Correspondence

DOI: 10.5582/ddt.2025.01093

Clinical significance of imeglimin in older patients with type 2 diabetes: Analysis of a national database and a long-term case suggesting the potential for sarcopenia prevention

Atsushi Ishimura[1,*], Kaori Hashimoto[2], Hirofumi Ogino[3]

[1] Laboratory of Clinical Pharmacy Assessment, Hoshi University, Tokyo, Japan;
[2] Pharmaceutical Department of Seihikarigaoka Hospital, Chiba, Japan;
[3] Division of Life Science Pharmaceutics, Nihon Pharmaceutical University, Saitama, Japan.

SUMMARY: We aimed to evaluate the clinical significance of imeglimin in older patients with type 2 diabetes. Prescription trends were analyzed using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (2021–2023). Prescriptions for imeglimin increased, with the highest usage among patients in their 70s, followed by those in their 60s, and a clear upward trend in those aged ≥ 80 years. We present the case of an 80-year-old woman with diabetes who repeatedly discontinued treatment. After initiating imeglimin (2000 mg/day), she continued therapy successfully, achieving stable HbA1c levels at approximately 7% over 30 months. Muscle mass indices (creatine kinase, creatinine, and estimated glomerular filtration rate), nutritional status (albumin), and inflammation (C-reactive protein) remained stable, and independent walking and quality of life were preserved. These findings suggest that imeglimin may support glycemic control and may help attenuate frailty and sarcopenia progression in older adults with diabetes.

Keywords: Imeglimin, type 2 diabetes, older adults, frailty, sarcopenia

1. Introduction

Medical care advances have enabled older adults with multiple comorbidities to live independently. However, they are vulnerable to physical, psychological, and social frailty, predisposing them to adverse health outcomes, including disability and mortality. The prevalence of frailty, a pre-disability state, is increasing. Sarcopenia, defined as the age-related loss of muscle mass and strength, is a major underlying cause of frailty. The prevalence of sarcopenia in older adults is approximately 1% in both men and women (*1*). Age-related decline in skeletal muscle is a key contributor to reduced muscle strength, with muscle mass decreasing at an annual rate of 1–2% from the 30s, with 30–40% loss by the 80s compared to that in the 20s. The importance of mitochondrial function in suppressing declines in the number of skeletal muscle stem cells has been highlighted (*2*). Mitochondria, present in nearly all cells except for erythrocytes, possess their own DNA and undergo replication, fusion, and fission. Mitochondrial dysfunction leads to impaired insulin secretion and contributes to the pathogenesis of type 2 diabetes (*3*). Consequently, patients with diabetes are at an increased risk of developing frailty and sarcopenia (*4*). Although multiple recent glucose-lowering agents have improved glycemic control among patients with type 2 diabetes (*5*), frailty and sarcopenia remain significant clinical challenges.

Imeglimin, a novel oral antidiabetic agent, was launched in September 2021 in Japan. While its chemical structure is similar to that of metformin, imeglimin belongs to a distinct class called "glimins" (*6*). Imeglimin enhances glucose-dependent insulin secretion by improving mitochondrial function (*7*). It can exert extrapancreatic effects on skeletal muscle and the liver by reducing oxidative stress (*8-10*). These unique mechanisms raise the possibility of imeglimin attenuating age-related decline in skeletal muscles, thereby contributing to the prevention of frailty in older adults. However, no previous studies have specifically examined the effects of imeglimin on reducing frailty risk. Therefore, in this study, we aimed to (*i*) investigate the real-world use of imeglimin in older adults in Japan using data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) and (*ii*) present a long-term case of an older patient with type 2 diabetes who maintained glycemic

control, muscle-related parameters (creatine kinase [CK], creatinine [CRE], estimated glomerular filtration rate [eGFR]), nutritional status (albumin [Alb]) (*11*), and inflammation (C-reactive protein [CRP]) (*12*) during imeglimin therapy.

2. Methods

2.1. Prescription trends of imeglimin by age group

We used open data from the NDB, first released in 2014 by the Ministry of Health, Labor, and Welfare. The NDB provides statistical data that reflect the current status of medical care and health checkups in Japan. In this study, we extracted prescription data for imeglimin from the NDB open data for the fiscal years 2021–2023 (*13*), corresponding to the period after its market launch. Prescription data were obtained from the category "prescription drugs" and included quantities stratified by sex, age group, and drug class, across outpatient (in-hospital and out-of-hospital) and inpatient settings. The proportion of prescriptions in each age group was calculated.

2.2. Case report

The patient was an octogenarian. In 2005, she was diagnosed with type 2 diabetes with an HbA1c level of 8.5%; dietary therapy was initiated. Pharmacotherapy was started in 2006 with voglibose (0.9 mg/day) and glimepiride (2 mg/day), resulting in an HbA1c improvement of 6.3%; however, treatment was discontinued by the patient in the same year. In 2009, during a municipal health checkup, her HbA1c level was 9.5%, and voglibose was restarted, but she discontinued treatment. In 2011, another health checkup revealed diabetes (HbA1c: 8.6%), leading to voglibose re-initiation; however, poor adherence prompted a switch to sitagliptin (50 mg/day), which reduced HbA1c to 6.9%. Subsequent weight gain necessitated the addition of metformin (500 mg/day) and pioglitazone (15 mg/day) in 2013. HbA1c levels stabilized in the 6% range until 2017, when the treatment was discontinued. In 2019, HbA1c increased to 11.4%, and treatment with dulaglutide (0.75 mg/week) and dapagliflozin (5 mg/day) was initiated, improving HbA1c to 7%. However, glycemic control worsened to 8%, and imeglimin (2000 mg/day) was introduced in 2022. Since then, no changes have been made to the regimen, and treatment has been continued. Informed consent was obtained from the patient in accordance with institutional and ethical guidelines.

3. Results and Discussion

Table 1 shows the proportion of imeglimin prescriptions by age group from 2021 to 2023. The total number of tablets dispensed increased from 58.15 million in 2022 to 143.31 million in 2023. In both years, patients in their 70s accounted for approximately 30% of all prescriptions, representing the largest proportion, followed by those in their 60s. The proportion of patients aged ≥ 80 years increased from 2022 to 2023.

Table 2 summarizes the clinical course after the initiation of imeglimin treatment. HbA1c levels were consistently maintained within the 7% range and improved to 7.1% after 30 months of therapy. CK and creatinine levels remained stable. Renal function assessed using CRE and eGFR showed no evidence of deterioration. Nutritional status (Alb) and inflammation (CRP) were stable throughout the observation period. Clinically, the patient maintained independent walking

Table 1. Proportion of imeglimin prescriptions by age group from 2021 to 2023

	under 10 years old	10s	20s	30s	40s	50s	60s	70s	80 years and older
FY2021	0	0	0	0	0	0	0	0	0
FY2022	0	0.0	0.6	2.5	9.4	20.2	22.7	29.0	15.6
FY2023	0	0.1	0.4	2.2	8.3	19.7	22.6	30.0	16.7

Table 2. Clinical course of the patient after initiation of imeglimin

	6 months before the start	at the start of treatment	6 months post-initiation	12 months post-initiation	18 months post-initiation	24 months post-initiation	30 months post-initiation
HbA1c (%)	8	8.4	7.5	7.2	7.6	7.5	7.1
CK (U/L)	49	52	40	48	51	45	51
CRE (mg/dL)	0.67	0.7	0.69	0.6	0.64	0.69	0.69
eGFR (mL/min/1.73 m^2)	63	60	61	61	66	61	61
Alb (g/dL)	4.5	4.4	4.6	4.6	4.6	4.4	4.4
CRP (mg/L)	0.06	0.13	0.22	0.11	0.06	0.04	0.03

HbA1c, hemoglobin A1c; CK, creatine kinase; CRE, creatinine; eGFR, estimated glomerular filtration rate; Alb, albumin; CRP, C-reactive protein.

ability and preserved quality of life.

This study combines an analysis of prescription trends using the NDB with a long-term case report to evaluate the clinical significance of imeglimin in older adults with type 2 diabetes. Our analysis demonstrated that imeglimin prescriptions increased substantially within a few years of its launch, specifically among patients in their 70s, with increasing use observed in those aged ≥80 years. These findings suggest that imeglimin is widely adopted in clinical practice for older patients, likely reflecting its favorable profile of low hypoglycemia risk and suitability in the context of preserved renal function. In Japan, recent trends in diabetes pharmacotherapy among older adults show an increasing use of agents associated with a lower risk of hypoglycemia, such as DPP-4 inhibitors and SGLT2 inhibitors (*14,15*), indicating a shift toward safer treatment options in this population. This shift is particularly relevant in the context of frailty and multimorbidity, which make older adults more susceptible to adverse drug events, including hypoglycemia.

In the patient, despite a history of repeated treatment discontinuation, imeglimin enabled sustained therapy with stable HbA1c control of approximately 7%. Importantly, no decline was observed in muscle-related parameters or renal function, with stable nutritional and inflammatory marker levels. The preservation of independent ambulation suggests that imeglimin may help maintain physical function and may attenuate the progression of frailty and sarcopenia, although further confirmation is needed. Diabetes increases the risk of frailty and sarcopenia (*16*), with mechanisms involving impaired insulin secretion and resistance, chronic inflammation (*17,18*), and oxidative stress-induced skeletal muscle damage (*19*). Imeglimin, by improving mitochondrial function and reducing oxidative stress (*8-10*), may mitigate these pathophysiological processes, thereby supporting muscle and systemic homeostasis. Notably, although imeglimin shares structural similarities with metformin, it exhibits distinct pharmacological properties. Metformin may not always be advantageous for sarcopenia, partly because of risks such as vitamin B12 deficiency and potential mitochondrial effects (*16*). By contrast, the mitochondrial protective action of imeglimin may help maintain skeletal muscle integrity. The present case provides clinical evidence supporting this hypothesis.

Nevertheless, this study has some limitations. First, as a single case report, the findings are limited, and causality between imeglimin therapy and the observed stability in clinical parameters cannot be established. Second, skeletal muscle mass and strength were assessed only indirectly *via* serum markers and renal function, without standardized assessments such as dual-energy X-ray absorptiometry, bioimpedance analysis, or handgrip strength. The lack of direct measurements was primarily due to constraints in the outpatient clinical setting, and therefore the present findings should be interpreted as merely suggestive. Third, lifestyle factors such as diet, physical activity, and nutritional status were not fully controlled during the 30-month observation period, and the potential positive influence of these factors on the outcomes cannot be ruled out. Moreover, because this study used aggregated data from the NDB Open Data, detailed patient-level information such as baseline characteristics, concomitant medications, and comorbidities could not be obtained. Although detailed individual-level analyses were not feasible in the present study, we acknowledge the importance of these characteristics and will consider incorporating such analyses in future investigations using datasets that allow linkage at the individual level. In addition, although our analysis demonstrated a substantial increase in imeglimin prescriptions after its launch, this trend only reflects growing clinical utilization and acceptance and does not indicate that imeglimin has superior efficacy or safety compared with other antidiabetic medications. Although the observation period of 30 months was relatively long, further follow-up with advanced age and analysis of multiple cases is required.

Our results suggest that imeglimin contributes to stable glycemic control in older adults with type 2 diabetes and may help attenuate the progression of frailty and sarcopenia. Future prospective studies with larger cohorts are needed to comprehensively evaluate the effects of imeglimin on muscle mass, muscle strength, physical function, and frailty-related outcomes, using standardized assessment tools and incorporating indicators of nutritional status and chronic inflammation. In addition, more rigorous study designs such as prospective cohort studies targeting older adults at high risk of frailty or sarcopenia, or randomized controlled trials with active comparators are essential to clarify the potential role of imeglimin as a therapeutic option for frailty prevention in older patients with diabetes.

Acknowledgements

This study was conducted with the support of the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant-in-Aid for Young Scientists (Grant Number: 25K21084). The authors express their gratitude for this support.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, Heshmat R. Prevalence of sarcopenia in the world: a systematic review and meta-analysis of general population

studies. J Diabetes Metab Disord. 2017; 16:21.
2. Motohashi N, Minegishi K, Aoki Y. Inherited myogenic abilities in muscle precursor cells defined by the mitochondrial complex I-encoding protein. Cell Death Dis. 2023; 14:689.
3. Kabra UD, Jastroch M. Mitochondrial dynamics and insulin secretion. Int J Mol Sci. 2023; 24:13782.
4. Anagnostis P, Gkekas NK, Achilla C, Pananastasiou G, Taouxidou P, Mitsiou M, Kenanidis E, Potoupnis M, Tsiridis E, Goulis DG. Type 2 diabetes mellitus is associated with increased risk of sarcopenia: A systematic review and meta-analysis. Calcif Tissue Int. 2020; 107:453-463.
5. Yokoyama H, Araki S, Yamazaki K, Kawai K, Shirabe SI, Oishi M, Kanatsuka A, Yagi N, Kabata D, Shintani A, Maegawa H. Trends in glycemic control in patients with insulin therapy compared with non-insulin or no drugs in type 2 diabetes in Japan: a long-term view of real-world treatment between 2002 and 2018 (JDDM 66). BMJ Open Diabetes Res Care. 2022; 10:e002727.
6. Theurey P, Vial G, Fontaine E, Monternier PA, Fouqueray P, Bolze S, Moller DE, Hallakou-Bozec S. Reduced lactic acidosis risk with imeglimin: Comparison with metformin. Physiol Rep. 2022; 10:e15151.
7. Hallakou-Bozec S, Vial G, Kergoat M, Fouqueray P, Bolze S, Borel AL, Fontaine E, Moller DE. Mechanism of action of imeglimin: A novel therapeutic agent for type 2 diabetes. Diabetes Obes Metab. 2021; 23:664-673.
8. Vial G, Lamarche F, Cottet-Rousselle C, Hallakou-Bozec S, Borel AL, Fontaine E. The mechanism by which imeglimin inhibits gluconeogenesis in rat liver cells. Endocrinol Diabetes Metab. 2021; 4:e00211.
9. Vial G, Chauvin MA, Bendridi N, Durand A, Meugnier E, Madec AM, Bernoud-Hubac N, Pais de Barros JP, Fontaine É, Acquaviva C, Hallakou-Bozec S, Bolze S, Vidal H, Rieusset J. Imeglimin normalizes glucose tolerance and insulin sensitivity and improves mitochondrial function in liver of a high-fat, high-sucrose diet mice model. Diabetes 2015; 64:2254-2264.
10. Fouqueray P, Leverve X, Fontaine E, Baquié M, Wollheim C, Lebovitz H, Bozec S. Imeglimin-a new oral antidiabetic that targets the three key defects of type 2 diabetes. J Diabetes Metab. 2011; 2:126.
11. Yanagita I, Fujihara Y, Iwaya C, *et al*. Low serum albumin, aspartate aminotransferase, and body mass are risk factors for frailty in elderly people with diabetes-a cross-sectional study. BMC Geriatr. 2020; 20:200.
12. Velissaris D, Pantzaris N, Koniari I, Koutsogiannis N, Karamouzos V, Kotroni I, Skroumpelou A, Ellul J. C-reactive protein and frailty in the elderly: A literature review. J Clin Med Res. 2017; 9:461-465.
13. Ministry of Health, Labour and Welfare. National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) Open Data. Available from: *https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html* (accessed 2025-8-20).
14. Niida Y, NishiokaY, Myojin T, Noda T, Takahashi Y, Imamura T. Trends in Diabetic Medication Use and Hypoglycemia Incidence Among Older Adults in Japan: A Retrospective Observational Study and a 10-Year Analysis Based on Level of Care Need Using Linked Medical and Long-Term Care Data. Cureus. 2025; 17:e87486.
15. Aoyama K, Okada A, Kaneko H, Azegami T, Suzuki Y, Meguro S, Fujiu K, Takeda N, Morita H, Node K, Yamauchi T, Nangaku M, Takeda N, Yasunaga H, Hayashi K. Evolving trends of antidiabetic agents stratified by age, kidney function and body mass index: Insights from a nationwide claims database. Diabetes Obes Metab. 2025; 28:701-710.
16. Morley JE, Malmstrom TK, Rodriguez-Mañas L, Sinclair AJ. Frailty, sarcopenia, and diabetes. J Am Med Dir Assoc. 2014; 15:853-859.
17. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Arch Intern Med. 2007; 167:635-641.
18. Akbaraly TN, Hamer M, Ferrie JE, Lowe G, Batty GD, Hagger-Johnson G, Singh-Manoux A, Shipley MJ, Kivimäki M. Chronic inflammation as a determinant of future aging phenotypes. CMAJ. 2013; 185:E763-E770.
19. Meng SJ, Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. Int J Mol Sci. 2010; 11:1509-1526.

Received September 8, 2025; Revised December 1, 2025; Accepted December 10, 2025.

**Address correspondence to:*
Atsushi Ishimura, Laboratory of Clinical Pharmacy Assessment, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan.
E-mail: ishimura.atsushi@hoshi.ac.jp

Released online in J-STAGE as advance publication December 13, 2025.