



Elderly Female of Type 2 Diabetes (T2D) and Dementia with Clinical Improvement by Imeglimin (Twymeeg)

Masaki OKADA¹, Hiroshi BANDO^{1,2iD*}, Noboru IWATSUKI¹, Kazuki SAKAMOTO¹, Tomoya OGAWA¹

¹Sakamoto Hospital, Higashi Kagawa city, Kagawa, Japan

²Tokushima University/Medical research, Tokushima, Japan

Corresponding Author: **Hiroshi BANDO, MD, PhD, FACP** [ORCID ID](#)

Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan;

Email: pianomed@bronze.ocn.ne.jp

Received date: 23 January 2023; **Accepted date:** 31 January 2023; **Published date:** 04 February 2023

Citation: Okada M, Bando H, Iwatsuki N, Sakamoto K, Ogawa T. Elderly Female of Type 2 Diabetes (T2D) and Dementia with Clinical Improvement by Imeglimin (Twymeeg). *Asp Biomed Clin Case Rep.* 2023 Feb 04;6(1):17-22.

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Abstract

Background: Recent diabetic focus includes imeglimin (Twymeeg).

Case Presentation: The case was an 83-year-old female with 19 years of type 2 diabetes (T2D) associated with recent treatment for dementia.

Result: HbA1c decreased from 10.0% to 6.6% for 4 months by Twymeeg 2000 mg/day. For neuropsychiatric symptoms in dementia, memantine and tiapride were provided and controlled. Furthermore, zinc acetate hydrate (Novelzin) was continued for T2D and dementia.

Discussion and Conclusion: Twymeeg administration was effective as the results of Trials of IMeglimin for Efficacy and Safety (TIMES) 2 and 3. Perspectives on the efficacy of zinc were discussed including Alzheimer's-Plus with low zinc (APLZ).

Keywords

Imeglimin (Twymeeg), Type 2 Diabetes, Zinc Acetate Hydrate, Novelzin, Trials of IMeglimin for Efficacy and Safety, Neuropsychiatric Symptoms in Dementia, Alzheimer's-Plus with Low Zinc

Abbreviations

T2D: Type 2 Diabetes; Novelzin: Zinc Acetate Hydrate; TIMES: Trials of IMeglimin for Efficacy and Safety; APLZ: Alzheimer's-Plus with Low Zinc

Introduction

Among non-communicable diseases (NCDs), type 2 diabetes (T2D) has been a crucial disease. The American Diabetes Association (ADA) proposed the latest guidelines as "Standards of Care in Diabetes" on Jan 1, 2023 [1]. The purpose would be to promote health for diabetic patients by refraining from various

comorbidities, macroangiopathy, microangiopathy and atherosclerotic cardiovascular disease (ASCVD) [2]. T2D has been more prevalent than before, and adequate management would be required over the world [3].

For T2D, fundamental therapeutic measures include

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nutritional, exercise, and pharmacological treatments. For decades, oral hypoglycemic agents (OHAs) have been surprisingly developed. Recent OHAs include sodium-glucose cotransporter 2 inhibitor (SGLT2i) and oral administration of glucagon-like-peptide 1 receptor agonist (GLP1-RA) [4]. Furthermore, the latest novel OHA is imeglimin (Twymeeeg) that shows dual efficacy of increasing insulin secretion and decreasing insulin resistance [5,6]. The characteristic point of imeglimin includes the similarity of molecules with metformin [7]. It has been the first-line OHA for a long time, used worldwide [8]. It has also shown enough efficacy on glucose variability, HbA1c, body weight, and cardiovascular influence [9]. Similar to metformin, imeglimin shows additional clinical beneficial effects for T2D [10].

On the other hand, recent focus concerning T2D includes dementia and/or mild cognitive impairment (MCI) associated with the involvement of zinc function. Zinc is present in all human tissues and fluids, and has been an indispensable component of various enzymes [11]. Zinc deficiency brings impaired taste and smell, increased risk of pneumonia, and decreased immune function [12]. Overlapping metabolic dysfunction has been suggested for T2D and Alzheimer's disease (AD) from a pathophysiological point of view [13]. Zinc concludes multifactorial functions for AD, and plays a role for enzymatic processing in amyloid precursor protein (APP) and for enzymatic degradation of amyloid- β (A β) [14]. When zinc homeostasis is disrupted in the brain, synaptic and memory deficits are brought on. Discussion has been found concerning the relationship between zinc levels in the blood, AD and related cognitive impairment [15]. Various accumulation of medical studies brought the certain link among diabetes, cognitive function and zinc [16].

From the combination of T2D, dementia and zinc mentioned above, our diabetic team had an impressive elderly female case with treatment of imeglimin. In this article, general clinical progress and some perspectives will be described.

Presentation of Cases

Medical History:

She was first diagnosed with T2D at the age of 63. She has been treated with oral hypoglycemic agents (OHAs), associated with HbA1c around 6.2-7.6% for years. When she underwent surgery at a university hospital for hip osteoarthritis at the age of 74, she was also treated for T2D in the diabetes mellitus (DM) department. Her HbA1c had been stable under 7.0% during 74-81 years old. From 2021, aged 81, her physical activity decreased and her HbA1c was above 8%. She also came to have a lot of snacks at home, and her condition did not improve. From 2022, her dementia symptoms became gradually worse, and she started to take medicine for dementia in our neurosurgery (NS) department. She often forgot the fact that she already had a regular meal; then she became a binge eater. Her diabetic treatment was transferred from university to our diabetic department in May 2022. Consequently, she started to receive treatment in the NS and DM departments in our hospital.

Physical Examinations:

Her physical examination in May 2022 showed the following: consciousness, alert, speech and conversation are normal in out clinic; vitals are normal ranges as pulse, BP, BT, respiration and SpO₂, unremarkable changes in the lung and heart, no symptom or signs of abdomen, neurological findings are intact. She did not have apparent hemiparesis or sensory disturbances in her extremities.

Biochemical laboratory test showed following data: Na 143 mEq/L, K 3.5 mEq/L, Cl 103 mEq/L, RBC 4.26 x 10⁶ / μ L, Hb 13.3 g/dL, Ht 39.2 %, MCV 92.2 fL (80-98), MCH 31.3 pg (27-33), MCHC 33.9 g/dL (31-36), WBC 7300/ μ L, Plt 25.9 x 10⁴ / μ L, TP 7.4 g/dL, Alb 4.4 g/dL, T-Bil 0.3 mg/dL, AST 15 U/L, ALT 24 U/L, LDH 158 U/L (124-222), r-GT 18 U/L, Uric Acid 5.9 mg/dL, BUN 18 mg/dL, Cre 0.49 mg/dL, eGFR 88.3 ml/min/1.73m², HDL 44 mg/dL, LDL 107 mg/dL, TG 194 mg/dL, T-Cho 190 mg/dL, arteriosclerotic index (AI) 3.3 (<4.0), CRP <0.6 mg/dL.

Chest X-P showed no remarkable specific changes. Electrocardiogram (ECG) revealed pulse 76/min, ordinary sinus rhythm, unremarkable ST-T changes.

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Urinalysis showed the results as glucose (+++), protein (-), urobilinogen (+/-), occult blood (+), pH 6.0, bilirubin (-), ketone bodies (-).

Medical Problems:

She had several medical problems in May 2022 as follows:

- T2D: Diabetic onset was 19 years ago. HbA1c value was 8.7% in first visit. Nutritional therapy was not satisfactory due to cognitive dysfunction (#2).
- Dementia: She developed symptoms and signs of dementia for a year. She was treated with memantine 5mg/day. The situation was almost stable.
- Hypertension: Anti-hypertensive agents (AHAs) were prescribed, which were amlodipine and candesartan. Her blood pressure was stable.
- Dyslipidemia: She has fatty liver and dyslipidemia, and formerly took anti-hypercholesterolemia medicine.
- Arteriosclerosis: Cerebral vascular accident (CVA) or lacunar infarct may exist, and then cilostazol (Pletal) has been prescribed.
- Osteoporosis: She continued to take alfacalcidol because of decreased bone mass density (BMD) for years.
- Femoral neck fracture: She developed bilateral femoral neck fracture in 2013 and 2020 with two

operations.

- Zinc prescription: She has T2D and dementia, as well as decreased serum zinc concentration. Consequently, zinc acetate hydrate (Novelzin) has been provided in NS department.

Clinical Course:

Her HbA1c value increased to 10.0% in June 2022, and then she started to take imeglimin (Twymeeeg) 2000mg/day. Clinical progress showed satisfactory decrease in blood glucose and HbA1c (**Fig-1**). After 4 months, HbA1c was 6.6% with decreased post-prandial blood glucose and HbA1c persisted around 7.0%.

Concerning symptoms and signs of dementia, her psychological situation was unstable. She was provided memantine 5mg/day before. In June 2022, she showed rather excited and aggressive air, and then memantine was increased to 10mg/day. However, she felt dizzy in August and then it decreased to 5 mg/day. After that, she developed tension, delirium and delusion, and then it was increased to 15-20 mg/day. In October 2022, she felt exacerbation of irritability and often quarreled with her family, and then she was given tiapride 50-100 mg/day. In December 2022, her psychological situation became stable. During her clinical progress, she continued to take metformin, alogliptin, amlodipine, candesartan and Novelzin.

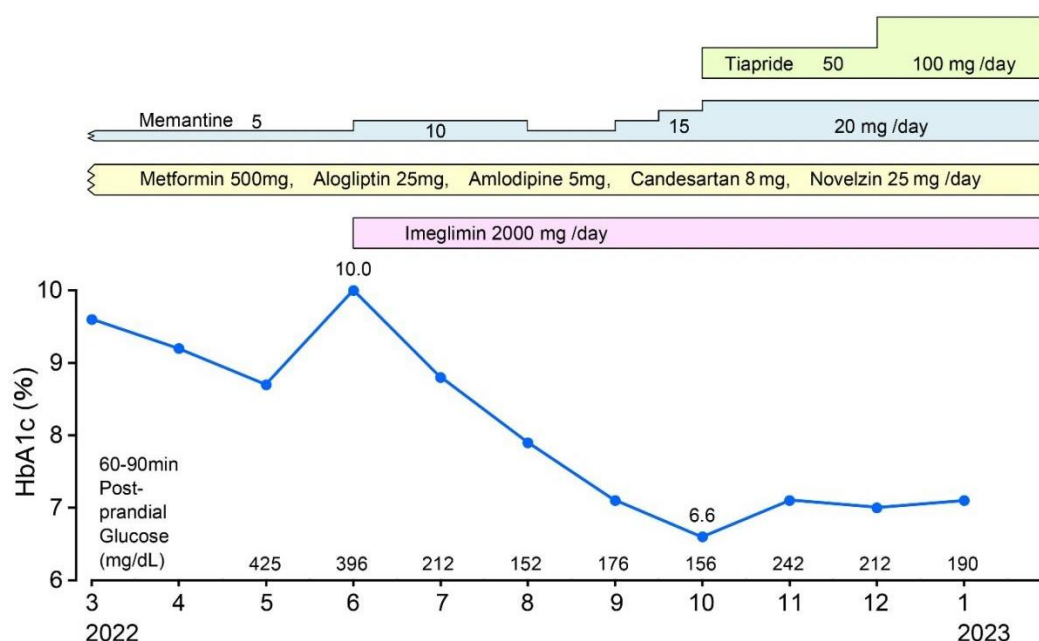


Fig-1: Clinical progress concerning HbA1c and medical treatment

Ethical Standards

The current case study was compiled with the previous standard ethical guidelines for the Helsinki Declaration. Moreover, commentary was included along with the standard protection rules for personal information. This principle has also been based on ethical rules in clinical practice and research against human subjects. Several guidelines are from the standard public proposal of the Japanese Ministry. This information is according to the Ministry of Health, Labor and Welfare, and Ministry of Education, Culture, Sports, Science Technology, Japan. Current authors and collaborators established an ethical committee for this investigation that exists at Sakamoto Hospital in Kagawa prefecture, Japan. It has some professional medical and legal persons, such as the president of the hospital, physicians, surgeon, head nurse, registered nutritionist, pharmacist and legal personnel. All members have discussed fully this case matter and recognized the agreement for the research protocol.

Discussion

For the current case, the characteristic aspects can be summarized as follows. The elderly patient was an 83-year-old woman who had several problems of T2D, dementia, hypertension, dyslipidemia, arteriosclerosis, osteoporosis, femoral neck fracture and zinc prescription. Among them, following three issues are especially recognized for discussion.

i) DM Dept: Imeglimin was administered for T2D, and HbA1c decreased sufficiently with clinical effects.

ii) NS Dept: Memantin and tiapride were used for controlling the unstable situation of dementia and anxiety.

iii) Zinc meds: T2D and dementia showed mutual relationship associated with zinc metabolism. Current case has continued to take zinc acetate hydrate (Novelzin).

Several consideration and perspective about these are described in this order.

Firstly, the current case showed decreased HbA1c from 10.0% to 6.6% for 4 months. Imeglimin has been known for its beneficial add-on therapy with other OHAs. For novel imeglimin, a series of large studies were found, which were called Trials of IMeglimin for

Efficacy and Safety (TIMES). They are TIMES 1, 2 and 3. Clinical effects were compared between combined therapy vs monotherapy for TIMES 2 [17]. Certain beneficial results were found concerning decreased HbA1c in the following. They are 0.46% for monotherapy of imeglimin, combination treatment of imeglimin and other OHAs, which are 0.70% for glinides, 0.56% for SU, 0.85% for alfa-GI, 0.67% for biguanides, 0.92% of DPP4-i, 0.57% for SGLT2i. Among these results, the most effective data was 0.92% for DPP4-4i. In addition, impressive results showed in TIMES 3 [18]. As to GLP-1RA as a subcutaneous injection, the combined effect of HbA1c was only 0.12%. The pharmacological route is similar between DPP4-I and GLP-1RA. However, clinical efficacy differs to a large extent as 0.92% and 0.12%, from TIMES 2 and 3. Certain action routes may differ or mitochondria pathways will be clarified from detailed pharmaco-physiological points of view in the future.

Secondly, the current case had both tests of MMSE (Mini-Mental State Examination) and HDS-R (Hasegawa's Dementia Scale-Revised) [19,20]. The results showed a light level of dementia, in which she occasionally had some episodes of memory and unstable feelings with her family. In response to her neuropsychiatric symptoms in dementia, medication doses of memantine and tiapride were controlled. This clinical management was successful in controlling the QOL of the patient and her families. From Jan 2023, her general irritability was relieved, and her family could lead stable lives. In the current case, no relationship seemed to be found between improving glucose variability with decreasing HbA1c and increasing and managing problems due to dementia. However, a recent report showed that T2D became an important risk factor for neuropsychiatric symptoms in early AD with an odds ratio of 3.48 [21].

Thirdly, this case showed decreased concentration of serum zinc and continued to take zinc acetate hydrate (Novelzin). For Alzheimer's disease (AZ), three subtypes were proposed by Bredesen [22]. They include i) inflammatory type; ii) non-inflammatory type; and iii) distinctive entity for younger cases that are associated with striking zinc deficiency. Consequently, it would be called the syndrome of

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Alzheimer's-plus with low zinc (APLZ). The hypothesis concerning AD was investigated in which zinc value is associated with cerebral deposition of β -amyloid protein ($A\beta$) [23]. Furthermore, serum zinc concentration and other AD factors were studied, such as white matter hyperintensities (WMHs) and AD-signature cerebral glucose metabolism (AD-CM). Subjects were 241 older adults with normal cognition. As a result, serum zinc concentration showed significant association with elevated $A\beta$ retention. As to the treatment of AD and mixed dementia, mono-type therapeutic measures would be inadequate. Then, a personalized multimodal program would be adequate [24]. Certain multimodal treatment includes personalized therapeutic methods for each perturbation to neuroplasticity. Especially, metabolic subsystem and neuroinflammation may influence hippocampal volume and clinical cognitive function.

Some limitations may be present concerning this article. Current case showed enough effects of imeglimin and memantine for T2D and dementia, associated with continuous intake of Novelzin. However, no apparent relationships were clarified among several factors, such as T2D, dementia, zinc, QOL, family cooperation and involvement of hospital team practice. Her future clinical progress will be followed up with careful attention.

In summary, a case report of an elderly female with T2D and dementia was presented who showed satisfactory clinical efficacy. Some perspectives were described concerning the relationship among T2D, dementia and zinc. This article is expected to become a useful reference for diabetic research.

Funding

There was no funding received for this paper.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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