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# The effects of vitamin D on glucose-insulin dynamics: mathematical model and simulation

## Abstract

**Background**: Maintenance of glucose level for diabetic people is very important and challenging. Many factors seem to affect the level of glucose in our body, out of which vitamin D is found to be one of the most important factors. It inspires us to develop a model that is capable of predicting the effect of vitamin D on glucose-insulin dynamics of human body.

**Objective**: The main objective of the study is to develop a model to capture the effect of vitamin D on the glucose-insulin dynamics of non-diabetic, T2DM and T1DM people.

**Method**: A minimal model previously developed by Bergman is extended to include the effects of vitamin D via parameters. Stability analysis and numerical simulation has been performed on the vitamin D model to analyze the behavior of the model. Comparisons are made to observe the blood glucose and insulin level in non-diabetic, T2DM and T1DM people.

**Result**: The model assess the changes in glucose-insulin dynamics after the induction of different values of vitamin D parameters in their respective range.

**Conclusion and future work**: The vitamin D model captured the glucose-insulin dynamics effectively and should be recommended in our daily routine, especially for the diabetic people. Further, the dosage of vitamin D may be calculated clinically because of the variation in the population and severity of the disease.

**Keywords:** diabetes, glucose-insulin dynamics, T1DM, T2DM, vitamin D, insulin sensitivity, insulin resistance

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**Abbreviations:** T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

## Introduction

Diabetes is the most widespread disease after cancer, and therefore extensive research is being carried out to develop drugs for its therapeutics. Diabetes mellitus is classified as T1DM (type 1 diabetes mellitus), T2DM (type 2 diabetes mellitus) and gestational diabetes. T1DM is an autoimmune disease in which the immune system attacks the insulin - producing β cells in the pancreas and destroys them. In T2DM, the pancreas usually produces enough insulin but for unknown reasons the body cannot use the insulin effectively a condition called insulin resistance. Insulin resistance is a risk factor for T2DM and recent studies have shown a strong relation among insulin resistance and vitamin D deficiency. Recent studies have shown that deficiency of vitamin D results in reduction of insulin secretion and thus in hyperglycemia, which leads to diabetes if it persists long.[1] Optimal profile of insulin release for diabetics has been discussed in.[2] Vitamin D deficiency was significantly associated with increased diastolic blood pressure, increased triglycerides levels, and reduced high density lipoprotein cholesterol and measurements of vitamin D may help to detect type 2 diabetic patients.[3] A review[4] states evidence of strong link between abnormal glucose-insulin dynamics and deficiency of vitamin D. Vitamin D also plays a role in the pathogenesis of T1DM and T2DM, with a special emphasis on the direct effects of vitamin D on pancreatic cells.[5] Vitamin D has both direct and indirect effects on various mechanisms related to the pathophysiology of T2DM and hypertension, including pancreatic beta cell dysfunction and impaired insulin action.[6] The causal link between vitamin D, T2DM and hypertension remains to be determined. Most of the researches have been done in the United States on persons suffering from either T1DM or T2DM.

Vitamin D is a powerful substance our body usually produces its own with the help of sunlight which makes our body produce a powdery substance which then converts to vitamin D. Vitamin D is obtained from exposure to sunlight, fortified foods and dietary supplements. When our skin is exposed to solar ultraviolet radiation (wavelength 290-350 *nm*), 7-dehydrocholesterol is converted to previtamin ($D_3$) which is rapidly converted to cholecalciferol ($D_3$). Ergocalciferol ($D_2$) obtained from food along with cholecalciferol ($D_3$) is converted into 25-hydroxyvitamin D in the presence of vitamin D-25-hydroxylase in the liver which is the major circulating metabolite and used to determine a patient's vitamin D status.[1,3–6] Almost all 25 - hydroxyvitamin D is bound to circulating DBP (vitamin D - binding protein) and is filtered by the kidneys and reabsorbed by the proximal convoluted tubules. The biologically inactive 25-hydroxyvitamin D must be converted in the kidneys to active 1, 25-hydroxyvitamin D by 1-alpha hydroxylase. Finally, the active 1, 25-hydroxyvitamin D can bind to VDR-RXR (vitamin D receptor - retinoic acid X - receptor complex) in the intestine, bone and parathyroid glands. VDRs are present in pancreatic β cells and vitamin D is essential for normal insulin secretion.[7] See Figure 1 for the mechanism of synthesis of vitamin D).

Sunlight exposure is just one of the factors out of many which influence vitamin D status, photochemical and photobiological sciences.[8] Studies have indicated that 25-hydroxyvitamin D (25(OH)D) level in obese people is lower than normal weight people. However relationship between 25(OH)D and fat mass are

found to be inconsistent.[9] Islet cell insulin secretion is reduced in vitamin D - deficient animals and can be corrected by vitamin D supplementation.[7,10,11] The impact of vitamin D deficiency on β cell function seen *in vitro* and *in vivo* in animal models has been matched by vitamin D studies in human volunteers undergoing hyperglycaemic clamps.[12] Epidemiological studies have shown that vitamin D deficiency might increase the incidence of an autoimmune disease such as T1DM.[13] Vitamin D appears to affect exclusively the insulin response to glucose stimulation, while it does not appear to influence basal insulinemia.[14,15] Vitamin D may have a beneficial effect on insulin action by stimulating the expression of insulin receptor thereby enhancing insulin responsiveness for glucose transport.[16] Association between low vitamin D level and decreased insulin sensitivity has been reported in cross-sectional studies.[12,16–22] Based on available data from recent studies, vitamin D supplementation is considered to be a potential and inexpensive therapy, which not only decreases the risk but also improves glycemic parameters in T2DM.[23] The positive effects of vitamin D on insulin secretion and sensitivity and secondary its action on inflammation can be seen through available clinical and epidemiological data.[24] Studies have shown that a low serum level of vitamin D increases the risk of developing diabetes.[25–27] A multivariate logistic regression model was used to predict the relationship between glucose control and vitamin D deficiency.[28] Recently in 2019,[29] it is quoted that sunlight exposure had a beneficial but insufficient effect on 25[OH]D levels and the same levels were documented in two consecutive summer seasons confirming that vitamin D supplementation in both summer and winter should be considered. It has been shown that there is an association of vitamin D deficiency with a myriad of acute and chronic illnesses including preeclampsia, childhood dental caries, periodontitis, autoimmune disorders, infectious diseases, cardiovascular disease, deadly cancers, type 2 diabetes and neurological disorders.[30–34]

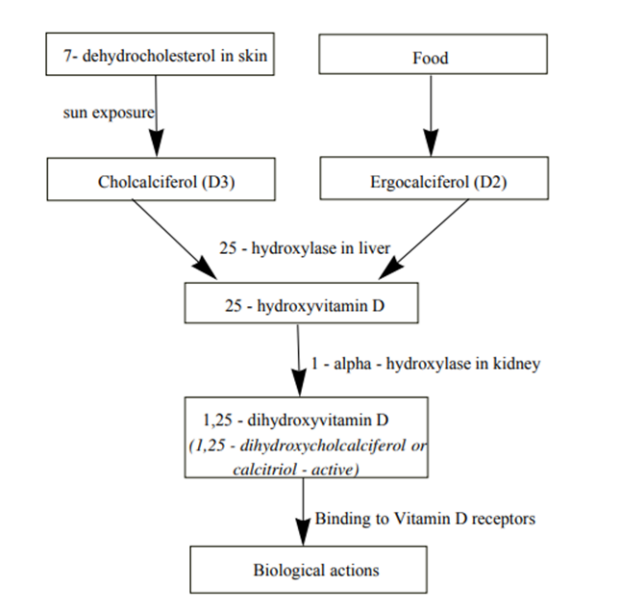


**Figure 1** Mechanism of synthesis of Vitamin D.

The purpose of the present study is to use the minimal model in order to predict the role of vitamin D on glucose-insulin regulatory system. The paper is divided into six sections. Section (1) contains the introduction of the work done till now in this area. In section (2), mathematical model is discussed by using vitamin D parameters. Positive and bounded solution of the model is given in the section (3). Stability is checked in section (4), analysis of model is done in section (5) and computer simulations are discussed in section (6). In section (7), discussion about the work done is given. Conclusion and future aspects of the work are presented in section (8).

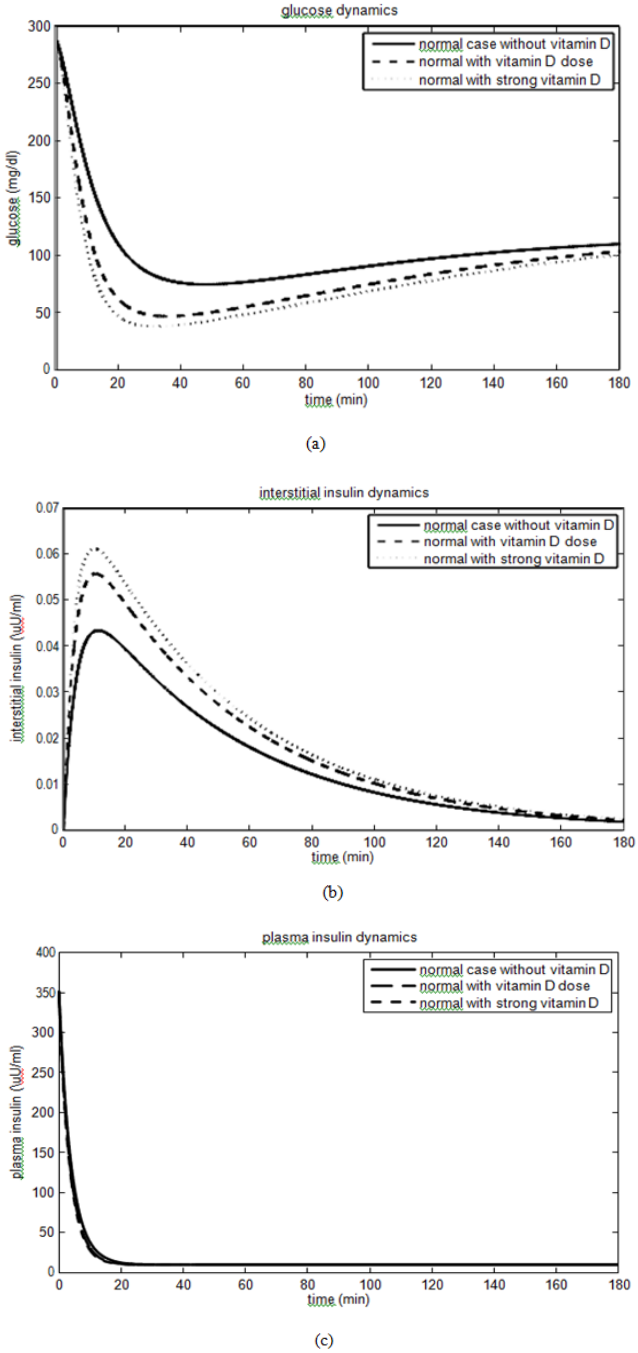


**Figure 2** Comparison of glucose concentration level of normal people for three different cases (without vitamin D, with mild dose of vitamin D and with strong dose of vitamin D) is shown in fig (a). High peak of interstitial insulin for case of strong dose of vitamin D as compared to other two cases (mild dose of vitamin D and without vitamin D) can be seen in fig (b). Plasma insulin concentration level for all three cases can be seen in fig (c).

## Mathematical model

Glucose is stored in liver and peripheral tissues including muscle tissues. Glucose utilization process is controlled by insulin, which

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enhances glucose uptake. Also, an increase in glucose concentration augments pancreatic release of insulin. This feedback loop leads to difficulties in interpretation of test results. To overcome this problem, the whole system is decomposed into two independent components:[35] (i) the effect of insulin to accelerate glucose uptake and (ii) the effect of glucose to enhance insulin secretion.

The two subsystems are described in mathematical terms and the mathematical model given by Bergman et al.[36] is given as:

$$\frac{dG(t)}{dt} = -X(t)G(t) - p_1\left(G(t) - G_b\right), G(0) = G_0 \quad (1)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3\left(I(t) - I_b\right), X(0) = X_0 \quad (2)$$

$$\frac{dI(t)}{dt} = p_5\left(G(t) - G_c\right) + t - p_4\left(I(t) - I_b\right); I(0) = I_0 \quad (3)$$

where, $G(t)\left[mg/dl\right]$ represents glucose concentration at time $t$, $X(t)\left[\min^{-1}\right]$ represents remote insulin concentration at time $t$, $I(t)\left[\mu U/ml\right]$ represents the interstitial insulin at time $t$, $G_c\left[mg/dl\right]$ represents the threshold level of glucose above which the endogenous insulin secretion will be stimulated, $G_b\left[mg/dl\right]$ represents the basal glucose level and $I_b\left[\mu U/ml\right]$ denotes the basal insulin level. The parameters $p_i\ (p_i > 0)$, i=1,2,3,4,5 are defined in Table 1.

To model the effects of vitamin D on glucose-insulin dynamics, we take into account four major factors:[33]

- vitamin D helps the cells in glucose uptake i.e. it increases glucose effectiveness
- it improves the insulin sensitivity of the body
- insulin secretion is increased due to vitamin D
- it decreases the insulin resistance.

To observe the changes in glucose-insulin dynamics due to the above said effects of vitamin D, four new parameters $v_j\ (v_j > 0)$, j=1,2,3,4 have been introduced in the model (1- 3) for which explanation is as follows:

$v_1\left[\min^{-1}\right]$ represents the effect of vitamin D on muscles and fat cells to utilize glucose so it is incorporated with parameter $p_1$ which represents glucose effectiveness.

$v_2$ deals with the effect of vitamin D on muscles and fat cells to increase insulin sensitivity, hence incorporated in the term containing $X(t)G(t)$.

Since vitamin D levels modulate the secretion of insulin by pancreas, hence $v_3\left[ml\left(\mu U\right)^{-1}\min^{-2}\right]$ is combined with $p_3$ which explains the same phenomena.

$v_4\left[\min^{-1}\right]$ represents the effect of vitamin D in increasing utilization of the insulin, therefore combined with parameter $p_4$.

After incorporating the above new parameters in the minimal model, the extended model is as below:

$$\frac{dG(t)}{dt} = -\left(1+v_2\right)X(t)G(t) - \left(p_1+v_1\right)\left(G(t) - G_b\right), G(0) = G_0 \quad (4)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + \left(p_3+v_3\right)\left(I(t) - I_b\right), X(0) = X_0 \quad (5)$$

$$\frac{dI(t)}{dt} = p_5\left(G(t) - G_c\right)^+ t - \left(p_4+v_4\right)\left(I(t) - I_b\right); I(0) = I_0 + I_b \quad (6)$$

The first term of the eqn.(6) contributes the plasma insulin concentration when the glucose concentration exceeds the threshold $G_c$, and is defined as

$$\left(G(t) - G_c\right)^+ t = \begin{cases} (G(t) - G_c)\,t, if G(t) > G_c \\ 0, if G(t) \le G_c \end{cases}$$

## Positive and bounded solutions of the model

### To show $G(t) > 0$

Eqn.(4) can be written as

$$\frac{dG(t)}{dt} + \left[\left(1+v_2\right)X(t) + (p_1+v_1)\right]G(t) = (p_1+v_1)G_b$$

$$\Rightarrow G(t) = \frac{(p_1+v_1)G_b\int_0^t f(u)\,du + G_0}{f(t)} \quad (7)$$

where

$$f(t) = e^{\int_0^t\left[\left(1+v_2\right)X(s) + (p_1+v_1)\right]ds} > 0$$

Since $p_1 > 0$, $v_1 > 0$, $G_b > 0$, $G_0 > 0$ and $f(u) > 0$, therefore right hand side of the eqn.(7) is positive. Hence $G(t) > 0$.

### To show $I(t) > 0$

Now eqn.(6) implies

$$\frac{dI(t)}{dt} = p_5\left(G(t) - G_c\right)^+ t - (p_4+v_4)(I(t) - I_b)$$

$$\frac{dI(t)}{dt} + (p_4+v_4)(I(t) - I_b) = p_5\left(G(t) - G_c\right)^+ t$$

The solution is given by

$$I(t) = I_b + I_0 e^{-(p_4+v_4)t} + \int_0^t p_5\left(G(u) - G_c\right)^+ e^{-(p_4+v_4)(t-u)}\,u\,du \quad (8)$$

Since the integral term in the right hand side of the eqn.(8) is positive,

$$I(t) \ge I_b + I_0 e^{-(p_4+v_4)t}, \forall\, t \ge 0 \quad (9)$$

which implies

$$I(t) \ge I_b > 0, \forall t \ge 0 \quad (10)$$

Hence, $I(t) > 0$.

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**Table 1** Values of the parameters

| Parameters | Units | Explanation | References |
|---|---|---|---|
| p1 | $\min^{-1}$ | represents glucose effectiveness | [34] |
| p2 | $\min^{-1}$ | fractional rate of insulin appearance in interstitial compartment | [34] |
| p3 | $(\min^{-2})(\mu U/ml)^{-1}$ | contribution of plasma insulin to the remote compartment from interstitial compartment | [34] |
| p4 | $\min^{-1}$ | clearance of plasma insulin | [34] |
| p5 | $(\min^{-2})(\mu U/ml)^{-1}(mg/dl)^{-1}$ | degree by which glucose exceeds threshold or baseline glucose level | [34] |

**Table 2** Values of parameters for normal

| Parameters | Without Vit. D | With mild dose of Vit. D | With strong dose of Vit. D | References |
|---|---|---|---|---|
| p1 | 0.399e-01 | 0.399e-01 | 0.399e-01 | [36] |
| p2 | 0.200e-01 | 0.200e-01 | 0.200e-01 | [36] |
| p3 | 0.4e-04 | 0.4e-04 | 0.4e-04 | [36] |
| p4 | 0.257 | 0.257 | 0.257 | [36] |
| p5 | 0.001 | 0.001 | 0.001 | [36] |
| G0 | 287 | 287 | 287 | [36] |
| I0 | 351 | 351 | 351 | [36] |
| v1 | 0 | 0.1e-04 | 0.3e-04 | [40] |
| v2 | 0 | 0.65 | 0.95 | [40] |
| v3 | 0 | 0.16e-04 | 0.24e-04 | - |
| v4 | 0 | 0.257e-01 | 0.3855e-01 | - |

**Table 3** Values of parameters for NIDD

| Parameters | Without Vit. D | With mild dose of Vit. D | With strong dose of Vit. D | References |
|---|---|---|---|---|
| p1 | 0.14e-01 | 0.14e-01 | 0.14e-01 | [41] |
| p2 | 0.200e-01 | 0.200e-01 | 0.200e-01 | [41] |
| p3 | 0.128e-05 | 0.128e-05 | 0.128e-05 | [41] |
| p4 | 0.129 | 0.129 | 0.129 | [41] |
| p5 | 0.1e-03 | 0.1e-03 | 0.1e-03 | [41] |
| G0 | 438 | 438 | 438 | [41] |
| I0 | 1322 | 1322 | 1322 | [41] |
| v1 | 0 | 0.28e-02 | 0.28e-02 | [40] |
| v2 | 0 | 0.75 | 0.85 | [40] |
| v3 | 0 | 0.512e-06 | 0.768e-06 | - |
| v4 | 0 | 0.129e-02 | 0.1.935e-01 | - |

**Table 4** Values of parameters for IDD

| Parameters | Without Vit. D | With mild dose of Vit. D | With strong dose of Vit. D | References |
|---|---|---|---|---|
| p1 | 0.16e-01 | 0.16e-01 | 0.16e-01 | [42] |
| p2 | 0.43e-01 | 0.43e-01 | 0.43e-01 | [42] |
| p3 | 0.38e-05 | 0.38e-05 | 0.38e-05 | [42] |
| p4 | 0.2676e-01 | 0.2676e-01 | 0.2676e-01 | [42] |
| p5 | 0.1e-06 | 0.1e-06 | 0.1e-06 | [42] |
| G0 | 300 | 300 | 300 | [42] |
| I0 | 51 | 51 | 51 | [42] |
| v1 | 0 | 0.28e-02 | 0.28e-02 | [40] |
| v2 | 0 | 0.75 | 0.75 | [40] |
| v3 | 0 | 0.152e-05 | 0.228e-0.5 | - |
| v4 | 0 | 0.26e-02 | 0.4008e-02 | - |

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**To show** $X(t) > 0$

Eqn.(5) can be written as

$$\frac{dX(t)}{d(t)} + p_2 X(t) = (p_3 + v_3)(I(t) - I_b)$$

$$\Rightarrow X(t) - X_0 e^{-p_2 t} = \int_0^t (p_3 + v_3) e^{-p_2 (t-u)} (I(u) - I_b) du$$

From eqn.(9),

$$I(t) - I_b \geq I_0 e^{-(p_4 + v_4)t}, \forall t \geq 0$$

After solving

$$X(t) - X_0 e^{-p_2 t} \geq \begin{cases} \frac{I_0 (p_3 + v_3)(e^{-(p_4+v_4)t} - e^{-p_2 t})}{p_2 - (p_4 + v_4)}, if p_2 \neq p_4 + v_4 \\ I_0 (p_3 + v_3) e^{-p_2 t} t, if p_2 = p_4 + v_4 \end{cases}$$

Since the right hand side of the above expression is positive, therefore

$$X(t) > X_0 e^{-p_2 t} > 0, \forall t \geq 0 \qquad (11)$$

Hence, $X(t)$ always exceeds the level X0 for all time t. It can be seen in Section (4).

**To show** $G(t)$ **is bounded**

From eqn.(4),

$$\frac{dG(t)}{dt} = -(1 + v_2) X(t) G(t) - (p_1 + v_1)(G(t) - G_b), G(0) = G_0$$

Therefore,

$$\frac{dG(t)}{d(t)} \leq -(p_1 + v_1)(G(t) - G_b)$$

Let $P(t) = \mathrm{G(t)} - \mathrm{G}_b$. Then,

$$\frac{dP}{dt} + (p_1 + v_1) P \leq 0$$

which implies

$$P(t) \leq P(0) e^{-(p_1 + v_1)t}, \forall \mathrm{t} > 0$$

$$G(t) - G_b \leq (G(0) - G_b) e^{-(p_1 + v_1)t}$$

$$< (G(0) - G_b), \forall t > 0$$

which implies

$$G(t) < G(0), \forall \mathrm{t} > 0.$$

Since $G(t) > 0$ and $G(t) \leq G(0)$, this implies $G(t)$ is bounded.

Hence we can conclude that all the solutions $G(t)$), $X(t)$, $I(t)$ are positive. They are also bounded above (and hence remain finite for all $t \geq 0$ ) is proved in the following section.

## Stability analysis of vitamin D model

**Theorem 1** (Comparison Theorem[37]): Let $\phi_{1,i}(t)$ be a solution of the ordinary differential equations

$$\frac{dx_i}{dt} = f_i(x, t), \mathrm{i} = 1, 2, \ldots . n$$

and $\phi_{2,i}(t)$ be a solution of a second system

$$\frac{dx_i}{dt} = g_i(x, t), i = 1, 2, \ldots . n$$

satisfying the same initial conditions $\phi_{1,i}(t_0) = \phi_{2,i}(t_0) = x_{i,0}, i = 1, 2, \ldots . n$, over the interval $a \leq t \leq b$. $f_i$, $g_i$ are defined on $U \times [a, b]$ and $U \subset R^n$ is an open domain. Hence $f_i, g_i : U \times [a, b] \to R$ are continuous functions such that $f_i < g_i$ $[f_i > g_i]$ on $U$. Then, $\phi_{1,i}(t) \leq \phi_{2,i}(t) [\phi_{1,t}(t) \geq \phi_{2,t}(t)]$ for all $t \in [a, b]$.

In the model (4–6), for conciseness of notation, define

$$g(t) = (G(t) - G_b), x(t) = X(t), i(t) = I(t) - I_b$$

$$q_1 = (p_1 + v_1), q_2 = (1 + v_2) G_b$$

$$q_3 = (p_3 + v_3), q_4 = (p_4 + v_4)$$

The eqns. (4–6) can be written in the form:

$$\frac{dg(t)}{dt} = -(1 + v_2) x(t) g(t) - q_2 x(t) - q_1 g(t) \qquad (12)$$

$$\frac{dx(\mathrm{t})}{dt} = -p_2 x(t) + q_3 i(t) \qquad (13)$$

$$\frac{di(t)}{dt} = p_5 H(g(t)) - q_4 i(t) \qquad (14)$$

Where $G_c = G_b$ (Preposition I.5,[38]) is taken in the eqn.(6) of the model to check the stability of the model at the equilibrium point. $H = H(g(t))$ is the unit step function:

$$H(g(t)) = \begin{cases} 0 if g(T) \leq 0 \\ 1, if g(T) > 0 \end{cases} \qquad (15)$$

Consider the system of eqns.(12–14), first term on the right-hand side of eqn.(14) is non-zero only when $g > 0$, any instability would arise only if g were maintained above zero i.e., $G > G_b$ for all $t \geq 0$.

Suppose $g(0) < 0$ (i.e., $G(0) < G_b$). Then $H = 0$, and from eqns.(12–14) we see that *g*, *x*, and *i* tends to zero, hence the system is stable for $G(0) < G_b$.

From eqn.(12), and using the Comparison Theorem, we have (where $H = 1$):

$$\dot{g} = -q_1 g - q_2 x - (1 + v_2) gx$$

$$\leq -q_1 g - q_2 x_{\min} - (1 + v_2) g x_{\min}$$

$$= -Qg - q_2 x_{\min}$$

where $Q = q_1 + (1 + v_2) x_{\min}$

$$g(\mathrm{t}) \leq \mathrm{g}(0) \mathrm{e}^{-Qt} - \frac{q_2 x_{\min}}{Q} (1 - e^{-Qt})$$

$$g(t) \to -\frac{q_2 x_{\min}}{Q} < 0 \; ast \to \infty$$

Since glucose level can't be negative at any time of day, hence it can be considered that $g(t)$ tends to zero after a finite time $T$, so that $g(t)$ passes through 0 after a time $T_G$, where $T_G \leq T$. Also at $t = T_G$, $H$ becomes zero. From this, it can be concluded that $g(0) > 0$ (i.e., $G(0) > G_b$).

From eqn.(14),

$$i = p_5 Hgt - q_4 i$$

$$i(t) = i(0)e^{-q_4 t} + p_5 e^{-q_4 t} \int_0^t H(g(s))\,\mathrm{sg}(s)\,\mathrm{ds} \qquad (16)$$

Now, the integral on the right in eqn.(16) is bounded above by

$$\int_0^{T_G} sg(s)\,ds < \infty$$

This shows that $i$ (t) is bounded: $i(t) \leq i_{\max}$ for $t \geq 0$.

Similarly, using eqn.(13) and Theorem 1, we have

$$\dot{x} = -p_2 x + q_3 i \leq -p_2 x + q_3 i_{\max}$$

$$x(t) \leq x(0)e^{-p_2 t} + \frac{q_3 i_{\max}}{p_2}(1 - e^{-p_2 t})$$

$$\leq x(0) + \frac{q_3 i_{\max}}{p_2}$$

$$\equiv x_{\max}$$

It can be seen from eqn.(16) that $i$ is bounded below : $i(t) \geq i_{min}$ for some finite $i_{\min}$ and $t \geq 0$. Therefore from eqn.(13) and using the Comparison Theorem,

$$\dot{x} = -p_2 x + q_3 i$$

$$\geq -p_2 x + q_3 i_{\min}$$

$$x(t) \geq x(0)e^{-p_2 t} + \frac{q_3 i_{\min}}{p_2}(1 - e^{-p_2 t}) \qquad (17)$$

which implies $x(t)\big(\equiv X(t)\big)$ is also bounded from above and below for $t \geq 0$.

Hence it can be concluded that if $G(0) < G_b$, the system (4–6) is stable. If $G(0) > G_b$, then the solution to eqn. (4) remain bounded for all $t \geq 0$.

## Analysis of model

Mathematical model will be analyzed in the neighborhood of equilibrium point to check its stability. Therefore, to determine the effect of vitamin D on glucose disappearance and insulin sensitivity after a glucose bolus at the equilibrium point, a modification has been introduced in the model (4–6) to include a glucose source. The model is given as:

$$\frac{dG(t)}{dt} = -(1+v_2)X(t)G(t) - (p_1 + v_1)(G(t) - G_b) + G_{in}(t),$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + (p_3 + v_3)(I(t) - I_b),$$

$$\frac{dI(t)}{dt} = p_5 (G(t) - G_c)^+ t - (p_4 + v_4)(I(t) - I_b),$$

where $G_{in}(t)$ is the glucose infusion rate per unit of volume at time $t$, which is assumed to be constant for stability analysis.

### Equilibrium condition

At equilibrium $(G, X, I) = (G^*, X^*, I^*)$, we have

$$X^* = \frac{(p_3 + v_3)(I^* - I_b)}{p_2}$$

$$G_{in}^* = (1 + v_2)X^* G^* + (p_1 + v_1)(G^* - G_b)$$

where $G_{in}^*$ represents the constant rate of injection of glucose

$$G^* = \frac{(p_1 + v_1)G_b + G_{in}^*}{\frac{(1+v_2)(p_3 + v_3)(I^* - I_b)}{p_2} + (p_1 + v_1)}$$

Define $I = I^* - I_b$, then the function $G^*(I)$ is given by

$$G^*(I) = \frac{(p_1 + v_1)G_b + G_{in}^*}{\frac{(1+v_2)(p_3 + v_3)I}{p_2} + (p_1 + v_1)} \qquad (18)$$

$G^*$ is a decreasing function of $I$ and

$$\lim_{I \to 0} G^*(I) = G_b + \frac{G_{in}^*}{(p_1 + v_1)} \qquad (19)$$

also

$$\lim_{I \to I_c} G^*(I) \to 0 \qquad (20)$$

where $I_c$ represents the threshold level of insulin.

Eqn.(19) shows that in absence of insulin, the presence of vitamin D does not lower the glucose concentration and a risk of hyperglycaemia may occur in case of T1DM and T2DM. On the other hand eqn.(20) represents the case of critical situation in which a patient dies if the level of insulin crossed the threshold level.

### Non-diabetic case

In non-diabetic people, $\beta$ cells which are secreted by pancreas work properly so plasma glucose and plasma insulin concentration are maintained and hence the blood sugar concentration does not cross the threshold level in the body.

Analysis of the stationary point of the model:

$$\frac{dG(t)}{dt} = 0; \frac{dX(t)}{dt} = 0; \frac{dI(t)}{dt} = 0$$

Gives the following:

$$X^* = \frac{(p_3 + v_3)(I^* - I_b)}{p_2}$$

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$$G_{in}^{*} = \frac{(1+v_2)(p_3+v_3)}{p_2}(I^{*} - I_b)G^{*} + (p_1+v_1)(G^{*} - G_b)$$

The glucose effectiveness $S_G$ is defined as

$$S_G = \frac{\partial G_{in}^{*}}{\partial G^{*}} = \frac{(1+v_2)(p_3+v_3)}{p_2}(I^{*} - I_b) + (p_1+v_1)$$

and the insulin sensitivity in presence of vitamin D $\left(S_{ID}\right)$ is defined as

$$S_{ID} = \frac{\partial^2 G_{in}^{*}}{\partial G^{*}\partial I^{*}} = \frac{(1+v_2)(p_3+v_3)}{p_2}$$

In the absence of vitamin D, insulin sensitivity $S_I$ becomes

$$S_I = \frac{p_3}{p_2} < S_{ID}$$

Hence it can be concluded that vitamin D improves insulin sensitivity, a result which was also found by.[16]

### T2DM (Type 2 diabetes mellitus)

Consider

$$G^{*} = \frac{(p_1+v_1)G_b + G_{in}^{*}}{\frac{(1+v_2)(p_3+v_3)(I^{*} - I_b)}{p_2} + (p_1+v_1)}$$

In case of T2DM, $I^{*} \approx 0$ Therefore,

$$G^{*} \approx \frac{(p_1+v_1)G_b + G_{in}^{*}}{(p_1+v_1) - \frac{(1+v_2)(p_3+v_3)I_b}{p_2}} \qquad (21)$$

where,

$$(p_1+v_1) > \frac{(1+v_2)(p_3+v_3)I_b}{p_2}$$

for the values of parameter described in Table 3. In the absence of vitamin D the above expression becomes

$$G^{*} \approx \frac{p_1 G_b + G_{in}^{*}}{p_1 - \frac{p_3}{p_2}I_b} \qquad (22)$$

$$I_b < \frac{p_1 p_2}{p_3}$$

For the values of parameter described in Table 3.

### T1DM (Type 1 diabetes mellitus)

People with T1DM depends totally on insulin injection as the $\beta$ cells are damaged fully and do not produce any insulin, hence in this case we can take $I^{*} \approx 0$ and $I_b = 0$ so that

$$G^{*} \approx G_b + \frac{G_{in}^{*}}{(p_1+v_1)} \qquad (23)$$

Eqn.(23) illustrates that in absence of insulin, even the presence of vitamin D does not lower the glucose level and a risk of hyperglycaemia may occur. Also if the amount of vitamin D increases the level of glucose in the plasma goes near to basal level and not less than basal.

## Computer simulations

The model was numerical simulated by using ode45 method in Matlab 2012b. To carry out the numerical simulation, the values of parameters $p_i$ $i$=1,2,3,4,5 are given in Tables 2–4. $G_b$ $\left[\sim 100\, mg/dl\right]$,[39] $G_c$ $\left[\sim 100\, mg/dl\right]$[39] have been taken for the numerical simulation of the model. Since two different level of dosages (mild and strong) of vitamin D have been considered, therefore $v_i$ , $i$ =1,2,3,4 has taken three set of values corresponding to the absence of vitamin D, mild dosage of vitamin D and strong dosage of vitamin D. The values of the new parameters $v_i$ , $i$=1,2,3,4 which was introduced to assess the effect of vitamin D on glucose-insulin dynamics are given in the Tables 2–4. Comparisons have been made in the glucose-insulin dynamics corresponding to these three different set of values. Graphs have been plotted for each case (non-diabetic, T1DM and T2DM) to capture the effect of vitamin D to lower down the glucose level near to basal value.

### Non-diabetic case

In non-diabetic case, the values of parameters $p_1$ , $p_4$ , $G_0$ , $I_0$ have been taken from the paper.[36] The values of parameters $p_2$ , $p_3$ , $p_5$ was taken same as the average normal values in humans. The values of parameters $v_1$ , $v_2$ have been picked from the paper[40] as the effect of parameters on the glucose-insulin dynamics is the same. The values of the parameters $v_3$ and $v_4$ have been considered as 40% (60%) and 10% (15%) for vitamin D dose (strong vitamin D dose). The parameters and their values for the non-diabetic case are given in Table 1. The effect of vitamin D on the glucose- insulin dynamics for the non-diabetic case is shown in Figure 2.

### T2DM case

In T2DM case, the values of the parameters ( $p_1$ to $I_0$ ) have been taken from the paper.[41] Glucose effectiveness ( $S_G$ ) and insulin sensitivity ( $S_I$ ) in this case was found lower than the non-diabetic case.[41] The parameter $p_2$ has mere effect on original minimal model so we set the value of $p_2$ the same as in the non-diabetic case, also $p_3$ was derived from $p_2 . S_I$ , where $S_I = (p_3 / p_2)$ was obtained by parametric estimation for the T2DM data with basal values ( $G_b$ and $I_b$ ) and peak glucose values comparable to the normal data. The parameter $p_5$ was taken as 10% of the $p_5$ value for the non-diabetic case. The values of the parameters $v_1$ , $v_2$ have been taken from the paper[40] as the effect of parameters on the glucose-insulin dynamics is the same. The values of the parameters $p_3$ and $p_4$ has been taken as 40% (60%) and 10% (15%) for vitamin D dose (strong vitamin D dose). The parameters and their values for the T2DM case are given in Table 2. The effect of vitamin D on glucose-insulin dynamics for T2DM people is shown in Figure 3.

### T1DM case

In T1DM case, we had considered $I_e = 0$ and $I_b = 0$ . The values of the parameters ( $p_1$ to $I_0$ ) have been chosen from the paper.[42] $S_G$

and $S_I$ in T1DM case was lower than in the non-diabetic case. Value of $p_2$ has been considered within the normal range and the parameters $p_4$, $I_0$ have been obtained by linear regression of log transformed T1DM data. The value of $p_5$ has been taken as very small, as the T1DM cases have lower response to pancreas.[40, 42] The values of parameters $v_1$, $v_2$ have been taken from the paper,[40] as the effect of parameters on the glucose-insulin dynamics is the same. The values of the parameters $p_3$ and $p_4$ have been taken as 40% (60%) and 10% (15%) for vitamin D dose (strong vitamin D dose). The parameters and their values for the T1DM case are given in Table 3. The effect of vitamin D on glucose-insulin dynamics for T1DM people is shown in Figure 4.

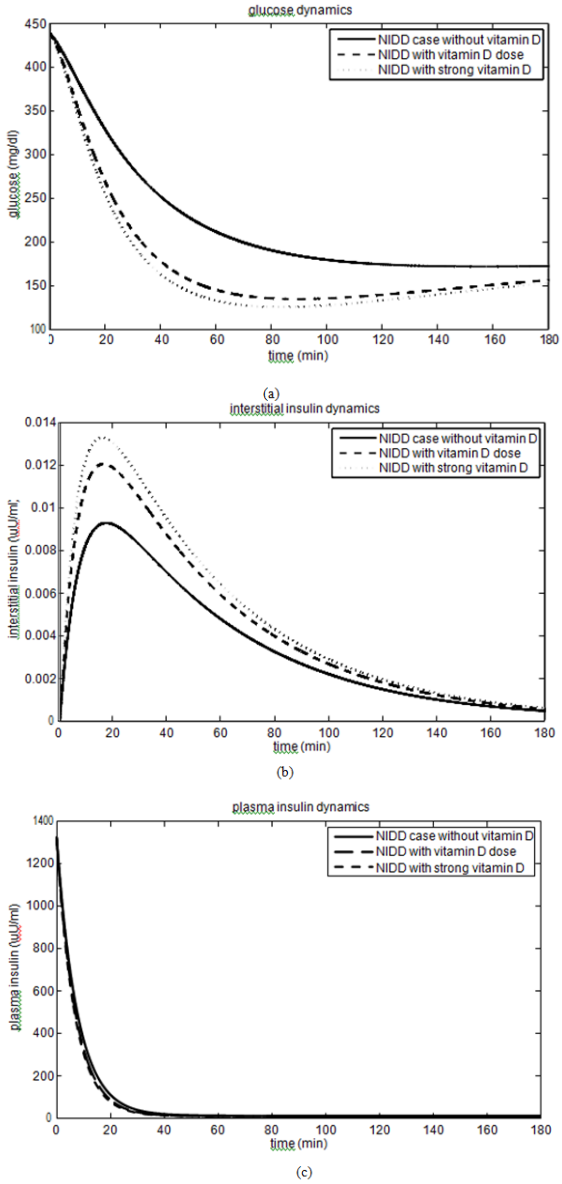


**Figure 3** Comparison of glucose concentration level of NIDD people for three different cases (without vitamin D, with mild dose of vitamin D and with strong dose of vitamin D) is shown in fig (a). High peak of interstitial insulin for case of strong dose of vitamin D as compared to other two cases (mild dose of vitamin D and without vitamin D) can be seen in fig (b). Plasma insulin concentration level for all three cases can be seen in fig (c).

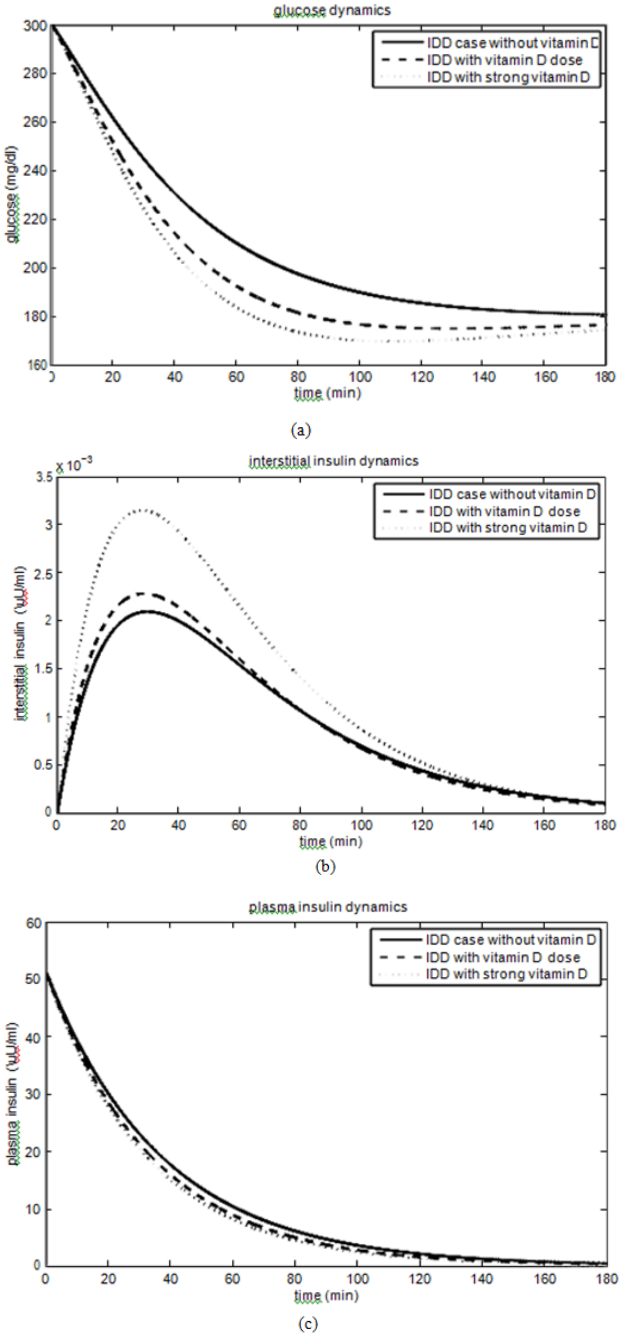


**Figure 4** Comparison of glucose concentration level of IDD people for three different cases (without vitamin D, with mild dose of vitamin D and with strong dose of vitamin D) is shown in fig (a). High peak of interstitial insulin for case of strong dose of vitamin D as compared to other two cases (mild dose of vitamin D and without vitamin D) can be seen in fig (b). Plasma insulin concentration level for all three cases can be seen in fig (c).

## Discussion

About 422 million people worldwide have diabetes, the majority living in low and middle income countries. Approximately 1.6 million deaths are directly attributed to diabetes each year. People having low income and suffering from diabetes are struggling to get the treatment involves insulin therapy which is very costly. This motivates us to find an approachable way to control the disease and make us focus on the vitamin D which not only increases the insulin sensitivity but

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gives a clear illustration of glucose-insulin dynamics. Vitamin D helps the muscles and fat cells to absorb glucose from plasma and increases the insulin sensitivity. To the best of our knowledge, it is the first mathematical model which incorporates the effects of vitamin D via parameters. In this paper, we have shown the level of glucose concentration decreased to 140 mg/dl from 180 mg/dl in T2DM people and from 190 mg/dl to 165 mg/dl in T1DM people after incorporating the vitamin D parameters (still not in the normal physiological range as vitamin d dose is not the solely responsible factor to control the glucose concentration). This illustration confirms that we should include a vitamin D dose in our daily routine (by the recommendation of a physician), especially for the persons who are involved in the industrial sector and do indoor jobs. Each individual should adjust the dosage of vitamin D according to his/her requirements.

## Conclusions and future work

In this paper, we discussed the glucose-insulin regulatory system model for diabetic persons using vitamin D effect via parameters. We have studied the mathematical model analytically and numerically. For the first time, effect of vitamin D has been dealt mathematically to discuss the situation of diabetes. Our results reveal that vitamin D has a great impact on the glucose-insulin regulatory system. The mathematical model captured the effect of vitamin D on glucose-insulin dynamics in which it is confirmed that the important parameters which determine insulin sensitivity, pancreatic responsivity and glucose effectiveness have a large impact on the model. In future, the present mathematical model can be extended further to incorporate the exact dose of vitamin D to capture the impact of vitamin D on glucose-insulin regulatory system, according to the severity of the disease. Such mathematical model will be of great help to the diabetic community which is currently increasing very rapidly.

### Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

### Contributory details

Ms. Saloni Rathee has contributed to the study design, numerical analysis and manuscript preparation. Ms. Nilam has contributed to the manuscript editing and review. Both have made equal contribution in the literature search.

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## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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