BPB Reports

Regular Article

Analysis of Metformin-Associated Lactic Acidosis using the Japanese Adverse Drug Event Report Database

Nanaka Ichihara,[a] Mika Maezawa,[a] Satoshi Nakao,[a,b] Koumi Miyasaka,[a] Sakiko Hirofuji,[a] Moe Yamashita,[a] Yuka Nokura,[a] Kensuke Matsui,[a] Hiroaki Uranishi,[c] Mayumi Kitamura,[d] Megumi Horibe,[d] Kazuhiro Iguchi,[e] and Mitsuhiro Nakamura[a,*]

[a]*Laboratory of Drug Informatics, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu, 501-1196, Japan;* [b]*Division of Pharmacy, Kyushu University Hospital, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan;* [c]*Division of Pharmacy, Nara Medical University Hospital, 840, Shijocho, Kashihara-shi, Nara, 634-8522, Japan;* [d]*Department of Nursing, School of Health Science, Asahi University, 1851 Hozumi, Mizuho, Gifu, 501-0296, Japan;* [e]*Laboratory of Community pharmacy, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu, 501-1196, Japan*

Received February 14, 2024; Accepted April 9, 2024

***Aim*: In 2010, the maximum dosage of metformin was increased in Japan to the maximum dosage approved in the United States. This study aimed to evaluate the impact of the revised dosage in the package insert on metformin-associated lactic acidosis (MALA) reports in Japanese patients using the Japanese Adverse Drug Event Report (JADER) database. *Methods*: Adjusted reporting odds ratios of MALA was evaluated using multiple logistic regression models. Trends were analyzed using the Mann–Kendall test and Pettitt's test. Receiver operating characteristic (ROC) curve analysis was used to estimate the metformin dose that influenced MALA development. *Results*: The JADER database contains 845,956 reports submitted between April 2004 and March 2023. The number of adverse event reports and mean dose increased after the 2010 revision of the package insert. According to the ROC curve for lactic acidosis, the cutoff value was 1000.0 mg/day. *Conclusions*: Increase in metformin doses owing to regulatory actions and the recommendation of the Japan Diabetes Society may have influenced the increased MALA reporting rate, suggesting a dose-dependent relationship between the drug and MALA. The cutoff for the daily dose of metformin associated with MALA was the current maintenance dose listed in the package insert. We believe that MALA development must be carefully monitored in Japan even at the dosage specified in the package insert.**

Key words lactic acidosis, metformin, adverse events, JADER

INTRODUCTION

Metformin is recommended worldwide as the first-line treatment for type 2 diabetes[1] due to its high efficacy, safety, and low cost.[2] However, metformin inhibits glycogenesis and glucose synthesis from lactic acid, glycerol, and amino acids. Additionally, there is a known risk of metformin-associated lactic acidosis (MALA) owing to an increased lactic acid level in the blood.[3]

The reported incidence of MALA is low, at less than 10 cases per 100,000 patients.[4] Moreover, while increased blood lactate levels have been observed in Japanese clinical trials,[5] there have been few reports of lactic acidosis (LA) in actual clinical practice. However, 25%–50% of patients who develop MALA die, making it a serious side effect.[6] Therefore, information on the risk of MALA occurrence is essential for healthcare professionals to enable early detection and take necessary preventive actions. Notably, MALA is listed as a potential side effect in the Japanese drug package insert.[7] The US Food and Drug Administration (FDA) has issued a safety announcement regarding the necessity of having boxed warnings about serious MALA.[8]

The maximum dose of metformin in the United States, both at the time of approval in 1994 and today, is 2250 mg/day.[8,9] However, due to concerns about the risk of MALA, regulatory actions such as dosage controls were implemented twice in Japan. Initially approved in 1961, the maximum dose of metformin was set at 1500 mg/day.[9] In 1977, following the frequent occurrence of LA with the biguanide phenformin,[10] a medication with similar effects, the maximum dose of metformin was reduced to 750 mg/day.[9] It was later reported that the frequency of MALA with metformin was much lower than that with phenformin and not different from the spontaneous frequency in patients with type 2 diabetes in the United States and Europe.[11] Because metformin exhibits dose-dependent effects,[12] the maximum dose was increased to 2250 mg/day in 2010 in Japan.[9]

Even after the revision of the dosage in the package insert, daily doses in Japan remained below 1000 mg/day.[13] The main reason for selecting lower doses of metformin is concern regarding the occurrence of MALA.[13] Few studies in Japan have comprehensively examined metformin dosage and the frequency of LA in actual clinical practice. Therefore, it is important to evaluate the impact and clarify the relationship

*To whom correspondence should be addressed. e-mail: mnakamura@gifu-pu.ac.jp

between the revised of metformin dosage and the occurrence of LA.

The Japanese Adverse Drug Event Report (JADER) database is a database that reflects actual clinical practice and is suitable for the analysis of infrequent adverse events (AEs) such as MALA. Moreover, JADER database has years of information on dose and AEs, making it suitable for evaluating the relationship between MALA and the metformin dosage, and providing an overview on the impact of document revisions. Our study aimed to use the JADER database to clarify dose associations and determine MALA risk doses calculated from the cutoff values, thereby aiding in the management of MALA.

METHODS

We searched the JADER database, published on the Pharmaceuticals and Medical Devices Agency (PMDA) website. It consists of four tables: (1) DEMO (patient information such as sex, age, and weight); (2) DRUG (drug information such as generic name, starting date of administration, dose, and "Drug Involvement" section, indicating the involvement of each reported drug in AEs, categorized as "suspected drug," "concomitant drug," or "interaction"); (3) REAC (AE information such as AE category and dates of the occurrence of AEs); and (4) HIST (primary disease information). We integrated these tables to create a relational database. Subsequently, we used the database to collect data reported from April 2004 to March 2023.[14] In this analysis, data identified as "Suspected Drug" were analyzed as drug involvement.

AEs in the JADER database were defined using codes based on the terminology used in the Medical Dictionary for Regulatory Activities/Japanese version 21.0 (MedDRA/J, www.pmrj.jp/jmo/php/indexj.php). For MALA, we used the preferred term "lactic acidosis" (preferred term code 10023676).

The data processing steps from data collection to analysis are summarized in Fig. 1. In JADER database, one fiscal year is defined as the period from April to March of the following year. Therefore, this survey defines the period from April to March as one year. The drug names in JADER database are largely entered in Japanese, but those entered in English as metformin were also incorporated into the analysis. Four combination products are commercially available: alogliptin/metformin, anagliptin/metformin, pioglitazone/metformin, and vildagliptin/metformin. Alogliptin/metformin and pioglitazone/metformin were included in the analysis because it is a single-dose formulation and the metformin dose can be calculated. However, the remaining two drugs were excluded from the analysis because these are two dose formulations of metformin, owing to which the dosage cannot be determined. The

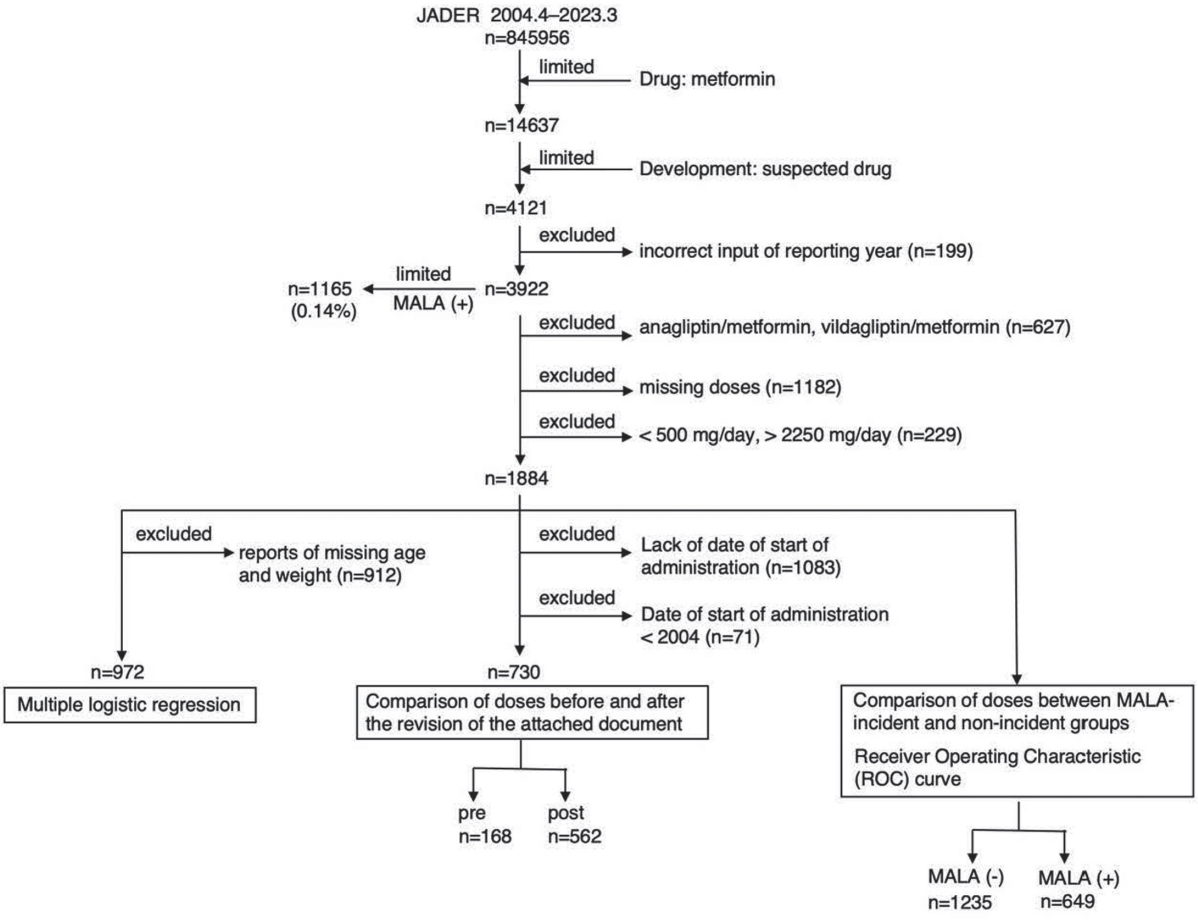

Fig. 1. Flowchart for Analysis of Metformin-Related Lactic Acidosis (MALA) using JADER

following AEs were excluded from the MALA dose-dependent testing: those lacking a calculated dosage and those with daily doses below 500 mg/day or above 2250 mg/day as per the recommended dosage in the package insert.[7] Our exclusion criteria align with those of previous studies, where doses below 500 mg/day were excluded.[15] For the analysis of the revised attachment, data including at least a record of years and months in the "Dose Start Date" field were considered.

Herein, we assessed the impact of regulatory actions by examining the change in the ratio of the number of AE reports included in this study to the total number of reports. The Mann–Kendall and Pettitt's tests were used to evaluate trends over time. Positive Kendall's τ values in the Mann–Kendall test indicate an increasing trend, while negative values indicate a decreasing trend. The Pettitt's test identifies a changing trend at an unknown time (t). The null hypothesis (H_0) posited that there was no change in the distribution of the sequence of random variables, and the alternative hypothesis (H_a) proposed that the distribution function $F_1(x)$ of the random variable from X_1 to X_t was different from the distribution function $F_2(x)$ of the random variable from X_{t+1} to X_T. Both tests were performed using the "trend" package in R ver. 4.0.2, with the significance level set at $P < 0.05$.

The reporting odds ratio (ROR) was used for signal detection. The ROR was calculated from a 2 × 2 contingency table and was regarded as a signal when the lower limit of the 95% confidence interval (CI) exceeded 1. Multiple logistic regression analysis was used to evaluate the effect of metformin dosage on the development of LA. The reporting year (Y), sex (S), age-stratified groups (<10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and >90 years) (A), weight (W) (<10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99, 100–109, 110–119, 120–129, 130–139, 140–149, 150–159, and >160 kg), and dose (D), were defined as independent variables. Only reports with complete information regarding the reporting year, sex, age, and weight were extracted from the JADER database. Age is entered in JADER database every 10 years and weight every 10 kg. For example, ages 10–20 y are processed as 15 y and weights 10–20 kg as 15 kg. The following formula was used:

$$\text{Log (odds)} = \beta_0 + \beta_1 Y + \beta_2 S + \beta_3 A + \beta_4 W + \beta_5 D$$

The dependent variable was the binary response indicating the absence or presence of MALA in each report. To comparatively evaluate the effect of these factors, we selected explanatory variables using a stepwise method. In the forward and backward direction, stepwise constructs successive models by adding terms based on a significance level of 0.05 and by removing terms based on a significance level of 0.05.

The final multiple logistic regression model was as follows:

$$\text{Log (odds)} = \beta_0 + \beta_1 Y + \beta_2 S + \beta_4 W + \beta_5 D$$

and the adjusted unit ROR was calculated. Multicollinearity diagnosis was performed using variance inflation factors (VIF). VIF was calculated with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[16] which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

In 2010, the package insert regarding the dosage of metformin was revised in Japan. Two regulatory action groups regarding LA AE reports were defined: pre-(April 2004–May 2010) and post-(June 2010–March 2023) revision groups. The mean metformin dose for both groups was calculated. In addition, patients administered metformin were classified into two groups—one with LA and the other without—and the mean dose for each group was determined. The t-test was used to compare the mean dose metformin. The receiver operating characteristic (ROC) curve was used to select the optimal cutoff value for determining the presence or absence of MALA. It was used to estimate the metformin dose that influences the onset of MALA. This curve plots the false-positive fraction (1-specificity) on the horizontal axis and the true-positive fraction (sensitivity) on the vertical axis. The cutoff point has the highest sensitivity while maintaining high specificity. The cutoff value maximizing the sum of the specificity was obtained using the Youden Index.

Data analysis was performed using the JMP Pro version 16 software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The JADER database contains 845,956 reports submitted between April 2004 and March 2023, from which we identified 1165 (0.14%) MALA events. The drug table was searched for "metformin hydrochloride" in the generic name, yielding 14,637 reports. A trend change in the number of reports of LA due to metformin use was observed in the year 2012 (k = 9), with a $P < 0.05$ for Pettitt's test and tau = 0.88 for the Mann–Kendall test with a $P < 0.05$ (Fig. 2).

Using a stepwise logistic regression model, we examined and selected significant MALA-related variables among demographic factors (reporting year, sex (female), weight, and dosage), with adjusted unit reporting odds ratios of 1.0772 (95% CI, 1.0421–1.1136), 0.7222 (95% CI, 0.5318–0.9809), 0.9843 (95% CI, 0.9756–0.9931), and 1.0009 (95% CI, 1.0006–1.0012), respectively (supplementary Table S1). The VIF in the final multiple logistic regression model for reporting year, sex, weight, and dose were 1.0360, 1.1565, 1.1618, and 1.0558, respectively.

The mean doses in the pre- and the post-revision groups were 644.3 ± 207.5 mg/day and 765.1 ± 396.1 mg/day, respectively. The mean dose in the post-revision group was significantly higher than that in the pre-revision group based on t-test ($P < 0.001$). The mean dose for the MALA-onset group (1029.7 ± 525.9 mg/day) was significantly higher than that for the non-onset group (787.7 ± 397.8 mg/day) based on t-test ($P < 0.001$). According to the ROC curve for LA (area under the ROC Curve (AUC)=0.64, sensitivity=0.5193, 1-specificity=0.2972), the cutoff value was 1000.0 mg/day (Fig. 3).

DISCUSSION

Although metformin-induced LA is rare, it is a highly lethal disease.[4-6] Therefore, prevention and early treatment are critical. However, there is currently insufficient information available on the prevention of MALA, leading to considerations such as avoiding the use of metformin itself.[13] Herein, we aimed to understand the relationship between MALA and dosage using the JADER database. Interestingly, our results suggested that the increase in metformin dosage following the

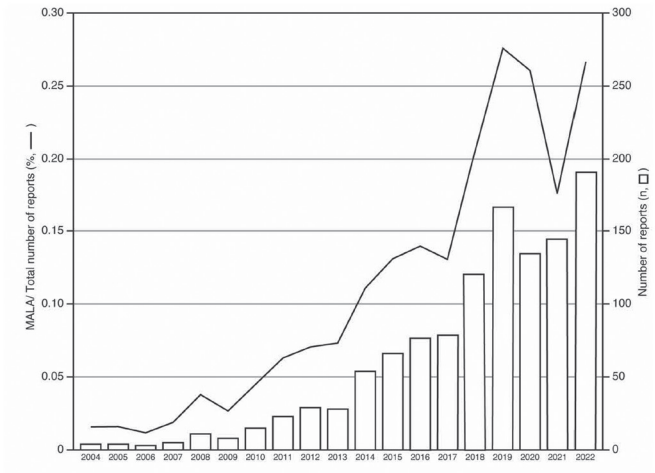

Fig. 2. Number of Reports and Reporting Ratio of Metformin-Associated Lactic Acidosis (MALA) in the JADER Database

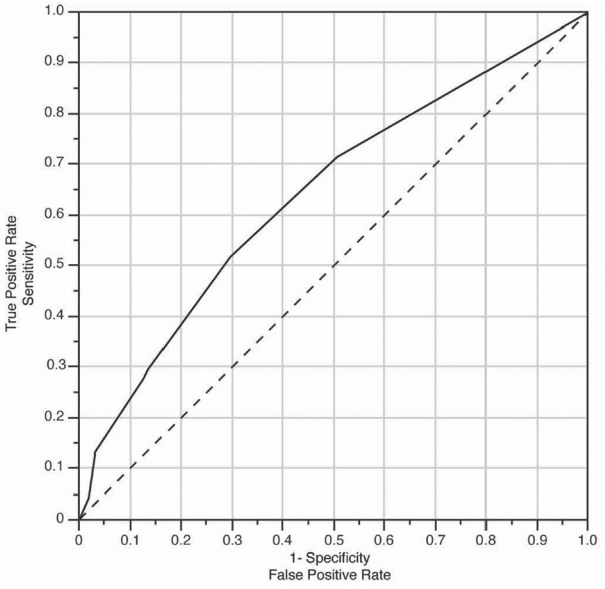

Fig. 3. Receiver Operating Characteristic Curve for Metformin-Associated Lactic Acidosis Related to Daily Dose of Metformin

revision of the package insert had an effect on the increased LA in Japan. In addition, the cutoff values calculated from the ROC curves suggested that the risk of LA increased at doses greater than or equal to 1000.0 mg/day. However, as the AUC of the ROC curve was 0.64, which is not a value generally considered a good discrimination, we believe that the reliability of the cutoff value in this study should be verified in a more in-depth epidemiological study.

It is known that there is a transient increase in the number of spontaneous reports of targeted adverse reactions following implementation of regulatory safety measures.[17] Notably, the Mann–Kendall and Pettitt's tests showed a characteristic upward trend in MALA reporting in 2012, possibly due to the package insert revision. Furthermore, in 2012, the Japan Diabetes Society published the first edition of its "Recommendations for the Proper Use of Biguanide Drugs."[18] The increase noted in MALA reporting since 2016 could be attributed to the FDA's announcement that metformin can be safely used in patients with mild and moderate renal dysfunction. Coincidentally, this announcement came at a similar time that the Japan Diabetes Society's publication of the second revision of "Recommendations for the Proper Use of Metformin" was published.[18,19] As for the increase noted after 2019, this might be attributed to the Japanese regulatory agency's announcement in 2019 that metformin can be safely used in some patients with mild-to-moderate renal dysfunction.[20] These increases could also be related to the increased number of metformin prescriptions.[21]

Clinically, a comparison of pre- and post-regulatory doses revealed significant differences, suggesting that the revision of the package insert had an effect. However, the mean dosage remained at 765.1 mg/day even after regulatory action. This is consistent with the results of a previous Japanese study that reported that the daily dosage remained below 1000 mg/day even after package insert revision.[13]

The association between high doses of metformin and the development of MALA remains controversial. Several studies have reported that the incidence of MALA does not differ from that of LA in patients with diabetes treated with other drugs.[11,22,23] Nagai *et al*. observed no significant difference in the incidence of MALA between metformin ≥1000 mg/day and <1000 mg/day using the Japanese Diagnosis Procedure Combination (DPC) database.[15] Korean cross-sectional study found no significant association between metformin dosage and hyperlactatemia.[24] Yokoyama *et al*. reported significantly elevated lactate levels (15.2 mg/dL) in high-dose patients compared to that in low-dose patients in a Japanese cohort, but no development of LA.[25] In contrast, a higher risk of LA was observed in patients with renal impairment with higher daily doses based on a population-based cohort study.[26] These divergent findings indicate that this issue remains unresolved in clinical practice.

In our study, we speculated that LA might have occurred within the dosage and administration ranges specified in the Japanese package inserts. Evaluation of the cutoff values calculated using Youden's index suggested that the risk of MALA increased when the daily dose of metformin exceeded 1000 mg/day in this study. However, the daily maintenance dose listed in the current package insert is 750–1500 mg/day [7] and the cutoff value falls within this range, suggesting that there is a risk of MALA even at the current maintenance dose.

The JADER database is a passive reporting system susceptible to confounding variables and biases, such as underreporting, over-reporting, lack of data on the denominator (number of patients in the population exposed to metformin), and confounders due to comorbidities. Spontaneous adverse event reporting databases such as JADER are considered suitable for investigating the number of adverse event reports and detecting signals, but not for investigating risk factors and incidence. Accurate assessment of risk factors requires identification of the population, for which it is desirable to use national or registry databases. On the other hand, it may be useful to investigate actual clinical AEs of rare adverse events such as MALA. Therefore, we used JADER in this study.

Reports of dose deviations from 500 to 2250 mg/day, calculated from the number of divided doses, were excluded from the analysis because the DOSE column of the DRUG table was considered to contain a mixture of daily and single doses. This is a limitation of JADER database. During the period under review, not only was the package insert revised regarding dosage and administration, but the FDA also revised the package insert, significantly changing the requirements for use in patients with renal dysfunction, among other things. Based on this, it has been suggested that the drug is particularly susceptible to reporting bias.[27] LA is affected by patients' liver and kidney functions; however, JADER database lacks detailed information on patient background. Therefore, interpreting the results of the JADER database requires great caution. In the future, it would be desirable to accurately calculate the cutoff value of metformin that affect the development of LA through studies using national databases, registry databases, or well-controlled epidemiologic studies. However, considering that MALA is a rare AE, we believe that our results are meaningful for clinicians.

Acknowledgment This research was partially supported by JSPS KAKENHI,Grant Numbers 23H05264, 21K11100, and 21K06646.

Ethical approval Ethical approval was not sought for this study because the study was a database-related observational study without directly involving any research subjects. All results were obtained from data openly available online from the PMDA website (www.pmda.go.jp). All data from the JADER database were fully anonymized by the relevant regulatory authority before we accessed them.

Conflict of interest The authors declare no conflict of interest.

REFERENCES

1) World Health Organization. “HEARTS-D: Diagnosis and management of type 2 diabetes.” <https://www.who.int/publications/i/item/who-ucn-ncd-20.1>, cited 13 February, 2024.
2) Clarke P, Gray A, Adler A, Stevens R, Raikou M, Cull C, Stratton I, Holman R. Cost-effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with Type II diabetes (UKPDS No. 51). *Diabetologia*, **44**, 298–304 (2001).
3) Statpeals. “Metformin-Associated Lactic Acidosis (MALA).” <https://www.ncbi.nlm.nih.gov/books/NBK580485/>, cited 13 February, 2024.
4) Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care*, **22**, 925–927 (1999).
5) Sumitomo Pharma. “Drug Interview Form Metogluco Tablets 250 mg, Tablets 500.” <https://sumitomo-pharma.jp/product/metgluco/attachment/interv.html> cited 13 February, 2024.
6) Kajbaf F, Lalau JD. Mortality rate in so-called “metformin-associated lactic acidosis”: a review of the data since the 1960s. *Pharmacoepidemiol. Drug Saf.*, **23**, 1123–1127 (2024).
7) Pharmaceuticals and Medical Devices Agency. “Metgluco Tablets 250 mg, Tablets 500 mg.” <https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/400093_3962002F2027_1_22>, cited 13 February, 2024.
8) U.S. FOOD & DRUG ADMINISTRATION. Glucophage (metformin hydrochloride) tablets [Label] <https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020357s034,021202s018lbl.pdf>, cited 13 February, 2024.
9) Pharmaceuticals and Medical Devices Agency. “Data on metgluco tablets 250 mg.” <https://www.pmda.go.jp/drugs/2010/P201000009/40009300_22200AMX00234_B100_1.pdf>, cited 13 February, 2024.
10) Gale EA, Tattersall RB. Can phenformin-induced lactic acidosis be prevented? *BMJ*, **2**, 972–975 (1976).
11) Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetes. *Diabetes Care*, **21**, 1659–1663 (1998).
12) Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am. J. Med.*, **103**, 491–497 (1997).
13) Kameda T, Kumamaru H, Nishimura S, Kohsaka S, Miyata H. Use of oral antidiabetic drugs in Japanese working-age patients with type 2 diabetes mellitus: dosing pattern for metformin initiators. *Curr. Med. Res. Opin.*, **36**, 749–756 (2020).
14) Pharmaceuticals and Medical Devices Agency. “ANNUAL REPORT FY 2016.” <https://www.pmda.go.jp/files/000221481.pdf>, cited 13 February, 2024.
15) Nagai Y, Kazumori K, Takeshima T, Iwasaki K, Tanaka Y. A claims database analysis of dose-dependency of metformin and incidence of lactic acidosis in Japanese patients with type 2 diabetes. *Diabetes Ther.*, **12**, 1129–1141 (2021).
16) Kanda Y. Investigation of the freely-available easy-to-use software “EZR” (Easy R) for medical statistics. *Bone Marrow Transplant.*, **48**, 452–458 (2013).
17) Hanatani T, Sai K, Tohkin M, Segawa K, Saito Y. Impact of Japanese regulatory action on metformin-associated lactic acidosis in type II diabetes patients. *Int. J. Clin. Pharm.*, **37**, 537–545 (2015).
18) The Japan Diabetes Society. “The Japan Diabetes Society. “Recommendation on the proper use of metformin Japan association for diabetes education and care.” <https://www.nittokyo.or.jp/uploads/files/recommendation_metformin_200318.pdf>, cited 14 March, 2024.
19) U.S. FOOD & DRUG ADMINISTRATION. “FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function.” <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain>, cited 13 February, 2024.
20) Ministry of Health. Labour and Welfare. “Pharmaceuticals and Medical Devices Safety Information No365.” <https://www.pmda.go.jp/files/000230983.pdf>, cited 13 February, 2024.
21) Shirabe S, Yamazaki K, Oishi M, Arai K, Yagi N, Sato M, Takeuchi M, Kai T, Maegawa H. Changes in prescription patterns and doses of oral antidiabetic drugs in Japanese patients with type2 diabetes (JDDM70). *J. Diabetes Investig.*, **14**, 75–80 (2023).
22) Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, Cederholm J, Eliasson B, Gudbjörnsdottir S. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. *BMJ Open*, **2**, e001076 (2012).
23) Bodmer M, Meier C, Krähenbühl ST, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care*, **31**, 2086–2091 (2008).
24) Lee EY, Hwang S, Lee Y-h, Lee SH, Lee YM, Kang HP, Han E, Lee W, Lee B-W, Kang ES, Cha BS, Lee HC. Association between metformin use and risk of lactic acidosis or elevated lactate concentration in type 2 diabetes. *Yonsei Med. J.*, **58**, 312–318 (2017).
25) Yokoyama S, Tsuji H, Hiraoka S, Nishihara M. Investigation of risk factors affecting lactate levels in Japanese patients treated with metformin. *Biol. Pharm. Bull.*, **39**, 2022–2027 (2016).
26) Eppenga WL, Lalmohamed A, Geerts AF, Derijks HJ, Wensing M, Egberts A, Smet PAGM, Vries FD. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care*, **37**, 2218–2224 (2024).
27) Flory JH, Hennessy S, Bailey CJ, Inzucchi SE. Reports of lactic acidosis attributed to metformin, 2015–2018. *Diabetes Care*, **43**, 244–246 (2020).