

## Effect of Vitamin D Supplementation on Pancreatic B -Cell Function in Patients with Type 1 Diabetes Mellitus and Vitamin D Deficiency: A Clinical Trial Study

Morteza Alijanpour Aghamaleki<sup>1</sup>, Mahmoud Hajiahmadi<sup>1</sup>, Mohammad Pornasrollah<sup>1</sup>, \*Zahra Oruji<sup>1</sup>, Faeze Aghajpour<sup>2</sup>

<sup>1</sup>Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.

<sup>2</sup>University of Mazandaran, Babolsar, IR Iran.

### Abstract

#### Background

Considering the increasing prevalence of type 1 diabetes mellitus (T1DM) as an autoimmune disease in recent years and the positive effects of vitamin D (VD) on this disease, especially the preventive effect of VD on progressive reduction of pancreatic  $\beta$ -cells, we aimed to investigate the effect of VD on pancreatic  $\beta$ -cell function in T1DM patients.

#### Materials and Methods

From Sep 2016 to Nov 2017, this single-blind clinical trial study was performed on patients who have affected with T1DM in the last five years, referred to Endocrinology Clinic of Amirkola Children's Hospital in Babol city of Iran. The patients with VD level less than 30 ng/mL were treated with 50,000 IU Pearl VD for 9 months. The patients' C-peptide, 25 (OH) D, HbA1c and total daily dose (TDD) insulin were compared at the beginning and end of the study. Data were analyzed using SPSS software version 22.0.

#### Results

By examining all 30 randomly selected children meeting the inclusion criteria, it was found that VD increased the C-peptide level (0.06 nmol/L), slightly improved the pancreatic  $\beta$ -cell function as well as decreased their HbA1c (0.64%), and TDD insulin levels (0.05 unit) although none of the relationships was significant. However, a significant decrease in HbA1c level was found in the female group ( $p=0.04$ ) as well as in the age group less than 10 years ( $p=0.007$ ).

#### Conclusion

VD intake had no significant effect on serum C-peptide levels and reduction of HbA1c and TDD insulin though a significant decrease in HbA1c level was observed in the female group and in the patients less than ten years.

**Key Words:** C-Peptide, Pancreatic B Cells, Pediatric, Type 1 Diabetes Mellitus, Vitamin D.

\*Please cite this article as: Alijanpour Aghamaleki M, Hajiahmadi M, Pornasrollah M, Oruji Z, Aghajpour F. Effect of Vitamin D Supplementation on Pancreatic B -Cell Function in Patients with Type 1 Diabetes Mellitus and Vitamin D Deficiency: A Clinical Trial Study. *Int J Pediatr* 2019; 7(2): 8977-84. DOI: [10.22038/ijp.2018.33805.2986](https://doi.org/10.22038/ijp.2018.33805.2986)

#### \*Corresponding Author:

Zahra Oruji (M.D), **Address:** Non-Communicable Pediatric Diseases Research Center, No 19, Amirkola children's hospital, Amirkola, Babol, Mazandaran Province, 47317-41151, IR Iran.

Email: [dr.oruji@yahoo.com](mailto:dr.oruji@yahoo.com)

Received date: Apr.14, 2018; Accepted date: Sep.12, 2018

## 1- INTRODUCTION

Diabetes is one of the most common endocrine diseases in the world (1). Type 1 diabetes mellitus (T1DM) is a type of diabetes that results from the progressive autoimmune destruction of pancreatic beta ( $\beta$ ) cells followed by low insulin secretion (2). T1DM makes up about 10% of diabetic cases (3), and about 15 million people around the world are suffering from this disease (3). Vitamin D (VD) is an important nutrient with widespread effects on differentiation, proliferation, apoptosis and cellular angiogenesis (4). Although VD is commonly known to regulate the calcium and phosphorus homeostasis in the body, 1,25-dihydroxyvitamin D is also known to regulate the expression of 200 different genes including the immune-regulatory gene (5). The presence of VD receptors in many organs and tissues of the body including immune system cells and pancreatic  $\beta$ -cells shows the widespread effects of this vitamin as an immune regulator in autoimmune diseases (6).

A study has shown a positive effect of VD on pancreatic islet cells and consequently insulin secretion, which is found in C-peptide tests (7). Various studies have suggested a relationship between VD deficiency and T1DM. This vitamin is needed for normal insulin secretion. Epidemiological studies have indicated a correlation between the average incidence of diabetes and sunlight exposure hours (8, 9). Other studies have demonstrated the reduced risk of T1DM as a result of taking VD during the first year of life. It is necessary to take sufficient VD in order to prevent the destruction of  $\beta$ -cells, and this vitamin may help prevent T1DM at a later stage in life. Consequently, the incidence of T1DM can be reduced by providing sufficient training to get VD and be exposed to the sunlight (10-12). Considering the identification of the active form of VD receptors in pancreatic  $\beta$ -cells and immune cells, the aim of this study

was to investigate the effects of VD supplementation intake in T1DM including the likelihood of increased insulin secretion or prevention of progressive reduction of pancreatic  $\beta$ -cell degradation, producing insulin. Obviously, the positive effects of VD on insulin secretion in patients with T1DM can reduce the long-term complications of diabetes and needed total daily dose (TDD) insulin.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This single-blind clinical trial study was performed on T1DM children in the last five years, referred to Endocrinology Clinic of Amirkola Children's Hospital (Babol City, North of Iran) from September 2016 to November 2017.

### 2-2. Methods

Children who suffered from T1DM for 6 months to 5 years and were treated with long-acting insulin (glargine), and fast-acting insulin (aspart) based on the Basal Bolus Insulin Protocol (BBIP) were selected as the sample and their C-peptide levels were initially tested. Insulin Lantus (glargine) was manufactured by SANOFI-Aventis Germany and Insulin Novorapid (aspart) was manufactured by NOVO NORDISK A/S, a Danish multinational pharmaceutical company. D-VITIN 50000U PEARL was manufactured by Zahravi Pharmaceutical Company in Iran. To check these levels, 3 ml of blood clots were needed. C-peptide was measured by the ELISA method using a DiaSorin kit manufactured in Italy, VD was measured by the ELISA method using the Ids kit made in England and Hemoglobin A1c (HbA1c) was measured by an enzymatic method using a Pishtazteb kit made in Iran, and the results were recorded.

### 2-3. Measuring tools

Children who had basal C-peptide levels  $> 0.2$  nmol/l were tested for VD levels.

Those with 25-hydroxyvitamin D (25[OH] D) levels less than 30 (ng/ml), indicating decreased level of VD were included in the study. Accordingly, 30 children were selected as the sample. Finally, after correcting the patients' levels of VD, their C-peptide, 25(OH) D, and HbA1C levels were checked again as well as their C-peptide, 25 (OH) D, HbA1C and TDD insulin were compared at the beginning and end of the study. A checklist containing name, age, gender, 25 (OH) D, HbA1C and C-peptide levels (before and after intervention) was used to collect the data.

#### 2-4. Statistical Analysis

Data were analyzed using SPSS 22.0 with the t-test and Mann–Whitney U test for compare ages less and more than 10 years old and paired t-test and Wilcoxon test for compare between other groups. P-value less than 0.05 was considered as significant level.

#### 2-5. Inclusion and exclusion criteria

Inclusion criteria were children diagnosed with T1DM in the last five years and referred to Endocrinology Clinic of Amirkola Children's Hospital as well as children with C-peptide level > 0.2 nanomoles (nmol) per litre (L), VD level < 30 ng per milliliter (mL), and calcium level > 8.5 Milligrams Per Decilitre (mg/dL) (13, 14). Exclusion criterion was unmodified vitamin D after a course of vitamin D deficiency treatment.

#### 2-6. Intervention

The patients with VD level between 20 and 30 (ng/ml) were VD insufficient and received D-VITIN 50,000 U PEARL per week for up to 6 weeks, and if their VD level was lower than 20 (ng/ml), indicating VD deficiency, they received D-VITIN 50,000 U PEARL for up to 8 weeks (13). All patients were visited and treated by a pediatric endocrinologist in Endocrinology Clinic of Amirkola Children's Hospital.

Then, the children's VD levels were re-tested and if, again, they were low, the weekly treatment was continued for a once based on VD levels until they became normal (more than 30 (ng/ml). If they failed to reach a normal level of this vitamin after another six-to-eight-week period of D-VITIN PEARL, the patients were excluded from the study. After correcting the patients' levels of VD, a single dose of VD was administered for each month until the end of the study (9 months), and finally, C-peptide, 25 (OH) D and HbA1C levels were checked again, and C-peptide, 25 (OH) D, HbA1C and TDD insulin were compared at the beginning and end of the study.

#### 2-7. Ethical consideration

This study has been approved by Local Ethics Committee of Babol University of Medical Sciences Ethics Committee (ID number: IR.MUBABOL.REC.1395.48), and registered by the Iranian Registry of Clinical Trials with this code: IRCT20180228038900N2.

### 3- RESULTS

Out of 30 children, 15 (50 %) of them were female and 15 (50%) were male. They consisted of 14 children (47%) less than 10 years old and 16 children (53 %) older than 10 years. Their mean age was  $10.97 \pm 3.66$  years and they were within the age range of 4-19 years. VD supplementation could significantly increase VD levels in patients to 26.98 ng/ml ( $P < 0.001$ ). **Table.1** presents the effect of VD on the factors under investigation in terms of gender. In males, the C-peptide and HbA1c levels decreased by 0.22 nmol/lit and 0.23%, respectively ( $p=0.13$  and 0.67, respectively), and the TDD insulin level increased by 3.43 ( $p=0.12$ ), none of which was significant. In females, the C-peptide level increased by 0.34 nmol/lit ( $p=0.09$ ), and the TDD insulin level decreased by 3.53 ( $p=0.10$ ), none of which was significant. However,

the HbA1c level significantly decreased by 1.04% in females ( $p=0.04$ ). **Table.2** displays the effect of VD on the factors under investigation in terms of age. In the children less than 10 years of age, the C-peptide level increased by 0.04 nmol/lit ( $p=0.70$ ), and the TDD insulin level decreased by 1.25 ( $p=0.45$ ), none of which was significant. However, the HbA1c level significantly decreased in this age group by 10.52% at the end of the study ( $p = 0.007$ ). In the children over 10 years of age, the C-peptide level increased by 0.06

nmol/lit ( $p=0.97$ ), the HbA1c level increased by 0.13% ( $P= 0.76$ ), and the TDD insulin level decreased by 1.00 ( $p=0.70$ ), none of which was significant.

**Table.3** illustrates the effect of VD on the serum levels of C-peptide, HbA1c and TDD insulin. VD led to an increase in the patients' C-peptide level by 0.06 nmol/L ( $p=0.82$ ), a decrease in HbA1c level by 0.064 ( $p=0.64$ ), and a decrease in TDD insulin level by 0.05 ( $p=0.97$ ), but none of the relationships was significant.

**Table-1:** The comparison of outcome variables including the VD, C-peptide and HbA1c levels, and the TDD level before and after VD treatment in T1DM patients in terms of gender

Gender	Variables	Before treatment	After treatment	P-value	Difference
Boys	VD level (ng/ml)	15.76±6.18	41.94±13.04	0.001	26.17±14.64
	C-peptide level (nmol/l)	0.69±0.9	0.46±0.53	0.13	-0.22±0.57
	HbA1c level (percent)	8.37±1.47	8.14±1.48	0.67	-0.23±2.09
	TDD level (unit)	24.57±18.01	28.00±10.23	0.12	3.43±8.20
Girls	VD level (ng/ml)	10.50±7.81	38.29±7.64	0.001	27.7±12.87
	C-peptide level (nmol/l)	0.58±0.34	0.92±0.87	0.09	0.34±0.69
	HbA1c level (percent)	9.13±1.98	8.09±1.47	0.04	-1.04±1.80
	TDD level (unit)	32.80±18.72	29.27±18.41	0.10	-3.53±7.84

VD: vitamin D; HbA1c: hemoglobin A1c; TDD: total daily dose.

**Table-2:** The comparison of outcome variables including the VD, C-peptide and HbA1c levels, and the TDD level before and after VD treatment in T1DM patients in terms of age group

Year	Variables	Before treatment	After treatment	P-value	Difference
≤ 10	VD level (ng/ml)	12.60±7.48	42.63±12.66	0.001	30.02±16.54
	C-peptide level (nmol/l)	0.37±0.20	0.41±0.35	0.70	0.04±0.42
	HbA1c level (percent)	9.16±0.85	7.64±1.57	0.007	-10.52±1.79
	TDD level (unit)	17.68±13.66	16.43±10.69	0.45	-1.25±6.05
>10	VD level (ng/ml)	13.60±7.58	37.91±8.37	<0.001	24.31±10.13
	C-peptide level (nmol/l)	0.86±0.85	0.93±0.92	0.97	0.06±0.87
	HbA1c level (percent)	8.39±2.24	8.53±1.25	0.76	0.13±1.81
	TDD level (unit)	38.31±17.03	39.31±18.43	0.70	-1.00±10.49

VD: vitamin D; HbA1c: hemoglobin A1c; TDD: total daily dose.

**Table-3:** A comparison of outcome variables including the VD, C-peptide and HbA1c levels, and the TDD level before and after VD treatment in T1DM patients

Variables	Before treatment	After treatment	P-value	Difference
VD level (ng/ml)	13.13±7.42	40.11±10.67	<0.001	26.98±13.57
C-peptide level (nmol/l)	0.63±0.67	0.69±0.75	0.82	0.06±0.69
HbA1c level (percent)	8.75±1.75	8.11±1.45	0.08	-0.64±1.96
TDD level (unit)	28.68±18.53	28.63±19.02	0.97	-0.05±8.64

VD: vitamin D; HbA1c: hemoglobin A1c; TDD: total daily dose.

#### 4- DISCUSSION

The current study showed that the intake of VD by children with T1DM had no significant effect on their serum C-peptide levels although this study emphasized that VD intake at least prevented the further decline of C-peptide level and progressive reduction of pancreatic  $\beta$ -cells. Bizzarri et al. in 2010 conducted a study on 34 T1DM patients with C-peptide  $>0.2$  nmol/l, who had undergone the treatment for less than three months. After following-up the patients for two years, they stated that there was no significant difference between the calcitriol group and placebo group in terms of the C-peptide level (15), which is consistent with our study. Gabbay et al. carried out a study in 2012 on 38 T1DM patients with C-peptide  $\geq 0.6$  nmol/l, suffering from diabetes for less than 6 months. After 18 months, supplementation of VD (cholecalciferol) decreased the rate of C-peptide decline, so that the cumulative incidence of progression to undetectable ( $\leq 0.1$ ng/mL) fasting C-peptide level reached 18.7% in the cholecalciferol group, and 62.5% in the placebo group. In other words, VD supplementation reduced the degradation rate of pancreatic  $\beta$ -cells (16). The final finding of Gabbay et al.'s study is also in line with that of our study, that is, the intake of VD supplements at least reduced the degradation rate of pancreatic  $\beta$ -cells and stopped the progressive decline of C-peptide though the patients studied here

had been suffering from diabetes for less than 6 months and definitely had healthier pancreatic  $\beta$ -cells in comparison with the patients of our study, who had been suffering from diabetes for more than 6 months. In addition, Fitas et al. in 2014 performed a study on 28 newly diagnosed T1DM patients with C-peptide  $\geq 0.2$  nmol/l, after 13.4 months, the group received cholecalciferol had significantly higher levels of C-peptide than the placebo group (17). A study was conducted by Sharma et al. on 52 T1DM children without considering a specific C-peptide level and specific duration of the onset of diabetes. After 6 months of follow-up, they found that the serum levels of C-peptide in children who had used VD supplements were significantly higher than those who had not used it (18). The studies of Fitas et al. (17), and Sharma et al. (18) indicated a statistically significant increase in the C-peptide level. Our study also showed an increase in the C-peptide level but not statistically significant.

The above-mentioned studies were different from our study due to their various inclusion criteria. All patients of our study had been suffering from T1DM and VD deficiency for at least 6 months; while the patients of the above-mentioned studies were only T1DM patients who were randomly divided into two groups, one receiving (D-Vitin 50,000) pearl and the other not receiving it. Sharma et al.'s study lasted for 6 months, which was shorter than the duration of our study. In

our study, VD intake resulted in a statistically insignificant decrease in HbA1c levels, which was also reported in the studies of Fitas et al., Gabbay et al., and Bizzarri et al.; they found that the intake of VD supplements did not significantly change the HbA1c level (15-17). However, in 2010 Aljabri et al. carried out a study on 18 T1DM patients who had VD levels less than 50 nmol/l. After a three-month follow-up, they observed that VD supplementation could significantly reduce the HbA1c levels (21). Mohammadian et al. fulfilled a study on 44 T1DM patients who had VD levels less than 50 nmol/l. After a three-month follow-up, they reported that the patients' HbA1c levels significantly decreased following their intake of VD supplements (20). Our study demonstrated the lowered HbA1c levels after VD intake, too, but the rate of decrease was not statistically significant. The different doses or formulations of VD and the shorter duration of this study, which lasted for 3 months, in comparison with our study, which lasted for 9 months, could account for the differences in the results of the studies.

Our study illustrated that VD reduces the TDD insulin level although this change was not statistically significant. Fitas et al., Gabbay et al. and Bizzarri et al. have also reported that VD replacement has no significant effect on the TDD insulin level (15-17); which is consistent with the current study. Pitocco et al. performed a study on 70 newly diagnosed T1DM patients with an average age of 13.6 years, and reported that the use of calcitriol for 3 and 6 months significantly decreases the insulin dose (21). Our study also revealed that VD supplements reduce the TDD insulin level, but the change is not statistically significant. The shorter duration and smaller sample size of our study compared to the study of Pitocco et al. cause the differences in the results. In

terms of gender and age, our study indicated significantly reduced HbA1c levels following the VD supplements in the female group and in the age group less than 10 years. The C-peptide level elevated and TDD insulin level decreased in the female group, while this difference was not statistically significant. The lack of a significant association between the VD level and HbA1c level at the age of over 10 years can be due to the presence of pubertal hormones during this age, which causes insulin resistance. In addition, the age of over than 10 years compared to the lower age groups, is the age at which the patients feel that they are entering new lives; therefore, they refuse to continue the treatment process because of their age and maturity, leading to a lack of proper control of their blood glucose and HbA1c levels. No article has been found to evaluate the effect of VD on the C-peptide, HbA1c and TDD insulin levels in terms of age and gender.

#### **4-1. Limitations of the study**

One of the limitations of the present study was the lack of body mass index (BMI) assessment in diabetic patients, which could be due to the small sample size and its consequent, the small number of diabetic patients with a high BMI. Another limitation was its duration longer than that of the previous studies, which made it very difficult for the researchers to follow-up the patients in order to check their regular intake of D-VITIN pearl and their repetition of the end-of-work tests. It is recommended to conduct a study on T1DM patients with normal levels of VD in order to investigate the effect of two preventive methods of VD intake (daily vs. monthly VD intake), and to compare these two groups in terms of their C-peptide, HbA1c and TDD insulin levels after a specific period. Further suggestion is to carry out a study with a larger sample size and longer duration and to determine the patients' BMI.

## 5- CONCLUSION

According to the results of the present study, the intake of VD by T1DM patients does not have a significant effect on the elevation of serum C-peptide levels and the reduction of HbA1c and TDD insulin levels although it can prevent a further decline in the C-peptide level. However, HbA1c level of females less than 10 years significantly decreased by VD consumption. Therefore, it is recommended to check the VD levels in T1DM patients regularly and administer an appropriate treatment for its deficiency followed by a required treatment to prevent its further decline and keep the patients' blood levels of VD at a normal level.

**6- CONFLICT OF INTEREST:** None.

## 7- ACKNOWLEDGMENT

We are grateful to the Clinical Research Development Committee of Amirkola Children's Hospital, Non-Communicable Pediatric Diseases Research Center of Babol University of Medical Sciences for their contribution to this study. This study was supported by a research grant and residency thesis of Dr Zahra Oruji from the Non-Communicable Pediatric Diseases Research Center of Babol University of Medical Sciences (Grant Number: 9542930).

## 8- REFERENCES

1. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on Type 2 diabetes prevention. *Diabetic Medicine: a journal of the British Diabetic Association*. 2007;24(5):451-63.
2. Harinarayan CV. Vitamin D and diabetes mellitus. *Hormones*. 2014;13(2):163-81.
3. McInerney. TK, Adam. HM, Campbell. DE, DeWitt. TG, Foy. JM, Kamat. DM, editors. *Textbook of pediatric* 20th Edition ed 2016.

4. Ban Y, Taniyama M, Yanagawa T, Yamada S, Maruyama T, Kasuga A, et al. Vitamin D receptor initiation codon polymorphism influences genetic susceptibility to type 1 diabetes mellitus in the Japanese population. *BMC medical genetics*. 2001;2:7.
5. Orbach H, Zandman-Goddard G, Amital H, Barak V, Szekanez Z, Szucs G, et al. Novel biomarkers in autoimmune diseases: prolactin, ferritin, vitamin D, and TPA levels in autoimmune diseases. *Annals of the New York Academy of Sciences*. 2007;1109:385-400.
6. Mazokopakis EE, Kotsiris DA. Hashimoto's autoimmune thyroiditis and vitamin D deficiency. *Current aspects. Hellenic journal of nuclear medicine*. 2014;17(1):37-40.
7. Paulett D C, Edward L G. Effect Of Vitamin D Supplementation On C-peptide and 25- hydroxyvitamin D Concentration at 3 and 6 Months. *Scientific Report*. 2015;5(10411):1-9.
8. Bener A, Alsaied A, Al-Ali M, Al-Kubaisi A, Basha B, Abraham A, et al. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. *Acta diabetologica*. 2009;46(3):183-9.
9. Bener A, Alsaied A, Al-Ali M, Hassan AS, Basha B, Al-Kubaisi A, et al. Impact of lifestyle and dietary habits on hypovitaminosis D in type 1 diabetes mellitus and healthy children from Qatar, a sun-rich country. *Annals of nutrition & metabolism*. 2008;53(3-4):215-22.
10. Mathieu C, Gysemans C, Giuliatti A, Bouillon R. Vitamin D and diabetes. *Diabetologia*. 2005;48(7):1247-57.
11. Mitri J, Pittas AG. Vitamin D and diabetes. *Endocrinology and metabolism clinics of North America*. 2014;43(1):205-32.
12. Penckofer S, Kouba J, Wallis DE, Emanuele MA. Vitamin D and diabetes: let the sunshine in. *The Diabetes educator*. 2008;34(6):939-40.
13. Sperling MA. *Pediatric Endocrinology E-Book*: Elsevier Health Sciences; 2014.
14. Beritta.M Svoren and Nicholas Jospe. *Diabetes Mellitus, Diabetes Mellitus in*

Children, The Endocrine System, Nelson Textbook of Pediatrics E-Book: Elsevier Health Sciences; 2016;589(6):2760-3.

15. Bizzarri C, Pitocco D, Napoli N, Di Stasio E, Maggi D, Manfrini S, et al. No Protective Effect of Calcitriol on  $\beta$ -Cell Function in Recent-Onset Type 1 Diabetes. *Diabetes care*. 2010;33(9):1962-3.

16. Gabbay MA, Sato MN, Finazzo C, Duarte AJ, Dib SA. Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual  $\beta$ -cell function in new-onset type 1 diabetes mellitus. *Archives of pediatrics and adolescent medicine*. 2012;166(7):601-7.

17. Layra Fitas A, Filipa Almeida A. Effect of Adjunctive Therapy with Cholecalciferol on Residual  $\beta$ -cell Function in recent-onset Type 1 Diabetes Mellitus:a Prospective Pilot Study. *ESPE DUBLIN*Ireland. 2014:18-20.

18. Sharma S, Biswal N, Bethou A, Rajappa M, Kumar S, Vinayagam V. Does

Vitamin D Supplementation Improve Glycaemic Control In Children With Type 1 Diabetes Mellitus? A Randomized Controlled Trial. *Journal of clinical and diagnostic research: JCDR*. 2017;11(9):SC15.

19. Aljabri KS, Bokhari SA, Khan MJ. Glycemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency. *Annals of Saudi medicine*. 2010;30(6):454-8.

20. Mohammadian S, Fatahi N, Zaeri H, Vakili MA. Effect of vitamin d3 supplement in glycemic control of pediatrics with type 1 diabetes mellitus and vitamin d deficiency. *Journal of clinical and diagnostic research: JCDR*. 2015;9(3):SC05.

21. Pitocco D, Crino A, Di Stasio E, Manfrini S, Guglielmi C, Spera S, et al. The effects of calcitriol and nicotinamide on residual pancreatic  $\beta$ -cell function in patients with recent-onset Type 1 diabetes (IMDIAB XI). *Diabetic Medicine*. 2006;23(8):920-3.