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Research Article

A PHARMACOKINETIC DOSE-VARIATION STUDY OF METFORMIN AND GEMIGLIPTIN PHARMACOVIGILANCE, AND THE CLINICAL PHARMACOLOGICAL SIGNIFICANCE OF RECENT ANTI-DIABETIC PHARMACEUTICALS

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ABSTRACT

Introduction: Anti-diabetic biguanides, like metformin, cause activation of AMP dependent protein kinase, and overcomes insulin resistance. Anti-dipeptidyl peptidase-4hypoglycaemic drugs, like gemigliptin, cause augmented beta-cell function by ameliorating the anti-beta cell apoptotic serum incretins, such as, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide.
Objectives: The objective of this study was to evaluate metformin and gemigliptin pharmacovigilance with pharmacokinetic dose-variation, and the clinical pharmacological significance of recent anti-diabetic pharmaceuticals.
Methods: In this study, new early grade type II diabetic, Group A = 50 patients, were prescribed oral 250 mg metformin once daily, for 43 days, and then 500 mg metformin once daily, for the next 43 days, and further; and Group B = 50 patients, were prescribed oral 25 mg gemigliptin once daily, for 43 days, and then 50 mg gemigliptin once daily, for the next 43 days, and further. The safety assessment was done by the monitoring of adverse drug reactions, like hypoglycaemia, weakness, gastrointestinal disturbances, abdominal pain and upper respiratory tract infections, in Group A, and nasopharyngitis, hypoglycaemia, gastrointestinal disturbances, headache, nausea, rashes, urticaria, oedema, and weakness, in Group B, with Adverse Event Case Report Forms, on days 0, 43, 86, and on further follow-ups, with statistical analysis of the study findings. The clinical pharmacological significance of metformin and gemigliptin was also analysed.
Results: In this study, there was absence of any significant occurrence of adverse drug reactions, on days 0, 43, 86, and on further follow-ups, with accelerating doses of metformin and gemigliptintherapy. The analysis demonstrated ample clinical pharmacological significance of metformin and gemigliptin.
Conclusions: Metformin and gemigliptin were safe and tolerable, with anti-diabetic pharmacotherapeutic drug-dose variations, with requisite clinical pharmacological significance.

INTRODUCTION

The American Association of Clinical Endocrinologists (AACE) provides guidelines for type II diabetes mellitus (T2DM) management, which emphasises on the individual goals of achieving haemoglobin A1C (HbA1C) level of ≤ 6.5%. The choice of anti-diabetic agents considers different patient characteristic factors, like glycaemic index, efficacy, impact on weight, undesirable adverse effects of pharmaco-therapeutic management, cardiovascular and renal co-morbidities, lifestyle, economy, and patient preferences. The predominant associated adverse effects of oral hypoglycaemic agents, include hypoglycaemia, weight gain due to hyperinsulinaemia, gastrointestinal symptoms, and hepato-

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renal toxicity. The prevailing increase in adverse drug reactions requires a safer anti-diabetic agent, the choice for which depends on the drug's potential for hypoglycaemia, weight gain, and long term adverse drug reactions.[1, 2]

Diagnostic Criteria of type II diabetes mellitus by American Diabetes Association include the following.

1. A fasting plasma glucose (FPG) level of 126 mg/dl (7.0 mmol/L) or higher, or.
2. A 2-hour plasma glucose level of 200 mg/dl (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), or.
3. A random plasma glucose of 200 mg/dl (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or.
4. A haemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol), or higher.[3]

Objectives

The objective of this study was to evaluate metformin and gemigliptin pharmacovigilance with pharmacokinetic dose-variation, and the clinical pharmacological significance of recent anti-diabetic pharmaceuticals.

METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements. An informed consent was obtained from each patient.

Selection criteria of the patients

Inclusion Criteria

The inclusion criteria were as follows : (i) patients of any gender, (ii) patients within 35 and 60 years, (iii) patientsof around 60 kg average body weight, (iv) patients presenting with new type II diabetes mellitus, of early grade, (v) type II diabetes mellitus American Diabetes Association diagnosis criteria,[2] (vi) co-operative and conscious patients, (vii) patients willing to undergo all pre and post- treatment investigations and willing to complete the entire course of treatment, (viii) patients who have given consent and are willing to go for a follow-up, (ix) patients not taking any previous anti-diabetic drug, (x) patients not taking any concomitant medication.

Exclusion Criteria

The exclusion criteria were as follows : (i)uncooperative or unconscious patients, (ii) patients below 35 and above 60 years, (iii) patients presenting with any grade other than moderate grade of diabetes, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high risk diseases or co-morbidities, (vi) cardiac, renal or any other associated complications or co-morbidities, (vii) any chronic disease intervening with the study data, (viii) pregnant or lactating women, (ix) paediatric or geriatric patients, (x) other associated medical illness or disorders, like uro-genital tract infections, having impact on study results, (xi) female patients using hormonal contraceptives.

Study Design

The study design was a multi-centre, prospective, randomized, open-labelled study; and a clinical pharmacological analytical study.

Study Population

The study population was 100 new global early grade type II diabetes mellitus patients.

Study Period

The study period was 1 year, fromJune, 2015 to July, 2015; from November, 2020 to July, 2021; and December, 2021.

Place of Study

The research study and the compilation of the study literature was conducted in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacovigilance, Pharmacogenomics, Internal Medicine, Endocrinology, Diabetology, Pathology, Clinical Pathology, and Molecular Diagnostics, in Dr.MoumitaHazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College and Hospitals, J.J.M. Medical College and Hospitals, Chigateri General Hospital, and Mahuya Diagnostic Centres and Doctors' Chambers.

Study Procedure

In this study, new early grade type II diabetic, Group A = 50 patients, were prescribed oral 250 mg metformin once daily, for 43 days, and then 500 mg metformin once daily, for the next 43 days, and Group B = 50 patients, were prescribed oral 25 mg gemigliptin once daily, for 43 days, and then 50 mg gemigliptin once daily, for the next 43 days.

The patients' characteristics, diabetic symptoms assessment, patients' disease and disease-related history were recorded with a study proforma. Then, thorough general physical examination and systemic examination were performed on the patients under study. The relevant blood, urine and other investigations were done to confirm the progressing health status of the patients being treated.

The efficacy assessment was done, by recording the fasting and the post-prandial blood sugar level, HbA1c level and urine routine examination findings including sugar and albumin levels and microscopy, after metformin or gemigliptin therapy.

The safety assessment was done by the monitoring of adverse drug reactions, with Adverse Event Case Report Forms, (i) on day 0, (ii) on day 43 (for any adverse effect between day 0 to day 43), (iii) on day 86 (for any adverse effect between day 43 to day 86), and (iv) on further follow-ups, after metformin and gemigliptin treatment. The safety assessment was done by the monitoring of adverse drug reactions, like hypoglycaemia, weakness, gastrointestinal disturbances, abdominal pain and upper respiratory tract infections, in Group A, and nasopharyngitis, hypoglycaemia, gastrointestinal disturbances, headache, nausea, rashes, urticaria, oedema, and weakness, in Group B, on days 0, 43, 86, and on further follow-ups, and the findings were statistically analysed.

Statistical Analysis

The observations recorded in this study, were statistically analysed by the Z Test for Proportions and the Test of

Significance with p values, with subsequent tabular representations. The clinical pharmacological significance of the long-time anti-diabetic pharmaceutical metformin and the recent anti-diabetic pharmaceutical gemigliptin was also analytically delineated.

RESULTS

The demographic characteristics of the patients were comparable. The comprehensive pharmacovigilance evaluation, corresponding to the pharmacokinetic step-wise dose-acceleration, was conducted on the new global early moderate grade, type II diabeticpatients, that is, among Group A = 50 patients, receivingoral 250 mg metformin once daily and Group B = 50 patients, receiving oral 25 mg gemigliptin once daily, for 43 days, and then Group A patients receiving oral 500 mg metformin once daily, and Group B patients receiving oral 50 mg gemigliptin once daily, for the next 43 days, and on further follow-ups.

As depicted in Table 1, on day 0,in both Group A and Group B, before the oral metformin and gemigliptin treatment, there was absence of any significant symptomatic observation of any previously occurring adverse effect-like symptom, such as, hypoglycaemia, abdominal pain, upper respiratory tract infections, nasopharyngitis, gastrointestinal disturbances, headache, nausea, rashes, urticaria, oedema, and weakness, which indicates the absence of any causal association of the occurrence of any adverse effect-like symptom to any previously existing factor, other than the drug metformin or gemigliptin.

As depicted in Table 2,both in Group A and Group B, there was absence of any significant occurrenceof adverse effects, such as, hypoglycaemia, abdominal pain, upper respiratory tract infections, nasopharyngitis, gastrointestinal disturbances, headache, nausea, rashes, urticaria, oedema, and weakness, on day 43 (occurrence of adverse effects between day 0 and day 43), after the oral 250 mg metformin or 25 mg gemigliptin treatment.

As depicted in Table 3, there was absence of any significant occurrence of adverse effects, such as, hypoglycaemia, abdominal pain, upper respiratory tract infections, nasopharyngitis, gastrointestinal disturbances, headache, nausea, rashes, urticaria, oedema, and weakness, on day 86 (occurrence of adverse effects between day 43 and day 86), after the oral 500 mg metformin or 50 mg gemigliptin treatment.

As depicted in Table 4, there was absence of any significant occurrence of adverse effects, such as, hypoglycaemia, abdominal pain, upper respiratory tract infections, nasopharyngitis, gastrointestinal disturbances, headache, nausea, rashes, urticaria, oedema, and weakness, on further follow-ups (occurrence of adverse effects after day 86), after the oral 500 mg metformin or 50 mg gemigliptin treatment.

Therefore, no significant adverse effects were observed among the patients due to the administration of oral metformin or gemigliptin, during step-wise accelerating dose-variations. This emphasises the safety and tolerability of both the pharmacotherapeutic approaches, among new early grade type II diabetic patients, who require these oral hypoglycaemic drug treatments, accompanied by step-wise dose acceleration, for appropriate control and stabilisation of serum glycaemic status.

Table 1 Day 0: The occurrence of any previously occurring adverse effect-like symptom beforeoral 250 mg metformin or 25 mg gemigliptin treatment

Any Previously Occurring Adverse Effect-Like Symptom On Day 0	Number of Patient Occurrencebefore 250 Mg Metformin Treatment n (%)	Number Of Patient Occurrence Before 25 mg Gemigliptin Treatment n (%)	Z Value	p Value
Hypoglycaemia	0 (0%)	0 (0%)	-	non-significant
Abdominal pain	0 (0%)	0 (0%)	-	non-significant
Upper respiratory tract infections	0 (0%)	0 (0%)	-	non-significant
Nasopharyngitis	0 (0%)	0 (0%)	-	non-significant
Gastrointestinal disturbances	0 (0%)	0 (0%)	-	non-significant
Headache	0 (0%)	0 (%)	-	non-significant
Nausea	0 (0%)	0 (%)	-	non-significant
Rashes	0 (0%)	0 (%)	-	non-significant
Urticaria	0 (0%)	0 (%)	-	non-significant
Oedema	0 (0%)	0 (%)	-	non-significant
Weakness	0 (0%)	0 (%)	-	non-significant

Table 2 Day 43 The occurrence of adverse effects after oral 250 mg metformin or 25 mg gemigliptin treatment

Adverse Effects on Day 43	Number of Patient Occurrence With 250 mg Metformin n (%)	Number of Patient Occurrence With 25 mg Gemigliptin n (%)	Z Value	p Value
Hypoglycaemia	0 (0%)	0 (0%)	-	non-significant
Abdominal pain	0 (0%)	0 (0%)	-	non-significant
Upper respiratory tract infections	0 (0%)	0 (0%)	-	non-significant
Nasopharyngitis	0 (0%)	0 (0%)	-	non-significant
Gastrointestinal disturbances	0 (0%)	0 (0%)	-	non-significant
Headache	0 (0%)	0 (%)	-	non-significant
Nausea	0 (0%)	0 (%)	-	non-significant
Rashes	0 (0%)	0 (%)	-	non-significant
Urticaria	0 (0%)	0 (%)	-	non-significant
Oedema	0 (0%)	0 (%)	-	non-significant
Weakness	0 (0%)	0 (%)	-	non-significant

Table 3 Day 86: The occurrence of adverse effects after oral 500 mg metformin or 50 mg gemigliptin treatment

Adverse Effects On Day 86	Number of Patient Occurrence With 500 mg Metformin n (%)	Number of Patient Occurrence With 50 mg Gemigliptin n (%)	Z Value	p Value
Hypoglycaemia	0 (0%)	0 (0%)	-	non-significant
Abdominal pain	0 (0%)	0 (0%)	-	non-significant
Upper respiratory tract infections	0 (0%)	0 (0%)	-	non-significant
Nasopharyngitis	0 (0%)	0 (0%)	-	non-significant
Gastrointestinal disturbances	0 (0%)	0 (0%)	-	non-significant
Headache	0 (0%)	0 (%)	-	non-significant
Nausea	0 (0%)	0 (%)	-	non-significant
Rashes	0 (0%)	0 (%)	-	non-significant
Urticaria	0 (0%)	0 (%)	-	non-significant
Oedema	0 (0%)	0 (%)	-	non-significant
Weakness	0 (0%)	0 (%)	-	non-significant

Table 4 Follow-ups: The occurrence of adverse effects after oral 500 mg metformin or 50 mg gemigliptin treatment

Adverse Effects on Follow-UPS	Number of Patient Occurrence With 500 mg Metformin n (%)	Number of Patient Occurrence With 50 mg Gemigliptin n (%)	Z Value	p Value
Hypoglycaemia	0 (0%)	0 (0%)	-	non-significant
Abdominal pain	0 (0%)	0 (0%)	-	non-significant
Upper respiratory tract infections	0 (0%)	0 (0%)	-	non-significant
Nasopharyngitis	0 (0%)	0 (0%)	-	non-significant
Gastrointestinal disturbances	0 (0%)	0 (0%)	-	non-significant
Headache	0 (0%)	0 (%)	-	non-significant
Nausea	0 (0%)	0 (%)	-	non-significant
Rashes	0 (0%)	0 (%)	-	non-significant
Urticaria	0 (0%)	0 (%)	-	non-significant
Oedema	0 (0%)	0 (%)	-	non-significant
Weakness	0 (0%)	0 (%)	-	non-significant

The analysis of the clinical pharmacological significance of the long-time anti-diabetic pharmaceutical metformin manifested its unfading beneficial effects, even in recent times, almost as the first-line or down-stream oral hypoglycaemic pharmacotherapeutic drug, with extremely steady drug safety and tolerability levels, along with its wide-spread conventional applications as an anti-diabetic drug. While, as a recent anti-diabetic pharmaceutical, gemigliptin, has manifested the clinical pharmacological pleiotropic potential of gemigliptin for a wide-ranged therapeutic applications, thus, re-emphasising the efficiency and suitability, in the anti-diabetic multi-system endocrinological pharmacotherapy, most importantly, preventing, as well as reducing the severe diabetic type II complications.

DISCUSSION

Metformin, an anti-diabetic biguanide, causes complex I inhibition, leading to activation of 5' adenosine monophosphate (AMP) activated protein kinase, in therapeutically irrelevant supra-pharmacological (>1 mM) metformin concentration, which may overcome insulin resistance and lower serum glucose levels. Metformin is effective, especially on HbA1C and weight, safe, inexpensive, and reduces the risk of cardiovascular events, and subsequent mortality. Recently, several hypotheses have described that metformin alters cellular redox balance, by a redox-dependent mechanism of action. Clinically relevant (50-100 μM) concentrations of metformin inhibit hepatic gluconeogenesis in a substrate selective manner both *in vitro* and *in vivo*, and lowers blood glucose, in turn, regulated by the distinct mechanisms of:

(a)Transcription: alterations in expression of gluconeogenic genes under the control of Forkhead box O (FOXO) and cAMP-responsive element-binding protein 1 (CREB) are often used as a readout of gluconeogenic regulation. The CREB–CREB-binding protein (CBP)–CREB-regulated transcription co-activator 2 (CRTC2) transcriptional complex increases expression of glucose-6-phosphatase (G6pc) and phosphoenolpyruvate carboxykinase 1 (Pck1), 2 gluconeogenic genes. The formation of this complex is stimulated by glucagon and catecholamines, as well as by fasting conditions. Additionally, the FOXO family of transcription factors stimulate G6pc and Pck1 expression. In response to insulin activation of AKT, FOXO proteins are phosphorylated and excluded from the nucleus, thus negatively regulating gluconeogenic gene expression.

(b)Allosteric mechanism: Hepatic gluconeogenesis is regulated by acetyl-coenzyme A (acetyl-CoA), an allosteric activator of pyruvate carboxylase. Pyruvate carboxylase catalyzes the conversion of pyruvate to oxaloacetate, a key anaplerotic reaction that supplies carbon for gluconeogenesis; it is also the first committed step in the gluconeogenic pathway. Following white adipose tissue (WAT) lipolysis, nonesterified fatty acids (NEFA) from the adipocyte are taken up by the liver, where β-oxidation produces acetyl-CoA, which subsequently binds to and allosterically activates pyruvate carboxylase. This extrahepatic mechanism of liver gluconeogenic regulation plays an important role in the maintenance of euglycemia, as hepatic insulin signaling is not sufficient to suppress hepatic gluconeogenesis.

(c)Substrate availability: Hepatic gluconeogenesis is also indirectly regulated by glycerol delivery to the liver by WAT lipolysis, which contributes about 20% to 30% of hepatic gluconeogenesis. In contrast to allosteric control of hepatic gluconeogenesis by NEFA-derived acetyl-CoA, glycerol from WAT lipolysis increases gluconeogenesis and HGP by a substrate-push mechanism. Glycerol enters the gluconeogenic

pathway when it is phosphorylated and converted to dihydroxyacetone phosphate (DHAP) by mitochondrial glycerol-3-phosphate dehydrogenase (GPD2). The reaction catalyzed by GPD2 is also redox-dependent and inhibited by an increase in the cytosolic redox state.

(d)Redox mechanisms: Redox regulation of hepatic gluconeogenesis is dependent on both the [NADH]:[NAD+] ratio and the nature of the gluconeogenic substrate. Redox balance is maintained by the continuous function of 2 redox shuttles: the malate-aspartate shuttle and the α-glycerophosphate shuttle. Perturbation of this balance of reducing equivalents can directly impact gluconeogenesis from redox-dependent substrates. Lactate, which reduces NAD+ to NADH during its conversion to pyruvate by lactate dehydrogenase, and glycerol, which feeds into the α-glycerophosphate redox shuttle through GPD2, are considered redox-dependent substrates. Conversely, alanine, pyruvate, and DHAP are redox-independent because their entry to the gluconeogenic pathway does not require NAD+ or NADH. Thus, a reduced cytosol, with a high [NADH]:[NAD+] ratio, will inhibit gluconeogenesis from lactate and glycerol, but not pyruvate, alanine, and DHAP. This regulatory mechanism is especially pertinent in the context of obesity and T2D due to dysregulated WAT lipolysis and increased glycerol supply to the liver. Therefore, inhibition of gluconeogenesis from glycerol may disproportionately benefit individuals with poorly controlled T2D with dysregulated WAT lipolysis. Metformin inhibition of GPD2 has been shown to increase cytosolic redox by disrupting the α-glycerophosphate redox shuttle, leading to an increase in the cytosolic redox state (increased cytosolic [NADH]:[NAD+]) resulting in inhibition of gluconeogenesis specifically from glycerol and lactate. Increased cytosolic redox state, due to metformin inhibition of glycerol-3-phosphate dehydrogenase, which is the only mechanism of action involved in substrate-selective (glycerol and lactate) inhibition of hepatic gluconeogenesis. While muscle and gut microbiota effect is scondary. Metformin has an oral bioavailability of about 60%, and accumulates in the small intestine, liver and kidney, due to the expression of OCT1, OCT3 and PMAT transporters in these tissues, causing an intestinal mechanism for metformin's glucose-lowering effects and the gastrointestinal side effects. In recent years, the clinical benefits of metformin have been linked to alterations in gut microbiome composition, intestinal glucose uptake, and hormone, eg. growth differentiation factor 15 (GDF 15), glucagon-like peptide-1 secretion. Metformin-induced activation of the integrated stress response pathway leads to GDF15 secretion, which improves glycaemic regulation and reduces appetite. Another mechanism implicating intestinal metformin action, includes augmented GLP-1 secretion, delayed gastric emptying, and altered enterocyte glucose metabolism.

A more recently proposed mechanism of action of metformin is increased cytosolic redox due to inhibition of hepatic GPD2 activity.[4]

The findings of a recent study in a racially diverse population demonstrate that diabetes is an independent risk factor associated with increased mortality in individuals withCOVID-19, whereas metformin treatment is associated with dramatically reduced mortality in subjects with T2D even after correcting for multiple covariates, with the possibility that metformin may provide a protective approach in high risk population. This effect remained even after correcting for age, sex, race, obesity, and hypertension orchronic kidney disease and heart failure.

In another study, metformin was associated with decreasedmortality in hospitalized COVID-19 patients with diabetes. In yet another study, metformin was also found to be associated with reducedrisk of early death.

In a very recent study, metformin was suggested to be associated with decreased mortality in women with COVID-19. Metformin has been shown to also have anti-inflammatory, anti-thromboticand excessive inflammatory responses, e.g.,cytokine storm as well as disseminated thromboembolic eventshave been recognized as deadly complications of COVID-19infection. By exerting some of its anti-fibrinolytic activities and inhibitinginflammatory cytokines, such as tumor necrosis factor alpha orinterleukin-6, suspected to play a role in the immuneresponse to COVID-19, metformin might improveoutcome. In fact, even prior to the COVID-19 pandemic, preadmission metformin use was found to be associated with reduced mortality in medical and surgical intensive care patients with T2D.[5]

The clinical pharmacological analysis of gemigliptinelucidated several hypotheses which have specified that DPP-4 inhibitors might accelerate beta cell regeneration, prevention from pancreas islet hypertrophy and insulin. Gemigliptin also causes augmented beta-cell function by ameliorating the anti-beta cell apoptotic serum incretins, such as, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. They might also improve the beta-cell function, which remains unaltered with the food intake, although some studies found no change in the incretin effect. They might even facilitate the adaptability of the beta-cells to insulin resistance, in consequence causing a glucose overload, with a decreasein the overall insulin exposure and the proinsulin-to-insulin ratio.[6, 7]

In this study, there was absence of any significant occurrence of adverse effects, on days 0, 43, 86 and further follow-ups, with varying dose-increase of metformin or gemigliptin therapy, thus emphasising on the safety and tolerability of both the oral hypoglycaemic drugs, among global type II diabetic patients. This study also strengthened the unfading clinical pharmacological implications of metformin and gemigliptin, in the treatment of type II diabetes mellitus.

CONCLUSION

As a conclusion, in this study, there was absence of any significant occurrence of adverse effects, on days 0,43, 86 and further follow-ups, with oral metformin or gemigliptin therapy. Therefore, through this study, it was concluded that gemigliptin was safe and tolerable, with varying drug doses increase. The qualitative analysis of the clinical pharmacological significance of these recently prevailing pharmaceuticals, metformin and gemigliptin, showed their much beneficial effects in the pharmacotherapy of type II diabetes mellitus.

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References

1. American Diabetes Association. Pharmacologic approaches to glycaemic treatment: Standards of medical care in diabetes – 2021. Diabetes Care 2021; 44 (Suppl. 1): S111–S124.
2. Mohan V, Mithal A, Joshi SR, Aravind SR, Chowdhury S. Remogliflozin Etabonate in the Treatment of Type 2 Diabetes: Design, Development, and Place in Therapy. Drug Des DevelTher 2020; 14: 2487–2501.
3. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes – 2020. Diabetes Care 2020; 43(Suppl. 1): S14-S31.
4. LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. Endocr Rev 2021; 42(1): 77–96.
5. Crouse AB, Grimes T, Li P, Might M, Ovalle F, Shalev A. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. Front Endocrinol 2021; 11: 600439.
6. Le TD, Nguyen NTP, Nguyen ST, Tran HTT, Nguyen LTH, Duong HH, Nguyen HM, Do BN. Sitagliptin increases beta-cell function and decreases insulin resistance in newly diagnosed Vietnamese patients with type 2 diabetes mellitus. Diabetes MetabSyndrObes: Targets Ther 2020; 13: 2119–2127.
7. Hazra M. A clinical pharmacological study of the prevalent prescription patterns of metformin, sitagliptin and gemigliptin among the early moderate grade new type II diabetes mellitus patients in global tertiary care hospitals. *Int J Pharm Sci Rev Res* 2021; 70(1): 180-184.

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