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Evaluation of Different Glycemic Control Regimens on the Prognosis of Coronary Heart Disease Combined with Type 2 Diabetes

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Abstract

Aim: To explore the safety and effectiveness of combining dapagliflozin and metformin with sitagliptin in patients with coronary heart disease and type 2 diabetes whose blood sugar control is below the standard. **Method:** From January 2022 to January 2023, 100 patients with poorly controlled blood sugar among those hospitalized with type 2 diabetes and coronary heart disease were selected. They were divided into an experimental group of 55 cases (combined with sitagliptin) and a control group of 45 cases (combined with insulin or glimepiride) based on dapagliflozin and metformin and followed up for 1 year. The rates of reaching blood sugar targets, heart function indicators, inflammatory factor results, and major adverse cardiovascular events were compared between the two groups. **Results:** After treatment, there was no statistical difference between the two groups in the 3-month, 6-month, and 12-month follow-up blood sugar indicators (FPG, 2hPG, HbA1c levels) and heart function indicators (NT-proBNP, LVEF, LVEDD) ($P > 0.05$). After 12 months of treatment, the levels of IL-6, CRP, and IL-8 in the observation group were lower than those in the control group, with a statistically significant difference ($P < 0.05$). After 12 months of treatment, the incidence of cardiovascular events was followed up, with the experimental group having a significantly lower rate of cardiac death than the control group ($P < 0.05$). The difference in other cardiovascular events was not statistically significant ($P > 0.05$). **Conclusion:** Combining sitagliptin with dapagliflozin and metformin in patients with coronary heart disease and type 2 diabetes who have poor blood sugar control can effectively manage blood sugar, reduce inflammation levels, and decrease the incidence of cardiac death, making it worthy of clinical application and promotion.

Keywords

Coronary Heart Disease, Type 2 Diabetes, Sitagliptin

1. Introduction

Type 2 diabetes, marked by persistent high blood sugar, relative insulin deficiency, and insulin resistance, is a significant risk factor for atherosclerosis and poses a considerable public health threat. It substantially raises the risk of coronary heart disease (CHD), with cardiovascular diseases being the primary cause of death among diabetics [1]. Moreover, diabetic patients with CHD have worse short-term and long-term outcomes compared to non-diabetics. Thus, actively managing blood sugar levels and minimizing cardiovascular events is essential for those with CHD and diabetes.

In clinical practice, oral hypoglycemic agents are commonly used as the primary regimen for glycemic control, with sodium-glucose cotransporter-2 inhibitors (SGLT2i) combined with metformin being the preferred treatment strategy [2]. This combined therapy not only effectively controls blood glucose levels but also significantly reduces the occurrence of cardiovascular events. Dipeptidyl peptidase-4 inhibitors (DPP-4i), a relatively new class of second-line hypoglycemic drugs including sitagliptin, vildagliptin, and saxagliptin, have been shown through large randomized controlled trials and observational studies to have a neutral overall cardiovascular safety profile for patients with or without coronary heart disease (CHD) combined with type 2 diabetes. Adding sitagliptin to standard treatment does not increase the risk of major adverse cardiovascular events (MACE) [3] [4]. However, there is currently a lack of real-world evidence regarding the cardiovascular safety and efficacy of combining metformin with SGLT2i and sitagliptin. This study aims to evaluate the effectiveness of sitagliptin on glycemic control, inflammatory markers, and cardiovascular events in patients with CHD and type 2 diabetes who have poor glycemic control with the combination of dapagliflozin and metformin.

2. Materials and Methods

2.1. Study Population

From January 2022 to January 2023, we selected 100 patients with poorly controlled blood glucose levels. They were admitted to our hospital for type 2 diabetes complicated with coronary heart disease. Based on their treatment regimen of combining SGLT-2 inhibitors and metformin, these patients were divided into two groups: an experimental group of 55 cases (combined with sitagliptin) and a control group of 45 cases (combined with insulin or glimepiride). A follow-up observation was conducted over one year. There was no statistically significant difference in general demographic data between the two groups ($P > 0.05$), as

shown in Table 1. This study was approved by the Ethics Committee of Central Hospital of Dalian University of Technology, with the ethical approval number: YN2022-063-15.

Table 1. Comparison of demographic characteristics between the two groups of patients ($\bar{X}$ ± S).

Item	Experimental Group (n = 55)	Control Group (n = 45)	t/χ^2 Value	P Value
Age (years)	56.72 ± 2.74	57.34 ± 2.62	−1.15	0.25
Gender (Male)	35 (63.6)	27 (60.0)	0.14	0.84
Weight (Kg)	68.86 ± 7.02	67.14 ± 6.39	1.27	0.21
Smoking history	30 (54.5)	25 (55.6)	0.01	0.92
Alcohol consumption history	26 (47.3)	18 (40)	0.53	0.47
Duration of type 2 diabetes (years)	6.67 ± 2.58	5.89 ± 2.26	1.59	0.12
HbA1c (%)	8.46 ± 0.75	8.68 ± 0.47	−1.71	0.09
FPG (mmol/L)	8.56 ± 1.24	8.83 ± 1.51	0.769	0.445
LDL-C (mmol/L)	3.31 ± 0.62	3.24 ± 0.49	0.62	0.54
Systolic blood pressure (mmHg)	145.82 ± 15.29	146.24 ± 14.81	0. 110	0.913
Diastolic blood pressure (mmHg)	90.63 ± 10.58	90.38 ± 10.22	0.095	0.925
Creatinine (mmol/L)	85.68 ± 15.46	85.43 ± 15.20	0.064	0.949
Use of coronary heart-disease related medication				
Antiplatelet agents	52 (94.5)	45 (100)	2.53	0.11
βblockers	48 (87.3)	40 (88.9)	0.06	0.81
ACEI/ARB	50 (90.1)	43 (95.6)	0.82	0.37
Statins	55 (100)	44 (97.8)	1.24	0.27

Note: HbA1c: glycosylated hemoglobin, FPG: fasting plasma glucose, LDL-C: low density lipoprotein-cholesterol, ACEI/ARB: angiotensin-converting enzyme inhibitors/Angiotensin II Receptor Antagonist Blocker.

2.2. Inclusion Criteria

1) Patients with a diagnosis of type 2 diabetes, meeting the World Health Organization (WHO) classification and diagnostic criteria for this disease.

2) Patients who have been treated with dapagliflozin combined with metformin for a course of ≥ 3 months, yet still have poorly controlled blood glucose, with HbA1c consistently > 7.0%.

3) Patients with coexisting coronary heart disease.

4) Patients with complete and comprehensive clinical data.

5) Patients who have provided informed consent for this study.

2.3. Exclusion Criteria

1) Patients with other types of diabetes.

2) Patients with severe complications such as diabetic nephropathy, severe arrhythmias, or acute heart failure.

3) Patients with other severe internal medical conditions and generally poor health status.

4) Patients with mental disorders or cognitive impairments who exhibit poor compliance and cannot cooperate with the study.

5) Patients with severe cardiac insufficiency and moderate to severe hepatic or renal dysfunction.

2.4. Treatment Methods

The experimental group received 100 mg of sitagliptin phosphate tablets orally each morning before breakfast, with ongoing monitoring of blood glucose and glycated hemoglobin levels. The control group was given insulin or 2 mg of glimepiride daily. Throughout the treatment period, patients' blood glucose levels were regularly monitored, and medication dosages were adjusted individually.

2.5. Observation Indicators and Evaluation Criteria

1) Blood Glucose Indicators: Venous blood samples were collected from patients before treatment and at 3, 6, and 12 months post-treatment, following standard procedures. The levels of fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), and glycated hemoglobin (HbA1c) were measured to compare differences in these indicators.

2) Cardiac Function Indicators: Fasting venous blood samples were collected from patients before treatment and at 3, 6, and 12 months post-treatment to measure the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Additionally, cardiac color Doppler ultrasound measured the left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) before treatment and at 3 months post-treatment.

3) Inflammatory Indicators: Fasting venous blood samples were collected from patients before treatment and at 12 months post-treatment. The levels of interleukin-6 (IL-6), interleukin-8 (IL-8), and high sensitivity C-reactive protein (hs-CRP) were detected using enzyme-linked immunosorbent assay (ELISA) before and after treatment.

4) Patients were followed for 12 months to observe the incidence of coronary heart disease attacks and hospitalizations during the treatment and follow-up period in both groups. The incidence of adverse cardiovascular events was statistically analyzed based on standards published by the American College of Cardiology (ACC), the American Heart Association (AHA), the U.S. Food and Drug Administration (FDA), and the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) [5]. These events included target vessel revascularization, heart failure due to coronary heart disease, non-fatal myocardial infarction, non-

fatal stroke, and cardiovascular-related death.

2.6. Statistical Methods

Data analysis was conducted using SPSS 25.0 statistical software. Normally distributed data were presented and analyzed using the t-test, while non-normally distributed data were expressed as median (P25, P75) and analyzed with the Mann-Whitney U test. Categorical data were expressed as cases (%) and compared using the chi-square test. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Comparison of Blood Glucose Levels between the Two Groups

After treatment, no statistically significant differences were observed in fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), and glycated hemoglobin (HbA1c) levels at 3, 6, and 12 months of follow-up between the two groups (P > 0.05), as shown in Table 2.

Table 2. Comparison of blood glucose levels at 3, 6, and 12 months post-treatment between the two groups ($\bar{X}$ ± S).

Follow-up Time	Indicator	Experimental Group (n = 55)	Control Group (n = 45)	t Value	P Value
3 months	FPG (mmol/L)	6.56 ± 1.24	6.31 ± 1.08	1.06	0.29
	2hPG (mmol/L)	10.24 ± 1.45	9.66 ± 1.87	1.75	0.08
	HbA1c (%)	7.21 ± 0.88	6.98 ± 0.74	1.40	0.16
		Experimental Group (n = 55)	Control Group (n = 45)	t Value	P Value
6 months	FPG (mmol/L)	6.68 ± 1.36	6.55 ± 1.34	0.46	0.64
	2hPG (mmol/L)	9.38 ± 1.05	9.46 ± 1.13	−0.37	0.72
	HbA1c (%)	6.74 ± 1.31	6.65 ± 1.07	0.37	0.71
		Experimental Group (n = 54)	Control Group (n = 39)	t Value	P Value
12 months	FPG (mmol/L)	6.24 ± 0.95	6.03 ± 0.84	1.10	0.27
	2hPG (mmol/L)	8.95 ± 1.74	8.50 ± 1.66	1.25	0.21
	HbA1c (%)	6.51 ± 0.75	6.38 ± 0.61	0.89	0.38

Note: 2hPG:2-hour postprandial plasma glucose.

3.2. Comparison of Cardiac Function Indicators between the Two Groups

After treatment, there were no statistically significant differences in the levels of NT-proBNP, LVEF, and LVEDD at 3, 6, and 12 months of follow-up between the two groups (P > 0.05), as shown in Table 3.

Table 3. Comparison of cardiac function indicators at 3, 6, and 12 months post-treatment between two groups ($\bar{X}$ ± S).

Follow-up Time	Indicators	Experimental Group (n = 55)	Control Group (n = 45)	t Value	P Value
3 months	NT-proBNP (pg/mL)	118.28 ± 30.54	126.77 ± 33.17	−1.33	0.19
	LVEF (%)	56.41 ± 8.37	55.18 ± 8.91	0.71	0.48
	LVEDD (mm)	48.75 ± 7.23	50.10 ± 7.62	−0.91	0.38
		Experimental Group (n = 55)	Control Group (n = 45)	t Value	P Value
6 months	NT-proBNP (pg/mL)	120.71 ± 28.64	124.51 ± 29.18	−0.66	0.51
	LVEF (%)	55.27 ± 7.15	54.83 ± 6.44	0.32	0.75
	LVEDD (mm)	47.15 ± 7.05	49.24 ± 7.95	−1.39	0.17
		Experimental Group (n = 54)	Control Group (n = 39)	t Value	P Value
12 months	NT-proBNP (pg/mL)	121.86 ± 30.73	124.95 ± 32.46	−0.47	0.64
	LVEF (%)	53.76 ± 6.47	53.27 ± 6.73	0.35	0.72
	LVEDD (mm)	48.57 ± 7.64	50.18 ± 8.03	−0.98	0.33

3.3. Comparison of Inflammatory Indicators between the Two Groups

Before treatment, there were no statistically significant differences in the levels of IL-6, CRP, and IL-8 between the two groups (P > 0.05). After 12 months of treatment, the experimental group showed significantly lower levels of IL-6, CRP, and IL-8 compared to the control group (P < 0.05). See Table 4.

Table 4. Comparison of inflammatory indicators between the two groups after 12 months of treatment ($\bar{X}$ ± S).

Group	IL-6 (μg/ml)		IL-8 (pg/mL)		hsCPR (mg/L)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Experimental Group (n = 54)	30.25 ± 5.06	18.57 ± 3.45	65.27 ± 7.09	33.06 ± 3.24	11.19 ± 1.27	5.28 ± 1.39
Control Group (n = 39)	31.49 ± 4.18	24.54 ± 3.84	65.73 ± 7.87	45.27 ± 2.88	10.72 ± 1.05	8.37 ± 1.84
t Value	−1.25	−7.85	−0.30	−18.77	1.89	−9.23
P Value	0.21	<0.001	0.77	<0.001	0.06	<0.001

3.4. Comparison of Cardiovascular Adverse Events between the Two Groups

After 12 months of treatment, the incidence of cardiovascular events was monitored in both groups. The incidence of cardiac death in the experimental group was lower than that in the control group, showing a statistically significant

difference ($P < 0.05$). No statistically significant differences were found in the incidence of other cardiovascular events ($P > 0.05$). See Table 5.

Table 5. Comparison of Major Adverse Cardiovascular Events (MACE) after 12 months of treatment between the two groups [cases (%)].

Cardiovascular Events	Target Vessel Revascularization Rate	Heart Failure	Non-fatal Myocardial Infarction	Non-fatal Stroke	Cardiovascular Death
Experimental Group (n = 55)	3 (5.45)	8 (14.55)	5 (9.09)	6 (10.90)	1 (1.82)
Control Group (n = 45)	3 (6.67)	6 (13.33)	6 (13.33)	3 (6.67)	6 (13.33)
χ^2 Value	0.06	0.03	0.46	0.54	5.04
P Value	0.80	0.66	0.50	0.46	0.03

4. Discussion

For patients with poorly controlled type 2 diabetes mellitus (T2DM) complicated by myocardial infarction, adding hypoglycemic agents to conventional insulin therapy is a common intervention. There are many hypoglycemic drugs available for combined therapy. Clinicians aim to find a safe and effective combination therapy that ensures blood glucose control while preventing and reducing cardiovascular events. For patients with T2DM and coronary heart disease (CHD), comprehensive measures are necessary to effectively control blood glucose levels, actively treat comorbid conditions, and use medication to alleviate CHD symptoms, reduce cardiovascular events, and slow the progression of diabetes and coronary atherosclerosis. These measures are crucial for reducing mortality and improving prognosis.

Sitagliptin is the most prescribed DPP-4 inhibitor (DPP-4I) worldwide. It works by inhibiting DPP-4 activity, reducing the inactivation of glucagon-like peptide-1 (GLP-1), which enhances the incretin effect and improves hyperglycemia. GLP-1 is often considered a major DPP-4 substrate that regulates cardiovascular function [6]. This clinical study found no significant differences in fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), and HbA1c levels between the two groups after treatment ($P > 0.05$). Additionally, no hypoglycemic events were reported in the experimental group during the study [7], supporting the clinical efficacy and safety of adding sitagliptin for Type 2 diabetes mellitus (T2DM) patients with inadequate insulin control.

hs-CRP is an acute-phase protein and inflammatory marker secreted by the liver, having prognostic value for patients with acute myocardial infarction (AMI). Recent research indicates that hs-CRP is positively correlated with coronary atherosclerosis development, and reducing hs-CRP levels can decrease cardiovascular events and microvascular obstructions [8]. Our study suggests that DPP-4 inhibitors can lower hs-CRP levels, indicating their anti-inflammatory effects.

IL-6, a cytokine produced by T lymphocytes, macrophages, and adipocytes, primarily stimulates the production of CRP and fibrinogen, promoting endothelial dysfunction and accelerating atherosclerosis [9]. Additionally, high levels of IL-6 are associated with an increased risk of myocardial infarction in healthy men. Therefore, reducing hs-CRP and IL-6 levels may inhibit atherosclerosis development, with sitagliptin potentially offering cardiovascular protection.

Current research indicates that peripheral blood levels of IL-8 are significantly elevated in patients with moderate or severe heart failure, suggesting that IL-8 can induce myocardial cell apoptosis and is involved in the development of heart failure [10]. Basic research indicates [11] that IL-8 causes cardiac damage through the following mechanisms: 1) IL-8 is directly toxic to myocardial cells; 2) IL-8 can increase inducible nitric oxide synthase activity, promoting the release of nitric oxide by endothelial cells, thereby damaging endothelial cells and reducing myocardial contractility; 3) IL-8 induces inflammatory responses after activating sphingomyelinase, lowering calcium ion concentration in myocardial cells.

Our study found no evidence that DPP-4 inhibitors increase NT-proBNP levels or cause differences in echocardiographic outcomes between groups. Prospective studies on the use of DPP-4 inhibitors in patients with type 2 diabetes and coronary heart disease have shown mixed results on the risk of hospitalization for heart failure. While saxagliptin was associated with a significantly increased risk of hospitalization for heart failure, sitagliptin and linagliptin showed no increased risk, and vildagliptin had a neutral effect on ventricular ejection fraction in patients with a history of heart failure [12].

5. Conclusion

This study found that adding sitagliptin to a metformin and dapagliflozin regimen can significantly improve blood glucose control, increase the rate of achieving glucose control targets in diabetic patients, and stabilize blood glucose levels. Regarding cardiovascular benefits, it can lower the risk of cardiovascular death but does not impact the rates of target vessel revascularization, heart failure, non-fatal myocardial infarction, and non-fatal stroke. The sitagliptin group also showed a reduction in inflammatory markers such as hs-CRP, IL-6, and IL-8, suggesting a potential benefit of sitagliptin. However, this conclusion requires further validation through larger-scale, real-world studies in diverse populations.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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