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Research Article

SITAGLIPTIN IN TYPE 2 DIABETES MANAGEMENT: A STUDY OF ADD-ON THERAPY IN BALI, INDONESIA

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ABSTRACT

Objectives: Dipeptidyl peptidase-4 (DPP-4) inhibitors are gaining popularity in several hospitals across Bali, particularly among patients with specific comorbid conditions, as they are included in Indonesia's National Formulary. In clinical practice, sitagliptin (SITA) is one of the most commonly used DPP-4 inhibitors. This observational study aims to assess the effectiveness of SITA as an add-on therapy in the treatment of Type 2 Diabetes Mellitus (T2DM) in Bali.

Methods: A hospital-based observational study was carried out at four different hospitals in Bali over the course of 2024. Data were obtained from the medical records of T2DM outpatients. Of the 354 medical records, 156 samples were obtained and categorized into four treatment regimens, including three groups receiving SITA as an add-on therapy and one comparator group (metformin+sulfonyl urea [SU]). Demographic and glycemic parameters were analyzed using ANOVA and *post hoc* Tukey Test.

Results: A significant difference was observed in the mean Hemoglobin A1c (HbA1c), HbA1c reduction, fasting plasma glucose reduction, and random plasma glucose (RPG) levels across the groups, with p-values of 0.04, 0.00, 0.03, and 0.03, respectively. *Post hoc* test showed that the combination of metformin and SITA was superior to reduce HbA1c compared to SU and SITA (p=0.04). The highest incidence of hypoglycemia was found in the Metformin and SU combination group, with 16.7%. However, there was no significant association between SITA and hypoglycemia statistically.

Conclusion: As a second- or third-line therapy, SITA therapy is effective in significantly lowering HbA1c and RPG levels, while also reducing the risk of hypoglycemia.

Keywords: Antidiabetic, Diabetes mellitus, Sitagliptin, Effectiveness, Safety.

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INTRODUCTION

Decreased insulin production and reduced cell sensitivity to insulin are characteristics of type 2 diabetes mellitus (T2DM) [1,2]. In 2019, the global prevalence of T2DM was reported at 9.3% and is expected to rise to 10.2% by 2030 [1,3]. The Bali Provincial Health Office recorded a total of 53.736 T2DM cases across all age groups in 2021 [4]. The 2018 Basic Health Research reported that the highest rates of DM in Bali were observed in four areas, such as Denpasar City, Badung Regency, Gianyar Regency, and Tabanan Regency [5,6].

Various drug regimens have been widely implemented to control blood glucose levels in T2DM, including the newer regimens, such as Dipeptidyl peptidase-4 inhibitor (DPP-4-i) [1,7]. A HbA1c level of ≥7.5% can increase the cardiovascular risk, so a combination of drugs with different mechanism of actions is required [2,8]. Diabetes treatment regimens continue to envolve each year. In 2019, the American Diabetes Association emphasized the advantages of combining DPP-4-i, which have demonstrated effective diabetes management with minimal side effects [8]. According to the Indonesia's National Formulary, DPP-4-i are classified as add-on therapies and are typically used alongside metformin or Sulfonyl Urea (SU) [9].

The mechanism of action of DPP-4-i is selectively blocked the enzyme DPP-4, therefore the activity of incretin hormones that help regulate blood glucose levels in prolonged [2,10,11]. One of the DPP-4-i available in Indonesia is sitagliptin (SITA). SITA offers effective blood glucose control even with irregular meal schedules, and its oral administration can help improve patient adherence to therapy [12,13]. The benefit of using SITA are low risk to causing hypoglycemia, does not impact to body weight, and effectively reduces HbA1c levels even in patients with Chronic Kidney Disease (CKD) [2,14]. One example of SITA use is as a third agent in combination with metformin and glimepiride, which has shown an HbA1c reduction of up to 0.84% [15] with minimal hypoglycemia episodes at 2.65% [16].

In Indonesia, SITA the use of SITA restricted only for combination therapy in the Indonesian national formulary, which lends further significance to the evaluation. The research that specifically focused on DPP-4-i studies conducted exclusively within Bali province is limited. Hence, this study sought to present an overview of SITA use in combination therapy for managing T2DM at public hospitals across Bali Province, Indonesia.

METHODS

This observational analytical study was designed with cross-sectional and retrospective data collection. Medical records were reviewed from four public hospitals in Bali between March 27th and June 30th, 2025. The study population included T2DM patients who received outpatient treatment from January to December 2024. A purposive sampling method was used. Inclusion criteria were: (1) Patients aged over 18 years, (2) availability of both pre- and post-treatment data on glycemic parameters (HbA1c, fasting plasma glucose (FPG), random plasma glucose (RPG), and (3) patients who were treated exclusively with oral antihyperglycemic agents. Exclusion criteria included pregnancy, a diagnosis of cancer, or CKD.

Data collection
Standardized form for data collection divides into two parts there are patient characteristics and glycemic profile. Sex, age, smoking status, body weight, height, and the type of therapy administered become the characteristics of the participants. The glycemic profile included laboratory results for HbA1c, FPG, and RPG. Hypoglycemia was defined as FPG and RPG levels <70 mg/dL. Optimal control was classified as HbA1c below 7%, FPG ranging from 70 to 99 mg/dL, and RPG between 140 and 180 mg/dL.

Data analysis
The characteristics data were analysed using descriptive methods. The data were gathered and displayed in tables and graphs, accompanied by descriptive summaries. The difference of effectiveness in each group was assessed using an analysis of variance (ANOVA) test and a Turkey *post hoc* test. The safety was evaluated through the percentage of hypoglycemia events occurring during the research period using binary logistic. A $p<0.05$ was considered statistically significant. We use SPSS version 30.0 for Windows for all analyses.

Ethical approval
This method was approved by the Institutional Ethical Committee of Tabanan Regional Public Hospital, with a research ethics permit issued under letter number 445/181/TIMKORDIK/RSUD/2025, dated March 20th, 2025. In addition, the research received approval from the Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (KE/FK/1807/EC).

RESULTS

A total of 156 patients were included in this study. We divided the treatment into four groups, including group 1 (metformin+SITA), group 2 (SU+SITA), group 3 (metformin+SU+SITA), and group 4 (metformin+SU) as illustrated in Fig. 1.

Samples were chosen through purposive sampling. A total of 198 patients were excluded from the study because they received other forms of therapy. Table 1 presents the characteristics of the participants.

Women have higher prevalence of T2DM than men. Individuals aged 45–59 years old, considered to be in their productive age group, are more vulnerable to developing T2DM when other risk factors, such as increased Body Mass Index (BMI), smoking, and poor lifestyle habits are present. Most of participants in the normal to overweight. Furthermore, 78.2% of the participants were classified as non-smokers.

According to the restrictions outlined in the 2023 National Formulary of the Republic of Indonesia, "SITA may be administered as an add-on therapy to metformin and SU, either as monotherapy or in combination." 37.8% of cases was using SITA as a third-line agent and 27.6% of cases as a second-line agent. The combination of metformin and SU was used as a comparator in 34.6% of cases. The most commonly used SU agent in combination therapy was glimepiride (50%). Table 2 displays the plasma glucose profiles of each treatment group.

We analyzed the differences of glucose profile parameters based on therapy group (Table 2) and continued to *post hoc* test to detect the significant difference in each group (Table 3). We applied the group 1 (Metformin and SITA combination) as a standard or references.

HbA1c was considered the primary laboratory parameter for assessing antidiabetic effectiveness. In this study, the combination of Metformin and SITA demonstrated effective HbA1c control, with an average level of 6.55±1.50% ($p=0.04$), while the greatest HbA1c reduction occurred in the Metformin+SU+SITA group: −2.19±1.45% ($p=0.00$). A *post hoc* analysis revealed that the difference was more pronounced in the reduction of HbA1c levels than in the HbA1c values. We found that the combination of metformin and SITA was better to reduce HbA1c compared to SU and SITA. This supports the role of SITA as an effective second-line agent in T2DM therapy.

Among the treatment groups, the lowest mean FPG level was observed in the metformin and SITA combination group (120.53±18.21 mg/dL), whereas the highest level was recorded in the triple therapy group comprising metformin, SITA, and SU (150.34±45.65 mg/dL) ($p=0.10$). Statistically significant reduction in FPG was observed in the metformin and SITA group (mean change: −33.87±49.36 mg/dL; $p=0.03$), representing the largest decrease among the treatment arms. Conversely, an increase in FPG was recorded in the metformin and SU group (3.43±57.30 mg/dL). However, we did not find the difference of GDP and GDP reduction in groups 2, 3, and 4 compared to group 1.

The lowest mean RPG level was observed in the metformin–SITA combination group (138.59±24.34 mg/dL), while the highest was found in the metformin–SITA–SU combination group (199.13±81.64 mg/dL). This difference was statistically significant ($p=0.03$). It has also been confirmed through *post hoc* test ($p=0.02$) for group 1 versus group 3. Nonetheless, the difference in the magnitude of glucose reduction across treatment groups was not statistically significant, either in ANOVA ($p=0.98$) and in the *post hoc* test.

Table 4 presents the frequency of hypoglycemia events across the different treatment groups. The highest incidence was observed in the metformin–glimepiride combination group, with 16.7% of participants experiencing hypoglycemia. No hypoglycemia events were reported in the SU–SITA combination group. In fact, there was no significant association with hypoglycemia events based on group 1 as a reference.

DISCUSSION

This study provides insights from the Balinese population, which may be informative for other regions in Indonesia. SITA is one of the T2DM medicine from the DPP-4-i class. Several studies found that SITA has a beneficial effect as cardioprotective among T2DM patients [17,18].

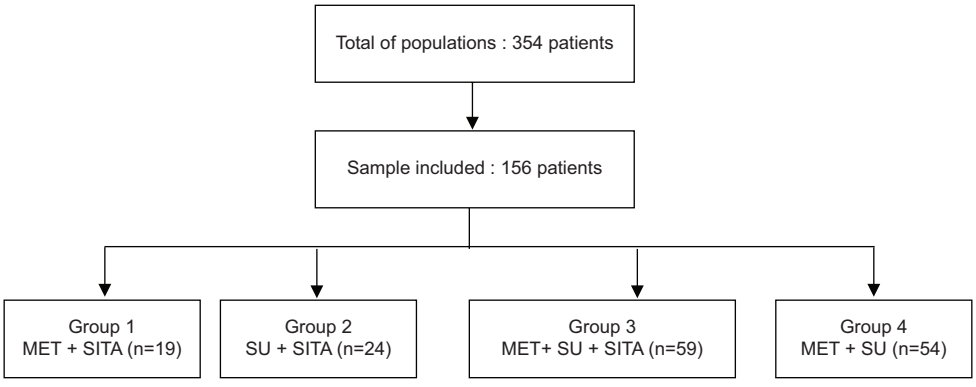

Fig. 1: The diagram of respondents group. MET: Metformin, SITA: Sitagliptin, SU: Sulfonylurea

Therefore, several guidelines recommend adding SITA to metformin therapy for T2DM patients who do not achieve adequate glycemic control with metformin alone [1,19,20]. However, there is a challenge in Indonesia related to SITA prescription in primary health care.

Our study explored the benefit of SITA as an add-on therapy agent to the primary outcome, which is the glycemic target parameter, including HbA1c, FPG, and RPG. We also assay the safety aspect through hypoglycemic events. The average age was 60.39±8.8 years old. There was a reduction of skeletal muscle mass in increasing age, which serves as the main site for insulin-dependent glucose storage. As glucose uptake into muscle becomes less efficient, compensatory hyperinsulinemia may occur, eventually leading to insulin resistance [8,21]. Natasya *et al*. found that HbA1c was significantly influenced by age [22]. In Prolanis study in West Java, Indonesia, the frequency of T2DM was high in 56–65 years [23]. In addition, SITA is reported to be safe in elderly patients [24,25].

Table 1: Characteristics of the participants

Characteristic	n (%)/mean±SD
Sex, male/female (n=156)	70 (44.9)/86 (55.1)
Age, years old (n=156)	60.39±8.80
Adult (20–39)	3 (1.9)
Middle age (40–64)	111 (71.2)
Elderly (>65)	42 (26.9)
BMI, kg/m^2 (n=144)	24.35±4.08
Thin (<18.5)	3 (1.9)
Normal (18.5–24.9)	83 (53.2)
Overweight (≥25)	58 (37.2)
Smoking status (n=156)	
Yes	34 (21.8)
No	122 (78.2)
Group of therapy (n=156)	
Group 1 (MET+SITA)	19 (12.2)
Group 2 (SU+SITA)	24 (15.4)
Group 3 (MET+SU+SITA)	59 (37.8)
Group 4 (MET+SU)	54 (34.6)
SU agent (n=156)	
Glimepiride	78 (50.0)
Gliquidone	28 (17.9)
Gliclazide	30 (19.2)
Glibenclamide	1 (0.6)

BMI: Body mass index, MET: Metformin, SITA: Sitagliptin, SU: Sulfonylurea

Our study was dominated by female, 55.1%. A previous study identified a significant correlation between gender and the prevalence of diabetes (p=0.004; OR=3.567; 95% CI: 1.575–8.077). This may be related to differences in body fat composition, as women generally have higher fat mass, predisposing them to elevated blood glucose levels [21]. The mean BMI in our participants was 24.35±4.08 kg/m^2 (normal-overweight range). An elevated BMI is linked to a greater risk of developing T2DM. In women, this risk becomes more pronounced within the BMI range of 27.5–29.99 kg/m^2 (HR=1.34), whereas for men, the risk increases significantly at a BMI of 30–39.99 kg/m^2 (HR=1.34) [26]. In this study, 1.9% of participants had a BMI <18.5 kg/m^2, indicating undernutrition among some T2DM patients. A total of 21.8% of patients were active smokers. Smoking is a well-established risk factor for both pre=diabetes and diabetes, contributing to impaired glucose metabolism and increased insulin resistance [27]. Interestingly, smoking status and smoking cessation have an impact on T2DM pharmacologic therapy, including DPP-4-i [28]. Moreover, the genetic aspect might influence our results [29,30], but we did not examine the genetic factors.

In Bali Province, SITA was most commonly used in combination with Metformin and SU. However, it was also frequently prescribed as a second-line antidiabetic agent. In this study, 37.8% of SITA use was in combination with Metformin and SU, with Glimepiride being the most frequently used SU (50%). This is consistent with the Indonesian National Formulary, which does not permit SITA as monotherapy. The Metformin-Glimepiride combination remains the most widely used glucose-lowering regimen in Denpasar [6]. In a comparative study involving 135 participants, 20% of those receiving this combination experienced hypoglycemia by week 15 [31]. Therefore, in this study,

Table 2: The differences of effectiveness parameters profile in each therapeutic group

Effectiveness parameters	Group 1 (MET+SITA) (n=19)	Group 2 (SU+SITA) (n=24)	Group 3 (MET+SU+SITA) (n=59)	Group 4 (MET+SU) (n=54)
HbA1c, % (n=127; *P*=0.04*)	6.5±1.50 (n=18)	8.02±2.24 (n=21)	7.85±1.84 (n=48)	7.33±1.67 (n=40)
ΔHbA1c, % (n=51; *P*=0.00**)	−1.77±2.51 (n=9)	0.81±1.84 (n=8)	−2.19±1.45 (n=23)	−1.02±2.16 (n=11)
FPG, mg/dl (n=132; *P*=0.10)	120.53±18.21 (n=17)	141.57±38.90 (n=23)	150.34±45.65 (n=50)	144.29±46.25 (n=42)
ΔFPG, mg/dl (n=144; *P*=0.03*)	−33.87±49.36 (n=15)	−11.88±56.20 (n=17)	−32.80±61.67 (n=47)	3.43±57.30 (n=35)
RPG, mg/dl (n=143; *P*=0.03*)	138.59±24.34 (n=17)	189.26±77.55 (n=23)	199.13±81.64 (n=53)	173.30±75.00 (n=50)
ΔRPG, mg/dl (n=129; *P*=0.98)	−16.8±33.44 (n=15)	−22.86±132.27 (n=22)	−21.32±97.82 (n=47)	−14.20±80.43 (n=45)

Each value represents in the mean±SD, *p<0.05, **p<0.01, MET: Metformin, SITA: Sitagliptin, SU: Sulfonylurea, FPG: Fasting plasma glucose, RPG: Random plasma glucose

Table 3: *Post hoc*-Tukey test

References	Comparator	p of *post hoc*					
		HbA1c	ΔHbA1c	FPG	ΔFPG	RPG	ΔRPG
Group 1 (MET+SITA)	Group 2 (SU+SITA)	0.06	0.04*	0.41	0.71	0.15	0.99
	Group 3 (MET+SU+SITA)	0.05	0.94	0.06	1.00	0.02*	0.99
	Group 4 (MET+SU)	0.43	0.81	0.21	0.17	0.35	1.00

*p<0.05, MET: Metformin, SITA: Sitagliptin, SU: Sulfonylurea, FPG: Fasting plasma glucose, RPG: Random plasma glucose

Table 4: Hypoglycemia events in each group

Hypoglycemic event	Group 1 (MET+SITA) (n=19) (%)	Group 2 (SU+SITA) (n=24) (%)	Group 3 (MET+SU+SITA) (n=59) (%)	Group 4 (MET+SU) (n=54) (%)
Hypoglycemia	1 (5.2)	0	4 (6.8)	9 (16.7)
None	18 (94.8)	24 (100)	55 (93.2)	45 (83.3)
p	Ref	0.99	0.82	0.24

Data given in n (%). Group 1 (MET+SITA) is the reference, MET: Metformin, SITA: Sitagliptin, SU: Sulfonylurea

SITA was used as an add-on agent, aiming to improve treatment adherence with minimal side effects – especially in Bali, where such research has not been conducted previously.

We found that the combination of metformin and SITA resulted in better control of HbA1c levels compared to the other groups (p=0.04). *Post hoc* testing demonstrated that the combination of metformin and SITA was superior in lowering HbA1c levels compared to the combination of SU and SITA (p=0.02). A study found that 21.2% of patients on SITA+Metformin achieved HbA1c <6.5% by week 30 [32]. Similarly, Kisioglu *et al*. reported that SITA significantly reduced HbA1c among patients with poor glycemic control on Metformin+SU: 6.8% at 3 months, 6.7% at 6 months, and 6.9% at 12 months [8]. Some studies found that SITA reduced HbA1c effectively among Japanese, including in the elderly population [24,33]. In a study by Patel *et al*., FPG decreased significantly across three test groups (SITA only, SITA+Metformin, and SITA+Metformin+Glimepiride) by day 60 [34]. Kim *et al*. also found that 81% of Korean T2DM patients responded to SITA, especially those younger and with lower BMI [35].

However, we could not detect the difference between each group according to FPG, whereas Srivastava *et al.* reported that the combination of metformin and SITA led to significantly greater reductions in both fasting and post-prandial blood glucose levels (p<0.01) [36]. In this study, a significant difference was observed in the RPG level. The combination of metformin and SITA demonstrating better RPG control compared to the triple therapy combination. It might be because the combination includes the SU agent as an antidiabetic oral. SU, a well-known stimulator of insulin release in the pancreas, therefore it affects the RPG. Notably, newer SU medicine has been developed as a safer antihyperglycemic agent [37,38]. In addition, the previous study indicated that combining a low dose SU with a DPP-4-i exerts a strong glucose-lowering effect by targeting the beta-cell pathway [39].

In the safety aspect, we found that there were no need to worry about hypoglycemia in each group. There was no significant difference of hypoglycemia events. However, a previous study found that patients in the Glimepiride group were more prone to experiencing multiple hypoglycemic episodes compared to those receiving SITA. Multivariate analysis showed that the adjusted incidence of hypoglycemia was significantly lower in the SITA group regardless of the definitions or types of hypoglycemic events [32]. Several studies also showed that SU induces hypoglycemic [40,41].

Based on our findings, healthcare professionals are encouraged to consider prescribing SITA as an add-on to metformin therapy. Our results were supported the international data that the prescription of DPP-4-i demonstrated an upward trend; in contrast, SU prescription was declining. In addition, the pharmacoeconomic study of SITA is required as a reference of government regulation in Indonesia's National Formulary [42].

CONCLUSION

Optimal glycemic control was achieved when SITA was added as a second-line treatment alongside metformin monotherapy. From a safety perspective, the combination of SITA and/or SU as an add-on of metformin appeared to be safe, as no hypoglycemia events were reported. Further studies are needed on the pharmacoeconomic aspects of using SITA as an add-on therapy.

Limitations of the study

The study was an outpatient study, then it was difficult to obtain sufficient laboratory reports. We realized that we could not gather complete data on characteristics, including T2DM duration, comorbid data, lifestyle, and history of other medication consumption.

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AUTHOR'S CONTRIBUTION

Anak Agung Ketut Purnama Sari was responsible for original draft preparation, editing, data collection, and validation. Phebe Hendra was responsible for supervision, technical, and material support. Dita Maria Virginia was responsible for the study's concept and design, conducting the statistical analysis, and critically revising the manuscript.

CONFLICTS OF INTEREST

There was no conflict of interest to disclose.

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