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ORIGINAL RESEARCH

A Multicenter, Open-Label, Single-Arm Trial of the Efficacy and Safety of Empagliflozin Treatment for Refractory Diabetes Mellitus with Insulin Resistance (EMPIRE-01)

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ABSTRACT

Introduction: Insulin resistance syndrome and lipoatrophic diabetes are characterized by severe insulin resistance and are often refractory to treatment. Trials assessing the efficacy of antidiabetes drugs for these rare conditions have been limited, however. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which lower glycemia independently of insulin action, have shown efficacy for type 2 diabetes with insulin resistance. We here investigated the efficacy and safety of the SGLT2 inhibitor empagliflozin for treatment of insulin resistance syndrome and lipoatrophic diabetes.

Methods: The trial was conducted at five academic centers in Japan and included seven patients with insulin resistance syndrome and one patient with lipoatrophic diabetes. Participants received 10 mg of empagliflozin daily. If the hemoglobin A_{1c} (HbA_{1c}) level was $\geq$ 7.0% (52 mmol/mol) after 12 weeks, the dose was adjusted to 25 mg. The study duration was 24 weeks, and the primary outcome was the change in HbA_{1c} level by the end of the treatment period. Safety evaluations were performed for all participants.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-023-01526-x.

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Results: By the end of the 24-week treatment period, the mean HbA_{1c} level for all eight patients had decreased by 0.99 percentage points (10.8 mmol/mol) (95% confidence interval [CI], 0.59 to 1.38 percentage points, 6.6 to 14.9 mmol/mol) and the mean fasting plasma glucose concentration had declined by 63.9 mg/dL (3.55 mmol/L) (95% CI 25.5 to 102.3 mg/dL, 1.42 to 5.68 mmol/L). Continuous glucose monitoring revealed a reduction in mean glucose levels from 164.3 ± 76.1 to 137.6 ± 46.6 mg/dL (9.13 ± 4.23 to 7.65 ± 2.59 mmol/L) as well as an increase in the time in range (70–180 mg/dL) from 58.9 ± 36.1% to 70.8 ± 18.3%. Seventeen mild adverse events were recorded in five individuals throughout the study period. No severe events were reported. The mean body mass showed a slight decrease and the mean serum ketone body concentration showed a slight increase during treatment.
Conclusion: Our results demonstrate that empagliflozin shows a certain level of efficacy and safety for treatment of insulin resistance syndrome and lipoatrophic diabetes.
Trial Registration: jRCTs2051190029 and NCT04018365.

Keywords: Empagliflozin; Genetic insulin resistance syndrome; Lipoatrophic diabetes; SGLT2 inhibitor; Type A insulin resistance syndrome; Type B insulin resistance syndrome

Key Summary Points

Why carry out this study?

Insulin resistance syndrome and lipoatrophic diabetes are both characterized by severe insulin resistance and are often refractory to treatment with antidiabetes drugs.

We hypothesized that sodium-glucose cotransporter 2 (SGLT2) inhibitors might be effective for treatment of these rare types of diabetes.

What was learned from the study?

Treatment with the SGLT2 inhibitor empagliflozin for 24 weeks led to a marked improvement in glycemic control in patients with these conditions.

Observed adverse events were all mild, with only a slight decrease in body mass and a slight increase in ketone bodies being apparent.

Empagliflozin appears to be both effective and safe for treatment of insulin resistance syndrome and lipoatrophic diabetes.

INTRODUCTION

Whereas type 1 and type 2 diabetes account for most cases of diabetes, various other types of diabetes have been identified, some of which are resistant to standard treatments for type 1 or type 2 disease. One such type of treatment-refractory diabetes is insulin resistance syndrome, which was formerly categorized as insulin receptor abnormalities [1, 2]. This syndrome has been traditionally classified into type A and type B, with the former being attributable to variants of the insulin receptor gene and the latter to autoantibodies to the insulin receptor [3, 4]. Given that variants of genes related to signaling downstream of the insulin receptor have also been associated with conditions similar to type A insulin resistance syndrome [5–7], genetic insulin resistance syndrome has been proposed as a category to encompass conditions triggered by variants of the insulin receptor gene or of genes for such downstream signaling proteins [2]. Individuals with lipoatrophic diabetes, which is characterized by a marked decrease or total loss of adipose tissue, also often manifest treatment-resistant diabetes due to severe insulin resistance, in addition to other metabolism-related disorders including dyslipidemia and hepatic steatosis [8, 9]. Lipoatrophic diabetes is categorized into genetic and acquired forms, with variants of various genes being responsible for the former [10, 11].

Both insulin resistance syndrome and lipoatrophic diabetes are rare conditions. In Japan, the number of cases of genetic insulin resistance syndrome and lipoatrophic diabetes being treated at specialized institutions was recently estimated to be approximately 100 for each [5, 12]. The annual number of newly diagnosed cases of type B insulin resistance syndrome in Japan is estimated to be around 20 [5]. Although case reports and case series related to the treatment of these atypical forms of diabetes have been published [5, 6, 13–15], prospective trials evaluating the effectiveness and safety of antidiabetes drugs for such patients are limited.

Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, exerts antidiabetic effects by attenuating glucose reabsorption in renal tubules through selective inhibition of SGLT2 [16]. In addition to its glucose-lowering action, empagliflozin has been shown to prevent the progression or onset of chronic kidney disease and heart failure [17–19], and it has been approved for the treatment of these conditions. Given that empagliflozin, like other SGLT2 inhibitors, reduces blood glucose levels independently of insulin action, it is expected to effectively lower glycemia even in individuals with severe insulin resistance [6, 13, 20]. However, limited information has been available regarding the efficacy of empagliflozin for forms of diabetes other than type 2. We have therefore now evaluated the efficacy and safety of empagliflozin treatment for individuals with treatment-refractory diabetes including insulin resistance syndrome and lipoatrophic diabetes.

METHODS

Study Design

This nonrandomized, prospective, open-label, multicenter trial was conducted at five academic centers in Japan (Tohoku University Hospital, Nihon University Hospital, Jichi Medical University Hospital, Kobe University Hospital, and Okayama University Hospital). The trial was performed in accordance with the 2013 Declaration of Helsinki [21] and International Conference on Harmonization Good Clinical Practice (ICHGCP) [22] guidelines. The study protocol and amendments were approved by the relevant institutional review board and an independent ethics committee at each study site. The trial was registered with the Japan Registry of Clinical Trials (jRCTs2051190029) and with ClinicalTrials.gov (NCT04018365). All participants provided written informed consent before entry into the study.

Individuals diagnosed with insulin resistance syndrome or lipoatrophic diabetes who were aged 20 years or older and had a hemoglobin A_{1c} (HbA_{1c}) level of at least 7% were recruited for the study. For detailed inclusion and exclusion criteria as well as the diagnostic criteria for insulin resistance syndrome and lipoatrophic diabetes, see the appendix in electronic supplementary material. Study participants were treated with empagliflozin at a starting dose of 10 mg once daily per os. After 12 weeks of treatment, the dose was increased to 25 mg if the HbA_{1c} level remained at or above 7.0% (52 mmol/mol). The total duration of the trial was 24 weeks. Participants were followed up every 4 weeks for monitoring of therapeutic effects and any adverse events.

After completion of this 24-week trial (EMPIRE-01 trial), empagliflozin treatment was continued for subjects who agreed to participate in a long-term safety trial for an additional 24 weeks (EMPIRE-02 trial). Results from the EMPIRE-02 trial will be reported separately.

Diagnosis Criteria for Insulin Resistance Syndrome and Lipodystrophic Diabetes

Type A insulin resistance syndrome is characterized by pronounced insulin resistance attributed to abnormalities of the insulin receptor gene. If testing for the insulin receptor gene is not feasible, clinical identification of type A insulin resistance syndrome is established by the absence of obesity or other causes of insulin resistance concomitant with the presence of fasting hyperinsulinemia (serum insulin concentration of $\geq$ 30 μU/ml).

Type B insulin resistance syndrome is characterized by pronounced insulin resistance caused by autoantibodies to the insulin

receptor. The presence of such autoantibodies serves as diagnostic confirmation for type B insulin resistance syndrome.

Non-A, non-B insulin resistance syndrome is characterized by pronounced insulin resistance arising from abnormalities of genes other than that for the insulin receptor. This classification encompasses cases with discerned causal genes such as *PIK3R1* (a form of genetic insulin resistance syndrome) as well as those without an identified causal gene.

In this protocol, cases suspected of having genetic insulin resistance syndrome but without *INSR* abnormalities were originally defined as non-type A, non-type B insulin resistance syndrome. This includes conditions triggered by abnormalities such as *PIK3R1*. Clinical diagnosis of non-A, non-B insulin resistance syndrome is established by the absence of obesity or other causes of insulin resistance as well as of abnormalities in the insulin receptor gene and of insulin receptor autoantibodies, and by the concomitant presence of fasting hyperinsulinemia (serum insulin level of $\geq$ 30 μU/ml). 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 [2]. Accordingly, Type-A insulin resistance syndrome and non-type A, non-typeB insulin resistance syndromes are collectively referred to as genetic insulin resistance syndrome.

Lipodystrophic diabetes manifests as diabetes resulting from insulin resistance and metabolic aberrations consequent to the congenital or acquired systemic or partial loss of adipose tissue, despite the absence of substantial weight loss or malnutrition.

Outcomes

The primary outcome was the change in HbA_{1c} level after treatment with empagliflozin for 24 weeks compared with baseline. Secondary outcomes included the percentage change in HbA_{1c} level from baseline after treatment for 12 or 24 weeks; the HbA_{1c} and fasting plasma glucose (FPG) levels as well as the insulin dosage every 4 weeks; the change in FPG concentration after treatment for 24 weeks compared with baseline; and the change in postprandial glucose levels assessed with a continuous glucose monitoring (CGM) device (FreeStyle Libre Pro, Abbott Diabetes Care, Alameda, CA, USA) after treatment for 20 weeks relative to baseline. In addition, mean sensor glucose, glucose management indicator (GMI), coefficient of variation (CV) of sensor glucose, time in range (70–180 mg/dL [3.9–10.0 mmol/L]), (> 180 mg/dL [> 10.0 mmol/L]), time below range (< 70 mg/dL [< 3.9 mmol/L]) were assessed with CGM at baseline and after treatment for 20 weeks.

For safety evaluation, the endpoints included adverse events (AEs) and adverse drug reactions (ADRs), the latter including hypoglycemia, urinary tract infection, genital infection, volume depletion including body weight loss, polyuria or pollakiuria, renal dysfunction, ketone body elevation, bone disease, cardiovascular disease, and malignant disease. AEs of special interest included liver dysfunction, renal dysfunction, metabolic acidosis, ketoacidosis, diabetic ketoacidosis, and lower limb amputation. Serious AEs are defined in the appendix in electronic supplementary material.

Sample Size Determination

Given the rarity of both insulin resistance syndrome and lipoatrophic diabetes, it was difficult to determine the sample size of the study on the basis of statistical power alone. Aiming to strike a balance between feasibility and a degree of scientific confidence, we set the sample size to eight.

Statistical Analysis

The change and percentage change in HbA_{1c} level as well as the change in FPG concentration at 24 weeks relative to baseline were assessed on an individual patient basis as well as summarized with sample size, mean, standard deviation (SD), minimum, median, and maximum values. The population means with 95% confidence intervals of these changes were

estimated. All statistical analysis was performed with the use of SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Participants

Seven individuals with insulin resistance syndrome and one with lipoatrophic diabetes participated in the trial. All the participants completed the 24-week treatment course. The characteristics of each participant and the study population as a whole are provided in Table S1 and Table 1, respectively. None of the seven individuals with insulin resistance syndrome were treated with insulin-like growth factor 1 (IGF1), which is approved for treating this syndrome in Japan. Four and three individuals with insulin resistance syndrome harbored variants of *INSR* and *PIK3R1*, respectively, whereas individuals with type B insulin resistance syndrome did not participate in the trial. The subject with lipoatrophic diabetes harbored a pathological variant of *BSCL2*.

Efficacy Evaluation

The mean HbA_{1c} level for all the participants was reduced by 0.99 percentage points (10.8 mmol/mol) (95% confidence interval [CI], 0.59 to 1.38 percentage points, 6.6 to 14.9 mmol/mol) after treatment for 24 weeks, from 8.46 ± 1.45% (68.4 ± 15.9 mmol/mol)(mean ± SD) at baseline to 7.48 ± 1.26% (57.6 ± 13.9 mmol/mol). The percentage change in HbA_{1c} level from baseline to after treatment for 24 weeks was − 11.54% (95% CI − 15.55% to − 7.53%). The time course of the mean HbA_{1c} level for all participants is shown in Fig. 1a, with the absolute change in this parameter being − 0.95 ± 0.78 percentage points (− 10.3 ± 8.81 mmol/mol) and the percentage change being − 10.51% (95% CI − 17.47% to − 3.55%) after treatment for 12 weeks. The time course of the HbA_{1c} level for each participant is shown in Fig. S1a.

Table 1 Baseline characteristics of the study participants (n = 8)

Characteristic	Value
Male/female	3/5
Age (years)	38.5 ± 8.3
Body mass index (kg/m^2)	22.3 ± 2.9
HbA_{1c} (%)	8.46 ± 1.45
HbA_{1c} (mmol/mol)	68.4 ± 15.9
FPG (mg/dL)	196.6 ± 66.2
FPG (mmol/L)	10.92 ± 3.68
Fasting IRI (μU/mL)	68.0 ± 84.6
Fasting CPR (ng/mL)	2.42 ± 0.87
TDD (U)	116.5 ± 38.8
TBD (U)	35.0 ± 7.1
Antidiabetic agents	
DPP4 inhibitors	2
Biguanides	7
Sulfonylureas	1
Thiazolidinediones	4
α-Glucosidase inhibitors	1
GLP-1 receptor agonists	2
Insulin	5

Date are n or mean ± SD values. TDD and TBD values are for the two patients treated with insulin. Abbreviations not defined in text: IRI, immunoreactive insulin; CPR, C-Peptide immunoreactivity; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1

The mean FPG concentration for all the participants was reduced by 63.9 mg/dL (3.55 mmol/L) (95% CI 25.5 to 102.2 mmol/L, 1.42 to 5.68 mmol/L) after treatment for 24 weeks, from 196.6 ± 66.2 mg/dL (10.92 ± 3.68 mmol/L) at baseline to 132.8 ± 34.6 mg/dL (7.38 ± 1.92 mmol/L). The time courses of FPG concentration for the study population as a whole and for each participant are shown in Fig. 1b and Fig. S1b, respectively.

Two participants were treated with multiple daily insulin injections. In one of these individuals, the total daily insulin dose (TDD) and total daily basal insulin dose (TBD) had decreased from 89 to 52 U and from 40 to 24 U, respectively, after treatment for 24 weeks. In the second individual, although the TDD had declined from 144 to 126 U after treatment for 24 weeks, there was no change in the TBD, which remained at 30 U. CGM analysis revealed that the average sensor glucose level had decreased from 164.3 ± 76.1 to 137.6 ± 46.6 mg/dL (9.13 ± 4.23 to 7.65 ± 2.59 mmol/L) between baseline and after treatment for 20 weeks, with the time in range showing a corresponding increase from 58.9 ± 36.1% to 70.8 ± 18.3% (Table 2).

Safety Evaluation

A total of 17 AEs was noted in five individuals (Table 3). All of these AEs were mild, with no serious AEs or events necessitating the discontinuation or suspension of treatment or a reduction in drug dose being reported. AEs observed in two or more individuals included nasopharyngitis, tenosynovitis, and diarrhea. Recovery or improvement from all AEs, with the exception of periarthritis as well as contact dermatitis at the area in which the CGM sensor was placed, was apparent by the end of the trial. One ADR (mild hypoglycemia) and one AE of special interest (liver dysfunction) were reported.

Given that treatment with SGLT2 inhibitors is associated with an increase in the serum concentration of ketone bodies and with a loss of body mass [23], we also examined changes in these two parameters. Time courses revealed a slight increase in the mean serum level of ketone bodies (Fig. 2a) and a slight decrease in mean body mass (Fig. 2b) over the course of the study treatment. The temporal changes in these parameters for each participant are shown in Fig. S2.

DISCUSSION

This trial is the first to investigate the efficacy and safety of empagliflozin in individuals with insulin resistance syndrome or lipoatrophic diabetes. It was conducted in accordance with ICHGCP guidelines, ensuring its quality. Treatment with empagliflozin was associated with a reduction in HbA_{1c} level from 8.46 ± 1.45% to 7.48 ± 1.26%, with the extent of this change being similar to that observed in trials performed with individuals with type 2 diabetes [24, 25]. The observed AEs were all mild, and no unanticipated AEs were reported. Our findings are thus indicative of the effectiveness and safety of empagliflozin for the treatment of diabetes associated with these rare conditions.

Medicines for diabetes have generally been tested for their efficacy and safety in individuals with type 1 or type 2 diabetes, with the result that they are officially approved only for these conditions. For the treatment of other types of diabetes, such drugs are thus administered off-label at the discretion of the physician. Whereas it is not feasible to study the effects of each antidiabetes drug for each category of diabetes, this situation is not only undesirable from a scientific viewpoint but also increases the psychological burden on patients with rare and refractory forms of diabetes [26].

Treatment of diabetes with SGLT2 inhibitors is sometimes associated with diabetic ketoacidosis (DKA), more often in individuals with type 1 diabetes than in those with type 2 diabetes [27, 28]. We did not observe DKA or a substantial increase in the serum level of ketone bodies during this trial. Nonetheless, DKA is a potentially concerning AE for the treatment of insulin resistance syndrome or lipoatrophic diabetes with SGLT2 inhibitors, given that insufficient insulin action in the body, whether due to insulin resistance or inadequate insulin secretion, is a contributing factor to DKA [29, 30]. Treatment with SGLT2 inhibitors is also associated with a mild reduction in body mass, and we observed a body mass reduction similar in extent to those reported in clinical trials for type 1 or type 2 diabetes [24, 25, 31–33].

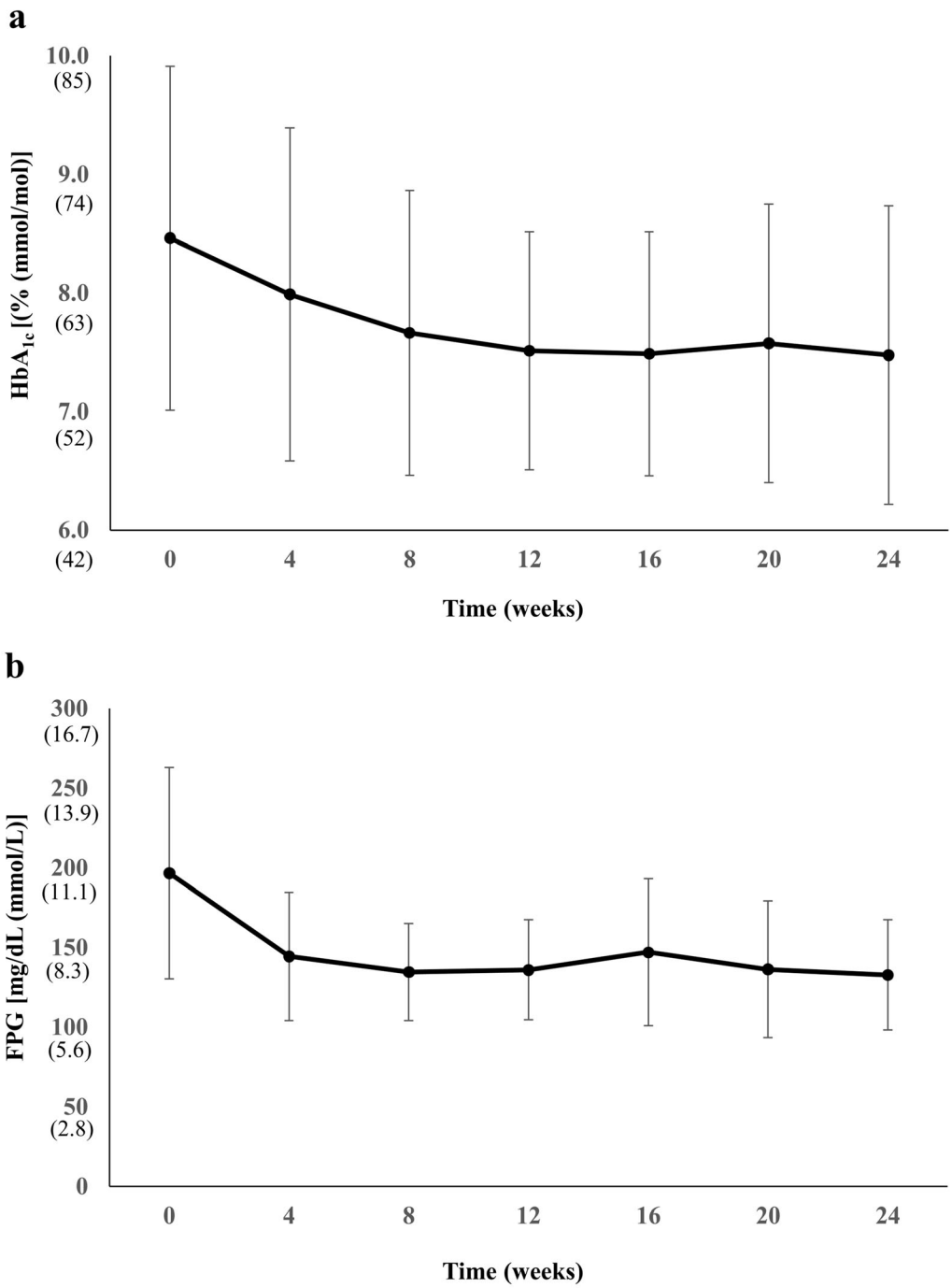

Fig. 1 Temporal changes in the mean HbA_{1c} level (**a**) and in the mean FPG concentration (**b**) during empagliflozin treatment for the study population. Data are means ± SD (n = 8)

Limitations of the present study include the small number of participants and its single-arm design. The rarity of the studied diseases limits the number of potential subjects, however. In Japan, IGF1 is the only medication officially approved for the treatment of insulin resistance syndrome. The trial that served as the basis for this approval was also conducted with only

Table 2 CGM metrics before and after empagliflozin treatment for 20 weeks

Metric	Baseline	Week 20
Mean sensor glucose (mg/dL)	164.3 ± 76.1	137.6 ± 46.6
Mean sensor glucose (mmol/L)	9.13 ± 4.23	7.65 ± 2.59
GMI (%)	7.23 ± 1.81	6.60 ± 1.12
CV of sensor glucose (%)	29.5 ± 4.6	29.3 ± 7.6
Time above range (%)	35.3 ± 40.6	20.5 ± 23.7
Time in range (%)	58.9 ± 36.1	70.8 ± 18.3
Time below range (%)	5.9 ± 7.9	8.7 ± 11.1

Date are means ± SD (n = 8). Abbreviations not defined in text: *GMI* glucose management indicator, *CV* coefficient of variation

eight patients [34]. In addition, although type B insulin resistance syndrome was included as a target disease for this trial, we were unable to recruit any individuals with this condition, largely because it typically presents with an acute onset and has a transient course, making it difficult to enroll subjects within a fixed trial period. Furthermore, in many of our analyses, we aggregated the results from all eight subjects, which included seven individuals with insulin resistance syndrome and one with lipoatrophic diabetes. Given the distinct pathologies of these two conditions, combining them for analysis might be problematic.

Table 3 AEs of the study treatment

Event	Number	Severity	Drug-related	Study treatment
Nasopharyngitis	3	Mild	No	Continued
AST of > 5 × ULN	1	Mild	No	Continued
ALT of > 5 × ULN	1	Mild	No	Continued
Contact dermatitis	1	Mild	No	Continued
Cough	1	Mild	No	Continued
Hypoglycemia	1	Mild	Yes	Continued
Hyperglycemia	1	Mild	No	Continued
Tenosynovitis	2	Mild	No	Continued
Infectious enteritis	1	Mild	No	Continued
Diarrhea	2	Mild	No	Continued
Nausea	1	Mild	No	Continued
Headache	1	Mild	No	Continued
Periarthritis	1	Mild	No	Continued

Abbreviations not defined in text: *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ULN* upper limit of normal

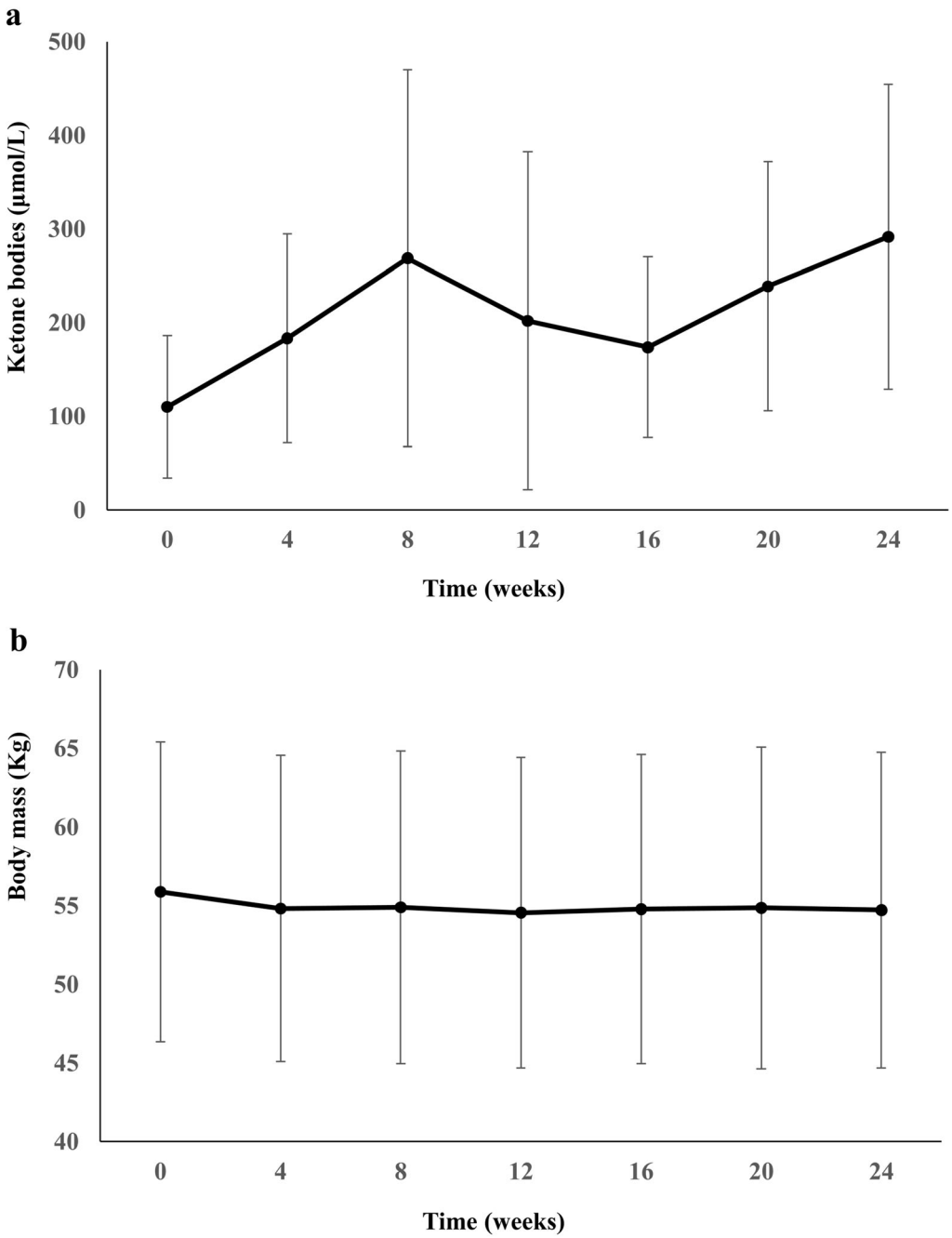

Fig. 2 Temporal changes in the mean serum level of ketone bodies (**a**) and in mean body mass (**b**) during empagliflozin treatment for the study population. Data are means ± SD (n = 8)

CONCLUSION

We have conducted a prospective trial in accordance with ICHGCP guidelines and obtained results indicative of the effectiveness and safety of empagliflozin for the treatment of diabetes associated with insulin resistance syndrome or lipoatrophic diabetes. The establishment of appropriate treatments for these rare

diseases will require further studies to analyze the detailed treatment responses in individual patients. In addition to their hypoglycemic action, SGLT2 inhibitors offer multiple clinical benefits including the prevention of heart failure and preservation of renal function. Further investigation is therefore warranted to determine whether treatment with empagliflozin also exerts such organ-protective effects in these rare and refractory conditions.

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Author Contributions. All authors were engaged in drafting the article, revising it critically, and approving the final version. Wataru Ogawa, Yushi Hirota, Yasumasa Kakei, and Takashi Omori conceived and designed the study. Yushi Hirota, Junta Imai, Hideki Katagiri, Ken Ebihara, Jun Wada, Junichi Suzuki, Tatsuhiko Urakami, and Wataru Ogawa contributed to the collection and interpretation of data. Yasumasa Kakei and Takashi Omori contributed to analysis of data. Wataru Ogawa, Yushi Hirota, Yasumasa Kakei, and Takashi Omori wrote the paper. All authors contributed to the discussion. All authors reviewed the manuscript critically for intellectual content and approved the final version.

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Data Availability. The datasets generated during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest. Yushi Hirota received the following remuneration and financial assistance: lecture fees from Eli Lilly Japan K.K. Sanofi, Terumo Corp., Sumitomo Pharma Co., Ltd., Abbott Japan LLC.), and research support from Sumitomo Pharma Co., Ltd., Kyowa Kirin Co., Ltd. and Medtronic Japan Co., Ltd. Junta Imai received the following financial assistance: scholarship donations from Nippon Boehringer Ingelheim Co., Ltd., Sumitomo Pharma Co., Ltd. (formerly Sumitomo Dainippon Pharma Co. Ltd.) and Mitsubishi Tanabe Pharma Co., Ltd. Hideki Katagiri received the following remuneration and financial assistance: lecture fees from Sumitomo Pharma Co.; research expenses (including those for contracted research, joint research, and clinical trials) and grants from Astellas Pharma Inc. and Taisho Pharmaceutical Co., Ltd. and scholarship donations from Sumitomo Pharma Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd. and Nippon Boehringer Ingelheim Co., Ltd. Jun Wada received the following remuneration and financial assistance: lecture fees from Astra Zeneca, Bayer Yakuhin Ltd., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd, Kyowa Kirin Co., Ltd., Novo Nordisk Pharma Ltd. and Mitsubishi Tanabe Pharma Co., Ltd.,; research expenses (including those for contracted research, joint research, and clinical trials) and grants from Bayer Yakuhin Ltd., Chugai Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Shionogi Pharmaceutical Co., Ltd., Sumitomo Pharma Co. and Mitsubishi Tanabe Pharma Co., Ltd.. Tatsuhiko Urakami received the following

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Ethical Approval. The trial was performed in accordance with the 2013 Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICHGCP) guidelines. The study protocol and amendments were approved by Kobe University Hospital Institutional Review Board and the relevant institutional review board at each study site (Tohoku University Hospital Institutional Review Board, The Institutional Review Board of Nihon University Hospital, Jichi Medical University Hospital Institutional Review Board, and IRB of Okayama University Hospital). The trial was registered with the Japan Registry of Clinical Trials (jRCTs2051190029) and with ClinicalTrials.gov (NCT04018365). All participants provided written informed consent before entry into the study.

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