

Relationship between serum Vitamin D concentration and Metabolic Syndrome among Iranian Adults Population

Hosseini-Nezhad ,A., Khoshnati Nikoo, M., Maghbooli, Z., Karimi, F., Mirzaei, K., Hosseini A., *Larijani, B.

Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran

Received 26 May 2009; Revised 31 Oct 2009; Accepted 4 Nov 2009

ABSTRACT

Background and the purpose of the study: There are increasing evidences about relationship between vitamin D metabolism and occurrence of diabetes mellitus. Vitamin D has a role in secretion and possibly the action of insulin and modulates lipolysis and might therefore contribute to the development of the metabolism. The aim of this study was to investigate the nature and strength of the association between vitamin D concentration and the metabolic syndrome (MS) in Iranian population.

Methods: A cross-sectional study was conducted on 646 healthy population who had no history of diabetes. The MS was defined according to WHO criteria. The concentrations of vitamin D, and parathyroid hormone (PTH) were also measured.

Results and major conclusion: Of the total 646 participants, the unadjusted prevalence of the MS was 18.3% (29% in men and 14.6% in women). The total prevalence of vitamin D deficiency was 72.3%. Amongst the men with vitamin D deficiency the prevalence of the MS was higher than those with normal vitamin D ($p=0.03$). In the logistic regression model, after age and sex adjustment, vitamin D deficiency predicted independently the metabolic syndrome ($p=0.001$). Vitamin D deficiency and the MS have a high prevalence among Iranian adult population. The finding of this investigation revealed that vitamin D deficiency may have an important role in metabolic syndrome and its components.

Keywords: metabolic syndrome, Vitamin D, Insulin resistance

INTRODUCTION

Metabolic syndrome (MS) refers to the cluster of several cardio-metabolic risk factors including abdominal obesity, hyperglycemia, dyslipidaemia and elevated blood pressure that are likely to be linked to insulin resistance (1). The clinical relevance of MS is that it identifies people who are at increased long term risk of cardiovascular disease and type 2 diabetes mellitus. Regardless of definition; large epidemiological surveys show that MS is common and age related and its prevalence in adult Iranian population aged 20 years and over are 27.46%-33.7% (2) and in US between 34.6% by National Cholesterol Education Program (NCEP) and 39.1% by International Diabetes Federation (IDF) reports (3). Indeed, MS becomes more prevalent with increase in the age; affecting half of adults aged 60 years and over (3-5).

Several investigations suggest that circulating concentrations of vitamin D may be inversely related to the prevalence of diabetes (6-10), the concentration of glucose (8,11-15), and insulin resistance (8, 11,13, 14). In addition, vitamin D deficiency may be a risk factor for the metabolic syndrome (11,16), that both

have a high prevalence in Iranian adult population (17-19). The goal of this study was to examine the nature and strength of the association between serum concentrations of vitamin D and the metabolic syndrome in a nationally representative sample of the Iranian population.

MATERIALS AND METHODS

Study's population

In this cross- sectional study, 646 healthy population residing in Tehran aged between 20-79 years, participated in Iranian multi-center osteoporosis study (IMOS) as previously described (19). In brief Individuals were selected using random cluster sampling by dividing city into multiple foci based on distribution of population. Trained operators met citizens at their homes in each focus. Blood samples of eligible persons, after filling an informed consent, were drawn and centrifuged within 30 min in their place of residency. Serum samples were transferred to the local participant laboratories and frozen and then sent to Endocrinology and Metabolism Research Center (EMRC) Laboratory, Tehran by mobile freezers.

The study protocol was approved by research ethics committee of Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences. After taking their informed consent, fasting blood samples were collected for measurement of glucose, total cholesterol, triglyceride, high density lipoprotein cholesterol, fasting blood sugar and vitamin D concentrations.

Laboratory measurements

Total cholesterol (TC), high density lipoprotein (HDL) cholesterol and triglyceride (TG) levels were determined by enzymatic methods. Dyslipidemia was defined as the presence of at least one of the reported lipid abnormalities. On the basis of the American Diabetes Association criteria (20), fasting blood sugar (FBS) ≥ 126 was considered as diabetes mellitus. The metabolic syndrome was defined according to WHO criteria (21). Based on WHO criterion MS diagnosed if glycemia was abnormal and two further criteria were present. These criteria were glucose intolerance or diabetes type 2 or insulin resistance due to HOMA-IR, $BMI > 30 \text{ kg/m}^2$ and $WHR > 0.9$ in men and > 0.85 in women, $TG \geq 150 \text{ mg/dl}$ or $HDL < 35$ in men and < 39 in women, on hypertension treatment or blood pressure $> 160/90 \text{ mmHg}$, microalbuminuria $\geq 20 \text{ mcg/min}$.

Serum vitamin D (25-hydroxy vitamin D3) was measured via radioimmunoassay using an IDS kit (England, Immunodiagnostic Systems Limited) with inter-assay and intra-assay CV 8.1% and 5.49% respectively. Serum levels of 25(OH) D was classified into two groups for deficiency status (Vitamin D $\leq 34.9 \text{ nmol/L}$ as deficiency, and Vitamin D $\geq 35 \text{ nmol/L}$ as normal) (19).

Blood pressures were measured two times using a standard calibrated mercury sphygmomanometer on the right hand of the participants remained seated for 15 minutes. The mean of two measurements was recorded as blood pressure. According to the JNC VII criteria, hypertension (HTN) was defined as systolic blood pressure $\geq 140 \text{ mmHg}$ or diastolic blood pressure $\geq 90 \text{ mmHg}$ or both (22).

Statistical analyses

Data were analyzed using SPSS software version 13. The Student t-test was used to compare the differences between two means. The chi-square test was used to compare the restrictive factors in two groups.

To evaluate the relationship between vitamin D and the metabolic syndrome regression model was used. The level of significance was set at a probability of 0.05 for all tests.

RESULTS

Of the total 646 participants who had no personal history of Diabetes, 72% were 40 years or older. The baseline characteristics of the participants are summarized in Table 1 and prevalence of metabolic

Table 1. Characteristics of the population under study

Variables	Men	Women	total
	(n=160)	(n=486)	
Age (year)	40, 47 \pm 15.7	50.1 \pm 13.13	47.62 \pm 14.46
BMI (kg/m ²)	24.89 \pm 4.01	27.4 \pm 4.9	26.65 \pm 4.84
Waist (cm)	95.52 \pm 11.53	94.34 \pm 13.39	94.89 \pm 12.55
Hip (cm)	106.39 \pm 8.35	109.19 \pm 10.24	107.89 \pm 9.49
Waist/hip ratio	0.89 \pm 0.06	0.86 \pm 0.07	0.87 \pm 0.07
Fasting glucose (mg/dl)	107.55 \pm 23.31	104.05 \pm 18.72	104.92 \pm 19.99
Triglyceride (mg/dl)	176.36 \pm 132.58	160.37 \pm 89.24	164.33 \pm 101.83
HDL-cholesterol (mg/dl)	32.65 \pm 9.78	44.99 \pm 14.66	41.92 \pm 14.61
Vitamin D (nmol/L)	32.57 \pm 21.69	30.92 \pm 18.09	31.33 \pm 21.45

All variables reported as Mean \pm S.D

Table 2. The prevalence of the constituents of the metabolic syndrome based on WHO criteria

	Men	Women	Total
	(n=160)	(n=486)	
Hyperglycemia	35.6%	33.3%	33.9%
Dyslipidaemia	70%	53.1%	57.3%
Central obesity	62.9%	39.7%	45.8%
HTN	10.6%	14.8%	13.8%

syndrome criteria based on WHO, are summarized in Table 2.

Using WHO criteria, the unadjusted prevalence of the metabolic syndrome was 18.3% (29.4% in males, 14.6% in females). The prevalence rates of the individual constituents of the metabolic syndrome, as defined by WHO are presented in table 2.

Among the components, dyslipidaemia had the highest prevalence which was 70% in men and 53.1% in women (Table 2).

Generally, male participants showed higher frequencies of hyperglycemia and dyslipidaemia than females.

In the total subjects the mean concentration of 25 (OH) D was $31.33 \pm 21.45 \text{ nmol/l}$ ($32.57 \pm 21.69 \text{ nmol/l}$ in males and $30.92 \pm 18.09 \text{ nmol/l}$ in females).

With regard to the vitamin D deficiency, total prevalence of vitamin D deficiency ($\leq 35 \text{ nmol/L}$) was 72.3% (73.1% in men, 72% in women).

Of important, just amongst the women aged 40 years and older, the prevalence of MS in vitamin D deficient group was higher than in normal vitamin D group (21% vs. 4.3%, $P=0.001$, respectively). However there was no significant difference in women aged less than 40 years with or without vitamin D deficiency (10.1% vs. 5.3%, respectively, $p=0.5$).

In the men with vitamin D deficiency, the prevalence of the MS was significantly higher than normal vitamin D group, in both age groups; < 40 years and ≥ 40 (for < 40 years old: 26% vs. 4.3%, $P=0.03$, respectively and for ≥ 40 years old 45.6% vs. 20%,

p=0.04, respectively).

Among the components, only obesity showed significantly higher prevalence in men of 40 years or older with vitamin D deficiency (87.7% in vitamin D deficient group and 30% in normal vitamin D group, p=0.05). There was not any significant correlation between other components and vitamin D deficiency in men. However; among the components of the MS in women aged ≥ 40 years with vitamin D deficiency, the prevalence of obesity, hyperglycemia, and HTN were significantly higher than women normal with vitamin D (obesity: 47.6% vs. 29.9%, p=0.002, hyperglycemia: 39.9% vs. 28.2%, p=0.02, HTN: 20.7% vs. 12%, p=0.04, respectively).

In the logistic regression model vitamin D deficiency independent of age and sex predicted the MS; had a significant relation with obesity (p=0.001) and after age adjustment vitamin D deficiency just in women showed relationship with HTN (p=0.03).

DISCUSSION

There are increasing evidences about the relationship between vitamin D metabolism and occurrence of diabetes mellitus. Vitamin D has a role in the secretion, and possibly the action of insulin (11) and modulates lipolysis (23, 24) and might therefore contribute to the development of the metabolic syndrome.

In this study prevalence of the metabolic syndrome among the men and women of ≥ 40 years with low vitamin D concentration were significantly higher. Similar studies have shown an inverse association between serum vitamin D and the presence of metabolic syndrome (16, 25).

From a clinical study of 126 participants it has been reported that, those with hypovitaminosis D were nearly three times as likely to have the metabolic syndrome compared with participants with normal vitamin D (30% vs. 11%, P < 0.001) (9).

Insulin resistance has been considered as a possible mechanism underlying the metabolic syndrome (26). Several studies have shown an inverse association between serum vitamin D and insulin resistance provide a possible explanation for findings of this study for an association between vitamin D deficiency and the prevalence of the metabolic syndrome (11-15).

There is ample evidence from animal studies that vitamin D is essential for normal insulin secretion which is impaired in the vitamin D deficient pancreas. A positive relation between serum vitamin D concentration and insulin sensitivity has been reported in a group of 34 men, including 7 subjects with diabetes (14) also found that serum vitamin D concentration was inversely associated with insulin concentration. In another study, that investigated insulin area under the curve in 134 elderly non-diabetic men, it was found an independent positive association between vitamin D concentration and insulin sensitivity (13). It has been reported that, in glucose-tolerant subjects, vitamin D concentration has a positive relation to

insulin sensitivity and a negative effect on β -cell function and these relations are independent of confounding factors (12).

In this study there was only a significant association between vitamin D deficiency and hyperglycemia in women. From several cohort studies (11-13, 27, 28) with varied baseline vitamin D status an association between vitamin D deficiency and impaired glucose mediated insulin release have been reported.

An accumulating data indicate that people with impaired glucose tolerance (13, 29) and diabetes (13, 30) have lower concentrations of vitamin D compared with those with normal glucose tolerance. Also, low concentrations of vitamin D are associated with β -cell dysfunction and impaired insulin secretion and action (13, 31).

In a meta analysis by Pittas et al., (32) through combining data from all studies on the association between vitamin D level and prevalent of type 2 DM (8, 9, 33, 34), it was found that the summary odds ratio (OR) was 0.54 (95% CI, 0.23 – 1.27) for the highest vs. the lowest vitamin D concentration (25-38 ng/ml vs. 10-23 ng/ml, respectively), but with significant heterogeneity among studies. In most (6, 7, 9, 13) case-control studies, patients with type 2 DM or glucose intolerance were found to have lower serum vitamin D concentration compared to controls without diabetes.

In some cross- sectional studies, in a variety of cohort studies, inverse associations between serum vitamin D and measured glycemia or the presence of type 2 DM have been reported (11, 12, 25).

Among the components of the MS in this study, obesity was associated with vitamin D deficiency without dependences on age and sex. Data of NHANES which is the largest cross-sectional study up to present time (25) show that, the components of the metabolic syndrome independently associated with low vitamin D were abdominal obesity and hyperglycemia, (8, 35).

Results of this study shows that, vitamin D deficiency independently predicted the metabolic syndrome. The modest effect of vitamin D deficiency on the metabolic syndrome in individual persons may translate into a dramatic effect in the population as a whole because of the high prevalence of hypovitaminosis D, which, in Iranian population (19), carries an attributable risk for type 2 diabetes mellitus and the metabolic syndrome.

The principal limitation of this study was its cross-sectional design, and thus the causative nature of the association cannot be established.

Further cohort investigations to determine the possible role of vitamin D in prevention of the metabolic syndrome are warranted. Because of the close interrelationships between vitamin D with insulin resistance and glucose homeostasis it is important to develop possible future approaches for prevention of the metabolic syndrome.

CONCLUSION

In conclusion vitamin D deficiency and the metabolic syndrome have a high prevalent among Iranian adult population and may have an important role in MS and its components. It is therefore imperative to make efforts to recognize individuals with MS early, so they may be targeted for intensive life style and risk factor management

to reduce cardio-metabolic risk.

ACKNOWLEDGEMENT

This study was supported by research grants from the Endocrinology and metabolism research center of Medical Sciences University of Tehran and the authors are grateful to EMRC for necessary facilities provided to carry the research work.

REFERENCES

1. Eckel, R.H., Grundy, S.M., Zimmet, P.Z. The metabolic syndrome. *Lancet*, 2005; 365: 1415-1428.
2. Azizi, F., Salehi, P., Etemadi, A., Zahedi-Asl, S. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. *Diabetes Res Clin Pract*, 2003; 61:29-37.
3. Ford, E.S. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the US. *Diabetes Care*, 2005; 28: 2745-2749.
4. Azadbakht, L., Mirmiran, P., Esmaillzadeh, A., Azizi, F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Iranian adults. *Am J Clin Nutr*, 2005;82:523-530.
5. Fakhrzadeh, H., Ebrahimpour, P., Nouri, M., Pourebrahim R, Heshmat R, Shoushtarizadeh P 'Larijani B Evaluation of prevalence of the metabolic syndrome in inhabitants of Tehran university of medical sciences population lab. *Iranian Journal of Diabetes & Lipid Disorders*, 2004; 3 (Suppl):71-80: Persian.
6. Isaia,G., Giorgino, R., Adami, S. High prevalence of hypovitaminosis D in female type 2 diabetic population (Letter). *Diabetes Care*, 2001; 24:1496.
7. Maghbooli, Z., Hossein-Nezhad, A., Karimi, F., Shafaei, A.R., Larijani, B.,Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. *Diabetes Metab Res Rev*. 2008;24:27-32.
8. Scragg, R., Sowers, M., Bell, C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the third National Health and Nutrition Examination Survey. *Diabetes Care*, 2004; 27:2813–2818
9. Maghbooli, Z., Hossein-Nezhad, A., Khoshnati, M., Adibi, H., Mohammadzadeh, N., Larijani, B., A study of bone mineral density in diabetic patients, *Iranian Journal of Public Health*, 2007;Suppl. 37-44.
10. Maghbooli, Z., Hossein-Nezhad, A., Shafaei, A.R., Karimi, F., Madani, F.S., Larijani, B. Vitamin D status in mothers and their newborns in Iran. *BMC Pregnancy and Childbirth*, 2007; 7:1-6
11. Chiu, K.C., Chu, A., Go, V.L., Saad, M.F. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr*, 2004; 79:820–825.
12. Baynes, K.C., Boucher, B.J., Feskens, E.J., Kromhout, D. Vitamin D, glucose tolerance and insulinaemia in elderly men. *Diabetologia*, 1997; 40:344 –347
13. Boucher, B.J., Mannan, N., Noonan, K., Hales, C.N., Evans, S.J. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. *Diabetologia*, 1995; 38:1239–1245.
14. Lind, L., Hanni, A., Lithell, H., Hvarfner, A., Sorensen, O.H., Ljunghall, S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. *Am J Hypertens*, 1995; 8: 894 –901
15. Ortlepp, J.R., Metrikat, J., Albrecht, M., Korff, A., Hanrath, P., Hoffmann, R. The vitamin D receptor gene variant and physical activity predicts fasting glucose levels in healthy young men. *Diabet Med*, 2003; 20: 451–454
16. Boucher, B.J. Inadequate vitamin D status: does it contribute to the disorders comprising syndrome 'X'? *Br J Nutr*, 1998; 79:315– 327
17. Larijani, B., Moayyeri, A., Keshtkar, A.A., Hossein-Nezhad, A., Soltani, A., Bahrami, A., Omrani, G.H., Rajabian, R., Nabipour, I. Peak bone mass of Iranian population: the Iranian Multicenter Osteoporosis Study. *J Clin Densitom*, 2006; 9:367-374.
18. Hashemipour, S.,Larijani, B., Adibi, H., Javadi, E., Sedaghat, M., Pajouhi, M., Soltani. A., Shafaei, A.R., Hamidi, Z., Fard, A.R., Hossein-Nezhad, A., Booya, F., Vitamin D deficiency and causative factors in the population of Tehran, *BMC Public Health*. 2004;4:38.
19. Hashemipour, S., Larijani, B., Adibi, H., Sedaghat, M., Pajouhi, M., Bastan-Hagh, M.H., Soltani, A., Javadi, E., Shafaei, A.R., Baradar-Jalili, R., Hossein-Nezhad, A. The status of biochemical parameters in varying degrees of vitamin D deficiency. *J Bone Miner Metab*, 2006;24:213-218.
20. American Diabetes Association Diagnosis and classification of diabetes mellitus *Diabetes Care*, 2004; 27(Suppl 1): S5-S10
21. Alberti, K.G., Zimmet, P.Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation *Diabet Med*, 1998 ;15:539-553
22. Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L. Jr., Jones, D.W.,

Materson, B.J., Oparil, S., Wright, J.T.Jr., Roccella, E.J. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on prevention detection, evaluation and treatment of high blood pressure for the National High Blood Pressure Education Program Coordinating Committee. *JAMA*, 2003; 289: 2560–2572.

23. Zemel, M.B., Hang, S., Greer, B., Dirienzo, D., Zemel, P.C. Regulation of adiposity by dietary calcium. *FASEB J*, 2000; 14: 1132-1138.
24. Saghafi, H., Hossein-nezhad, A., Rahmani, M., Larijani, B., Relationship between Lipid Profile and Bone Turnover in Pre and Postmenopausal Women, *Iranian Journal of Public Health*, 2008; Suppl.23-29
25. Ford, E.S., Ajani, U.A., Mc Guire, L.C., Liu, S. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care*, 2005; 28:1228–1230
26. Reaven, G.M., Banting. Lecture 1988: Role of insulin resistance in human disease. *Diabetes*, 1988; 37:1595–1607
27. Borissova, A.M., Tankova, T., Kirilov, G., Dakovska, L., Kovacheva, R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int J Clin Pract*, 2003; 57:258-261
28. Lind, L., Pollare, T., Hvarfner, A., Lithell, H., Sorensen, O.H., Ljunghall, S. Long- term treatment with active vitamin D (alphacalcidol) in middle- aged men with impaired glucose tolerance. Effects on insulin secretion and sensitivity, glucose tolerance and blood pressure. *Diabetes Res*, 1989; 11:141-147
29. Tanaka, Y., Seino, Y., Ishida, M., Yamaoka, K., Yabuuchi, H., Ishida, H., Seino, S., Seino, Y., Imura, H. Effect of vitaminD3on the pancreatic secretion of insulin and somatostatin. *Acta Endocrinol (Copenh)*, 1984; 105:528–533.
30. Executive summary of the 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). *JAMA*, 2001;285:2486–2497.
31. Holick, M.F. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. *Curr Opin Endocrinol Diabetes*, 2002;9:87–98.
32. Pittas, A.G., Lau, J., Hu, F., 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; 92:2017-2029.
33. Wareham, N.J., Byrne, C.D., Carr, C., Day, N.E., Boucher, B.J., Hales, C.N. Glucose intolerance is associated with altered calcium homeostasis: a possible link between increased serum calcium concentration and cardiovascular disease mortality. *Metabolism*, 1997; 46:1171-1177
34. Snijder, M., van, Dam, R., Visser, M., Deeg, D., Seidell, J., Lips, P. To: Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. *Diabetologia*, 2007; 48:1247-1257.
35. Parikh, S.J., Edelman, M., Uwaifo, G.I., Freedman, R.J., Semega-Janneh, M., Reynolds, J., Yanovski, J.A. The relationship between obesity and serum 1, 25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab*, 2004; 89: 1196-1199