Reasons for Metformin Non-Use in Type 2 Diabetes Mellitus in a Hospital: A Retrospective Observational Study

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Research Article

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Abstract

Objective: To investigate and analyze the reasons for metformin non-use in a hospital.

Methods: Research-related non-probability physicians and patients filled questionnaire.

Results: Physicians’ main influencing factors were severe liver and kidney dysfunction; gastrointestinal adverse reactions and 11 other causes. Secondary factors included the appearance of hypoglycemia and other adverse reactions (e.g., skin rash). Patients’ main reasons included: worry about drug’s influence on liver and kidney function, gastrointestinal adverse reactions, hypoglycemia, and further weight loss, etc. Statistical analysis showed metformin has certain effects on the mean blood glucose and the mean glycated hemoglobin levels.

Conclusion: Based on the research results, we can design more targeted medication education programs.

Introduction

Diabetes affects 2% of the population, consumes 5% of the health service budget, creates appreciable interference with aspects of patients’ lives, such as employment, and thereby, poses a significant burden to individuals and society. In 2017, the annual cost incurred by patients diagnosed with diabetes was estimated at $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity. After adjusting for inflation, the economic costs of diabetes increased by 26% from 2012 to 2017 [1], and this increase is attributed to the increased prevalence of diabetes and the increased cost per person with diabetes [2]. The prevalence of diabetes in China, a country with a vast population, increased from 0.67% in 1980 to 10.4% in 2013 [3].

Scientific and technological developments have improved the understanding and diagnosis of diabetes. Guidelines for diabetes prevention and treatment recommend adherence to the principle of combining prevention and treatment strategies, based on evidence-based medicine, and focusing on the applicability and practical value of clinical interventions. These guidelines play an important role in standardizing clinical medical practice and improving the current situation of diabetes prevention and control in China. The practice guideline updates are crucial to understand the emerging international trends in the prevention, diagnosis, monitoring, and treatment of diabetes and its chronic complications as well as the new evidences for practicing evidence-based medicine. Therefore, it is important that health services, especially primary care institutions, follow the latest guidelines.

The 2017 edition of the type 2 diabetes prevention guidelines of the Chinese Diabetes Society and the 2018 edition of guidelines by the American Diabetes Association recommended changes in the indications for glucose-lowering drug selection with regard to metformin should be updated throughout the treatment course unless there are contraindications; thus, the 2017 treatment guidelines expanded the range of application of metformin [1, 3, 4, 5]. Many large clinical studies, including the UK Prospective Diabetes Study (UKPDS), have revealed that metformin is a multi-mechanism glucose-lowering agent with adequate efficacy [6, 7, 8, 9] that is currently a first-line treatment for overweight or obese patients with type 2 diabetes. Metformin can not only inhibit the decomposition of liver glycogen and improve insulin resistance safely and effectively in lowering blood sugar[10], but also has other effects, such as controlling body weight [11], improving polycystic ovary syndrome [12], inhibiting tumor growth [13, 14, 15], regulating the lipid profile and blood pressure [16, 17], reducing hypercoagulability, improving vascular reactivity, and reducing the incidence of and mortality from cardiovascular diseases [18, 19].

This research was conducted for the screening of eligible physicians and patients and used a research questionnaire for ascertaining real-world metformin usage in primary care hospitals. The study aimed to evaluate the causes for metformin non-use through an analysis of the causes identified with Pareto law analysis and to reveal whether the use of metformin strictly complies with the updated latest guidelines and instructions. We aimed to provide supporting data for clinical pharmacists to focus on the development of medication education programs for the relevant physicians and patients with regard to metformin use. Simultaneously, the study was intended to eliminate relevant misinterpretations of this drug usage by physicians and patients to promote the rational and standardized use of this drug, improve medication compliance, and maximize the clinical effect of this drug.

Objectives
In this non-probability sampling survey, we used a basic-level hospital HIS (Hospital Information System) to obtain diabetes-related prescription information for all patients with type 2 diabetes who were treated from January 1, 2018 to December 31, 2018. Metformin usage was retrospectively analyzed, and physicians whose prescriptions did not adhere to the guidelines for investigations and patients with diabetes who had unused metformin prescriptions were evaluated to ascertain the reason for the deviation from the guideline.

**Study Subjects**

This retrospective study was approved by the Ethics Committee of Beijing Changping District Hospital of Integrated Traditional Chinese and Western Medicine and included clinicians who dealt with type 2 diabetes and all patients with type 2 diabetes who were treated at the study center during the study period. The study inclusion and exclusion criteria are described in Box 1. The stripping and shedding criteria were as follows: adverse events, lack of efficacy, loss of follow-up, automatic withdrawal of subjects, and incomplete data that could affect the efficacy evaluation.

**Box 1 Participant inclusion and exclusion criteria**

| Participant inclusion criteria | Participant exclusion criteria |
|-------------------------------|-------------------------------|
| ► Patients with definite diagnosis of type 2 diabetes in HIS system from January 1, 2018 to December 31, 2018, all those with ICD code E11.901 were included. | ► Patients with contraindications to metformin, namely: 1) Moderate (grade 3B) and severe renal failure or insufficiency [Cr < 45mL/min or eGFR < 45mL/min (min 1.73m2)], 2) Diseases that can cause hypoxia (especially acute or chronic disease exacerbation), such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock, 3) Severe infection and trauma, major surgical operations, clinical hypotension, etc., 4) Those who are known to be allergic to metformin, 5) Acute or chronic metabolic acidosis, including DKA with or without coma (DKA requires insulin treatment), 6) Alcoholics, 7) Patients who have received intravascular injection of iodized contrast agent may temporarily stop using this product, 8) Uncorrected deficiency of vitamin B12 and folic acid. |
| ► Provision of consent to participate in the survey independently. | ► Patients who are not routinely managed by our hospital, i.e. those who come to our hospital temporarily for medical treatment due to other matters such as tourism, |
| | ► Samples of pregnant women and children under 10 years old, |
| | ► People with difficulty in completing visits and follow-up due to cognitive and communication barriers. |

**4. Research methods**

4.1. Extraction of the study variables

The following information was extracted from the hospital records

1. General information: Patient's name, ID number, sex, age, clinical diagnosis, and date that diabetes was diagnosed.
2. Information on metformin use: Whether metformin was used and the dose and prescribing frequency.
3. Patient's health status: Blood glucose control, complications, and liver and kidney function.

4.2. Compared the glycemic control of metformin users and non-users and the metformin use and non-use among patients with type 2 diabetes.
4.3. Statement

All methods were performed in accordance with the relevant guidelines and regulations. All participating patients in this study signed the informed consent form and filled out the questionnaire.

5. Questionnaire development

Data from a mixed-methods systematic review was used to investigate the reasons why physicians and patients were not using metformin. The physicians’ questionnaire included four sections: 1. Demographic information, including the participants’ age, sex, number of years qualified, and the specialty, 2. Participants’ description of situations wherein metformin was not used for treating type 2 diabetes. 3. Participants’ knowledge of and willingness to understand the latest version of the guidelines and instructions. 4. Participants’ analysis of why they did not receive the latest version of guidelines and instructional knowledge update as well as preferences for how they wished to obtain relevant information. Sections 1 and 3 used closed questions to collect quantitative data. Sections 2 and 4 contained two open-ended questions to allow the participants to answer without restriction. The in-built survey logic ensured that participants were shown pertinent questions based on their previous answers. The patient questionnaire was divided into two parts: demographic information, including age, sex, years since being diagnosed with type 2 diabetes, clinical diagnosis, test value, of liver and kidney function and blood sugar control and subjective factors underlying the reasons for the patients’ failure to use metformin. Prior to the study completion, participants were encouraged to share any additional information that they deemed relevant in order to capture useful insights that were unaddressed elsewhere in the questionnaire. The final versions of the questionnaires can be found in the Online Supplementary File 1 and File 2.

6. Data storage

All electronic data were stored in password-protected computer files that were only accessible to study investigators. Participants who disclosed personal details were additionally protected by coding in data files, and these password-protected files will be retained for 10 years, in conformance with ethical policies.

7. Data analysis

Pareto's law was applied in cause analysis to identify the main, secondary, and general influencing factors. The specific method involved calculating the number and percentage of cause distributions and then sorting them from high to low. A cumulative percentage \( \leq 80\% \) indicated the main reason, which is represented by "A", the secondary reason, with a cumulative percentage of 80%–90% represented by "B", and the general reason with a cumulative percentage >90% represented by "C" [20].

Demographic data was tabulated, and a primary descriptive analysis of the data was performed using IBM SPSS Statistics, V26.0. Count data was presented as percentages, the measurement data was expressed as average value, and multivariate logistic analysis was used for regression analysis. \( P < 0.05 \) was considered statistically significant. Cronbach's coefficient was used to evaluate the internal consistency of the questionnaire. Factor analysis was used to evaluate structure validity.[21].

Results

8.1. Questionnaire results and analysis of physician surveys

A total of 111 clinician participants completed the questionnaire survey, most of them are young and middle-aged physicians. 52.25% of the physicians surveyed had read the latest guidelines, and 63.06% understood the clinical status of metformin has been further improved. Endocrinologists had a better understanding of this drug and their adherence to the latest version of the guidelines was better than that of physicians in other specialties. Correlation analysis, regression analysis and F test show that there is no significant correlation between sexes age division, physician level, years of experience and the reasons why doctors did not choose metformins.

Table 1 shows that, physicians consider severe liver and kidney dysfunction, gastrointestinal adverse reactions, severe infection and trauma, etc. 11 factors as the main factors to consider stopping metformin. In addition, the appearance of hypoglycemia and other adverse reactions were secondary factors. Alcoholism, vitamin B12, and uncorrected folate deficiency are the general factors.
A few physicians considered older age, and stable chronic heart failure, with regular cardiac and renal function examinations, in their decision making.

Table 1
Physician perceptions of metformin not being used

| Concrete reasons for not using metformin                                                                 | Comments (n) | Percentage (%) | Cumulative percentage (%) | Influence degree |
|-----------------------------------------------------------------------------------------------------------|--------------|----------------|---------------------------|------------------|
| Patients with contraindications to metformin, namely: Moderate (grade 3B) and severe renal failure or insufficiency [Cr < 45mL/min or eGFR < 45mL/min (min 1.73m2)];                      | 86           | 9.11           | 9.11                      | A                |
| Gastrointestinal intolerance                                                                             | 79           | 8.37           | 17.48                     | A                |
| Severe infections and trauma, major surgical procedures, clinical hypotension, etc. Metformin must be discontinued 48 hours prior to elective surgery using conventional, spinal or epidural anesthesia | 73           | 7.73           | 25.21                     | A                |
| Severe liver insufficiency                                                                               | 72           | 7.63           | 32.84                     | A                |
| Diseases that can cause hypoxia (especially acute or chronic disease exacerbation), such as decompensated heart failure, respiratory failure, recent myocardial infarction, shock;  | 67           | 7.10           | 39.94                     | A                |
| Acute and chronic metabolic acidosis, including DKA with or without coma                                  | 65           | 6.89           | 46.83                     | A                |
| Pregnant women                                                                                            | 65           | 6.89           | 53.72                     | A                |
| Patients strongly refuse because of certain obsessions                                                   | 61           | 6.46           | 60.18                     | A                |
| Patients younger than 10 years old                                                                       | 57           | 6.04           | 66.22                     | A                |
| Over underweight patients                                                                                | 54           | 5.72           | 71.94                     | A                |
| Intravascular injection of iodized contrast agent                                                         | 53           | 5.61           | 77.55                     | A                |
| Patients prone to hypoglycemia                                                                           | 48           | 5.08           | 82.63                     | B                |
| Other adverse reactions, such as rash, etc                                                               | 48           | 5.08           | 87.71                     | B                |
| Alcoholics                                                                                                | 37           | 3.92           | 91.63                     | C                |
| Vitamin B12 or folic acid deficiency has not been corrected                                              | 36           | 3.81           | 95.44                     | C                |
| Elderly patients                                                                                         | 23           | 2.44           | 97.88                     | C                |
| Stable chronic heart failure patients with regular cardiac and renal function examinations                | 20           | 2.12           | 100.00                    | C                |

### 8.2. Results and analysis of patient questionnaire

A total of 10,508 patients participated in the survey, and 3,730 of these patients completed the questionnaires. From Table 2, we can infer that the main reasons for refusal to use metformin included concerns about the influence of the drug on liver and kidney function, gastrointestinal adverse reactions, hypoglycemia, etc. Secondary factors were forgetting to take medication, over-interpreting medicine specifications, and obsessing that new drugs are better than old ones. The general influencing factors included the fear that drugs may affect planned conception and difficulty in purchasing the drug locally, etc.
### Table 2
Patient perceptions of metformin not being used

| Concrete reasons for not using metformin                                                                 | Comments (n) | percentage(%) | Cumulative percentage(%) | Influence degree |
|----------------------------------------------------------------------------------------------------------|--------------|--------------|--------------------------|-----------------|
| Worry about the effects on kidney function                                                              | 1086         | 25.29        | 25.29                    | A               |
| Worry about gastrointestinal discomfort                                                                  | 466          | 10.85        | 36.14                    | A               |
| Worry about the effect on liver function                                                                 | 439          | 10.22        | 46.36                    | A               |
| Worry about hypoglycemia                                                                                | 436          | 10.15        | 56.51                    | A               |
| Fear of further weight loss                                                                             | 375          | 8.73         | 65.24                    | A               |
| Because of the nature of work or lifestyle, patients think it is troublesome to take drugs and difficult to stick to them | 283          | 6.59         | 71.83                    | A               |
| Hold a subjective view that if diabetes improves, they can stop taking medicine                          | 260          | 6.05         | 77.88                    | A               |
| Forget to take medicine                                                                                 | 140          | 3.26         | 81.14                    | B               |
| Over-interpretat medicine specification                                                                  | 135          | 3.14         | 84.28                    | B               |
| Patients believed that the new diabetes drug was more effective than the old drug metformin            | 135          | 3.14         | 87.43                    | B               |
| Have a pregnancy plan and worry about the effects of medication                                         | 121          | 2.82         | 90.24                    | C               |
| Difficulty in purchasing the drug locally                                                               | 106          | 2.47         | 92.71                    | C               |
| Health product marketers discourage the use of western medicine                                         | 82           | 1.91         | 94.62                    | C               |
| Economic reasons                                                                                        | 81           | 1.89         | 96.51                    | C               |
| The idea tends to be non-drug therapy                                                                    | 73           | 1.70         | 98.21                    | C               |
| Like to use Traditional Chinese medicine, resist western medicine                                       | 71           | 1.65         | 99.86                    | C               |
| Others                                                                                                  | 6            | 0.14         | 100.00                   | C               |

#### 8.3. Results and analysis of diabetes control at different ages and stages with or without metformin

Analysis of diabetes control and comparison among different age ranges and treatments course, outpatient and inpatient care, and whether metformin drugs subgroups of mean blood sugar, mean glycated hemoglobin (HbA1c), and complications, as shown in Tables 3.
| Table 3 | Results of blood sugar, HbA1c and complications at different ages and stages with or without metformin |
|---------|-----------------------------------------------------------------------------------------------------|
|         | Outpatients taking metformin | Outpatients without taking metformin | Hospitalized patients taking metformin | Hospitalized patients without taking metformin |
|         | a1 | a2 | n1/n* (%) | a1 | a2 | n1/n* (%) | a1 | a2 | n1/n* (%) | a1 | a2 | n1/n* (%) |
| Mean data | | | | | | | | | | | | |
| **Age (years)** | | | | | | | | | | | | |
| 10~17 | 8.8 | 7.6 | 0/2 (0.00%) | | | | | | | | | |
| 18~24 | 6.49 | 8.45 | 0/11 (0.00%) | 8.81 | 9.75 | 0/5 (0.00%) | 8.55 | 8.68 | 0/6 (0.00%) | 8.05 | 8.7 | 0/2 (0.00%) |
| 25~34 | 6.8 | 8.58 | 11/230 (4.78%) | 9.3 | 8.9 | 8/119 (6.72%) | 6.97 | 7.98 | 3/37 (8.11%) | 8.75 | 8.97 | 2/32 (6.25%) |
| 35~44 | 6.77 | 8.55 | 75/550 (13.64%) | 9.16 | 8.65 | 39/225 (17.33%) | 8.26 | 8.28 | 13/84 (15.48%) | 8.93 | 8.93 | 10/57 (17.54%) |
| 45~54 | 6.57 | 8.54 | 153/1012 (15.12%) | 9.2 | 8.55 | 106/473 (22.41%) | 7.69 | 8.25 | 39/211 (18.48%) | 8.36 | 8.66 | 24/130 (18.46%) |
| 55~64 | 6.5 | 8.55 | 294/1899 (15.48%) | 8.95 | 8.51 | 219/964 (22.72%) | 7.45 | 8.17 | 77/397 (19.40%) | 8.61 | 8.7 | 56/368 (15.22%) |
| 65~74 | 6.29 | 8.6 | 225/1336 (16.84%) | 8.85 | 8.34 | 205/646 (31.73%) | 7.31 | 8.00 | 67/278 (24.10%) | 8.5 | 8.54 | 56/286 (19.58%) |
| 75~ | 6.15 | 8.34 | 131/652 (20.09%) | 9.02 | 8.42 | 113/327 (34.56%) | 7.15 | 7.99 | 39/184 (21.20%) | 8.46 | 8.64 | 45/258 (17.44%) |
| **Course of the disease (years)** | | | | | | | | | | | | |
| 0~2 | 6.04 | 8.49 | 13/1756 (0.74%) | 9.14 | 8.55 | 14/703 (1.99%) | 7.91 | 8.30 | 0/265 (0.00%) | 8.64 | 8.71 | 0/191 (0.00%) |
| 3~4 | 6.46 | 8.51 | 92/1730 (5.32%) | 8.92 | 8.48 | 40/698 (5.73%) | 7.29 | 8.02 | 0/142 (0.00%) | 8.33 | 8.67 | 1/127 (0.79%) |
| 5~9 | 6.8 | 8.64 | 283/1416 (19.99%) | 8.99 | 8.46 | 307/917 (33.48%) | 7.51 | 8.23 | 18/291 (6.19%) | 8.46 | 8.54 | 43/383 (11.23%) |
| 10~14 | 6.88 | 8.51 | 272/416 (65.38%) | 8.92 | 8.39 | 72/127 (56.69%) | 7.13 | 8.08 | 20/171 (11.70%) | 8.63 | 8.8 | 41/163 (25.15%) |
| 15~19 | 7.05 | 8.32 | 78/161 (48.45%) | 8.86 | 8.6 | 74/113 (65.49%) | 7.00 | 7.73 | 130/185 (70.27%) | 8.53 | 8.56 | 45/109 (41.28%) |
| 20~24 | 6.3 | 8.48 | 95/134 (70.90%) | 9.14 | 8.69 | 108/120 (90.00%) | 7.49 | 8.05 | 48/105 (45.71%) | 8.71 | 8.71 | 34/87 (39.08%) |

**a1 Blood sugar**

**a2 HbA1c**

**n1 The number of type 2 diabetes patients complications at the corresponding age or course**

**n* Number of type 2 diabetes patients of corresponding age or course**

An independent sample t-test shows the mean blood glucose level showed no significant difference \((P>0.05)\) between subgroup but the hospitalized samples showed a significant difference in the mean HbA1c \((P<0.05)\). Specific analysis showed that the significance of hospitalization for the mean HbA1c was 0.01 \((T = 3.928, P = 0.001)\), and the specific comparison showed that the mean HbA1c value of outpatients (8.53) was significantly higher than that of inpatients (8.38).
The influence of hospitalization and metformin on mean blood glucose level and mean HbA1c were studied using a two-way analysis of variance. Hospitalization did not show a significant difference \( (F=1.408, P = 0.235) \) in mean blood glucose level but metformin showed significant effects \( (F=1441.405, P = 0.001) \), indicating that the drug will affect the difference of mean blood glucose. Hospitalization was significant \( (F = 15.994, P = 0.001) \) in mean HbA1c, indicating that whether hospitalization will cause a difference in the mean HbA1c. Metformin showed significant effects \( (F = 15.936, P = 0.001) \), indicating that the main effect exists and that metformin will cause a difference in the mean HbA1c. Specific differences were analyzed by single-factor ANOVA.

**Discussion**

The physicians participating in the survey are mainly young and middle-aged and the attending doctors with 5-14 years of experience. The ones with the above characteristics will be the main targets for clinical pharmacists to deliver the latest relevant guidelines. Related analysis and regression analysis revealed that departments, sexes, age divisions, physician level, and years of employment did not have an impact on the reasons why doctors did not choose metformins.. Therefore, it was not possible to specifically analyze the impact of independent variables on dependent variables.

From the perspective of physicians, severe liver and kidney dysfunction, gastrointestinal adverse reactions and 11 other causes were listed as the main influencing factors. Despite the low proportion, it should be noted that elderly patients and patients with stable chronic heart failure under the condition of regular heart and kidney function checks have been described as non-contraindications in the latest version of the guidelines and instructions. Some doctors still choose this method, which shows that they have not fully kept up with the latest use descriptions of metformin.

With regard to the patient samples, the main reasons for refusing to use metformin included the following: concern about the influence of the drug on liver and kidney function, gastrointestinal adverse reactions, hypoglycemia, and further weight loss, etc. As we all know, metformin has certain requirements for liver and kidney function but does not cause further damage and reasonable weight loss can improve insulin resistance to a certain extent. The results show that the patients lacked reliable access to scientific knowledge of medicine. Therefore, clinical pharmacists should guide and educate patients with type 2 diabetes according to the above-specified medication errors in order to promote the patients’ deep scientific understanding and reasonable use of this drug. Patients with gastrointestinal adverse reactions can be made to develop tolerance for the adverse reactions by initiating low metformin doses and gradually increasing the drug dose or by using extended-release formulations [22,23].

The independent samples \( t \)-test revealed that there is no significant difference in blood glucose levels but a significant difference in the mean HbA1c between inpatient and outpatient treatment.

A two-way analysis of variance indicates that metformin has certain effects on the mean blood glucose and the mean HbA1c.

**10. Strengths and Limitations**

This is the first study to investigate the perceptions of physicians with regard to the reasons for metformin not being used among patients with type 2 diabetes. Moreover, alongside the data from physicians presented in this article, this study provides an overview of the patients’ reasons for refusal to use metformin. In the context of the changes to the guidelines and specifications (the expanded scope for the application of metformin and its improved clinical status), it is particularly interesting to have conducted this study to see how district hospitals are implementing the latest version of the guidelines and specifications.

It was not possible to contact all physicians and patients due to the privacy policy. Physicians who resigned from the hospital before starting the survey would have been unaware of the questionnaire. Furthermore, some patients who came to the hospital infrequently and left no contact information would have been difficult to contact to obtain valid questionnaire information, and some patients, for various reasons, were unwilling to cooperate to complete the questionnaire. It is impossible to determine the accuracy of information, such as the course of diabetes, in the case of some psychiatric patients who cannot communicate normally, and their medical history can only be narrated by their family members, therefore, the risk of bias remains unknown and should be considered when interpreting the results.

**Conclusion**
There is room for improvement for physicians, especially those who are not endocrinologists, to better align themselves with the latest guidelines for the management of patients with type 2 diabetes. Accordingly, we advise that health administration departments and hospital leaders should increase the number of more relevant knowledge training workshops to promote more standardized knowledge and to increase the input of information construction with literature download as the main body to update diagnosis and treatment behavior. From this survey, it can be clearly seen that clinical pharmacists, who constitute a bridge for information transmission, should not only serve the endocrinology department, but also promote endocrine-related pharmaceutical care to non-endocrine departments with patients who have diabetes. In terms of drug understanding of patients with type 2 diabetes, due to the lack of medical literacy, there is still some misunderstanding about metformin; thus, there is still a long way to go for physicians, and clinical pharmacists need to do to further correct and guide patients to correct the understanding bias to use drugs more scientifically and rationally.

Declarations

Ethics approval

The Medical Sciences Human Research Ethics Committee, Beijing ChangPing District Hospital of Traditional Chinese Medicine and Western Medicine, China (Reference No.: 2018-01).

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References

1. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care, 2018,41(5):917-928.
2. American Diabetes Association. Introduction: Standards of medical care in Diabetes-2020. Diabetes Care, 2020,43(Suppl 1)(Suppl 1):S1-S2.
3. Diabetes Branch of Chinese Medical Association. Guidelines for the Prevention and Treatment of Type 2 diabetes (2017 edition)[J]. Chinese Journal of Diabetes, 2018,10(1):4-67.
4. American Diabetes Association. Introduction: standards of medical care in Diabetes—2018. Diabetes Care, 2018,41(Suppl 1)(Suppl 1):S73-S85.
5. Yiming Mu, Linong Ji, Chunlin Li, et al. Expert Consensus on metformin clinical Application (2018 edition). Chinese Journal of Diabetes, 2019,27(3):161-173.
6. Benoit Viollet, Bruno Guigas, Nieves Sanz Garcia, et al. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond), 2012,122(6):253-270.
7. Ricardo Lage, Carlos Diéguez, Antonio Vidal-Puig, Miguel López. AMPK: a metabolic gauge regulating whole-body energy homeostasis. Trends Mol Med, 2008,14(12):539-549.
8. Kimberly A Coughlan, Rudy J Valentine, Neil B Ruderman, Asish K Saha. AMPK activation: a therapeutic target for type 2 diabetes? Diabetes Metab Syndr Obes, 2014,7(7):241-253.
9. Gregory R Steinberg, Bruce E Kemp. AMPK in health and disease. Physiol Rev, 2009,89(3):1025-1078.
10. Qingfeng Cheng, Shumin Yang, Changhai Zhao, et al. Efficacy of metformin-based oral antidiabetic drugs is not inferior to insulin glargine in newly diagnosed type 2 diabetic patients with severe hyperglycemia after short-term intensive insulin therapy. J Diabetes, 2015,7(2):182-191.
11. Linong Ji, Hongmei Li, Xiaohui Guo, et al. Impact of baseline BMI on glycemic control and weight change with metformin monotherapy in Chinese Type 2 diabetes patients: Phase IV open-label trial. PLOS ONE, 2013,8(2):e57222.

12. Jinman Chen, Chenglai Xia, Jie Yang. Meta-analysis of effects of ethinyl estradiol cyproterone tablets combined with metformin on hormone levels in patients with polycystic ovary syndrome. Chin J Clin Pharm, 2017,26(5):308-314.

13. Sei Yoshida, Sungki Hong, Tsukasa Suzuki, et al. Redox regulates mammalian target of rapamycin complex 1 (mTORC1) activity by modulating the TSC1/TSC2-Rheb GTPase pathway. J Biol Chem, 2011,286(37):32651-32660.

14. Issam Ben Sahra, Claire Regazzetti, Guillaume Robert, et al. Metformin, independent of AMPK, induces mTOR inhibition and cell-cycle arrest through REDD1. Cancer Res, 2011,71(13):4366-4372.

15. Heather A Hirsch, Dimitrios Iliopoulos, Kevin Struhl. Metformin inhibits the inflammatory response associated with cellular transformation and cancer stem cell growth. Proc Natl Acad Sci U S A, 2013,110(3):972-977.

16. J. Ma, L.Y. Liu, P.H. Wu, et al. Comparison of metformin and repaglinide monotherapy in the Treatment of New Onset type 2 diabetes mellitus in China. J Diabetes Res, 2014,2014:article ID 294017.

17. Hye Yeon Sin, Jin Yub Kim, Ki Hwa Jung. Total cholesterol, high density lipoprotein and triglyceride for cardiovascular disease in elderly patients treated with metformin. Arch Pharm Res, 2011,34(1):99-107.

18. Juan Pablo Domecq, Gabriela Prutsky, Aaron Leppin, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. J Clin Endocrinol Metab, 2015,100(2):363-370.

19. Xiaoyan Xing, Yufeng Li, Zuodi Fu, et al. The effect of metformin on lowering blood pressure in patients with primary hypertension with hyperinsulinemia. Chin J Intern Med, 2010,49(1):14-18.

20. Yexin Sun, Genzhi Yang, Zhu Zhu, et al. Sampling analysis of drug precursors in outpatient department of our hospital. Chin Pharm, 2017,20(3):527-530.

21. Timothy David Noblet, John F Marriott, Taryn Jones, et al. Perceptions about the implementation of physiotherapist prescribing in Australia: a national survey of Australian physiotherapists. BMJ Open, 2019,9(5):e024991, DOI: 10.1136/bmjopen-2018-024991.

22. Linong Ji, Jing Liu, Jing Yang, et al. Comparative effectiveness of metformin monotherapy in extended release and immediate release formulations for the treatment of type 2 diabetes in treatment-naïve Chinese patients: analysis of results from the CONSENT trial. Diabetes Obes Metab, 2018,20(4):1006-1013.

23. Lawrence Blonde, George E Dailey, Serge A Jabbour et al. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin, 2004,20(4):565-572.

Figures
Figure 1

Consolidated Standards of Reporting Trials (CONSORT) chart.

Supplementary Files

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