AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

METABOLIC DYSFUNCTION AND ATRIAL REMODELING: THE LINK BETWEEN ETIOLOGY AND PATHOGENESIS IN ATRIAL FIBRILLATION

Panjiyev Jonibek Abdumajidovich

Department of Preclinical Sciences of the Asian International

University, Bukhara, Uzbekistan

Abstract : Atrial fibrillation (AF) increasingly emerges as a metabolic disease rather than an isolated electrophysiological disorder. Metabolic dysfunction—including obesity, insulin resistance, dyslipidemia, mitochondrial injury, chronic inflammation, and epicardial adipose tissue (EAT) expansion—creates a structural and electrophysiological atrial substrate that predisposes to AF. Etiologic metabolic stressors induce oxidative injury, abnormal intracellular calcium cycling, ion-channel remodeling, gap junction disruption, mitochondrial dysfunction, fibroblast activation, and autonomic imbalance. Together, these mechanisms generate conduction heterogeneity, ectopic firing, rotor stabilization, and progressive atrial cardiomyopathy. This review integrates metabolic etiologies with mechanistic pathways of AF pathogenesis, providing a comprehensive conceptual model linking systemic metabolism to atrial arrhythmogenesis. Understanding AF as a metabolic-inflammatory-fibrotic disorder offers new opportunities for prevention and personalized therapy.

Keywords : Atrial fibrillation, Rate control, Rhythm control, Obesity, insulin resistance, reentry circuits

Atrial fibrillation is the most common type of cardiac arrhythmia. It is due to abnormal electrical activity within the atria of the heart, causing them to fibrillate. It is characterized as a tachyarrhythmia, which means that the heart rate is often fast. This arrhythmia may be paroxysmal (less than seven days) or persistent (more than seven days). Due to its rhythm irregularity, blood flow through the heart becomes turbulent and has a high chance of forming a thrombus (blood clot), which can ultimately dislodge and cause a stroke. Atrial fibrillation is the most common sustained arrhythmia worldwide. Historically, AF was considered primarily an electrophysiological disorder driven by pulmonary vein (PV) triggers and reentry circuits. However, modern evidence demonstrates that atrial cardiomyopathy, driven largely by metabolic dysfunction, forms the substrate on which AF develops. Major metabolic drivers—obesity, insulin resistance, visceral adiposity, dyslipidemia, hypertension, systemic inflammation, OSA, mitochondrial dysfunction—induce molecular and structural remodeling of the atria long before AF appears clinically.

Thus AF is no longer viewed as a standalone rhythm disturbance, but as the final common pathway of metabolic injury. This article unifies etiological metabolic factors with mechanistic atrial remodeling, forming a single, integrated etiopathogenic model.

ETIOLOGY: METABOLIC FACTORS CONTRIBUTING TO AF

1. Obesity and Visceral Adiposity

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Obesity is one of the strongest etiologic factors for AF. Key mechanisms:

a) Increased epicardial adipose tissue (EAT)

EAT directly surrounds atrial myocardium and secretes:

- Pro-inflammatory cytokines: IL-6, TNF-α
- Fibrosis mediators: TGF-β1
- Adipokines: leptin (pro-arrhythmic), adiponectin (anti-inflammatory, decreased in obesity)

EAT thickness correlates linearly with AF burden.

b) Increased atrial wall stress : Visceral fat increases blood volume → atrial stretch → mechanoelectric remodeling.

c) Lipotoxicity : Excess fatty acids accumulate in atrial myocytes → ceramide formation → apoptosis and fibrosis.

2. Insulin Resistance and Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) and insulin resistance (IR) are strong, independent risk factors for atrial fibrillation (AF). Their arrhythmogenic effect arises from metabolic toxicity, oxidative injury, calcium mishandling, mitochondrial dysfunction, microvascular rarefaction, inflammatory signaling, and electrophysiological remodeling. Together, these processes create a substrate that favors both triggered activity and reentry, accelerating the development of atrial cardiomyopathy.

a) Advanced Glycation End-Products (AGEs) and RAGE Signaling – Expanded

Chronic hyperglycemia promotes non-enzymatic glycation of proteins and lipids, forming AGEs. These accumulate in atrial tissue and induce pathogenic effects through:

1. AGE–RAGE (Receptor for AGE) Activation

AGEs bind to RAGE on:

- atrial myocytes
- fibroblasts
- endothelial cells
- immune cells

This activates:

- NF-κB signaling → transcription of pro-inflammatory cytokines
- JNK and p38 MAPK pathways → apoptosis + oxidative stress

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

- TGF-β1 upregulation → fibroblast-to-myofibroblast transformation

2. Consequences

- Chronic inflammation: ↑ IL-6, IL-1β, TNF-α → amplifies local injury
- Interstitial fibrosis: TGF-β1 stimulates excessive collagen I/III deposition
- Extracellular matrix stiffening: AGEs crosslink collagen → loss of atrial compliance
- Conduction abnormalities: Heterogeneous fibrosis creates conduction block zones → reentry substrate

3. Microvascular damage

AGEs injure atrial microcirculation → ischemia → ROS generation → further fibrosis.

Net effect: AGE–RAGE signaling converts hyperglycemia into a chronic pro-fibrotic, pro-arrhythmic state.

b) Calcium Handling Abnormalities – Deepened Explanation

Calcium dysregulation is a central electrophysiological mechanism linking diabetes to AF. Insulin resistance profoundly disrupts intracellular Ca^{2+} cycling.

1. Reduced SERCA2a Activity

Insulin signaling normally promotes the expression and function of SERCA2a, responsible for reuptake of Ca^{2+} into the sarcoplasmic reticulum (SR).

IR/T2DM cause:

- ↓ SERCA2a expression
- ↑ phospholamban (PLB) inhibition of SERCA2a
- hyperglycemia-induced oxidative modification of SERCA2a

→ SR refilling slows → cytosolic Ca^{2+} remains elevated → electrical instability.

2. RyR2 Hyperphosphorylation and SR Ca^{2+} Leak

Diabetes increases:

- CaMKII-δ activation (via ROS and O-glcNAcylation)
- PKA activity (via β-adrenergic overdrive in metabolic syndrome)

These kinases hyperphosphorylate RyR2 → the channels become "leaky".

Consequences:

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

- spontaneous SR Ca^{2+} release events ("sparks")
- delayed afterdepolarizations (DADs)
- triggered activity → PV ectopy → AF initiation

3. NCX (Na^{+}/Ca^{2+} exchanger) dysregulation

Due to excess cytosolic Ca^{2+}:

- NCX works in *forward mode*, extruding Ca^{2+} and generating inward depolarizing current → promotes DADs.

4. Mitochondrial Ca^{2+} dysregulation

Altered Ca^{2+} fluxes → mitochondrial Ca^{2+} overload → ROS → further injury.

Net effect: Diabetes creates a Ca^{2+}-unstable atrial myocyte prone to ectopic firing.

c) Mitochondrial Injury – Fully Expanded

Mitochondria are severely affected by metabolic disturbances in diabetes. Their dysfunction directly contributes to arrhythmogenesis.

1. Glucotoxicity and Lipotoxicity

Hyperglycemia + elevated free fatty acids (FFA) cause:

- excessive electron flux through the electron transport chain (ETC)
- formation of superoxide (O_2^-) and other ROS
- mitochondrial membrane potential collapse
- cardiolipin oxidation (impairs ETC function)

2. Oxidative Stress and mtDNA Damage

ROS attack:

- mtDNA → mutations and deletions
- mitochondrial proteins → impaired ATP synthesis
- membrane lipids → permeability transition pore (mPTP) opening

This triggers:

- further ROS
- release of cytochrome c
- mitochondrial apoptosis pathways

3. ATP Depletion

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Low ATP impairs:

- Na^+/K^+-ATPase → depolarized resting membrane potential
- Ca^{2+} pumps → exacerbates Ca^{2+} mishandling
- gap junctions (energy-dependent) → ↓ Cx40, Cx43 conductivity

→ conduction slowing → increased reentry risk.

4. Mitochondrial Fragmentation

T2DM increases:

- Drp1 activity (fission protein)
- decreases Mfn2 (fusion protein)

Fragmented mitochondria produce more ROS and less ATP, amplifying electrical instability.

5. Mitochondrial–NLRP3 Axis

Damaged mitochondria release:

- mtDNA
- cardiolipin
- ROS

These activate the NLRP3 inflammasome, inducing:

- IL-1β & IL-18 release
- fibroblast proliferation
- gap junction remodeling
- enhanced arrhythmogenicity

Net effect: Mitochondrial dysfunction links metabolism to persistent atrial remodeling.

3. Dyslipidemia

Patients with high LDL and low HDL show increased AF risk.

- Oxidized LDL accumulates in atrial tissue → inflammation.
- HDL deficiency reduces antioxidant capacity.

4. Hypertension and Renin-Angiotensin-Aldosterone System (RAAS) Overactivation

RAAS activation causes: atrial stretch, oxidative stress, aldosterone-induced fibrosis, connexin down-regulation. All contributing to AF substrate formation.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

PATHOGENESIS: HOW METABOLIC DYSFUNCTION PRODUCES ATRIAL REMODELING

Atrial remodeling occurs on 3 levels: Electrical, Structural, Metabolic/Inflammatory

1. Electrical Remodeling

a) Abnormal Calcium Cycling

Central mechanism.

Obesity, diabetes, ROS → RyR2 phosphorylation (CaMKII-δ activation) → abnormal Ca^{2+} leak → DADs
DADs → triggered activity → AF initiation.

b) Ion-Channel Remodeling

Metabolic stress changes expression of key channels:

- ↓ ICa-L (L-type Ca^{2+} current) → APD shortening
- ↑ IK1 (inward rectifier K^{+} current) → hyperpolarization
- ↓ INa (sodium current) → conduction slowing

These changes stabilize reentry circuits.

c) Gap Junction Abnormalities

EAT inflammation reduces connexins:

- ↓ Cx40 / ↓ Cx43
  → slowed conduction
  → heterogeneous propagation
  → substrate for reentry and rotor anchoring

2. Structural Remodeling

a) Fibrosis — the final common pathway

Metabolic-driven fibrosis is largely mediated by: TGF-β1, Angiotensin II, Aldosterone, Galectin-3, Inflammatory cytokines (IL-6, TNF-α)

Fibrosis consequences:non-uniform conduction, local conduction block, reentry circuits, rotor stabilization

b) Adipocyte infiltration into myocardium

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Epicardial adipocytes penetrate myocardium → creating electrically inert islands → conduction discontinuities.

3. Metabolic & Inflammatory Remodeling

a) ROS Overproduction

Major sources:

- mitochondrial ETC leakage
- NADPH oxidase
- xanthine oxidase

Effects:

- oxidation of RyR2 → Ca^{2+} leak
- degradation of sodium channels
- fibroblast activation

b) NLRP3 Inflammasome Activation

Key pathway in AF.

Activation triggers:

- lipotoxicity
- hyperglycemia
- ROS
- mitochondrial DNA fragments

Consequences:

- release of IL-1β and IL-18
- fibroblast proliferation
- electrical remodeling

c) Autonomic Nervous System Imbalance

Metabolic syndrome → increased sympathetic tone
OSA → vagal hyperactivity at night

Both lead to: triggered ectopy, shortening of refractory period, PV automaticity

Conclusion

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

Atrial fibrillation (AF) should not be viewed merely as an isolated electrophysiological disorder but rather as the final common phenotype of chronic metabolic stress acting on an electrically vulnerable atrial substrate. A growing body of translational and clinical evidence demonstrates that obesity, insulin resistance, dyslipidemia, mitochondrial dysfunction, obstructive sleep apnea, and hypertension initiate a multidimensional cascade—metabolic, inflammatory, structural, and electrical—culminating in the development and persistence of AF. From a clinical standpoint, this paradigm mandates a shift in therapeutic thinking. The future of AF management extends beyond rhythm-control strategies and ablation: it lies in aggressive metabolic modulation. Early intervention with structured weight reduction, glycemic optimization, lipid correction, RAAS blockade, SGLT2 inhibitors, mineralocorticoid receptor antagonists, and targeted anti-inflammatory therapies has demonstrated substantial reductions in AF burden and recurrence rates. Moreover, modification of epicardial fat volume, improvement in cardiorespiratory fitness, and management of OSA with CPAP therapy emerge as essential pillars of integrated care.Recognizing AF as a metabolic and inflammatory cardiomyopathy not only reframes its pathogenesis but opens pathways for precision medicine, enabling identification of high-risk phenotypes, individualized interventions, and earlier prevention of atrial remodeling. Ultimately, AF prevention and durable rhythm control will depend on treating the metabolic disease that precedes the arrhythmia, rather than reacting to its late electrical consequences.

Used literature :

1. Markides V, Schilling RJ. Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. Heart. 2003 Aug;89(8):939-43

2. Ren J, et al. Mitochondrial dysfunction and AF. J Mol Cell Cardiol. 2023.

3. Kadhim K, et al. NLRP3 inflammasome activation in AF. Heart Rhythm. 2021.

4. Lavie CJ, et al. Epicardial fat, inflammation, and AF. J Am Coll Cardiol. 2020.

5. Pathak RK, et al. Metabolic interventions reduce AF burden. JACC EP. 2021.

6. Anderson ME. CaMKII and atrial arrhythmias. Circ Res. 2020.

7. Choi YJ, Choi EK, Han KD, Jung JH, Park J, Lee E, Choe W, Lee SR, Cha MJ, Lim WH, Oh S. Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among Asian patients with hypertrophic cardiomyopathy: A nationwide population-based study. Int J Cardiol. 2018 Dec 15;273:130-135.

8. Bai CJ, Madan N, Alshahrani S, Aggarwal NT, Volgman AS. Sex Differences in Atrial Fibrillation-Update on Risk Assessment, Treatment, and Long-Term Risk. Curr Treat Options Cardiovasc Med. 2018 Aug 27;20(10):79.

9. Dan GA, Iliodromitis K, Scherr D, Marín F, Lenarczyk R, Estner HL, Kostkiewicz M, Dagres N, Lip GYH. Translating guidelines into practice for the management of atrial fibrillation: results of an European Heart Rhythm Association Survey. Europace. 2018 Aug 01;20(8):1382-1387.

10. Laäs DJ, Naidoo M. Oral anticoagulants and atrial fibrillation: A South African perspective. S Afr Med J. 2018 Jul 25;108(8):640-646.