MITO RISING Perspective | Scientific Review 2026

# Imeglimin: Beyond Glycemic Control

## From Mitochondrial Metabolic Regulation to the Biology of Recovery

**Mitochondrial Function · $NAD^+$ Metabolism · Skeletal Muscle · Inflammation · Biological Aging**

Shigeki Takemoto, MD, PhD Founder, MitoQure | MITO RISING

## 1. What Is Imeglimin?

Imeglimin is a first-in-class oral antidiabetic agent belonging to a novel pharmacological class known as the *glimins*.

Originally discovered by Merck Serono in Switzerland, subsequently developed by Poxel in France and Sumitomo Pharma in Japan, imeglimin received its first regulatory approval in Japan on June 23, 2021, and was introduced into clinical practice under the brand name Twymeeg®.

What makes imeglimin particularly interesting is its distinctive pharmacological profile involving mitochondrial metabolism.

Unlike glucose-lowering agents that primarily target a single aspect of glucose homeostasis, imeglimin addresses two fundamental abnormalities associated with type 2 diabetes:

- Impaired glucose-dependent insulin secretion
- Increased insulin resistance

Its actions involve pancreatic $\beta$-cells, the liver, and skeletal muscle, with mitochondrial metabolic regulation considered an important underlying mechanism.

## 2. A Dual Mechanism of Action

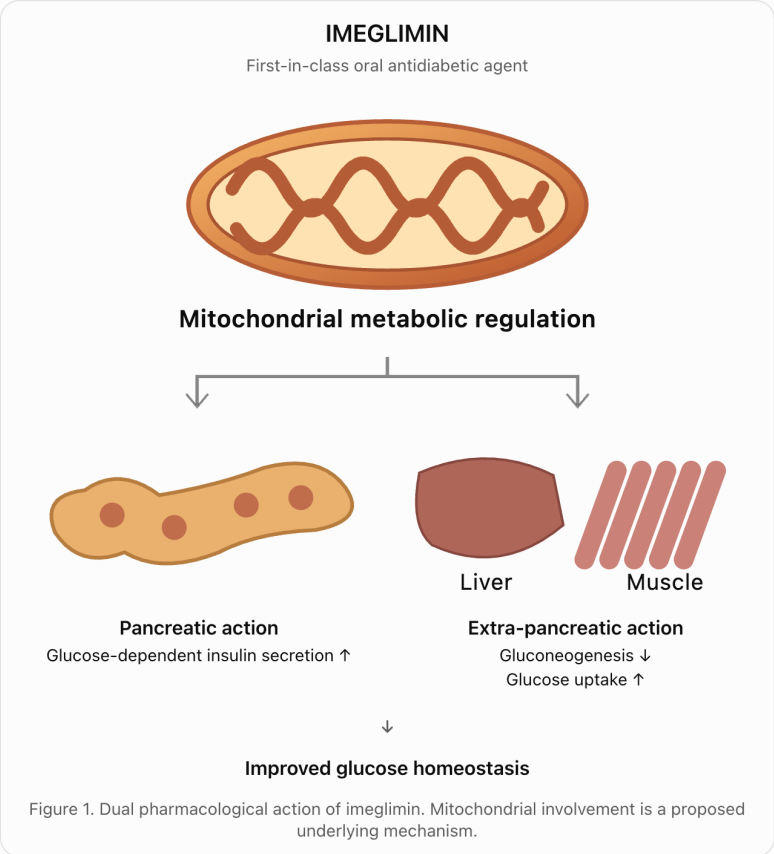


Figure 1. Dual pharmacological action of imeglimin. Mitochondrial involvement is a proposed underlying mechanism.

### Pancreatic β-cells

Imeglimin enhances glucose-dependent insulin secretion, potentially through the regulation of intracellular $NAD^+$ metabolism, ATP availability, and calcium-dependent signaling.

Experimental studies using pancreatic islets from diabetic rats have demonstrated increased intracellular $NAD^+$ levels and increased expression of NAMPT, a key enzyme in the $NAD^+$ salvage pathway.

CD38-dependent signaling also appears to contribute to its insulin-secretory effects.

These findings suggest that imeglimin may influence the metabolic machinery through which pancreatic β-cells sense glucose and respond to metabolic demand.

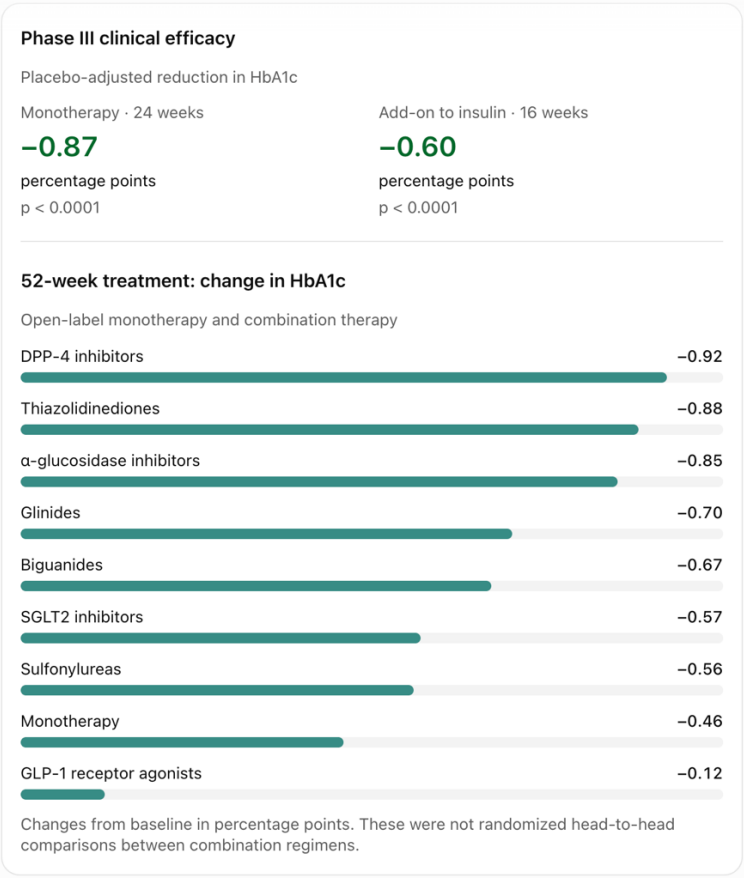
### Liver and skeletal muscle

Imeglimin also improves glucose metabolism outside the pancreas by reducing hepatic gluconeogenesis and enhancing glucose uptake in skeletal muscle.

These complementary actions address both insufficient insulin secretion and insulin resistance.

## 3. Established Clinical Evidence

The Japanese phase III clinical trials demonstrated significant improvements in glycemic control in patients with type 2 diabetes.

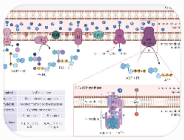



The clinical data establish imeglimin as an effective glucose-lowering agent. However, they do not establish an anti-aging effect or a direct improvement in whole-body mitochondrial function.

## 4. Imeglimin as a Mitochondrial Metabolic Modulator

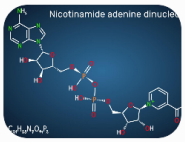
The scientific significance of imeglimin may extend beyond glucose regulation.

Experimental studies suggest that imeglimin can influence several interconnected components of mitochondrial biology.



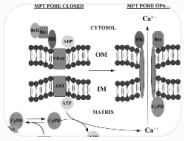
**Mitochondrial respiratory regulation**

Experimental models have demonstrated reduced complex I activity, restoration of complex III activity, and reduced mitochondrial ROS production.



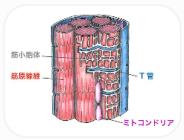
**NAD⁺ metabolism**

Imeglimin may influence NAD⁺ availability through the NAMPT-dependent salvage pathway, potentially affecting metabolic signaling and cellular adaptation.




**Mitochondrial protection**

Experimental findings suggest modulation of oxidative stress and mitochondrial permeability transition pore (mPTP) opening, with potential implications for cellular survival.



**Mitochondrial biogenesis and adaptation**

Animal studies have reported increased PGC-1α expression and improved maximal respiratory capacity in skeletal muscle.

The distinction is important. Increasing mitochondrial activity is not necessarily beneficial under every physiological condition. Healthy mitochondria must continuously adapt their metabolic activity to changing energy demands and cellular stress.

## 5. Emerging Research: Beyond Diabetes

Recent experimental and observational investigations have expanded the scientific interest in imeglimin.

| Research domain | Emerging findings |
|---|---|
| $NAD^+$ metabolism | NAMPT-dependent $NAD^+$ regulation |
| Skeletal muscle | $NAD^+$, SIRT1, SIRT3, PGC-1$\alpha$ and GLUT4-related pathways |
| Oxidative stress | Reduced mitochondrial ROS in experimental models |
| Cellular inflammation | Modulation of NLRP3 inflammasome and IL-1$\beta$ signaling |
| Pancreatic $\beta$-cells | Preservation of mitochondrial morphology and cellular survival |
| Liver metabolism | Improved mitochondrial and fatty acid metabolism in animal models |
| Biological aging | Exploratory clinical research hypothesis |

Three recent studies are particularly relevant to the development of Mitochondrial Recovery Medicine.

**Ishiguro et al., 2025 — Skeletal muscle and exercise adaptation**

Experimental research examining imeglimin and resistance exercise identified changes in $NAD^+$, sirtuins, PGC-1$\alpha$, and GLUT4. These findings suggest a potential interaction between pharmacological metabolic regulation and exercise-induced adaptation. An additional increase in muscle mass, however, was not clearly demonstrated.

**Satheesan et al., 2025 — Circulating mitochondrial DNA and inflammation**

A prospective observational study reported reductions in circulating cell-free mitochondrial DNA and selected inflammatory biomarkers during imeglimin-containing treatment regimens. The independent contribution of imeglimin remains uncertain because of the nonrandomized design and concurrent therapies.

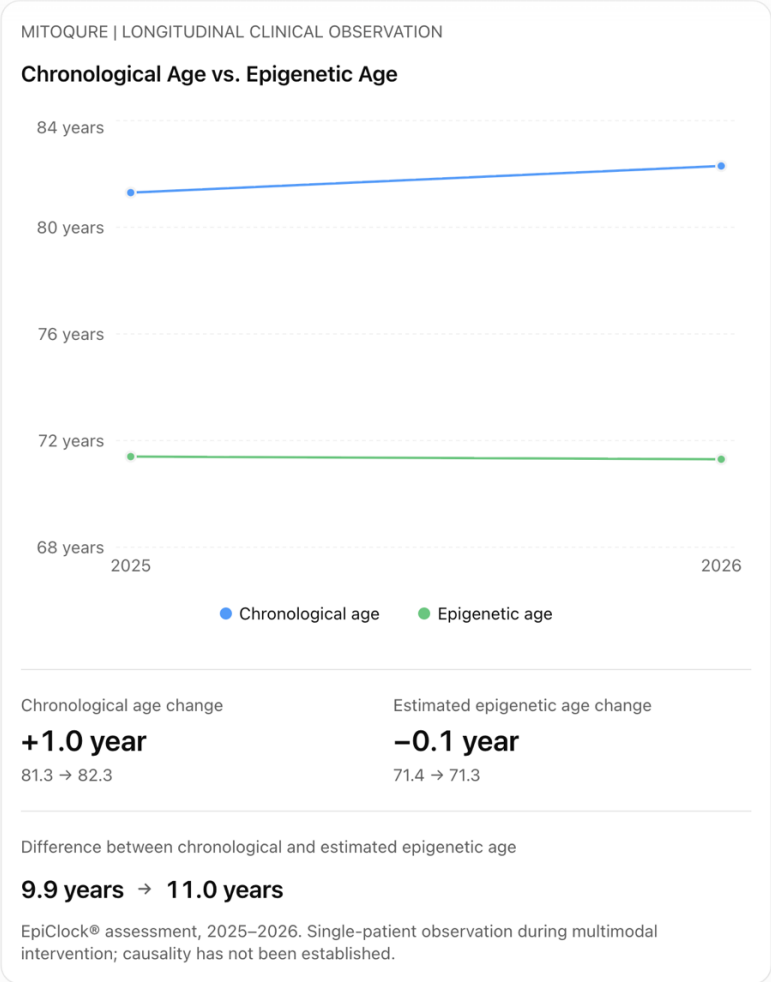
**Lee et al., 2024 — Mitochondrial stress and NLRP3 signaling**

Cell-based experiments identified effects involving mitochondrial ROS, mPTP opening, NLRP3 inflammasome activation, and IL-1$\beta$ production. These findings provide a mechanistic connection between mitochondrial stress regulation and innate immune signaling, although clinical benefits against chronic inflammation remain unproven.

# 6. Clinical Observation: Imeglimin and Epigenetic Aging

At Juraku Internal Medicine Clinic, we have observed favorable changes in fatigue, muscle strength, walking performance, and daily physical activity among selected patients receiving imeglimin for type 2 diabetes.

One particularly interesting observation involves a woman in her early eighties receiving imeglimin as part of a multimodal clinical intervention.




While her chronological age increased by one year, her estimated epigenetic age remained essentially unchanged.

This observation does not demonstrate that imeglimin reversed biological aging. Multiple simultaneous interventions, improved metabolic control, lifestyle changes, and measurement variability may have contributed to the result.

Nevertheless, it raises an important scientific question:

**Can mitochondrial metabolic modulation, as part of comprehensive clinical care, help preserve physiological function and influence biomarkers associated with biological aging?**

## 7. Imeglimin and Mitochondrial Recovery Medicine

Within my proposed framework of Mitochondrial Recovery Medicine, mitochondrial health is not defined solely by ATP production.

It is defined by the ability of biological systems to respond to stress, repair damage, adapt to change, and restore physiological function.

This dynamic property is what I describe as **Recovery Capacity**.

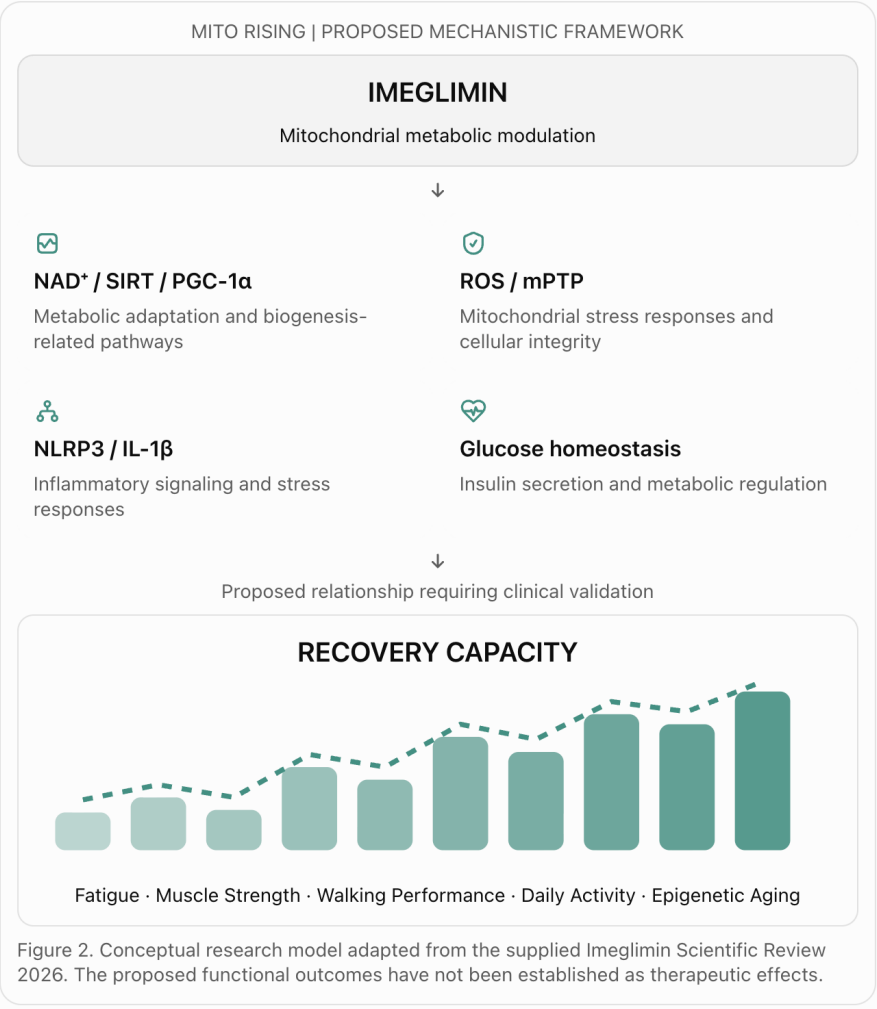



Figure 2. Conceptual research model adapted from the supplied Imeglimin Scientific Review 2026. The proposed functional outcomes have not been established as therapeutic effects.

### The 4R Framework of Mitochondrial Recovery Medicine

| Strategy | Potential relevance to imeglimin |
|---|---|
| **REPAIR** | Modulation of oxidative stress and cellular damage responses |
| **REPROGRAM** | Regulation of mitochondrial metabolism and stress adaptation |
| **REPLACE** | Imeglimin does not directly replace mitochondria |
| **RECOVER** | Investigation of whether metabolic changes translate into functional recovery |

Among these four strategies, **Reprogram** currently represents the most direct conceptual connection to imeglimin pharmacology.

Whether such metabolic reprogramming can lead to meaningful functional recovery remains a question for clinical research.

## 8. Clinical Use and Safety Considerations

According to the Japanese prescribing information revised in January 2026, imeglimin is approved for the treatment of type 2 diabetes.

The standard adult dosage is 1,000 mg twice daily, administered orally in the morning and evening.

Because absorbed imeglimin is eliminated predominantly through the kidneys as unchanged drug, renal function is an important determinant of drug exposure.

| eGFR (mL/min/1.73 m²) | Recommended dosage in Japan |
|---|---|
| ≥45 | 1,000 mg twice daily |
| 15–44 | 500 mg twice daily |
| 10–14 | 500 mg once daily, only when benefits outweigh risks |
| Below 10, including dialysis | Not recommended |

Important safety considerations include hypoglycemia, gastrointestinal adverse effects, severe appetite loss, vomiting, and dehydration.

Particular caution is required in older adults and patients receiving insulin, sulfonylureas, or metformin. The possibility of lactic acidosis also warrants attention in susceptible patients, despite its absence in the clinical trials described in the prescribing information.

Imeglimin is contraindicated in type 1 diabetes, severe ketosis, diabetic coma or precoma, severe infection, major trauma, and the perioperative period, as well as in patients with known hypersensitivity to its ingredients.

**Imeglimin is not an approved treatment for aging, sarcopenia, mitochondrial disease, or rejuvenation.**

# 9. MitoQure Clinical Research 2027

## Imeglimin, Mitochondrial Stress Regulation, and Recovery Capacity

Our next objective is to investigate whether metabolic changes during imeglimin treatment are associated with measurable improvements in physiological function.

The proposed longitudinal assessment framework integrates conventional metabolic biomarkers with functional and molecular measurements.

| Assessment domain | Proposed measurements |
|---|---|
| Glucose metabolism | HbA1c, glycated albumin, CGM |
| Subjective recovery | Fatigue VAS, validated questionnaires |
| Muscle strength | Handgrip strength, five-times sit-to-stand test |
| Physical performance | Gait speed, SPPB |
| Daily activity | Step counts, activity monitoring |
| Mitochondrial stress | Circulating cell-free mtDNA |
| Inflammation | Selected inflammatory biomarkers |
| Biological aging | EpiClock® assessment |

Assessments at baseline and at 3, 6, and 12 months, with selected molecular and epigenetic measurements at appropriate intervals, could provide a multidimensional understanding of individual recovery trajectories.

Controlled studies will ultimately be necessary to distinguish the effects of imeglimin from those of improved glycemic control, physical activity, nutritional interventions, and other treatments.

## 10. Conclusion — From Glucose Regulation to the Biology of Recovery

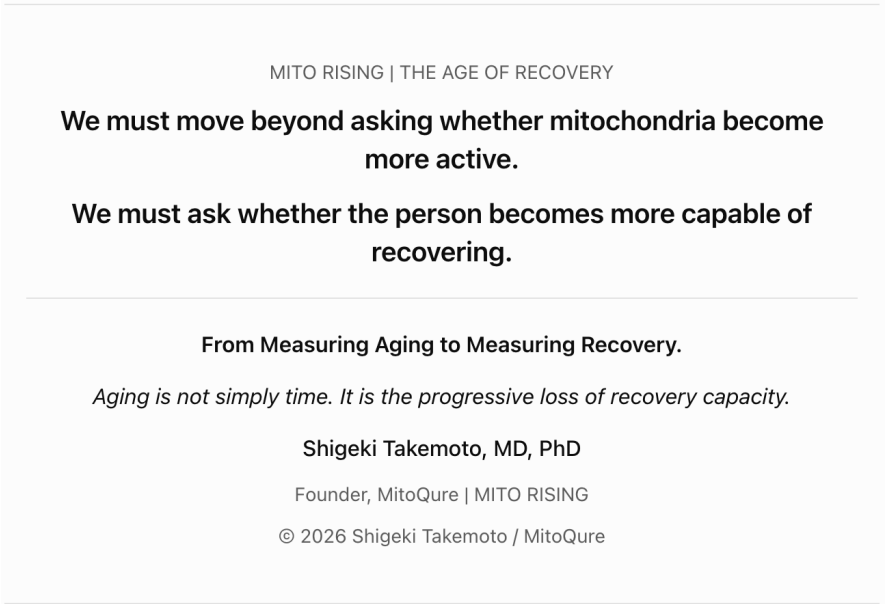
Imeglimin represents an important example of how mitochondrial biology is entering modern clinical pharmacology.

Its established role is the treatment of type 2 diabetes. Its broader effects on mitochondrial metabolism, cellular stress responses, and inflammatory signaling provide opportunities for translational research.

The next scientific challenge is to determine whether these molecular effects can translate into meaningful improvements in human physiological resilience.

The ultimate goal is not merely to lower blood glucose, increase ATP production, or change an epigenetic clock.

It is to understand whether the human body can maintain and restore its capacity to function.



# Scientific references


| Reference | Research focus |
|---|---|
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| Vial et al. *Diabetes*. 2015;64:2254-2264. | Mitochondrial metabolism |
| Sanada et al. *Scientific Reports*. 2022;12:13220. | Pancreatic β-cell protection |
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| Lee et al. *Journal of Pharmacological Sciences*. 2024. | NLRP3 inflammasome |
| Ishiguro et al. *Journal of Diabetes and Its Complications*. 2025. | Skeletal muscle and exercise |
| Satheesan et al. *Frontiers in Endocrinology*. 2025. | Circulating mtDNA and inflammation |
| Twymeeg® Prescribing Information, January 2026, 6th edition. | Clinical efficacy and safety |
| Twymeeg® Pharmaceutical Interview Form, January 2026, 13th edition. | Pharmacology and clinical evidence |


*Scientific disclaimer: This article integrates established clinical evidence, experimental findings, clinical observations, and proposed research hypotheses. Recovery Capacity Theory and its application to imeglimin remain investigational frameworks. No anti-aging or rejuvenation benefit of imeglimin has been established in humans.*

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