

Original Research Article

Vitamin D and Insulin Resistance in metabolic syndrome

Abstract

Poor vitamin D status is frequently linked with nearly all elements of the metabolic syndrome. There is insufficient evidence of beneficial effect to recommend vitamin D supplementation as a means of improving insulin resistance. **The aim of this study** was to determine the relation between vitamin D deficiency and insulin resistance in patients with metabolic syndrome.

Materials and Methods:

Ninety patients with metabolic syndrome received 200,000 IU vitamin D intramuscularly every 4 weeks for 12 weeks. Serum 25-hydroxy vitamin D [25(OH) D] , fasting blood sugar, Hb A1c, homeostasis model assessment of insulin resistance(HOMA IR), serum lipid profiles anthropometric factors and blood pressure were assessed before and after intervention.

Results: After intervention, Serum 25-hydroxy vitamin D [25(OH) D] concentration increased in all subjects (14.5 ± 2.2 vs. 32 ± 5.5 (P .0001)). There was a significant decrease of HOMA-IR (3.05 ± 0.34 vs $2.08 \pm .25$ (P=0.003) in patients with vitamin D deficiency before supplementation.

In conclusion vitamin D supplementation improve IR in patients with metabolic syndrome with vit D deficiency .So, vitamin D supplementation based on baseline 25(OH)D is recommended .

Keywords: Insulin resistance, vitamin D

INTRODUCTION:

Vitamin D, in addition to its role in calcium and bone metabolism, has pleiotrophic effects in many cell types in many life forms. These include a potential role in the actions of insulin and development of obesity. Thus, not

surprisingly hypovitaminosis D has been linked with hypertension, atherogenic dyslipidaemia and increased CVD risk [1]. Low skin exposure to sunlight, low dietary intake of vitamin D, high body mass index (BMI), and genetic predispositions may contribute to the occurrence of Hypovitaminosis D [2]. Measurement of Serum 25-OH-vitamin D is the generally accepted tool to assess vitamin D status [2]. Although suboptimal vitamin D levels almost always asymptomatic, population based screening for vitamin D deficiency is not recommended, but test for vitamin D deficiency in patients with high-risk conditions such as osteoporosis, chronic kidney disease, hyperparathyroidism, or a malabsorption syndrome is recommended [3].

Obesity is one of the leading global health risk factors for morbidity and mortality, accounting for 4.8% of deaths worldwide [4]. Insulin resistance (IR) indicates decreased response to insulin-mediated cellular actions [5] with subsequent reduction in tissue glucose uptake and impairment in insulin suppressive effect on hepatic glucose output [6], in addition to its effect on protein and lipid metabolism and on vascular endothelial function and genes expression [7]. IR is the most common metabolic alteration related to obesity [8], representing a significant link between obesity and other metabolic risks such as cardiovascular diseases [9].

HOMA is a vastly used clinical and epidemiological tool to assess β - cell function and insulin resistance [10]. Although, if used appropriately, it closely mirrors the glucose clamp technique in the assessment of insulin sensitivity [11], it only shows what is occurring with glucose homeostasis in the fasting state [10]. There is conflicting data about the role of vitamin D supplementation on HOM -IR as a reflection of insulin resistance.

Aim of the study:

The aim of this study was to determine the effect of vitamin D supplementation on insulin resistance in patients with metabolic syndrome.

MATERIALS AND METHODS:

A prospective study was conducted in Alfayum University on 90 patients with metabolic syndrome were recruited from the outpatient clinic of internal medicine during the period from January 2015 to January 2016, with the approval of the local ethics committee . Written informed consent was obtained from the participants

Inclusion criteria for participants with metabolic syndrome are: the presence of any **three** of the following five traits [12]:

- Abdominal obesity, defined as a waist circumference in men ≥ 102 cm (40 in) and in women ≥ 88 cm (35 in)
- Serum triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides
- Serum HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women or drug treatment for low HDL-C
- Blood pressure $\geq 130/85$ mmHg or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) ≥ 100 mg/dL or drug treatment for elevated blood glucose

Patients were excluded if they were pregnant, lactating, taking any glucose lowering medications, using any anti-hypertensive or lipid lowering medications or had chronic liver or renal disease

BMI was calculated as weight/height² (kg/m²). Resting systolic blood pressure (SBP) and diastolic BP (DBP) were measured while the participants were seated using a standard sphygmomanometer with an appropriate size cuff. Lipid profile (total cholesterol, triglycerides, HDL-C and LDL-C) were assessed. Fasting morning blood was drawn for measurement of glucose, insulin, calcium, phosphorus, HbA1c, and 25-hydroxyvitamin D [25(OH) D and IR was assessed on the basis of the homeostasis model assessment of IR (HOMA-IR), using the following formulae: $HOMA-IR = [fasting\ insulin\ (mU/l) \times fasting\ glucose\ (mg/l) / 405]$. Patients were assigned to consume vitamin D supplements (200,000 IU) by intramuscular injection every 4 weeks for 12 weeks. Follow up of serum calcium, phosphorus levels were done regularly. The level of serum 25-hydroxy vitamin D [25(OH) D] was measured at the beginning and end of the study. Plasma total 25(OH)D

concentrations were measured in duplicates by using IDS enzyme immunoassay (IDS-EIA, Immunodiagnostic Systems INC., Scottsdale, AZ). We used the cut-off value for deficiency of 25(OH)D levels below 20 ng/ml following the Endocrine Society Clinical Practice guidelines [13].

Statistical analysis:

All collected data were expressed as mean $\pm$ SD and analyzed by using SPSS version 12 using the following tests: Student t test, Chi-square test, $P > 0.05$ was considered nonsignificant, $P < 0.05$ was considered significant $P < 0.001$ was considered highly significant.

RESULTS:

Of the 90 obese patients included in the study; 40(44.4%) were males and 50(55.6%) were females, with a mean age of 55.6 ± 8 years, 20 patients of the studied 90 patients (22.22%) were vitamin D deficient (25-hydroxyvitamin D < 20 ng/ml).

Comparing with the baseline, plasma 25(OH) D level significantly increased in the all studied subjects who received vitamin D (14.5 ± 2.2 vs. 32 ± 5.5 ($P = .001$), however, there was no significant effect on HOMA –IR nor TG (as shown in table 1). In vitamin D deficient patient HOMA-IR showed a decrement pattern [3.05 ± 0.34 vs 2.08 ± 0.25 ($P = 0.003$)], in addition to a significant change in TG concentration ($p < 0.04$) after 12 w of vitamin D supplementation, as shown in table 2

Also, there was statistically significant decrease in HBA1C levels after vitamin D supplementation for 12 w in all participants [5.7 ± 0.08 vs 5.6 ± 0.13 ($P = 0.01$)] , in addition to patients with vitamin D deficiency [5.8 ± 0.12 vs 5.6 ± 0.2 ($P = 0.03$)].(as shown in tables 1 and 2)

124 **Table 1: Different variables of all participants before and after vitamin**
125 **D supplementation**

	Before	After	P value
Vit D(ng/ml)	17.2±1.2	39.5±7.2	0.001
Weight (kg)	88.7±20.2	77.1 ± 17.5	0.01
Waist (cm)	101.3 ± 18.2	100.2 ± 16.8	0.72
BMI	34 .7 ± 2.7	34.4 ±3.2	0.31
SBP (mm HG)	136±19.7	133±18.2	0.62
DBP(MM hg)	85.3 ± 7.2	84 ± 7.7	0.75
HBA1C	5.7 ± 0.08	5.6 ± 0.13	0.01
T Cholesteol (mg/ dl)	188 ± 22.7	187.5 ± 20.2	0.81
TG (mg/dl)	179.2 ± 52	164.3 ± 20	0.12
HOMA IR	2.9 ±0.49	2.7 ± 0.36	0.5

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127 **Table 2: Different variables of patients with vitamin D deficiency before**
128 **and after vitamin D supplementation**

	Before	After	P value
Vit D(ng/ml)	14.5± 2.2	32.00± 5.2	0.001
Weight (Kg)	88.2± 41	87.5±	0.16
Waist (cm)	101.2± 23.5	99.8 ± 16.8	0.72
BMI	34 .7 ± 2.7	34.4 ±3.2	0. ±42
SBP (mm HG)	132±11.2	130±17.2	0.42
DBP (mm HG)	83.3±7.8	82.2±6.9	0.72
HBA1C	5.8 ± 0.12	5.6 ± 0.2	0.03
T Cholesterol (mg/dl)	192±19.2	190±18.3	0.62
TG (mg/ dl)	194±38	164±13	0.04
HOMA IR	3.05 ± 0.34	2.68 ± 2.5	0.03

129

130 **DISCUSSION:**

131 Our analyses revealed that vitamin D deficient patients with low serum
132 25(OH) D concentrations at baseline and increases in serum 25(OH)D
133 concentrations during follow up contribute to decrement pattern of
134 HOMA-IR

Kayeniyil et al.[14] **Gagnon et al.**[15], **Skaaby** [16] observations seem consistent with our observation of the effect on baseline serum 25(OH)D on metabolic syndrome as they reported low probability for onset of metabolic syndrome with increase in baseline 25(OH)D concentrations.

Moreover, **Belenchia et al** [17] and **Kelishadi et al** [18] concluded that the correction of poor vitamin D status may be effective in treatment of obesity and its associated insulin resistance.

Some of the proposed mechanisms for vitamin D's role in improving insulin resistance in obesity include inflammation reduction [19] and improving peripheral and hepatic uptake of glucose, [20] in addition, vitamin D modulates nuclear peroxisome proliferative activated receptor (PPAR) which has a key factor in the IR [21].

In contradiction to our results; **Carrillo E. et al** [22] found that vitamin D supplementation in adults induced an early improvement in peak power, and elevated vitamin D status was associated with reduced waist-to-hip ratio in spite of insignificant effect on HOMA-IR

Moreover, **Mousa, et al.** [23] **Harris, et al.** [24] **Wamberg , et al.** [25] **Salehpour, et al.** [26] and **Beilfuss, et al.** [27] concluded that neither measures of insulin resistance, secretion nor glycaemic indices were influenced by vitamin D supplementation. This provides evidence that vitamin D supplementation has no significant effect on glucose and insulin metabolism in overweight and obese individuals.

In addition, two meta-analyses [28,29] reported nonsignificant effect of vitamin D supplementation on IR.

In line with these results, we observed statistically significant decrease in HBA1C levels after vitamin D supplementation for 12 w in all participants, in addition to patients with vitamin D deficiency. These results come in agreement with the meta-analysis done by **Poolsup et al.** [29] who confirmed an improvement in HbA1c levels after vitamin D supplementation in pre-diabetics. On the other hand, another meta-analysis [30] could not confirm this effect but in diabetic patients

These conflicting results may be explained by the variability in the analytic approach, follow up time, consideration of confounders, and baseline serum 25(OH)D concentrations.

Our study also revealed improvement in triglyceride concentrations after vitamin D supplementation in vitamin D deficient patients only, a finding which was not present on comparing all the studied subjects after vitamin D supplementation.

These results are in agree with **Ford et al** [31] **Saedisomeolia et al** [32] and **Chaudhuri et al** [33] who reported a negative correlation between serum levels of 25(OH) D and triglycerides levels in patients with metabolic syndrome and type 2 diabetes.

Suggested mechanisms include positive effect of vitamin D on serum calcium with subsequent reduction of hepatic triglyceride production [34], reduction in parathyroid hormone level with increase in triglyceride tissue uptake [35], upregulation of VLDL cholesterol gene receptors [33] and reduction of insulin resistance via reduction of pro-inflammatory cytokines [36].

On contrary, **Ponda et al** [37] **Saeidlou et al** [38] **Rusconi et al** [39] and **Andersen et al** [40] could not confirm any correlation between vitamin D supplementation and improvement of triglyceride levels neither in obese children nor in adults.

Conclusion and Recommendations: vitamin D supplementation improves IR in patients with metabolic syndrome with vit D deficiency. So, vitamin D supplementation based on low baseline 25(OH) D is recommended.

REFERENCES:

1. **Richard C Strange, Kate E Shipman, and Sudarshan Ramachandran.** Metabolic syndrome: A review of the role of vitamin D in mediating susceptibility and outcome. *World J Diabetes*. **2015** Jul 10; 6(7): 896–911.
2. **Kuhn T, Kaaks R, Teucher B, et al.** Dietary, lifestyle, and genetic determinants of vitamin D status: a cross-sectional analysis from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Germany study. *Eur J Nutr*. **2014**;53(3):731–41.

- 201 3. **Kurt A. Kennel, Matthew T. Drake, and Daniel L. Hurley.**
202 Vitamin D Deficiency in Adults: When to Test and How to Treat.
203 Mayo Clin Proc. **2010** Aug; 85(8): 752–758.
- 204 4. **WHO.** Global health risks. Geneva: BMJ Publishing Group, **2009**.
- 205 5. **Ferrannini E., Galvan A. Q., Gastaldelli A., et al.** Insulin: new roles
206 for an ancient hormone. European Journal of Clinical Investigation.
207 **1999**;29(10):842–852.
- 208 6. **Schwartz B., Jacobs D. R., Jr., Moran, et al.** Measurement of
209 insulin sensitivity in children: comparison between the euglycemic-
210 hyperinsulinemic clamp and surrogate measures. Diabetes Care.
211 **2008**;31(4):783–788.
- 212 7. **Rasmussen-Torvik L. J., Pankow J. S., Jacobs D. R., et al.**
213 Heritability and genetic correlations of insulin sensitivity measured by
214 the euglycaemic clamp. Diabetic Medicine. **2007**;24(11):1286–1289.
- 215 8. **Weiss R., Kaufman F. R.** Metabolic complications of childhood
216 obesity: identifying and mitigating the risk. Diabetes Care.
217 **2008**;31(supplement 2):S310–S316.
- 218 9. **Sinaiko A. R., Steinberger J., Moran A., et al.** Influence of insulin
219 resistance and body mass index at age 13 on systolic blood pressure,
220 triglycerides, and high-density lipoprotein cholesterol at age 19.
221 Hypertension. **2006**;48(4):730–736.
- 222 10. **Wallace TM, Levy JC, Matthews DR.** Use and abuse of HOMA
223 modeling. Diabetes Care **2004**; 27: 1487–1495.
- 224 11. **Bonora E, Targher G, Alberiche M, et al** Homeostasis model
225 assessment closely mirrors the glucose clamp technique in the
226 assessment of insulin sensitivity: studies in subjects with various
227 degrees of glucose tolerance and insulin sensitivity. Diabetes Care
228 **2000**; 23: 57–63
- 229 12. **Grundy SM, Cleeman JI, Daniels SR, et al.** Diagnosis and
230 management of the metabolic syndrome: an American Heart
231 Association/National Heart, Lung, and Blood Institute Scientific
232 Statement. Circulation **2005**; 112:2735.
- 233 13. **Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.** Evaluation,
234 treatment, and prevention of vitamin D deficiency: an Endocrine

- Society clinical practice guideline. *J Clin Endocrinol Metab.* **2011** Jul;96(7):1911-30.
14. **Kayaniyil S, Vieth R, Harris SB, et al.** Association of 25(OH)D and PTH with metabolic syndrome and its traditional and nontraditional components. *J Clin Endocrinol Metab.* **2011** Jan;96(1):168-75.
15. **Gagnon, C. et al.** Effects of Combined Calcium and Vitamin D Supplementation on Insulin Secretion, Insulin Sensitivity and β -Cell Function in Multi-Ethnic Vitamin D-Deficient Adults at Risk for Type 2 Diabetes: A Pilot Randomized, PlaceboControlled Trial. *Plos One.* 9(10), 1–12 **(2014)**.
16. **Skaaby T.** The Relationship of Vitamin D Status to Risk of Cardiovascular Disease and Mortality. *Dan Med J* 62 (2). 2 **2015**.
17. **Belenchia, A. M., Tosh, A. K., Hillman, L. S., et al.** Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. *Am. J. Clin. Nutr.* **97**, 774–781 **(2013)**.
18. **Kelishadi, R., Salek, S., Salek, M., et al.** Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial. *J. Pediatr. (Rio. J.).* 90,28–34 **(2014)**.
19. **Flores M.** A role of vitamin D in low-intensity chronic inflammation and insulin resistance in type 2 diabetes mellitus? *Nutr Res Rev* **2005**;18:175–82.
20. **Maestro B, Davila N, Carranza MC, et al.** Identification of a vitamin D response element in the human insulin receptor gene promoter. *J Steroid Biochem Mol Biol* **2003**;84:223–30.
21. **Ojuka EO.** Role of calcium AMP kinase in the regulation of mitochondrial biogenesis and GLUT4 levels in muscle. *Proc Nutr Soc.* **2004**;63:275–8.
22. **Carrillo, A. E. et al.** Impact of vitamin D supplementation during a resistance training intervention on body composition, muscle function, and glucose tolerance in overweight and obese adults. *Clin. Nutr.* 32,375–381 **(2013)**.
23. **Mousa A, Naderpoor N, de Courten MP, et al.** Vitamin D supplementation has no effect on insulin sensitivity or secretion in vitamin D-deficient, overweight or obese adults: a randomized placebo-controlled trial. *Am J Clin Nutr.* **2017** Jun;105(6):1372-1381.

24. **Harris, S. S., Pittas, A. G. & Palermo, N. J.** A randomized, control-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. *Diabetes Obes. Metab.* 14, 789–794 (2012).
25. **Wamberg, L. et al.** Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels- results from a randomized trial. *Eur J Intern Med.* 24(7), 644–649 (2013).
26. **Salehpour, A. et al.** Does vitamin D3 supplementation improve glucose homeostasis in overweight or obese women? A doubleblind, randomized, control-controlled clinical trial. *Diabet. Med.* 30, 1477–1481 (2013).
27. **Beilfuss, J., Berg, V., Sneve, M., et al.** Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alpha and insulin resistance in overweight and obese subjects. *Cytokine.* 60, 870–874 (2012).
28. **Jamka M, Woźniewicz M, Jeszka J, et al.** The effect of vitamin D supplementation on insulin and glucose metabolism in overweight and obese individuals: systematic review with meta-analysis. *Sci Rep.* 2015;176(1):R1–R14
29. **Poolsup N, Sukomboon N, Plordplong N.** Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis. *Diabet Med.* 2016;33(3):290–299.
30. **Krul-Poel YH, Ter Wee MM, Lips P, et al.** The effect of vitamin D supplementation on glycaemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Eur J Endocrinol.* 2017;176(1):R1–R14.
31. **Ford ES, Ajani UA, McGuire LC, et al.** Concentrations of serum vitamin D and the metabolic syndrome among US adults. *Diabetes Care.* 2005;28(5):1228–30.
32. **Ahmad Saedisomeolia, Ehsaneh Taheri, Mahmoud Djalali, et al.** Association between serum level of vitamin D and lipid profiles in type 2 diabetic patients in Iran. *J Diabetes Metab Disord.* 2014;13:7.
33. **Jaydip Ray Chaudhuri, K. Rukmini Mridula, Alluri Anamika, et al.** Deficiency of 25-Hydroxyvitamin D and Dyslipidemia in Indian Subjects. *J Lipids.* Volume 2013 (2013), Article ID 623420.

34. **Martins D, Wolf M, Pan D, et al.** Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med.* **2007**;167(11):1159–65.
35. **B. Lacour, C. Basile, T. Drueke, et al.** Parathyroid function and lipid metabolism in the rat. *Mineral and Electrolyte Metabolism*, vol. 7, no. 3, pp. 157–165, **1982**.
36. **Ginsberg HN, Zhang Y-L, Hernandez-Ono A.** Regulation of plasma triglycerides in insulin resistance and diabetes. *Arch Med Res.* **2005**;36(3):232–40.
37. **Ponda MP, Huang XX, Odeh MA, et al.** Vitamin D may not improve lipid levels: a serial clinical laboratory data study. *Circulation.* **2012**;126(3):270–7.
38. **Sakineh Nouri Saeidlou, Davoud Vahabzadeh, Fariba Babaei, et al.** Seasonal variations of vitamin D and its relation to lipid profile in Iranian children and adults. *J Health Popul Nutr.* **2017**; 36: 21
39. **Rusconi RE, De Cosmi V, Gianluca G, et al.** Vitamin D insufficiency in obese children and relation with lipid profile. *Int J Food Sci Nutr.* **2015**;66(2):132–4.
40. **Andersen R, Brot C, Mejborn H, et al.** Vitamin D supplementation does not affect serum lipids and lipoproteins in Pakistani immigrants. *Eur J Clin Nutr.* **2009**;63(9):1150–3.