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Original Research Article

Vitamin- D Supplementation with Moderate Exercise Enhance Plasma Insulin Levels in Prediabetes and Type 2 Diabetes Patients

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Conflict of interest: Nil

Abstract:

The aim of the study is to investigate the relationship between the supplementation of vitamin -D with moderate exercise (ME) on plasma insulin level in Indian subjects of Pre and Type 2 diabetes mellitus. Several observational studies suggest that vitamin-D plays a role in the pathogenesis of pre and Type2 diabetes. We investigate the effect of ME with Vitamin-D supplementation in the pathogenesis of diabetes.

Method: The Plasma Insulin and vitamin- D levels were measured using Radioimmunoassay and ELISA. We measured plasma Insulin level in the Indian subjects of age group (30-50 years) of N30, before and after vitamin- D supplementation with ME for the following groups. Vitamin- D deficient with Pre diabetes mellitus (PDM), vitamin -D deficient with Type 2 diabetes mellitus (T2DM), vitamin- D deficient with non-diabetes mellitus (NDM) and ME alone.

Result: We observed that, plasma Insulin level were significantly ($P<0.05$) increased after supplementation of vitamin- D with moderate exercise when compare to and ME alone.

Conclusion: This study suggests that Vitamin- D supplementation with moderate exercise may improve insulin secretion from β cells in Vitamin -D deficient with PDM and T2DM cases.

Keywords: Vitamin-D, Pre diabetes, Insulin, Type 2 diabetes.

Introduction

The rapid increase in prevalence of diabetes has become a major distress for India and the World. The initial Pre diabetes is prevalent in the global population progression to diabetes can occur because of worsening insulin resistance, Pancreatic β-cell dysfunction or both. In case without intervention, Pre diabetes is likely to become Type-2 diabetes, with in short period[1]. The β-cell dysfunction is an important contributor to the pathogenesis of type 2 diabetes[2,3].

Rickets and osteomalacia can be prevented and treated with vitamin D, which is essential for bone and mineral metabolism[4-8]. There have been many studies on possible extra-skeletal effects of vitamin D due to the fact that vitamin D receptors (VDRs) are expressed in practically every tissue and cell[9-17]. Epidemiological research has demonstrated a strong interest in vitamin D due to the association between low 25-hydroxyvitamin D (25[OH]D]) concentrations and a number of acute and chronic illnesses[18,19].

Several observational studies have related vitamin D deficiency (VDD) to Type-2 diabetes[20] and metabolic syndrome[21]. Advantageous effects of vitamin D have been demonstrated on both insulin sensitivity and β-cell function in several animal model studies[22-24]. Furthermore, other studies have suggested an interesting involvement of vitamin D in the impairment β-cell secretion[25-26]. 2010. However, published clinical trials shows supplementation of Vit D in subjects with Type-2-diabetes and Prediapetes have inconsistent results[27]. A greater improvement in the insulin sensitivity [28] and metabolic syndrome after exercise[29-30].was reported. However, in some cases Type- 2 diabetes and Pre diabetes single exposure of Vit D or ME alone could not show significant effect for this reason and based on earlier studies we hypothesized that combine effect of VitD supplementation along with moderate exercise assign potential effect on β-cell function. Further, no previous study has examined the combine effect of (ME+ Vit D) on insulin secretion in Vitamin D deficient diabetes patients. Hence, this study has been undertaken.

There is general agreement that providing toddlers and newborns with 400 IU of vitamin D daily can prevent nutritional rickets[31]. More debatable are the possible extra-skeletal effects of vitamin D and the skeletal effects of vitamin D insufficiency in adults and older individuals (aged >65 years). Some people believe that taking vitamin D supplements is pointless[32]. Others, however, have argued that people should strive to reach 25-hydroxyvitamin D (25OHD) concentrations comparable to those found in some tribes in equatorial Africa with a sun exposure lifestyle that may be similar to that of early humans[33-37]. This is because the vitamin D intake requirement is much higher than what the general population currently achieves.

Vitamin D supplementation only demonstrated a non-significant trend to delay the progression of prediabetes into T2DM in the large D2d RCT of individuals with prediabetes. People who got vitamin D (4,000 IU per day) and had a high risk of developing T2DM were purposefully included in the trial. In the ITT analysis, the vitamin D group's hazard ratio for developing T2DM was 0.88 (95% CI 0.75-1.04; P = 0.12) higher than that of the placebo group. However, in a post hoc analysis, those with a baseline BMI under 30 mg/m2, severe vitamin D deficiency at baseline, complete adherence to medication throughout the study, or blood 25OHD above 100 nmol/l during the study[38] showed a significant benefit.

Materials and method:

The outpatients and inpatients were collected from the Nandha Medical College and Hospital Erode, Tamilnadu. Prior written and informed consent was obtained from every patient and the study was approved by the Intuitional ethical committee. The subjects were divided into four groups. Vitamin- D deficient with Pre diabetes mellitus (PDM), vitamin - D deficient with Type 2 diabetes mellitus (T2DM), vitamin- D deficient with non-diabetes mellitus (NDM) and Mild exercise (ME) alone. Abnormal BMI patients were excluded. Moderate exercise (ME): Mild walking morning 1 hr daily Vitamin D supplementation given 5000 IU per day given.

Blood samples were collected and the Plasma Insulin and vitamin- D levels were measured in control and experimental group using Radioimmunoassay and ELISA

Results

In this study before and after supplementation of vit D or moderate exercise or both, the vitamin D and insulin level were analyzed. We observed that, plasma Insulin level were significantly (P<0.05) increased after supplementation of vitamin- D with moderate exercise in Vitamin- D deficient with Prediabetes mellitus (PDM), vitamin-D deficient with Type 2 diabetes mellitus (T2DM), vitamin- D deficient with non-diabetes mellitus (NDM) which is shown in figure 1-7. One way ANOVA used to analyze the data.

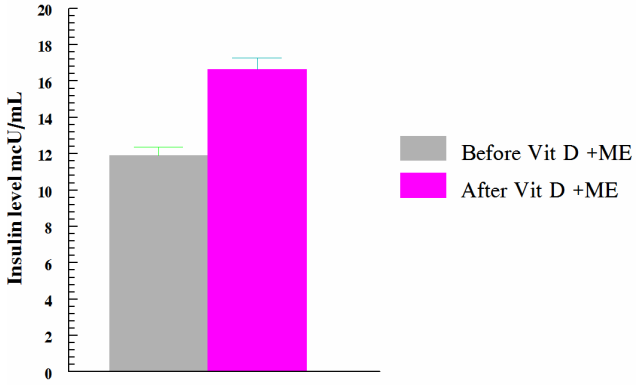

Figure 1: Vitamin- D deficient with non-diabetes mellitus (NDM) Supplement Vit D+ ME (Moderate Exercise) Result: mean ±SEM (n=30), significant(P<0.05)

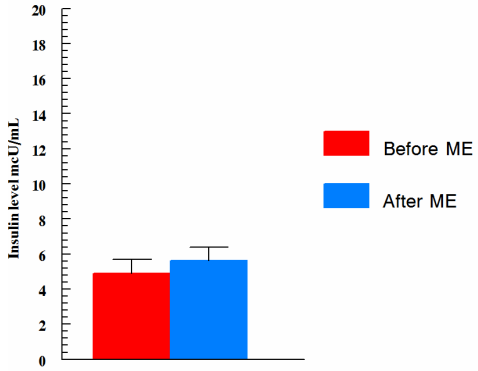

Figure 2: Vitamin-D deficient with Prediabetes mellitus (PDM) supplement Moderate exercise (ME) alone Result: mean ±SEM (n=30), non-significant

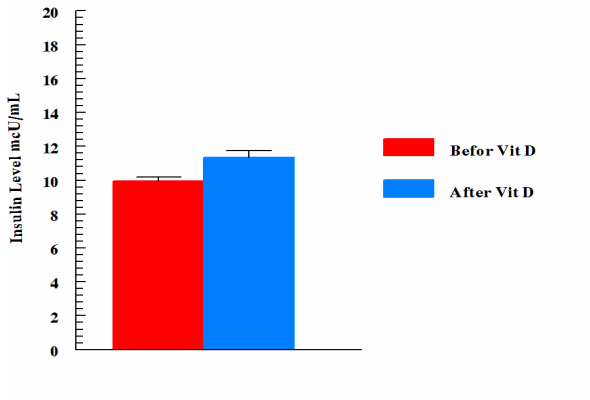

Figure 3: Vitamin- D deficient with Prediabetes mellitus (PDM) Supplement Vit D alone Result: mean ±SEM (n=30), non-significant

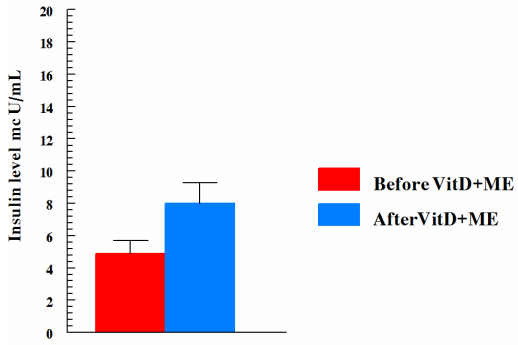

Figure 4: Vitamin- D deficient with Prediabetes mellitus (PDM) Supplement Vit D+ME (Moderate exercise) Result: mean ±SEM (n=30), significant(P< 0.05)

In this study after supplementation of Vit D with moderate exercise significantly increases the plasma insulin level. Similarly earlier studies reported that after aerobic training (AT) and resistance training (RT) significantly larger improvements in beta cell function in overweight adults[39] and in mice[40].

Vitamin D supplementation increases the beta cell insulin secretion in animal and human models[41]. However compare to pervious study in this study we observed that combined effect of supplementation Vita D with ME shows better performance of beta cell - insulin secretion compare to single exposure Vit D or ME alone.

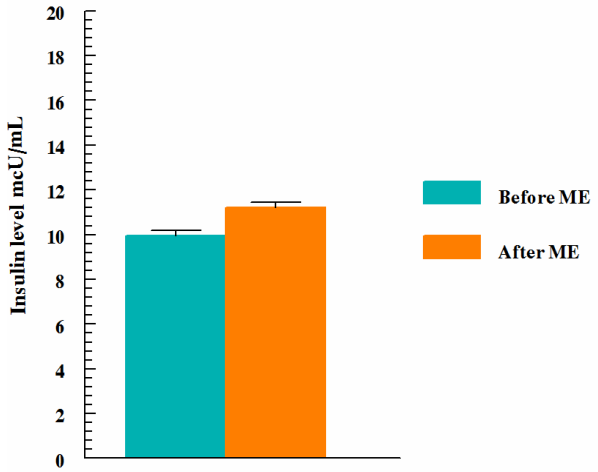

Figure 5: Vitamin -D deficient with Type 2 diabetes mellitus (T2DM) Supplement ME (Moderate exercise) Result: mean ±SEM (n=30), non-significant

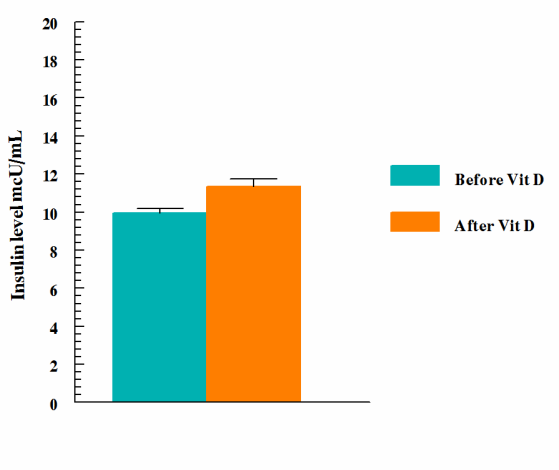

Fig 6: Vitamin -D deficient with Type 2 diabetes mellitus (T2DM) Supplement Vit D alone Result: mean ±SEM (n=30), non-significant

However, the exact mechanisms of vitamin D effect on insulin secretion in the presence of glucose are not yet fully understood and need further studies, but it has been reported that vitamin D directly increases insulin secretion in beta cells[42]. The mechanism may occur due to the presence of vitamin D receptors (VDR) on pancreatic β cells in the islets of Langerhans [30]. Faure et al. have reported that vitamin D enhances Ca2+ entry or Ca2+ mobilization in β cells, which could indirectly amplify insulin secretion[43]. In addition current research supports a direct effect of vitamin D on insulin formation and release because due to the presenceof the vitamin D response element in the human insulin gene promoter and the transcriptional activity of the human insulin gene caused by 1, 25-dihydroxyvitamin D (the active form of vitamin D)[44-45].

Huang HH et al have reported exercise has an effect on the pancreatic islets by stimulating insulin production and/or secretion in diabetic animals[40]. Conversely, exercise on *β*-cell health indicate exercise partially spared the *β*-cells from diabetes.However, the exact mechanisms of exercise effect on insulin secretion in beta cell not yet fully understood and need further studies

Conclusion

This study concludes that in Vitamin D deficient diabetes cases vitamin D supplementation not only sufficient to enhance the insulin secretion the is a moderate exercise also required with the supplementation of Vit D

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Institutional Ethical Committee approval:

Nandha Medical College and Hospital, Erode College's intuitional Ethical Committee assessed and approved the survey project. Informed consent obtained from all the participants.

Author Contributions: Dr. A.S.kumar — conceptualization, data curation, investigation, methodology, project administration, visualization, writing—original draft, writing—review and editing, **Dr. G. M. Thirumalai Raaja** — conceptualization, methodology, writing—original draft, writing—review and editing, **Dr Paramasivan N** —conceptualization, visualization, supervision, writing—original draft, **Dr A.Chandrabose**—methodology, writing—original draft, writing—review and editing.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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References

1. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care. 2007;30(3):753–759.
2. Kahn S, Hull R, Utzschneider K. Mechanisms linking obesity to insulin resistance and to type 2 diabetes. Nature 2006; 444:840–846
3. Ferrannini E, Gastaldelli A, Miayzaki Y, Matsuda M, Pettiti M, Natali A, Mari A, DeFronzo R. Predominant role of reduced beta-cell sensitivity to glucose over insulin resistance in impaired glucose tolerance. Diabetologia 2003; 46:1211–1219
4. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiological Reviews 2016. 96 365–408.
5. Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. Nature Reviews Disease Primers 2017. 3 17101
6. Uday S, Fratzl-Zelman N, Roschger P, Klaushofer K, Chikermane A, Saraff V, Tulchinsky T, Thacher TD, Marton T, Högler W. Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg. BMC Pediatrics 2018; 18: 183.
7. Uday S, Högler W. Nutritional rickets and osteomalacia in the twenty-first century: revised concepts, public health, and prevention strategies. Current Osteoporosis Reports 2017; 15:293–302.
8. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Mäkitie O, et al Global consensus recommendations on prevention and management of nutritional rickets. Journal of Clinical Endocrinology and Metabolism 2016; 101: 394–415.
9. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, Lieben L, Mathieu C, Demay M. Vitamin D and human health: lessons

from vitamin D receptor null mice. Endocrine Reviews 2008; 29:726–776.
10. Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, Murad MH, Kovacs CS. The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. Endocrine Reviews 2012; 33:456–492.
11. Pilz S, Verheyen N, Grübler MR, Tomaschitz A, März W. Vitamin D and cardiovascular disease prevention. Nature Reviews Cardiology 2016; 13:404–417.
12. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Reviews in Endocrine and Metabolic Disorders 2017; 18:153–165.
13. Trummer C, Pilz S, Schwetz V, Obermayer-Pietsch B, Lerchbaum E. Vitamin D, PCOS and androgens in men: a systematic review. Endocrine Connections 2018; 7 R95–R113.
14. Muscogiuri G, Altieri B, Annweiler C, Balercia G, Pal HB, Boucher BJ, Cannell JJ, Foresta C, Grübler MR, Kotsa K, et al Vitamin D and chronic diseases: the current state of the art. Archives of Toxicology 2017; 91:97–107.
15. Zittermann A, Pilz S, Hoffmann H, März W. Vitamin D and airway infections: a European perspective. European Journal of Medical Research 2016; 21:14.
16. Wagner CL, Hollis BW. The implications of vitamin D status During pregnancy on mother and her developing child. Frontiers in Endocrinology. 2018; 9: 500.
17. Keane JT, Elangovan H, Stokes RA, Gunton JE. Vitamin D and the liver-correlation or cause? Nutrients; 2018;10: 496.
18. Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, Khan H, Baena CP, Prabhakaran D, Hoshen MB, et al Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. BMJ. 2014; 348 g1903.
19. Gaksch M, Jorde R, Grimnes G, Joakimsen R, Schirmer H, Wilsgaard T, Mathiesen EB, Njølstad I, Løchen ML, März W, et al Vitamin D and mortality: individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. PLoS ONE. 2017; 12 e0170791.
20. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab. 2007 Jun; 92(6):2017–29.
21. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143–3421.
22. Bourlon PM, Faure-Dussert A, Billaudel B. The de novo synthesis of numerous proteins is decreased during vitamin D3 deficiency and is gradually restored by 1, 25-dihydroxyvitamin D3 repletion in the islets of Langerhans of rats. The Journal of endocrinology.1999 Jul; 162(1):101– 9.
23. Cade C, Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat in vivo. Endocrinology. 1986 Jul; 119(1):84–90
24. Clark SA, Stumpf WE, Sar M. Effect of 1,25 dihydroxy vitamin D3 on insulin secretion. Diabetes.1981 May; 30(5):382–6.
25. Hyppönen E, Power C: Vitamin D status and glucose homeostasis in the 1958 British birth cohort: the role of

obesity. Diabetes Care 2006; 29: 2244–2246.
26. Pittas AG, Dawson-Hughes B: Vitamin D and diabetes (review). J Steroid Biochem Mol Biol 2010; 121: 425–429.
27. Gedik O, Akalin S. Effects of vitamin D deficiency and repletion on insulin and glucagon secretion in man. Diabetologia. 1986 Mar; 29(3):142–5
28. Houmard J, Tanner C, Slentz C, Duscha B, McCartney J, Kraus W. Effect of the volume and intensity of exercise training on insulin sensitivity. J Appl Physiol 2004; 96:101–106
29. Rynders CA1, Weltman JY, Jiang B, Breton M, Patrie J, Barrett EJ, Weltman A. Effects of exercise intensity on postprandial improvement in glucose disposal and insulin sensitivity in prediabetic adults. J Clin Endocrinol Metab. 2014 Jan;99(1):220-8.
30. Johnson J, Slentz C, Houmard J, Samsa G, Duscha B, Aiken L, McCartney J, Tanner C, Kraus W. Exercise training amount and intensity effects on metabolic syndrome (from Studies of a Targeted Risk Reduction Intervention through Defined Exercise). Am J Cardiol 2007; 100:1759.
31. Munns, C. F. et al. Global consensus recommendations on prevention and management of nutritional rickets. J. Clin. Endocrinol. Metab. 2016;101: 394–415.
32. Bolland, M. J., Grey, A. & Avenell, A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018;6: 847–858.
33. Luxwolda, M. F., Kuipers, R. S., Kema, I. P., Dijck-Brouwer, D. A. & Muskiet, F. A. Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l. Br. J. Nutr. 2012;108: 1557–1561.
34. Luxwolda, M. F. et al. Vitamin D status indicators in indigenous populations in East Africa. Eur. J. Nutr. 2013;52: 1115–1125.
35. Holick, M. F. & Grant, W. B. Vitamin D status and ill health. Lancet Diabetes Endocrinol. 2014;2: 273–274.
36. Bouillon, R., Lips, P. & Bilezikian, J. P. Vitamin D supplementation and musculoskeletal health. Lancet Diabetes Endocrinol. 2019; 7:85–86.
37. Lips, P., Bilezikian, J. P. & Bouillon, R. Vitamin D: giveth to those who needeth. JBMR 2020;4, e10232.
38. Dawson-Hughes, B. et al. Intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: a secondary analysis from the Vitamin D and Type 2 Diabetes (D2d) Study. Diabetes Care 2020;43: 2916–2922.
39. AbouAssi H1, Slentz CA2, Mikus CR1, Tanner CJ3, Bateman LA1, Willis LH1, Shields AT3, Piner LW1, Elliott-Penry LE1, Kraus EA1, Huffman KM1, Bales CW1, Houmard JA3, Kraus WE The Effects of Aerobic, Resistance and Combination Training on Insulin Sensitivity and secretion in Overweight Adults from STRRIDE AT/RT: A Randomized Trial. J Appl Physiol.1985; 2015
40. Huang HH1, Farmer K, Windscheffel J, Yost K, Power M, Wright DE, Stehno-Bittel L. Exercise increases insulin content and basal secretion in pancreatic islets in type 1 diabetic mice. Exp Diabetes Res. 2011; 2011:481427.
41. Jeddi S, Syedmoradi L, Bagheripour F, Ghasemi A. The effects of vitamin d on insulin release from isolated islets of rats. Int J Endocrinol Metab. 2015 Jan 30;13(1):e20620.
42. d'Emden MC, Dunlop M, Larkins RG, Wark JD. The in vitro effect of 1 alpha,25- dihydroxyvitamin D3 on insulin production by neonatal rat islets. Biochem Biophys Res Commun. 1989;164(1):413–8
43. Faure A, Sutter BC, Billaudel B. Is 1,25-dihydroxyvitamin D3 the specific vitamin D3 metabolite active on insulin release and calcium handling by islets

from vitamin D3-deprived rats? Diabete Metab. 1991;17(2):271–8
44. Maestro B, Davila N, Carranza MC, Calle C. 2003. Identification of a vitamin D response element in the human insulin receptor gene promoter. J Steroid Biochem Mol Biol. 84:223-30.
45. Maestro B, Molero S, Bajo S, Davila N, Calle C. 2002. Transcriptional activation of human insulin receptor gene by 1,25-dihydroxyvitamin D(3). Cell Biochem Funct. 20:227-32