Original Article

Effect of Verapamil on Glycemic Control in Type 2 Diabetic Hypertensive Patients in Saudi Arabia: A Quasi Experimental Study

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ABSTRACT

Background: Type 2 diabetes is a common chronic disease that continues to increase in prevalence globally and is a major healthcare burden. Diabetes and hypertension frequently occur concurrently, and the use of antihypertensive agents is common in diabetic patients. One antihypertensive agent, verapamil, has tentatively shown potentially positive effects on glycemic control in assorted pre-clinical models. **Aim:** To evaluate the effect of verapamil on glycemic control in hypertensive type 2 diabetic patients. **Methods:** Type 2 diabetic hypertensive patients were recruited from King Fahad Medical City, Riyadh, KSA, to receive oral verapamil therapy. Blood pressure and glycometabolic parameters, including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), C-peptide, and homeostatic model assessment insulin resistance (HOMA-IR), were monitored at baseline and after 6 months of verapamil therapy. **Results:** Thirty-five patients (16 male, 19 female) with a mean age of 57.2 years were recruited. The use of verapamil was associated with non-significant decreases in HbA1c, FPG, C-peptide, and HOMA-IR. However, a sub-group of 17 participants showed a decrease in HbA1c that was ≥0.5%. Univariate logistic regression showed that baseline BMI, HOMA-IR, and C-peptide were significantly ($P < 0.05$) associated with HbA1c reductions of ≥0.5%. **Conclusion:** Verapamil is metabolically neutral and allows the stabilization of glycometabolic parameters in type 2 diabetic individuals. Additional research exploring the mechanism behind the variable response to verapamil therapy is warranted.

Keywords: *C-peptide, diabetes, HbA1c, hypertension, verapamil*

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases, and it continues to increase in prevalence as a global health problem due to rapid economic development, aging populations, and unhealthy lifestyles.[1] Diabetes carries a significant disease burden for the individual and society and is projected to increase at an alarming rate.[2] Globally, according to the recent IDF Atlas, diabetes prevalence in adult patients aged 20–79 years was estimated to be 9.3% (527 million people) and predicted to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[3] According to the IDF, Saudi Arabia was one of the top 10 countries for diabetes prevalence in 2011 and is projected to stay in the top 10 by 2030.[4] In 2011, the prevalence of diabetes in Saudi adults' males and females was 34.1% and 27.6%, respectively.[5] In another study a prevalence rate of 25.4% for subjects aged ≥30 years and 40.2% for subjects aged ≥45 years was reported.[6] A more

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recent study in 2019 found that more than 25% of the adult Saudi population has diabetes, and this figure is projected to increase by more than double by 2030.[7]

Type 2 diabetes accounts for the vast majority (around 90%) of diabetic cases worldwide (463 million people).[2] In 2011, a study performed in KSA to determine the prevalence of type 2 diabetes, found that in people who were 30 years old and above, the overall prevalence was 31.6% with male preponderance.[8] A systematic review done to highlight the prevalence and future projections of type 2 DM in KSA found that the prevalence of type 2 diabetes is 32.8% and the predicted prevalence will be 35.4% in 2020; 40.4% in 2025 and 45.4% in 2030.[9]

There are many classes of anti-diabetic medications available to reverse the hyperglycemia observed in type 2 diabetes patients. These medications have different mechanisms of action and target several pathophysiological components of the disease. However, current glucose-lowering drugs provide inadequate blood glucose control.[10,11]

Verapamil, one of the first-generation L-type calcium channel blockers, has been widely used in clinical practice to treat hypertension and other cardiac conditions. Although verapamil has not yet proven its systemic effect on DM. Animal studies have shown promising results from verapamil in enhancing β-cell survival and function and improving glucose profile.[12] Limited human studies have hinted at a possible effect of verapamil in improving overall glucose profile.[13-16] In 2020, the first systematic review critically examined all relevant human studies to assess whether verapamil-based treatment was associated with improved glycometabolic control in patients with type 2 diabetes. The review indicated that plasma glucose levels were lowered significantly by verapamil-based treatment in patients with type 2 diabetes (mean change -13 ± 5.29 mg/dL; $P = 0.049$), and that HbA1c values are not affected by verapamil use (mean change - 0.10 ± 0.12%; $P = 0.453$).[17] Recently, a randomized, double blind, placebo-controlled evaluated the efficacy and safety of oral verapamil in non-insulin type 2 diabetic patients.[18] Patients were randomized to receive 120 mg verapamil-SR (120 mg) or placebo, and the result showed a significant reduction in HbA1c mean level in non-insulin user patients receiving 120 mg verapamil of 0.5% after 3 months ($P = 0.047$).[18]

Therefore, a study of the dual therapeutic potential of verapamil is important to assess and clarify the ability of verapamil to improve glycometabolic response and its blood pressure control effect in diabetic hypertensive patients.

The available human studies are very limited; however, such studies have shown or suggested a possible effect of the antihypertensive verapamil on improving patient glycemic control. However, the role of verapamil remains unclear due to variability in sample size and study design. The opportunity to examine the effects of verapamil in type 2 DM patients by assessing endogenous insulin secretion and/or insulin sensitivity underpinned the rationale of this study. The aim of this work is to evaluate the effect of verapamil on glycemic control in hypertensive type 2 diabetic patients.

Methodology

An open, uncontrolled interventional quasi experimental study was conducted in a tertiary-care hospital, Riyadh (the capital of Saudi Arabia), on 35 hypertensive patients with type 2 DM.

Patients with type 2 DM based on 2016 American Diabetes Association (ADA) guidelines were included.[19] More over those with BP > 140/90 mm Hg, ≥18 years of age, and a body mass index (BMI) >18 were also considered eligible for this study. Patients with reproductive potential willing to use medically acceptable birth control until 3 months after the completion of the treatment period were also included. Informed consent was obtained from all participants. Patients were excluded if they were on insulin therapy for less than 12 months; had cardiac medical conditions that in the opinion of the investigator, would interfere with the safe completion of the trial, for example, uncompensated heart failure, fluid overload, myocardial infarction, or evidence of ischemic heart disease or left ventricular dysfunction; hypotension (systolic pressure <90 mm Hg); PR interval prolongation on electrocardiogram (ECG) or bradyarrhythmia (e.g. sick sinus syndrome, AV block); and atrial flutter or fibrillation within the 12 weeks before the intervention. Patients were also excluded if they had secondary hypertension, resistant hypertension, a history of epilepsy, cancer, cystic fibrosis, sickle cell anemia, diabetes secondary to pancreatic disease, untreated hypothyroidism or active Grave's disease with hyperthyroidism, evidence of active infection, advanced or end stage organ failure, or a psychiatric or medical disorder that would prevent giving informed consent. Pregnant females and patients on medication known to interact with verapamil or contraindicated to be taken with verapamil were also excluded.

Baseline laboratory tests for fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), fasting C-peptide, lipid profile, and renal and liver function were ordered before verapamil initiation.

Recruited patients were initiated on 120 mg verapamil slow-release (half a tablet; ISOPTIN SR®) once daily,

and the dose was adjusted to the desired therapeutic response. Weekly patient follow up was maintained for a period of 24 weeks after verapamil initiation. Subjects were contacted weekly after starting verapamil via telephone for an assessment of adverse events, concomitant medications, diabetes management, habits/lifestyle, and compliance with medication. Patients were also allowed to contact the investigator as needed during the study's duration.

Follow-up visits were requested from the patients after 12 weeks to assess medication compliance, blood pressure, pulse rate, clinical and adverse events, concomitant medications, and to request laboratory tests such as lipid profile, renal, and liver function tests. Another follow-up visit was done on week 24 (end of study visit) to check all of the baseline laboratory tests, as well as blood pressure, pulse rate, medication compliance, adverse events, and concomitant medications.

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is an important indicator of insulin resistance. It was calculated according to the following formula: fasting insulin (microU/L) x fasting blood C-peptide. A decreased HOMA-IR level would indicate improvement in insulin sensitivity and the efficacy of the intervention. Adherence was assessed using the Arabic version of the Morisky Medication Adherence Scale (MMAS-8).[20] Adherence was also confirmed by pharmacy refill data or medical records.

Statistical analysis

The data were manually entered in Excel 2016 and then imported into Stata 16.1 (Stata Corp-College Station, TX, USA) for analysis. A normality test (Shapiro-Wilk) was performed to check the distribution of data, and appropriate parametric/non-parametric statistical tests were applied accordingly. Non-normal data were compared with the Wilcoxon signed-rank test for matched pairs, and normal data were compared with a paired *t*-test. Factors affecting the response to verapamil were assessed using a univariate logistic regression analysis. A sample size of 35 achieves 80% power to detect a mean of paired differences of 0.5% in the HbA1c values with an estimated standard deviation of differences of 1 and with a significance level (alpha) of 0.05 using a two-sided paired *t*-test.

Ethical approval

An ethical approval for this study was granted from the Institutional Review Board at King Fahad Medical City, Riyadh, Saudi Arabia, reference number 16-172 on 16 September 2016, with registration number with KACST, KSA: H-01-R-012.

Personal identifying data shall only be collected when necessary for research. The data collected will be only be used for this proposal. Data stored securely so that only authorized users (the investigators) are permitted access to the database; secondary disclosure of personal identifiable data is not allowed.

Results

During the study period, 35 participants were enrolled into the study. The mean age was 57.2 ± 7.7 years, and 54.3% (n = 19) of participants were female. The duration of diabetes was from 4 to 20 years, and half of them (n = 17, 48.6%) were on insulin. All participants had a normal ECG (normal sinus rhythm) and normal ejection fraction (EF) (65.51 ± 5.75%). Demographic and clinical characteristics are presented in Table 1. Most of the participants (n = 30) had an

Table 1: Baseline characteristics of participants

Baseline characteristics	Number of participants=35
Age (mean±SD)	57.2±7.7 years
Females *n* (%)	19 (54.3)
Education level *n* (%)	
Illiterate	12 (34.3)
Primary school	10 (28.6)
Intermediate school	8 (22.9)
High school	2 (5.7)
university	3 (8.6
Exercise performance *n* (%)	
No exercise	21 (60)
One hour/week	5 (14.3)
2 hours/week	1 (2.9)
3 hours/week	5 (14.3)
7 hours/week	3 (8.3)
Insulin user *n* (%)	17 (48.6)
Smoking *n* (%)	3 (8.6)
BMI (mean±SD)	34±5.8 kg/m^2
EF (mean±SD)	65.5±5.7%
Pulse (mean±SD)	108.9±7.7 beats per minute
Systolic blood pressure (mean±SD)	156.2±7.5 mmHg
Diastolic blood pressure (mean±SD)	91.4±4.1 mmHg
Mean arterial blood pressure (mean±SD)	113±4.5 mmHg
Duration of Diabetes (mean±SD)	13±5.6 years
HbA1c (mean±SD)	8.4±1.3%
C-peptide (mean±SD)	0.9±0.3 nmol/L
HOMA-IR (mean±SD)	2.3±0.8
FPG (mean±SD)	8.7±2.1 mmol/L
Diabetic neuropathy *n* (%)	8 (22.9)
Diabetic retinopathy *n* (%)	4 (11.4)

BMI: body mass index, EF: ejection fraction, HbA1c: glycated haemoglobin, HOMA-IR: homeostatic model assessment insulin resistance, FPG: fasting plasma glucose

education level lower than high school, and 60% were not performing any exercise. The majority of patients were on metformin (100%), sitagliptin (40%), aspirin (80.0%), calcium carbonate (74.4%), and cholecalciferol (vitamin D_3) (74.4%). All participants had normal renal and liver function tests at baseline assessment.

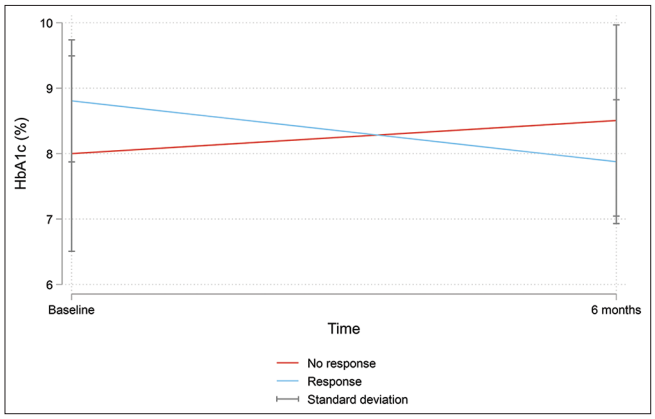

Figure 1: Change in mean HbA1c in responders and non-responders after six months of treatment with verapamil

Table 2: Glycometabolic parameters values (HbA1c, FPG, C-peptide, and HOMA-IR) before and after Verapamil

Parameter	Baseline	After 6 months	*P*
HbA1c (%) Mean±SD	8.4±1.3	8.2±1.9	0.25
FPG (mmol/L) Mean±SD	8.7±2.1	8.2±2.1	0.11
C-Peptide (nmol/L)*	0.92 (04)	2.04 (1.57)	0.06
HOMA-IR*	2.4 (1.13)	2.04 (1.57)	0.05

*Expressed as Median (IQR). HbA1c: glycated haemoglobin, FPG: fasting plasma glucose, HOMA-IR: homeostatic model assessment insulin resistance

All glycometabolic parameters values (HbA1c, FPG, C-peptide, and HOMA-IR) decreased after using verapamil; however, the decrease was not statistically significant as shown in Table 2, where HbA1c and FPG were normally distributed and expressed as mean ± SD while C-peptide and HOMA-IR were not-normally distributed and expressed as median (Interquartile range IQR).

A sub-analysis was conducted to examine the effect of verapamil on each participant's HbA1c. Accordingly, the study group was divided into responders and non-responders, where responders were defined as participants who achieved a reduction of ≥ 0.5% in HbA1c value following 6 months of verapamil therapy. Around half of the participants (n = 17, 48.6%) were considered responders based on this definition. The responders had a statistically significant favorable response to verapamil with a mean reduction of 0.9 ± 0.4% in HbA1c from their baseline values ($P < 0.001$, Figure 1). Conversely, participants classified as non-responders exhibited a significant increase in HbA1c values relative to their baseline values with a mean difference of -0.5 ± 0.80% in HbA1c ($P < 0.001$, Figure 1).

A univariate analysis was conducted for factors affecting the response to verapamil in the responders group. The result showed that baseline BMI, HOMA-IR, and C-peptide were significantly higher in the responders group [Table 2]. However, none of these factors was significant on multivariate analysis [Table 3].

Table 3: Logistic regression for factors affecting response to verapamil therapy in responders group

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender	0.7 (0.18-2.66)	0.60	0.8 (0.17-1.97)	0.98
Age	0.98 (0.90-1.07)	0.66	0.45 (0.96-1.22)	0.99
Baseline HbA1c	1.7 (0.95-3.02)	0.07	1.26 (1.3-12.2)	0.09
Baseline FPG	1.04 (0.75-1.42)	0.83	0.24 (0.08-0.97)	0.45
Baseline C-peptide level	1.1 (0.1-1.3)	0.01*	1.2 (0.001-403)	0.97
Baseline HOMA-IR	6.16 (1.62-23.49)	0.01*	5.7 (0.08-412)	0.42
Sitagliptin	1.78 (0.45-6.97)	0.41	4.2 (0.65-9.6)	1.00
Insulin	0.35 (0.09-1.37)	0.13	0.24 (0.06-0.97)	0.43
Baseline BMI	1.24 (1.06-1.45)	0.01*	1.95 (1.130-3.37)	0.16
Metformin dose	0.48 (0.18-1.27)	0.14	1.08 (0.08-1.9)	1.00
Duration of diabetes	1.04 (0.92-1.17)	0.56	28.23 (13.2-44)	0.99
Education	1.44 (0.81-2.56)	0.21	9.04 (1.1-23)	0.98
Exercise	1.12 (0.80-1.56)	0.50	3.67 (2.1-28)	0.97
Smoking	2.27 (0.19-27.58)	0.52	1.97 (1.23-4.33)	0.46
Neuropathy	1.08 (0.22-5.22)	0.93	15.35 (0.022-23.36)	0.32
Retinopathy	1.07 (0.13-8.56)	0.95	0.003 (0.001-1.22)	0.058

HbA1c: glycated haemoglobin, FPG: fasting plasma glucose, HOMA-IR: homeostatic model assessment insulin resistance, BMI: body mass index

The patients tolerated verapamil well. After 3 months of verapamil therapy, one patient reported nausea (2.85%), another reported fatigue (2.85%), and one experienced a headache (2.85%). After 6 months, two patients (5.71%) reported constipation, one reported dizziness (2.85%), one reported fatigue (2.85%), and another experienced a headache (2.85%). All of the adverse events were transient and spontaneously resolved, with no treatment interruption required.

The mean liver function test (AST, ALT, bilirubin, and albumin), renal function test (serum creatinine and GFR), and mean lipid profile (cholesterol, LDL, HDL, TG) at baseline, 3 months, and after 6 months of intervention were within normal levels.

There were no changes in anti-diabetic medication throughout the study period. Also, there were no changes in anti-hypertensive medication except for verapamil. The dose of verapamil was changed from 120 mg to 240 mg in eight patients, as they required a higher dose to control their blood pressure.

Medication adherence level at baseline was high, ranging from 6 to 8. The majority of participants (32, 91.4%) had high adherence levels with a maximum score of 8. It remained high after 3 and 6 months, ranging from 7 (2 patients) to 8 (33 patients). There was a non-significant change in the adherence score with no difference in adherence between responders and non-responders. The mean of BMI at baseline, after 3 months, and at 6 months of intervention were very similar.

Discussion

In this study, the effect of verapamil on glycometabolic parameters in type 2 diabetic patients was evaluated after 6 months of verapamil use. We found that the use of verapamil in type 2 diabetic patients was associated with a decrease in HbA1c, FPG, C-peptide, and HOMA-IR; however, the decrease did not reach a statistically significant level ($P \geq 0.05$). Seventeen patients significantly achieved the required response to verapamil, which is defined as a 0.5% decrease in HbA1c level.

The coexistence of hypertension and diabetes is very common and blood pressure control is an established strategy for preventing microvascular and macrovascular events in people with type 2 diabetes.[21,22] Therefore, identifying the dual therapeutic potential of an antihypertensive drug that can improve glycometabolic response in diabetic patients' therapy is an appealing strategy. In addition, using combination therapy is very common in treating hypertension. Therefore, adding an antihypertensive drug that has a positive effect on blood glucose may help control blood glucose levels in diabetic patients.

Based on previous research, it was uncertain whether verapamil had any useful antidiabetic activity and/or whether any antidiabetic activity was a consequence of a direct effect on the pancreatic production of insulin.[15,23] Therefore, the current clinical trial was designed to measure the effects of verapamil on C-peptide, a biochemical marker for endogenous insulin secretion, in addition to the biochemical parameters that reflect glycemic control, namely HbA1c, FPG, and HOMA-IR, in type 2 diabetic hypertensive patients.

In 2021, a randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of oral verapamil administration on 44 non-insulin type 2 diabetic patients.[18] The included patients were on two oral antidiabetic medications (sitagliptin and metformin). There was no disclosure regarding the blood pressure condition of the participants, their verapamil tolerance, and relevant side effects such as hypotension. Patients were randomized to receive either 120 mg verapamil-SR (120 mg) or placebo, and there was a significant reduction in HbA1c mean level in patients receiving 120 mg verapamil after 3 months ($P = 0.047$).

Since our patients were on insulin and have high BMI, they had more insulin resistance and consequently less residual pancreatic function, making a direct comparison between the two studies very difficult. In addition, insulin use may affect the negative response of HbA1c to verapamil, a factor that should be considered in designing future studies.

Verapamil has no effect on FPG, which has also been reported by Malayeri *et al*.[18] However, three more studies have shown a significant positive effect of verapamil use on FPG.[13,14,23] Sample size would be the most probable reason to this discrepancies in the effect of verapamil on FPG.

To the best of our knowledge, no previous study has measured the impact of verapamil on HOMA-IR values. In addition, theoretically, the insulin level or C-peptide level should be available to calculate the HOMA-IR and compare it with the current study's results. A study reported that C-peptide levels were not significantly different between the placebo and verapamil treatment groups in noninsulin-dependent diabetes participants; however, the participants' exact C-peptide values were not reported.[13] Verapamil showed a good effect on both BP and pulse rate, and it was well tolerated by most patients, as previously reported.[16,18,23,24] All adverse events in this study and previous studies were

transient and resolved spontaneously, and treatment was not interrupted, even in studies that detected a higher percentage of adverse effects. In addition, verapamil tolerability was similar to the control group, which may reflect that the reported side effects were not related to verapamil use; nevertheless, the detected adverse effects did not significantly interrupt the study.

Medication adherence has been identified as a key issue in healthcare outcomes.[25] Adherence rate was high in the current study (94.3%); a similar result (90%) was reported by Rubio-Guerra *et al*.[24]

Lower adherence rate (67%) has been reported in a previous study.[14] However it is difficult to make direct comparison with this study since medication adherence was self-reported and could not be confirmed by pharmacy refill data or medical records as was the case in the current study.

Recruitment criteria limited the overall sample size. However, the size was appropriate for the level of power/treatment effect. A larger sample size and controlling variables such as BMI, insulin use, and duration of diabetes would have strengthened the subgroup analysis. Data remain very limited on the glycometabolic effect of verapamil-based treatments, so further prospective, longitudinal clinical trials, preferably multicenter studies, are needed to investigate the glycometabolic effect of verapamil on type 2 diabetes. It will be also interesting to evaluate whether early initiation of verapamil will have a beneficial effect in preserving endogenous insulin secretion and preventing disease progression in diabetic hypertensive patients.

Conclusion

In this work, verapamil was shown to be metabolically neutral. It stabilizes the glycometabolic parameters with no adverse glycemic effects in type 2 diabetes. Extending the verapamil use was able to maintain the significant reduction in HbA1c levels in the responder participants. Several factors could have affected the change in HbA1c levels, such as BMI, HOMA-IR, and C-peptide, and these should be taken into consideration in designing future studies.

Ethical approval

An ethical approval for this study was granted from the Institutional Review Board at King Fahad Medical City, Riyadh, Saudi Arabia, reference number 16-172 on 16 September 2016, with registration number with KACST, KSA: H-01-R-012.

Declaration

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Nil.

Conflicts of interest

There are no conflicts of interest.

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