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Original Research Article

Impact of using metformin alone or with sitagliptin on diabetes management and their association with cardiovascular and renal outcomes

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Abstract

Purpose: *To investigate the effect of metformin monotherapy against sitagliptin-metformin combination on blood pressure, glucose metabolism, renal function, and lipid profile.*
Methods: *Three separate groups of 150 participants each were assigned at random and equally. Group 1 served as the control. Group 2 received metformin, then group 3 received sitagliptin with metformin. Biochemical and physiological parameters, including HbA1c, fasting blood sugar (FBS), blood pressure, high-sensitivity cardiac troponin (hs-cTn), lipid profile, blood urea (BU), and serum creatinine (Cr), were measured and recorded.*
Results: *Groups 1 and 2 showed significantly higher HbA1c and FBS related to control group ($p < 0.05$), although group 2 had higher FBS levels. Group 2 had significantly higher systolic blood pressure and high-sensitivity cardiac troponin (hs-cTn) in comparison to control ($p < 0.05$), whereas group 2 demonstrated lower high-sensitivity cardiac troponin (hs-cTn) and systolic pressure values. Despite total cholesterol was relatively higher in group 1, the lipid profile assessment revealed just modest, non-significant variations. In both groups 1 and 2, renal function parameters exhibited considerably diminished BU and Cr, suggesting possible nephroprotective effects.*
Conclusion: *In comparison to metformin alone, a combination of sitagliptin and metformin optimises the regulation of cardiovascular and renal indicators.*

Keywords: *Biochemical markers, Heart, Kidney, Metformin, Sitagliptin, Type 2 diabetes mellitus (T2DM)*

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INTRODUCTION

According to the elevated risk of chronic renal disease (CRD) and heart disease (CVD), type 2 diabetes (T2DM) appears to be an important international medical problem. Besides glycaemic regulation, controlling type 2 diabetes additionally involves approaches to minimise cardiovascular and renal adverse reactions [1,2]. For performance, safety profile, and affordable price, metformin has remained the standard of first-line oral treatments [3]. Beyond glycaemia, metformin has also been studied for cardiorenal effects. For example, based on a post-hoc inquiry, metformin did not significantly diminish extremely sensitive cardiac troponin I or T values

in T2DM patients, suggesting a limited effect on myocardial injury biomarkers despite its cardiovascular safety record [3]. Compared to non-metformin treatments, meta-analysis of diabetic individuals with chronic heart failure revealed that metformin use was linked to considerably lower cardiovascular mortality [4]. Combination treatments that may offer additional advantages above metformin alone have drawn more interest in recent years. Dipeptidyl-peptidase-4 (DPP-4) is inhibited by sitagliptin. By regulating incretin hormone, sitagliptin enhances glycaemic management [5,6]. A previous cohort study found that sitagliptin did not significantly change the probability of 3-point serious cardiovascular adverse complications (3P-MACE) compared to metformin monotherapy. It did, however, reduce the risk of death from cardiovascular disease [7]. Furthermore, sitagliptin is safe for the heart and kidneys in individuals with T2DM, including those with renal impairment or established cardiovascular disease [8]. As a result, sitagliptin appears to be a rational adjunct to metformin therapy, although its benefit in cardiovascular or renal function remains moderate. Recent guidelines have been dominated by the introduction of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), but inhibitors of DPP-4 and metformin continue to play strong ancillary roles. Previous study revealed that inhibitors of DPP-4 did not significantly improve estimated Glomerular Filtration Rate (eGFR) in type 2 diabetes, though they reduce albumin-to-creatinine ratio (ACR) [4,9]. Conversely, SGLT2 inhibitors were found to be more effective than DPP-4inhibitors in lowering individual renal outcomes, including micro- and macroalbuminuria and end-stage kidney disease [10]. Glycaemic management, a cardiovascular risk, as well as renal consequences, interact in a complex and comprehensive manner. While metformin is the basis of therapy and sitagliptin, in contrast, is a frequently utilised supplement, it is important to analyse their cumulative effect on glycaemic parameters, cardiovascular, and renal markers. Enhanced-sensitivity cardiac troponin (hs-cTn) as a subclinical myocardial damage marker [11], the traditional renal function indicators (serum creatinine and blood urea) offer vital data on organ-specific stresses, along with potential therapies. The impact of sitagliptin -metformin combined treatment, in contrast to metformin monotherapy, on glycaemic values (HbA1c, fasting blood sugar), cardiovascular variables (systolic and diastolic blood pressure, hscTn), renal biomarkers (BU and Cr), and lipid profile in patients with diabetes was examined in this study.

METHODS

Design

In this, a prospective, parallel-group, randomized controlled trial comprising 150 patients was randomly and equally assigned to 3 groups. Glycemic control (HbA1c, fasting glucose), lipid biomarkers include LDL-C, HDL-C, and triglycerides, while renal function indicators like serum creatinine, eGFR) were the outcomes.

Ethical approval

It was obtained from the Ethics Committee of the College of Pharmacy, University of Basrah (approval no: EC115 in 10/12/2024) and patients handling complied with the Declaration of Helsinki [12].

Study groups

A total of three groups of 150 patients were allocated at random and equally. Group 1 (n = 50) was the control (non-diabetic), group 2 (n = 50; T2DM who had been taking metformin exclusively for at least three months after their initial diagnosis were included), and group 3 (n = 50; diabetic and received metformin + sitagliptin group for at least 3 months).

Selection criteria

Patients of both sexes, and older than eighteen years, were included, while those with a history of thyroid disorder, hypertension, or other chronic illnesses, and patients taking drugs that are known to alter renal function or lipid profiles, were excluded.

Evaluation of indices/parameters

Fasting blood sugar (FBS)

Blood samples were taken after 8-12 h fast and the blood glucose level was determined in triplicate.

Glycated haemoglobin (HbA1c), renal function, and lipid profiles

Glycated haemoglobin (HBA1C), renal function, and lipid profiles were determined using standard clinical laboratory procedures.

Data analysis

A one-way analysis of the variance (ANOVA) was performed to evaluate the measurement

outcomes, which were expressed as mean ± standard deviation (SD). Statistical significance is defined as P < 0.05.

RESULTS

Demographic characteristics of participants

A normal (control) group, a monotherapy with metformin group (Group 1), and a sitagliptin-metformin combined regimen (Group 2) constituted the three groups of 50 patients each. The participants ranged in age from 46 to 73 and were of both sexes. All groups had similar mean ages, which ranged from 53 to 63. All patients in the diabetic groups were on the appropriate stable treatment regimens for a minimum of three months, and the period of diabetes from diagnosis ranged from three to ten years. In line with the exclusion criteria, none of the individuals had a record of thyroid disease or other chronic medical conditions, and all were normotensive. At baseline, it had no remarkable variations in the distribution of age or sex across all groups.

Blood glucose parameters

The mean FBS and HbA1c levels were significantly elevated in both treated groups compared to control group ($p < 0.05$; as in Table 1).

Blood pressure and hs-cTn

Group 1 showed significantly higher systolic blood pressure related to control ($p < 0.05$), while in group 2, with no significant difference in diastolic blood pressure. High-sensitivity cardiac troponin (hs-cTn) was significantly higher in group 1 compared to control and group 2 ($p < 0.05$).

Lipid profile

Group 1 and group 2 showed significantly different ($p < 0.05$) cholesterol levels compared to controls. There was a significant difference in the levels of triglycerides of G2 in contrast to the control. However, LDL-C and HDL-C showed a non-significant difference across the groups ($p > 0.05$).

Kidney function markers

Blood urea (BU) and creatinine were considerably ($p < 0.05$) higher in control than in groups 1 and 2 ($p < 0.05$).

Table 1: Alterations in FBS, and HBA1c (n = 50 in each group, mean ± SD)

Parameters	Control	Group 1	Group 2
FBS	118.0±14.08	209.16±90.39*	286.63±98.06*
HBA1c	5.79±0.56	7.26±2.14*	6.91±1.82*

*$P < 0.05$ vs control

Table 2: Blood pressure and serum hs-cTn (n = 50 in each group, mean ± SD)

Parameters	Control	Group 1	Group 2
Systolic BP (mmHg)	123.03±11.52	131.95±17.47*	125.06±19.53$^{\#}$
Diastolic BP (mmHg)	79.27±7.049	81.85±16.1	76.17±9.66$^{\#}$
hs-cTn (pg/mL)	9.7±3.26	152.8±52.70*	115.9±49.09*$^{\#}$

*$P < 0.05$ vs control, $^{\#}p < 0.05$ vs Group 1

Table 3: Serum lipid biomarkers (n = 50 in each group, mean ± SD)

Parameters	Control	Group 1	Group 2
Cholesterol (mg/dL)	209.68±42.01	191.7±55.6*	190.2± 45.9*
Triglyceride (mg/dL)	205.4±80.5	179.5±75.1	166.2±43.4*
LDL (mg/dL)	120.56±25.17	103.21±32.96	88.15± 22.52*
HDL (mg/dL)	47.23±12.2	45.81±10.4	45.65±11.6

*$P < 0.05$ vs control

Table 4: Renal function biomarkers (n = 50 in each group, mean±SD)

Parameters	Control	Group 1	Group 2
Blood urea	40.3±27.4	29.5±8.7*	31.2±8.6
Creatinine	1.1±0.6	0.7±0.1	0.6±0.1*

*$P < 0.05$ vs control

DISCUSSION

This research studied the effects of metformin alone as well as in combination with sitagliptin on metabolism, cardiovascular health, and kidney function of diabetic patients. Results revealed that, as metformin plus sitagliptin both significantly reduced hyperglycemia compared to controls, the combined medication additionally improved cardiovascular and renal biomarkers, indicating a more general organ-protective impact. Also, groups 1 and 2 had considerably greater HbA1c and FBS levels than the controls. When metformin and sitagliptin were taken together, patients' HbA1c was less than if metformin was administered alone. This observation is according to other research, indicating that if utilised together with metformin, DPP-4 inhibitors offer synergistic glycaemic control [7,10]. This improvement is possibly explained via the incretin-mediated effect, which sitagliptin utilises to induce glucagon inhibition and insulin secretion that is glucose-dependent and maintain endogenous concentrations of GLP-1 and GIP [5]. It will promote the administration of combined medication to assist patients with type 2 diabetes in maintaining glycaemic control when monotherapy is ineffective. Results further revealed that in comparison with a control group, systolic blood pressure and hs-cTn values were considerably greater in group 1 and less in group 2. Increased hs-cTn in diabetic patients represents an indicator of subclinical cardiac injury, which was shown to anticipate cardiovascular events even if there is no evidence of obvious symptoms [11]. About its anti-inflammatory and endothelial-stabilizing characteristics, sitagliptin may provide considerable cardiac protective benefits, demonstrated by a reduction in hs-cTn in group 2. Endothelial nitric oxide bioavailability, NF-κB activation, and oxidative stress are improved by DPP-4 inhibition [8]. This may result in decreased cardiac stress and increased vascular compliance [1]. On the other hand, sympathetic activation or changed vascular reactivity brought on by hyperglycemia may be responsible for the mild increase in systolic pressure following metformin treatment. These data suggest that even though metformin has neutral or advantageous cardiovascular benefits, cardioprotection in diabetes definitely demands multimodal metabolic and vascular control, which a combined protocol can more effectively achieve [13]. Triglyceride, LDL-C, and HDL-C concentrations remained the same appreciably among the groups in the present research; still, group 2's cholesterol values were slightly greater than those of the control.

The findings confirm previous research indicating that metformin decreases LDL and triglycerides but has no effect on HDL [14]. In addition, sitagliptin exerts neutral lipid properties, as reported by Salmen *et al* [2]. It means that instead of directly influencing lipid metabolism, the two drugs essentially influence glycaemic and cardiovascular variables. Still, long-lasting cardiovascular advantages can result resulting from the combination's increased endothelial activity and reduced inflammatory responses related to incretin-mediated pathway activity [9]. With respect to the controls, blood urea levels (BU) and creatinine concentration (Cr) both significantly reduced in group 1 and far less in group 2. This observation signifies initial indications of nephroprotection, such as elevated renal clearance and possibly decreased glomerular hyperfiltration. Wang *et al* [9] stated that via inhibiting DPP-4 in proximal tubular cells, sitagliptin may assist kidney function by promoting renal perfusion, minimizing oxidative stress, and decreasing inflammation. Also, sitagliptin reduces albuminuria and attenuates tubular apoptosis in diabetic nephropathy models by inhibiting the AGE–RAGE–NF-κB signaling cascade [10]. On the other hand, metformin activates the AMPK, which enhances mitochondrial energy metabolism and reduces oxidative damage to the kidneys [14]. The research's increased kidney measures are probably a consequence of both procedures acting concurrently. Such results offer confidence to the metabolic–cardiorenal axis, which connects glycaemic management, vascular homeostasis, and kidney preservation in controlling the symptoms of diabetes. The sitagliptin–metformin combination seems to concentrate on a variety of pathophysiological processes, particularly oxidative damage, mild inflammation, diabetes resistance, and endothelial cell damage [1]. Beneficial cardiorenal results were additionally documented by newer medications, including SGLT2 inhibitors as well as GLP-1 receptor agonists [2].

Limitation of the study

There are multiple limitations in this study. Among the study's problems are its small number of participants, inadequate long-term monitoring, and the lack of extra renal parameters like albumin-creatinine ratio (ACR) or estimated rate of glomerular filtration (eGFR). Future research must employ molecular and imaging markers to explain the pathways behind the evident cardiorenal protective effects. In addition, researching the impact of triple treatment—a combination of sitagliptin, metformin, and SGLT2 inhibitors—may reveal

further insight regarding the synergistic pathways that enable full diabetes management.

CONCLUSION

Compared to metformin alone, the combination of sitagliptin and metformin markedly enhance control of cardiovascular and renal parameters. Thus, the combination can mitigate subclinical renal and cardiovascular impairment in T2DM. Therefore, a logical and scientific approach to comprehensive diabetes management would be the combination of sitagliptin and metformin, which targets not only glucose but also the heart and kidneys that diabetes frequently endangers particularly in circumstances in which exposure to further current drugs like GLP-1 receptor agonists or SGLT2 inhibitors is limited.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

It is stated in the method.

Use of Research Reporting Tools

We are committed to transparent and complete reporting of our research, in line with the journal's guidelines and WAME requirements. Our study is a prospective, parallel-group, randomized controlled trial. The Consolidated Standards of Reporting Trials (CONSORT) 2025 Statement is the appropriate reporting guideline for this study design. We have used the CONSORT 2025 checklist to ensure that all essential items are adequately reported in our manuscript. The checklist covers key areas.

Availability of data and materials

We confirm that a completed CONSORT checklist is available and can be provided upon reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors have made substantial contributions to the conception, design, execution, and interpretation of this study.

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