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Role of Serum Endothelin-Converting Enzyme-1 (ECE-1), Adenosine Monophosphate-Activated Protein Kinase (AMPK), and Oxidized Low-Density Lipoprotein (Ox-LDL) in the Pathophysiology and Theoretical Diagnostic Framework of Type 2 Diabetic Mellitus Patients with Acute Myocardial Infarction: A Narrative Review (Article Review)

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دور كل من إنزيم محول الإندوثيلين-1 المصلي (ECE-1)، وبروتين كيناز المنشط بـ AMP (AMPK)، والبروتين الدهني منخفض الكثافة المؤكسد (Ox-LDL) في اطار تشخيصي نظري لمرضى السكري من النوع الثاني المصابين بالاحتشاء القلبي الحاد:مراجعة سردية (مراجعة مقالية)

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) significantly increases the risk of acute myocardial infarction (AMI) through mechanisms including vascular dysfunction, oxidative stress, and inflammation. Conventional diagnostic tools, such as electrocardiography and troponins, often exhibit limited efficacy in patients with T2DM due to atypical symptom presentation.

Materials and Methods: This narrative review synthesizes published evidence from basic, preclinical, and clinical studies on the structure, functions, and interplay of a panel of serum biomarkers — endothelin-converting enzyme-1 (ECE-1), adenosine monophosphate-activated protein kinase (AMPK), and oxidized low-density lipoprotein (ox-LDL) — in the pathophysiology of AMI in the context of T2DM (T2DM-AMI). This narrative review synthesizes published evidence from basic, preclinical, and clinical studies on the structure, functions, and interplay of a panel of serum biomarkers — ECE-1, AMPK, and ox-LDL — in the pathophysiology of AMI in the context of T2DM (T2DM-AMI). No original patient data, clinical cohorts, or laboratory measurements are presented. The diagnostic potential discussed is derived from mechanistic and correlational studies and remains theoretical.

Results: ECE-1 promotes vasoconstriction via endothelin-1 (ET-1), AMPK serves as a master regulator of cellular energy balance, and ox-LDL is a key driver of atherosclerosis. Their interactions highlight a vicious cycle of metabolic and vascular damage. Based on published mechanistic and correlational evidence, combining these biomarkers may theoretically improve early diagnosis and personalized treatment; however, this remains hypothetical pending clinical validation in prospective cohorts containing original patient data. No quantitative diagnostic metrics (sensitivity, specificity, AUC-ROC, or cutoff thresholds) for the proposed biomarker panel are available from the current literature. Similarly, no quantitative comparison with existing diagnostic standards (high-sensitivity troponin or electrocardiography) is provided, as such validation studies have not yet been conducted.

Conclusion: The panel of ECE-1, AMPK, and ox-LDL shows theoretical diagnostic potential for T2DM-AMI based on existing mechanistic studies. However, because this is a narrative review without original patient data, clinical cohorts, or laboratory measurements, clinical validation in prospective studies is required before any diagnostic application can be recommended. However, without established diagnostic criteria, quantitative metrics (sensitivity, specificity, AUC-ROC, cutoff values), or direct quantitative comparison with current standards (hs-troponin, ECG), the term "diagnosis" remains aspirational. Clinical validation studies reporting these quantitative measures are urgently needed.

Keywords: Type 2 Diabetic Mellitus, Serum Endothelin, AMPK, ECE-1, Myocardial Infarction, Narrative review, Hypothesis-generating, Theoretical framework

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, and type 2 diabetes mellitus (T2DM) is a major contributor to its escalating prevalence. T2DM is characterized by chronic hyperglycemia, insulin resistance, and relative insulin deficiency. These metabolic derangements accelerate atherosclerosis and dramatically increase the risk of acute myocardial infarction (AMI). Patients with T2DM are more likely than non-diabetic individuals to suffer an AMI [1]. The atypical presentation of AMI in this cohort, often characterized by silent or unrecognized symptoms, frequently leads to delayed diagnosis and, consequently, more severe complications and poorer outcomes [1-3]. Given the heightened cardiovascular risk in this population, novel diagnostic strategies are urgently needed.

Currently, the diagnosis of AMI relies on clinical symptoms, electrocardiogram (ECG) findings, and elevated cardiac troponins. However, the diagnostic accuracy of these methods can be compromised in T2DM patients, due to atypical presentations and confounding comorbidities. For instance, diabetic neuropathy can mask typical anginal pain, while pre-existing ECG abnormalities and chronic kidney disease can complicate the interpretation of ECG and troponin results, respectively [4]. Furthermore, these traditional markers primarily indicate myocardial necrosis rather than the underlying pathophysiological processes. T2DM accelerates arterial stiffening and endothelial dysfunction through a confluence of metabolic stress, oxidative stress, and chronic inflammation. Therefore, biomarkers that reflect these upstream processes might theoretically enable earlier diagnosis and guide targeted therapies, but this remains hypothetical and requires validation in diagnostic accuracy studies [5].

This review examines ECE-1, AMPK and Ox-LDL as potential biomarkers for AMI in T2DM. ECE-1 catalyzes the production of endothelin-1 (ET-1), a potent vasoconstrictor that contributes to vascular fibrosis [5]. AMPK maintains energy balance and mitigates inflammation. Ox-LDL promotes endothelial damage and plaque formation. Their interplay—ox-LDL upregulating ECE-1 and down regulating AMPK—exacerbates T2DM-AMI pathology [6]. **The aim of the present review** is to elucidate their roles and interrelationships based on mechanistic evidence, and to explore their theoretical diagnostic utility, acknowledging that no diagnostic validation has yet been performed [6]. It is important to clarify that this narrative review does not provide quantitative diagnostic metrics (e.g., sensitivity, specificity, AUC-ROC, or cutoff thresholds) for the proposed biomarkers, nor does it offer a direct quantitative comparison with existing diagnostic standards such as high-sensitivity troponin or electrocardiography. Such data are not yet available in the published literature. Therefore, the use of the term "diagnosis" in the title reflects the theoretical potential of these biomarkers based on pathophysiological mechanisms, not an established clinical diagnostic utility.

MATERIALS AND METHODS:

This narrative review synthesizes published evidence from basic, preclinical, and clinical studies on the structure, functions, and interplay of a panel of serum biomarkers — endothelin-converting enzyme-1 (ECE-1), adenosine monophosphate-activated protein kinase (AMPK), and oxidized low-density lipoprotein (ox-LDL) — in the pathophysiology of AMI in the context of

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T2DM (T2DM-AMI). No original patient data, clinical cohorts, or laboratory measurements are presented. The diagnostic potential discussed is derived from mechanistic and correlational studies and remains theoretical. Explicitly stated this is a "narrative review" with no original patient data, cohorts, or lab measurements.

2.1. Review Design

This is a narrative (non-systematic) review. Unlike a systematic review or meta-analysis, this paper does not follow PRISMA guidelines, nor does it employ a systematic search strategy with predefined inclusion/exclusion criteria. The aim of this narrative review is to synthesize and discuss published mechanistic, preclinical, and clinical evidence regarding the roles of ECE-1, AMPK, and ox-LDL in the pathophysiology of T2DM-AMI, and to explore their theoretical diagnostic potential.

2.2. Literature Search (Narrative Approach)

A non-systematic literature search was conducted using the following electronic databases: PubMed, Google Scholar, and Scopus. The search was performed between October, 2025 till March, 2026. The following search terms were used in various combinations: "Endothelin-converting enzyme-1" OR "ECE-1", "AMP-activated protein kinase" OR "AMPK", "oxidized low-density lipoprotein" OR "ox-LDL", "type 2 diabetes mellitus" OR "T2DM", "acute myocardial infarction" OR "AMI", "biomarkers", "diagnosis", "endothelial dysfunction", "oxidative stress", and "inflammation".

2.3. Selection Criteria (Narrative Approach)

Articles were considered for inclusion if they were published in peer-reviewed journals in English, presented original or review data on the structure, function, or pathophysiology of ECE-1, AMPK, or ox-LDL in the context of T2DM, AMI, or cardiovascular disease. No formal inclusion/exclusion criteria were applied, and no quality assessment or grading of evidence was performed, consistent with the narrative nature of this review. Preference was given to recent publications (last 10-15 years), but seminal older papers were also included where relevant.

2.4. Data Extraction and Synthesis

Data were extracted manually from selected articles by the author. The synthesis was organized thematically around each biomarker (ECE-1, AMPK, ox-LDL), followed by a discussion of their interrelationships. No quantitative meta-analysis was performed.

2.5. Limitations of the Methodology

This narrative review has several methodological limitations: (1) no systematic search strategy was used, which may introduce selection bias; (2) no quality assessment of included studies was performed; (3) no grading of evidence strength (e.g., GRADE criteria) was applied; (4) no original patient data or laboratory measurements are presented. Therefore, the conclusions are hypothesis-generating rather than definitive.

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RESULTS

1. Endothelin Converting Enzyme -1 (ECE-1)

1.1 Structure of ECE-1

Endothelin-1 (ET-1) is a 21-amino-acid peptide essential for vascular homeostasis. Despite a short plasma half-life (1.5–4 minutes), ET-1 exerts prolonged effects due to strong receptor binding and downstream signaling. Its clearance is mediated by receptor- B (ETB) uptake, enzymatic degradation, and hepatic clearance. Among the endothelin peptides, ET-1 is the most potent isoform and a key mediator of vasoconstriction in T2DM and AMI. The biological effects of ET-1 are mediated by two receptor subtypes: ETA and ETB. ETA receptors, located on vascular smooth muscle cells, mediate vasoconstriction and cell proliferation. In contrast, ETB receptors on endothelial cells promote vasodilation through the release of nitric oxide (NO) and prostacyclin, while also facilitating ET-1 clearance. The balanced regulation of these receptors is essential for vascular health; an imbalance can precipitate disease [7].

ECE-1 is a zinc-activated metallopeptidase that converts the 38-amino-acid precursor, Big ET-1, into the active 21-amino-acid ET-1. There are four isoforms of ECE-1 (ECE-1a, ECE-1b, ECE-1c and ECE-1d), each with distinct subcellular localizations and functions. Notably, ECE-1c is responsible for significant ET-1 production in vascular tissues, linking it closely to T2DM and AMI. Alterations in ECE-1 activity can lead to endothelial dysfunction and exacerbate inflammation, processes that are central to these pathologies [8]. The isoforms feature zinc-containing domains that facilitate ET-1 creation at the plasma membrane, within intracellular vesicles, and in the Golgi apparatus. Pathophysiological states arise when the ECE-1/ET-1 axis is dysregulated in T2DM and AMI [9]. In T2DM, chronic hyperglycemia, oxidative stress, and inflammation elevate ECE-1 levels, promoting ET-1 release. This results in endothelial dysfunction, increased vascular stiffness, accelerated atherosclerosis, and diabetic microvascular complications. Similarly, in AMI, high levels of ET-1 worsen ischemia-reperfusion injury, promote adverse cardiac remodeling, and destabilize atherosclerotic plaques, contributing to heart failure [9].

The elevated action of ECE-1, specifically ECE-1a and ECE-1c at the endothelial membrane, is significant in increasing ET-1 production under these conditions. Thus, based on mechanistic evidence, ECE-1 has been suggested as a potential biomarker and a target for vascular and metabolic diseases. However, diagnostic accuracy studies have not yet been conducted [10]. The isoforms ECE-1a and ECE-1c are typically found at the cell surface and in early endosomes, enabling rapid, cell-surface production of ET-1 [11]. In contrast, ECE-1b resides in the trans-Golgi network, processing intracellular big ET-1 for secretion. ECE-1d is primarily located in early endosomes, where it is involved in intracellular signaling and the degradation of other neuropeptides. This differential localization allows for precise regulation of ET-1, which is critical for both normal physiology and disease states [12].

1.2.Physiological Functions of ECE-1

ECE-1 a protein of (753–770 amino acids) cleaves big ET-1 to generate active ET-1, thereby regulating vascular tone, proliferation, fibrosis, and inflammation [13]. In a healthy state,

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ET-1 vasoconstrictive effects are balanced with NO. However, oxidative stress disrupts this equilibrium , favoring ET-1 dominance [12]. ETA receptor activation leads to vasoconstriction, while ETB receptors are primarily responsible for ET-1 clearance, mainly in the lungs [13].

1.3. Role of ECE-1 in the Pathophysiology of Type 2 Diabetes

The pathophysiological changes and vascular complications in T2DM are strongly associated with ECE-1, which catalyzes ET-1 production [14]. Diabetes causes endothelial dysfunction earlier than other complications which increases the risks for cardiovascular problems and microvascular problems such as retinopathy, nephropathy and neuropathy. The ECE-1-mediated increase in ET-1 is a major contributor to generalized endothelial dysfunction [15].

Chronic hyperglycemia, is a major driver of increased ET-1 production. The heightened activity of ECE-1 in high-glucose conditions is partly mediated by the activation of the protein kinase C (PKC)-delta isoform. Evidence indicates that dysglycemia leads to the activation of the endothelin system [15]. Researchers suggest that inhibiting this PKC isoform could prevent the hyperglycemia-associated rise in ET-1, highlighting ECE-1';s crucial role in diabetic vascular damage. Consequently, ECE-1 is viewed not only as a marker of diabetes but also as a key enzyme in the development of its vascular complications. Monitoring this pathway's activity could help clinicians assess disease severity in diabetic patients [16].

Hyperglycemia in diabetic people causes oxidative stress, making NO less available and leading ET-1 to rise which stops the normal relaxation of blood vessels. As T2DM progresses, the decline in NO bioavailability, coupled with sustained ET system activation, promotes adverse vascular remodeling and growth of atherosclerotic plaques in the vessel walls [17]. The ability of ET-1 to induce vascular proliferation, fibrosis, and inflammation contributes significantly to many diabetic vascular problems. Though a direct action of ECE-1 on insulin resistance is lacking in the literature, it is clear that the role of ECE-1 in T2DM links it to problems that promote insulin resistance, including higher levels of free fatty acids and dysregulated production of adipokines. Therefore, the activity of ECE-1 in the body follows the metabolic abnormalities present in T2DM.[18-19]. All figures (1-4) in this review are conceptual/schematic diagrams created by the author for illustrative purposes. They are not derived from or adapted from any specific published figure unless explicitly stated. The mechanistic data underlying these diagrams are supported by the cited references[20].

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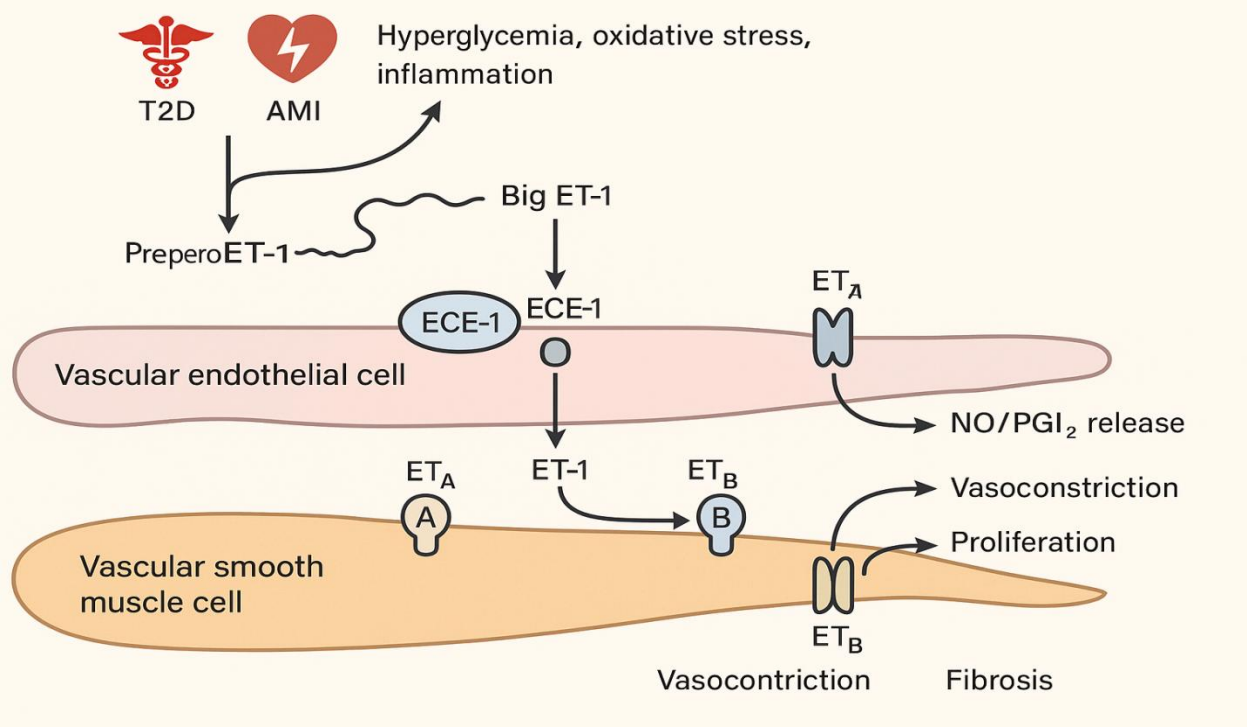

Figure 1: "Mechanistic Role of Endothelin-Converting Enzyme-1 (ECE-1) in Linking Type 2 Diabetes Mellitus and Acute Myocardial Infarction through Endothelin-1 Signaling" [18].

Figure 1 illustrates how hyperglycemia, oxidative stress, and inflammation in T2DM and AMI lead to increased production of preproET-1. This is converted to Big ET-1 and then to active ET-1 by ECE-1 on the vascular endothelium. ET-1 acts on ETA and ETB receptors on vascular smooth muscle cells to cause vasoconstriction, proliferation, and fibrosis, contributing to hypertension and increased cardiovascular risk.

2. Adenosine Monophosphate Activated Protein Kinase (AMPK)

AMPK is a highly conserved serine/threonine kinase that acts as a cellular energy sensor. It is activated by low energy states (e.g., elevated AMP:ATP or ADP:ATP ratios), triggering pathways to restore homeostasis. In addition to glucose uptake, fatty acid oxidation, protein synthesis, and mitochondrial function, AMPK plays a key role in metabolism, regulating glucose uptake, fatty acid oxidation, protein synthesis, and mitochondrial function.[20].

2.1. Structural Characteristics, Activation Mechanisms, and Physiological Roles in Metabolic Regulation

AMPK exists as a heterotrimeric complex composed of a catalytic α subunit and regulatory β and γ subunits. Gene diversity (α1, α2; β1, β2; γ1, γ2, γ3) allows for twelve possible isoform combinations, leading to tissue-specific expression and function [20]. Complexes containing the α2 subunit are predominantly found in tissues with high energy demand, such as skeletal muscle, heart, and liver. In contrast, α1-containing complexes are ubiquitously

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expressed. This isoform diversity enables AMPK to fine-tune its response to metabolic stress across different tissues [21].

Most AMPK protein is present in the cytoplasm and at the plasma membrane, where it interacts with important energy-related molecules; however, some isoforms may be found elsewhere in the cell. If energy is limited (for example, there is high AMP/ADP or more free intracellular calcium), the binding of AMP/ADP to the γ-subunit activates Thr172 phosphorylation which raises AMPK activity. Further rules in the cell come from post-translational modifications, among them are ubiquitination and acetylation which control AMPK's functions inside the cell.[21].

Cells use and store energy in the body by using AMPK to increase metabolic reactions that produce ATP and inhibit those that use it. AMPK promotes glucose uptake in muscle and adipose tissue. At the same time, it helps cells use blood sugar, making the body respond better to insulin [22]. When AMPK is present, it stops the production of new fats by turning off the rate-limiting enzyme ACC and decreasing malonyl-CoA. It accomplishes this by boosting the work of the CPT1 which transports fats into the mitochondria. Protein production is stopped in the body when AMPK turns off mTOR, allowing energy conservation. The AMPK receptor improves mitochondrial function and helps create new mitochondria, increasing energy production capacity [23]. On top of that, it helps activate autophagy, whereby the body clears away damaged parts and proteins to keep cells healthy under challenging metabolic conditions. AMPK integrating energy-sensing functions with metabolic and homeostatic pathways indicates it is essential for energy balance and thus makes it an important target for therapeutics used in diabetes, obesity and cardiovascular diseases.

AMPK is responsible for keeping the body's metabolism stable, serving as a kind of fuel gauge that checks AMP-ATP and ADP-ATP amounts. It decreases use of ATP in making fats and proteins, yet activates ATP-producing pathways such as fatty acid oxidation and glycolysis. Problems with this process are linked to the typical metabolic disturbances seen in type 2 diabetes (T2DM). AMPK works in glucose metabolism by allowing GLUT4 to move to cells, making insulin work better and preventing too much glucose production in the liver, protecting against both too high and too low blood sugar. Lipid metabolism allows for a rise in the rate of liver fatty acid breakdown and a decrease in cholesterol production, lipogenesis and triglyceride build-up, all of which suppresses basal adipocyte activity. Thus, AMPK enhances mitochondria production, aids in functioning under stressed conditions, decreases harmful oxidant species and lowers pro-inflammatory pathways such as TNF-α-mediated NF-κB and therefore, helps stop chronic inflammation and oxidative damage in diabetes, as well as in CVD. In addition, cellular proliferation and senescence are controlled by AMPK, implying that changes in metabolism are linked to aging and the growth of chronic diseases. Therefore, AMPK has been proposed as a therapeutic target for metabolic illnesses such as T2DM, obesity and CVD, although this remains experimental. by helping balance the body's energy, adjusting the metabolism and extending the life of the cells. [25].

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2.2. AMPK in the Pathophysiology of Type 2 Diabetes and Its Interaction with ECE-1 and Ox-LDL

AMP-activated protein kinase (AMPK) helps to keep cells energized and is closely related to the development of Type 2 Diabetes (T2D) and connected heart complications. AMPK becoming less active is a main trait of T2D and causes insulin resistance, faults in beta cells and increases the chances of metabolic syndrome. High nutrition levels and frequent inflammation suppress AMPK's activity in muscle, the liver and adipose tissue.[24]. Such suppression leads to impaired insulin action because it reduces the amount of glucose that goes into cells, raises hepatic glucose production and increases problems with lipid metabolism. AMPK may influence which pancreatic beta-cells function and persistent halting of AMPK in stressful situations can make beta-cells secrete less insulin and become more likely to die. Additionally, AMPK helps exercise and the use of metformin reduce the risk of diabetes, as both actions increase AMPK activity to improve glucose management and lipid metabolism.[25]. In patients experiencing Type 2 Diabetes (T2D) along with Acute Myocardial Infarction (AMI), serum AMPK measurements are especially important, showing the heavy strain present when an old disease suddenly confronts an acute condition. In these cases, people with T2D get a double shock: their previous metabolic imbalances are made much worse by the sudden serious metabolic and energy shortages triggered by myocardial ischemia. Therefore, AMPK levels in the blood of these high-risk patients represent the difficult circle formed by chronic diabetes and current heart problems Providing insight into the body's energy system's struggles.[26].

The preservation of heart tissue during ischemia depends on AMPK activation in acute myocardial infarction. A decline in ATP creates ischemia and as a result, AMPK turns on, boosting the body's intake of glucose, helping make energy with sugar and preventing protein synthesis. It helps to trigger autophagy which clears damaged organelles and improves the cells' resilience.[26]. Improper AMPK activation in diabetics weakens their hearts, making them more likely to suffer heart damage when there is ischemia. In reperfusion, the work of AMPK is dependent on the circumstances; at first, activation is helpful, but excessive or extended activation in some cases may add to reperfusion injury. AMPK contributes to the remodeling that happens after a heart attack, influencing hypertrophy, fibrosis and responses of the mitochondria all of which matter for the heart over a long period.[26].

AMPK, Ox-LDL and ECE-1 interact to show that T2D and AMI involve a complex relationship among metabolic stress, inflammation and vascular damage. Ox-LDL reduces AMPK activity by raising the secretion of inflammatory cytokines such as TNF-α and preventing AMPK from being phosphorylated. This suppression worsens abnormal metabolism, increases cell damage from oxidative stress and contributes to damage of the blood vessels, resulting in the formation of foam cells and increased atherosclerosis.[27]. In other words, activation of AMPK can counteract the harmful effects of Ox-LDL by forming more antioxidants and other substances, blocking inflammatory processes (e.g., NF-κB) and reducing cholesterol generation by aiming at HMG-CoA reductase. AMPK is also able to affect scavenger receptors, thus

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lowering the absorption of Ox-LDL and reducing both atherosclerosis and endothelial dysfunction.[27].

While a direct regulatory link between AMPK and ECE-1 has not been established, their functions are likely coordinated through shared anti-inflammatory and antioxidant pathways. Activation of AMPK may suppress the increased expression and production of ECE-1 and ET-1 by lowering inflammatory and oxidative stress through NF-κB.[27]. As a result, excessive ET-1 in T2D and AMI conditions might decrease which can relax blood vessels, decrease inflammation and prevent excess fibrosis. Similarly, continuing high ET-1 signals, resulting from more ECE-1 activity, might lead to inflammation which decreases AMPK activity and can intensify both metabolism- and circulation-related issues.[28]

A decrease in AMPK points to poor regulation of metabolism, an increase in oxidative stress and problems with blood vessels in both T2D and AMI. A further rise in Ox-LDL and more ECE-1/ET-1 signaling emphasizes this disorder, causing harm to the vessel walls, increased atherosclerosis and cardiac changes. Activating AMPK with a therapeutic strategy might regulate metabolism, minimize the harmful effects from Ox-LDL and manage ECE-1, making it a compelling therapeutic target for patients with T2D and AMI, Adapted from [29].

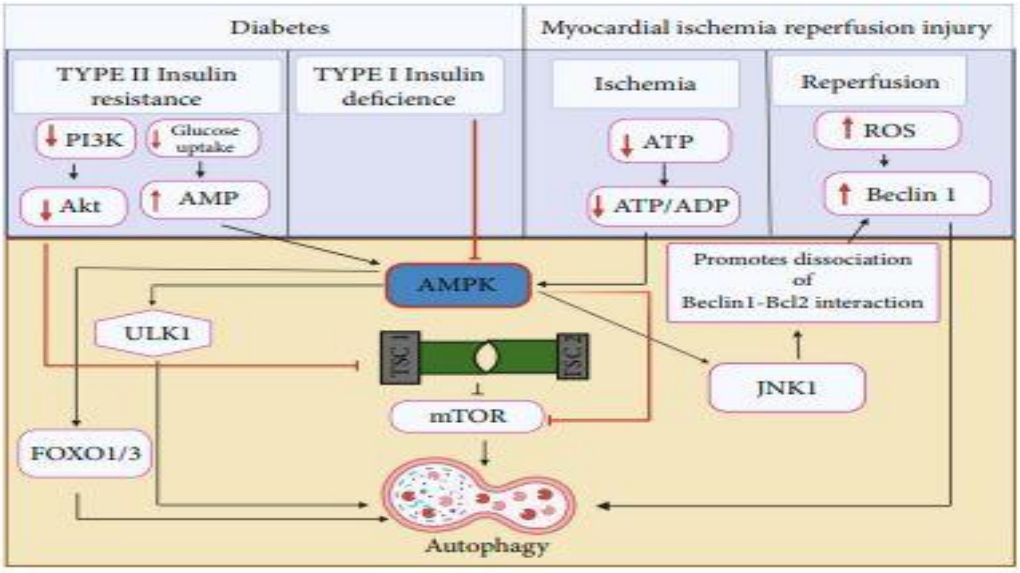

Figure 2: AMPK as a Central Regulator Linking Diabetes-Induced Insulin Signaling Dysfunction and Acute Myocardial. Adapted from [26]. This illustrates AMPK's role in autophagy during ischemia-reperfusion injury.

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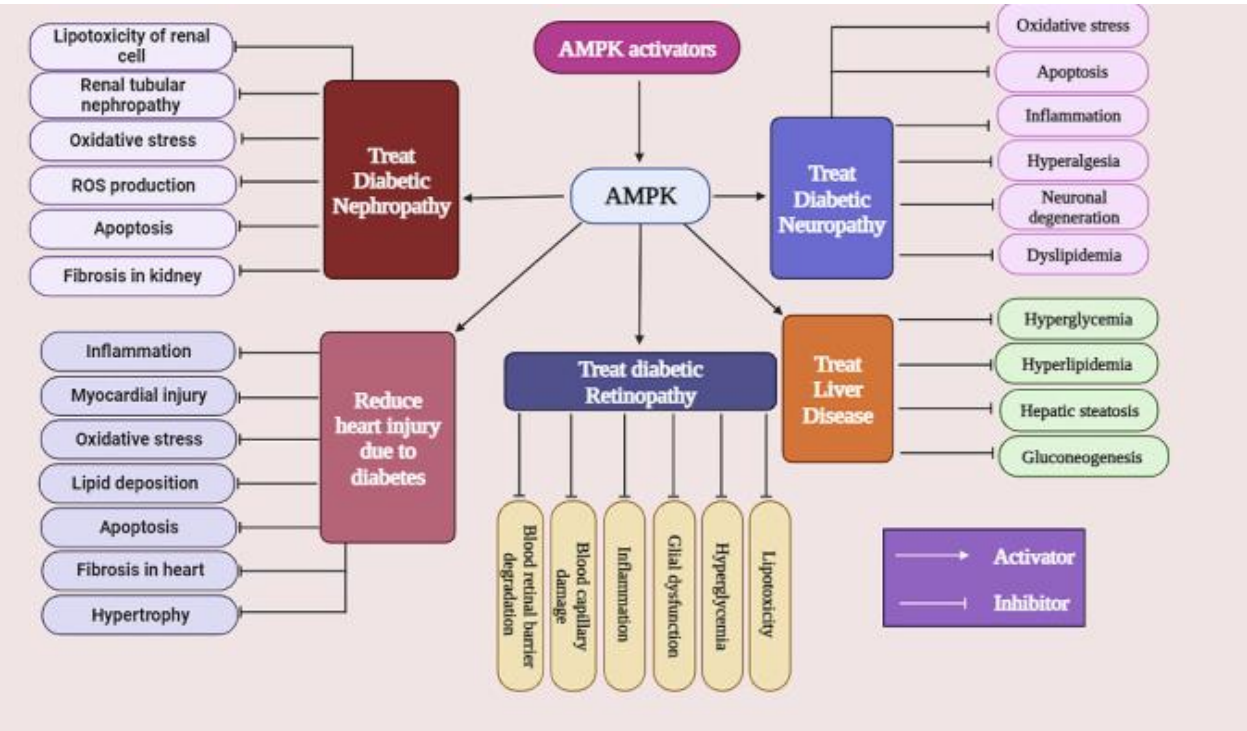

Figure 3: Role of AMPK signaling in treating different diabetic complications ([26])

This **Figure 3** illustrates the multifaceted role of AMP-activated protein kinase (AMPK) signaling in improving diabetes complications, with a focus on cellular and systemic diseases. AMPK signaling stands out as a central regulator that reverses the complications of diabetes by enhancing cell elasticity, restoring metabolic homeostasis, and mitigating oxidative and inflammatory damage. Its activation treats interrelated diseases throughout the organs, making it a promising therapeutic target for comprehensive diabetes management.[29].

3. Oxidized Low-Density Lipoprotein (Ox-LDL)

Low-Density Lipoprotein (LDL) is a class of lipoprotein particles responsible for transporting cholesterol from the liver to different parts of the body. When everything in the body is functioning normally, cells absorb LDL using the LDL receptor pathway. Oxidized LDL (Ox-LDL) is produced when LDL attaches below the artery lining and is affected by oxidative action. Ox-LDL plays a major role in starting and advancing the buildup of plaque in the arteries, making it an important cause of heart disease [30]. In this type of diabetes, hyperglycemia, excess oxidative stress and dyslipidemia help promote the oxidation of LDL. Oxidized low-density lipoprotein (Ox-LDL) is important where dyslipidemia, oxidative stress and vascular inflammation are involved. While native LDL is an important protein for transporting cholesterol and making hormones, its oxidized form is considered more suitable for signaling disease than for functioning in normal metabolism. The following section combines what is known now about Ox-LDL's removal from the body, T2D is influenced by its negative effects on cell lipid balance.

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3.1. Structure and Formation of Ox-LDL

LDL particles are composed of a core of cholesterol esters surrounded by phospholipids and a single large protein, apolipoprotein B-100 (apoB-100). Oxidation by reactive oxygen species (ROS) and reactive nitrogen species (RNS) modifies both the lipid and protein components of LDL, generating lipid peroxides (e.g., malondialdehyde) and altering the structure of apoB-100 [30]. These modifications prevent Ox-LDL from being recognized by the native LDL receptor and instead promote its uptake by scavenger receptors on macrophages and endothelial cells [31].

3.2. Pathophysiological Significance in Type 2 Diabetes

Oxidized low-density lipoprotein (ox-LDL) is a pathologically modified form of LDL. Oxidation alters apolipoprotein B-100 and lipids, enabling binding to scavenger receptors such as SR-A, CD36, and LOX-1 on macrophages and endothelial cells. Under physiological conditions, Ox-LDL has no known function; instead, it is recognized as a key indicator of oxidative stress, suggesting that antioxidants are insufficient. Ox-LDL is essential in atherosclerosis because it leads macrophages to absorb cholesterol, causes the formation of "foam cells," creates problems in the endothelial layer, increases vascular smooth muscle cell activity, causes ongoing inflammation and saturates ways to remove excess cholesterol (ABCA1, ABCG1), so more cholesterol is maintained Because of the fast-paced changes in glucose, cholesterol and oxidative stress seen in diabetics, LDL oxidation happens much faster. A rise in Ox-LDL in diabetic individuals contributes to heart and blood vessel disease by increasing dysfunction in veins, reducing nitric oxide production, increasing expression of adhesion molecules, accelerating the formation of foam cells, extending vascular inflammation and stimulating vascular smooth muscle cells to migrate and reproduce.[32].

Ox-LDL plays a role in cardiac problems by forming weak plaques that can rupture, increasing matrix metalloproteinase secretion that destroys their protective caps, bringing about vascular smooth muscle cell death that weakens the plaques, and damaging heart muscle cells with oxidative stress working as a sign of higher risk for cardiovascular events, particularly in patients with diabetes.[33]. When Ox-LDL interacts with LOX-1 receptors at the molecular level, it has been suggested to potentially upregulate ECE-1, leading to higher endothelin-1 production and increased vasoconstriction, oxidative stress, and inflammation. However, direct evidence linking Ox-LDL to ECE-1 upregulation remains limited and requires further investigation. This process is opposed by AMP-activated protein kinase which increases the movement of cholesterol out of cells, reduces damaging ROS and decreases inflammatory NF-κB activity. In Type 2 diabetes, having too many nutrients for a long time makes AMPK less active which favors ECE-1/endothelin-1 and leads to more oxidized LDL-related damage to blood vessels. Ox-LDL appears to play a central role linking abnormal metabolism, vascular inflammation, and cardiac complications in diabetes, suggesting several potential therapeutic targets, all of which require experimental validation. [30].

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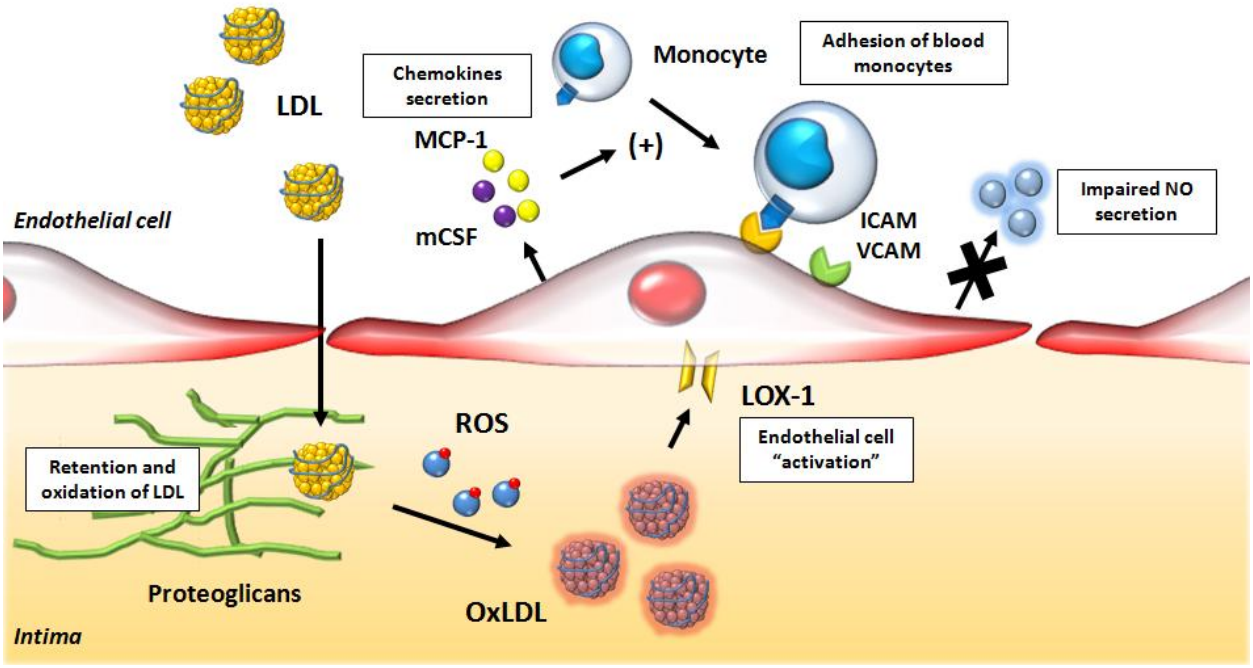

Figure 4: Role of Oxidized LDL in Atherosclerosis [30].

Figure 4 shows that Oxidized LDL (Ox-LDL) is taken up by endothelial cells (ECs) mainly through the action of overexpressed LOX-1 in human atherosclerotic lesions, leading to important changes in the ECs. The MCP-1 chemokine is triggered by LOX-1 and the MAPK pathway, while ICAM-1 and VCAM-1 adhesion molecules are turned on by LOX-1 through NF-κB activation. In addition, OxLDL-LOX-1 pathways block production of nitric oxide and encourage EC death by turning on NF-κB and AP- pathways. Overall, they increase endothelial dysfunction, attract more inflammatory cells and allow plaques inside the arteries to grow faster [33].

DISCUSSION

4. Clarification on the Nature of Claims Made in This Review

Before discussing the interrelationships between ECE-1, AMPK, and ox-LDL, it is important to clarify the evidentiary basis of this review. All claims regarding the diagnostic or therapeutic potential of these biomarkers are based exclusively on mechanistic and correlational evidence from basic science, preclinical, and observational studies. No diagnostic accuracy studies (e.g., prospective cohorts reporting sensitivity, specificity, or AUC-ROC values) have been published for this biomarker panel in T2DM-AMI patients. Therefore, statements such as "could serve as a biomarker," "may improve diagnosis," or "shows diagnostic potential" are speculative and hypothesis-generating. They should not be interpreted as evidence-based clinical recommendations. The primary value of this review is to synthesize current mechanistic knowledge and to identify gaps for future research, not to claim established diagnostic utility.

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4.1. Relationship and Interplay Between ECE-1, AMPK and Ox-LDL

The interplay between ECE-1, AMPK, and Ox-LDL forms a critical pathophysiological axis in T2DM and AMI. Ox-LDL significantly inhibits AMPK activity by inducing oxidative stress and inflammation. This creates a deleterious feedback loop: high levels of Ox-LDL impair AMPK's protective functions, which in turn exacerbate Ox-LDL-mediated cellular damage [34]. Furthermore, impaired AMPK function in T2DM may indirectly promote Ox-LDL formation by altering lipid metabolism and cellular stress responses. The measurement of Ox-LDL levels can help quantify the burden of oxidative stress-driven atherogenesis, a key risk factor for AMI in patients with T2DM [35].

4.2. Absence of Quantitative Diagnostic Metrics and Comparison with Current Standards

This narrative review does not report sensitivity, specificity, AUC-ROC values, or cutoff thresholds for the ECE-1, AMPK, and ox-LDL panel because such quantitative diagnostic studies have not yet been performed in T2DM-AMI cohorts. Furthermore, no direct quantitative comparison with existing diagnostic standards (high-sensitivity cardiac troponin, electrocardiography) is provided. The available literature is limited to mechanistic, correlational, and observational studies without diagnostic validation. Consequently, any statement regarding the "diagnostic" value of these biomarkers remains theoretical and hypothesis-generating. Future research should prioritize prospective cohort studies designed to establish quantitative performance metrics, including optimal cutoff values, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC-ROC), as well as head-to-head comparisons with current clinical standards.

4.3. Limitations of This Narrative Review and the Need for Original Validation Studies

The present work is a narrative review that synthesizes existing mechanistic and correlational evidence from the published literature. It does not include original patient data, clinical cohorts, or prospective diagnostic validation. Therefore, all statements regarding the diagnostic "potential" of ECE-1, AMPK, and ox-LDL for T2DM-AMI are hypothesis-generating rather than confirmatory. As acknowledged in the abstract, clinical validation in large, prospective cohorts with direct measurement of these biomarkers is essential before any clinical application can be recommended. This limitation does not undermine the heuristic value of this review but rather highlights a critical direction for future research. Without original data, no definitive conclusions about diagnostic accuracy (sensitivity, specificity, or predictive values) can be drawn.

This review has several methodological weaknesses that must be acknowledged. ***First,** no systematic search strategy was employed. The literature search was narrative and non-systematic, relying on PubMed, Google Scholar, and Scopus without predefined search protocols, inclusion/exclusion criteria, or PRISMA guidelines. This introduces potential selection bias, as relevant studies may have been unintentionally omitted.***Second**, no quality assessment of the included studies was performed. Tools such as the Cochrane Risk of Bias tool for randomized trials, QUADAS-2 for diagnostic accuracy studies, or the Newcastle-Ottawa Scale

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for observational studies were not applied. Consequently, the strength of the evidence underlying the reported findings has not been formally evaluated.***Third**, no grading of evidence strength (e.g., GRADE criteria) was conducted. Statements regarding the diagnostic potential of ECE-1, AMPK, and ox-LDL are based on mechanistic and correlational evidence, not on high-quality diagnostic accuracy studies.***Fourth,** as noted in previous sections, this review contains no original patient data, clinical cohorts, or laboratory measurements. All conclusions are derived from published literature. Given these methodological limitations, the findings of this narrative review should be considered hypothesis-generating rather than conclusive. Future research should employ systematic reviews, meta-analyses, and prospective diagnostic accuracy studies to validate the theoretical framework proposed here.

4.4. Assay Availability, Measurement Methods, and Standardization Challenges

For any biomarker to be clinically useful, reliable and standardized assays must be available. Currently, the measurement of ECE-1, AMPK, and ox-LDL in serum presents several challenges.

ECE-1: Commercial ELISA kits for human ECE-1 are available from several suppliers (e.g., Cloud-Clone Corp, MyBioSource, Cusabio). However, these kits are primarily research-use-only (RUO) and not FDA-approved or CE-marked for diagnostic purposes. No standardized reference ranges or cutoff values have been established for ECE-1 in T2DM-AMI patients. Furthermore, ECE-1 exists in four isoforms with different subcellular localizations, and most commercial kits do not distinguish between them.

AMPK: AMPK is an intracellular kinase that is typically measured in tissue lysates rather than serum. While serum AMPK levels can be detected by ELISA, the physiological significance of circulating AMPK is poorly understood. Most published studies measure AMPK phosphorylation (activation state) in platelets, mononuclear cells, or cardiac tissue rather than serum levels. Therefore, serum AMPK as a diagnostic biomarker for T2DM-AMI lacks established biological plausibility and requires further mechanistic validation.

Ox-LDL: Ox-LDL is the most clinically advanced of the three biomarkers. Several commercial ELISA kits are available (e.g., Mercodia, Cloud-Clone Corp, Abcam). Some studies have reported reference values, and ox-LDL has been investigated in multiple cardiovascular cohorts. However, standardization remains problematic because different assays use different antibodies (e.g., against malondialdehyde-modified apoB-100 versus other epitopes), leading to variable results across studies.

4.5. Cost-Effectiveness and Feasibility in Resource-Limited Settings

Even if technical assay challenges are overcome, the clinical adoption of any new biomarker panel depends on cost-effectiveness and feasibility, particularly in resource-limited settings where T2DM and AMI burdens are highest.

Estimated Costs: Commercial ELISA kits for ox-LDL typically cost 300-600 $ per kit (96 wells), translating to 3-6 $ per sample plus labor and equipment costs. ECE-1 kits are similarly priced. AMPK kits range from 400-800 $ per kit. A panel combining all three biomarkers would cost approximately 15-25 $ per patient for consumables alone, not including instrument

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maintenance, personnel, and quality control. In comparison, high-sensitivity troponin assays cost approximately 2-5 $ per sample and are widely available on automated clinical chemistry platforms.

Feasibility in Resource-Limited Settings: ELISA-based measurements require specialized equipment (plate readers, washers, incubators), trained personnel, stable electricity, and cold chain storage for reagents. These requirements are often unavailable in low- and middle-income countries, particularly in rural areas. Point-of-care testing for troponin is increasingly available, but no point-of-care tests exist for ECE-1, AMPK, or ox-LDL.

Cost-Effectiveness: No cost-effectiveness studies have been published for this biomarker panel. Given the modest additional diagnostic information that might be provided beyond existing standards (hs-troponin, ECG), it is unlikely that a three-biomarker ELISA panel would be cost-effective unless it demonstrates superior diagnostic accuracy in prospective trials. Future studies should include formal cost-effectiveness analyses using incremental cost-effectiveness ratios (ICERs) and quality-adjusted life years (QALYs).

4.6. Confounding Factors Affecting ECE-1, AMPK, and Ox-LDL Levels

Several demographic, clinical, and pharmacological factors may influence serum levels of ECE-1, AMPK, and ox-LDL, potentially confounding their diagnostic utility in T2DM-AMI.

Age: Age is a major determinant of vascular function and oxidative stress. Endothelin-1 levels increase with age in healthy individuals, and ECE-1 activity may be similarly affected. Ox-LDL levels also rise with age due to accumulated oxidative damage. Age-matched control groups are essential in diagnostic validation studies.

Renal Function: Chronic kidney disease (CKD) is common in T2DM and affects biomarker levels through multiple mechanisms. ET-1 and its precursors are cleared by the kidneys, and ECE-1 levels may be elevated in CKD independent of cardiac status. Ox-LDL levels are also increased in CKD due to enhanced oxidative stress and reduced clearance. AMPK signaling is dysregulated in CKD. Therefore, renal function (eGFR, creatinine) must be measured and adjusted for in any diagnostic study.

Other Comorbidities: Hypertension, dyslipidemia, obesity, and heart failure independently affect all three biomarkers. Hypertension increases ET-1 and ECE-1 expression. Dyslipidemia directly affects LDL oxidation. Obesity is associated with reduced AMPK activity. Studies must either exclude patients with these comorbidities or adjust for them statistically.

Medications: Several commonly used medications affect these biomarker pathways:

- **Metformin** activates AMPK, potentially altering serum AMPK levels or activity
- **Statins** reduce LDL cholesterol and may decrease ox-LDL formation
- **ACE inhibitors and ARBs** interact with the endothelin system
- **Insulin and oral hypoglycemics** affect metabolic pathways that regulate AMPK.

4.7. Comparison with Emerging Biomarkers Further Along in Validation

The diagnostic potential of ECE-1, AMPK, and ox-LDL for T2DM-AMI must be evaluated in the context of other emerging biomarkers that have progressed further in clinical validation.

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ST2 (Suppression of Tumorigenicity-2): ST2 is a member of the interleukin-1 receptor family. Soluble ST2 (sST2) is a well-established biomarker for myocardial stress, fibrosis, and adverse remodeling in AMI and heart failure. sST2 is measured by FDA-approved assays (e.g., Presage ST2 assay) and is included in clinical guidelines for risk stratification in heart failure. Multiple studies have validated sST2 in T2DM patients with cardiovascular disease. Compared to ECE-1 and AMPK, sST2 has superior clinical validation, established cutoff values (>35 ng/mL), and reimbursement pathways.

GDF-15 (Growth Differentiation Factor-15): GDF-15 is a stress-responsive cytokine elevated in AMI, heart failure, and T2DM. It is measured by commercial ELISA kits and has been evaluated in large cohorts such as the FRISC-II and GUSTO IV trials. GDF-15 improves risk prediction beyond conventional biomarkers and is being integrated into multimarker panels. Its assay standardization is more advanced than for ECE-1 or serum AMPK.

MicroRNAs (miRNAs): Circulating miRNAs (e.g., miR-1, miR-133, miR-208, miR-499) have emerged as highly sensitive and specific biomarkers for AMI. They are detectable in serum and plasma using RT-PCR, and some panels have shown diagnostic accuracy comparable to troponin. miRNAs are stable, and their expression patterns distinguish between T2DM patients with and without cardiovascular complications. Compared to ECE-1 and AMPK, miRNAs have a larger evidence base and are closer to clinical translation.

Comparison with the Proposed Panel: The biomarkers proposed in this review (ECE-1, AMPK, ox-LDL) are mechanistically plausible but lack the clinical validation, standardized assays, and large cohort data that support ST2, GDF-15, and miRNAs. Ox-LDL is the most advanced among the three, but even ox-LDL has not achieved the regulatory approval or clinical adoption of these other emerging biomarkers. Therefore, the ECE-1/AMPK/ox-LDL panel should be viewed as an early-stage, hypothesis-generating candidate requiring substantial further validation rather than a clinically ready alternative to more established emerging biomarkers.

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Table 1: Comparison of Proposed Biomarkers with Established and Emerging Alternatives

Feature	ECE-1	AMPK (serum)	Ox-LDL	hs-Troponin (current standard)	ST2	GDF-15	miRNAs
Commercial assay available	Yes (RUO)	Yes (RUO)	Yes (RUO)	Yes (FDA/CE approved)	Yes (FDA approved)	Yes (RUO)	Yes (RUO)
Standardized reference ranges	No	No	Limited	Yes	Yes	Limited	No
Validated in large T2DM-AMI cohorts	No	No	Limited	Yes	Yes	Yes	Moderate
Established cutoff values	No	No	No	Yes	Yes	No	No
Point-of-care testing available	No	No	No	Yes	No	No	No
Cost per sample (USD)	$5-10	$5-10	$3-6	$2-5	$10-15	$5-10	$10-20
Guideline recommended	No	No	No	Yes	Yes (for HF)	No	No

RUO = Research Use Only; HF = heart failure.

CONCLUSIONS

The methodological limitations of this narrative review , including the absence of a systematic search strategy, quality assessment, and grading of evidence , mean that all findings are hypothesis-generating rather than conclusive. Future systematic reviews following PRISMA guidelines and prospective diagnostic accuracy studies reporting sensitivity, specificity, and AUC-ROC values are urgently needed.This narrative review identifies ECE-1, AMPK, and ox-LDL as candidate biomarkers with theoretical diagnostic potential for T2DM-AMI based on pathophysiological mechanisms. However, no quantitative diagnostic metrics (sensitivity, specificity, AUC-ROC, cutoff values) are available, and no quantitative comparison with existing standards (hs-troponin, ECG) has been made. Therefore, the term "diagnosis" in the title is used to indicate potential rather than established clinical utility., revealing underlying mechanisms of vascular stress, metabolic dysregulation, and oxidative damage that extend beyond simple myocardial necrosis. Their interrelationships form a feedback loop of stress and inflammation. However, because this is a narrative review without original patient data, clinical

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cohorts, or laboratory validation, the clinical utility of these biomarkers remains unproven. Key limitations of the current literature include its reliance on correlative data from observational studies and a lack of prospective, interventional trials. Future research should focus on validating these biomarkers in large, prospective cohorts of T2DM patients with direct, original measurements to establish their diagnostic and prognostic utility for AMI. Furthermore, exploring therapeutic strategies that modulate these pathways — such as AMPK activators or ECE-1 inhibitors — could pave the way for more personalized interventions, but such strategies remain experimental at this stage.

Acknowledgments: The authors are grateful to all the researchers who support us to achieve this study.

Conflict of interests. The authors declare that they have no conflict of interests regarding the publication of this work.

Methodological Note : This paper is a narrative (traditional) review. Readers should be aware of the following methodological features:

- No systematic search protocol was registered.
- No PRISMA checklist was followed.
- No quality assessment tools (e.g., QUADAS-2, Cochrane Risk of Bias, Newcastle-Ottawa Scale) were applied.
- No GRADE assessment of evidence strength was performed.
- No original patient data, clinical cohorts, or laboratory measurements are included.

For definitive diagnostic validation of ECE-1, AMPK, and ox-LDL in T2DM-AMI, prospective cohort studies with quantitative performance metrics are required.

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الخلاصة

المقدمة: يُعد داء السكري من النوع الثاني عاملاً رئيسياً يرفع بشكل كبير احتمالية الإصابة باحتشاء عضلة القلب الحاد، وذلك عبر مسارات مرضية تشمل اختلال الوظيفة البطانية، والإجهاد التأكسدي، والعمليات الالتهابية. أما الوسائل التشخيصية التقليدية المتمثلة في تخطيط كهربية القلب وقياسات التروبونين، فغالباً ما تكون فعاليتها محدودة لدى مرضى السكري من النوع الثاني، ويعود ذلك إلى أن الأعراض تظهر لديهم بشكل غير نمطي مقارنة بغيرهم من المرضى.

طرق العمل: تعتمد هذه المراجعة السردية على تجميع المعطيات المنشورة في الأدبيات العلمية المستمدة من الدراسات الأساسية وما قبل السريرية وكذلك الدراسات السريرية، وذلك فيما يتعلق ببنية ووظائف وتداخلات ثلاث مؤشرات حيوية موجودة في المصل، وهي: إنزيم المحول للإندوثيلين-1(ECE-1) ، وكيناز البروتين المنشط بـ(AMP (AMPK ، والبروتين الدهني منخفض الكثافة المؤكسد-(ox LDL).ويركز البحث على دور هذه المؤشرات في الآليات المرضية المرتبطة باحتشاء عضلة القلب الحاد لدى المصابين بداء السكري من النوع الثاني. من المهم التنبيه إلى أن هذا العمل لا يتضمن أي بيانات أصلية مستمدة من مرضى، ولا يعرض أي نتائج من مجموعات سريرية، ولا يقدم قياسات مخبرية جديدة. إن الإمكانية التشخيصية التي يناقشها البحث تستند فقط إلى أدلة مستخلصة من دراسات آلية ودراسات ارتباطية، ولذلك تبقى هذه الإمكانية في إطارها النظري غير المثبت سريرياً حتى الآن.

النتائج : يؤدي إنزيم ECE-1 إلى تضيق الأوعية الدموية من خلال تحفيزه لإنتاج الإندوثيلين-1(ET-1) ، بينما يعمل بروتين AMPK كمنظم مركزي لتوازن الطاقة داخل الخلايا، ويُعد الـ ox-LDL محركاً أساسياً في نشوء تصلب الشرايين. وتُظهر التداخلات بين هذه المؤشرات الثلاثة وجود حلقة مرضية مغلقة تتفاقم فيها الأضرار الاستقلابية والوعائية. وبناءً على الأدلة المنشورة المستمدة من الدراسات الآلية والارتباطية، فإن دمج هذه المؤشرات الحيوية قد يؤدي – من الناحية النظرية – إلى تحسين التشخيص المبكر وتخصيص العلاج لكل مريض على حدة، إلا أن هذا الافتراض لا يزال مجرد فرضية نظرية تنتظر التحقق السريري من خلال دراسات مستقبلية جماعية تتضمن بيانات أصلية مستمدة من مرضى حقيقيين. تجدر الإشارة إلى أنه لا توجد في الأدبيات العلمية الحالية أي مقاييس كمية تشخيصية (مثل معايير الحساسية، أو النوعية، أو المساحة تحت منحنى الخاصية التشغيلية، أو قيم القطع التشخيصية) للمجموعة المقترحة من المؤشرات الحيوية. كما أنه لا تتوفر أي مقارنة كمية بين هذه المؤشرات والمعايير التشخيصية الحالية (كالتوربونين عالي الحساسية أو تخطيط كهربية القلب)، وذلك ببساطة لأن دراسات التحقق السريري اللازمة لم تجر بعد.

الاستنتاجات: استناداً إلى ما توصلت إليه الدراسات الآلية المتاحة حالياً، فإن مجموعة المؤشرات الحيوية المكونة من ECE- 1 و AMPK و ox-LDL تمتلك إمكانات تشخيصية نظرية لمرضى السكري من النوع الثاني المصابين باحتشاء عضلة القلب الحاد. لكن يجدر التأكيد على أن هذا العمل هو مراجعة سردية لا تحتوي على بيانات أصلية مستمدة من مرضى، ولا تشمل مجموعات سريرية، ولا تقدم قياسات مخبرية جديدة. ولهذا السبب، لا يمكن التوصية بأي تطبيق تشخيصي لهذه المؤشرات إلا بعد إجراء دراسات تحقق سريري مستقبلية جماعية. كما أن مصطلح "تشخيص" الوارد في عنوان هذا البحث لا يزال طموحاً نظرياً في غياب معايير تشخيصية محددة، وغياب المقاييس الكمية (مثل الحساسية، والنوعية، والمساحة تحت المنحنى، وقيم القطع)، وعدم وجود مقارنة كمية مباشرة مع المعايير التشخيصية الحالية كالتوربونين عالي الحساسية وتخطيط كهربية القلب. إن الحاجة ملحة وماسة إلى إجراء دراسات تحقق سريري توفر هذه المقاييس الكمية بشكل موثوق.

الكلمات المفتاحية: داء السكري من النوع الثاني , الإندوثيلين المصلي, وكيناز البروتين المنشط بـAMPK) AMP , إنزيم المحول للإندوثيلين-1, احتشاء عضلة القلب . مراجعة سردية، توليد الفرضيات، إطار نظري .