ORIGINAL ARTICLE

CONTENTS

Molecular docking analysis of the interaction between metformin/glimepiride combination and organic cation transporter in diabetic patients

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ABSTRACT

Aim: This study aimed to evaluate the interaction of glimepiride/metformin with organic cation transporter protein-1 (OCT-1) using molecular docking technology, as well as to determine the drug's effect on serum OCT-1 levels in patients compared to healthy individuals. This may contribute to understanding the efficacy of this treatment in controlling blood glucose levels.

Materials and Methods: Molecular docking technology was used to determine the interaction of the glimepiride/metformin combination with organic cation transporter 1 (OCT-1). The study included 50 women: 26 with type 2 diabetes and 24 healthy women as a control group. ELISA was used to determine the levels of organic cations in the participants' serum.

Results: The results showed a high binding energy of -10.2 kcal/mol between the glimepiride/metformin combination and the OCT-1 protein, indicating the drug's efficacy in treating diabetes. These results confirm the findings of the clinical trial on OCT-1, which showed that the protein level in patients was (511.6 ± 120.3), similar to the concentration in the control group (558.8 ± 39.2), indicating that most of the drug had entered the cells.

Conclusions: The results suggest that the glimepiride/metformin combination is a recommended treatment option for lowering blood glucose levels and treating type 2 diabetes.

KEY WORDS: organic cation, type 2 diabetes, molecular docking, glimepiride

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INTRODUCTION

The protein-protein interaction is important in explaining the actions of several molecules as well as the structure for identification. Molecular docking was used for the interaction; this method explains the association with the active site [1, 2]. The presented method is very important in knowing the action of drugs that are used for treating diseases; the most important model used is diabetes [3, 4]. Several parameters were used to identify it is relation to diabetes and drug that used in treated diabetes [5, 6]. Diabetes is also associated with metabolic syndrome [7]. Most people with type 2 diabetes are obese and have insulin resistance, which reduces the cells' response to insulin [8, 9]. At the onset of the disease, beta cells increase insulin secretion to compensate, but over time, they become unable to maintain this level, leading to disease progression [10]. Genetic factors also play a role in the development of the disease [9, 11]. Many drugs are used to treat diabetes, the first line of treatment being the diabetes drug metformin [12, 13]. Metformin works by preventing the liver from producing glucose, reducing glucose production, and increasing energy expenditure in fat, liver, and muscle cells by activating AMP-activated protein kinase, which helps these tissues absorb and utilize glucose well [12, 14, 15]. Glimepiride, a type of medication called a sulfonylurea, helps control type 2 diabetes by stimulating the pancreas to secrete more insulin [16]. Many medications require transporter or carrier proteins. They facilitate the transport of many drugs and natural substances across cell membranes and organelles. One such transporter protein is the organic cation transporter OCT1 (SLC22A1), which is primarily expressed in the liver [17]. OCT-1 facilitates the uptake of cationic metabolites and drugs in the liver and plays a role in their distribution and transport within hepatocytes [18, 19]. Glimepiride increases the number of glucose transporters on the surface of muscle and adipose tissue cells, helping these cells absorb glucose more efficiently. It also promotes insulin-mediated glycogen synthesis and lipogenesis, and reduces glucose production in the liver. Its blood glucose-lowering effect is based on increased insulin

secretion and improved glucose utilization by the body Glimepiride is rapidly and completely absorbed when taken orally [20]. Combination of drugs are important to lowering blood glucose, for example metformin which is long been used for treating diabetes can be combined with other medications [21, 22]. Also, sulfonylurea drug with metformin or Glimepiride with metformin [23-25]. Although patients use these drugs to manage diabetes, their effectiveness in lowering blood sugar levels varies. This study was conducted to examine the effectiveness of various drugs in treating diabetes by examining how strongly they bind to receptors and comparing predicted results with actual receptor levels.

AIM

This study aimed to evaluate the interaction of glimepiride/metformin with organic cation transporter protein-1 (OCT-1) using molecular docking technology, as well as to determine the drug's effect on serum OCT-1 levels in patients compared to healthy individuals. This may contribute to understanding the efficacy of this treatment in controlling blood glucose levels

MATERIALS AND METHODS

This study included 50 women aged between 40 and 60 years with a body mass index (BMI) between 25.55 and 30.53.

The study was divided into two groups:

Group G1: 26 women diagnosed with type 2 diabetes, taking metformin with glimepiride.

Group G2: 24 healthy women, as a control group.

Patients with diabetes were diagnosed in the Diabetes and Endocrinology Department at Baghdad Teaching Hospital – Medical City. Diabetologists diagnosed 26 women with type 2 diabetes after assessing their symptoms and measuring their glycated hemoglobin (HbA1c) levels. The study also included a control group with normal HbA1c levels and no prior history of diabetes. All necessary approvals were obtained from the hospital and university for the study protocol.

CRITERIA FOR EXCLUSION

Women with chronic conditions, including heart, kidney, liver, bone, and tumor diseases, gastrointestinal diseases, hypertension, metabolic disorders, type 1 diabetes, and smokers, were excluded. women taking medications that could affect the study results were also excluded, with the exception of metformin and glimepiride.

SAMPLE COLLECTION AND ANALYSIS

Ten milliliters of venous blood were collected from each participant. A whole blood sample was immediately placed in an EDTA tube for glycated hemoglobin (HbA1c) level determination. The isolated serum was aliquoted into tiny containers. On the same day, spectrophotometry assessments were done on lipid and FBS levels in a segment of the extracted serum. The researchers aliquoted the residual serum into labeled storage vials and refrigerated it at -20°C to further measure the OCT-1 protein using the enzyme-linked immunosorbent assay (ELISA).

STATISTICAL WORK

Graph pad prism 10 and SPSS version 26 were used. Confidence interval 95% was used, One Way ANOVA analysis in combined with Tukey's multiple comparison tests were used to assess the significance level among the studied groups. other statistical toles was used like Reserve operator characteristic

ETHICAL APPROVAL

The ethical have been approved by the committee of College of Science for Women according to the reference 5302/22 in 2024/8/21

RESULTS AND DISCUSSION

MOLECULAR DOCKING

The researchers obtained the three-dimensional structure of OCT1 at a crystal resolution of 3.57 Å from the Protein Data Bank (PDB ID: 8ET6), which represents the native, unmutated form of the protein. Structural and physicochemical data for the drug compounds were obtained from PubChem. These compounds were then converted into the PDBQT format suitable for docking simulations using Open Babel, integrated into the PyRx platform.

THE MOLECULAR BOND OF GLIMEPIRIDE WITH THE ORGANIC CATION TRANSPORTER 1

The AutoDock program was used to analyze the molecular docking of glimepiride with the OCT-1 transporter protein. AutoDock was used to evaluate its binding affinity and location within the active site. Table 1 shows the optimal binding pose with a binding energy of -8.8 kcal/mol, indicating a strong and stable interaction between glimepiride and OCT-1. Other docking poses showed binding energies between -8.6 and -8.0 kcal/mol, supporting the stability of the molecule within the

Table1. Results of molecular docking of glimepiride with OCT1 protein

Ligand	Binding Affinity kcal/mol	RMSD	Interaction type	Amino Acids Residue
Glimepiride	-8.8	0	hydrogen bonds	SER-382
			carbon-hydrogen bonds Interaction	PHE-379
			van der Waals interactions	VAL-385, TYR-361, ARG-439, ILE-248, ILE-365, CYS-436, PHE-380, VAL -40 and LEU-248
			π-interactions such as π-sigma interactions	MET-368, and TYR -381
			π-alkyl interactions	TYR - 36, VAL-37,and LEU-384
			bi-anion interacts	ASP-378

Source: Compiled by the authors of this study

Table 2. Results of molecular docking of metformin and glimepiride with OCT-1 protein

Ligand	Binding affinity	RMSD/ lower and upper bound	Interaction type	Amino acids residue
Metformin + Glimepiride	-10.2	0	hydrogen bonds interactions	TYR-36, VAL-37, SER-358, ASP-474, and TYR-361
			Pi-sigma interactions	PHE-446
			van der Waals interactions	GLY-38, VAL-40, LYS-214, GLN-362, GLN-447, PHF-159, CYS-473, GLY-477, GLN-241, ALA-383, SER-382, ILE-365, ARG-439, and TRP-354
			Pi-alkyl interactions	PHE-379, LEU-248, and CYS -450
			alkyl interactions	PHE-379

Source: Compiled by the authors of this study

Table 3. Clinical data in patients having diabetes mellitus and control group

Parameter	G1:N=26 (Mean±SD)	G2:N=24 (Mean±SD)	P- Value
Age	49.3±7.2	44.6±6.2	0.7
BMI	29.9±3.1	26.2±1.8	0.005
FBG (mg/dl)	150.9±48.08	86.56±10.61	0.0001
HbA1C	8.361±1.568	5.246±0.388	0.0001
TG(mg/dl)	189.6±86.18	138.4±81.96	0.09
Cholesterol (mg/dl)	212.9±40.93	184.6±41.51	0.05
LDL(mg/dl)	125.7±36.45	110.6±40.75	0.2
HDL(mg/dl)	48.42±9.222	46.28±5.418	0.4
VLDL(mg/dl)	37.91±17.24	27.67±16.40	0.09

*Note: *For groups and presenting them with the symbols below:*
G1: Diabetic patients taking metformin with glimepiride;
G2: control group
Source: Compiled by the authors of this study

Table 4. Mean ± SD value of 1-OCT for studied groups

Parameters		G1	G2
OCT-1 (Pg/ml)	Mean± Std. deviation	511.6± 120.3	558.8± 39.2
	Lower 95% CI of mean	459.6	535.1
	Upper 95% CI of mean	563.6	582.5
	P Value	P= 0.1	

*Note: *For groups and presenting them with the symbols below:*
G1: Diabetic patients taking metformin with glimepiride;
G2: control group
Source: Compiled by the authors of this study

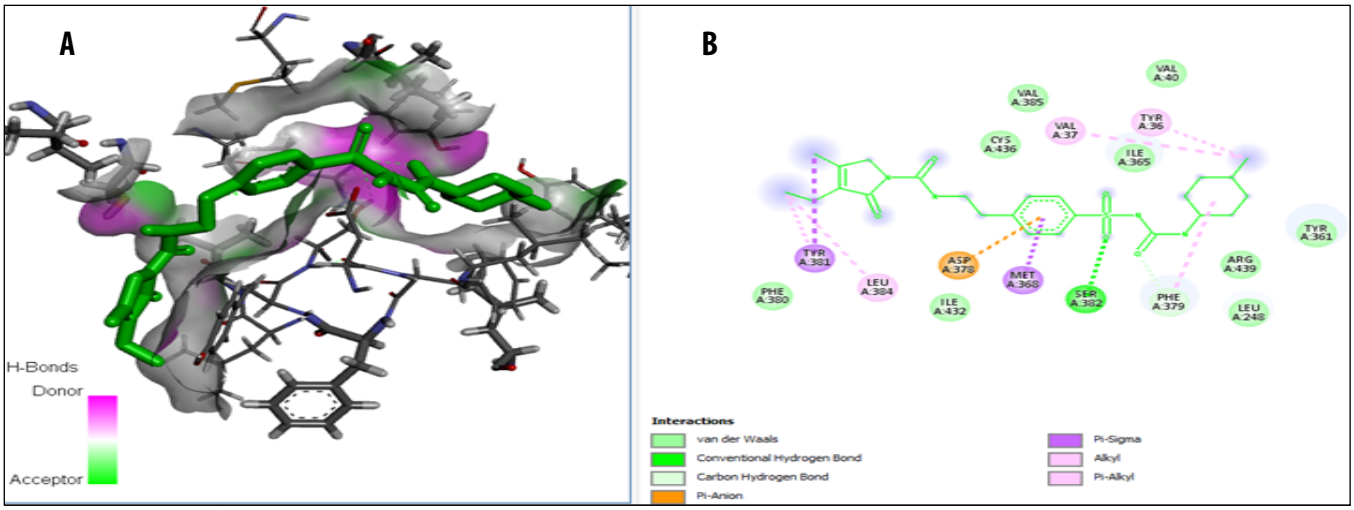

Fig. 1. A: Three-dimensional representation of the glimepiride interaction within the active site of the OCT-1 protein.
B: Two-dimensional representation of the glimepiride interactions with amino acid residues in the active site
Source: Own materials

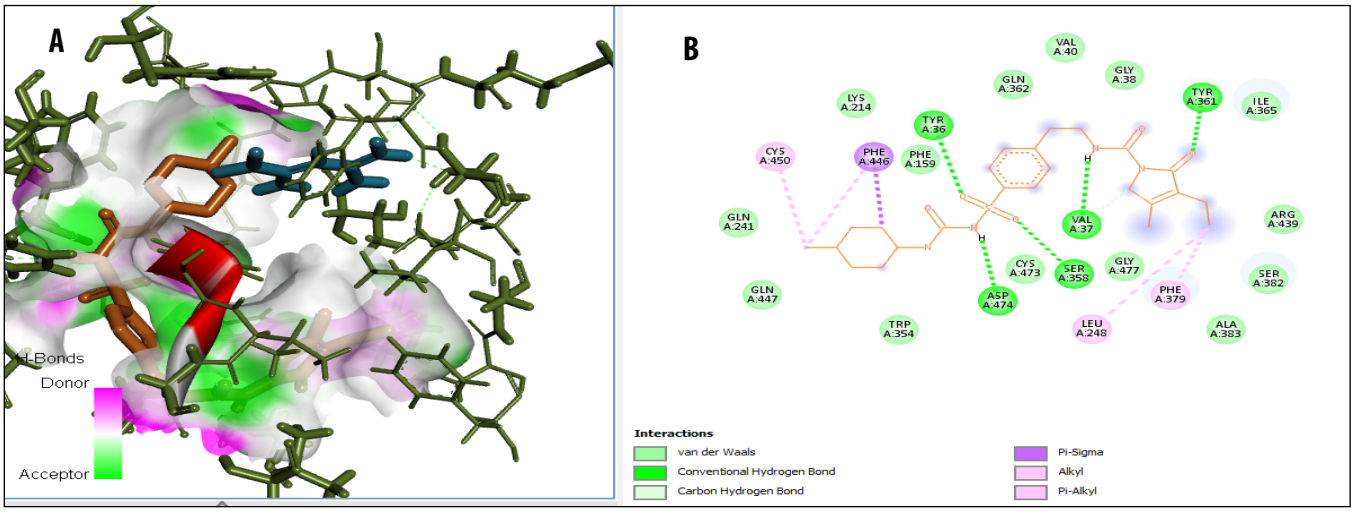

Fig. 2. A: 3D representation of metformin (shown in blue) and glimepiride (shown in red) interaction within the active site of OCT-1 protein.
B: Two-dimensional representation of the interactions of metformin and glimepiride with amino acid residues in the active site
Source: Own materials

active site. The optimal pose yielded an RMSD value of 0.0, confirming it as the reference structure. Figure 1. A-B shows that glimepiride localizes well within the protein's active pocket and identifies a set of key interactions with the surrounding amino acid residues. These include hydrogen bonds with SER-382, carbon-hydrogen bonds with PHE-379, and van der Waals interactions with VAL-385, TYR-361, ARG-439, ILE-248, ILE-365, CYS-436, PHE-380, VAL-40, and LEU-248. Interactions that contribute to enhancing the stability of glimepiride within the active site were observed: bi-sigma interactions with MET-368 and TYR-381, bi-alkyl interactions with TYR-36, VAL-37, and LEU-384, and a dianionic interaction with ASP-378. These results suggest that glimepiride exhibits a potent and effective binding to the OCT1 transporter protein, demonstrating its ability to influence protein function.

Molecular docking of metformin and glimepiride to the transporter protein OCT1, Using a molecular docking program, significant differences were found when the carrier protein was bound to metformin alone and then to both metformin and glimepiride. As previously demonstrated, the binding results with metformin were relatively weak, while the binding of glimepiride and metformin showed stronger results or binding forces of -8.5 and -10.2 kcal/mol. This improvement is likely due to the enhanced interactions facilitated by the presence of glimepiride with metformin, as the two molecules formed a network of interactions that included traditional hydrogen bonds with amino acids (such as TYR-36, VAL-37, SER-358, ASP-474, and TYR-361). Pi-sigma interactions were also evident with the amino acid PHE-446. In addition, van der Waals

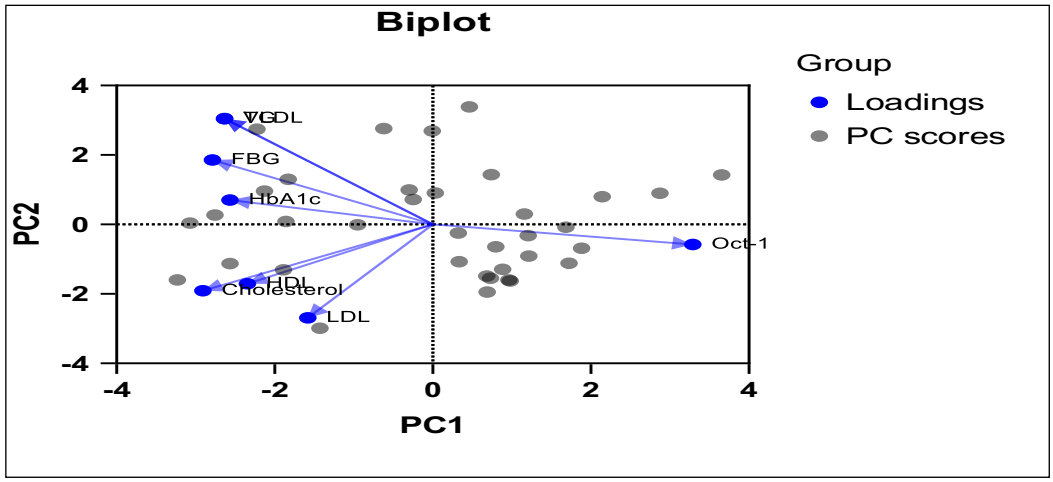

Fig. 3. Principle component analyses of metabolic parameters
Source: Own materials

interactions were recorded with (GLY-38, VAL-40, LYS-214, GLN-362, GLN-447, PHF-159, CYS-473, GLY-477, GLN-241, ALA-383, SER-382, ILE-365, ARG-439, and TRP-354), Pi-alkyl interactions were observed with (PHE-379, LEU-248, and CYS-450), and alkyl interactions occurred with the amino acid (PHE-379) as shown in Table 2 and Figure 2. A-C. These diverse and overlapping interactions reflect the compound's ability to stabilize itself within the binding site, enhancing the drug's interaction with the OCT-1 protein. This also suggests a potential synergistic effect on the transport or cellular uptake of the two drugs when used together, supporting their combined use in the clinical treatment of type 2 diabetes patients

In review patients with type 2 diabetes can receive glimepiride alone or in combination with other antidiabetic drugs. It can also be used as adjunctive therapy with insulin [26]. other study confirmed the clinical significance of glimepiride as a stimulant for insulin secretion from the pancreas, thereby improving blood glucose control [27]. A previous study evaluated the use of oral hypoglycemic medications to improve treatment practices. The results of this study showed that glimepiride was the optimal choice due to its superior pharmacokinetic properties in terms of safety and efficacy. However, its use was less common (28%) compared to glibenclamide, which was more commonly used (42.1%). Furthermore, the study found that the glibenclamide dosage was inadequate, and two cases of hypoglycemia were reported after prolonged use[28]. A recent computational study has shown that glimepiride has a high affinity for binding to human glucose transporter inhibitors and human aldose reductases, supported by molecular docking analysis and molecular dynamics simulation[29].

BIOCHEMICAL PARAMETERS

The clinical data of patients with diabetes mellitus and the control group are presented in Table 3. Age distribution ensured that age-related factors did not influence any statistically significant differences in the other variables. The results of the statistical analysis showed that age is not a statistically significant variable, due to the homogeneity of ages among the sample members. study results showed clear and statistically significant differences between groups G1 and G2 with regard to body mass index (BMI). indicating that individuals in group G1 experienced greater weight gain than individuals in groups G2. However, one study supports the idea that the drug has anti-obesity effects because it found that patients with type 2 diabetes who take metformin have a lower body mass index[30]. However, the results of this study showed the opposite: the mean body mass index (BMI) of patients using metformin with glimepiride (G1) was higher than the mean BMI of the healthy control group (G2). The lower BMI in the G2 group was an expected outcome, as these individuals did not suffer from any metabolic disorders and were likely to have followed healthy lifestyles that contributed to maintaining a normal weight. The higher BMI in the G1 group may be attributed to other factors, including poor adherence to treatment, lower levels of physical activity, or a difference in treatment duration.

Clinical parameters like HbA1c and FBG have been studied. The level of both studied parameters showed significant elevation in the patient group as compared to the control group. Use The combination treatment demonstrated the ability to control blood glucose and enhance cellular sensitivity to insulin. A previous study confirmed that glimepiride had a significant effect on blood glucose control [31]. Also, using the combination drugs improved blood glucose level [32]. A previous

study involving 76 patients compared the metformin/glimepiride and metformin/glibenclamide groups. The metformin/glimepiride group demonstrated greater effectiveness in controlling blood sugar levels, with a reduction in the number of hypoglycemic episodes among patients with uncontrolled type 2 diabetes[33]. According to a previous study that found individual patient responses to glimepiride vary, the ABCC8 gene polymorphism (rs757110) may affect insulin and glucose levels throughout the treatment period, underscoring the importance of tailoring treatment to each individual patient to maximize effectiveness and minimize risks [34]. The study did not show significant differences in lipid profile between the two groups, suggesting that the treatment did not significantly affect these parameters, as its effect depends on individual factors such as body weight and blood sugar control.

OCT1 protein levels were determined in the volunteer subject, as shown in Table 4. Molecular docking analysis revealed that glimepiride exhibited a good affinity for the OCT1 transporter protein's site, indicating a stronger binding affinity for this protein. A decrease in serum OCT1 concentrations was observed in diabetic patients receiving metformin-glimepiride, supporting the hypothesis of its important role in extracellular insulin transport via the OCT1 transporter protein. Its lower serum levels, compared to normal levels in healthy individuals, suggest increased cellular uptake. These results indicate that glimepiride possesses pharmacological properties that make it more effective in influencing insulin uptake via this protein. Previous research has shown that the OCT1 transporter protein facilitates the pharmacological efficacy of metformin by transporting it from intestinal cells to the portal circulation and allowing it to enter liver cells [25, 31]. These data underscore the importance of studying the properties and functions of the OCT1 transporter to understand the mechanisms of different drug responses in patients with type 2 diabetes.

Principle component analyses have been done to identify the contribution of the metabolic parameters in the disease Figure 3, Lipid profile, FBG, and HbA1c contributed toward the negative side of PC1 that indicates their association to the diabetic group; in contrast, OCT-1 loaded in the positive direction, which is related to the control group, and it is level related to the drug used.

CONCLUSIONS

The results of the molecular docking study indicate that glimepiride treatment, particularly when used in combination with metformin, exhibits high binding energy to the OCT1 protein, suggesting a stronger interaction that may contribute to improved drug uptake and intracellular efficacy. These biochemical findings support this hypothesis, as the group of patients receiving the glimepiride-metformin combination showed OCT1 protein levels similar to those observed in healthy individuals in the control group. Overall, these results highlight the importance of integrating clinical analysis with molecular docking techniques to better understand patient response to treatment and pave the way for designing personalized treatment plans based on each patient's molecular and physiological characteristics.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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