SUPPLEMENTARY MATERIAL

A multicenter, open-label, single-arm trial of the efficacy and safety of empagliflozin treatment for refractory diabetes mellitus with insulin resistance (EMPIRE-01)

Yushi Hirota[1], Yasumasa Kakei[2], Junta Imai[3], Hideki Katagiri[3], Ken Ebihara[4], Jun Wada[5], Junichi Suzuki[6], Tatsuhiko Urakami[6], Takashi Omori[7], Wataru Ogawa[1]

[1]Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[2]Clinical and Translational Research Center, Kobe University Hospital, Kobe, Japan
[3]Department of Metabolism and Diabetes, Tohoku University Graduate School of Medicine, Miyagi, Japan
[4] Division of Endocrinology and Metabolism, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan
[5] Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University, Faculty of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[6]Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan
[7]Division of Clinical Biostatistics, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Correspondence: Wataru Ogawa, MD, PhD, Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. Tel.: +81-78-382-5860. Fax: +81-78-382-2080. Email: ogawa@med.kobe-u.ac.jp

SUPPLEMENTARY APPENDIX

Inclusion Criteria and Exclusion Criteria

The inclusion criteria for the trial were as follows:

1. Diagnosis of insulin resistance syndrome (type A, type B, or non–type A, non–type B*) or lipodystrophic diabetes prior to consent.
2. Instruction on the use and dosage of antihyperglycemic agents, dietary therapy, and exercise therapy for at least 12 weeks before registration.
3. An HbA_{1c} value of □7.0% during the screening period.
4. Washout period of at least 12 weeks prior to registration for individuals currently receiving SGLT2 inhibitors.
5. Age of 20 years or older at the time of consent.
6. Receipt of sufficient explanation regarding the purpose, nature, anticipated pharmacological effects, and risks of the clinical trial, and provision of written consent in person.

The exclusion criteria for the trial were as follows:

1. History of acute coronary syndrome (including non–ST-elevation myocardial infarction, ST-elevation myocardial infarction, and unstable angina), stroke, or transient ischemic attack within 3 months prior to consent.
2. Serum ALT, AST, or alkaline phosphatase levels exceeding three times the upper limit of normal during the screening period and suspected liver dysfunction.
3. Systemic corticosteroid therapy at the time of consent (with the exception of individuals with type B insulin resistance syndrome).
4. A change in dose of thyroid hormone medication within 6 weeks prior to consent.
5. Unstable condition of endocrine disorders other than diabetes.
6. Hematologic disorders or other conditions that cause hemolysis or instability of red blood cells (such as malaria, babesiosis, and hemolytic anemia).
7. Premenopausal status with the final menstruation occurring within 1 year prior to consent, breastfeeding or pregnancy, or childbearing potential (no hysterectomy or oophorectomy) in women who do not intend to use a contraception method defined in the study and do not consent to regular pregnancy testing during the trial period.
8. History of alcohol or substance abuse within 3 months before consent that could hinder participation in the study.

9. Conditions that render administration of the investigational drug difficult.
10. Renal impairment as indicated by an estimated glomerular filtration rate of <45 mL min^{-1} 1.73 m^{-2} during the screening period.
11. Manifestation of hypersensitivity reactions to empagliflozin or its excipients, or lactose intolerance.
12. Severe ketoacidosis, diabetic coma or precoma, severe infection, perioperative status, or serious trauma during the screening period, or deemed inappropriate for participation in the study for other reasons by a study investigator.

Serious AEs

Serious AEs are defined as any of the following AEs:

1. Death
2. Any event that may lead to death
3. Events that require hospitalization or prolongation of a hospital stay for treatment (not applicable to hospitalization or prolongation of hospitalization for reexamination or follow-up)
4. Disability
5. An event that may lead to disability
6. Congenital disease or abnormality in later generations
7. Other events that are as serious as 1 to 6

*In this protocol, cases suspected of having genetic insulin resistance syndrome but without *INSR* abnormalities are defined as non-type A, non-type B insulin resistance syndrome. This includes conditions triggered by abnormalities such as *PIK3R1*. After the creation of this protocol, the Japan Diabetes Society proposed a new disease classification that defines insulin resistance syndrome caused by gene mutations as genetic insulin resistance, regardless of the type of causative gene [1]. Accordingly, in the main text of this paper, Type-A insulin resistance syndrome and non-type A, nontypeB insulin resistance syndromes are collectively referred to as genetic insulin resistance syndrome.

Reference

1. Ogawa W, Araki E, Ishigaki Y, et al. New classification and diagnostic criteria for insulin resistance syndrome. Diabetol Int. 2022; 13:337–43.

Fig. S1 Time courses of HbA_{1c} (**a**) and FPG (**b**) levels for individual patients during empagliflozin treatment.

Supplementary Figure 1

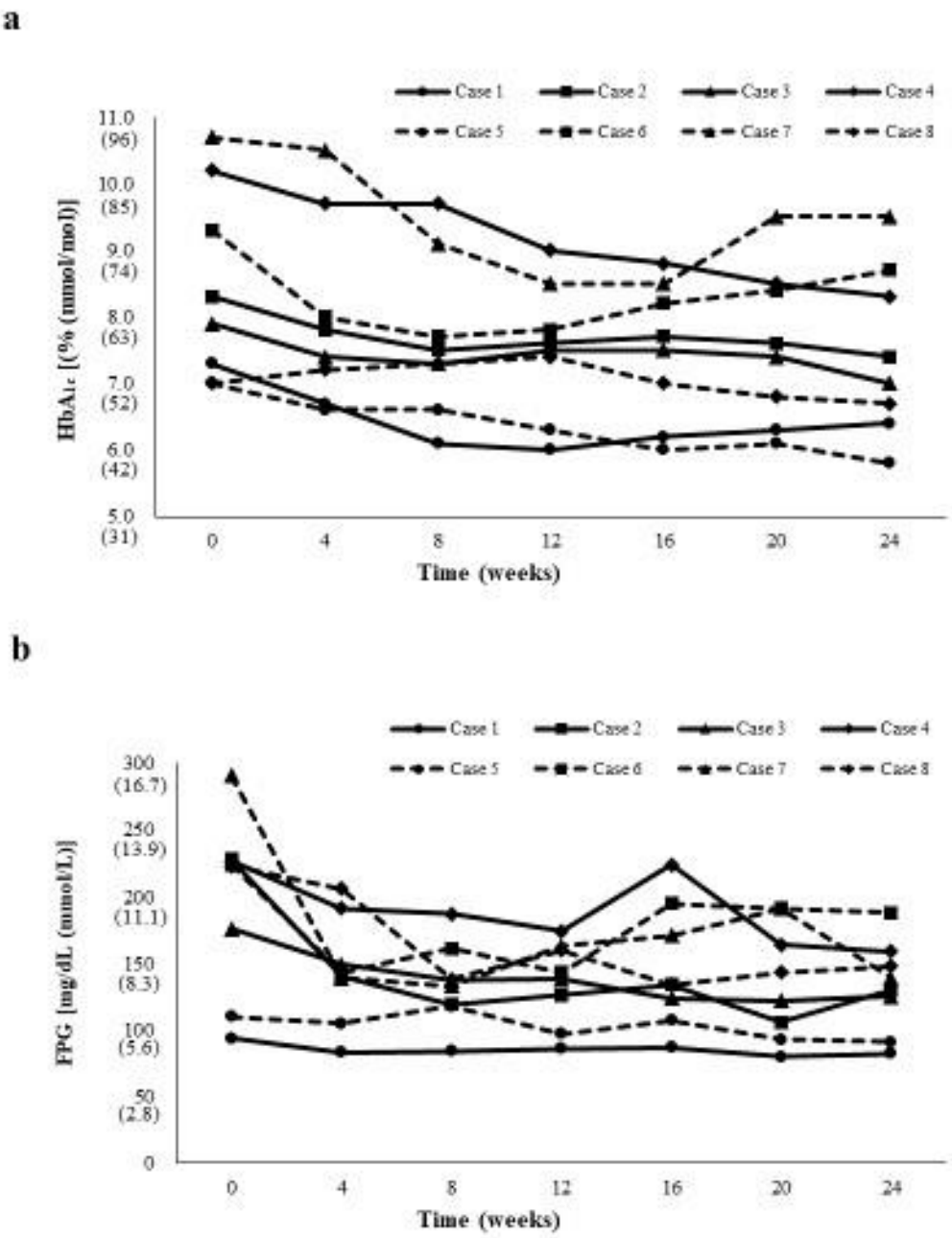
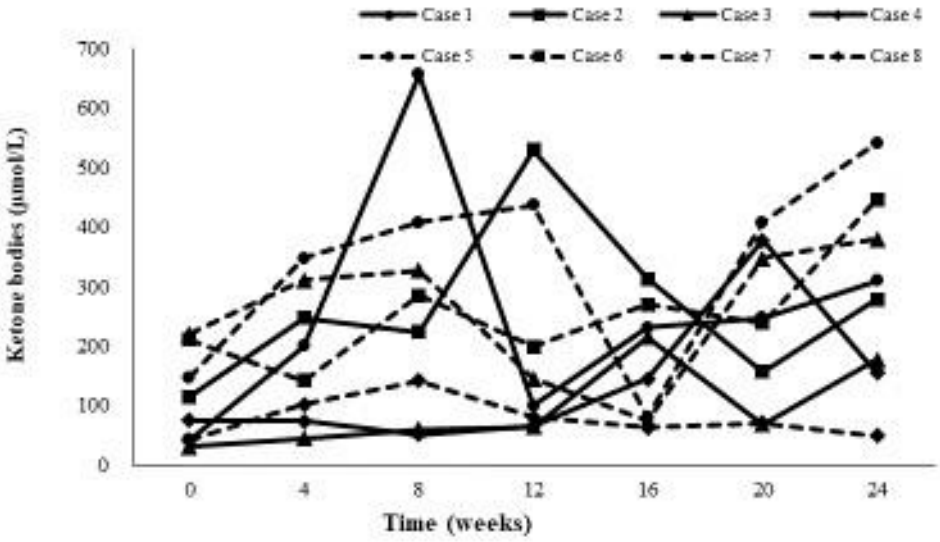


Fig. S2 Time courses of the serum concentration of ketone bodies (**a**) and body mass (**b**) for individual patients during empagliflozin treatment.

Supplementary Figure 2

a



b

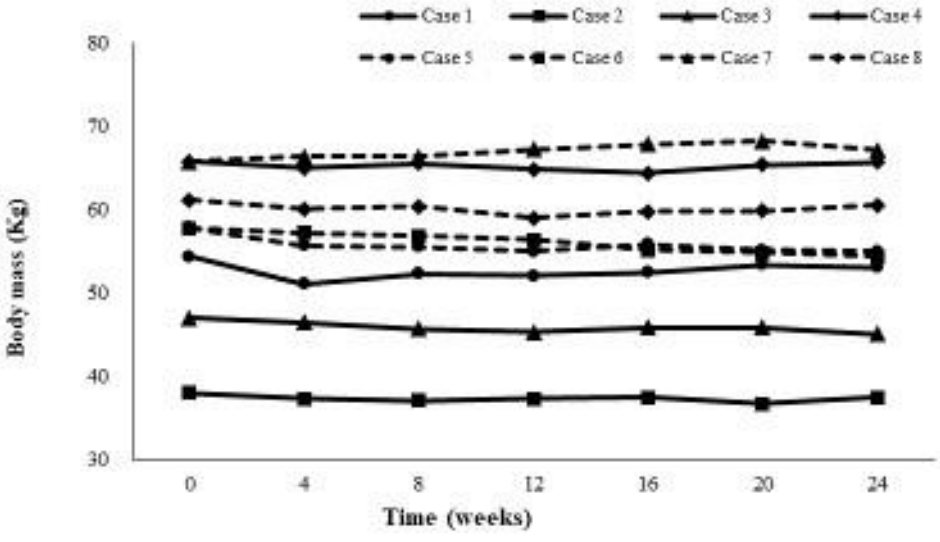


Table S1 Clinical information for the study patients with insulin resistance syndrome or lipodystrophic diabetes

Case	Disease	Mutation	Age/ sex	Height (cm)/body mass (kg)	Body mass index (kg/m^2)	HbA_{1c} (%/ mmol/mol)	FPG (mg/dL/ mmol/L)	Therapy for diabetes
1	Insulin resistance syndrome	*INSR* Asn489Ser Heterozygous	36/F	166.4/54.3	19.6	7.3/56	94/5.22	Metformin 1500 mg
2	Insulin resistance syndrome	*PIK3R1* Arg649Trp Heterozygous	39/F	142.1/37.9	18.8	8.3/67	228/12.67	Metformin 2250 mg Insulin lispro 49 U Insulin glargine 40 U
3	Insulin resistance syndrome	*PIK3R1* Lys653Ter Heterozygous	33/M	152.8/46.9	20.1	7.9/62	176/9.78	Teneligliptin 20 mg
4	Lipodystrophic diabetes	*BSCL2* Arg275Ter Homozygous	42/M	180.5/65.7	20.2	10.2/87	227/12.61	Metformin 1500 mg Teneligliptin 20 mg Pioglitazone 30 mg Glimepiride 2 mg Miglitol 150mg

5	Insulin resistance syndrome	*PIK3R1* Arg649Trp Heterozygous	22/M	155.6/57.8	24.0	7.5/58	101/6.31	Metformin 1500 mg Pioglitazone 60 mg
6	Insulin resistance syndrome	*INSR* Leu999del Heterozygous	42/F	151.3/57.7	25.2	9.3/78	224/12.44	Metformin 2250 mg Acarbose 150 mg Insulin lispro 114 U NPH insulin 30 U
7	Insulin resistance syndrome	*INSR* Arg120Gln Heterozygous	49/F	161.3/65.7	25.3	10.7/93	291/16.17	Metformin 500 mg Pioglitazone 15 mg Dulaglutide 0.75 mg/week
8	Insulin resistance syndrome	*INSR* Arg120Gln Heterozygous	45/F	155.8/61.1	25.2	7.0/52	223/12.39	Metformin 500 mg Pioglitazone 15 mg Dulaglutide 0.75 mg/week