ISSN 2321 – 7359 EISSN 2321 – 7367

discovery

Medical Science

The International Weekly Journal for Medicine

Inter-Arm Blood Pressure Difference and Severe Vitamin D Deficiency

Shashi K Agarwal

Agarwal Health Center, Edison, NJ, USA

Correspondence to: Shashi K. Agarwal, Email: usacardiologist@gmail.com; Mobile: 732-895-3200

Publication History
Received: 11 May 2014
Accepted: 04 July 2014
Published: 09 July 2014

Citation
Shashi K Agarwal. Inter-Arm Blood Pressure Difference and Severe Vitamin D Deficiency. *Medical Science*, 2014, 10(37), 31-36

ABSTRACT

An inter-arm blood pressure difference of more than 15 mm Hg (IAD) is associated with increased cardiovascular events and premature mortality. IAD is common in hypertensive patients. The underlying pathology appears to be atherosclerotic arterial disease involving the upper extremities. Vitamin D deficiency has been associated with increased atherosclerosis, partly due to its vascular inflammatory effects. Vitamin D deficiency is extremely common in hypertensive patients. This study reveals that severe vitamin D deficiency is associated with an increased incidence of IAD in hypertensive patients.

Keywords: hypertension, cardiovascular disease, vitamin D, Inter-arm blood pressure, atherosclerosis, inflammation

Abbreviations: ASH: American Society of Hypertension; BP: Blood pressure; HTN: Hypertension; IAD: Interarm blood pressure difference; JNC-7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

1. INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide (CDC, 2013; WHO, 2013). Recently, a large body of research has suggested that adequate levels of Vitamin D are necessary for optimal cardiovascular health (Lee et al, 2008) Several studies have found that that vitamin D deficiency is associated with hypertension (Kristal-Bonch et al, 1997; Forman et al, 2007) and cardiovascular diseases (Wang et al, 2008; Kim et al, 2008), including stroke (Pilz et al, 2008), heart failure (Pilz et al, 2008), cardiac arrhythmias (Chavan et al, 2007),

© 2014 discovery publication. All rights reserved

CARDIOVASCULAR DISEASE

- Cardiovascular disease is a major cause of morbidity and mortality worldwide.
- Adequate levels of Vitamin D are necessary for optimal cardiovascular health.
- Inter-arm difference of 15 mm or more is associated with a 2.5 greater risk of peripheral vascular disease, a 1.7 fold increase in cardiovascular mortality, and a 1.6 higher risk of all-cause death.
- Severe vitamin D deficiency appears to be associated with inter-arm blood pressure difference and may play a patho-physiological role in its development.

coronary artery disease (Watson et al, 1997), and myocardial infarction (Giovannucci et al, 2008). It deficiency has also been linked to several cardiovascular risk factors, including obesity (Foss, 2009), diabetes (Baz-Hecht et al, 2010), metabolic syndrome (Martini et al, 2006), hyperlipidemia (Lind et al, 1995), peripheral arterial disease (Melamed et al, 2008), and chronic renal disease (Mehrotra et al, 2009). Its deficiency has also been linked to excess all cause and cardiovascular mortality (Dobnig et al, 2008).

The actions of vitamin D on the cardiovascular system are multiple and complex. Its blood pressure effects are related to increased intracellular calcium resulting in a decreased renin activity (Li, 2003). It improves myocardial contractility (Green et al, 2006) and reduces myocardial hypertrophy (Wu et al, 1996). It also affects endothelial function, smooth muscle reactivity and vascular calcification, thereby influencing atherosclerotic coronary (Ian et al, 2009; Watson et al, 1997) and peripheral vascular disease (Hatton et al, 1994). Vascular dysfunction and accelerated atherosclerosis in vitamin D deficiency (Brewer et al, 2011) has also been linked to its inflammatory effects (Li et al, 2002; Dusso et al, 2005; Guillot et al, 2010). Segmental peripheral atherosclerotic processes in the subclavian arteries have been implicated as the underlying patho-physiology in the causation of inter-arm blood pressure difference (Shadman et al, 2004). This study was done to see if there was a link between vitamin D deficiency and atherosclerotic peripheral vascular disease resulting in an inter-arm blood pressure difference in patients with hypertension.

2. METHODS

We studied 189 consecutive hypertensive patients who had recent vitamin D levels available. Hypertension was diagnosed by standard blood pressure measurement techniques, using an appropriate-sized cuff at the level of the right atrium, with the patient rested for 5 minutes, and with the back supported. Measurements were taken in each arm using the same sphygmomanometer. Systolic blood pressure was categorized as follows: Normal: less than 120/80 mmHg; Pre-HTN: 120 to 139/80 to 89 mmHg; HTN: 140/90 mmHg or greater: Stage 1: 140 to 159/90 to 99 mmHg, Stage 2: 160/100 mmHg or greater. All patients had been diagnosed with hypertension with at least 2 consecutive elevated BP measurements (≥140 mm Hg systolic and/or 90 mm Hg diastolic or ≥130/80 mm Hg in the presence of diabetes mellitus or chronic kidney disease). All patients were on lifestyle changes recommendations and conventional anti-hypertensive patients, consistent with JNC 7 (Chobanian et al, 2003) and ASH guidelines (Gradman et al, 2010). Vitamin D was measured as serum levels of 25(OH) D by a commercial laboratory. The generally accepted values are classified as follows: Vitamin D deficiency: below 20 ng/mL (50 nmol/L), Vitamin D insufficiency: 21-29 ng/mL (52-72 nmol/L), Vitamin D "sufficient": 30 ng/mL (75 nmol/L) or greater, Vitamin D toxicity: over 150 ng/mL (374 nmol/L), (CSPHR, 2009; Holick, 2007; Lee et al, 2008). We further classified vitamin D deficiency as follows: mild deficiency was present if the levels were between 20 ng/mL and 11 ng/mL and severe deficiency existed if the levels were below at or below10 ng/mL.

3. RESULTS

Of the 189 hypertensive patients, 50 (26%) had IAD. Of these 50, 15 (30%) had severe vitamin d deficiency (Vitamin D levels at or below10 ng/mL). and 19 (38%) had less severe deficiency. Of the 139 (74%) without IAD, 23 (17%) had severe vitamin deficiency and 49 (35%) had less severe deficiency. 106 (56%) of 189 patients had vitamin d deficiency of 20 ng/mL or less. Of these 106, 38 (36%) had severe deficiency and 68 (64%) had less severe deficiency. Of the 38 with severe deficiency, 15 had IAD (39%) and 23 (61%) had no IAD. Of the 68 with less severe deficiency, 19 (28%) had IAD and 49 (72%) had no IAD. Overall, patients with IAD had a 30% incidence of severe vitamin deficiency compared to 17% in patients without IAD (Figure 1).

4. DISCUSSION

Vascular dysfunction and inflammation resulting in development and progression of atherosclerosis has been implicated in vitamin D deficiency associated peripheral vascular disease. The association of inter-arm difference in blood pressure and severe vitamin D deficiency in our patients suggests a causal association.

Shashi K Agarwal,
Inter-Arm Blood Pressure Difference and Severe Vitamin D Deficiency,
Medical Science, 2014, 10(37), 31-36,
http://www.discovery.org.in/md.htm

© 2014 discovery publication. All rights reserved

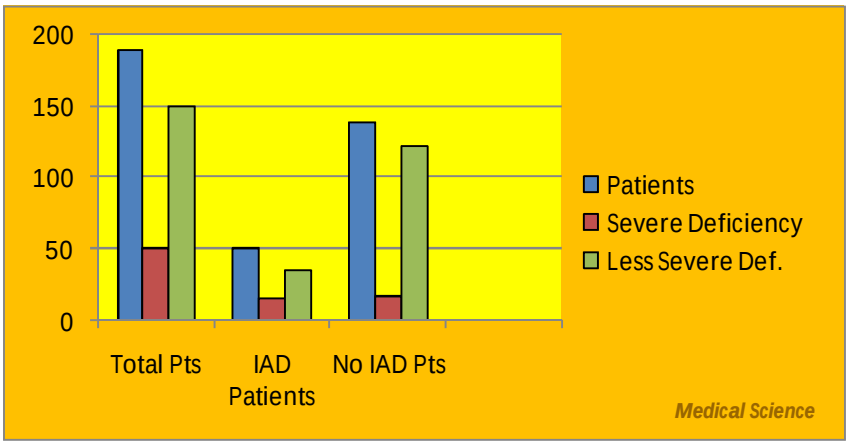

Figure 1

Hypertensive patients with incidence of severe vitamin deficiency

4.1. Inter-arm BP difference

Inter-arm BP difference of more than 10 mm/Hg is common (Fotherby et al, 1993; Lane et al, 2002; Cassidy et al, 2001). A difference of 15 mm or more is not benign (Clark et al, 2007). Its presence is associated with a 2.5 greater risk of peripheral vascular disease, a 1.7 fold increase in cardiovascular mortality, and a 1.6 higher risk of all-cause death (Clark et al, 2012). Causes of inter-arm blood pressure difference include atherosclerosis, vasculitis, fibromuscular hyperplasia, connective tissue disorders, radiation arteritis, thoracic outlet compression, dissecting aortic aneurysm, and congenital abnormalities (Osler, 1915; Geisbock, 1905). Clinically noticed inter-arm blood pressure difference is invariably as a result of stenosis involving the subclavian arteries (Shadman et al, 2004) due to atherosclerosis (Kay et al, 1930).

4.2. Vitamin D

4.2.1. Vitamin D deficiency related health disorders

Vitamin D deficiency is now a worldwide epidemic. Besides cardiovascular diseases, its deficiency has also been linked with neonatal tetany, rickets, osteopmalacia and osteoporosis, its deficiency has recently been linked to several other diseases, including autoimmune diseases such as multiple sclerosis, Crohn's disease, lupus, rheumatoid arthritis, colorectal cancer and chronic lymphocytic leukemia (Ramgopalan et al, 2010). Its deficiency may play a role in the pathogenesis of diabetes mellitus (Harris et al, 2005), depression (Hoogendijk et al, 2008), active tuberculosis (Nnoaham et al, 2008), periodontal disease (Amano et al, 2009), and some cancers (Lappe et al, 2007). Deficiency is also associated with an increase in overall general mortality (Zittermann et al, 2009).

4.2.2. Causes of Vitamin D deficiency

Vitamin D deficiency is usually a result of poor exposure to sunlight, presence of dark pigmented skin or excessive use of sunscreens (Rashid et al, 1983). Adequate sun exposure may also be denied due virtually complete covering of the skin for medical, social, cultural, or religious reasons (Gannage-Yared et al, 2000; Brand et al, 2008). Vitamin D deficiency may also occur in infants, adolescents and pregnant and lactating women due to increased needs (Gultekin et al, 1987; Prentice et al, 1998; Ramagopalan et al. 2010). Individuals with fat malabsorption syndromes, inflammatory bowel disease, obesity and gastric bypass surgery may also become vitamin D deficient (Wortsman et al, 2000, Lo et al, 1985; Compher et al, 2008; Reid, 1998).

4.2.3. Treatment of Vitamin D deficiency

Vitamin D deficiency is easily treatable (Lee et al, 2008). Reversing the deficiency has been associated with improvement in cardiovascular disorders (Goel et al, 2011; Pfeifer et al, 2001). Besides 30 minutes of direct exposure of sunlight to the arms and face (Holick, 1994) sources of vitamin D include fatty fish, such as salmon, mackerel, herring and sardines (Nakamura Nakamura et al, 2000) organ meats such as liver (Mavroidi et al, 2013), and fortified foods (Calvo et al, 2004). The generally recommended daily dose of vitamin D is 400 IU (NIH, 2013). Cardiovascular patients with vitamin D deficiency should be prescribed a daily oral vitamin D dose of 1,000 to 2,000 IU (Bischoff-Ferrari et al, 2006). Several doses of 50,000 IU may be initially required to raise the serum levels (Stechschulete et al, 2009). Supplementation is extremely safe with rare instances of toxicity. Prolonged massive intake may result in hypercalcemia (Hathcock et al, 2007), confusion and cardiac arrhythmias (Favus et al, 1996).

5. CONCLUSION

This study indicates that patients with IAD are twice more likely to have severe vitamin D deficiency when compared to those without IAD. IAD is attributed to atherosclerosis of the peripheral arteries. Substantial evidence connects atherosclerosis to vascular inflammation. Patients with low vitamin D levels exhibit higher levels of inflammation. This may explain the association noted in this study. Patients with severe vitamin D deficiency should be checked for inter-arm blood pressure difference.

Shashi K Agarwal,
Inter-Arm Blood Pressure Difference and Severe Vitamin D Deficiency,
Medical Science, 2014, 10(37), 31-36,
http://www.discovery.org.in/md.htm

© 2014 discovery publication. All rights reserved

SUMMARY OF RESEARCH

Hypertension is a common disease and is a major risk factor for major cardiovascular events. The presence of inter-arm blood pressure difference of more than 15 mm/Hg is ominous and is related to sublclavian atherosclerosis. Vitamin D deficiency has reached pandemic levels worldwide. Our data suggests that severe vitamin D deficiency is causally related to inter-arm blood pressure difference. Further studies are needed to evaluate the beneficial role of vitamin D supplementation in these patients.

FUTURE ISSUES

1.Can vitamin D supplementation play a role in preventing atherosclerotic peripheral vascular disease in patients with hypertension?
2.Should patients with vitamin D deficiency take anti-inflammatory agents?

DISCLOSURE STATEMENT

The author has no conflicts of interest to disclose.

REFERENCES

1. Amano Y, Komiyama K, Makishima M. Vitamin D and periodontal disease. *J Oral Sci*. 2009, 51(1), 11-20 [PMID: 19325195]
2. Baz-Hecht M, Goldfine AB. The impact of vitamin D deficiency on diabetes and cardiovascular risk. *Curr Opin Endocrinol Diabetes Obes*. 2010, 17(2), 113-9 [PMID: 20150805]
3. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr.* 2006, 84(1), 18–28 [PMID: 16825677]
4. Brand CA, Abi HY, Couch DE, Vindigni A, Wark JD. Vitamin D deficiency: a study of community beliefs among dark skinned and veiled people. *In J Rheum Dis*. 2008, 11, 15-23
5. Brewer LC, Michos ED, Reis JP. Vitamin D in atherosclerosis, vascular disease, and endothelial function. *Curr Drug Targets*. 2011, 12(1), 54-60 [PMID: 20795937]
6. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the US and Canada: current status and data needs. *Am J Clin Nutr.* 2004, 80(6 Suppl.), 1710S–6S [PMID: 15585792]
7. Cassidy P, Jones K. A study of inter-arm blood pressure differences in primary care. *J Hum Hypertens*. 2001, 15(8), 519-522 [PMID: 11494088]
8. CDC: http://www.cdc.gov/nchs/fastats/Icod.htm; accessed February 12, 2013
9. Chavan CB, Sharada K, Rao HB, Narsimhan C. Hypocalcemia as a cause of reversible cardiomyopathy with ventricular tachycardia. *Ann Intern Med*. 2007, 146(7), 541–542 [PMID: 17404364]
10. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; 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. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*, 2003, 42(6), 1206-52 [PMID: 14656957]
11. Clark CE, Campbell JL, Powell RJ, Thompson JF. The inter-arm blood pressure difference and peripheral vascular disease: cross-sectional study. *Family Practice*, 2007, 24(5), 420-426 [PMID: 17670807]
12. Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in SBP between arms with vascular disease and mortality: a systematic review and meta-analysis. *Lancet*, 2012, 379(9819), 905-914
13. Compher CW, Badellino KO, Boullata JI. Vitamin D and the bariatric surgical patient: a review. *Obes Surg*., 2008, 18(2), 220-4 [PMID: 18176832]
14. Council on Science and Public Health Report 4. Appropriate supplementation of vitamin D. American Medical Association, Annual Meeting, Chicago, Illinois; June 2009
15. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all cause and cardiovascular mortality. *Arch intern Med*, 2008, 168(12), 1340-1349 [PMID: 18574092]
16. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol*. 2005, 289(1), F8–F28 [PMID: 15951480]
17. Favus MJ, Christakos S. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 3rd ed. Philadelphia, PA: Lippincott Raven, 1996
18. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension*, 2007, 49(5), 1063–1069 [PMID: 17372031]
19. Foss YJ. Vitamin D deficiency is the cause of common obesity. *Med Hypotheses,* 2009, 73(1), 123 [PMID: 19054627]
20. Fotherby MD, Panayiotou B, Potter JF. Age-related differences in simultaneous interarm blood pressure measurements. *Postgrad Med J*. 1993, 69(809), 194-196 [PMID: 8497433]
21. Gannage-Yared MH, Chamali R, Yaacoub N, Halaby G. Hypovitaminosis D in a sunny Country: Relation to Life Style and Bone Markers. *J Bon and Min Res.,* 2000, 15(9), 1856-1862 [PMID: 10977006]
22. Geisbock F. Die Bedeutung der Blutdruckmessung fur die praxis. *Deutsches Arch f klin Med*., 1905, 83, 363
23. Giovannucci E, Liu U, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*. 2008, 168(11), 1174–1180 [PMID: 18541825]
24. Goel RK, Harbans Lal. Role of Vitamin D Supplementation in Hypertension. *Indian J Clin Biochem*., 2011, 26(1), 88–90 [PMID: 22211023]
25. Gradman AH, Basile JN, Carter BL, Bakris GL; American Society of Hypertension Writing Group. Combination therapy in hypertension. *J Am Soc Hypertens*. 2010, 4(1), 42-50 [PMID: 20374950]
26. Green JJ, Robinson DA, Wilson GE, Simpson RU, Westfall MV. Calcitriol modulation of cardiac contractile performance via protein kinase C. *J Mol Cell Cardiol*. 2006, 41(2), 350-359 [PMID: 16815434]
27. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. *Joint Bone Spine*, 2010, 77(6), 552-7 [PMID: 21067953]

© 2014 discovery publication. All rights reserved

28. Gultekin A, Ozalp I, Hasanoglu A, Unal A. Serum 25-hydroxycholecalciferol levels in children and adolescents. *Turk. J. Pediatr*., 1987, 29(3), 155-162 [PMID: 3506361]
29. Harris SS. Vitamin D in type 1 diabetes prevention. *J Nutr*. 2005, 135(2), 323-325 [PMID: 15671235]
30. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr*. 2007, 85(1), 6–18 [PMID: 17209171]
31. Hatton DC, Xue H, DeMerritt JA, McCarron DA. 1,25(OY)2 vitamin D3-induced alterations in vascular reactivity in the spontaneously hypertensive rat. *Am J Med Sci*. 1994, 307(suppl 1), S154-S158 [PMID: 8141157]
32. Holick MF. McCollum award lecture, 1994: Vitamin D-new horizons for the 21stcentury. *Am. J. Clin. Nutr*., 1994, 60(4), 619-630
33. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007, 357(3), 266-281 [PMID: 17634462]
34. Hoogendijk WJG, Lips P, Dik MG, Deeg DJH, Beekman ATF, Penninx BWJH. Depression Is Associated With Decreased 25-Hydroxyvitamin D and Increased Parathyroid Hormone Levels in Older Adults. *Arch Gen Psych*., 2008, 65(5), 508-512 [PMID: 18458202]
35. Ian H de Boer, Bryan Kestenbaum, Abigail B Shoben, Erin D Michos, Mark J Sarnak, David S Siscovick. 25-Hydroxyvitamin D Levels Inversely Associate with Risk for Developing Coronary Artery Calcification. *J Am Soc Nephrol*. 2009, 20(8), 1805–1812 [PMID: 19443637]
36. Kay WE, Gardner KD. Comparative blood pressures in the two arms. *Calif Western Med*. 1930, 33(2), 578–579 [PMID: 18741473]
37. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol*. 2008, 102(11), 1540–1544 [PMID: 19026311]
38. Kristal-Boneh E, Froom P, Harari G, Ribak J. Association of calcitriol and blood pressure in normotensive men. *Hypertension*, 1997, 30(5), 1289–1294 [PMID: 9369290]
39. Lane D, Beevers M, Barnes N, Bourne J, John A, Malins S, Beevers DG. Inter-arm differences in blood pressure: when are they clinically significant? *J Hypertens*. 2002, 20(6), 1089-1095 [PMID: 12023677]
40. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *The American journal of clinical nutrition*, 2007, 85(6), 1586–91 [PMID: 17556697]
41. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency: an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol*., 2008, 52(24), 1949-56 [PMID: 19055985]
42. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D Deficiency. An Important, Common, and Easily Treatable Cardiovascular Risk Factor? *J Am Coll Cardiol*, 2008, 52(24), 1949-1956 [PMID: 19055985]
43. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest*. 110(2), 229–238, 2002 [PMID: 12122115]
44. Li YC. Vitamin D regulation of therenin-angiotensin system. *J Cell Biochem*. 2003, 88(2), 327-31 [PMID: 12520534]
45. Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. *Am J Hypertens*. 1995, 8(9), 894–901 [PMID: 8541004]
46. Lo CW, Paris PW, Clemens TL, Nolan J, Holick MF. Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes. *Am J Clin Nutr*., 1985, 42(4), 644-649 [PMID: 4050723]
47. Martini LA, Wood RJ. Vitamin D status and the metabolic syndrome. *Nutr Rev*. 2006, 64(11), 479–486 [PMID: 17131943]
48. Mavroeidi A, Aucott L, Black AJ, Fraser WD, Reid DM, Macdonald HM. Seasonal Variation in 25(OH)D at Aberdeen (57°N) and Bone Health Indicators- Could Holidays in the Sun and CodLiver Oil Supplements Alleviate Deficiency? *PLoS One*, 2013, 8(1), e53381 [PMID: 23308207]
49. Mehrotra R, Kermah DA, Salusky IB, Wolf MS, Thadhani RI, Chiu YW, Martins D, Adler SG, Norris KC. Chronic kidney disease, hypovitaminosis D, and mortality in the United States. *Kidney Int*. 2009, 76(9), 977-83 [PMID: 19657329]
50. Melamed ML, Muntner P, Michos ED, Uribarri J, Weber C, Sharma J, Raggi P. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease. *Arterioscler Thromb Vasc Biol*. 2008, 28(6), 1179-85 [PMID: 18417640]
51. Nashimoto M, Hori Y, Yamamoto M. Serum 25-hydroxyvitamin D concentrations and related dietary factors in peri- and postmenopausal Japanese women. *Am J Clin Nutr*. 2000, 71(5), 1161–5 [PMID: 10799378]
52. NIH. "Dietary Supplement Fact Sheet: Vitamin D". Office of Dietary Supplements, National Institutes of Health. URL: http://dietarysupplements.info.nih.gov/factsheets/vitamind.asp.
53. Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol*. 2008, 37(1), 113-119 [PMID: 18245055]
54. Osler W. Modern Medicine. Lea & Febiger: Philadelphia, 1915
55. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D (3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab*. 2001, 86(4), 1633-7 [PMID: 11297596]
56. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, März W. Low vitamin d levels predict stroke in patients referred to coronary angiography. *Stroke*, 2008, 39(9), 2611-2613 [PMID: 18635847]
57. Pilz S, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, Boehm BO, Dobnig H. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large crosssectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab*. 2008, 93(10), 3927-3935 [PMID: 18682515]
58. Prentice A. Calcium requirements of breast-feeding mothers. *Nutr. Revs.*, 1988, 56, 124-127
59. Ramagopalan SV, Heger A, Berlanga AJ, Maugeri NJ, Lincoln MR, Burrell A, Handunnetthi L, Handel AE, Disanto G, Orton SM, Watson CT, Morahan JM, Giovannoni G, Ponting CP, Ebers GC, Knight JC. A ChIP-seq-defined genomewide map of vitamin D receptor binding: Associations with disease and evolution. *Genome Res.,* 2010, 20(10), 1352-60 [PMID: 20736230]
60. Rashid A, Mohammed T, Stephens WP, Warrington S, Berry JL, Mawer EB. Vitamin D state of Asians living in Pakistan. *Br Med J.*, 1983, 286(6360), 182-184 [PMID: 6401520]
61. Reid IR. The roles of calcium and vitamin D in the prevention of osteoporosis. *Endocrinol Metab Clin North Am*., 1998, 27(2), 389-98 [PMID: 9669144]
62. Shadman R, Criqui MH, Bundens WP, Fronek A, Denenberg JO, Gamst AC, McDermott MM. Subclavian artery stenosis: prevalence, risk factors, and association with cardiovascular diseases. *J Am Coll Cardiol*., 2004, 44(3), 618–623 [PMID: 15358030]
63. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: bone and beyond, rationale and recommendations for supplementation. *Am J Med*. 2009, 122(9), 793–802 [PMID: 19699370]

© 2014 discovery publication. All rights reserved

64. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*, 2008, 117(4), 503–511 [PMID: 18180395]
65. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation, 1997, 96(6), 1755-1760 [PMID: 9323058]
66. WHO: http://www.who.int/mediacentre/factsheets/fs310/en/index.html; accessed Feb 12, 2013
67. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000, 72(3), 690-3 [PMID: 10966885]
68. Wu J, Garami M, Cheng T, Gardner DG. 1,25(OH)2 vitamin D3 and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. *J Clin Invest*., 1996, 97(7), 1577-1588 [PMID: 8601621]
69. Zittermann A, Gummert JF, Börgermann J. Vitamin D deficiency and mortality. *Curr Opin Clin Nutr Metab Care*, 2009, 12(6), 634-9 [PMID: 19710612]

Medical Science

© 2014 discovery publication. All rights reserved