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RESEARCH PAPER

Vitamin D and calcium supplementation in type 2 diabetes mellitus: clinical outcomes and molecular docking insights into insulin receptor interaction

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Abstract
Vitamin D and calcium play essential roles in glucose metabolism and insulin secretion, though the epidemiological evidence remains inconclusive and their direct molecular interaction with the insulin receptor remains unclear. This study aimed to investigate the effects of vitamin D and calcium supplementation on glycemic control and insulin sensitivity in Iraqi patients with type 2 diabetes mellitus (T2DM) and explore the potential binding affinity of vitamin D3 to the insulin receptor through molecular docking analysis. A total of 300 vitamin D-deficient T2DM patients were assigned to three groups based on the treatment protocol: Group A (metformin only), Group B (metformin + vitamin D), and Group C (metformin + vitamin D and calcium). Glycemic parameters, including fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), fasting insulin (FI), and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), were evaluated before and after eight months of supplementation. Results showed that vitamin D supplementation significantly improved insulin secretion and sensitivity showing decreased FBG and HbA_{1c} with increased FI in group B patients, with Group C demonstrating the most pronounced improvements in FBG, HbA_{1c}, FI, and HOMA-IR. Molecular docking analysis revealed a strong binding affinity (-7.5228381 Kcal/Mol) of vitamin D3 to the insulin receptor, suggesting a potential direct role in insulin signaling. In conclusion, these findings highlight the combined benefits of vitamin D and calcium in improving glycemic control and insulin function in T2DM patients while providing novel molecular insights into vitamin D3's interaction with the insulin receptor.

Keywords Type 2 diabetes mellitus · Vitamin d · Calcium · Insulin sensitivity · Glycemic control · Molecular docking · Insulin receptor

Introduction

Vitamin D is a fat-soluble hormone precursor (prohormone) which regulates the uptake of calcium in the small intestine and interacts with parathyroid hormone to promote bone mineralization and sustain calcium homeostasis in the bloodstream. Furthermore, new epidemiological research have found links between low vitamin D levels and a variety of illness states, most likely due to its anti-inflammatory and immune-modulating capabilities, as well as potential impacts on cytokine levels. Vitamin D acts via a vitamin D receptor (VDR) that is found in all nucleated cells. Its primary biological function is to promote enterocyte development and calcium uptake in the intestines, which enables calcium homeostasis (Brannon et al. 2008). Moreover, extra-skeletal effects of vitamin D deficiency are expected

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because VDRs are found not just in the small intestine but also in the bowel, bone marrow cells triggered lymphocytes of the T and B types, single-nuclear cells, beta cells of the islet, and essential organs like the heart, brain, gonads, prostate, skin and breasts (Adams and Hewison 2010).

Varying groups have varying ideal levels of vitamin D for skeletal or extra-skeletal health. For the health of bones, the Institute of Medicine (IOM) determined that a blood level of 20 ng/mL was optimal (Institute of Medicine, Food and Nutrition Board 2011). Other organizations, however, such as the American Geriatrics Society (AGS), the International Osteoporosis Foundation (IOF), the Endocrine Society (ENDO), and the National Osteoporosis Foundation (NOF) concurred that a minimum of 30 ng/mL was required for preventing illness (Chang and Lee 2019), this has later become the most acceptable reference levels for evaluation of vitamin D deficiency.

Calcium (Ca) is an important element that plays a variety of biological roles, involving bone and teeth mineralization, blood coagulation, muscular contraction, nerve impulse exchange, and cell signaling transmission (Becerra-Tomás et al. 2014; Rooney et al. 2016; Sing et al. 2016). Furthermore, Ca plays an important function in insulin secretion and glucose homeostasis (Zaccardi et al. 2015; Mears 2004). Insulin release is controlled by Ca levels in pancreatic β-cells (Zaccardi et al. 2015). Furthermore, increasing cytosolic Ca influences glucose absorption in the myocyte (Ojuka et al. 2002). As a result, aberrant Ca homeostasis may be associated with insulin action abnormalities and glucose homeostasis problems, leading to T2DM development (Zhu et al. 2019).

Type 2 diabetes mellitus (T2DM), previously referred to as non-insulin-dependent or adult-onset diabetes, is the most prevalent form of diabetes mellitus and is believed to result from a continuous defect in insulin secretion atop a foundation of insulin resistance, arising from the body's inefficient utilization of insulin. Over time, insulin levels may become insufficient, leading to inadequate glucose regulation. The underlying causes of elevated blood glucose levels in T2DM encompass both insulin resistance and deficiency. Despite extensive research, the precise etiological factors behind T2DM remain elusive, with identified risk factors including excess body weight, physical inactivity, poor nutrition, ethnicity, family history of diabetes, a previous history of gestational diabetes, and advancing age (World Health Organization 2016; Standards of Medical Care in Diabetes 2014, 2015; Olokoba et al. 2012).

Low vitamin D levels have been linked to insulin resistance and decreased pancreatic β-cell activity. Vitamin D has a crucial role in regulating β-cell activity, as evidenced by the presence of vitamin D receptors in β-cells and decreased insulin secretory capability in mice missing a functioning receptor. The processes through which Ca consumption influences the danger of diabetes are uncertain. Improper control of Ca within cells, which affects the release and sensitivity of insulin was proposed as a possible way for explaining the link relating to Ca deficiency to the danger of diabetes. The primary function of vitamin D is to aid intestinal calcium uptake. Insufficient calcium absorption, due to deficiency of vitamin D or inadequate consumption of Ca, might explain the observed relationships. Data supports the concept that calcium helps normalize glucose intolerance caused by vitamin D deficiency in vivo (Chiu et al. 2004; Borissova et al. 2003; Pittas 2006).

The existing research does not provide sufficient evidence to establish solid conclusions concerning the relationship between calcium and vitamin D consumption and the occurrence and treatment of type 2 diabetes. Particular investigations with careful monitoring of intakes of Ca and larger vitamin D doses are required to clarify impact on homeostasis of insulin and glucose. Since trials supplementing Ca and vitamin D among individuals having T2DM have presented inconsistent outcomes, we aimed to explore the potential role of Ca and vitamin D supplementation on the glucose levels and management in a group of Iraqi patients with newly diagnosed T2DM. The importance of the findings of this study lies in their contribution to a better understanding of the ways that could achieve a good management of diabetes, thus minimizing the risk of many of the devastating complications of diabetes leading to better quality of life for diabetic patients.

Methods

Study subjects

The study involved 300 vitamin D deficient subjects with newly diagnosed T2DM with an age range of (36–48) years old. The patients' population was separated into three distinct groups, the first group (group A) included 100 patients receiving only 500 mg metformin twice daily and following a balanced healthy diet with restriction of sugars and carbohydrates. The second group (group B) included 100 patients receiving 500 mg metformin twice daily with a 50.000 IU (1250 mcg) dose of vitamin D3 (as cholecalciferol) once a week for two months followed by 2.000 IU (50 mcg) dose of vitamin D3 daily for six months. The third group (group C) included 100 patients receiving the same treatment as group B but with an additional 1000 mg calcium as calcium citrate given daily. Additionally, 200 apparently healthy subjects with normal vitamin D levels and with an age range of (37–46) years old were also enrolled in the study as a control group (group D). All the patients were instructed to

follow a healthy and balanced diet with restriction of sugars and carbohydrates. The treatment strategy was supervised by a specialist physician. All the biochemical parameters were reevaluated after an eight-month treatment period.

Ethical statement

This study was designed as an investigator-initiated, university-approved research trial. At the time of initiation, the study was reviewed and approved by the Scientific and Ethics Committee of the College of Applied Sciences–University of Technology (Approval No. 51124, Date: 18/March/2023). The study was not prospectively registered in an international clinical trials registry, as institutional regulations did not mandate such registration for university-driven, non-funded projects involving standard-of-care medications and nutritional supplements. Nevertheless, all procedures were conducted in strict compliance with the principles of the Declaration of Helsinki, with independent ethics committee approval and informed consent obtained from all participants in the presence of a trained healthcare professional who served as an independent witness to ensure ethical compliance. Each instance of consent was documented separately for each participant by the research team, stating the participant's unique identifier, date, and a clear statement that the participant provided their verbal consent in the presence of the witnessing staff member.We acknowledge that future studies should be prospectively registered in recognized clinical trials registries to enhance transparency and comparability.

Ethical safeguards: Group A patients were not left untreated. They received standard-of-care management for newly diagnosed T2DM, including metformin therapy and dietary counseling, which aligns with national and international guidelines. Their vitamin D deficiency was closely monitored, and at the end of the eight-month trial period, patients in Group A were offered vitamin D supplementation to correct their deficiency. This approach was reviewed and approved by the institutional ethics committees (Approval No. 51124), which determined that the design posed no undue risk to participants. Thus, the trial maintained both scientific rigor and ethical responsibility.

Exclusion criteria

The following subjects were excluded from the study since their associated conditions may have an effect on the results of the study: type 1 diabetic subjects, any known inflammatory conditions, subjects with liver diseases, subjects with kidney diseases, subjects with pancreatic diseases, subjects with hypertension, subjects with malignant diseases, pregnant subjects, subjects taking vitamin D and/or calcium supplementation, subjects with dysfunctional thyroid or parathyroid, and subjects with recent surgeries.

Collection of blood samples

Five milliliters of venous blood were taken from all of the study subjects by vein puncturing using plastic disposable syringes. The blood was transferred into gel and EDTA tubes. Serum samples isolated from gel tubes were used for measurement of FBG, FI, Ca and vitamin D. Whole blood samples were used for HbA_{1c} measurement. The samples collected were analyzed immediately.

Measurement of FBG, FI, HbA_{1c}, Ca and vitamin D

Fasting glucose and calcium were tested in serum of all the research individuals using the Humalyzer 2000 semi-automated photometer provided with Glucose liquicolor and Calcium liquicolor kits manufactured by Human Diagnostics. HbA_{1c} was measured using Hipro Hurricane Specific Protein Immunoassay Analyzer provided with Hipro® Glycosyclated Hemoglobin kit manufactured by Hipro Biotechnology. Fasting insulin and vitamin D levels in the research subjects' serum were analyzed using the fully automated Maglumi 800 Chemiluminescence Immunoassay Analyzer provided with MAGLUMI Insulin (CLIA) and MAGLUMI vitamin D (CLIA) kits manufactured by Snibe Diagnostic.

HOMA-IR calculation

HOMA-IR index was calculated using the following formula (Matthews et al. 1985): HOMA-IR = (FI × FBG)/405. Where FI is the fasting insulin expressed in mIU/L or µIU/mL and FBG is the fasting blood glucose expressed in mg/dL.

Statistical analysis

Biochemical data were analyzed and processed using Microsoft Excel (2019), GraphPad Prism 9 and SPSS (statistical package for social sciences) software, version (25). In order to assess the results of this study, the mean (average) value, standard deviation (SD), P-value (probability) and pearson correlations were calculated.

Molecular docking

To begin our study, we obtained the three-dimensional structure of vitamin D3 (PubChem CID: 5280795) from the PubChem database, ensuring its atomic coordinates reflected real-world geometry (Kim et al. 2023). Simultaneously, the crystallographic structure of the target protein

Table 1 Levels of FBG, FI, HbA_{1c}, Vit. D and Ca in the patients and control groups before treatment initiation

Parameters	Patients (N = 300) Mean ± SD	Control (N = 200) Mean ± SD	*p*-value	Reference range
FBG (mg/dL)	191.2 ± 33.4	90.5 ± 5.7	0.000*	70–110
FI (μIU/mL)	4.7 ± 1.6	9.9 ± 1.8	0.000*	4.03–23.46
HbA_{1c} (%)	8.6 ± 1.2	4.8 ± 0.3	0.000*	3.8–5.8
Vit. D (ng/mL)	11.3 ± 5.7	36.4 ± 3.2	0.000*	30–100
Ca (mg/dL)	7.8 ± 0.4	9.3 ± 0.6	0.000*	8.2–10.4

*Significant at the levels of ($p \leq 0.05$)

receptor (PDB ID: 1144) was retrieved from the Protein Data Bank (Till et al. 2001), providing a high-resolution blueprint of its active site. With these structural foundations in place, we employed Molecular Operating Environment (MOE) software (version 2022.02) (Chemical Computing Group Inc 1010) to simulate molecular docking and predict binding sites, aiming to rigorously assess how vitamin D3 interacts with the receptor at an atomic level.

Preparing the receptor involved careful steps to mirror biological conditions. Solvent molecules were retained to preserve a hydrated environment around the binding site, mimicking natural cellular settings. To focus computational resources, dummy atoms and spatial constraints were strategically placed to define the binding pocket's boundaries, guiding the ligand's exploration. Docking simulations utilized MOE's Triangle Matcher algorithm, chosen for its ability to efficiently sample diverse ligand conformations. Recognizing that both the ligand and receptor can flex during binding, we incorporated Induced Fit refinement—a method that iteratively adjusts their shapes to identify optimal fits. This approach generated 20 distinct binding poses for vitamin D3, each ranked by stability using the GBVI/WSA dG scoring function (ΔG, kcal/mol). The top-ranked poses, representing the most thermodynamically favorable interactions, were further analyzed. Finally, UCSF Chimera (Pettersen et al. 2004) enabled detailed visualization of 3D interaction profiles, such as hydrogen bonds and hydrophobic contacts, alongside energy score validation, ensuring a robust and nuanced evaluation of the ligand-receptor complexes.

This streamlined workflow balanced precision with biological realism, capturing the dynamic interplay between vitamin D3 and its target receptor.

Results

Clinical investigation

This study involved the investigation of vitamin D and Ca supplementations effect on newly diagnosed T2DM patients. The levels of FBG, FI, HbA_{1c}, vitamin D and Ca were measured in the patients before treatment initiation and their results are shown in Table 1. The results of the same biochemical parameters in the patients' subgroups after an eight-month treatment period are shown in Table 2.

It is clear from Table 1 that there is a significant increase in levels of both FBG and HbA_{1c} in patients in comparison to the control group. Moreover, the concentration of FI is significantly lower in the patients' group in comparison to controls.

The levels of both vit. D and Ca are also significantly lower in the patients in comparison to controls. Accordingly, the patients had vitamin D deficiency with a vast majority also having Ca deficiency. Vitamin D deficiency is estimated based on the most commonly used reference range in clinical practice which is divided into three categories (insufficiency < 30 ng/mL, deficiency < 20 ng/mL and sufficient > 30 ng/mL). Differences of opinion exist as to the definitions of vitamin D insufficiency and deficiency; however, the optimal vitamin D level depends on the level at which health outcomes start to appear (Kennel et al. 2010).

The results in Table 2 show that there is a significant reduction in both FBG and HbA_{1c} in patients taking only vitamin D supplement with metformin (group B) compared to patients taking only metformin (group A). However, group C patients taking a combination of vitamin D and Ca supplements with metformin showed a more significant reduction in both FBG and HbA_{1c} compared to both groups A and B.

Levels of FI showed a significant increase in group B patients taking only vitamin D supplement compared to patients with vitamin D deficiency (group A). However,

Table 2 Levels of FBG, FI, HbA_{1c}, Vit. D and Ca in the patients' subgroups after treatment

Parameters	Group A (Mean ± SD)	Group B (Mean ± SD)	Group C (Mean ± SD)	Group D (Mean ± SD)	*p*-value	Reference range
FBG (mg/dL)	116.9 ± 3.4	108.1 ± 2.2	94.2 ± 4.4	90.5 ± 5.7	0.000*	70–100
FI (μIU/mL)	5.2 ± 1.9	7.8 ± 1.4	10.7 ± 1.5	9.9 ± 1.8	0.000*	4.03–23.46
HbA_{1c} (%)	6.2 ± 0.6	5.8 ± 0.3	5.2 ± 0.1	4.7 ± 0.3	0.000*	3.8–5.8
Vit. D (ng/mL)	10.1 ± 4.4	32.3 ± 0.7	34.1 ± 1.7	36.4 ± 3.2	0.000*	30–100
Ca (mg/dL)	7.9 ± 0.2	8.6 ± 0.3	9.7 ± 0.4	9.3 ± 0.6	0.000*	8.2–10.4

*Significant at the levels of ($p \leq 0.05$)

Table 3 Number and percentage of insulin resistant subjects estimated based on HOMA-IR index

HOMA-IR index		
Study subjects	IR N (%)	Normal N (%)
Before treatment		
Patients (N = 300)	300 (100)	0 (0)
After treatment		
Group A (N = 100)	89 (89)	11 (11)
Group B (N = 100)	64 (64)	36 (36)
Group C (N = 100)	49 (49)	51 (51)

IR; insulin resistance, N; number of subjects, IR: HOMA-IR > 1.9 (Bonora et al. 2000)

Table 4 The correlation between vit. D and the biochemical parameters in the patients group

Vitamin D vs parameters	Correlation (r)	*p-value*
FBG	−0.802	0.000*
FI	0.643	0.000*
HbA_{1c}	−0.691	0.000*
Ca	0.855	0.000*

*Correlation is significant at the level of ($p \leq 0.05$), (r): Pearson correlation

levels of FI showed a much higher significant increase in group C patients taking a combination of vitamin D and Ca supplements compared to both groups A and B.

Levels of both vitamin D and Ca were also significantly increased to be within the reference range in the patients of both groups B and C compared to group A. However, the levels of vitamin D and Ca were significantly higher in patients of group C compared to group B patients.

Using the hyperinsulinemic-euglycemic clamp methodology, Bonora et al. (2000), reported an extremely strong association with the HOMA-IR index. Thus, HOMA-IR is regarded as a legitimate tool to measure sensitivity to insulin in epidemiological investigations. Table 3 shows the number of insulin resistant subjects in the study subgroups estimated based on the calculation of HOMA-IR index.

Before the treatment protocol, all of the patients were insulin resistant. After the eight-month treatment period, 89% of the patients in group A were still insulin resistant, showing only an 11% reduction after treatment with only metformin. Group B patients taking only vitamin D supplement with metformin showed a 36% improvement in the insulin resistance cases with 64 (64%) subjects remaining insulin resistant. Group C patients taking a combination of vitamin D and Ca supplements with metformin showed a 51% improvement in the cases with only 49 (49%) subjects remaining insulin resistant.

Table 5 The correlation between Ca and the biochemical parameters in the patients group

Ca *vs* Parameters	Correlation (r)	*p*-value
FBG	−0.669	0.000*
FI	0.597	0.001*
HbA_{1c}	−0.522	0.003*
Vitamin D	0.855	0.000*

*Correlation is significant at the level of ($p \leq 0.05$), (r): Pearson correlation

Table 6 Energy score for the top 10 docked complexes

Complex no	Receptor	Ligand	S (Kcal/Mol)	RMSD
1	1I44	Vitamin D	−7.5228381	2.1319113
2			−7.2613168	0.7940402
3			−7.0081496	1.4972949
4			−6.9905033	1.6353804
5			−6.9508772	1.6513594
6			−6.9300814	1.6856979
7			−6.8630137	1.3657146
8			−6.6865296	1.0318153
9			−6.6781001	2.426187
10			−6.5900908	1.5049146

The associations between vitamin D, Ca and other biochemical parameters are evaluated based on calculations of pearson correlations (r) shown in Tables 4 and 5 respectively.

According to Table 4, both FBG and HbA_{1c} levels were negatively correlated in a statistical significant manner with vitamin D. Additionally, there is a statistically significant positive association between vitamin D and both Ca and FI levels.

According to Table 5, both FBG and HbA_{1c} levels were negatively correlated in a statistical significant manner with Ca. Additionally, there is a statistically significant positive association between Ca and both vitamin D and FI levels.

In-silico investigation

When we studied how vitamin D3 interacts with the insulin receptor (using the structure labeled 1I44), the docking simulations produced 20 different protein–ligand complex poses. These "poses" were ranked by how strongly they bind, using a scoring method called GBVI/WSA dG. Among the top 10 fits, the binding strength (measured as ΔG) ranged from − 7.52 to -6.59 kcal/mol—a scale where lower values mean tighter binding (Table 6). The strongest match, Complex 1, had a score of -7.52 kcal/mol, hinting it's the most stable. However, complex1 didn't align perfectly with the receptor's shape, showing a slight "misfit" (RMSD of 2.13 Å). On the other hand, Complex 2 docked into place much better (RMSD of 0.79 Å), even though its binding strength was weaker (-7.26 kcal/mol). The mix of misfits passing from 0.79 to 2.43 Å—suggests vitamin D3 isn't rigid; it can flex and adapt to the receptor.

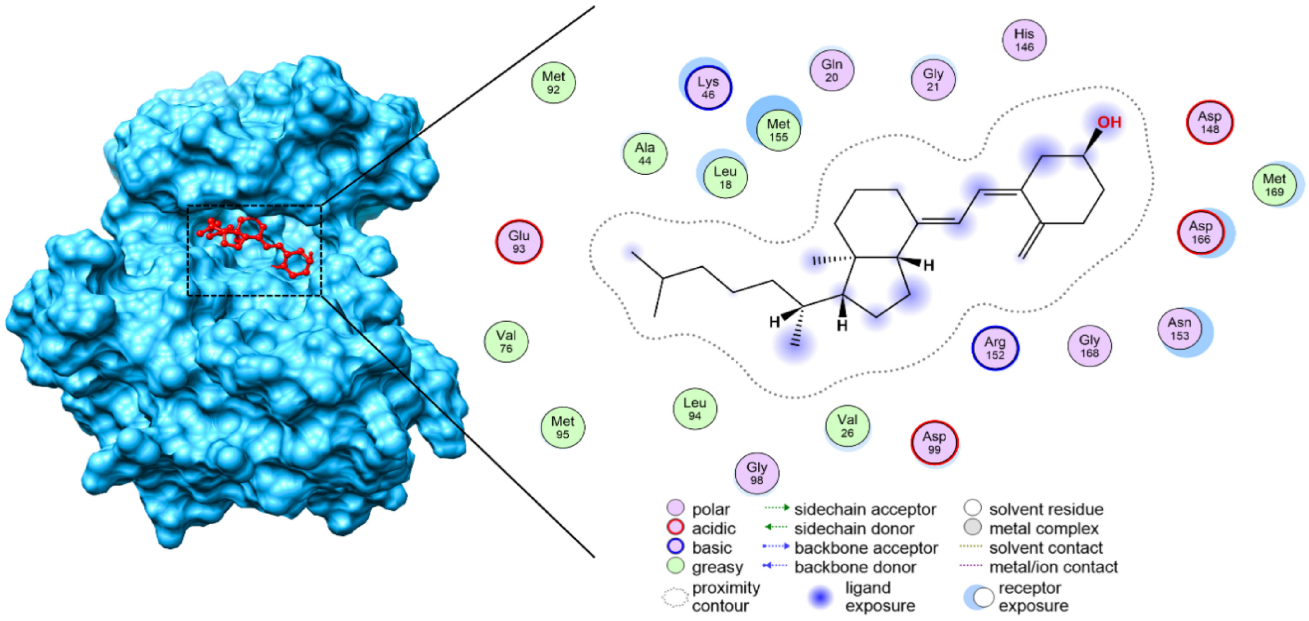


Fig. 1 The top binding pose and interaction profile of ligand Vitamin D with the insulin receptor tyrosine kinase (PDB ID: 1I44)

A closer examination of the top-ranked binding pose (Complex 1) using UCSF Chimera (Fig. 1) unveiled essential molecular interactions that stabilize the vitamin D3-receptor complex. Hydrogen bonds acted as precise bridges between the ligand and critical residues, while hydrophobic contacts formed water-excluding clusters, and π-stacking interactions aligned aromatic groups in the tyrosine kinase domain. These structural features directly reflected the energy scores derived computationally, reinforcing the thermodynamic efficiency of this binding configuration. Together, these observations underscore how specific atomic-level interactions harmonize with energetic predictions to define a stable and favorable binding mode.

Collectively, the data suggests that vitamin D3 adopts multiple stable conformations within the receptor's binding site, with energy scores and structural deviations reflecting a balance between binding affinity and conformational adaptability.

Discussion

The results of the present study are consistent with many of the previous results and findings confirming the existence of vitamin D deficiency in patients with T2DM. Vitamin D deficiency and T2DM are linked by an extensive amount of research (Maddaloni et al. 2018), which might be caused by impacts of vitamin D on sensitivity to insulin, homeostasis of glucose, secretion of insulin and inflammatory reactions throughout the body. Yet, the precise nature of this association as well as its practical significance are unknown. Vitamin D regulation is undeniably critical for skeletal health, particularly bone mineralization. Furthermore, several investigations demonstrated that lowered concentrations of vitamin D are linked to previously unknown clinical illnesses such as cardiovascular disease, resistance to insulin, metabolic syndrome and type 2 diabetes. These disorders may arise as an outcome of vitamin D insufficiency. (Lips et al. 2017a). Nevertheless, the primary clinical investigations attempted to validate this concept had contradictory findings.

The activity of beta cells, homeostasis of glucose and resistance to insulin were found to be related in an inverse manner to serum vitamin D levels, indicating a decreased risk of both metabolic syndrome and T2DM (Kayaniyil et al. 2010a; Maki et al. 2012). Many clinical investigations have connected deficiency of vitamin D to the emergence of resistance to insulin in various groups, not just in adults (Gannage-Yared et al. 2009), but additionally in youngsters (Olson et al. 2012). In general, results from observational research clearly suggest a relationship between low vitamin D level and the development of type 2 diabetes (Afzal et al. 2013a; Song et al. 2013). These relationships between vitamin D, glucose homeostasis and insulin levels were proved statistically by the calculations of pearson correlations performed in our study (Table 4).

The current study also found that the patients' category exhibited decreased serum Ca levels than the control category. This can at least in part be explained by the decreased blood levels of vitamin D, that is recognized for its function in homeostasis of calcium. In addition to its structural function in the skeleton, calcium is a vital element required for a variety of crucial biological activities. Ca may have

a significant function in several glucose homeostasis-related activities. Ca modulates intracellular activities that are mediated by insulin in tissues like fat and muscle, as well as pancreatic beta cell secretion and insulin receptor phosphorylation. Additionally, calcium inhibits certain regulating genes that produce cytokines associated with inflammation linked to insulin resistance (Pittas et al. 2007; Ojuka 2004). For effective insulin-mediated actions, intracellular Ca concentrations must fall within a restricted limit. Variations in cytoplasmic Ca levels in insulin-responsive tissues contribute to peripheral insulin resistance (Zemel 1998) via an abnormal signal transduction cascade, resulting in decreased glucose transporter function. These relationships between Ca, glucose homeostasis and insulin levels were also proved statistically by the calculations of pearson correlations performed in our study (Table 5).

Findings of the current investigation further supported the results of the earlier studies mentioned above and the role of vitamin D and Ca on the glycemic status, control, insulin release and sensitivity is clearly evident, as the results showed a significant enhancement in glycemic status and control in the group of patients given vitamin D supplement as evident by the levels of FBG and HbA_{1c}. Group B patients also showed an increase in insulin release and improvement in insulin sensitivity as shown by the calculations of insulin resistance by the HOMA-IR index. Our results also showed that adequate Ca levels are of vital importance, as was evident from the group of patients given a combination of vitamin D and Ca (group C). The results of group C showed a much higher improvement in terms of glycemic status and control and also in terms of insulin release and sensitivity compared to the patients of both groups A and B. This improvement is thus suggested to be traced back to the effect of Ca.

In cross-sectional investigations, reverse relationships between serum vitamin D and assessments of glycemia or a diagnosis of type 2 diabetes were observed in a number of cohorts (Chiu et al. 2004; Ford et al. 2005; Hypponen and Power 2006). In most but not all case–control studies, patients with T2DM or glucose intolerance are found to have lower serum vitamin D concentration compared to controls without diabetes (Aksoy et al. 2000; Isaia et al. 2001).

Several carefully constructed, randomized studies assessed the impact of supplementing with vitamin D3 on glucose homeostasis in patients in danger of T2DM and found contradictory findings. Sollid et al. (2014) performed a controlled clinical study with roughly 500 prediabetic participants to compare vitamin D and placebo for T2DM prevention. Participants were given 20,000 IU cholecalciferol once a week, and following a year of supplementation, there were no significant variations in inflammatory and diabetic indicators, or basal serum vitamin D levels. Forouhi et al. (2016) examined the impact of four months of cholecalciferol or ergocalciferol supplements (both 100,000 IU/month) against placebo in a large, random study involving 340 prediabetes or susceptible T2DM participants evaluated by the Cambridge Risk Score (Griffin et al. 2000). Following vitamin D administration, there were no variations in concentrations of HbA_{1c} across the different categories. Their findings were consistent with recent research by Davidson et al. (2013). The authors supplied a group of African and Latino American patients having prediabetes with low levels of vitamin D at start for a one-year period. In comparison to the placebo, they employed a cholecalciferol dosage that raised blood concentrations of vitamin D into the higher-normal limit. The authors discovered no impact on sensitivity and secretion of insulin, nor percentage of participants that acquired T2DM (Davidson et al. 2013).

Several investigations have found a beneficial impact on glycemic indicators. In a comparable manner, Gagnon et al. (2014) found an improvement in sensitivity to insulin indicators after conducting a study that included prediabetics only. In the past, they offered a daily dose of 1200 mg calcium carbonate and 2000–6000 IU vitamin D to participants having intolerance to glucose or newly confirmed diabetes, yet no observed impact on sensitivity to insulin, secretion, or activity of beta cell was found. Therefore, there is some intriguing proof that vitamin D has a positive impact on beta cell function even though the majority of clinical randomized studies have not demonstrated an advantageous impact of supplementation with vitamin D on control of glycemic, sensitivity to insulin indices, and type 2 diabetes incident (Sollid et al. 2014; Forouhi et al. 2016; Griffin et al. 2000; Davidson et al. 2013; Gagnon et al. 2014; Tuomainen et al. 2015; Wagner et al. 2016) in participants susceptible for the disease. Actually, a group of overweight or obese and at danger of T2DM (n = 92) prediabetic participants demonstrated a considerable enhancement in insulin secretion in 2011, according to Mitri et al. (2011a). For four months, they received calcium carbonate and 2000 IU of cholecalciferol everyday as supplements instead of a placebo. The fact that the aforementioned trials were not intended to evaluate glucose homeostasis and that the findings are consistent with post hoc analysis is a significant limitation.

A study by Tang et al. (2018) found no correlation between vitamin D administration and the risk of type 2 diabetes. Nonetheless, the researchers proposed that vitamin D supplement may have a dosage response impact on improving the metabolism of glucose and insulin in persons without diabetes. They hypothesized that greater dosages of vitamin D supplements could be beneficial for the main avoidance of type 2 diabetes.

In conclusion, studies varied greatly with regard to characteristics of participants, supplementation type, length, and

methodology. Notably, maintaining the course of therapy would have been crucial in disputing these findings (Muñoz-Torres et al. 2019).

Gulseth examined how supplementation affected sensitivity and secretion of insulin in individuals having T2DM whose baseline vitamin D blood concentration was replete (38.0+12.6 nmol/L) (Gulseth et al. 2017). No apparent improvement in secretion of insulin or management of glycemia was found, even though the blood concentration of vitamin D increased considerably. This might be explained by the fact that the participants were replete at baseline. According to one research, eight individuals with prediabetes who received 10,000 IU of vitamin D3 per day for eight weeks saw a substantial improvement in their insulin sensitivity ($P=0.012$) (Nazarian et al. 2011). These trials indicate that supplementation of vitamin D could enhance sensitivity to insulin in individuals with poor basal vitamin D status who are at higher risk for type 2 diabetes.

Santos conducted a thorough assessment of the research on glycemic management and vitamin D levels (Santos et al. 2018). It was established that a negative association was found between blood 25OHD and HOMA-IR. Glycemic control and insulin sensitivity metrics including A1c, HOMA-IR, and the quantitative insulin sensitivity check index (QUICKI) were not improved by supplements, according to the majority of research. The analyzed trials found no discernible glycemic advantage from vitamin D supplementation or replenishment, despite the fact that improved glycemic management is linked to increased vitamin D status in individuals with type 2 diabetes (Sacerdote et al. 2019).

Plenty of observational research about calcium consumption and the prevention of type 2 diabetes were located. The relationship between calcium consumption and type 2 diabetes has been studied in several groups. The largest are four cohort investigations conducted in China and the United States that showed a negative correlation between the incidence of type 2 diabetes in women with dietary or total calcium consumption, but not in men. The Japanese study discovered a negative correlation among those who consumed more vitamin D (Pittas et al. 2006; Dam et al. 2006; Villegas et al. 2009; Kirii et al. 2009).

In a Spanish investigation, over 500 postmenopausal women with no diabetes who received a greater quantity of vitamin D3 in the form of an enriched milk complemented with 900 mg of calcium and vitamin D3 (600 IU) daily demonstrated a reduction in glycated hemoglobin and fasting plasma glucose following the intervention (Reyes-Garcia et al. 2018). Another research also found that elevated calcium consumption had a positive impact on both the glycemic profile and insulin sensitivity (Das and Choudhuri 2021). These outcomes also support the conclusions of our investigation.

The molecular docking results of this study provide novel insights into the direct interaction between vitamin D3 and the insulin receptor, which has not been extensively explored in previous research. While numerous investigations have shown the role of vitamin D in glucose metabolism and insulin sensitivity, our findings contribute to a structural and mechanistic perspective, demonstrating the way of vitamin D3 action and its impact at the molecular level.

The docking simulations revealed that vitamin D3 binds favorably to the insulin receptor's active site, with strong binding free energy values (ΔG) ranging from -7.52 to -6.59 kcal/mol. The best-ranked binding pose demonstrated key molecular interactions, including hydrogen bonding and hydrophobic interactions, which contribute to the stability of the vitamin D3-insulin receptor complex. These findings suggest that vitamin D3 may play a direct role in modulating insulin receptor activity, potentially enhancing insulin signaling.

Previous studies have primarily focused on the indirect effects of vitamin D on insulin secretion and sensitivity, often attributing these effects to its role in calcium homeostasis and immune modulation (Kayaniyil et al. 2010b; Afzal et al. 2013b). However, direct molecular interactions between vitamin D3 and the insulin receptor have not been reported. Our study is among the first to provide computational evidence supporting this direct interaction, adding a new dimension to the understanding of vitamin D's role in glucose metabolism.

Most prior research has linked vitamin D deficiency to impaired beta-cell function and insulin resistance, often through observational and clinical studies (Maddaloni et al. 2018; Lips et al. 2017b). Some studies have suggested that vitamin D receptor (VDR) activation may influence insulin secretion, but they have not explored whether vitamin D3 directly interacts with the insulin receptor itself. The molecular docking approach used in our study provides the first computational validation of this potential interaction, offering a mechanistic explanation for the clinical improvements observed with vitamin D supplementation.

Furthermore, our results, not just align with previous studies showing a correlation between vitamin D levels and insulin sensitivity, but they go beyond correlation by demonstrating a possible direct structural interaction (Pittas et al. 2007; Mitri et al. 2011b). The findings support the hypothesis that vitamin D3 may contribute to insulin receptor activation, rather than solely influencing glucose metabolism through calcium-dependent pathways.

The significant reduction in FBG and HbA_{1c}, coupled with an increase in FI observed in groups receiving Ca and

vitamin D supplements, suggests improved sensitivity and secretion of insulin. Additionally, the strong correlation between vitamin D and calcium levels with insulin sensitivity parameters further emphasizes their interdependent roles in glucose metabolism. These clinical and laboratory results are supported by computational findings that may in part provide an explanation for the beneficial effect of both vitamin D and Ca supplements on insulin release and sensitivity. The ability of vitamin D3 to stably interact with the insulin receptor suggests a plausible mechanistic pathway through which vitamin D exerts its beneficial effects on glucose metabolism. Moreover, the superior improvements seen in participants receiving both Ca and vitamin D indicate that calcium plays an additional role in insulin signaling and its supplementation may further potentiate the impact of vitamin D on the homeostasis of glucose (Pittas et al. 2007). These findings support the important role of both vitamin D and Ca in the management of diabetic patients.

The reasons or explanation of the difference in the results with previous studies may be attributed to the duration of treatment, type and dose of supplement and/ or characteristics of the study subject which is beyond the scope of the present study. It is thus recommended to investigate the effect of different types of supplements with different doses and different treatment durations in order to achieve a better understanding of the optimal dose and type of supplement combined with a proper treatment duration.

The findings of the present study open new avenues for further experimental validation using biochemical and cellular assays to confirm the direct binding of vitamin D3 to the insulin receptor. Future studies should investigate whether this interaction translates into functional changes in insulin receptor activation and downstream signaling pathways. Additionally, structural modifications of vitamin D3 analogs could be explored to enhance its affinity for the insulin receptor, potentially leading to novel therapeutic approaches for improving insulin sensitivity in diabetic patients.

Conclusions

The integration of clinical, laboratory, and molecular docking data in this study proves the hypothesis that supplements of Ca and vitamin D can improve sensitivity and secretion of insulin in patients with T2DM. While vitamin D supplementation alone improved insulin release, sensitivity, and glycemic control, the co-administration of calcium resulted in a significantly greater effect, underscoring the critical role of calcium in insulin regulation and highlighting the importance of monitoring these nutrients in T2DM patients to optimize metabolic management and mitigate the risk of diabetes-related complications. Molecular docking analysis provided computational evidence suggesting a potential direct interaction between vitamin D3 and the insulin receptor, reinforcing its possible role in modulating insulin signaling. To further validate these findings, future studies with larger cohorts and extended follow-up periods are warranted to refine supplementation strategies for the effective management of T2DM.

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Declarations

Conflict of interest The authors of the present study declare that they have no financial or other competing interests.

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