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Potential Effects of Levels of Vitamin C and Vitamin D in Serum on Diabetic Cardiovascular Diseases Prevention

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Abstract. Diabetes, as one of the major causes of global death, is affecting people worldwide and increasing the risk of cardiovascular diseases. Recent research indicated that vitamin C and vitamin D supplements can lower blood glucose levels and blood pressure to help prevent diabetic cardiovascular disease. However, the impact of the serums level of vitamin C and vitamin D on reducing the diabetic cardiovascular disease risk have not been fully illustrated. This paper aimed to investigate the association between vitamin C, vitamin D serum levels and cardiovascular disease complicated by diabetic mellitus. This study used data from the NHANES 2017-2018, and Multiple Linear Regression and Logistic Regression methods were implied. The study found that for plasma fasting glucose, vitamin D in serum was found to have a significant influence (p=0.0374). For blood pressure, significant correlations were observed with vitamin D in serum ($p_{Systolic} < 0.0001,\ p_{Diastolic} = 0.0240$) and with vitamin C in serum ($p_{Systolic} < 0.0001,\ p_{Diastolic} = 0.0089$). Furthermore, the impact of vitamin D serum levels on decreasing diabetic cardiovascular disease risks had a precondition, with serum content below sufficient standard 75 nmol/L provided by American's Endocrine Society. SHAP was also applied in this paper as an interpretation was to support the findings. Future studies will explore the appropriate serum levels of vitamin C and vitamin D for clinical treatment.

Keywords: Diabetic cardiovascular disease, Vitamin C, Vitamin D, Plasma fasting glucose, Blood Pressure.

1. Introduction

Diabetes remains a pressing global health concern, with cardiovascular disease (CVD) remaining a leading cause of death in the diabetic population [1]. From 2009 to 2019, the death rate attributable to high Blood Pressure (BP) increased by 34.2%, with the actual number of deaths rising to 65.3% [2].

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CVD is known as the most prominent cause of morbidity and mortality across the world. It is estimated that nearly 18 million global deaths are due to CVD in 2019 by the World Health Organization (WHO) [3].

Diabetes patients have higher risks of developing cardiovascular diseases [4-8], with a risk of 32.2% being affected by CVD [9]. It composed more than half of the mortality causes among diabetes patients [9-12]. Common risk factors of CVD are closely related to diabetes, including dysfunctions in the circulatory, nervous, and urinary systems. Hypertension, as one of the most correlating factors [13,14], inflicts 30% of Type I diabetes and 60% of Type II diabetes patients, increasing the risk of CVD among diabetes patients by damaging the glomerular basement membrane and leading to nephrotic syndromes [15]. Blood pressure is one of the factors for estimating the CVD prevalence risk; regulating blood pressure might lower the risks of CVD.

A meta-analysis of randomized controlled trials suggested that vitamin C supplements significantly decreased the serum level of fasting blood glucose [16], postprandial glycemia, and blood pressure [17]. The observed effect ostensibly attributable to a deficiency in this nutrient but could potentially stemmed from heightened vitamin C requirements among individuals with diabetes [18]. Carter et al. and Mazloom Z mentioned the lower level of vitamin C in the serum of diabetes patients [19,20], but further studies are still required. Vitamin D's role in normalizing extracellular calcium enabled insulin secretion [21]. Increasing evidence indicates the association between vitamin D deficiency and insulin resistance, leading to higher blood glucose levels [22]. Though some research highlights the potential relationship between the serum level of vitamin D and the complications of diabetes [23], the evidence is still insufficient.

Although the cardiovascular and coronary heart disease mortality of type 2 diabetes patients decreased year by year, the mortality rate was still much higher than that of non-diabetic patients, which highlights the current absence of highly effective clinical strategies to mitigate cardiovascular mortality in diabetes patients [24]. The research on the influence of vitamins on diabetes and CVD remain inadequate, with obscure and inconsistent findings based on different study methods. More significantly, to our best knowledge, there is lack of studies connecting the diabetes and CVD controls when estimating the effects of vitamins. Therefore, an anomaly-detected, population-based study on influential factors is essential to prevent cardiovascular diabetes complications. The study may shed light on the CVD risk control among diabetes patients.

2. Method

2.1. Samples

NHANES (National Health and Nutrition Examination Survey) uses a multistage, probability sampling design to estimate the health and nutritional status of people in the United States. NHANES 2017-2018 data is picked from Center for Disease Control and Prevention's National Center for Health Statistics site [25]. Diabetic and cardiovascular detection indicators as well as basic physical information are extracted from the datasets. The diabetic health was surveyed with the question "Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes" and average blood pressure after three readings is calculated for cardiovascular health. The Systolic Blood Pressure (SBP) $\geq$ 80mm Hg and Diastolic Blood Pressure (DBP)$\geq$ 120mm Hg is served as a stratifying standard. Age and BMI are potential confounding variables that may contribute to unforeseen outcomes and warrant meticulous consideration such as affecting BG and BP, so they are included in the models as covariates.

2.2. Variables and Outcomes

This study examines serum levels of Vitamin C, Vitamin D (D2 and D3), and their potential correlations with fasting blood glucose (FBG) levels, as well as systolic and diastolic blood pressure (BP). Age and BMI are considered as covariates.

Fasting Blood Glucose (FBG): Quantitatively measured by the UV In vitro test with the Roche/Hitachi cobas c311 system.

Vitamin D2 and D3 (SVD2+D3): Quantitatively measured via high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS).

Vitamin C (SVC): Measured by ultra-high performance liquid chromatography (UPLC) with electrochemical detection.

Systolic and Diastolic BP: Measured three times after 5 minutes of seated rest, with readings taken from the right arm unless contraindicated.

2.3. Shapley Additive Explanations

Shapley Additive Explanation (SHAP) is a method of model post-hoc interpretation, that constructs an additive explanatory model, where all features are treated as "contributors". The core idea is to calculate the marginal contribution of features to the outputs of the model and explain the model we use from both global and local levels. In this study, Multiple Linear Regression model is put in the black box. A positive SHAP value suggested a positive contribution of the feature values on the predicted outcomes and larger values mean the feature has a greater effect.

2.4. Main Models

Study effects were assessed using Multiple Linear Regression and Logistic Regression methods to evaluate the effects of Vitamin C and Vitamin D on diabetic cardiovascular disease. Besides, Multiple Linear Regression's kernel function was utilized to illustrate the distribution of feature plots and the SHAP values, where greater SHAP values suggest a more positive contribution of the feature values on the predicted outcomes.

3. Results

3.1. Associations between Vitamins C & D Serum Levels and BP & FBG

Total participants (n=2250) in NHANE cohort have a mean age of 45.10 (SD = 20.64) and a median BMI of 28.93(kg/m^2) (SD = 7.43). Participants are divided into four groups: Diabetes with CVD Risks, Diabetes Only, CVD Risks Only and No Diabetes nor CVD Risks (see Table 1). Older people have higher risks to develop a diabetes with the mean age of diabetes groups 62.31 (SD = 13.01) and no diabetes groups 42.32 (SD = 20.31). The average BMI levels in four groups all exceeded the standard BMI (18.5-25kg/m^2) by World Health Organization (WHO), and BMI parameters also indicated significance differences between the diabetes with median 32.69(SD = 7.92) and no diabetes groups 28.33(SD = 7.17).

The average SVC among four groups all satisfied to the standard (0.6-1.0 mg/L) made by American Association for Clinical Chemistry (AACC). The average SVC in Diabetes and CVD risk group 0.79 mg/dL was found generally lower than that in other three groups, suggesting that the shortage of SVC may be a key factor that increase the cardiovascular diabetic disease risk. Moreover, the impact of vitamin C on individual symptoms remained to be discussed. For SVD, the average level in four groups all failed to meet the sufficient standard (≥ 75 $nmol/L$) made by American's Endocrine Society. However, higher SVD was found in diabetes groups with average level of 73.44 (32.41) than that in no diabetes groups 65.61 (30.73).

Table 1. Column with variables of different groups by mean and standard deviation analysis.

Variable	Diabetes and CVD risk (n=158)	Diabetes and No CVD risk (n=157)	No diabetes and CVD risk (n=965)	No diabetes and No CVD risk (n=970)	Total (n=2276)
Age	61.29 (12.42)	63.43(13.33)	43.05(20.69)	41.63(20.00)	45.10(20.64)
BMI(kg/m^2)	32.45(8.18)	32.92(7.70)	28.48(7.36)	28.14(6.96)	28.93(7.43)

Table 1. (continued).

Vitamin D in serum(nmol/L)	72.52(33.31)	74.43(31.73)	66.52(31.21)	64.77(30.34)	66.69(31.08)
Vitamin C in serum(mg/L)	0.79(0.42)	0.88(0.67)	0.90(0.46)	0.86(0.44)	0.87(0.46)

The means and standard deviations of BMI, age, SCV and SCD levels in each group Legend. The number outside the bracket is the mean and the one in the bracket is the standard deviation. Multiple linear regression model was used to the analysis with BMI and age serving as covariates, the results are shown in Table 2. For plasma fasting glucose, SVD was negatively correlated had significant influence($p = 0.0374$) . For systolic and diastolic blood pressure, significant effect was both found in SVD ($p_{Systolic} < 0.0001,\ p_{Diastolic} = 0.0240$) and SVC ($p_{Systolic} < 0.0001,\ p_{Diastolic} = 0.0089$). Those factors were all negatively correlated with blood pressure. The result suggests that both vitamin D and vitamin C are helpful for Cardiovascular Health while vitamin D is also helpful to lower the risk of diabetes.

Table 2. Relationship between factors and Diabetes and CVD risk.

Factors	Estimate	Spearman correlation coefficient	p-value	Outcome
BMI(kg/m^2)	0.7416	0.3033	< 0.0001	Plasma fasting glucose
Age	0.4722	0.4281	< 0.0001	
Vitamin D in serum(nmol/L)	-0.0505	0.0971	0.0374	
Vitamin C in serum(mg/L)	-1.7072	-0.0856	0.2596	
BMI(kg/m^2)	0.3074	0.2816	< 0.0001	Systolic blood pressure
Age	0.5031	0.5647	<0.0001	
Vitamin D in serum(nmol/L)	-0.0464	0.0790	< 0.0001	
Vitamin C in serum(mg/L)	-1.9431	-0.0953	0.0074	
BMI(kg/m^2)	0.2109	0.1863	<0.0001	Diastolic blood pressure
Age	0.1102	0.2153	<0.0001	
Vitamin D in serum(nmol/L)	-0.0205	-0.0005	0.0240	
Vitamin C in serum (mg/L)	-1.4807	-0.1012	0.0089	

Using logistic regression, significance impact of SVC and SVD was found on cardiovascular diabetic participants. 75 nmol/L of SVD was discovered as the turning point, which was also the standard threshold for sufficient SVD worldwide. When the SVD was below the sufficient standard, the probability of having diabetic cardiovascular disease would also decrease (0.006%) with the increased SVD (see Figure 1). However, excess content (above standards) may have a negative effect on lowing diabetic and CVD risks, with a forward correlated (0.08%) fitting curve shows in second graph of Figure 1. Furthermore, the logistic regression model shows a high precision of 95% in SVD $< 75\ \ nmol/L$, 92% in SVD$\geq 75\ \ nmol/L$, showing the reliability of model results.

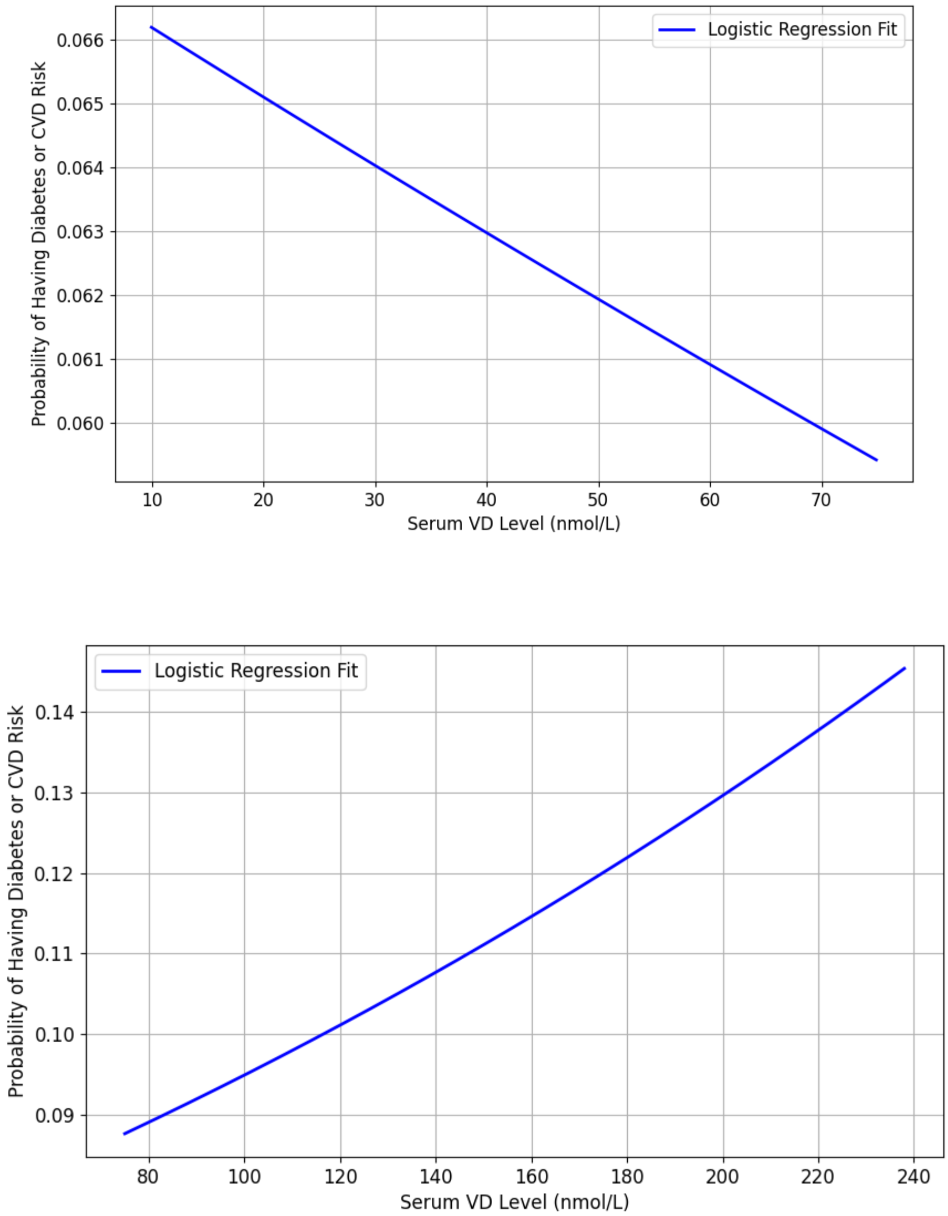

Figure 1. Logistic Regression Fit for Serum VD Level and Health Risks (VD < 75 nmol/L and VD ≧ 75 nmol/L).

3.2. SHAP values

According to the graphs of the visualized SHAP values for the Multiple Linear Regression, bluer dots represent lower feature values and red dots represent higher feature values. Clear contribution coefficients are shown by SHAP values. Since the color of the accumulated dots are bluer when the SHAP values are smaller (see Figure 2), advanced age and higher BMI both contributed to higher FBG (SHAP value of age = 9.75, SHAP value of BMI = 5.51) and BP (SHAP value of age = 10.39 and 2.28, SHAP value of BMI = 2.28 and 1.56), indicating that elder or more obese people are more likely to have higher blood glucose level and blood pressure.

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Negative SHAP values observed for higher feature values of SVC implied an inverse relationship with FBG (SHAP value = -1.57) and BP (SHAP value = -1.44 and -0.64) in prediction as shown in Figure 2. Thus, lower SVC may correlate with elevated fasting blood glucose and blood pressure, potentially increasing risks for diabetes and cardiovascular diseases.

The distribution of higher feature values of SVD indicated negative impacts on FBG (SHAP value = -0.80) and BP (SHAP value = -0.91 and -0.69) (see Figure 2), particularly among individuals with higher vitamin D levels. Negative SHAP values for SVD concerning fasting blood glucose and blood pressure suggested that as vitamin D levels rise, fasting blood glucose and blood pressure tend to decrease.

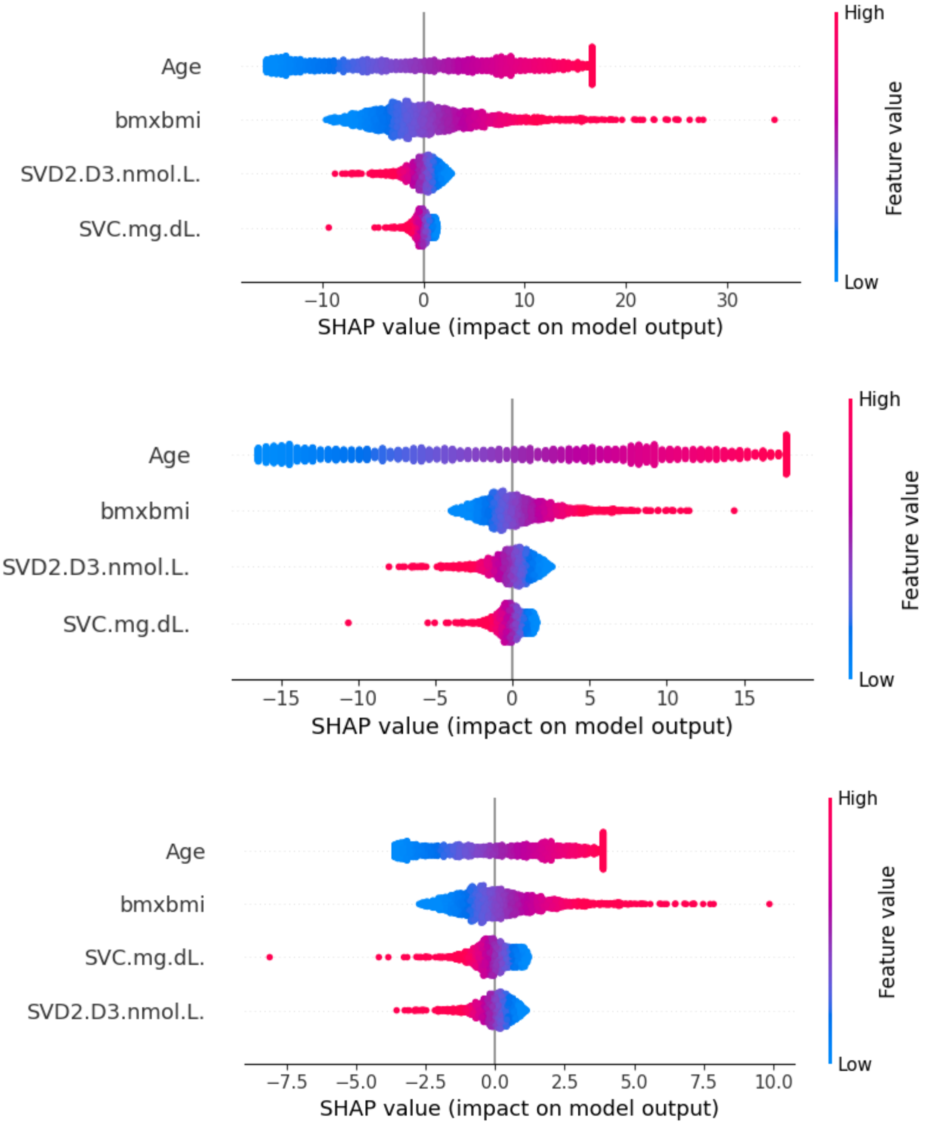

Figure 2. SVR for the Blood Glucose Level, Systolic Blood Pressure and Diastolic Blood Pressure.

4. Discussion

In our research, the serum levels of vitamin C and vitamin D exhibited an inverse correlation with blood pressure, which is consistent with several studies [26-29]. It might because vitamin C mitigate oxidative damage to blood vessels, thereby promoting their elasticity and facilitating glutathione (GSH) synthesis to mitigate hypertension according to the free radical theory [30,31]. Vitamin D functions include vasodilation [32], inhibition of cellular proliferation and myocardial hypertrophy [33], and prevention of vascular calcification through ion balance [34]. Moreover, it was observed in our study that a low serum vitamin D level was associated with elevated blood glucose levels, a relationship potentially elucidated through its effects on pancreatic beta cells and insulin sensitivity [35]. This correlation is substantiated by prior investigations [36,37].

The positive correlation, shown in the logistic regression model, between vitamin D serum level and probability of having cardiovascular diabetic disease when SVD level is greater than the normal. It might be due to the overdose of vitamin D would cause metabolic dysfunctions. Some participants could have imbalanced and unhealthy diets that lead to the abnormally high level of vitamin D, which causes hypercalcemia and other symptoms of toxicity, resulting in negative impacts on blood pressure and blood glucose level.

The relationship between vitamin C levels in serum and blood glucose levels was not significant in this study, which is inconsistent with some studies suggesting a negative association [38,39]. A possible explanation was the effects of other confounding variables excluded from the study. Physical activities and daily diets could affect the metabolism mechanisms, and intake and absorbed amounts of nutrients, which influence the blood glucose level and blood pressure afterwards [40].

The partial definition of CVD risks might also partly cause results deviation. Due to the limited data without a definite diagnosis of CVD, only hypertension was considered as a factor that increases the CVD risk. Besides, the number of samples was marginally inadequate when being divided into the group of having both diabetes and CVD risks. A larger sample size might depict a more pronounced picture of the correlations.

Despite the growing body of research on the roles of vitamins in relieving health issues, there remains a notable lack of comprehensive studies estimating the effects of vitamin C and vitamin D on reducing diabetic cardiovascular disease risks, and the study aims to fill the gap. The significance of this research lies not only in discovering vitamins' potentials but also in their implications for clinical practice. The results suggest that vitamin C and vitamin D levels in serum are vital on preventing CVD in diabetic patients. Thus, to maintain healthy vitamin C and vitamin D levels and prevent the complication, dietary improvements, vitamin supplements control, and medications might be required to facilitate metabolism efficiency.

5. Conclusion

Based on the results and discussions above, the conclusions of this research are listed as follows:

Vitamin D in serum was negatively correlated with plasma fasting glucose with significant influence.

The serum levels of vitamin C and vitamin D present an inverse correlation with systolic and diastolic blood pressure.

It was concluded that higher vitamin C and vitamin D levels in serum might be beneficial in diabetic CVD prevention by lowering both blood glucose levels and blood pressure. The effect of vitamin D has a turning point. When the content level was below that threshold, the probability of having diabetic cardiovascular disease decreases while the serum vitamin levels increased.

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Nanchen Hu, Fan Xia, Hanna Li contributed equally to this work and should be considered co-first authors.

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