	I: Control; II: 5A; III: ELK-2A2K2E; IV:5A-C1; V: ELK-2A2K2E+5A-C1; VI: ELKA-CH1; VII: ELK-2A; VIII: 5A-CH1
13	Tian et al. (2017)	Mice LDLr-/- C57BL/6	7 wk	male	HFD	8 wk	Sc-D-4F and D-4F	1 mg/ kg/ day	IP	6 wk	I: Control; II: Sc-D-4F; III: D-4F (n=8/group)

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No	Authors (Year)	Animal Models	Age	Gender	Diet	Diet Duration	Peptide Type	Dose	Route	Duration	Groups and Samples
14	Edmunds et al. (2019)	Mice ApoE -/- C57BL/6	12 wk	female	WD	6 wk	RG54	12 mg/ kg	IP	3x/ wk for 6 mg	I: NaCl; II: Liraglutide; III: ApoA-I; IV: RG54 (n=9)
15	Suematsu et al. (2019)	Mice ApoE -/- C57BL/6 and CETP Tg	6 wk	male	HFD	2x/wk for 16 wk	FAMP and i-FAMP-D1	FAMP (50 mg/ kg), i-FAMP-D1 (50 mg/ kg)	IP	3x/ wk for 16 wk	I: Control; II: FAMP; III: i-FAMP-D1 (n=6/group)
16	Wu et al. (2020)	Mice LDLr-/- C57BL/6	6-8 wk	male	HCD	12 wk	Rev-D-4F	2.1 mg/ kg	IV	9 wk	I: PBS; II: ST; III: MNC@M-ST; IV: AP; V: MNC@M-AP; VI: MNC@M-ST/AP (n=6/group)

AP, Apolipoprotein; ApoA-I, Apolipoprotein A-I; ApoE, Apolipoprotein E; CETP, Cholesteryl Ester Transfer Protein; DMPC, R)-(+)-1,2-dimyristoyl-sn-glycero-3-phosphocholine; EV, empty vector; FA, filtered air; FAMP, Fukuoka University ApoA-I MPs; HCD, high cholesterol; diet; HD, high dose; HFD, high-fat diet; HFHSC, High Fat High Sucrose diet with added Cholesterol; IP, intraperitoneal; kg, kilogram; LD, low dose; LDLr, low-density lipoprotein receptor; mg, milligram; MNC@M, Fe3O4 magnetic nanoclusters coated with anchored leukocyte membrane fragments; MLV, multilamellar vesicle; NaCl, Natrium Chloride; PBS, phosphate buffer saline; PO, peroral; POPC, palmitoyl oleoyl phosphatidyl choline; Rev-D-4F, reverse-D-4F; rHDL, reconstituted-HDL; Sc, Scrambled; SM, sphingomyelins; ST, Simvastatin; SQ, subcutaneous; Tg6F, transgenic 6F; UFP, ultrafine particle; ULV, unilamellar vesicle; WD, western diet; Wk, week; WT, wild-type; µg, microgram; *= p<0.05; **=p<0.01; ***=p<0.001.

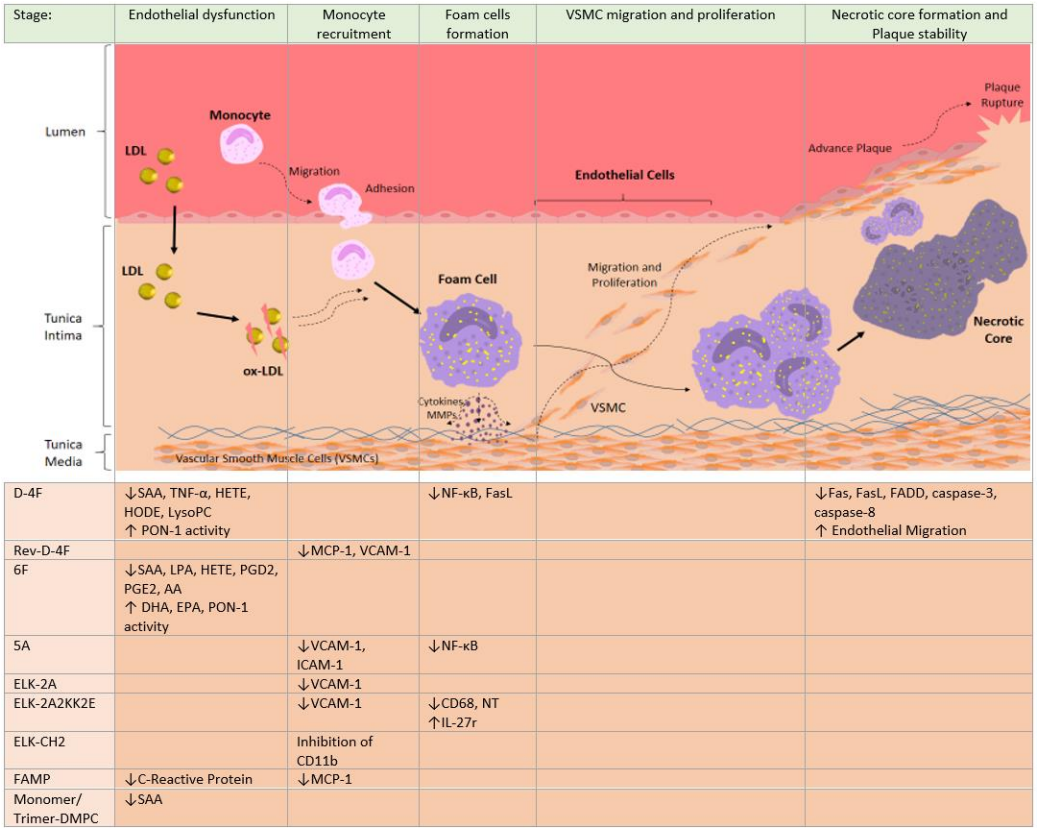

Figure 3. The Role of ApoA-I MPs against atherosclerosis.
AA, Arachidonic Acid; CD, Cluster of Differentiation; DHA, Docosahexaenoic Acid; EPA, Eicosapentaenoic Acid; FADD, Fas-Associated Death Domain; FAMP, Fukuoka University Apolipoprotein A-I Mimetic Peptide; FasL, Fas Ligand; HETE, Hydroxyeicosatetraenoic Acid; HODE, Hydroxyoctadecadienoic Acid; ICAM-1, Intercellular Adhesion Molecule 1; IL, Interleukin; LDL, Low Density Lipoprotein; LPA, lysophosphatidic Acid; LysoPC, Lysophosphatidylcholine; MCP-1, Monocyte Chemotactic Protein 1; NF-κB, Nuclear Factor Kappa B; NT, Nitrotyrosine; Ox-LDL, Oxidized Low Density Lipoprotein; PGD2, Prostaglandin D2; PGE2, Prostaglandin E2; PON-1, Paraoxonase-1; Rev-D-4F, Reverse-D-4F; SAA, Serum Amyloid A; VCAM-1, Vascular Cell Adhesion Molecule 1; VSMCs, Vascular Smooth Muscle Cells

Intraperitoneal administration of L-4F peptide significantly reduced plaque formation,[14] while oral and subcutaneous administration had no significant effect.[12,15]

The Rev-D-4F peptide was utilized by Wu et al. (2020). Rev-D-4F is an analog of the peptide D-4F. Intravenous administration of this peptide in conjunction with self-driven bioinspired nanovehicles in the form of Fe_3O_4 magnetic nanocluster (MNCs) coated by Simvastatin (ST) and associated with leukocyte membrane fragments (MNC@M-ST-AP) could reduce plaque formation.[13]

In contrast to the previous study, Chattopadhyay et al. (2013) demonstrated oral administration of L-6F and 6F peptides from transgenic tomatoes using transgenic tomatoes constructed with Empty Vector (EV) and a vector expressing 6F peptide could significantly reduce plaque formation.[16]

Other studies utilized intraperitoneal administration of various peptides, including 5A, ELK-2A2K2E, 5A-C1, ELK-2A2K2E and 5A-C1 combination, ELKA-CH2, ELK-2A, and also 5A-CH.[18] Ditiatkovski et al. (2017) evidenced a significant reduction of plaque formation, particularly in the aortic arch than other locations of histological lesions.[18] Regarding treatment duration, ELK-2A2K2E peptide did not affect thoracal and abdominal aortic plaque during week 16.[18] On the other hand, Schwendeman et al. (2015) used a combination of 5A peptide with SM and POPC with HDL reconstruction (5A-SM and 5A-POPC rHDL). When compared to 5A-SM, 5A-POPC rHDL significantly reduced atherosclerotic plaque formation.[22]

Discussion

In this systematic review, 16 studies that developed ApoA-I MPs for the treatment of atherosclerosis in mice were examined. Depending on peptide type, administration route and time, and location of histological lesions, the majority of ApoA-I MPs could reduce atherosclerotic plaque. In addition, this systematic review describes the potential mechanism of ApoA-I MPs against the formation of atherosclerotic plaques. As the HDL metabolism regulator (HDL remodeling, cholesterol efflux, and RCT) and anti-inflammatory agent, it decreases the formation of atherosclerosis plaques by reducing plaque formation.

Apolipoprotein A-I as HDL Metabolism Regulator

ApoA-I MPs help to increase the pre-β1-HDL formation and improve the RCT mechanism. In the early stages of RCT, these nanoparticles play an important role as acceptors of free cholesterols from ABCA1.[4] The lipid-poor pre-β1-HDL is gradually enlarged due to cholesterol uptake and esterification catalyzed by the LCAT. The enlarged HDL contributes to the lipid core, which can receive phospholipids and free cholesterol from peripheral tissue via Adenosine Triphosphate Binding Cassette G1 (ABCG1). These HDL molecules release cholesterol ester into the hepatocytes via scavenger receptor class B type I (SR-BI) or transfer them to LDL via a CETP-mediated mechanism involving transfer protein (PLTP) and diverse lipases for HDL remodeling.[4]

A previous study showed that D-4F could increase cholesterol removal from foam cells and plasma pre-β1-HDL formation and regulate cholesterol levels.[11] Subcutaneous administration of L-4F also could reduce atherosclerosis formation by upregulation of ABCA1 and ABCG1 expression in the macrophages, liver, and aortic walls, as well as SR-BI expression in the liver and aortic walls.[14] Moreover, the L-4F peptide significantly increased cholesterol efflux,[14] but this peptide became less unstable by oral administration due to digestion by intestinal proteases compared to the D-4F.[14,15] Previous studies have shown that oral administration of D-4F is safe and well-tolerated.[24]

On the other hand, the 5A peptide is a bi-helix amphipathic peptide with high specificity for ABCA1-mediated cholesterol efflux and low cytotoxicity.[25] This mimetic peptide could stimulate a 3.5-fold increase in ABCA1-mediated cell efflux and a 2.5-fold increase when combined with phospholipid.[25] The 5A-C1 peptide significantly increased cholesterol

efflux.[18] and 5A-POPC was also found to increase cholesterol efflux by ABCG1. To this end, 5A-POPC binds to HDL and LDL and increases the transfer of cholesterol from LDL to HDL.[25]

The other type of peptide is ELK/ELKA. ELK-2A2K2E significantly increases cholesterol efflux.[17, 18] Moreover, Fukuoka University ApoA-I MPs (FAMP) were reported to demonstrate two roles in HDL metabolism, especially in the production of pre-β-HDL metabolism. FAMP could increase cholesterol efflux through ABCA1-dependent or -independent mechanism to produce new pre-β HDL particles.[26] Furthermore, incubation of FAMP with human HDL or plasma could produce both small HDL particles and ApoA-I-rich particles. These particles migrated as pre-HDL on agarose electrophoresis.[27]

Apolipoprotein A-I as Anti-Inflammatory Agent

Most ApoA-I MPs play a role as an anti-inflammatory agent. ApoA-I functions as an anti-inflammatory agent through the uptake of oxidized lipids, which is facilitated by the high affinity of active peptides for oxidized fatty acids, sterols, and phospholipids.[4] ApoA-I MPs, as anti-inflammatory agents in monocyte chemotactic activity (MCA) and atherosclerosis, have a high affinity against oxidized fatty acids, cholesterol, and phospholipids. ApoA-I MPs can also inhibit MCA stimulation mediated by LDL. ApoA-I MPs also play a role in stimulating endothelial nitric oxidase synthase (eNOS), thus leading to vasodilated blood vessels.[28]

Studies of ApoA-I MPs had been developed from a physicochemical and biological aspect (in vitro) into animal models (in vivo). Recent studies have examined various ApoA-I MPs as anti-inflammatory agents (Figure 3).[11,12,17,18]an apolipoprotein A-I mimetic peptide, on nuclear factor-κB (NF-κB D-4F and L-4F peptides have been proven to regulate various plasma and tissue biomarkers to prevent or reduce atherosclerosis. D-4F had a role as an atheroprotective agent through oxidative stress and inflammation inhibition.[11] Rev-D-4F was also developed as ApoA-I MP against atherosclerosis. This peptide significantly inhibited VCAM-1 and MCP-1, which play a role in monocyte adhesion and chemotaxis.[12]

Another type of ApoA-I MPs, 6F, was proven to reduce the total plasma cholesterol, triglycerides, SAA, LPA, 5-HETE, 15-HETE, PGD2, PGE2, and AA. LPA has been shown to alter the secretion of apoB-containing lipoproteins from hepatocytes, accelerating atherosclerosis in a mouse model.[29]

Oxidation of LDL generates lysophosphatidylcholine, which is the main substrate for the lysophosphatidic acid (LPA The Tg6F also could decrease systemic inflammation and dyslipidemia in WD-induced mice by preventing the increase of SAA and LPA levels in the small intestine.[16]

In addition, ELK-2A2K2E could decrease CD68, VCAM-1, and NT expression and raise RCT value via cholesterol and fecal bile acid. ELKA-CH2 was observed to be a selective CD11b inhibitor in monocytes. Furthermore, ELK-2A has been demonstrated to be a selective inhibitor of VCAM-1 expression in endothelial cells.[17, 18] Monocyte CD11b expression can be suppressed by ABCA1-dependent or -independent mechanisms.[25] Moreover, ELK-2A and ELKA-CH2 could increase IL-27 expression.[18]

However, no research has been conducted on the safety and tolerability of other ApoA-I MPs. Concerning its applicability, the primary issue with ApoA-I MPs is their high production costs.[30]

Conclusions

ApoA-I MPs can inhibit atherosclerosis through RCT and anti-inflammatory pathways. Nonetheless, the characteristics of eligible items are extremely diverse. Administration of ApoA-I MPs could reduce the formation of atherosclerotic plaques in mice models, depending on the peptide type and method of administration. Some ApoA-I MPs also affect the lipid profile and other biomarkers in the plasma and tissue. Several ApoA-I MPs (4F, 5A, ELKs, and FAMP) inhibit atherosclerosis by increased of cholesterol efflux in the RCT

pathway.

A recent study revealed no results regarding the safety and toxicity of ApoA-I MPs except for the D-4F peptide. Several types of ApoA-I MPs, however, have not been evaluated for cholesterol efflux or RCT value; therefore, additional research is required. Moreover, research on ApoA-I MPs safety, toxicity, and human clinical trials is required to support the development of ApoA-I MPs as a new therapy for atherosclerosis in humans.

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