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Efficacy and Safety of Dipeptidyl Peptidase-4 (DPP-4) Inhibitor in Patient Type 2 Diabetes Mellitus with Renal Disorder: A Narrative Review

Anjeli Khairunnisa[1], Widya Kardela[1], Sri Oktavia[1]
School of Pharmaceutical Science Padang (STIFARM Padang), West Sumatera, Indonesia, 25147

Abstract:
Background*: The careful selection of oral antidiabetic drugs for diabetic patients with comorbid kidney disorder is very important so that the drugs used are appropriate and in accordance with the patient's body condition so as to achieve maximum therapeutic effect and minimal side effects. DPP-4 Inhibitor belongs to the class of anti-diabetic drugs that have good efficacy in the treatment of diabetes with low side effects at all stages of kidney disease. DPP-4 Inhibitors have minimal risk for hypoglycemia, besides that they have the advantage of not changing body weight.*
Methods*: This narrative review article aims to describe the efficacy and safety of DPP-4 type 2 diabetes mellitus drugs in type 2 diabetes mellitus patients who have comorbid kidney disorders.*
Results*: Literature search was carried out systematically using 3 databases, namely PubMed, ScienceDirect and Google Scholar in the last 20 years, namely 2001-2021. The inclusion criteria were based on articles that discussed the efficacy and safety of DPP-4 inhibitor drugs in patients with comorbid kidney disorders.*
Conclusion: *A review of these articles proves that DPP-4 inhibitor drugs are effective, and side effects are well tolerated in diabetic patients with comorbid kidney disorders.*
Key Word*: Efficacy, safety, DPP-4 inhibitor, type 2 diabetes mellitus.*

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I. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder because the pancreas does not produce enough insulin or the body cannot use the insulin it produces effectively[1].

One way to control blood glucose levels is through inhibition of dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitors can be used as monotherapy or in combination and can be used as first, second, and third line therapy[2,3]. DPP-4 inhibitors are recommended as second-line therapy in patients who are poorly controlled with metformin, thiazolidinediones, or sulfonylureas[2,4]. Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) are a new class of antidiabetic drugs with a very favorable profile, and the side effects are well tolerated. Dipeptidyl peptidase-4 (DPP-4) inhibitors are safe for long-term use with a low incidence of adverse events (AEs), including hypoglycemia[5–8], gastrointestinal disturbances, edema[6] and neutral to body weight[2,7–12].

Kidney disorders and kidney failure are both serious health problems, although they each present in different ways. Patients with chronic kidney disease (CKD) often have no symptoms or signs, until the remaining kidney function is less than 15%[13]. One of the most common causes of CKD is type 2 diabetes mellitus (T2DM). In controlling glucose in people with T2DM with CKD, there are important things to consider in the selection of oral antidiabetic drugs (OAD), which is related to the risk of hypoglycemia because an increase in the incidence of hypoglycemia will also increase the incidence of cardiovascular complications and can prolong the work of OAD, because most the drug is excreted in the kidneys. In addition, the role of OAD in inhibiting the progression of CKD, as assessed by a worsening of the glomerular filtration rate (GFR) and/or albuminuria, is also an important aspect that needs to be considered in selecting OAD in T2DM patients with CKD[14].

Groups of OAD that do not cause hypoglycemia include: DPP-4 inhibitors, biguanides, thiazolidinediones (TZD), alpha-glucosidase inhibitors, sodium glucose co-transporter 2 (SGLT-2) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists. While the OAD groups that can cause hypoglycemia are: sulfonylureas (SU), and glinides [2]. Sulfonylureas (SU) drugs are known to have a high potential to cause hypoglycemia in patients with impaired kidney function. Metformin from the biguanide group has the potential to cause lactic acidosis and nephrotoxicity, while glitazone can worsen water and sodium retention in patients with impaired renal function[15].

Based on this, this review article was written to describe the efficacy and safety of DPP-4 inhibitors type 2 diabetes mellitus drugs for type 2 diabetes patients with comorbid kidney disorders.

Table 1: DPP-4 inhibitor drugs group

DPP-4 inhibitor drugs group	
Vildagliptin	Anagliptin
Sitagliptin	Gemigliptin
Saxagliptin	Teneligliptin
Linagliptin	Evogliptin
Allogliptin	Trelagliptin
Omarigliptin	

II. Methods

Data extraction: For the narrative review of this article, identification of full-text articles in English was carried out by searching on PubMed, ScienceDirect and Google Scholar in the last 20 years, namely 2001-2021. The keywords used were ((Efficacy) AND (safety)) AND (DPP-4 inhibitor)) AND (comorbid))).

Study selection: Inclusion criteria in this review were with the following characteristics: efficacy and safety of DPP-4 inhibitors diabetes mellitus drugs against type 2 diabetes mellitus patients, and comorbid kidney disorder. The exclusion criteria were article titles that did not match the topic, review articles, case studies, not research articles, articles with other groups of OAD, articles without comorbidities, and paid articles. The process and stages of the narrative review in this review use PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analysis) diagrams as documentation of the process of searching, filtering and selecting articles to obtain articles that can be used in the narrative review of this article. The PRISMA diagram can be seen in Figure 1. Quality assessment in this review was to exclude and include research that would be included based on quality. The assessment of the quality of the articles used was based on the following: title, abstract, research design, exclusion and inclusion criteria. When the screening process has been passed, data extraction was carried out so that it is known that each article that has been screened has met the requirements for use. Data extraction was then developed, tested, and filtered.

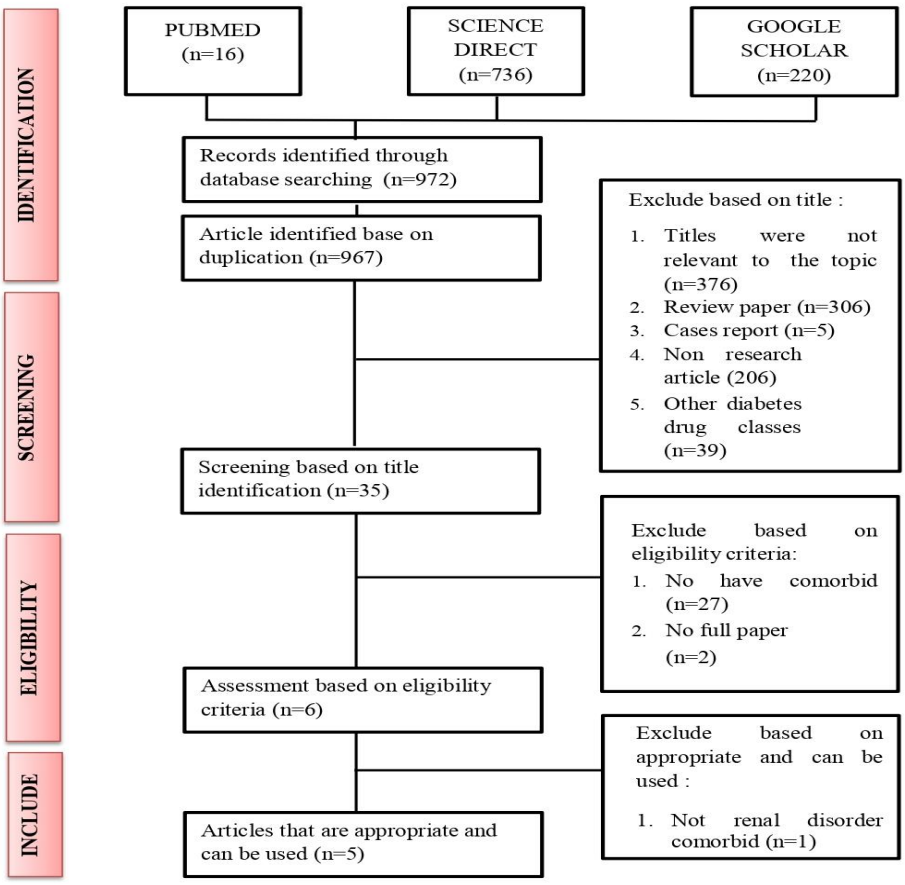

Figure 1. PRISMA Diagram

III. Result

It can be seen in Figure 1, the first stage is identification. A total of 972 articles were found through the 3 databases used (PubMed, ScienceDirect, and Google scholar) based on keywords that matched this review. Then further identification was carried out to eliminate 972 articles based on duplication. A total of 5 articles were found to have articles similar to other databases, so this article was removed and the remaining were 967 articles. The screening stage was then carried out based on the title of the article, as many as 932 articles were omitted due to several reasons such as: 376 titles were not in accordance with the topic, 5 titles were case studies, 306 titles were review articles, 206 titles were non-research articles, 39 titles were research articles that did not use type 2 diabetes drugs, the DPP-4 inhibitors. From the title screening, 35 articles were obtained.

Furthermore, an assessment was carried out based on eligibility criteria, as many as 29 articles were excluded, 27 articles did not have comorbidities and 2 articles were not full text. Then one article was excluded with comorbid non-kidney disorders. Thus, 5 articles were finally selected in the last 10 years, namely 2011-2021. Afterwards, further review was carried out by making an extraction table consisting of titles, methods, drug use, efficacy parameters, safety parameters, results and conclusions. The PRISMA diagram is used in this review as evidence and documentation of the steps taken by the author in identifying, screening until articles meet the eligibility criteria for use in this article review.

Efficacy of DPP-4 inhibitor

A. Hemoglobin A1c (HbA1c) decreased in patient type 2 diabetes mellitus with renal disorder

a.) Vildagliptin

Vildagliptin (50 mg/day) was compared with placebo in patients with moderate or severe kidney impairment. Its efficacy persisted for 52 weeks of treatment. Decreased HbA1c of vildagliptin vs placebo (-0.7% vs -0.3%) moderate renal impairment and (-0.7% vs -0.1%) severe renal impairment from baseline 7.8%. Patients who achieved HbA1c <7%, vildagliptin vs placebo (36% vs 26%) moderate renal impairment, and (53% vs 17%) severe renal impairment[16].

b.) Linagliptin

Linagliptin (5 mg/day) was compared with placebo in patients with mild or moderate renal impairment baseline HbA1c 8.0-8.2%. After 24 weeks of treatment the decrease in HbA1c with linagliptin vs placebo (-0.67% vs -0.07%) mild renal impairment and (-0.53% vs -0.07%) moderate renal impairment[7].

c.) Sitagliptin

Sitagliptin (100 mg/day) was compared with dapagliflozin (5-10 mg/day) in patients with mild renal insufficiency at baseline 7.7-7.8%. After 24 weeks of treatment the decrease in HbA1c with sitagliptin vs dapagliflozin in mild renal insufficiency 0.51%[17] vs 0.36%[18]. In patients on metformin background, HbA1c decreased (-0.50% vs -0.35%) sitagliptin vs dapagliflozin. And in patients with metformin background therapy in combination with a sulfonylurea HbA1c decreased (-0.40% vs -0.45%) sitagliptin vs dapagliflozin[18]. Patients who achieved HbA1c <7%, sitagliptin group vs. dapagliflozin group (42.6% vs 27.0%) [17] and (41.1% vs 28.2%)[18].

d. Omarigliptin

Omarigliptin (12.5-25 mg/day) was compared with placebo in patients with moderate or severe renal impairment. In patients with moderate renal impairment (Omarigliptin vs placebo) HbA1c decreased (-0.68% vs -0.06%) from baseline 7.7% and in patients with severe renal impairment HbA1c decreased (-0.80% vs -0.88%) from baseline 7.7%. Patients who achieved HbA1c <7% with omarigliptin vs placebo (31.1% vs 34.2%)[19].

B. Fasting plasma glucose (FPG) decreased in patient type 2 diabetes mellitus with renal disorder

a.) Vildagliptin

Vildagliptin was compared with placebo with a baseline of 9.1 mmol/l for moderate renal impairment and 8.2 mmol/l for severe renal impairment. FPG value (-0.9 mmol/l) with vildagliptin in moderate renal impairment and (-1.8 mmol/l) in severe renal impairment. While the decrease in FPG from placebo was not explained[16].

b.) Linagliptin

Linagliptin was compared with placebo in patients with mild or moderate renal impairment in the baseline range of 9.0 – 9.5 mmol/l. In the mild renal impairment category, it decreased -1.2 mmol/l and -0.3 mmol/l in moderate renal impairment[7].

c.) Sitagliptin

Sitagliptin was compared with dapagliflozin in patients with mild renal insufficiency[17,18]. The baseline FPG was 9.0 mmol/l in the sitagliptin group and 9.2 mmol/l in the dapagliflozin group. FPG decreased (-0.9 mmol/l vs -1.1 mmol/l) sitagliptin vs dapagliflozin[17]. In another review article, baseline FPG was 163.2 mmol/l in the sitagliptin group and 165.0 mmol/l in the dapagliflozin group. Decreased FPG (-16.2 mmol/l vs -22.7 mmol/l) sitagliptin vs dapagliflozin, in patients on metformin therapy background. While the decrease in FPG in patients without background therapy or with metformin + sulfonylurea therapy was not explained[18].

d.) Omarigliptin

Omarigliptin was compared with placebo in patients with moderate renal impairment or severe renal impairment. Baseline FPG 9.5 mmol/l, decreased FPG value (-1.4 mmol/l vs -1.1 mmol/l)) in the omarigliptin vs placebo group[19].

Table 2 : Parameter of efficacy and safety endpoint

Ref.	Parameter Of Efficacy And Safety	
	Efficacy Endpoints	**Safety Endpoints**
[16]	1. HbA1C 2. FPG	1. AEs (Any AEs, Drug related AEs, Discontinuations due to AEs, Serious AEs) 2. Common AEs
[7]	1. HbA1C 2. FPG	1. AEs (Any AEs, Drug related AEs, Serious AEs) 2. Common AEs
[17]	1. HbA1C 2. FPG 3. 2-h PPGE 4. 2-h PPG 5. PP insulin 6. PP glucagon	1. AEs (Any AEs, Drug related AEs, Serious AEs, Discontinuations due to AEs) 2. Percentages of patients meeting predefined limits of changes (PDLC) in laboratory parameters 3. Vital sign 4. Body weight
[19]	1. HbA1C 2. FPG	1. AEs (Any AEs, Drug related AEs, Serious AEs) 2. Physical examination (Vital sign) 3. Laboratory blood chemistry (ALT,AST, total bilirubin, creatine kinase, alkaline phosphatase) 4. Lipid panel 5. Haematology 6. Urinalysis 7. Electrocardiogram
[18]	1. HbA1C 2. 2h-PPGE 3. 2-PPG 4. FPG	1. AEs (Any AEs, Drug related AEs, Serious AEs) 2. Hypoglycemia 3. Genital mycotic infection (GMI) 4. Urinary tract infection (UTI)

Safety of DPP-4 inhibitor

a.) Any adverse events (AEs)

Overall the percentage of each incidence of adverse events (AEs) was higher in the placebo group than in the DPP-4 inhibitors[16–19], except in the linagliptin group vs placebo with mild and moderate renal impairment[7].

b.) Drug-related AEs

The incidence of drug-related AEs with DPP-4 inhibitors (vildagliptin, linagliptin, omarigliptin) was the same as that of placebo[7,16,19], except for a comparison between the sitagliptin vs dapagliflozin (7.8% vs 13.7%) [17] and (7.6 vs 15.0) had higher drug-related AEs for dapagliflozin[18].

c.) Serious AEs

There was no significant difference between the DPP-4 inhibitors and control groups (placebo and dapagliflozin) [7,16–19].

d.) Genital mycotic infection

For sitagliptin 0.9% vs dapagliflozin 8.3%[18] and not rated in other articles.

e.) Urinary tract infection

The highest incidence was in the comparison group, vildagliptin vs placebo (5.7% vs 7.9%) in moderate renal impairment and (6.4% vs 10.9%) in severe renal impairment[16], and sitagliptin vs dapagliflozin (1.0% vs 2.5%) with mild renal insufficiency[18].

f.) Deaths

There was death (0.8% vs 0.0%) in the vildagliptin vs placebo group with moderate renal impairment and (3.2% vs 1.6%) with severe renal impairment[16]. In the omarigliptin vs placebo group (0.9% vs 0.9%) with moderate renal impairment and (1.9% vs 2.8%) with severe renal impairment[19].

g.) Hypoglycemia

The incidence of hypoglycemia was low, there was no significant difference between treatment groups[7,16,19]. In the 24-week omarigliptin group without insulin therapy background, there was no hypoglycaemia and low hypoglycemia at 54 weeks[19]. The study group on metformin therapy had a low incidence of hypoglycemia (3.3% vs. 3.3.6%) and (2.7% vs. 4.0%) sitagliptin vs. dapagliflozin. Meanwhile, against the background of sulfonylurea therapy, the incidence of hypoglycemia increased significantly (15.8% vs 16.0%) [17] and (15.0% vs 11.8%) [18] sitagliptin vs dapagliflozin.

h.) Body weights

Weight loss in the omarigliptin group was -0.6 kg and the placebo group was -1.5 kg from the baseline 80.0 - 84.2 kg[19]. In another study, body weight gain from baseline (83.3 – 85.2 kg) was higher in the dapagliflozin group (2.48 kg) than the sitagliptin group (1.44 kg)[18].

IV. Discussion

Efficacy is the ability of a drug to achieve a desired effect. Meanwhile, drug safety refers to the frequency of drug side effects, namely physical or laboratory toxicity that may occur related to the drug, which appears during treatment and does not exist before treatment, or becomes worse during treatment[20]. The monitoring of drug safety aspects must always be carried out to evaluate the consistency of its safety profile or risk-benefit ratio, where the benefit must be greater than the risk to support the safety assurance of circulating drugs[21]. Assessing the efficacy and safety of drugs is very important, especially in conditions of renal impairment, because patients with impaired renal function often have pharmacokinetic parameters, such as drug absorption, distribution, protein binding, biotransformation and renal excretion, which are different from patients with normal renal function. Most of the drug and its metabolites are eliminated through the kidneys, so adequate renal function is required to avoid drug toxicity. Patients may also exhibit an altered pharmacodynamic response to the drug administered because of the physiologic and biochemical changes associated with renal impairment. Selection and appropriate dosage of drugs for patients with chronic kidney disease (CKD) is important to avoid unwanted drug effects and to ensure optimal results[22].

From the article searches carried out, there are 5 articles that report the efficacy and safety of DPP-4 inhibitor drugs used in patients with mild, moderate to severe renal impairment and renal insufficiency compared with other antidiabetic drugs. Kidney damage category based on estimated glomerular filtration rate (eGFR) value. Where the value of eGFR in normal kidney conditions (≥90 ml/min/1.73 m²), mildly decreased (60-89 ml/min/1.73 m²), mildly to moderately decreased (45-59 ml/min/1.73 m²), moderately to severely decreased (30-44 ml/min/1.73 m²), severely decreased (15-29 ml/min/1.73 m²) and kidney failure eGFR <15 ml/min/1.73 m² [23,24]. The DPP 4 inhibitor class of drugs is an oral type 2 diabetes drug that can be given to patients with normal kidney conditions or those with mild to terminal kidney disorders (all stages of chronic kidney disease)[3,14,25], but the use of these DPP-4 drugs must use dose adjustments, because most of the metabolism occurs in the liver and kidneys and then into active metabolites which are then eliminated in the urine, except for linagliptin does not require dose adjustment in patients with normal renal function and with all stages of CKD [10], due to its complete elimination via bile[9,26,27]. The DPP-4 inhibitors used include sitagliptin 100 mg/day, omarigliptin 12.5 and 25 mg/day, vildagliptin 50 mg/day and linagliptin 5 mg/day. The dose of drug use per day from each research article is in accordance with the recommended dose[2].

The efficacy assessment according to the diabetes diagnostic criteria was based on the results of the fasting plasma glucose (FPG) test, plasma glucose 2-hours after the oral glucose tolerance test (OGTT) and HbA1c[2,28]. Among other blood tests, the HbA1c level test has several advantages over others. The HbA1c examination does not require the patient to fast, the results of the examination are not influenced by the patient's short-term lifestyle (food, drink and physical activity) because HbA1c describes the patient's long-term average blood sugar for 2-3 months[29].

The 5 articles overall assessed the efficacy of DPP-4 inhibitor drugs by examining HbA1c and FPG. In addition, there are 2 articles that examined 2-hour incremental postprandial glucose excursion (2h-PPGE), and 2-hour postprandial glucose (2h-PPG)[17,18]. And 1 article assessed 2-hour postprandial area under the curve (AUC_{0-120}) insulin (2h-PP insulin) and 2-hour postprandial area under the curve (AUC_{0-120}) glucagon (2h-PP glucagon) and PP insulin ratio: PP glucagon[17]. **(Table 2).**

In general, 24, 52 and 54 week studies of DPP-4 inhibitors have shown similar or better efficacy than placebo and another antidiabetic drug (dapagliflozin). The highest percentage difference in HbA1c reduction

between DPP-4 inhibitors vs placebo was in the group taking vildagliptin (-0.7% vs -0.3%) in moderate renal impairment, (-0.7% vs -0.1%) in severe renal impairment[16]. The range of decline in HbA1c DPP-4 inhibitors is around 0.5-0.8% [3,6], 0.5-0.9% [2] and 0.79-0.94% [30]. The decrease in HbA1c of DPP-4 inhibitor drugs from 5 articles reviewed was 0.3-0.8%[7,16–19].

Safety assessment based on all adverse events (AEs). Adverse events (AEs) are any unwanted medical events in patients or clinical research subjects who are given a pharmaceutical product and do not necessarily have a causal relationship with the treatment. Therefore, an adverse events can be in the form of an unfavorable and undesirable event (including abnormal laboratory results), symptoms, or diseases associated with the use of a medicinal product, whether or not considered to be related to the drug product[31,32]. Safety assessments included exposure levels, common side effects and changes in laboratory tests, serious or unexpected AEs or other significant adverse events including assessment of patients who discontinued the study (prematurely discontinued) due to AEs, and patients who died[33].

Overall drug safety was concluded based on any AEs, serious AEs, drug-related AEs, mortality, genital mycotic infection (GMI), urinary tract infection (UTI), incidence of hypoglycemia and body weight. Drug-related AEs were higher in dapagliflozin compared to DPP-4 inhibitors[17,18], whereas in the DPP-4 inhibitors vs placebo group the results were almost the same[7,16,19]. 4 articles assessed the number of patients who died in the trial, in 2 articles that conducted a 24 week trial with mild renal impairment no patient died (0.0% vs. 0.0%)[17,18]. In the vildagliptin vs placebo group, there was one death in the moderate renal impairment group. Patients in the vildagliptin treatment group, died suddenly at home for no apparent reason, this death was not suspected due to drug-related studies. In patients with severe renal impairment, there were three deaths (3.2%) in the vildagliptin group. One death was due to renal failure, 2 days after the last dose of the study drug, one was due to septic shock 1 month after discontinuation of the study, and the third was due to aortic surgery. There was one death in the placebo group with severe renal impairment (1.6%) due to complications of renal impairment. None of the deaths was thought to be related to the study drug[16]. In the omarigliptin vs placebo group with mild renal impairment, one patient in the omarigliptin group died of acute heart failure and in the placebo group one patient died of cardiac arrest[19].

Hypoglycemia is the side effect that most often occurs due to blood glucose lowering therapy in DM patients and intensive control can result in the risk of severe hypoglycemia. If this condition occurs, it will be very dangerous and can be life-threatening because blood glucose is the only source of energy in the brain, so that a decrease in levels from normal can directly affect and disrupt brain function[34]. There are 2 group with low incidence of hypoglycaemia, on the background of the drug metformin (3.3% vs. 3.3.6%)[17] and (2.7% vs. 4.0%)[18] in the study group sitagliptin vs dapagliflozin. When against a background of sulfonylurea drugs, rates of hypoglycemia were higher (15.8% vs 16.0%)[17] and (15.0% vs 11.8%)[18] in the sitagliptin vs dapagliflozin study group.

The 54-week study of omarigliptin (12.5-25 mg/day) versus placebo in a randomized, placebo-controlled, parallel-group, double-blind, and multicentre study, reported weight loss (-0.6% vs -1.5%) without other OAD drugs therapy background[19], and in the sitagliptin vs dapagliflozin group there was weight gain (1.44% vs 2.48%) against a sulfonylurea background[18]. Sulfonylureas are drugs that are widely used throughout the world, these drugs increase the risk of hypoglycemia and weight gain which are major problems in CKD patients[10]. Sulfonylureas drugs work by stimulating the release of insulin in pancreatic beta cells, increasing the sensitivity of beta cells to glucose, and lowering glucose levels in the blood. In addition, sulfonylureas also cause suppression of high overnight hepatic glucose output so that they can lower fasting blood glucose concentrations even more, but have an increased risk of hypoglycemia[34].

Other reported AEs include infection, cutaneous or vascular AEs, pancreatitis, cardiac disorders, peripheral oedema, decreased blood glucose, tremor, hyperhidrosis, diarrhea, hypertension, hyperkalemia[16], cough, hyperglycemia, upper respiratory tract infections[7], dizziness, and nasopharyngitis[7,16]. For diabetic patients with chronic kidney disease, they have a higher risk of cardiovascular disease[10]. In general, the DPP-4 inhibitors group showed the same or better efficacy and safety than placebo and other antidiabetic drugs.

V. Conclusion

DPP-4 inhibitors are effective and safe for use in patients with type 2 diabetes who have comorbid renal impairment at all stages, are at low risk of hypoglycemia, and generally well tolerated AEs.

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