

## Negative Correlation Found between Insulin Resistance and Vit D Levels in Obesity

Kaushik Kar<sup>1</sup>, Satwika Sinha<sup>2</sup>

<sup>1</sup>Associate Professor, Department of Biochemistry, Calcutta National Medical College, Kolkata, India

<sup>2</sup>Assistant Professor, Department of Biochemistry, Calcutta National Medical College, Kolkata, India

### Original Research Article

\*Corresponding author

Satwika Sinha

#### Article History

Received: 01.11.2017

Accepted: 14.11.2017

Published: 30.11.2017



**Abstract:** Vitamin D deficiency probably takes a part in the development of insulin resistance. Insulin resistance also markedly affects the obese population. In this study, 123 obese persons were selected, and homeostatic model assessment (HOMA-IR) was measured in them. Vitamin D was also measured in all participants. Among participants with HOMA-IR >2.7, significantly higher BMI and lower vitamin D were observed; furthermore, inverse relation observed between insulin resistance and vitamin D in them.

**Keywords:** Obesity, BMI, HOMA-IR, Vitamin D.

### INTRODUCTION

Apart from calcium homeostasis vitamin D has proved its role in many biological functions [1,2]. Vitamin D deficiency is a potential risk factor of many diseases, substantiated by some authors [3,4]. Concurrence of low level of vitamin D and insulin resistance can take place, furthermore vitamin D may have a significant part in insulin secretion as well as its deficiency can promote type 2 diabetes mellitus proposed by some studies [5]. Those studies also suggested several pathophysiological mechanisms of vitamin D related insulin resistance [1,5,6].

Vitamin D exerts its activity by binding with vitamin D receptors, located inside nucleus.

Presently, those receptors have been identified in other tissues, of which skeletal muscles and adipose tissues are of special significance, since they are the main determinants of peripheral insulin uptake and sensitivity [1,2,7]. Some researchers indicated the common risk factors like sedentary life style and obesity to develop vitamin D deficiency and type 2 diabetes [8]. Furthermore, epidemiological data have linked low vitamin D levels to cardiovascular diseases and type 2 diabetes [9]. The mechanisms by which obesity and its comorbidities are related to vitamin D deficiency are poorly understood.

In the present study, we determined the prevalence of insulin resistance and vitamin D status in obese population. Furthermore we tried to find out any correlations between them.

### Study design

This hospital based, cross sectional, non-interventional study was conducted during the period of November 2016 to April 2017, during the period of reduced sunlight in the Department of Biochemistry, Calcutta National Medical College, Kolkata, and West Bengal, India.

### Selection of case group

The study group primarily included 123 (one hundred twenty three) obese patients attending endocrinology and General Medicine Outdoor Patient Department. Obese patients were selected by calculation of BMI. This is performed by standardized protocol based on height and weight measurements. Overweight was defined as a BMI of 25-29.99 kg/m<sup>2</sup> and obesity was defined as a BMI 30 kg/m<sup>2</sup> or higher according to WHO criteria [10].

### Exclusion criteria of case group

## MATERIALS AND METHODS

Known case of diabetes mellitus, parathyroid diseases, use of an anticonvulsant or systemic glucocorticoids; use of a vitamin D or calcium supplements, hepatic disease, renal disease, or malabsorptive disorder; disorder of bone or calcium metabolism (including known vitamin D deficiency); patients with cardiovascular or respiratory diseases, hypothalamic disease; or genetic disorder that predisposes to obesity (such as Prader-Willi syndrome), pregnancy.

**Sample collection**

The amount of blood collected in absolute fasting after 9 hours with all aseptic precautions in 2 parts was 5 ml. The first part collected in ethylene diamine tetraacetic acid (EDTA) vial for estimation of glycated haemoglobin (HbA<sub>1c</sub>). The second part collected was allowed to clot, serum was separated for estimation of Fasting Plasma Glucose (FPG), insulin and vitamin D.

**Measurements of biochemical analytes**

HbA<sub>1c</sub>, the index of long term glycemic control, was determined with Micromat II (Biorad) instrument based on boronate affinity chromatography [11]. FPG was analysed using reagent kit (Merck) by Glucose Oxidase method [12]. Serum insulin was determined by ELISA with monoclonal antibody based reagent (Monobind) [13].

Insulin resistance was estimated using homeostatic model assessment (HOMA-IR). The HOMA-IR was calculated as follows: HOMA-IR: (Fast Plasma Glucose (mmol/L) × Insulin (µIU/mL))/22.5 [14].

The cutoff value was set as 2.7. Subjects were classified into two groups according to HOMA-IR: the insulin resistant group as Group 1 (HOMA- IR > 2.7) and the non-resistant group (HOMA-IR < 2.7) as Group 2.

Serum 25 (OH)D concentrations were measured using a commercially available radioimmunoassay kit (Minividas Biomeriux, France). According to the report of the Institute of Medicine, vitamin D status is categorized as: risk of deficiency < 12 ng/mL, risk of inadequacy 12-19 ng/mL, sufficiency 20-50 ng/mL [15].

**STATISTICAL METHODS USED**

Statistical analysis was done by independent t test and correlation coefficient linear regression plot, p value <0.05 was considered as significant.

**Data collection and processing for statistical analysis:**

- Statistical analysis was aimed
- To assess the significance of difference between the mean values of Fasting plasma glucose(FPG), HbA<sub>1c</sub>, Serum insulin and vitamin D, HOMA-IR, BMI.
  - To find out any correlations between HOMA-IR and vitamin D status in group 1(HOMA-IR>2.7).

**RESULTS**

One hundred and twenty two obese subjects were participated in the study. Group 1 included sixty seven subjects (37 females and 30 males) and group 2 included fifty five subjects (30 females and 25 males). The mean age was 45±11.26 yrs, on the other hand in group 2, mean age was 44±10.32 yrs.

**Table -1**

	FPG (mg/dl)	HbA <sub>1c</sub> %	Insulin(µIU/ml)	BMI	Vitamin D(ng/mL)	HOMA-IR
HOMA-IR<2.7 N=55 Group 2	Mean-95.70 SD-6.40 SEM-0.86	Mean-5.19 SD-0.21 SEM-0.028	Mean-7.20 SD-0.32 SEM-0.043	Mean-27.93 SD-0.66 SEM-0.089	Mean-17.34 SD-0.86 SEM-0.116	Mean-1.69 SD-0.15 SEM-0.020
HOMA-IR>2.7 N=67 Group 1	Mean-104.31 SD-8.54 SEM-1.04	Mean-5.44 SD-0.39 SEM-0.047	Mean-16.58 SD-2.08 SEM-0.254	Mean-31.6 SD-1.49 SEM-0.182	Mean-9.26 SD-2.37 SEM-0.289	Mean-4.26 SD-0.71 SEM-0.086
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

**Table -2**

	HOMA-IR>2.7
HOMA-IR and Vitamin D	Sample size= 67 Correlation coefficient(r)= (-0.77)
P value	P<0.0001

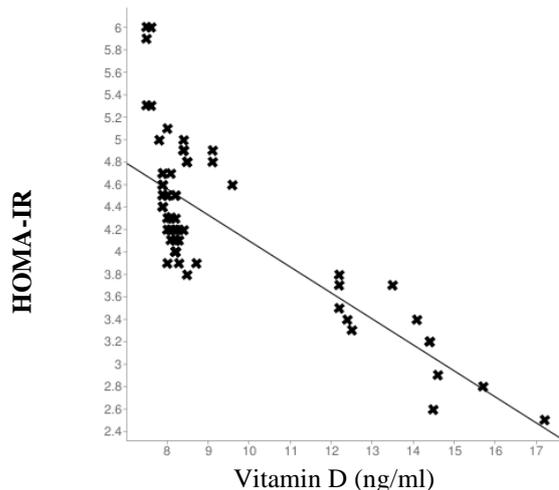


Figure-1

Table 1 shows that there is significant higher BMI values and lower 25(OH)D in group 1 in comparison to group 2. The mean FPG, insulin and HbA<sub>1c</sub> levels were also significantly higher in group 1 when compared to group 2. Furthermore, Table 2 shows, significant negative correlation between HOMA-IR and vitamin D status in group Figure 1 reveals significant negative correlations between HOMA-IR and vitamin D levels in group 1.

## DISCUSSION

The most significant finding in this study is that the low serum vit D was inversely correlated with insulin resistance in obese subjects in insulin resistant group.

Some authors accumulated the evidence of lower 25(OH)D in obese subjects [6,14]. This association may be explained by the storage of vitamin D in adipose tissue because of its high lipid solubility and decreased exposure to obese subjects to sunlight [6,8,16]. Some authors also noticed the improvement of metabolism of glucose, calcium and vitamin D with increased physical activity as well as decrease in body weight. Some studies have been conducted to find out the association between hypovitaminosis D and insulin resistance. However, ethnicity, dietary intake, physical activity and obesity are potential confounders that may affect the relationship between vitamin D and type 2 diabetes mellitus [17]. Vitamin D, obesity and insulin resistance were selected as a common parameters by some researchers [16,18,19]. It is still an issue whether low 25(OH)D concentrations directly affects the pathogenesis of insulin resistance or BMI also contributes. Kabadi *et al.* [20] have shown that the contributory effects of vitamin D deficiency and obesity cause an increased risk of insulin resistance. Some other studies didn't find any association between HOMA-IR and 25(OH)D levels after adjusting BMI [21]. Some authors highlighted that 25(OH)D and insulin resistance

are probably depends on bodyweight [22]. Obesity is definitely a risk to develop insulin resistance [23], furthermore increased fat accumulation is associated with decreased serum 25(OH)D concentrations [17,6,19,24].

In our study, insulin resistance is associated with the low 25 (OH)D levels. The significantly increased levels of FPG, HbA<sub>1c</sub> and insulin in the group 1 may indicate a long-term muscle insulin resistance. Furthermore, higher prevalence of hypovitaminosis D and restricted physical activity in obese subjects suggested the significant role of maintenance of a normal vitamin D concentrations and an modification of life style in prevention of obesity and diabetes. We have selected the study population who does not differ in ethnicity, dietary intake, physical activity and obesity to minimize the confounding factors.

Dong *et al.* Observed that 25(OH) D levels were inversely related to BMI, waist circumference, total fat mass, and percentage of fat mass in a group of adolescents [25].

Several possibilities have been emphasized to explain the lower 25(OH)D levels observed in obesity, including decreased sun exposure due to sedentary lifestyle, poor diet, and decreased bioavailability of vitamin D(3) from cutaneous and dietary sources because of its deposition in body fat compartments [26]. Vitamin D receptors and vitamin D-binding proteins are known to exist in pancreatic tissue, furthermore calcium plays an essential role in  $\beta$ -cell insulin secretion Thus insulin resistance plays a significant role in hypovitaminosis of 25(OH)D [27,28]. Mechanism links between vitamin D and insulin sensitivity have been proposed by some authors. A vitamin D response element in the insulin receptor gene promoter might affect insulin receptor protein expression [29].

Furthermore, 1,25-dihydroxyvitamin D<sub>3</sub>, the active form of vitamin D, induces increased transcription and protein expression of the insulin receptors [30].

## CONCLUSION

The focus on treatment of insulin resistance and intensification of physical activity in obese subjects will encompass the normalization of vitamin D levels. On the other end, future studies are needed to determine the clinical sequelae of lower 25(OH)D levels in obese subjects, the amount and duration of treatment necessary to replenish 25(OH)D in them, and whether treatment with vitamin D can improve primary clinical endpoints such as insulin resistance.

## REFERENCES

1. Sung CC, Liao MT, Lu KC, and Wu CC. Role of vitamin D in insulin resistance. *BioMed Research International*. 2012 Sep 3;2012.
2. Mackawy AM, Badawi ME. Association of vitamin D and vitamin D receptor gene polymorphisms with chronic inflammation, insulin resistance and metabolic syndrome components in type 2 diabetic Egyptian patients. *Meta gene*. 2014 Dec 31;2:540-56.
3. Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y. Vitamin D in systemic and organ-specific autoimmune diseases. *Clin Rev Allergy Immunol*. 2013;45(2):256–266.
4. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and metaanalysis. *Clin Endocrinol Metab*. 2007;92:2017–2029.
5. Forouhi NG, Ye Z, Rickard AP. Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes in individuals with prediabetes but not with normal glucose tolerance. *Diabetologia*. 2012;55(8):2173–2182.
6. Mezza T, Muscogiuri G, Sorice GP, Prioletta A. Vitamin D deficiency: a new risk factor for type 2 diabetes? *Ann Nutr Metab*. 2012;61(4):337–348.
7. Candido FG, Bressan J. Vitamin D: Link between osteoporosis, obesity and diabetes? *Int J Mol Sci*. 2014;15(4):6569–6591.
8. Mezza T, Muscogiuri G, Sorice GP, Prioletta A. Vitamin D deficiency: a new risk factor for type 2 diabetes? *Ann Nutr Metab*. 2012;61(4):337–348.
9. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *The American journal of clinical nutrition*. 2004 Dec 1;80(6):1678S-88S.
10. Adult Treatment Panel III. Third report of the National Cholesterol Education Program Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults. *Circulation*. 2002;106(25):3143–3421.
11. Herold DA, Boyd JC, Bruns DE, Emerson JC, Burns KG, Bray RE, Vandenhoff GE, Freedlender AE, Fortier GA, Pohl SL. Measurement of glycosylated hemoglobins using boronate affinity chromatography. *Annals of Clinical & Laboratory Science*. 1983 Nov 1;13(6):482-8.
12. Raabo E, Terkildsen TC. On the enzymatic determination of blood glucose. *Scand J Clin Lab Invest* 1960;12:402-7.
13. Andersen L, Dinesen B, Jørgensen PN, Poulsen F, Røder ME. Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem*1993;39:578-82.
14. Brock K, Cant R, Clemson L, Mason RS, Fraser DR. Effects of diet and exercise on plasma vitamin D levels in Vietnamese immigrant elderly in Sydney, Australia. *J Steroid Biochemical Mol Biol*. 2007;103(3-5):786–792.
15. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Washington DC: The National Academies Press; 2011. Dietary reference intakes for calcium and vitamin D in Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D and Calcium.
16. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000;72(3):690–693.
17. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willet WC. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care*. 2006;29(3):650–656.
18. Lu L, Yu Z, Pan A. Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle aged and elderly Chinese individuals. *Diabetes Care*. 2009;32(7):1278–1283.
19. Ou HY, Karnchanasorn R, Lee LZ, Chiu KC. Interaction of BMI with vitamin D and insulin sensitivity. *Eur J Clin Invest*. 2011;41(11):1195–1201.
20. Kabadi SM, Lee BK, Liu L. Joint effects of obesity and vitamin D insufficiency on insulin resistance and type 2 diabetes mellitus: Results from the NHANES 2001-2006. *Diabetes Care*. 2012;35(10):2048–2054.
21. Gulseth HL, Gjelstad IMF, Tierney AC. Serum vitamin D concentration does not predict insulin action or secretion in European subjects with the metabolic syndrome. *Diabetes Care*. 2010;33(4):923–929.
22. Muscogiuri G, Sorice GP, Prioletta A, Policola C, Casa S, Pontecorvi A, Giaccari A. 25-Hydroxyvitamin D Concentration Correlates With Insulin-Sensitivity and BMI in Obesity. *Obesity*. 2010 Oct 1;18(10):1906-10.
23. Miñambres I, Sánchez-Hernández J, Sánchez-Quesada JL, Rodríguez J, de Leiva A, Pérez A. The association of hypovitaminosis d with the metabolic syndrome is independent of the degree of obesity. *ISRN endocrinology*. 2012 Oct 24;2012.

24. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. *Calcif Tissue Int.* 1998;43(4):199–201.
25. Dong Y, Pollock N, Stallmann-Jorgensen IS, Gutin B, Lan L, Chen TC, Keeton D, Petty K, Holick MF, Zhu H. 2010. Low 25-hydroxyvitamin D levels in adolescents: race, season, adiposity, physical activity, and fitness. *Pediatrics* 125:1104–1111.
26. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *The American journal of clinical nutrition.* 2000 Sep 1;72(3):690-3.
27. Lee SO, Clark SA, Gill RK, Christakos SY. 1, 25-Dihydroxyvitamin D<sub>3</sub> and pancreatic beta-cell function: vitamin D receptors, gene expression, and insulin secretion. *Endocrinology.* 1994 Apr 1;134(4):1602-10.
28. Sooy K, Schermerhorn T, Noda M, Surana M, Rhoten WB, Meyer M, Fleischer N, Sharp GW, Christakos S. Calbindin-D28k controls [Ca<sup>2+</sup>]<sub>i</sub> and insulin release evidence obtained from calbindin-D28k knockout mice and β cell lines. *Journal of Biological Chemistry.* 1999 Nov 26;274(48):34343-9.
29. Maestro B, Dávila N, Carranza MC, Calle C. Identification of a Vitamin D response element in the human insulin receptor gene promoter. *The Journal of steroid biochemistry and molecular biology.* 2003 Feb 28;84(2):223-30.
30. Maestro B, Campión J, Dávila N, Calle C. Stimulation by 1, 25-dihydroxyvitamin D<sub>3</sub> of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. *Endocrine journal.* 2000;47(4):383-91.