ความชุกและปัจจัยที่สัมพันธ์กับการสั่งยา Metformin อย่างไม่สมเหตุสมผลในโรงพยาบาลลำปาง

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The prevalence of and factors associated with inappropriate metformin prescription in type 2 DM patients with contraindications: a case study in Thailand

Abstract

Objectives: To explore the prevalence of and factors associated with inappropriate metformin prescription in type 2 DM patients with contraindications.

Design, setting, participants: A cross-sectional study including type 2 DM patients aged ≥30 who visited the outpatient department at Lampang Hospital in 2017 and were prescribed metformin at least once. Data from electronic medical records (EMR) were used to identify diabetic patients using ICD10 codes, together with other covariates. Inappropriate prescription was defined as patients receiving metformin over the maximum daily doses indicated for each of the risks. The risks were categorized into the following 3 groups: 1) Metformin prescription not recommended in patients with CKD stage 4 or above, chronic liver disease, or heart failure; 2) A maximum daily dose of 1,000 mg in patients with CKD stage 3b; and 3) A maximum daily dose of 2,550 mg in patients without the abovementioned conditions.

Outcomes measured: Primary outcome: prevalence of inappropriate metformin prescription in type 2 DM patients with contraindications.

Results: Among 5,812 DM patients, the prevalence of inappropriate metformin prescriptions was 15%. Of these, 8.6% were prescribed metformin over the maximum dose of 2,550 mg per day. In CKD stage 3b group, 46% received inappropriate prescriptions. The specialty of physician and the length of work experience were found to be associated with inappropriate metformin prescription

Conclusion: This study has revealed a high prevalence of inappropriate metformin prescription, indicating a remaining concern that requires further action to reduce the incidence of the drug misuse.

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บทคัดย่อ

Metformin เป็นยาลดระดับน้ำตาลที่ถูกแนะนำอย่างกว้างขวาง ในฐานะยากลุ่มแรกในการรักษาผู้ป่วยเบาหวานชนิดที่ 2 ยา Metformin มีข้อห้ามใช้ในผู้ป่วยโรคไตเรื้อรัง โรคหัวใจล้มเหลว และโรคตับเรื้อรัง อย่างไรก็ตาม ยังมีความรู้น้อยมากเกี่ยวกับความชุกการจ่ายยา Metformin อย่างไม่สมเหตุสมผล การศึกษานี้มีวัตถุประสงค์เพื่อสำรวจความชุกและปัจจัยที่สัมพันธ์กับการใช้ยา Metformin อย่างไม่สมเหตุสมผลในผู้ป่วยเบาหวานชนิดที่ 2 ที่มีข้อห้าม

การศึกษาภาพตัดขวางนี้รวมผู้ป่วยเบาหวานชนิดที่ 2 อายุตั้งแต่ 30 ปีขึ้นไป ซึ่งรับบริการที่แผนกผู้ป่วยนอก โรงพยาบาลลำปางในปี พ.ศ. 2560 และได้รับการจ่ายยา Metformin อย่างน้อย 1 ครั้ง ข้อมูลจากเวชระเบียนอิเล็กทรอนิกส์ถูกใช้ในการยืนยันผู้ป่วยเบาหวาน โดยใช้รหัส ICD10 รวมถึงปัจจัยอื่นๆ การใช้ยาอย่างไม่สมเหตุสมผลนิยามจากการที่ ผู้ป่วยได้รับยา Metformin เกินขนาดสูงกว่าระดับยาสูงสุดต่อวัน ตามความเสี่ยง โดยความเสี่ยงถูกแบ่งออกเป็น 3 กลุ่ม คือ 1) การจ่ายยา Metformin ไม่แนะนำในผู้ป่วยโรคไตเรื้อรัง ระดับ 4 ขึ้นไป โรคตับเรื้อรัง หรือโรคหัวใจล้มเหลว; 2) ระดับยาสูงสุดต่อวันที่ 1,000 มิลลิกรัมต่อวัน ในกลุ่มผู้ป่วยโรคไตเรื้อรัง ระดับ 3 บี; และ 3) ระดับยาสูงสุดต่อวันที่ 2,550 มิลลิกรัมต่อวัน ในผู้ป่วยที่ไม่มีข้อบ่งชี้ข้างต้น การทดสอบไคร์สแควร์ถูกใช้ทดสอบความสัมพันธ์ระหว่างการจ่ายยาอย่างไม่สมเหตุสมผล และปัจจัยที่เกี่ยวข้อง

จากผู้ป่วยเบาหวานจำนวน 5,812 คน พบความชุกของการใช้ยา Metformin อย่างไม่สมเหตุสมผลอยู่ 15% ในกลุ่มนี้ 8.6% ถูกจ่ายยา Metformin เกินระดับสูงสุด 2,550 มิลลิกรัมต่อวัน ในกลุ่มผู้ป่วยไตวายเรื้อรังระดับ 3 บี พบว่า 46% ได้รับการจ่ายยาอย่างไม่สมเหตุสมผล สาขาเฉพาะทางของแพทย์และระยะเวลาในการทำเวชปฏิบัติ ถูกพบว่ามีความสัมพันธ์กับการจ่ายยา Metformin อย่างไม่สมเหตุสมผล

การศึกษานี้เผยให้เห็นถึงความชุกที่สูงของการใช้ยา Metformin อย่างไม่สมเหตุสมผล อันชี้ให้เห็นถึงความน่ากังวลที่ยังเหลืออยู่ ที่ต้องการปฏิบัติการเพื่อลดการเกิดการใช้ยาผิดพลาด

คำหัส : Metformin, การใช้ยาอย่างไม่สมเหตุสมผล, เบาหวาน

Introduction

Metformin is a glucose-lowering agent that is widely recommended as a first-line therapy to treat patients with type 2 Diabetes Mellitus (DM) (1, 2). This is owing to its effectiveness in reducing blood sugar and also that it is inexpensive (3). Moreover, evidence has shown that long-term use of metformin is associated with a reduction in diabetic complications such as DM foot and diabetic retinopathy (4). In addition, literature has indicated the benefits of metformin in reducing diabetes-related morbidities and mortalities (1).

Metformin is contraindicated in patients with chronic kidney disease (CKD) because it is eliminated unchanged in the urine and accumulates in the kidneys. This results in a rise of lactic acidosis, which increases the risks of multisystem organ dysfunction, including coma, seizure, cardiovascular events (hypotension, ventricular fibrillation), and carries a high mortality risk (5). A study from Denmark and the UK showed the incidence rates of lactic acidosis increased with decreasing baseline renal function in both coun-

tries (6).

Apart from CKD, metformin is also contraindicated in patients with congestive heart failure and impaired hepatic function, as a result of the increased risk of lactic acidosis (1).

Recent recommendations from the American Diabetes Association and the US Food and Drug Administration suggest that the daily dose of metformin should not exceed 2,550 mg, while the maximum dose should be reduced by half when the estimated glomerular filtration rate (eGFR) is between 30-44 ml/min/1.73m^2. The use of metformin is not recommended in patients with eGFR<30 ml/min/1.73m^2, chronic liver disease, or heart failure (2, 7). These recommendations are reflected in the clinical practice guidelines from the Thai Clinical Practice Guidelines for Diabetes (8). Thai Rational Drug Use (RDU) recommend not to start metformin in type 2 DM with CKD of at least stage 3b, heart failure, and chronic liver disease(9).

Although the maximum doses of metformin per day are clearly indicated for patients with different risks, prescription of the drug higher than the maximum limits remains a concerning common occurrence. A study in 2009 investigated inappropriate metformin use in the Thai population and showed that 19.3% of type 2 DM patients who received metformin had at least one contraindication, with chronic renal impairment being the most common (78%) (10).

While there is very little research examining the prevalence of inappropriate metformin prescription, even the existing evidence was published approximately a decade ago and may be obsolete. This study aims to explore the prevalence of and factors associated with inappropriate metformin prescription in type 2 DM patients with contraindications.

Method

Population and samples

This cross-sectional study included type 2 DM patients aged ≥30 who were prescribed metformin at least once. Data from electronic medical records (EMR) were used to identify patients with DM diagnosed using ICD10 codes of E10-E14, who visited the outpatient department at Lampang Hospital from January to December 2017. Samples were excluded if they did not have information about eGFR or metformin prescription dose.

Metformin's contraindications

Metformin's contraindications in type 2 DM patients were defined as co-morbidities of CKD at least stage 3b, heart failure, or chronic liver disease (7) (2). Co-morbidities were defined as patients having ICD10 diagnoses (11). For heart failure, the codes used were I50.0, I50.1, I50.9, and for chronic liver disease, the ICD10 codes used were K70-K77. The EMR of those with the diagnoses of heart failure and chronic liver disease was double-checked to confirm the presence of the diseases. CKD was defined by eGFR, with values of 30-44 defining CKD stage 3b, and values lower than 30 defining CKD stage 4. An eGFR was defined as the eGFR value which appeared in the EMR at Lampang Hospital. The eGFR was calculated using the CKD-EPI formula (12).

Inappropriate prescription

Inappropriate prescription was defined as patients receiving metformin over the maximum daily doses indicated for each of the risks. The risks were categorized into the following 3 groups: 1) Metformin prescription not recommended in patients with CKD stage 4 or above, chronic liver disease, or heart failure; 2) A maximum daily dose of 1,000 mg in patients with CKD stage 3b; and 3) A maximum daily dose of 2,550 mg in patients without the abovementioned conditions (2, 7).

Data collection

Data, including hospital number, last metformin prescription date, visiting date, metformin prescription dose, birth date, sex, the medical specialty and duration of work of the physicians who prescribed metformin, the department of the clinic where the patient received metformin, the last eGFR, and co-morbidities (chronic liver disease, heart failure), were retrieved from EMR.

Clinical outcomes

The primary and secondary outcomes were the prevalence of inappropriate metformin prescription in type 2 DM patients with contraindications and factors associated with inappropriate metformin prescriptions.

Statistical analyses

Baseline characteristic were expressed as numbers and proportions, means, and standard deviations. The prevalence of inappropriate metformin prescription in type 2 DM patients with contraindications is presented in terms of frequency and percentage. Factors associated with inappropriate metformin prescriptions were analyzed by a chi-square test, with a significance level of 0.05.

Ethics approval

This research was approved by the Ethics Committee at Lampang Hospital.

Results

A total of 5,812 samples were identified. The majority of patients were female, 3,444 (53.9%). Most of them were aged in the ranges 50-<60, 1,777 (30.6%) and 60-<70, 2,040 (35.1%). Five percent of the samples had at least one absolute contraindication for metformin prescription, with heart failure as the most common (3.2%). It is also noted that 498 (8.6%) of the samples were prescribed metformin over the maximum limit of 2,550 mg per day, as shown in Table 1.

Table 1: Demographic characteristics of samples

Characteristics	N (%)
Total	5,812 (100)
Sex	
Male	2,368 (40.7)
Female	3,444 (59.3)
Age (years)	
30-<50	768 (13.2)
50-<60	1,777 (30.6)

Characteristics	N (%)
60-<70	2,040 (35.1)
≥70	1,227 (21.1)
eGFR (ml/min/1.73m²)	
≥45	5,515 (94.9)
30-44	235 (4.0)
<30	62 (1.1)
Chronic liver diseases	70 (1.2)
Heart failure	183 (3.2)
eGFR <30 or presence of chronic liver disease or heart failure	293 (5.0)
Number of patients receiving metformin >2,550 mg per day	498 (8.6)

Table 2 demonstrates the prevalence of inappropriate metformin prescription. As seen, the prevalence of inappropriate metformin prescription was 15%. Among 293 patients with absolute contraindications for metformin, the average metformin dose prescribed was 1,609.4 mg/day. In the CKD stage 3b group, the mean metformin prescription was 1,930 mg/day, while the maximum dose recommended should not exceed 1,000 mg/day. For patients who did not have any contraindication, however, 15% of the patients still received metformin over the maximum limit of 2,550 mg/day, with the average dose being 3,002.5 mg/day. Table 2: Inappropriate use of metformin

Table 2: Inappropriate use of metformin

Contraindications	Inappropriate metformin prescribed (mg per day)	Number of inappropriate used / total samples (%)	Prescribed metformin dose (mg per day) (Mean(SD))
No contraindication	>2,550	478/5,306 (9.0)	3,002.5 (31.6)
CKD stage 3b	>1,000	99/213 (46.5)	1,930.8 (460.3)
CKD stage 4 or above or Chronic liver disease or Heart failure	Any dose	293/293 (100)	1,609.4 (681.5)
Total		870/5,812 (15.0)	

Statistical analyses revealed an association between inappropriate metformin prescription and the specialty of the physicians, their work experience, and the clinics. As seen in Table 3, inappropriate prescription rates were prominent among internists (16.3%) and family physicians (15.4%), while in the other specialties the rate was 12.5% and in general practitioners 11.4%. In addition, there are differences in the inappropriate prescription rates among physicians whose work experience was <3 years (11.3%), those with 3-20 years (16%), and those with more than 20 years (15.6%).

Table 3: Association between the prevalence of inappropriate metformin prescription and covariates

Characteristics	N	Inappropriate prescription (%)	P-value
Sex			
Male	2,368	341 (14.4)	0.314
Female	3,444	529 (15.4)	
Age group			
30-<50	768	119 (15.5)	
50-<60	1,777	260 (14.6)	0.929
60-<70	2,040	310 (15.2)	
≥70	1,227	181 (14.8)	
Specialty of physicians			
Internal medicine	3,656	595 (16.3)	
General practitioner	1,164	133 (11.4)	<0.001
Family medicine	623	96 (15.4)	
Other	369	46 (12.5)	
Work experience of physicians (years)			
<3	1,103	125 (11.3)	
3-20	3,207	511 (16.0)	<0.001
≥20	1,502	234 (15.6)	
Clinics			
Internal medicine	3,587	586 (16.3)	
Primary care practice	1,877	244 (13.0)	<0.001
Other	348	40 (11.5)	

Discussion

Since 2016, the Thai Rational Drug Use (RDU) has introduced guidelines to reduce drug misuse (9). They recommended that metformin should not be prescribed in type 2 DM patients with CKD stage 4, and that type 2 DM patients with CKD stage 3b should not have metformin prescribed over 1,000 mg per day. However, this study has revealed a high prevalence of inappropriate metformin prescription of 15%, indicating a remaining concern that requires further action to reduce the incidence of the drug misuse.

Concerning the prevalence of inappropriate metformin prescription in patients with an absolute contraindication, this study reports a low prevalence of 5.04%, compared with 19% as shown in the previous Thailand study in 2009 (10). This

evidence represents a decrease in the prevalence of inappropriate prescriptions of metformin over time. One explanation could possibly be owing to the effectiveness of Thai RDU to promote rational drug prescription. Qualitative research may be recommended to explore the extent to which components of the RDU program influence rational metformin prescriptions among physicians, in order to inform on how to improve rational drug prescription further.

An issue worth noting is that among all absolute contraindications, a high prevalence of inappropriate prescription was found among the samples in heart failure (3.2%) and chronic liver disease (1.2%), compared with only 1.1% in CKD stages 4-5. However, Thai RDU guidance covers only CKD stages 4-5, not heart failure or chronic liver disease. Hence, more attention should be paid to heart failure and chronic liver disease as contraindications for prescribing metformin among DM patients.

As already noted, the maximum metformin dose of 2,550 mg should never be exceeded, regardless of whether the physicians have information about the co-morbidities of the patients or not. Nonetheless, this study found 8.6% of inappropriate metformin prescriptions in this group. This evidence shows that some physicians may not know about the stipulated maximum dose of metformin. RDU campaigns may need to focus more on the information about the maximum dose of daily metformin that should be prescribed to reduce the drug misuse.

While Thai RDU clearly states the maximum daily dose of 1,000 mg in patients with CKD stage 3b, almost half of these patients still received metformin over the recommended dose, with an average of 1,930.8 mg/d. One explanation might be the difficulty in real practice to obtain eGFR values during the out-patient service time, which prevents physicians from knowing the current stage of the patients' kidney function. Therefore, they were likely to be unaware of contraindications in using metformin.

A pop-up alarm on a computer screen is a method generally used to prevent prescription errors in hospitals. Using a pop-up notification in diabetic patients highlighting their existing contraindications could be one way to prevent inappropriate prescription when physicians look at the computer screen. Nevertheless, overuse of the pop-up alarm potentially increases the odds of users becoming desensitized or even immune to the appearance of alerts, also known as alarm fatigue (13). Strategies that could improve the effectiveness of alarms may be to customize alerts, present only the most severe conditions, increase alert specificity, and improving the interface design.

As the prevalence of the adverse consequence – lactic acidosis – among patients who receive metformin above the maximum level is considered very rare (6, 14), some physicians may not be worried about the reduced maximum dose in CKD and all other contraindications. This issue has received increasing attention because a higher-than-maximum dose of metformin could possibly be prescribed if subsequent harm is proven to be outweighed by its benefits (15, 16). More information about the prevalence of undesirable outcomes of metformin overdose and judgment

about balance between risks and benefits, is required to clarify this important issue.

Evidence from this study indicates that physicians' specialties and work experience are associated with the rate of inappropriate prescription; i.e., physicians with more than 3 years of work experience, internists and family physicians, are prone to prescribed metformin incorrectly. An explanation for this could be the very small incidence of lactic acidosis found among those who received metformin overdose in real clinical practice. As little to no adverse effect of drug overdose perceived from direct clinical experience could essentially outweigh the theoretical harm, physicians with long work experience may be inclined to prescribe metformin slightly over the indicated maximum dose, compared with recent medical graduates. Interventions to reduce inappropriate prescription could be tailored, focusing on these targeted groups to decrease the drug misuse.

This study employed the definition of the diagnoses of heart failure and chronic liver disease using ICD10 retrieved from the EMR. However, doing so might result in an underestimation of the prevalence because, in practice, physicians sometimes do not record the diagnosis of heart failure and chronic liver disease. To overcome this study's limitation, diagnosing heart failure and chronic liver disease based on the clinical, radiological, and laboratory findings may be considered.

While evidence from this study indicates the situation in the setting of a provincial hospital, other healthcare settings may experience different influences. This is because problems about inappropriate prescription of metformin involve many doctors – internists, FM, GP, others – and seem to affect a wide range of healthcare providers. Future studies should explore this further with larger sample sizes and in other healthcare settings, such as medical school hospitals, other provincial hospitals, and community hospitals, to gain a better understanding of the situation.

Health literacy of the patients, about their knowledge of particular conditions related to metformin prescription, also plays an important role in reducing drug misuse (17). As metformin is among the most common sugar-lowering drug prescribed, information about maximum doses of metformin associated with particular medical conditions should be delivered to patients; this includes a general maximum dose of 2,550 mg per day, reduced maximum daily dose of 1,000 mg in patients with CKD stage 3b, and no prescription in those with heart failure, chronic liver disease, and CKD stage 4 and above. Improving patients' knowledge could potentially raise their awareness when a higher-than-maximum dose of metformin was prescribed so that prompt notification to their physicians about drug misuse could be done.

While the study selected only type 2 DM patients with metformin prescription to explore the incidence of drug misuse, it is acknowledged that excluding type 2 DM patients with no metformin prescription might somehow overestimate the incidence of inappropriate prescription. This is because, in one way, appropriate metformin prescription can be interpreted as patients not receiving the drug when physicians noticed the contraindication. With respect to this, some type 2 DM patients without metformin prescription could

also be counted as the denominator, which in turn would reduce the incidence of inappropriate prescription. Future research, expanding the scope of sample selection to explore the incidence of inappropriate prescription, is recommended.

Conclusion

This study has revealed a high prevalence of inappropriate metformin prescription; inappropriate prescription is inclined to appear among family physicians or internists, or those who have long experience of medical practice. These information could be in assistance of devising the intervention to reduce the incidence of the drug misuse in the future.

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