RESEARCH ARTICLE

Differential Impact of Metformin Combined with Sitagliptin or Pioglitazone on Glycemic Control and Adipokine Regulation in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) involves insulin resistance and pancreatic β-cell dysfunction, with adipose tissue dysfunction playing a key role through imbalanced adipokines like leptin and adiponectin. The leptin-to-adiponectin ratio emerges as a sensitive marker of metabolic risk. While metformin is first-line therapy, combining it with sitagliptin or pioglitazone may differentially influence insulin sensitivity and adipokine profiles.

Aim: to assess how metformin plus sitagliptin and metformin plus pioglitazone affect adipokine levels, insulin resistance, and glycemic control in patients with T2DM.

Methods: This is a comparative observational study that enrolled 134 T2DM patients already stabilized on combination therapy for no more than 6 months including 68 on metformin 1000 mg/day + sitagliptin 50 mg twice daily; and 66 on metformin 1000 mg/day + pioglitazone 15 mg/day. Blood samples were collected after overnight fasting and were used to measure glucose, HbA1c, insulin, insulin resistance, pancreatic β-cell function, adiponectin, and leptin.

Results: The baseline characteristics of patients in both groups were not different significantly. The pioglitazone group showed lower fasting glucose (132.6±32.4 vs. 147.5±44.8 mg/dL, p=0.03), insulin (12.9±6.2 vs. 16.9±8.7 µU/mL, p=0.002), HOMA-IR (4.4±2.7 vs. 6.2±4.4, p=0.004), leptin (21.9±9.1 vs. 25.8±10.7 ng/mL, p=0.02), and LAR (4.3±2.3 vs. 5.2±2.5, p=0.03). LAR value is shown to be positively correlated with HOMA-IR in the studied groups (p<0.001).

Conclusion: In patients with T2DM, metformin plus pioglitazone was linked to a higher improvement in insulin sensitivity and adipokine balance than metformin plus sitagliptin. For determining the clinical significance of these differences, additional longitudinal studies evaluating cardiovascular outcomes are necessary, even though these findings point to a more favorable metabolic profile.

Keywords: Adiponectin, Leptin, Metformin, Pioglitazone, Sitagliptin.

INTRODUCTION

As a rising global health concern, type 2 diabetes mellitus (T2DM) is closely linked to obesity and long-term overnutrition. It is marked by a high risk of microvascular and macrovascular complications, such as retinopathy, nephropathy, neuropathy, and heart diseases [1,2]. In 2024, 589 million adults, approximately 1 in 9, worldwide had diabetes. By 2050, that figure is expected to rise to 853 million. Most of these cases are presented as T2DM, which is constitutes more than 90% of all diabetes cases and is the main cause of the rapidly rising global diabetes burden [3]. A complex relationship between genetic and environmental factors causes impaired glucose homeostasis, insulin resistance, and progressive pancreatic β-cell dysfunction in the pathophysiology of T2DM [4]. Additionally, it is becoming more widely acknowledged that adipose tissue is an active endocrine organ that is crucial to the pathophysiology of the condition through dysregulation of special signaling proteins called adipokines. Dysregulated adipokine, abnormal secretion linked to obesity, is commonly associated with insulin resistance, persistent low-grade inflammation, and the development of T2DM [5,6]. The two main adipokines that affect insulin resistance and glucose metabolism are leptin and adiponectin. The leptin-adiponectin ratio (LAR) may be a more informative biomarker for early assessment of patients at higher risk of metabolic dysregulation, unstable glycemic control. Its screening is regarded as a primary prevention strategy of the cardiometabolic disorders than either hormone alone.

These molecules are considered potential biomarkers for monitoring, diagnosis, and treatment of T2DM [7].

A significant percentage of T2DM patients do not meet recommended glycemic targets despite the availability of several antidiabetic treatments.

In addition to contributing to increasing β-cell dysfunction and worsening insulin resistance, persistent poor glycemic control accelerates the development of microvascular and macrovascular complications. These difficulties highlight the significance of optimizing combination therapies that address underlying metabolic disorders, achieve optimal glycemic control, while addressing related metabolic and oxidative abnormalities. Therefore, therapeutic approaches that enhance insulin sensitivity, maintain β-cell function, lower oxidative stress, and rebalance adipokines may be particularly effective [8]. Currently, a number of pharmaceuticals are used to help patients with T2DM maintain better glycemic control and lower blood glucose fluctuations.

These include sodium-glucose cotransporter-2 (SGLT2) inhibitors, incretin-based treatments (like dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists) and insulin sensitizers (like metformin and thiazolidinediones). These medications can lessen metabolic stress and enhance glycemic control but many patients still experience glycemic variability [9]. Additionally, issues like side effects, cost, fluctuations in weight, and inconsistent patient reactions may restrict their clinical application. These limitations emphasize how crucial it is to find treatment approaches that address underlying metabolic disorders like insulin resistance and adipose tissue dysfunction in addition to raising glucose levels.

Sitagliptin and pioglitazone are, in fact, two antidiabetic agents commonly used in the management of T2DM, but they work through different mechanisms. Thus, they could differentially affect the metabolic pathways related to insulin resistance and adipose tissue dysfunction. Pioglitazone, which acts as a peroxisome proliferator-activated receptor (PPAR) agonist, not only increases insulin sensitivity but it also affects the process of adipocyte differentiation and the secretion of adipokines. This might result in higher levels of adiponectin and better metabolic equilibrium [9].

On the other hand, sitagliptin that is a DPP-4 inhibitor functions by activating incretin hormones and stimulating the release of insulin in a glucose-dependent fashion. This mainly results in an improvement in glycemic control and, unlike pioglitazone, it does not have an effect on insulin resistance directly [10].

Based on this difference in mechanism of action, and the fact that drug combination is the preferred strategy for treating patients with T2DM, we hypothesize that these drugs when combined with metformin might result in different effects on adipokine patterns, especially on LAR, which is now considered a very sensitive indicator of metabolic risk. However, the clinical application of these drugs might be affected by limitations such as the weight gain and fluid retention associated with pioglitazone, as well as the very rare cases of pancreatitis reported with DPP-4 inhibitors. Thus, the aim of this study was to investigate the effect of either pioglitazone or sitagliptin combined with metformin therapy on insulin resistance as well as differences in adipokine secretion profiles among patients with T2DM. Furthermore, this study also examined the differences between these combinations concerning their influence on metabolic parameters and adipose tissue dysfunction, to provide a clear understanding of the roles of these combinations regarding the enhancement of insulin sensitivity for better individualized therapy.

PATIENTS AND METHODS

Study design, period, and ethical considerations

The current work is a comparative observational study that was carried out at the consultation unit of AL-Wafaa Center for Diabetes and Endocrine Disorders, Mosul/Nineveh, during October to December 2025. The ethical approval was obtained from The Research Committee of Nineveh Health Directorate with code number 2025248. The purpose of conducting this research was explained to all participants and their consent was obtained before inclusion to the study. The participants were subjected to medical examination by consultants to approve their inclusion and to avoid variables affecting the outcome of the study.

Patients, Materials and Methods

Study participants

The study included a total of 134 patients with T2DM divided into two treatment groups. Group 1 (Metformin plus sitagliptin group), this group comprised 68 patients (33 males and 35 females) treated with metformin (1000 mg/day) in combination with sitagliptin (50 mg/twice daily). Group 2 (Metformin plus pioglitazone group), included 66 patients (32 males and 34 females) who were receiving metformin (1000 mg/day) in combination with pioglitazone (15 mg/once daily). Exclusion criteria included patients under insulin treatment regimen or other antidiabetic agents different from those studied, as well as patients on chronic medications due to cardiovascular diseases like heart failure; renal or any other chronic or systemic illnesses that could have an effect on glucose metabolism or adipokine levels. Pregnant and lactating women were also excluded. Basic demographic data were collected from each participant. These are age, sex, body mass index (BMI), duration of diabetes, duration of treatment, and family history of diabetes

Laboratory methods

After an overnight fast, 5 ml. of venous blood were collected from each participant using disposable syringes.

The blood samples were divided into two portions. Two milliliters were transferred into EDTA tubes for the measurement of glycated hemoglobin (HbA1c). HbA1c was determined using the turbidimetric inhibition immunoassay (TINIA) method on a Cobas c111 autoanalyzer with commercially available kits supplied by Roche Diagnostics (Germany). The remaining blood was placed into plain tubes, allowed to clot, and centrifuged at 3000 rpm for 10 minutes to obtain serum. Fasting serum glucose was measured photometrically using the Cobas c111 autoanalyzer and Roche diagnostic kits (Germany). Serum insulin, adiponectin and leptin levels were determined using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Insulin resistance and pancreatic beta-cell function were assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) and Homeostasis Model Assessment of beta-cell function (HOMA-B) respectively.

Statistical analysis

GraphPad Prism 8.4.2 was used for analysis of the study data. Continuous variables presented as mean ± standard deviation (SD), while categorical variables are expressed as numbers. Comparisons between the two study groups were carried out using the unpaired t-test for continuous variables and the chi-square test for categorical variables. Pearson's correlation analysis was used to assess the relationship between LAR and insulin resistance as estimated by HOMA-IR. A p value of ≤ 0.05 was considered statistically significant.

Ethical statement

Ethical approval was obtained from The Research Committee of Nineveh Health Directorate with code number 2025248.

RESULTS

Baseline characteristics of the study groups

A total of 134 patients with T2DM were included in the study. Group 1 consisted of 68 patients treated with metformin plus sitagliptin, while Group 2 included 66 patients treated with metformin plus pioglitazone. There were no significant differences between the two groups regarding age, sex distribution, body mass index (BMI), duration of diabetes, duration of treatment, and family history of diabetes (Table 1).

Glycemic Status and Insulin Resistance

The glycemic parameters of both groups are shown in Table 2. Fasting serum glucose was significantly higher in Group 1 compared with Group 2 (147.5 ± 44.8 vs. 132.6 ± 32.4 mg/dl, p=0.03). However, there was no significant difference in HbA1c levels between the two groups (p=0.3). Serum insulin levels were significantly higher in Group 1 than in Group 2 (16.9 ± 8.7 vs. 12.9 ± 6.2 µU/ml, p=0.002). Similarly, HOMA-IR values were significantly elevated in Group 1 compared with Group 2 (6.2 ± 4.4 vs. 4.4 ± 2.7, p 0.004), indicating greater insulin resistance in patients receiving sitagliptin with metformin. No significant difference was observed in HOMA-B between the two groups.

Table 1
Baseline demographic and clinical characteristics of patients with T2DM in the two treatment groups

Variable	Group 1	Group 2	P-value
Number (M/F)	68 (33/35)	66 (32/34)	0.9
Age (years mean ± SD)	47.7±8.1	48.9±9.3	0.44
Duration of Diabetes (months)	11.1±3.5	11.6±3.8	0.43
Duration of treatment (months)	4.7±1.1	4.5±1.2	0.54
Family history (Y/N)	32/36	32/34	0.8
BMI (kg/m^2)	30.6±6.4	30.1±5.3	0.61

BMI: body mass index, F: female, M: male, N: no, Y: yes, Group 1: Sitagliptin + metformin, Group 2: Pioglitazone + metformin.

Table 2
Comparison of glycemic parameters and insulin resistance indices between the two treatment groups

Parameter	Group 1 (mean ± SD)	Group 2 (mean ± SD)	P-value
FSG (mg/dl)	147.5±44.8	132.6±32.4	0.03
HbA1c (%)	7.2±1.5	6.9±1.5	0.3
Insulin (µU/ml)	16.9±8.7	12.9±6.2	0.002
HOMA-IR	6.2±4.4	4.4±2.7	0.004
HOMA-B	86.7±54.1	80.5±51.1	0.5

Data are significant when p value is ≤0.05, using unpaired t. test. Group 1: Sitagliptin + metformin. Group 2: Pioglitazone + metformin.

Adipokine Levels

Adipokine levels in the studied groups are presented in Table 3. Serum adiponectin levels were slightly higher in Group 2 than in Group 1; however, this difference did not reach statistical significance. In contrast, serum leptin levels were significantly higher in Group 1 compared with Group 2 (25.8 ± 10.7 vs. 21.9 ± 9.1 ng/ml, p=0.02). The LAR was also significantly higher in Group 1 than in Group 2 (5.2 ± 2.5 vs. 4.3 ± 2.3, p=0.03), suggesting a less favorable adipokine profile in patients treated with sitagliptin combined with metformin (Table 3).

Table 3
Adipokine profile in patients receiving metformin plus sitagliptin (Group 1) or metformin plus pioglitazone (Group 2)

Parameter	Group 1	Group 2	P-value
Adiponectin (µg/ml)	5.1±1.3	5.6±2.1	0.13
Leptin (ng/ml)	25.8±10.7	21.9±9.1	0.02
LAR	5.2±2.5	4.3±2.3	0.03

Data are expressed as mean ± SD, and are significant when p value is ≤0.05, using unpaired t. test.

Correlation between LAR and insulin resistance

LAR and HOMA-IR showed a strong positive correlation in both treatment groups, according to Pearson's correlation analysis. LAR and HOMA-IR showed a significant positive correlation in Group 1 ($p<0.0001$). Similarly, there was a significant positive correlation ($p<0.001$) between these parameters in Group 2. Regardless of the type of treatment, these results show that higher LAR values are linked to increased insulin resistance (Fig 1).

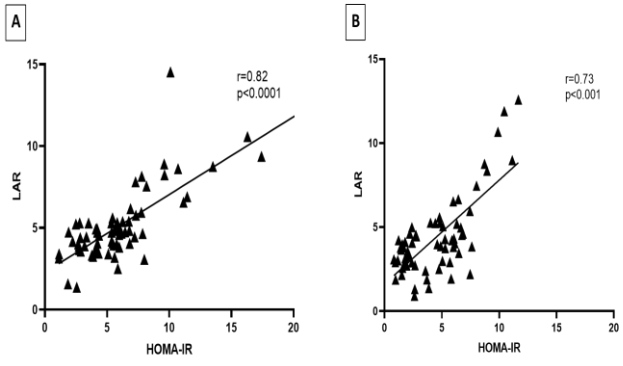

Fig 1. Correlation between leptin-to-adiponectin ratio (LAR) and insulin resistance (HOMA-IR) in the two treatment groups. Pearson's correlation between serum LAR and HOMA-IR. A: Group 1 (sitagliptin + metformin); B: Group 2 (pioglitazone + metformin). LAR and HOMA-IR showed a strong positive correlation in both treatment groups at $p<0.0001$.

DISCUSSION

With a focus on glycemic indices, insulin resistance, and adipokine profiles, the current study assessed the various metabolic effects of metformin in combination with either sitagliptin or pioglitazone in patients with T2DM. Age, sex distribution, BMI, the duration of diabetes and treatment were all well matched between the two groups at baseline, which decreased the possibility that these variables would have influenced the results. As a result, the treatment regimens are more likely to be responsible for the differences found in this study. Comparative data indicates that pioglitazone and sitagliptin are both useful treatments option. A 52-week randomized controlled trial reported that sitagliptin and pioglitazone, as add-on therapies in patients with poorly controlled T2DM on metformin and sulfonylureas, were equally effective in reducing HbA1c, although modest differences were observed in lipid indices, systolic blood pressure, weight gain, and fasting glucose reduction, which was slightly greater with pioglitazone. This encourages personalized treatment choices based on baseline metabolic rates [11]. However, the current study's findings showed that the groups under investigation differed significantly in terms of fasting glucose, insulin resistance indicators, and adipokine balance. When compared to patients receiving metformin plus sitagliptin (Group 1), patients treated with metformin plus pioglitazone (Group 2) showed significantly lower fasting serum glucose, circulating insulin levels, and HOMA-IR values, suggesting a greater improvement in insulin sensitivity in Group 2. These results match with the known mechanism of action of pioglitazone as a PPAR-γ agonist, which increases insulin sensitivity by reducing lipotoxicity and inflammation, redistributing fat from visceral to subcutaneous depots, and differentiating adipocytes [12]. This is supported by a recent randomized multicenter study carried out in China that showed, when compared to metformin alone, a fixed-dose combination of pioglitazone and metformin improved glycemic control, insulin resistance, lipid profile, and inflammatory markers [13]. The lower HOMA-IR values observed in the pioglitazone group are consistent with its established role as a PPAR-γ agonist that enhances peripheral insulin sensitivity and improves adipose tissue function. Unlike pioglitazone, sitagliptin mainly lowers blood sugar by inhibiting DPP-4, which increases glucose-dependent insulin secretion through incretin [14]. The higher circulating insulin levels and HOMA-IR values seen in the metformin plus sitagliptin group in the current study may be explained by this insulinotropic mechanism. Metformin and sitagliptin combination therapy offers good glycemic control with a favorable safety and tolerability profile, according to an evidence-based review of phase III clinical trials. However, sitagliptin may modulate adipokine secretion and adipose tissue function less effectively, in comparison to pioglitazone, because of its limited direct effects on

insulin sensitivity [15]. HbA1c levels, however, did not significantly differ between the two treatment groups in the present study, despite significant differences in fasting glucose and insulin resistance indices. Given that HbA1c measures cumulative glycemic exposure rather than transient metabolic changes, this result most likely reflects the cross-sectional design of the study and the relatively short treatment duration. The current study's adipokine analysis showed that patients receiving metformin plus sitagliptin had significantly higher leptin concentrations and LAR values, while those receiving metformin plus pioglitazone had a more favorable adipokine profile. The pioglitazone group had somewhat higher levels of adiponectin, but this difference was not statistically significant. Pioglitazone dramatically lowers leptin levels and raises adiponectin concentrations, effects not consistently seen with metformin alone, according to a meta-analysis of ten randomized controlled trials [16]. Notably, weight gain brought on by pioglitazone has been documented without corresponding increases in leptin levels, indicating either decreased leptin secretion per unit fat mass or enhanced leptin sensitivity [17]. Pioglitazone positively modulates the distribution of adipose tissue and the balance of adipokines, according to additional mechanistic evidence. In comparison to glimepiride-treated patients, a four-month intervention on 32 pioglitazone-treated patients improved hepatic insulin sensitivity, increased HDL cholesterol, and decreased C-reactive protein levels while also significantly lowering the visceral-to-subcutaneous fat ratio and LAR [18]. Additionally, a robust and significant increase in adiponectin levels with pioglitazone treatment was confirmed by a meta-analysis comparing pioglitazone with metformin [19]. These results demonstrate pioglitazone's ability to enhance adipose tissue function outside of glycemic control. The observed reduction in LAR in the pioglitazone group may reflect improved adipokine balance associated with enhanced insulin sensitivity, which supports the mechanistic role of adipose tissue dysfunction in the pathophysiology of T2DM. LAR has become a sensitive indicator of metabolic dysfunction due to the strong correlation between insulin resistance, decreased adiponectin bioavailability, and leptin resistance. The substantial positive correlation between LAR and HOMA-IR found in both treatment groups supports the idea that adipose tissue dysfunction plays a part in the pathophysiology of insulin resistance in type 2 diabetes. Apart from their roles in the development of type 2 diabetes, a case-control study found that the plasma levels of both leptin and adiponectin can reveal the severity of coronary artery diseases; however, leptin may be a more accurate indicator of the severity of CAD than either LAR or adiponectin alone [20]. Clinical data further demonstrates pioglitazone's potential cardiometabolic advantages by confirming its capacity to raise adiponectin levels even in the absence of full insulin normalization [21, 22].

All of these results point to the fact that while metformin plus sitagliptin successfully modulates glycemic control through insulinotropic mechanisms, metformin plus pioglitazone offers more extensive metabolic benefits by improving insulin sensitivity and correcting adipokine imbalance. Patients with significant insulin resistance and obesity may benefit most from these pleiotropic effects, which may lower their long-term cardiometabolic risk. Larger longitudinal studies should be the main focus of future research in order to better understand how adipokine-related biomarkers, in particular the leptin-to-adiponectin ratio, predict metabolic outcomes and direct treatment choices in T2DM patients. Such studies could aid in overcoming present gaps in our knowledge of adipose tissue dysfunction and facilitate the creation of more focused and customized treatment plans. Lastly, it is important to note that our study has a number of limitations, such as a cross-sectional design and a relatively short treatment period that may underestimate long-term effects on adipokine dynamics and glycemic control. Despite these limitations, this study offers the first direct comparison of metformin plus sitagliptin and metformin plus pioglitazone, offering a groundwork for future longitudinal and mechanistic investigations.

CONCLUSIONS

This study shows that in patients with T2DM, metformin plus pioglitazone is linked to a better adipokine profile and a greater improvement in insulin sensitivity than metformin plus sitagliptin. These results imply that treatments aimed at adipose tissue dysfunction and insulin resistance may provide metabolic advantages beyond glycemic control. For evaluating metabolic risk and treatment response, LAR may be a helpful biomarker. To validate the clinical implications of these findings and their possible influence on long-term cardiometabolic outcomes, more longitudinal research is necessary.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Author contribution

IOK performed the experimental work, data collection, and drafted the manuscript. SHM and MHA conceived and designed the study, supervised the research, and contributed to data analysis and

interpretation. SHM and MHA also critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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