

Association of dyslipidaemia in patients with varying degrees of Vitamin D deficiency in the Asian population

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Abstract

Objective: To investigate the associations of dyslipidaemia with varying levels of 25 hydroxy vitamin D3 deficiency.

Methods: This cross-sectional study was conducted at the Pakistan Institute of Medical Sciences, Islamabad, Pakistan, from July 2016 to January 2017, and comprised patients having varying levels of 25 hydroxy vitamin D3 deficiency. Patients were stratified according to the severity of deficiency and had their serum fasting lipid profiles measured. SPSS 20 was used for data analysis.

Results: Of the 175 participants, 124(70.9%) were female and 51(29.1%) were male. The overall mean age of the patients was 47.7±12.2 years (range: 18-65 years). A very strong inverse correlation was found between vitamin D levels and low-density lipoprotein cholesterol ($p<0.001$) and a similar trend was obtained for vitamin D and total cholesterol ($p<0.001$). With regards to triglycerides, a modest inverse correlation was found ($p=0.05$). No significant association was documented between 25 hydroxy vitamin D3 levels and high-density lipoprotein cholesterol ($p=0.3$).

Conclusion: An inversely proportional relationship was found between total cholesterol, low-density lipoprotein cholesterol and triglycerides against varying levels of vitamin D deficiency.

Keywords: Vitamin D, Dyslipidaemia, LDL, HDL, Total cholesterol, Triglycerides. (JPMA 67: 1843; 2017)

Introduction

In recent years, the activated form of vitamin D is now considered by researchers to be a hormone rather than a vitamin. The presence of the vitamin D receptor has been found in over 36 different tissues of the body, thus potentially expanding vitamin D actions on nearly all cell systems and organs (e.g. immune cells, brain, breast, colon and prostate).

The maintenance of normal function of many non-skeletal tissues such as muscle (including heart muscle), immune function, and inflammation as well as cell proliferation and differentiation is also thought to be dependent on vitamin D. Its use as an adjunctive treatment for tuberculosis, psoriasis, and multiple sclerosis or for the prevention of certain cancers has also been postulated. Furthermore, vitamin D insufficiency may increase the risk of type 1 diabetes mellitus, cardiovascular disease (insulin resistance, hypertension, or low-grade inflammation), or brain dysfunction (e.g., depression) owing to its diverse effects on various tissues.¹

Although there is no consensus on optimal levels of 25-hydroxyvitamin D (25[OH]D) as measured in serum, but

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vitamin D deficiency is defined by most experts as a 25(OH)D level of less than 20ng per millilitre (50 nmol per litre)² and with the use of such definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.³

In practice, vitamin D levels between 21-30 ng/ml are described as being insufficient, 11-20 ng/ml as being deficient, and levels <10 ng/ml as being severely deficient.

We planned to assess the frequency of varying levels of different lipid parameters, namely total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), in patients who have low levels of vitamin D. Furthermore, we analysed the aforementioned levels with regards to varying degrees of vitamin D deficiency, particularly to see whether the lipid profile worsens with lower levels of 25[OH]D3.

Secondly, identifying dyslipidaemias in patients with hypovitaminosis D would enable us to address a major modifiable risk factor for coronary artery disease (CAD) and cerebrovascular accidents (CVA), allowing us to institute treatment which may help prevent the aforementioned, thus considerably lowering morbidity and mortality. We understand the statistical limitations of a cross-sectional study at the outset, but hoped that the results obtained would give precedence to well-

organised clinical trials.

Patients and Methods

This cross-sectional study was conducted at the outpatient department (OPD) of the Pakistan Institute of Medical Sciences, Islamabad, Pakistan, from July 2016 to January 2017, and comprised patients having varying 25(OH)D3 deficiency levels. The sample size was calculated with a confidence level of 95%, an anticipated population proportion of 32.9%⁴ and absolute precision of 7%. Since local data for similar research was not available, we relied on an anticipated patient population gauged from literature.⁴

Patients were excluded if they had pre-existing hyperlipidaemia, history of familial hyperlipidaemias, diabetes mellitus, chronic metabolic conditions (chronic

renal failure, chronic liver failure), morbid obesity (body mass index (BMI) > 30), were cigarette smokers, had received vitamin D supplements during the preceding year or those on statin therapy.

All of the aforementioned conditions were excluded on the basis of clinical presentation, including history, physical examination and existing medical records.

Permission was taken from the institutional ethics committee and samples were collected by non-probability consecutive sampling. Demographic parameters were recorded on a questionnaire and the degree of vitamin D deficiency, as reported by the hospital laboratory, was documented. Lipid profile samples were taken and sent to the lab and the reports were verified by the hospital pathologist, which were thereafter transferred to the prescribed questionnaire (Annexure).

SPSS 20 was used for data analysis. Quantitative variables, including serum lipid measurements, lab values of 25(OH)D3, age and BMI were presented by mean and standard deviation (SD) and frequencies and percentages were calculated for qualitative variables such as gender.

Effect modifiers (e.g. age, BMI and gender) were controlled by stratification.

Results

Of the 175 participants, 124(70.9%) were female and 51(29.1%) were male. The overall mean age of the patients was 47.7±12.2 years (range: 18-65 years). Moreover, 54(30.9%) patients were in the 48-57 years age category.

Gender did not have any significant bearing on the levels of vitamin D deficiency (p=0.35). No significant association was found between vitamin D levels and age (p=0.68) or BMI (p=0.75).

The mean BMI was 26.21±3.25, with 96(54.9%) patients falling in the overweight category.

The mean 25(OH)D3 measured in our patients was 15.5±8.165 ng/ml(range: 1.3-29.9ng/ml). The various

ANNEXURE

PROFORMA

To assess the association of hyperlipidaemias in patients with varying levels of vitamin D deficiency in the Asian population.

Test ID number: _____ Hospital ID: _____ Date: _____

Name: _____ Age: _____

Sex: Male Female

Height (m): _____ Weight (kg): _____ BMI: _____

25(OH)D3 Levels _____ (ng/dl)

< 10 (Severe Deficiency)

10 - 20 (Deficiency)

20 - 30 (Insufficiency)

Fasting Lipid Profile

Serum Cholesterol _____ mg/dl

HDL Cholesterol _____ mg/dl

LDL Cholesterol _____ mg/dl

Triglycerides _____ mg/dl

HDL: High-density lipoprotein

LDL: Low-density lipoprotein

25(OH)D3: 25 hydroxyvitamin D3

Table-1: Vitamin D levels vs. Lipid Profile parameters.

Vitamin D Levels and Categories of Deficiency	HDL-Cholesterol		LDL-Cholesterol		Triglycerides		Total Cholesterol	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
25(OH)D3 levels (ng/ml) <10 Severe Deficiency	40	10	150	50	181	127	222	53
11-20 Deficiency	44	12	124	46	154	73	192	52
21-30 Insufficiency	43	10	94	38	147	94	166	44

HDL: High-density lipoprotein

LDL: Low-density lipoprotein

25(OH)D3: 25 hydroxyvitamin D3.

levels of vitamin D deficiency were almost equally distributed among the study subjects with 55(31.4%) having vitamin D levels <10 ng/dl, 65(37.1%) between 11-20 ng/dl and 55(31.4%) had levels between 21-30 ng/dl.

Analysis of the respective components of the lipid profile showed that the mean LDL cholesterol was 122.89 ± 49.8 mg/dl (range: 39-347mg/dl) which fell in the borderline range as per ACC/AHA Guidelines (American College of Cardiology/ American Heart Association).⁵ Besides, 110(62.8%) patients had serum LDL in either the borderline or raised ranges.

The mean HDL cholesterol was 42.09 ± 10.97 mg/dl (range: 18-82mg/dl) which is a strong cardiovascular risk indicator.

Furthermore, 34(19.4%) patients had desired ranges of HDL >50mg/dl and 141(80.6%) had an HDL cholesterol level that was either borderline or raised.

The mean TG concentration was 160.36 ± 99.82 mg/dl (range: 96-899 mg/dl), which fell in the borderline category. Also, 47(26.9%) patients had normal/desirable TG concentrations (<100 mg/dl) while 128(73.1%) had concentrations that were either raised or borderline.

Mean TC concentration was 193.53 ± 54.19 mg/dl (range: 96-499mg/dl) which were desirable. Also, 107(61.1%) patients had desirable levels of TC, while the number of patients in the borderline and raised categories was 34(19.4%) each.

When results for various levels of hypovitaminosis D were tabulated, it was found that mean LDL-C levels were considerably higher in patients with lowest levels of vitamin D, and lower in patients who had less severe deficiency.

When TGs were assessed, the trend was similar to that noted for LDL-C, with patients having the most severe deficiency of vitamin D having the highest mean levels of TG. The same results were obtained for TC with an inverse relationship noted between 25(OH)D3 levels and serum TC.

The same trend was not as consistent with HDL-C levels, but patients with severe vitamin D deficiency did document the lowest levels of HDL cholesterol (Table).

A very strong inverse correlation was found between vitamin D levels and LDL-C ($r=-0.451$, $p<0.001$) and a similar trend was obtained for vitamin D and TC ($r=-0.422$, $p<0.001$).

With regards to TG, a modest inverse correlation was found ($r=-0.148$, $p=0.05$). No significant association was

documented between 25(OH)D3 levels and HDL-C ($p=0.3$).

It was anticipated that the BMI of the study population would correlate with the parameters of the lipid profile, but no statistically significant association was documented ($p=0.8$).

Analysis of the various concentrations of plasma lipids in various degrees of hypovitaminosis D revealed that with the exception of HDL-C, patients with lower levels of vitamin D had greater elevations in their lipid concentrations.

The mean LDL-C in the group having severe vitamin D deficiency was 150 ± 49.786 mg/dl, while it was 93.96 ± 37.823 mg/dl in the group having levels of vitamin D between 21-30 ng/dl.

Mean TC in patients with vitamin D concentrations <10 ng/dl was 222.35 ± 52.542 mg/dl, while in patients with insufficiency it was 166.09 ± 43.923 mg/dl.

Similarly, the mean TG concentration was 180.82 ± 127.267 mg/dl in patients with severe vitamin D deficiency, and 166.09 ± 43.923 mg/dl in patients with insufficiency.

Discussion

Over the last three to four decades, the global scientific understanding of vitamin D3 has grown immensely, with the active form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), being elevated to the status of a hormone. The contribution of vitamin D3 towards generalised good health, both by virtue of its role as a vitamin and an essential dietary component, and the metabolic effects of 1,25(OH)2D3 as a steroid hormone, cannot be highlighted enough. With the discovery of the vitamin D receptor (VDR), we have come to know that the scope of action of 1,25(OH)2D3 extends beyond the target tissues required for calcium homeostasis, and that 1,25(OH)2D3 is a pluripotent steroid hormone which initiates the physiologic responses of >36 target tissues with cells bearing the VDR. Furthermore, decades of dedicated research have led to the knowledge that in addition to the endocrine production of 1,25(OH)2D3 by the kidneys, there are at least more than 10 target organs which are active in its paracrine production. It has been estimated that the expression of almost 500 out of the approximately 20,488 genes in the human genome may be regulated by the VDR.⁶

Vitamin D and its effects on various body tissues has been a subject of great debate, with an ever increasing understanding of the mechanism by which the vitamin D-VDR axis interacts. There is little doubt about the

importance of vitamin D for the regulation of multiple bodily functions and the scope of improving health with correction of vitamin D deficiencies. The newly defined roles of vitamin D via the VDR on the immune system, hormonal regulation and cellular proliferation have been examined widely. There also exists an established relationship between vitamin D and lipid metabolism, although various studies have yielded slightly conflicting results with regard to different lipid parameters.^{1,7,8}

According to a study conducted in Norway, there was a cross-sectional association between serum 25(OH)D3 and serum lipids, and a longitudinal association over 14 years between serum 25(OH)D3 and TGs, which may explain the relation between low serum 25(OH)D3 concentrations and mortality.⁹

In October 2011, an article was published in the European Journal of Endocrinology which examined the association of serum 25(OH)D3 concentrations in association with the metabolic syndrome and its components (central obesity, hypertension, low HDL-C, hypertriglyceridaemia, glucose impairment and insulin resistance) and impairment of flow-mediated vasodilatation (FMD) and increased carotid intima-media thickness (cIMT) which are markers of subclinical atherosclerosis.⁹ Two conclusions were drawn from this: one, that higher 25(OH)D3 was significantly associated with reduced presence of metabolic syndrome; and, two, that obesity, central obesity, hypertension, hypertriglyceridaemia, low HDL, insulin resistance and metabolic syndrome were all associated with increased odds of having low 25(OH)D3.

The abovementioned study¹⁰ was in addition to another similar piece of research carried out in the United States in a population of adolescents in which they also concluded that low levels of serum 25(OH)D3 is strongly associated with hypertension, hyperglycaemia and the metabolic syndrome independent of adiposity.¹¹

Another study in Turkey measured the impact of vitamin D insufficiency on the epicardial coronary flow velocity and endothelial function. Their findings revealed that the incidence of slow coronary flow (SCF) was significantly higher in patients who were vitamin D-deficient and a linear regression analysis showed that vitamin D deficiency was independently correlated with FMD and cIMT. It reported a strong association between vitamin D deficiency and the SCF phenomenon. In addition, vitamin D deficiency was associated with endothelial dysfunction and subclinical atherosclerosis.¹²

A recent publication revealed the association of low vitamin D levels and increased risk of non-alcoholic fatty liver disease (NAFLD) among non-obese adults. NAFLD is suggested to be the hepatic manifestation of insulin resistance and the metabolic syndrome. The study was carried out in Turkey among 613 patients and the researchers found lower vitamin D levels among the patients with fatty liver disease compared to the control group. Moreover, the vitamin D levels were decreasing with advancing stages of NAFLD among non-obese subjects. It thus concluded that low vitamin D was an independent risk factor for NAFLD.¹³

On the basis of the data analysed in our study, we found significantly raised LDL and TG and dangerously low HDL levels in our patients. The TC in the vast majority was normal.

However, when varying levels of vitamin D deficiency were tabulated against the various parameters mentioned above, results opened a new perspective. It was found that with worsening levels of vitamin D deficiency, LDL, TG and TC levels rose steadily. Patients having severe vitamin D deficiency had the highest LDL, TG and TC levels. Those with mild insufficiency were found to have comparatively lower levels of the aforementioned lipids.

A possible confounding factor, namely body weight, was also taken into account since an increased BMI would theoretically be associated with both low vitamin D and raised lipids. However, we found that vitamin D levels were not consistently lower in groups with greater BMIs and no significant correlation was noted.

The trend was not consistent with regards to HDL-C status, as we did not find that patients with lower vitamin D had lower HDL or vice versa.

Hyperlipidaemia is a major modifiable cardiovascular risk and leads to serious morbidity and mortality. Control of lipid parameters with replacement with 25(OH)D3 would be an interesting avenue to explore.

Limitations of this study included its cross-sectional design and the fact that causation could not be inferred from the identified associations. Future longitudinal studies of 25(OH)D3 and the components of the lipid profile are needed. The possibility of residual confounding from unmeasured confounders exists. The male-to-female ratio was not equal, thus generalised results pertaining to gender cannot be given.

Conclusion

Patients with hypovitaminosis D had an overall increased

frequency of serum LDL and TG while they had low serum HDL levels. All three factors are documented for increased cardiovascular risk. An inversely proportional relationship was observed between categories of vitamin D deficiency and LDL, TGs and TC.

Disclosure: None.

Conflict of Interest: None.

Source of Funding: None.

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