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Original Research Article

Comparing the efficacy and renal safety of metformin and imeglimin in diabetic rats

Charang Ngammoiran[1]*, Thongam Ramananda Singh[1], Laishram Elizabeth Devi[2], L. Tarinita Devi[1], Usham Dharmaraja Meetei[1]

[1]Department of Pharmacology, Regional Institute of Medical Sciences, Imphal, Manipur, India
[2]Department of Pharmacology, Shija Academy of Health Sciences, Imphal, Manipur, India

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***Correspondence:**
Dr. Usham Dharmaraja Meetei,
E-mail: pharmangam17@gmail.com

ABSTRACT

Background: Diabetic kidney disease (DKD) represents a significant cause of end-stage kidney disease and is closely linked to substantially higher rates of cardiovascular morbidity and mortality. As a result, there is a need for therapies that can prevent DKD, improve patient compliance, reduce side effects, and be cost-effective.
Methods: Healthy male albino rats (150-200 g) were screened, and hyperglycemia was induced in 24 rats, and after one week, hyperglycemia was confirmed. The rats were then divided into four groups (Groups 1, 2, 3, and 4) (n=6). Group 1 was designated as diabetic control group, while nephrotoxicity was induced in the remaining rats. Group 1 and Group 2 (toxic control group) were treated with vehicle. Group 3 (metformin group) was treated with metformin, and Group 4 (imeglimin group) received imeglimin, both at a dose of 180 mg/kg/day for two weeks.
Results: On day 21, there was a significant reduction in serum urea and creatinine levels in Group 3 ($p<0.05$ and $p<0.05$, respectively) and Group 4 ($p<0.001$ and $p<0.001$, respectively) when compared with Group 1. Also, both Groups 3 and 4 showed a significant reduction in serum urea ($p<0.001$, $p<0.001$) and creatinine ($p<0.001$, $p<0.001$) levels when compared with Group 2. However, the glycemic control by imeglimin did not significantly differ from that of metformin on day 21.
Conclusions: Imeglimin was more effective in improving renal function parameters, demonstrating greater renal safety compared to metformin.

Keywords: Diabetes mellitus, Metformin, Imeglimin, Glycemic control, Diabetic kidney disease, Renal safety

INTRODUCTION

Diabetes mellitus (DM) is a multiple metabolic condition characterized by impaired glucose homeostasis and hyperglycemia resulting from defective insulin secretion, defective insulin action or both. If left untreated or uncontrolled for an extended period, it may lead to multi-organ system damage affecting kidneys, eyes, nerves and blood vessels.[1]

Hence, there is a need for integrated care in the treatment of diabetes to effectively manage plasma glucose levels while prioritizing the identification and management of diabetes-related complications and modifying risk factors for diseases associated with this condition.[2]

The most recent estimates indicate that as of 2021, there are approximately 537 million people (aged 20-79 years) living with diabetes worldwide. It is projected that this number will increase to 643 million by 2030 and 783 million by 2045.[3] This increasing prevalence of DM

worldwide is a significant public health concern that is creating unmanageable pressures on individuals, their caregivers, healthcare systems and society as a whole.[1]

In recent years, many new drugs have been developed to treat type II DM in addition to conventional hypoglycemic agents like insulin, sulfonylureas and biguanides like metformin. The recently developed drug for the treatment of Type II DM is imeglimin, the first of a new class of medicines called "glimins", a tetrahydro-triazine-containing agent.[4]

Acute kidney injury (AKI) and diabetes significantly increase the risk of diabetic kidney disease (DKD). During AKI, hypoxia-inducible factor (HIF)-1 activation, inflammation and reactive oxygen species (ROS) trigger necrosis and apoptosis in renal tubular cells. Incomplete repair can lead to persistent renal tubular inflammation, fibrosis and progression to DKD. DKD poses a significant healthcare challenge. It affects as many as 50% of people living with diabetes, represents a major cause of end-stage kidney disease (ESKD) necessitating dialysis or renal transplantation and is closely linked to substantially higher rates of cardiovascular morbidity and mortality. Key characteristics of DKD include thickening of the glomerular and tubular basement membranes, mesangial expansion, glomerular hypertrophy, podocyte effacement, glomerulosclerosis, tubular interstitial fibrosis and inflammation. It typically begins with microalbuminuria, progressing to macroalbuminuria, and leading to a gradual decline in kidney function.[5-7]

Hyperglycemia is a commonly known risk factor of DKD through various metabolic disruptions. These include increased oxidative stress, renal polyol formation, protein kinase C (PKC) as well as mitogen-activated protein kinases (MAPKs) activation, and the accumulation of advanced glycation end products (AGEs). Other important risk factors of DKD are obesity, hypertension, dyslipidemia and inflammation.[8]

Metformin is considered the gold standard drug treatment option for Type II DM. It acts by decreasing the production of glucose in the liver and increasing the utilization of glucose in the body through the activation of AMP-activated protein kinase (AMPK).[9] Recent studies have reported that metformin can potentially prevent or reduce endoplasmic reticulum (ER) stress, epithelial-mesenchymal transition and oxidative stress in patients with DKD. Additionally, it can promote the expression of HIF and autophagy in renal tissue, thereby protecting it.[10]

Imeglimin is one of the recently developed oral antidiabetic drugs used in Type II DM. It reduces postprandial hyperglycemia, normalizes glycated haemoglobin (HbA1c) and improves beta-cell function by increasing insulin sensitivity and reducing insulin resistance and hepatic gluconeogenesis. At the cellular and molecular level, imeglimin restores balance in respiratory chain activity by partially inhibiting Complex I and correcting deficiencies in Complex III activity. This dual action reduces the production of ROS, alleviates oxidative stress, and prevents the mitochondrial permeability transition pore opening, thus protecting cells from death. There is some evidence indicating that imeglimin may be a promising new therapeutic agent for various diabetes-induced vascular disorders like nephropathy, retinopathy and neuropathy, as it has been found to improve endothelial dysfunction and vascular network.[4,11-13]

As diabetes-related kidney disease becomes more common, it is essential to carefully check how well different treatments work and how safe they are for the kidneys. Metformin is a well-known medicine, but researchers are still studying whether imeglimin is safe for the kidneys and if it can help protect kidney function in people with diabetes. And till now, hardly any report compares the renal safety of metformin and imeglimin. Thus, keeping this in mind, the present study is undertaken in an attempt to compare the glycemic control and the renal safety of metformin and imeglimin in diabetic rats, and the findings from this may contribute to improving therapeutic strategies for diabetes management, especially for patients at risk of developing or experiencing diabetic nephropathy (DN).

METHODS

Male albino rats weighing between 150-200 g were obtained from the Central Animal House, Regional Institute of Medical Sciences, Imphal, Manipur, after the approval from the Institutional Animal Ethics Committee and kept in the animal room in Department of Pharmacology, RIMS, Imphal, 7 days before the experiment for acclimatisation. The animals were housed in groups of six per polypropylene cage under natural light-dark cycle at room temperature with free access to standard food and water.

Study design

Non-randomised controlled experimental study. The sample size was 24.

Duration of study

The study duration was 2 years (April 2023 to March 2025).

Exclusion criteria

Female albino rats, albino rats with blood glucose <126 mg/dl after induction of diabetes.

Drugs and chemicals

Streptozotocin (Sisco Research Laboratories Pvt. Ltd., 60 mg/kg.), Nicotinamide (Sisco Research Laboratories Pvt. Ltd, 120 mg/kg), Gentamicin (Abaris Healthcare Pvt. Ltd, 80 mg/kg/day), Metformin (USV Private Limited, 180

mg/kg/day), Imeglimin Hydrochloride (Examed Pharmaceuticals, Valsad, Gujarat, 180 mg/kg/day).

Experimental design

The animals were put on standard diet and water ad libitum. After overnight fasting, all animals were screened for fasting blood glucose, serum urea and creatinine levels. Male albino rats with fasting blood glucose level: 70-99 mg/dl, serum urea level: 15-22 mg/dl and serum creatinine level: 0.4-0.8 mg/dl were selected.[14,15] Type II DM was induced in these male albino rats using streptozotocin (STZ) and nicotinamide, following the methods outlined by Shirwaikar et al.[16] Among these, 6 rats served as the diabetic control group while nephrotoxicity was induced in the remaining rats following the methods outlined by Singh et al.[17]

Induction of diabetes and nephrotoxicity

All the rats were given intraperitoneal (i.p) injection of 120 mg/kg nicotinamide dissolved in 0.9% normal saline (NS) and after 15 minutes, 60 mg/kg STZ freshly dissolved in 0.1M citrate buffer with pH 4-4.5 was given by i.p route.[16] Drugs were given at a uniform volume of 0.5 ml/100 gm of body weight/day by i.p route.

After 1 week of STZ and nicotinamide injection, Type II DM induction in rats was confirmed with overnight fasting blood samples. 24 rats with blood glucose level ≥126 mg/dl were considered as diabetic and included in study. The diabetic rats were divided in 4 groups (group 1, 2, 3 and 4) and nephrotoxicity was induced with gentamicin 80 mg/kg/day dissolved in 0.9% NS in the 3 groups (group 2, 3 and 4) while group 1 was given 0.9% NS. Drugs were given at a uniform volume of 0.5 ml/100 gm/day by i.p injection for 8 consecutive days (day 1 to 8).[17]

Group 1 (diabetic control group) and Group 2 (toxic control group) were treated with 1% carboxymethyl cellulose (CMC) in distilled water (D/W) orally (p.o.) from day 1 to 14 (2 weeks). Group 3 (diabetic with nephrotoxicity group treated with metformin) were treated with metformin at the dose of 180 mg/kg/day p.o. from day 1 to 14 (2 weeks). Group 4 (diabetic with nephrotoxicity group treated with imeglimin) were treated with imeglimin at the dose of 180 mg/kg/day p.o. from day 1 to 14 (2 weeks). The doses of metformin and imeglimin were extrapolated from adult human dose and then suspended in 1% CMC in D/W.[18] All the drugs were given at a uniform volume of 1ml/100gm/day p.o. for a period of 2 weeks. (Table 1).

Table 1: After induction of diabetes.

Groups	Diabetic control group	Toxic control group	Diabetic with nephrotoxicity group treated with Metformin	Diabetic with nephrotoxicity group treated with Imeglimin
	(Group 1)	(Group 2)	(Group 3)	(Group 4)
Nephrotoxicity Day 1 to 8 (i.p)	0.9% NS	Gentamicin	Gentamicin	Gentamicin
Treatment Day 1 to 14 (p.o.)	1% CMC in D/W	1% CMC in D/W	Metformin in 1% CMC in D/W	Imeglimin in 1% CMC in D/W
Total duration	2 weeks	2 weeks	2 weeks	2 weeks

Gentamicin 80 mg/kg/day in 0.9% NS, Metformin and Imeglimin both at 180 mg/kg/day in 1% CMC in D/W. Drugs given at uniform volume of 0.5ml/100g/day for i.p. and 1ml/100g/day for p.o. route.

Blood collection

Blood was collected from the retro-orbital venous plexus using a capillary tube under light ether anaesthesia to assess the following parameters:[19]

Fasting blood glucose estimation on day 0 (for baseline glucose level), after 1 week (to confirm Type II DM induced by STZ - nicotinamide administration) and at the end of 3 weeks.

Serum urea and creatinine estimation on day 0 (for baseline serum urea and creatinine levels) and at the end of 3 weeks. The blood samples were allowed to stand at room temperature for 30 minutes and then centrifuged at 3000 rpm for 10 minutes and stored at -300C till analysis.[20]

Biochemical estimation

Blood glucose

Fasting blood glucose was estimated by enzymatic method by using glucometer (Contour plus, ASCENSIA Diabetes Care India Pvt. Ltd., Thane, Maharashtra).

Renal function parameters

Serum urea estimation done by commercially available diacetyl monoxime (DAM) kit (PATHOZYME DIAGNOSTICS, Kagal, Maharashtra) as per manufacturer instructions using semi-autoanalyzer.

Serum creatinine was estimated using commercially available alkaline picrate kits (Jaffe's Method, ERBA diagnostics Mannheim GmbH, Germany and

manufactured by TRANSASIA BIO-MEDICALS LTD. Mahakuma Namchi, South Sikkim) as per manufacturer instructions using semi-autoanalyzer.

Statistical analysis

The data obtained in the study was expressed as mean ± standard deviation (SD) and analysed for statistical significance using one-way analysis of variance (ANOVA) followed by Bonferroni test using IBM SPSS (statistical package for social sciences) software version 21 (IBM Corp., Armonk, NY, USA). P<0.05 was taken as significant.

Waste disposal

Waste materials, including cotton swabs, gloves, needles and disposable syringes were collected in appropriate containers and disinfected at the source using a 1% hypochlorite solution. Sharp waste was shredded following chemical disinfection. The treated materials were then sent to the institute's waste management plant for further processing.

RESULTS

Effect of metformin and imeglimin treatment on blood glucose level

As depicted in Table 2, all the four groups (Groups 1, 2, 3 and 4), showed increase in blood glucose values after one week of induction of diabetes (on 7th day) from the normal range taken for the study. No significant difference was seen, with p>0.05 in blood glucose values, when group 1 was compared to groups 2, 3 and 4 on 7th day.

The blood glucose values of group 1, 2, 3 and 4 on 21st day were 277.50±11.72, 282.16±31.37, 203.83±32.0 and 185.66±50.39 mg/dl, respectively. There was a significant difference in blood glucose levels when groups 1 and 2 were compared with group 3 (p<0.05, p<0.05 respectively) and group 4 (p<0.001, p<0.001 respectively) on 21st day. When group 3 was compared to group 4 on 21st day, there was no significant difference present (p>0.05) in blood glucose levels.

Table 2: Changes in blood glucose in different treatment groups.

Groups		Diabetic control group	Toxic control group	Diabetic with nephrotoxicity group treated with Metformin	Diabetic with nephrotoxicity group treated with Imeglimin
		(Group 1)	(Group 2)	(Group 3)	(Group 4)
Blood glucose (mg/dl)	Day 0	90.16±9.47	99±6.95	95.33±7.22	96.66±5.27
	Day 7	236±18.54	242.16±15.11*	237.66±17.23*	241.16±20.61*
	Day 21	277.50±11.72	282.16±31.37	203.83±32.0†‡	185.66±50.39††‡‡§
ANOVA					
		Day 0	Day 7	Day 21	
Df		3	3	3	
F		1.536	0.149	12.660	
P		0.236	0.929	0.000	

The results were expressed in mean±SD, with p<0.05 considered significant (n=6). *p>0.05 when group 1 compared to group 2, group 3 and group 4 on day 7; ††p<0.001, †p<0.05, when group 1 compared to group 3 and group 4 on day 21; ‡‡p<0.001, ‡p<0.05 when group 2 compared to group 3 and group 4 on day 21; §p>0.05, when group 3 compared to group 4 on day 21 (One way-ANOVA followed by Bonferroni test).

Table 3: Changes in serum urea in different treatment groups.

Groups		Diabetic control group	Toxic control group	Diabetic with nephrotoxicity group treated with Metformin	Diabetic with nephrotoxicity group treated with Imeglimin
		(Group 1)	(Group 2)	(Group 3)	(Group 4)
Serum urea (mg/dl)	Day 0	19.16±1.47	18.5±2.07	17.5±2.16	20.16±1.47
	Day 21	52±6.63	64.16±3.48*	41.33±7.60*†	31.16±1.94**†‡
ANOVA					
		Day 0	Day 21		
Df		3	3		
F		2.267	40.909		
P		0.112	0.000		

The results were expressed in mean±SD, with p<0.05 considered significant (n=6). **p<0.001, *p<0.05 when group 1 compared to group 2, 3 and 4 on day 21; †p<0.001 when group 2 compared to group 3 and 4 on day 21; ‡p<0.05 when group 3 compared to group 4 on day 21 (One-way ANOVA followed by Bonferroni test).

Effect of metformin and imeglimin treatment on renal parameters

Assessment of kidney function parameters showed elevated levels of serum urea and creatinine in all the groups from the normal range taken for the study and showed significant differences among all the groups (p=0.000).

As depicted in Table 3, the serum urea values of groups 1 and 2 on the 21st day were 52±6.63 mg/dl and 64.16±3.48 mg/dl, respectively. When group 2 was compared with group 1 on 21st day, serum urea level was significantly increased (p< 0.05). The serum urea values of Groups 3 and 4 were 41.33±7.60 mg/dl and 31.16±1.94 mg/dl respectively. On the 21st day, both group 3 (p<0.05) and group 4 (p<0.001), showed a significant reduction in serum urea levels when compared with the group 1. There was a significant reduction in serum urea levels in groups 3 (p<0.001) and 4 (p<0.001) when compared with the group 2. When group 3 was compared with group 4, serum urea showed a significant increase (p<0.05) on the 21st day.

As depicted in Table 4, the serum creatinine values of Groups 1 and 2 on the 21st day were 1.37±0.16 mg/dl and 1.74±0.05 mg/dl, respectively. When group 2 was compared with group 1 on 21st day, serum creatinine level was significantly increased (p<0.001). The serum creatinine values of Groups 3 and 4 were 1.14±0.15 mg/dl and 0.91±0.04 mg/dl respectively. On the 21st day, both Group 3 (p<0.05) and Group 4 (p<0.001) showed a significant reduction in serum creatinine levels when compared with the group 1. When group 3 was compared with group 4, there was a significant increase (p<0.05) in serum creatinine on the 21st day.

Table 4: Changes in serum creatinine in different treatment groups.

Groups		Diabetic control group	Toxic control group	Diabetic with nephrotoxicity group treated with Metformin	Diabetic with nephrotoxicity group treated with Imeglimin
		(Group 1)	(Group 2)	(Group 3)	(Group 4)
Serum Creatinine (mg/dl)	Day 0	0.71±0.03	0.67±0.03	0.70±0.03	0.73±0.03
	Day 21	1.37±0.16	1.74±0.05*	1.14±0.15**†	0.91±0.04*†‡
ANOVA					
		Day 0		Day 21	
Df		3		3	
F		2.710		54.639	
P		0.072		0.000	

The results were expressed in mean±SD, with p<0.05 considered significant (n=6). *p<0.001, **p<0.05 when group 1 compared to group 2, 3 and 4 on day 21; †p<0.001 when group 2 compared to group 3 and 4 on day 21; ‡p<0.05 when group 3 compared to group 4 on day 21 (One-way ANOVA followed by Bonferroni test).

DISCUSSION

DM is a multiple metabolic condition characterized by impaired glucose homeostasis and hyperglycemia and DKD poses a significant healthcare challenge.[1,6] Among the various pathways contributing to the pathogenesis of DKD, oxidative stress is recognized as a key driver of disease progression. Hence, there is a need for integrated care in the treatment of diabetes to effectively manage plasma glucose levels while prioritizing identifying and managing diabetes-related complications and modifying risk factors for diseases associated with this condition.[2]

Metformin is considered the gold standard drug treatment option for Type II DM, while imeglimin is one of the recently developed oral antidiabetic drugs used in Type II DM.[9,11] Metformin reduces hepatic glucose production and enhances glucose utilization by activating AMPK.[9] Recent studies have reported that metformin can potentially prevent or reduce ER stress, epithelial-mesenchymal transition and oxidative stress in patients of DKD. Additionally, it can promote the expression of HIF and autophagy in renal tissue, thereby protecting it.[10] Imeglimin reduces postprandial hyperglycemia, normalizes HbA1c, and improves beta-cell function by increasing insulin sensitivity, resistance, and hepatic gluconeogenesis. At the cellular and molecular level, imeglimin restores balance in respiratory chain activity by partially inhibiting Complex I and correcting deficiencies in Complex III activity. This dual action reduces the production of ROS, alleviates oxidative stress, and prevents the mitochondrial permeability transition pore opening, thereby protecting cells from death. Therefore, imeglimin shows promise as a therapeutic agent for addressing residual risks associated with the progression of DKD.[11-13]

This study used a rat model of STZ-Nicotinamide-induced Type II DM followed by gentamicin-induced nephrotoxicity to compare the renoprotective effects of metformin and imeglimin on the development and progression of DKD. The rats exhibited Type II DM, as indicated by increased fasting blood sugar. Also, the model showed increased levels of serum urea and creatinine after drugs-induced diabetes and nephrotoxicity, similar to a study done by Nasiri et al.[21]

Various studies have reported that metformin and imeglimin reduce oxidative stress, enhance mitochondrial function, and protect against cell damage, highlighting their potential benefits in managing DKD. However, till now, there is hardly any study that compares the renal safety of metformin and imeglimin

This study showed that metformin significantly decreased serum urea and creatinine levels in diabetic rats with gentamicin-induced nephrotoxicity, which is consistent with the findings of a study done by Madhag et al which showed a significant reduction in serum urea level and creatinine level in the diabetic rat models.[22,23] They showed that metformin alone or in combination with Empagliflozin mitigates diabetes-associated renal complications. Similarly, Mohammad et al showed that metformin reduced serum urea, creatinine, inflammatory cytokines, and renal levels of leucine-rich α-2-glycoprotein-1 (LRG1), transforming growth factor-β1 (TGF-β1), activin-like kinase1 (ALK1) and vascular endothelial growth factor (VEGF) in diabetic rats and improved histopathology by reducing glomerular enlargement, narrowing of Bowman's space, and VEGF immunostaining. This study also shows that imeglimin significantly reduces serum urea and creatinine levels in diabetic rats with gentamicin-induced nephrotoxicity. In the clinical research conducted by Uto et al the safety of imeglimin on kidney function was assessed by tracking estimated glomerular filtration rate (eGFR), which remained stable after six months, indicating no harm to renal function.[24] Albuminuria improved in some patients, with one patient showing reduced severity of kidney damage from macroalbuminuria to microalbuminuria, suggesting imeglimin may benefit DN. In another study, imeglimin rapidly improved cardiac and vascular dysfunction by reducing oxidative stress and increasing nitric oxide (NO) bioavailability. It also improved myocardial perfusion and positively impacted the structure of the myocardium and kidneys after 90 days of treatment. Imeglimin also decreased albuminuria and interstitial fibrosis in the rodents tested.[25]

In this study, there was elevated blood glucose level from the standard baseline range in diabetic control, toxic control, metformin treated and imeglimin treated groups on the 7th day showing all groups developed hyperglycemia after induction of diabetes. On the 21st day, there was a significant difference in blood glucose level in metformin and imeglimin treated groups compared with the diabetic control and toxic control groups. However, no significant difference was seen when metformin treated group was compared to imeglimin treated group, consistent with previous studies.[26,27]

Nishiyama et al compared the effects of different treatments on blood glucose levels in db/db mice.[28] Treatment with imeglimin alone (db/db Imeg) or metformin alone (db/db Met) similarly resulted in insignificant changes in blood glucose levels or insulin secretion compared to the control group. But, the combination therapy (db/db Imeg + Met) demonstrated notable improvements, including better glucose tolerance with blood glucose levels, significantly decreasing 15 minutes after glucose loading. This group also showed enhanced glucose responsiveness with a 1.3-fold increase in insulin secretion and a reduced area under the curve (AUC) for blood glucose during the insulin tolerance test, suggesting improved glucose regulation through the synergistic effects of the combination therapy.

Imeglimin and metformin both significantly reduced HbA1c at 12 weeks compared to baseline. However, imeglimin showed a further significant reduction in HbA1c from 12 to 24 weeks, whereas metformin did not demonstrate a statistically significant additional reduction during this period. Neither affected body weight. Both reduced glucose levels during the Oral glucose tolerance test (OGTT), but only imeglimin significantly enhanced insulin and C-peptide secretion, improving β-cell function over time. Imeglimin uniquely increased GIP levels and demonstrated a time-dependent shift in incretin-driven insulin secretion, correlating with GLP-1 at 12 weeks and GIP at 24 weeks. Overall, imeglimin provided unique beta-cell and incretin-related benefits with sustained HbA1c reductions.[29]

Results of the present study showed that imeglimin at a dose of 180 mg/kg/day has more favourable serum urea and creatinine levels changes in diabetic rats and, therefore, has more renal safety as compared to metformin at a dose of 180 mg/kg/day. The metformin and imeglimin treated groups showed significant reduction in blood glucose level compared with both the diabetic control and toxic control groups. In contrast, when the metformin treated group was compared to the imeglimin treated group on the 21st day, the blood glucose levels had no significant difference.

The limitation of this study is the lack of comprehensive parametes, such as histopathological analysis and inflammatory markers to provide a more detailed comparison of the renoprotective effects of metformin and imeglimin.

CONCLUSION

The present study evaluated and compared the efficacy and renal safety of metformin and imeglimin in gentamicin induced nephrotoxicity in streptozotocin-nicotinamide induced diabetic animal models, although the glycemic control was not significantly different, imeglimin showed better renal safety than metformin.

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