SYSTEMATIC REVIEW

# The Differences in Efficacy of Vildagliptin as a Single Drug With Vildagliptin as a Combination With Metformin in Type 2 Diabetes Mellitus: A Systematic Review

Rada Citra Saputra[1], Iin Novita Nurhidayati Mahmuda[2]

[1] Medical Student, Faculty of Medicine, Muhammadiyah University of Surakarta, 57169 Gonilan, Kartasura, Sukoharjo, Central Jawa, Indonesia
[2] Internal Medicine Department, Faculty of Medicine, Muhammadiyah University of Surakarta, 57169 Gonilan, Kartasura, Sukoharjo, Central Jawa, Indonesia

## ABSTRACT

**Introduction:** In America, the prevalence of diabetes mellitus about 8.6% or 21 million adults in 2016. In Indonesia, the prevalence of diabetes mellitus has increased 2% from 2013-2018 for people aged more than 15 years. Vildagliptin was an oral antihyperglycemic drug class Dipeptidyl Peptidase-4 inhibitor which has been approved for use in type 2 diabetes mellitus. However, the benefits and risks of vildagliptin may be different for monotherapy and in combination especially with metformin. This systematic review will explain the efficacy of vildagliptin as monotherapy and vildagliptin in combination with metformin in type 2 diabetes patients. These findings can be used to develop treatment recommendations for type 2 diabetes mellitus sufferers. **Methods:** Data collection techniques for systematic review using Pubmed and Science direct for terms related to efficacy vildagliptin as single drug and efficacy vildagliptin as combination with metformin in HbA1c, FPG, risk hypoglycemia and weightloss of T2DM. The journals matched with the restriction criteria and PICO. The quality of the journals is tested using GRADE method. **Results:** Journal searches found 741 journals, 8 of which were eligible for systematic review with high quality journal by GRADE method. The review of 8 journals found that vildagliptin as combination with metformin has good efficacy and can reduce HbA1c (8.1±0.6% to 6.9±0.1%), FPG (141±15mg/dl to 106±4mg/dl), and lower risk of hypoglycemia and weightloss about 4.67±5.8kg for lowdose combination and 4.29±6.7kg for highdose combination. **Conclusion:** Vildagliptin is more effective in combination with metformin in T2DM patients than vildalgiptin as single drug.

**Keywords:** Type-2 diabetes mellitus, Vildalgiptin, Metformin, HbA1c, Combination

**Corresponding Author:**
Iin Novita Nurhidayati Mahmuda, M.Sc.
Email: innm209@ums.ac.id
Tel: +6281393050635

## INTRODUCTION

Diabetes mellitus was a chronic disease that occured when the pancreas was insufficient to produce insulin or when the body could not effectively used the produced insulin (1). In America, in 2016 the prevalence of diagnosed type-2 diabetes mellitus was 8.6% or as many as 21 million adults (2). A recent United States analysis of the prevalence of diagnosed diabetes showed an increase among adults aged 20-79 years (3). In Indonesia, the prevalence of diabetes mellitus in 2018 when compared to 2013 has increased by 2%. This was based on a doctor's diagnosis in the population aged 15 years and over. Meanwhile, the prevalence of diabetes mellitus for all ages in Indonesia was slightly lower than the prevalence of diabetes mellitus over the age of 15, which was 1.5%. The highest prevalence of diabetes mellitus was in the province of DKI Jakarta at 3.4% and the lowest prevalence of diabetes was in the province of East Nusa Tenggara. The prevalence of diabetes mellitus in the province of Central Java was 2.1% (4).

Vildagliptin was an oral antihyperglycemic drug class Dipeptidyl Peptidase-4 (DPP-4) inhibitor that has been approved as monotherapy and combination therapy in type-2 diabetes mellitus (5). Vildagliptin could prevent the inhibition of the degradation of the hormone incretin glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). As a result, there was an increase in blood glucose control such

as glycated hemoglobin (HbA1c), and levels of fasting plasma glucose (FPG), as well as an increase in the function of alpha-cells and beta-cells (6). Meanwhile, metformin was well recognized as a first-line therapeutic recommendation in the treatment of type 2 diabetes mellitus (7). Metformin worked to low blood sugar levels by reducing glucose production in the liver, reducing intestinal absorption, and increasing insulin sensitivity. Metformin could also reduce basal and post prandial blood sugar (8).

Based on research (Godoy et al. 2015), the results of HbA1c reduced from 8.3% to 7.2% with vildagliptin therapy. Meanwhile, based on research (Rhee et al. 2017) with metformin therapy, there was reduction of HbA1c by 1.0-2.0% and in research (Odawara and Sagara. 2016) vildagliptin-combined metformin therapy could reduce the value of HbA1c from 7.6-8.0% to 6.8-7.2 % with good tolerance and reduced risk of hypoglycemia and body weight so this systematic review would review the differences of efficacy vildagliptin as single drug with vildagliptin as combination drug with metformin in the treatment of type 2 diabetes mellitus. Hopefully, it could provide a reference in the treatment of type 2 diabetes mellitus.

## MATERIALS AND METHODS

### Information sources and search design

We used data retrieval techniques through two e-databases, they were Pubmed and Sciencedirect. Keywords that we used in the e-database are efficacy OR "therapeutic equivalency" OR "clinical equivalencies" OR "generic equivalencies" AND vildagliptin AND metformin AND type 2 diabetes mellitus OR "noninsulin-dependent diabetes mellitus" OR "non-insulin dependent diabetes mellitus ".

### Eligibility criteria and study selection

In our review, we included randomized controlled trials (RCTs) assesing efficacy of vildagliptin as single drug or vildagliptin as combination with metformin in patient type-2 diabetes mellitus which ages >20 years old and they had minimal outcome was HbA1c. Articles we chosen were articles that were limited in the last 10 years.

We entered search results and duplicate articles in Microsoft Excel, then we screened duplicate titles and abstract to exclude as irrelevant articles. Then, we retrieved full texts of potentially eligible articles to perform full text screening. All the filtered articles were reviewed by four reviewer and feasible to be reviewed.

### Data items and data collection

Our common outcome was the change value of hemoglobin A1c (HbA1c%) from baseline to final results. While, other outcome that possible to be entered in our review were FPG, bodyweightloss, and risk of hypoglicemia that counted from baseline to final result.

To assess outcome efficacy, we extracted data by taking studies which assessing the used of vildagliptin as singledrug or as combination with metformin. Data extraction from the articles was divided into two. First, was articles that compared between the efficacy of vildagliptin as singledrug and placebo/sitagliptin. Second, was articles that compared between the efficacy of vildagliptin as combination with metformin and glimepirid as combination with metformin or placebo as combination with metformin or metformin as single therapy.

### Risk of bias and quality of evidence

We used a system adopted by the Cochrane's collaboration called GRADE (Grading of Recommendations, Assessment, Development, adn Evaluations). It was a methode that used by systematic reviewers and guideline developers to assess quality of evidence and to decide recommendation of a drug intervention in certain disease. GRADE analyze performed with five difference steps to determine final assessment result of articles quality that contained risk of bias assessment. First step was determining grade of articles value based on the study design of the articles, such as Randomized Controlled Trials with "high" grade value and Observational Study with "moderate" grade value. Second step, downgrade or upgrade for each articles. The articles would be downgrade if there were risk of bias, inconsistency result, indirectness of evidence, imprecision of results, and publication bias. Otherwise, the articles would be upgrade if there were large magnitude of effect, all plausible confounding would reduce the demonstrated effect or increase it if no effect was observed, and dose-response gradient. Third step, determine final grade for each articles. Forth step, consider other factors that affected to strenght of intervention recommendations. Last step, made recommendation based on quality of evidence that has been found.

## RESULTS

### Search results

We recorded the articles that we got as many as 741 articles, 167 articles from Pubmed and 577 articles from Sciencedirect. We eliminated 398 duplicate articles. We screened titles and abstracts then eliminated irrelevant titles (n = 292) and abstracts (n = 69). Finally, we rated 37 full text articles and found 8 articles that fit our criteria by eliminating 29 articles because 20 articles with irrelevant intervention, seven articles with irrelevant outcome, and two articles with incomplete final data. (Fig.1)

### Characteristics of studies

Eight articles with a total population of 1,213 patients

consisting of 618 female patients and 595 male patients. Population age contained in all articles is type 2 diabetes mellitus patient aged >45 years. There was one article that took type-2 diabetes mellitus patients after undergoing kidney transplant surgery, one article with type-2 diabetes mellitus patients who had kidney failure, and six articles that took type-2 diabetes mellitus patients without having comorbids. There was one study that provides drug interventions with different doses. All of the studies obtained carried out the provision of interventions with different durations. The control interventions in each study were placebo and sitagliptin in the vildagliptin study as a single drug. Meanwhile, the study of vildagliptin in combination with metformin had control interventions with glimepirid + metformin, placebo + metformin, and metformin. (Table.II)

**Risk of bias assessment**

We used GRADE (Grade of Recommendations, Assessment, Development, and Evaluations) method to assess the risk of bias contained in eight articles. There were no change in the quality of evidence from initial grade to final grade because there was no risk of bias in all articles. In the eight articles had no downgrade factors among limitations in study design and/or execution, inconsistency of results, indirectness of evidence, Imprecision of results, and publication bias. First, limitations in study design and/or execution because all articles included execution in their study design such as allocation concealment dan lack of blinding—particularly. Second, Inconsistency of results because all articles had consistent result with theory effect of an intervention. Third, Indirectness of evidence because all articles had direct of evidence between intervention and its comparison. Forth, Imprecision of results because all articles had almost similar amount of patients and had a good result in the patients of type-2 diabetus mellitus. Fifth, Publication bias because all articles had passed publication and there were many available articles with the similar topic. However, there were four of the eight articles that found upgrade factor, it was All plausible confounding would reduce the demostrated effect or increase it if no effect was observed because two of four articles eliminated things that could affect interventions and Dose-response gradient because two of four articles used different doses in one group so the efficacy would be also different. Eight articles that have met the grade of evidence according to GRADE method and data analysis of the characteristics of the article, demographic data of respondents, and data on the results of the intervention could be used as a recommendation for the appropriate article and could be used as a worthy article with the same assessment on differences in vildagliptin as a single drug and vildagliptinn as a combination drug with metformin. (Table I)

**Analysis of glycated hemoglobin (HbA1c)**

Overall, vildagliptin as a single drug and vildagliptin as a combination drug can reduce the value of HbA1c. In four articles vildalgiptin as a single drug showed that vildagliptin was shown to reduce HbA1c from baseline. However, the decrease in HbA1c vildagliptin as a single drug was not significant compared to its placebo comparison (-0.1% HbA1c from baseline and $p$ = 0.098 after 52 weeks; -0.5 ± 0.4% HbA1c from baseline and $p$ = 0.081 after four months) (9) (10) and sitagliptin (-0.56 ± 0.13% HbA1c from baseline and $p$ = 0.874 after 24 weeks) (11). However, the decrease in HbA1c in the vidagliptin group as a single drug and had a significant value at the third month of treatment with a reduction in HbA1c value of -0.6 ± 0.5% and $p$ = 0.016(10). In fact, the largest decrease in HbA1c ≤6.5% was in the vildagliptin group compared to its comparison, namely sitagliptin, with a value of $p$ = 0.050 (11). (Table III)

Vildagliptin which is used in combination with metformin there is one article which states that vildagliptin as a metformin combination is not significant to its comparison, namely glimepirid combined with metformin with p value ≥ 0.05 (12). However, when compared with baseline, the vildagliptin group in combination with metformin experienced a decrease in HbA1c -3.23% with p ≤ 0.01 (12). Meanwhile, three other studies stated that the vildagliptin group as a combination with metformin experienced a significant decrease with its comparison, the placebo combination of metformin (-0.51 ± 0.11% HbA1c with $p \leq 0.001$ after 24 weeks; the final value of HbA1c was 6.9 ± 0.1% with $p \leq 0.01$ after 12 weeks) (6)(13) and metformin monotherapy (-1.0 ± 0.2% HbA1c with $p \leq 0.001$ after 12 weeks) (7). (Table III)

**Fasting plasma glucose (FPG)**

A reduction in FPG from each baseline was found across the vildagliptin group as a single drug and the vildalgiptin group as a combination drug with metformin. In the vildaglitpin group as a single drug, the reduction in FPG was not significant compared to its comparators, namely placebo (-0.1% FPG with $p$ = 0.343 after 52 weeks; -16.4 ± 16.6mg / dl FPG with $p$ = 0.081 after three months and -7.3 ± 21.3 mg / dl FPG with $p$ = 0.161 after four months) (9) (10) and sitagliptin (-0.47 ± 0.37mmol / l FPG with $p$ = 0.185 after 24 weeks) (11). (Table.III)

The reduction in FPG in the vildagliptin group as a combination drug with metformin was significant to the comparison, there is metformin combination glimepirid (-48.25% FPG with $p \leq 0.01$ after three months) (12), placebo combination metformin (-0.69mmol/l or 12.4mg / dl FPG with $p \leq 0.001$ after 24 weeks with vildaliptin bd and -0.58mmol/l or

**Table I : Grade of Evidence**

| No. | Author and Year | Downgrade faktor | | | | | Upgrade factor | | | Final Grade |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Limitation in study design | Inconsis-tency of results | Indirect-ness | Impre-cision of results | Publica-tion bias | Large Effect | All plau-sible con-founding | Dose-re-sponse gradient | |
| 1. | Foley et al. 2011 (9) | - | - | - | - | - | - | - | - | High |
| 2. | Kothny et al. 2015 (11)ran-domised, multicentre, dou-ble-blind, 24 week study con-ducted in 87 centres across Brazil and the USA. Patients with type 2 diabetes, either drug naive or treated with any glucose-lowering agents, who had inadequate glycaemic control (HbA<inf>1c</inf> 6.5–10.0% [48–86 mmol/mol] | - | - | - | - | - | - | + | - | High |
| 3. | Haidinger et al. 2014 (10) | - | - | - | - | - | - | + | - | High |
| 4. | Rizzo et al. 2012 (15)sita-gliptin and vildagliptin, known to have different efficacy on mean amplitude of glycemic excursions (MAGE | - | - | - | - | - | - | - | - | High |
| 5. | Mokta et al. 2018 (12) | - | - | - | - | - | - | - | - | High |
| 6. | Pan et al. 2012 (6) | - | - | - | - | - | - | - | + | High |
| 7. | Derosa et al. 2017 (13) | - | - | - | - | - | - | - | - | High |
| 8. | Strózik *et al.* 2015 (7) | - | - | - | - | - | - | - | + | High |

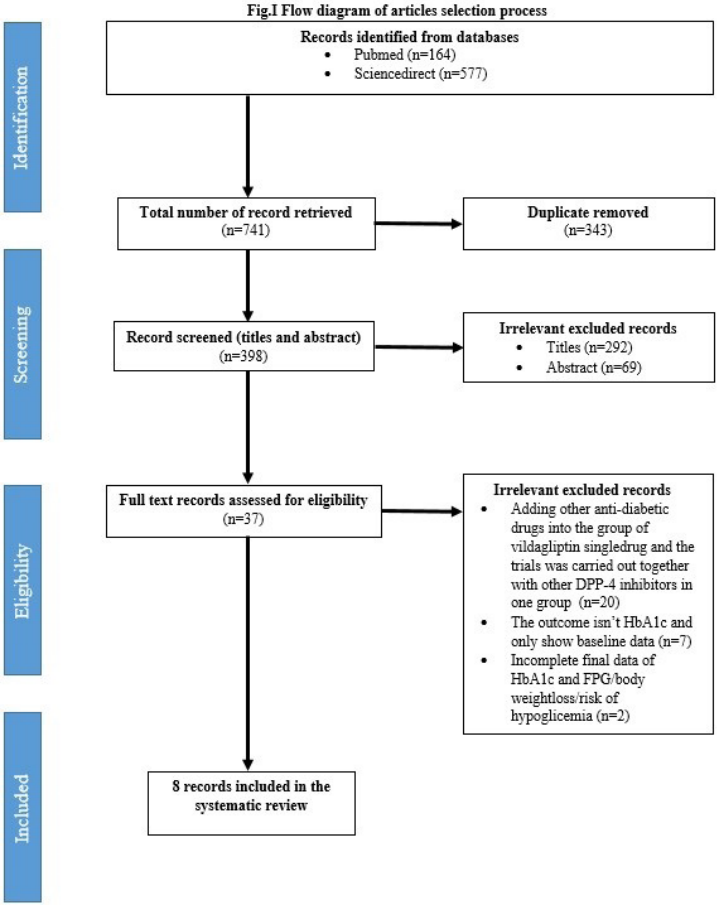


**Figure 1 : Flowchart PRISMA.** We identified articles through database Pubmed and Sciencedirect. We eliminated dupplicate articles, title and abstract not relevant, and full-text articles not relevant. Finally, we got 8 articles that eligible to reviewing.

**Table II : Characteristics of Articles**

| No | Author (Year) | Study Design | Duration of Intervenion | Population (N) | Gender (N) | | Age (year) | Journal Name |
|---|---|---|---|---|---|---|---|---|
| | | | | | Male | Female | | |
| 1. | Foley et al. 2011 (9) | Randomised clinical trial, a double-blind (RCT) | 64 weeks | 59 | 35 | 24 | 57.4±9.4(V) and 57.0±6.7(P) | Diabetologia |
| 2. | Kothny et al. 2015 (11) randomised, multicentre, double-blind, 24 week study conducted in 87 centres across Brazil and the USA. Patients with type 2 diabetes, either drug naive or treated with any glucose-lowering agents, who had inadequate glycaemic control (HbA<inf>1c</inf> 6.5–10.0% [48–86 mmol/mol] | Multicentre, Randomised, parallel-arm, double blind, clinical trial (RCT) | 26 weeks | 148 | 71 | 77 | 66.7±8.8(V) and 66.9±9.6(S) | Diabetologia |
| 3. | Haidinger et al. 2014 (10) | A prospective, randomized, open-label PROBE (parallel group with a blinded end point) study (RCT) | 15 weeks | 33 | 24 | 9 | 64.25±8.7(V) and 63.0±8.4(P) | Diabetes Care |
| 4. | Rizzo et al. 2012 (15)sitagliptin and vildagliptin, known to have different efficacy on mean amplitude of glycemic excursions (MAGE | A prospective 16-week, single-center, double-blind, randomizes,, placebo-controlled, phase II trial. (RCT) | 16 weeks | 90 | 43 | 47 | 60±8.8 (V) and 60±8.5 (S) | American Journal of Transplantation |
| 5. | Mokta et al. 2018 (12) | Randomized, prospective, comparative and interventional study (RCT) | 29 months | 217 | 119 | 108 | 50.88±9.30(VM) and 49.41±8.87(GM) | Journal of The Association of Physicians of India |
| 6. | Pan et al. 2012 (6) | Multi-centre, randomized, double-blind, parallel-group study. Placebo-controlled study (RCT) | 24 weeks | 438 | 205 | 233 | 54.2±9.62(V2); 53.7±10.0(V4); 54.5±9.68(P) | Diabetes, obesity, and Metabolism |
| 7. | Derosa et al. 2017 (13) | Multicenter, randomized, double-blind, placebo controlled study (RCT) | 8±2 months and 12 months | 167 | 85 | 82 | 54.2±8.3(VM) and 52.4±7.1(PM) | Elsevier |
| 8. | Stryzik et al. 2015 (7) | Randomized parallel group (RCT) | 12 weeks | 61 | 23 | 38 | 51.4±7.2(M15); 45.9±4.6(M15W1); 58.2±2,7(M3); 49.3±4.4(M3W1) | Elsevier |

Notes: Vildagliptin (V), Placebo (P), Sitagliptin (S), Vildagliptin+Metformin (VM), Glimepiride+Metformin (GM), Vildagliptin bd (V2), Vildagliptin qd (V4), Placebo+Metformin (PM), Metformin 1500mg (M15), Metformin 1500mg+Vildagliptin 100mg (M15W1), Metformin 3000mg (M3), Metformin 3000mg+Vildagliptin 100mg (M3W1).

-10.4 mg / dl FPG with p = 0.001 after 24 weeks with vlidagliptin qd; final decrease in FPG 106 ± 4 mg/dl with p ≤0.05 after 12 weeks) (6)(14), and metformin monotherapy (-1.11 ± 0.19mmol/l and -0.71 ± 0.24mmol / l FPG with p ≤ 0.001 after 12 weeks) (7). (Table III)

**Risk of hypoglycemia and body weightloss**

The combination treatment of vildagliptin with metformin shows a much better side effect profile compared to metformin combination glimepiride such as lower weight loss and a lower incidence of hypoglycemia (12). Only one patient on 2x50mg vildagliptin developed hypoglycemia and no patient had severe hypoglycemia in each group. These results suggest that vildagliptin may be the optimal therapeutic option, which can be added to metformin for better glucose control without an increased risk of severe hypoglycemia and a slight tendency to lose weight (6). There have been reports of weight loss and body mass index on vildagliptin and metformin therapy after 9 and 12 months of treatment (13). Combined vildagliptin treatment with metformin resulted in significant weight loss, namely 4.67 ± 5.8kg at the low-dose combination and 4.29 ± 6.7kg at the high-dose combination (7).

## DISCUSSION

Vildagliptin, a dpp-4 inhibitor, was an oral antihyperglycemic drug that was discovered in 2007

**Table III : Intervention Research Results**

| No. | Author (Years) | Intervention (N) | Comparison (N) | Outcome | Summary of results |
|---|---|---|---|---|---|
| 1. | Foley et al. 2011 (9) | Vildagliptin 100mg/day (n=29) | Placebo (n=30) | HbA1c and FPG | After 52 weeks of treatment, the vildagliptin group experienced a decrease in the mean value of HbA1c and FPG from the baseline by -0.1% HbA1c and -0.1% FPG, with a significance value of p = 0.098 (HbA1c) and p = 0.343 (FPG) |
| 2. | Kothny et al. 2015 (11) randomised, multicentre, double-blind, 24 week study conducted in 87 centres across Brazil and the USA. Patients with type 2 diabetes, either drug naive or treated with any glucose-lowering agents, who had inadequate glycaemic control (HbA<inf>1c</inf> 6.5–10.0% [48–86 mmol/mol] | Vildagliptin 50mg/day (n=83)<br><br>after 2 weeks of receiving placebo. | Sitagliptin 25mg/day (n=65)<br><br>after 2 weeks of receiving placebo. | HbA1c and FPG | After 24 weeks of treatment, the vildagliptin group experienced a decrease in the mean HbA1c and FPG values from the baseline by -0.56 ± 0.13% and 0.47 ± 0.37mmol / l, with a significance p value = 0.874 (HbA1c) and p = 0.185 (FPG) . but for the number of patients with a reduction in HbA1c ≤6.5% the most was the vildagliptin group with a significance p value = 0.050 |
| 3. | Haidinger et al. 2014 (10) | Vildagliptin 50mg/day (n=17) | Placebo 1x/day (n=16) | HbA1c and FPG | After 4 months of treatment, at 3 months the vildagliptin group experienced a decrease in the mean HbA1c value of -0.6 ± 0.5% with a significance p value = 0.016 and FPG -16.4 ± 16.6mg/dl with a significance p value = 0.081. whereas at the 4th month the decrease in the mean value of HbA1c-0.5 ± 0.4% with p value = 0.081 and FPG -7.3 ± 21.3mg/dl with a significance p value = 0.161 |
| 4. | Rizzo et al. 2012 (15)sitagliptin and vildagliptin, known to have different efficacy on mean amplitude of glycemic excursions (MAGE | Vildagliptin 2x50mg/day (n=45) | Sitagliptin 100mg/day (n=45) | HbA1c and FPG | After 12 weeks of treatment, the vildagliptin group experienced a significant reduction in mean HbA1c and FPG values with p ≤0.001 from their respective baselines. However, it did not experience a significant reduction when compared with sitagliptin |
| 5. | Mokta et al. 2018 (12) | Vildagliptin 2x50mg and Metformin 2x1g/day (n=111) | Glimepiride 1x2mg/day and Metformin 2x1g/day (n=106) | HbA1c and FPG | After 3 months of treatment, there was no significant difference between the two groups with p ≥ 0.05. However, compared to baseline, the vildagliptin group experienced a decrease in mean HbA1c -3.23% (p ≤0.01) and FPG -48.25% (p ≤0.01) |
| 6. | Pan et al. 2012 (6) | • Vildagliptin 2x50mg/day and metformin 1500mg/day(n=146)<br>• Vildagliptin 4x50mg/day and metformin 1500mg/day (n=148) | Placebo and metformin 1500mg/day (144) | HbA1c and FPG | After 24 weeks of treatment, both vildagliptin groups experienced a reduction in HbA1c compared to placebo with a significance p value ≤0.001 (-0.51 ± 0.11%) for vildagliptin bd and FPG with a significance p value ≤ 0.001 (-0.69mmol/l or 12.4mg/dl) for vilagliptin bd and p=0.001 (-0.58mmol/l or -10.4 mg/dl) for vildagliptin qd against placebo |
| 7. | Derosa et al. 2017 (13) | Vildagliptin 2x50mg/day and Metformin 2500±500mg/day | Placebo and Metformin 2500±500mg/day | HbA1c andFPG | After 12 weeks of treatment, the vildagliptin group experienced a significant reduction in mean HbA1c with p ≤0.01 (final value 6.9 ± 0.1%) and FPG with significance value p ≤0.05 (final value 106 ± 4mg/dl) compared with the placebo group. |
| 8. | Stryzik et al. 2015 (7) | • Vildagliptin 100mg/day dan Metformin 1500mg/day (n=15)<br>• Vildagliptin 100mg/day and Metformin 3000mg/day (n=17) | • Metformin 1500mg/day (n=13)<br>• Metformin 3000mg/day (n=16) | HbA1c | After 12 weeks of treatment, the group with the vildagliptin combination experienced a significant reduction in HbA1c with a significance p ≤0.001 with a reduction of -1.0 ± 0.2% and FPG experienced a significant decrease in the combination group with a significance p value ≤0.001 with a reduction of 1.11 ± 0.19mmol/l and 0.71 ± 0.24mmol/l) |

and was effective at lowering blood glucose, not causing weight gain or increasing the risk of hypoglycemia (16). Vildagliptin was strong and selective in blocking DPP-4 in GLP-1 and GIP to become inactive GLP-1. Vildagliptin has shown efficacy treatment as a single drug and as combination with other anti-diabetic drugs or insulin (17).

Research by Foley et al. 2011 and Research Haidinger et al. 2014 has different results, according to research by Foley et al. 2011 reduction of HbA1c and FPG compared with control (placebo) did not get any significant results with $p$ value = 0.098 (HbA1c) and $p$ value = 0.343 (FPG). Meanwhile, according to research by Haidinger et al. 2014 there was a significant reduction of HbA1c with $p$ value = 0.016. However, the FPG value did not perform significant reduction with $p$ value = 0.081. The condition of increased glucose toxicity in type 2 diabetes mellitus was associated with increased of FPG which could reduce the function of pancreatic beta cells and any agents that reduced of FPG estimated to improve pancreatic beta cell function. Foley et al, 2011. The HbA1c reduction seen with vildagliptin 50mg / day in a patient with severe renal failure was similar to the HbA1c reduction seen with 2x50mg / day vildagliptin in a patient with good renal function (11).

Research by Kothny et al. 2015 and research by Rizzo et al. 2012 were an articles with the same intervention and control (sitagliptin). Based on the results of the two articles, the reduction of HbA1c and FPG were not significant. Research by Kothny et al. 2015 obtained $p$ value = 0.874 (HbA1c) and $p$ value = 0.185 (FPG). However, for the largest number of patients with reduction of HbA1c ≤6.5% was the vildagliptin group with a significant of $p$ value = 0.050 compared with sitagliptin. The reduction value from each baseline keep showing significant results.

Research by Mokta et al. 2018 in the intervention group (vildalgiptin + metformin) and control group (glimepririd + metformin), the two groups had no significant difference ($p \geq 0.05$). However, in the case of hypoglycemia, the vildagliptin group was better than the comparison group (glimepiride) with a significant of $p$ value ≤ 0.01 and in the body weight changed between the two groups, the vildagliptin group was better (0.69 kg) than the glimepiride (2.07 kg) with a significant of p value ≤ 0.01.

Research by Pan et al. 2012 used two difference interventions vildagliptin as combination metformin 1500mg/day, they were vildagliptin 2x50mg/day and vildagliptin 4x50mg/day. Treatment during 24 weeks showed a reduction of HbA1c compared with placebo had significant of $p$ value ≤0.001 for vildagliptin 2x50 mg/day and reduction of FPG with $p$ value ≤0.001 for vildagliptin 4x50mg/day.

Research Derosa et al. In 2017 the vildagliptin group showed reduction of HbA1c mean value with $p$ value ≤0.01 significantly and reduction of FPG with significant of $p$ value ≤0.05. The article of Stryzik et al. 2015 used vildagliptin after 12 weeks of treatment, group with vildagliptin as combination had significant reduction of HbA1c with a significant of $p$ value ≤0.001 and reduction of FPG in the combination group with a significant of $p$ value ≤ 0.001.

Metformin that used as combination therapy, especially with vildagliptin, was effective to get glycemic control (18). The combination of two drugs was a good treatment for insulin resistance and vildagliptin to improve pancreatic beta cell dysfunction (19). Metformin worked mainly in the liver to reduce glucose production and worked in the intestines to increase glucose utilization. In the liver, metformin inhibited mitochondria that cause AMP-K activation, increased insulin sensitivity, and reduced c-AMP so that reduced the expression of gluconeogenic enzymes (20). In the intestine, Metformin worked to reduce glucose absorption. In addition, metformin reduced basal and postprandial blood glucose (8).

The efficacy of vildagliptin as combination with metformin might be more potential in patients with uncontrolled type 2 diabetes mellitus. The best efficacy with vildagliptin 2x50 mg occured because metformin increased the effect of vildagliptpin to increase intake of GLP-1 levels. Only one patient in 2x50mg vildaglptin group developed hypoglycemia and no patient had severe hypoglycemia in each group. Vildagliptin could be added to metformin treatment for better glucose control without an increased risk of severe hypoglycemia and weight loss (6).

HbA1c reduction was very effective and good in the vildagliptin-combined metformin group at 6, 9 or 12 months of treatment. Even, FPG had better improvement at 12th month. There was also a reduction of body weight and body mass index in vildagliptin and metformin therapy after 9 and 12 months (13).

Improvement of glucose control was the result of synergistic mechanism of action from vildagliptin and metformin and could enhance stimulation of postprandial insulin secretion. Vildagliptin increased the intake of GLP-1 levels through inhibition of the DPP-4 enzyme, furthermore, metformin could simultaneously increase GLP-1 synthesis or induce expression of dependent islet genes and respond to incretin receptors. Metformin had potential effect of insulin transporting glucose beyond insulin receptor binding

and phosphorylation. There was significant difference in body weight and body mass index change during 12 weeks. Treatment of vildagliptin as combination with metformin resulted in significant weight loss, that were 4.67 ± 5.8kg at the low-dose combination and 42.9 ± 6.7kg at the high-dose combination (7).

## CONCLUSION

Vildagliptin as a combination drug with metformin was more effective in reducing the value of HbA1c, FPG, and lower risk of hypoglycemia and weight loss compared with vildagliptin as a single drug. Therefore, the metformin combination vildagliptin could be recommended as a good therapeutic choice in patients with type 2 diabetes mellitus and also considered other clinical aspects of these patients.

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