Baghdad Journal of Biochemistry and Applied Biological Sciences

NARRATIVE REVIEW

2025, VOL. 6, NO. 3, 148-152, e-ISSN: 2706-9915, p-ISSN: 2706-9907

The Role of 13-Hydroxyoctadecadienoic Acid, 15-Lipoxygenase, and Peroxisome Proliferator-Activated Receptor Alpha Gene Polymorphism (rs1800206) in Acute Coronary Syndrome: Pathophysiological Insights and Biomarker Relevance

Abdullah Abdulsattar Raeef[1]*, Hassan H. Al-Saeed[2], Sami Mekhlif Mishlish[3]

[1]Department of Medical Laboratories Techniques, College of Health and Medical Technology, University of Al-Maarif, Al-Anbar, Iraq
[2] Department of chemistry and biochemistry, College of medicine/Al-Nahrain University, Iraq
[3] University of Anbar, College of Medicine, Department of Medicine, Iraq

Article's Information

Received: 27.05.2025
Accepted: 17.06.2025
Published online: 20.06.2025
Published: 10.07.2025

* Corresponding authors.

E-mail:
Abdullah.abdulsatta@uoa.edu.iq

Pages:148-152

https://doi.org/10.47419/bjbabs.v6i03.401

Abstract

Acute Coronary Syndrome (ACS) represents a spectrum of life-threatening cardiovascular conditions characterized by sudden myocardial ischemia. This review synthesizes current knowledge on the pathophysiological roles of 13-hydroxyoctadecadienoic acid (13-HODE), 15-lipoxygenase (15-LOX), and peroxisome proliferator-activated receptor alpha (PPAR-α) in ACS development, with particular emphasis on the PPAR-α rs1800206 (Leu162Val) polymorphism. Emerging evidence highlights the dual role of 13-HODE as both a pro-inflammatory mediator and angiogenic factor, while 15-LOX drives oxidative stress and contributes to plaque destabilization. The PPAR-α pathway emerges as a critical regulator of lipid metabolism and vascular inflammation, with the rs1800206 variant modifying disease susceptibility and therapeutic responses to fibrates. The authors further explore established and novel biomarkers, including high-sensitivity troponin, CK-MB, hs-CRP, and atherogenic lipid profiles, which collectively enhance ACS diagnosis and risk stratification. The integration of these molecular and genetic markers provides a framework for understanding the complex interplay between inflammation, oxidative stress, and metabolic dysregulation in ACS. Therefore, the findings have value in the clinic since they increase therapy choices for PPAR-α and draw attention to the potential for personalized medicine in ACS. This literature review endeavors to push precision medicine for ACS, by reviewing the specific mechanisms of 13-HODE, 15-LOX and PPAR-α polymorphisms and showing how this information can be applied to help patients.

Keywords: Acute Coronary Syndrome, 13-HODE, Myocardial Injury, 15-LOX, PPAR-alpha.

1. Introduction

Cardiovascular diseases CVDs cause the most deaths and one of the main ways they do this is through acute coronary syndrome (ACS). Many contributing factors to ACS are endothelial dysfunction, inflammation, lipids in the blood and genetic predisposition [1,2]. The presence of classical risks like diabetes, smoking and hypertension does much of the work in cardiovascular disease, but molecules such as PPAR-α, 15-LOX and 13-HODE are also key players in lipid regulation and vascular inflammation [3,4].

Reduced blood supply to the heart muscle causes the group of diseases known as acute coronary syndrome (ACS). The main types of acute coronary syndrome involve ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. Angina describes the pain, discomfort or pressure people feel in their chest when there is reduced blood flow and this pain may move to the arms or jaw. Many people explain it as an uncomfortable pressure in their chest. Either a new angina episode or chronic angina that appears after 20 minutes rest is classified as class III or IV by the Canadian Cardiovascular Society. MIs which include NSTEMI and STEMI, happen when parts of the myocardium become necrotic following a blockage in blood flow. Analysis of the ECG is what sets MIs apart from each other. Nearly all cases of STEMI are accompanied by ST segment elevation on the ECG, but NSTEMI will have no such feature, though other changes might be read as ischemic. Even though the symptoms are the same for NSTEMI and STEMI, STEMI results in a worse heart injury than NSTEMI [5].

ACS is diagnosed with the combination of how the patient presents, ECG changes and an increase in a specific type of blood test. ACS can make someone feel chest pain, have difficulty breathing, feel lightheaded, break out in sweats or become pale. A patient's personal experience of these symptoms can change according to age, gender and other cultural elements. Because disease symptoms may be different in these groups, doctors should keep a close eye for it. Ischemic can cause the ECG to show abnormal changes to the heart's muscle. Evidence of elevated or depressed ST segments, the appearance of T wave changes or the markers Q wave presence may suggest ACS. Lastly, an MI is frequently diagnosed by biomarkers released into the bloodstream with myocardial damage, such as troponin T and I and creatine kinase myocardial band (CK-MB) [6].

1. The Role of 15-Lipoxygenase (15-LOX) in ACS

A class of non-heme iron-containing dioxygenases known as the mammalian Lipoxygenases (LOXs) catalyze the stereospecific oxidation of arachidonic acid and other polyunsaturated fatty acids to produce a range of physiologically active substances. One of the fatty acid dioxygenases in the lipoxygenase family is 15 15-lipoxygenase (15-LOX). Nevertheless, the focus was shifted to competing members of the family, namely
12 (ω-hydroxyeicosatetraenoic acid) protein phosphatase, which likewise preferentially hydroxylates fatty acids at the 15-position [7].

Numerous investigations have linked cardiovascular disorders to 15-LOX. It has been demonstrated that the human coronary artery atherosclerotic plaques exhibit elevated 15-LOX activity. Furthermore, in many animal models, the development of atherosclerosis is linked to 15-LOX bioactive lipid mediators. On the other hand, animals who have their 15-LOX activity inhibited develop atherosclerotic plaque and other cardiovascular problems such as heart failure, ischemic stroke, and coronary stenosis. The idea that elevated 15-LOX activity in vascular tissues is a risk factor for cardiovascular events is supported by these data. 15-LOX activity may act as a mediator between atherogenesis, immunological response, and arterial wall remodeling by influencing vascular inflammation and atherogenesis [8].

Through the synthesis of different lipoxygenated mediators, 15-lipoxygenase (15-LOX) contributes to the mediation of inflammatory reactions and the enhancement of immunological activities. However, 15-LOX also controls oxidative stress by producing 15-HETE, which has antioxidant qualities by squelching free radicals and deactivating the enzymes that produce reactive oxygen species, such as lipoxygenase and xanthine oxidase. Therefore, 15-LOX activity is a two-pronged sword that may have anti-inflammatory and antioxidant effects in addition to pro-inflammatory ones. Notably, the 15-LOX pathway prevents oxidative stress and inflammation while preserving the equilibrium of inflammatory responses to encourage positive reactions [4].

In ACS patients, elevated 15-LOX levels suggest a state of enhanced oxidative stress and inflammation, further implicating this enzyme as a contributor to plaque rupture and ACS pathogenesis [9].

2. 13-HODE and Vascular Inflammation

The omega-6 polyunsaturated fatty acid 13-Hydroxyoctadecadionoic acid (13-HODE, C18H34O3) is hydroxylated at position 13 of the chain [10]. Lipids, known as HODEs are of significant interest to researchers studying disease and physiology. By activating receptors like peroxisome proliferator-activated receptors (PPARs), initiating cell signaling pathways involved in metabolic regulation, and regulating pro-inflammatory responses and cell death, they carry out a variety of biological tasks [11].

Investigations are conducted on 13-HODE's (hydroxy octadecadienoic acid) complex involvement in illness development. It has been demonstrated that 13-HODE accelerates the

development of cardiovascular disorders, cancer, and neuro degeneration. A strong pathogenic factor influencing the course of illness states that 13-HODE levels are abnormal in several disease disorders. Through the PPARγ/Stat3 pathway, 13-HODE is known to be a strong pro-angiogenic agent in malignancies, up-regulating the production of vascular endothelial growth factor (VEGF) in macrophages. In models of prostatic intraepithelial neoplasia, macrophage-derived 13-HODE may enhance neoplastic development by promoting the angiogenic switch in pre-neoplastic lesions [12].

3. Peroxisome Proliferator-Activated Receptors (PPARs): Functions and Isoforms

Nuclear hormone receptors called PPARs control genes related to inflammation, glucose balance, and lipid metabolism. The liver, heart, and skeletal muscle all have high levels of PPAR-α expression, which regulates fatty acid β-oxidation and lowers inflammatory reactions [13,14]. PPAR-α affects gene transcription essential for lipid management and vascular health by binding to PPREs and heterodimerizing with RXR [15].

A subfamily of nuclear receptor proteins known as peroxisome proliferator-activated receptors (PPARs) is essential for controlling inflammation and the metabolism of fats and carbohydrates in animals. Three primary isoforms of PPARs have been identified: PPARα, PPARβ/δ, and PPARγ. The discovery that certain activating substances triggered a subpopulation of peroxisomal enzymes in mouse tissues suggested that the matching protein could regulate genes, which predicted the presence of PPARα. These three mammalian proteins were eventually identified as belonging to an evolutionarily conserved family and given the names α, β/δ, and γ after differentiating the effects of fibrate hypo lipidemic drugs on PPARα gene expression in the liver and heart in comparison to other malfunctioning PPARs [16].

Numerous human health and disease conditions are linked to PPARs. The expression of genes related to fatty acid oxidation, ketogenesis, and triglyceride level modulation is a major function of PPAR-α in the regulation of lipid and glucose metabolism. One of the most important regulators of fatty acid catabolism in skeletal muscle is PPAR-β/δ. Adipose tissue is the primary site of PPAR-γ expression, which is essential for the expression of genes related to triglyceride synthesis, fatty acid absorption, and adipocyte development [17].

In the vascular endothelium, PPAR Alpha activation promotes the synthesis of the vasodilator nitric oxide and suppresses the expression of the vasoconstrictor endothelin-1 (ET-1). Additionally, PPAR Alpha regulates the production of growth factors and oxidative stress, both of which affect endothelial function and vascular smooth muscle cell (VSMC) activity. PPAR Alpha synthetic ligands inhibit the development of atherosclerotic lesions and reduce the resulting inflammatory response. Another important regulator of energy balance in cardiomyocytes that affects the onset of heart failure is PPAR Alpha. Finally, ligands for PPAR Alpha modulate insulin sensitivity and oxidative stress by interacting with other signaling pathways in the context of vascular function and systemic energy metabolism[15].

4. Genetic Polymorphism rs1800206 (Leu162Val) in PPAR-α

At position 162, the PPAR-α gene's *rs1800206 SNP* causes a leucine-to-valine substitution (Leu162Val). In addition to changing receptor activation, this mutation may have an impact on lipid profiles, inflammation, and cardiovascular outcomes [18]. Higher triglycerides and different reactions to fibrate treatment have been linked to carriers of the Val162 variation. Significant differences in PPAR-α levels associated with this *SNP* are seen in patient group with ACS, suggesting its significance in disease severity and susceptibility [19].

5. Biomarkers of Myocardial Injury and Inflammation

6.1. Troponin and CK-MB

Troponin and CK-MB are established biomarkers for myocardial infarction. Troponin, specifically cTnI and cTnT, reflects cardiomyocyte injury with high specificity and sensitivity. Elevated CK-MB levels complement troponin findings and assist in early diagnosis [20,21].

6.2. High Sensitivity CRP (hs-CRP)

hs-CRP, an acute-phase reactant, has emerged as a robust marker of systemic inflammation and cardiovascular risk. Elevated hs-CRP levels in ACS patients reflect ongoing inflammation and predict adverse outcomes [22]. The link between hs-CRP, 13-HODE, and 5-LOX pathways underscores an inflammatory network central to ACS pathology.

6.3. Lipid Profile Alterations

Dyslipidemia, a critical risk factor in ACS, is reflected in altered levels of total cholesterol, LDL, HDL, and triglycerides. LDL and low HDL

levels are consistently associated with ACS incidence and severity. A study showed that the LDL levels elevated in ACS patients and reduced HDL compared to controls, with differences more marked in NSTEMI and STEMI subgroups[23,24].

7. Pathophysiological Integration

The coordinated activity of 13-HODE, 15-LOX, and PPAR-α forms a critical axis influencing endothelial function, lipid oxidation, and inflammatory responses. The *rs1800206* polymorphism may enhance susceptibility to ACS by modifying PPAR-α activity, altering gene expression in lipid metabolism pathways, and weakening anti-inflammatory responses [25]. The interplay of these molecular factors with classic risk elements accelerates atherogenesis and plaque instability.

8. Clinical Implications and Therapeutic Insights

Targeting the PPAR-α pathway via agonists (e.g., fibrates) offers promising therapeutic avenues. Identification of individuals harboring the *rs1800206* polymorphism can optimize treatment strategies and risk stratification. Similarly, monitoring of 13-HODE, 15-LOX, and hs-CRP levels may guide early intervention and prognosis [13,26].

Conclusion

In summary, this review commands attention to important roles of 13-HODE, 15-LOX, and PPAR-α in the pathogenesis of ACS, where the polymorphism of rs1800206 may influence susceptibility to disease and treatment responses. Existing pathways and biomarker links allow for better evaluation and forecast of both ACS and further ACS-related events. By changing treatment for these pathways, we might end up with personalized treatments, especially focusing on PPAR-alpha.

Acknowledgments: We would like to acknowledge the University of Al Maarif /Iraq/Anbar for providing the laboratories to complete the practical part of the research.

DECLARATIONS

1-Authors' contributions.

Contributor Role	Degree of Contribution		
	Lead	**Equal**	**Supporting**
Conceptualization	AAR	HHS	SMM
Data curation	AAR		
Formal analysis	AAR		
Funding acquisition	AAR		
Investigation		HHS	
Methodology	AAR	HHS	
Project administration	AAR	HHS	SMM
Resources	AAR		
Software	AAR	HHS	
Supervision		HHS	SMM
Validation		HHS	
Visualization	AAR	HHS	
Writing-original draft	AAR		
Writing-review & editing		HHS	SMM

2-Ethical approval: The study was approved by the institutional review board (IRB) of the College of Medicine/Al-Nahrain University with reference I.D (20231005).

3-Conflicts of Interest: The authors declare that they have no conflicts of interest.

4-Funding resources: No funding resources.

References

[1] Surya A. Machine Learning and Ensemble Approach Onto Predicting Heart Disease. arXiv preprint.https://doi.org/10.48550/arXiv:211108667. 2021.

[2] Di Cesare M, Perel P, Taylor S, Kabudula C, Bixby H, Gaziano TA, et al. The heart of the world. Global heart. 2024;19(1):11. doi: 10.5334/gh.1288

[3] Kobe MJ. Structural and Kinetic Investigations of 15-Lipoxygenase-2: Louisiana State University and Agricultural & Mechanical College; 2015. https://www.proquest.com/openview/a826604a327416abf2ef21e00ad7f138/1?pq-origsite=gscholar&cbl=18750&diss=y

[4] Mitra S. Insights into 5-Lipoxygenase Active Site and Catalysis: Louisiana State University and Agricultural & Mechanical College; 2015. https://digitalcommons.lsu.edu/gradschool_dissertations/3000

[5] Singh A, Museedi AS, Grossman SA. Acute coronary syndrome. 2017. PMID: 29083796

[6] Kumar A, Cannon CP, editors. Acute coronary syndromes: diagnosis and management, part I. Mayo Clinic Proceedings; 2009: Elsevier. https://doi.org/10.4065/84.10.917

[7] Erba F, Mei G, Minicozzi V, Sabatucci A, Di Venere A, Maccarrone M. Conformational dynamics of lipoxygenases and their interaction with biological

membranes. International journal of molecular sciences. 2024;25(4):2241. https://doi.org/10.3390/ijms25042241

[8] Snodgrass RG, Zezina E, Namgaladze D, Gupta S, Angioni C, Geisslinger G, et al. A novel function for 15-lipoxygenases in cholesterol homeostasis and CCL17 production in human macrophages. Frontiers in immunology. 2018;9:1906. https://doi.org/10.3389/fimmu.2018.01906

[9] Manicone AM, McGuire JK. Matrix metalloproteinases as modulators of inflammation. Seminars in cell & developmental biology. 2008;19(1):3441.DOI.10.1016/j.semcdb.2007.07.003.

[10] Umeno A, Sakashita M, Sugino S, Murotomi K, Okuzawa T, Morita N, et al. Comprehensive analysis of PPARγ agonist activities of stereo-, regio-, and enantio-isomers of hydroxyoctadecadienoic acids. Bioscience Reports. 2020;40(4): https://doi.org/10.1042/BSR20193767.

[11] Yessoufou A, Wahli W. Multifaceted roles of peroxisome proliferator-activated receptors (PPARs) at the cellular and whole organism levels. Swiss Medical Weekly. 2010;140(3738):w13071.DOI.10.4414/smw.2010.13071.

[12] Spindler SA, Sarkar FH, Sakr WA, Blackburn ML, Bull AW, Lagattuta M, et al. Production of 13-hydroxyoctadecadienoic acid (13-HODE) by prostate tumors and cell lines. Biochemical and biophysical research communications. 1997;239(3):775.https://doi.org/10.1006/bbrc.1997.7471

[13] Cheng HS, Tan WR, Low ZS, Marvalim C, Lee JYH, Tan NS. Exploration and development of PPAR modulators in health and disease: an update of clinical evidence. International journal of molecular sciences. 2019;20(20): https://doi.org/10.3390/ijms20205055.

[14] Wagner K-D, Wagner N. PPARs and myocardial infarction. International journal of molecular sciences. 2020; https://doi.org/10.3390/ijms21249436.

[15] Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. Journal of hepatology. 2015;62(3):720-33. https://doi.org/10.1016/j.jhep.2014.10.039

[16] Changizi Z, Kajbaf F, Moslehi A. An overview of the role of peroxisome proliferator-activated receptors in liver diseases. Journal of Clinical and Translational Hepatology. 2023;11(7):1542. doi: 10.14218/JCTH.2023.00334

[17] Berger J, Moller DE. The mechanisms of action of PPARs. Annual review of medicine. 2002;53(1):409-35. https://doi.org/10.1146/annurev.med.53.082901.104018

[18] Uthurralt J, Gordish-Dressman H, Bradbury M, Tesi-Rocha C, Devaney J, Harmon B, et al. PPARα L162V underlies variation in serum triglycerides and subcutaneous fat volume in young males. BMC medical genetics. 2007;8:1-11. https://doi.org/10.1186/1471-2350-8-55.

[19] Blackett PR, Sanghera DK. Genetic determinants of cardiometabolic risk: a proposed model for phenotype association and interaction. Journal of clinical lipidology. 2013;7(1):65-81. https://doi.org/10.1016/j.jacl.2012.04.079

[20] Chaulin AM. Biology of cardiac troponins: Emphasis on metabolism. Biology. 2022;11(3):429.https://doi.org/10.3390/biology11030429

[21] Papadaki M, Marston SB. The importance of intrinsically disordered segments of cardiac troponin in modulating function by phosphorylation and disease-causing mutations. Frontiers in physiology. 2016;7:508. https://doi.org/10.3389/fphys.2016.00508

[22] Banait T, Wanjari A, Danade V, Banait S, Jain J. Role of high-sensitivity C-reactive protein (Hs-CRP) in non-communicable diseases: a review. Cureus. 2022;14(10). DOI: 10.7759/cureus.30225

[23] Mormone A, Tortorella G, Esposito F, Caturano A, Marrone A, Cozzolino D, et al. Advances in pharmacological approaches for managing hypercholesterolemia: a comprehensive overview of novel treatments. Biomedicines. 2024;12(2):432. https://doi.org/10.3390/biomedicines12020432

[24] Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, et al. The role of lipids and lipoproteins in atherosclerosis. Endotext [Internet]. 2019. PMID: 26844337

[25] Han L, Shen W-J, Bittner S, Kraemer FB, Azhar S. PPARs: regulators of metabolism and as therapeutic targets in cardiovascular disease. Part I: PPAR-α. Future cardiology. 2017;13(3):259-78. https://doi.org/10.2217/fca-2016-0059

[26] Kersten S. Integrated physiology and systems biology of PPARα. Molecular metabolism. 2014;3(4):354-71. https://doi.org/10.1016/j.molmet.2014.02.002