NAD^+ Metabolism in Cardiac Health, Aging, and Disease (Abdellatif et al., *Circulation*, 2021)

What is NAD^+?

- Nicotinamide adenine dinucleotide (NAD^+) is a critical coenzyme in cellular metabolism.
- It regulates **redox reactions, mitochondrial function, energy metabolism, DNA repair, and cell signaling**.
- NAD^+ serves as a substrate for enzymes like **sirtuins, PARPs, and CD38**, all of which influence cardiac health.

Why it Matters in the Heart

- **Aging and Disease**: NAD^+ levels decline with normal aging, and more steeply in conditions like **obesity, diabetes, and hypertension**—all major cardiovascular risk factors.
- **Pathophysiology**: Reduced NAD^+ impairs mitochondrial function, weakens stress responses, and promotes inflammation and fibrosis, accelerating cardiac aging and dysfunction.
- **Heart Failure**: In particular, low NAD^+ is implicated in **heart failure with preserved ejection fraction (HFpEF)**, a condition strongly associated with aging and comorbidities.

Mechanisms of NAD^+ Depletion

1. **Reduced biosynthesis** – impaired salvage and de novo pathways.
2. **Increased consumption** – overactivation of PARPs (from DNA damage) and CD38 (inflammation, immune signaling).
3. **Mitochondrial dysfunction** – both a cause and consequence of NAD^+ loss.

Therapeutic Implications

- **NAD^+ Repletion Strategies**:

    - Dietary precursors (nicotinamide riboside [NR], nicotinamide mononucleotide [NMN], nicotinic acid).
    - CD38 inhibitors.
    - Exercise and caloric restriction (physiological NAD^+ boosters).
- **Preclinical Evidence**: Supplementation restores cardiac NAD^+ pools, improves diastolic function, reduces fibrosis, and enhances mitochondrial efficiency.
- **Clinical Trials**: Early human studies show NAD^+ precursor supplementation is well tolerated and improves markers of metabolic and cardiovascular health, though larger trials are needed.

Key Takeaway for Clinicians

Declining **NAD^+ metabolism is a hallmark of cardiac aging and disease**. Interventions that restore NAD^+ show promise in improving mitochondrial function, reducing inflammation, and treating conditions like HFpEF. While not yet standard therapy, NAD^+ repletion is an emerging, biologically rational strategy that may soon complement conventional cardiovascular care.

Study Link: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.056589