The Study of Serum Vitamin D Level In Patient With Pulmonary Hypertension And Right Ventricular Systolic Dysfunction Detected by Transthoracic Echocardiography

Ali Jaber Al-Mamoori

Department of Medicine; Faculty of Medicine, University of Babylon, Iraq.
Email: minaaligaber@gmail.com

Abstract

Objective: To aim the vitamin D level in patient with pulmonary hypertension and right ventricular systolic dysfunction.

Patients and methods: This case-control study was conducted on twenty five patients with pulmonary hypertension who were admitted to Merjan Teaching Hospital in Al-Hilla, Babylon-Iraq, during the period from June to December 2016. There were 13 males and 12 females among the patients; ages of them ranged from 39 to 80 years with a mean age of 59.50±11.881 years. The controls were equal in number to the patients and were relatives of them; they were healthy with respect to any cardiac or pulmonary morbidity; and were matched by age and gender. Blood samples were collected from both groups to estimate the level of vitamin D and transthoracic echocardiographic studies were done for them to evaluate right ventricular systolic pressure (RVSP) and tricuspid annular plane systolic excursion (TAPSE) to assess right ventricular systolic function.

Results: The study results demonstrated that there was a statistically significant difference between patients and controls regarding vitamin D level, right ventricular systolic pressure (RVSP) and tricuspid annular plane systolic excursion (TAPSE).

Conclusion: Vitamin D deficiency is more frequent and prevalent among patients with Pulmonary hypertension and right ventricular systolic dysfunction compared to con- trol group of subjects. Future large scale studies are therefore warranted to validate benefit of supplementing vitamin D in patients at risk for pulmonary hypertension who are likely to be vitamin D deficient.

Keywords: Vitamin D, pulmonary hypertension, right ventricular systolic pressure , tricuspid annular plane systolic excursion, right ventricular systolic function,.

دارسة حول مستوى فيتامين (د) في الدم لدى مرضى ارتفاع ضغط الدم الرئوي وعدم كفائة البطين الأيمن الإنقباضية المشخصين بواسطة فحص صدى القلب

علي جابر المعموري

كلية الطب، جامعة بابل

الخلاصة

الهدف: لفحص مستوى فيتامين (د) لدى مرضى ارتفاع ضغط الدم الرئوي وعدم كفائة البطين الأيمن الانقباضي المشخصين بواسطة فحص صدى القلب.

طريقة العمـــل: أجريت هذه الدراسة على خمسة وعشرين مريضا مع ارتفاع ضغط الدم الرئوي الذين تم إدخالهم في مستشفى مرجان التعليمي في الحلة، بابل – العراق، خلال الفترة من حزيران إلى ديسمبر ٢٠١٦. كان هنـــاك ١٣ ذكور و ١٢ إناث من بين المرضى. تراوحت أعمارهم من ٣٩ إلى ٨٠ سنة مع متوسط عمر ٥٩.٥٠ ± ١١.٨٨١ سنة. وكانت مجموعة المقارنة أشخاص طبيعيون مساوين في العدد للمرضى وكانوا أقارب المرضى؛ كانوا اصحاء فيما يتعلق بأي أمراض القلب أو الامراض الرئوية ,وكانوا مطابقين للمرضى بالسن ونوع الجنس. جمعـــت عينـــات الدم من المجموعتين لتقدير مستوى الفيتامين "د" ودراسات صدى القلب من أجل تقييم الضغط الانقباضـــي البطـــين الأيمن و الانحراف الانقباضي للصمام ثلاثي الشرفات.

النتائج: أظهرت نتائج الدراسة وجود فروق ذات دلالة إحصائية بين المرضى و مجموعة المقارنـــة فيمـــا يتعلـــق بمستوى فيتامين (د) و الضغط الانقباضي البطين الأيمن والانحراف الانقباضي للصمام ثلاثي الشرفات.

الاستنتاج: نقص فيتامين (د) هو أكثر تواترا وانتشار افي المرضى الذين يعانون من ارتفاع ضغط الدم الرئـــوي و وعدم كفاءة البطين الأيمن الانقباضي مقارنة مع مجموعة الضبط. بالتالي فإن الدراسات علـــى نطـــاق واســـع فـــي المستقبل مطلوبة للتحقق من فائدة اعطاء فيتامين (د) في المرضى المعرضين لخطر ارتفاع ضـــغط الـــدم الرئـــوي الذين من المرجح أن يكون فيتامين (د) ناقصا.

الكلمات المفتاحية: فيتامين(د)، ارتفاع ضغط الدم الرئوي، الضغط الانقباضي البطين الأيمن, عدم كفاءة البطين الأيمن الانقباضي و الانحراف الانقباضي للصمام ثلاثي الشرفات.

1-Introduction

Vitamin D has a significant role in the regulation of musculoskeletal stability and home- ostasis of the body [1] . The pathogenesis of many chronic illnesses such as diabetes, elevated blood pressure and several types of infections have been linked to deficiency of vitamin D [2] . Blood pressure control appears to be having an association with vitamin D via numerous paths and is inversely associated with serum renin activity [3]. Vitamin D can block the action of renin, and this seems to be resulting from elevated intracellular calcium levels [4]

Lack of vitamin D triggers the renin-angiotensin-aldosterone pathway and increases the susceptibility to hypertension [5] . Vitamin D has an effect on vascular endothelial growth factor and endothelin expression and can predispose to endothelial dysfunction [6] .

Deficiency of Vitamin D weakens its protective effects against fibrosis, myocardial fiber thickening and anti-apoptosis, leading to cardiac wall thickening and finally dilatation. It has been also noticed that deficiency of vitamin D causes myocardial hypertrophy and extracellular matrix deposition in myocardium. Harmful effects connected to vitamin D excess include hyperphosphatemia, hypercalcaemia, elevated matrix metalloproteinase and arterial stiffness [7]

Pulmonary hypertension signifies a group of disorders that leads to various pulmonary vascular changes like vasoconstriction, endothelial and smooth muscle tissue proliferation that ensues to a persistently elevated pulmonary arterial pressure [8] . This results in right sided cardiac failure and a significant decrease cardiac output with subsequent mortality [9] . As the main pathological mechanisms of elevated pulmonary arterial pressure are linked to vasoconstriction, thrombosis and inflammation, it can be suggested that vitamin D deficiency may exert an incorrect outcome on the progress of pulmonary hypertension [10] (Heidari, B. et al 2015). In addition, activation of renin-angiotensin-aldosterone pathway that results from vitamin D lack is connected to an elevated pulmonary arterial pressure [2] .

A significant target tissue for vitamin D special effects on genomic and non-genomic levels is the cardiac muscle. Cardiac muscle cells express vitamin D receptors, and some researches in rodents showed that this vitamin has a protective effect regarding cardiac muscle hypertrophy and malfunction [11] .

Vitamin D-mediated cardiovascular illness is a subject of extensive discussions by many researchers; for example, Pilz *et al [12]* had measured the level of vitamin D in Caucasian patients as they were referred for coronary angiography and they concluded that the deficiency of this vitamin is associated with myocardial dysfunction, cardiac failure, and sudden cardiac death.

Some evidences demonstrated that vitamin D possesses three principal cardiac-protective mechanisms: Suppressing renin gene expression; presence of vitamin D receptors in cardiac myocytes, besides that lack of vitamin D activates secondary hyperparathyroidism, which in turn indorses cardiac hypertrophy [13]

The main objective of this study is to inspect the influence of vitamin D deficiency on the prevalence of pulmonary hypertension.

2-Patients and methods

This case-control study was conducted on twenty five patients with pulmonary hyperten- sion who were admitted to Merjan Teaching Hospital in Al-Hilla, Babylon-Iraq, during the period from June to December 2016. There were 13 males and 12 females among the patients; ages of them ranged from 39 to 80 years with a mean age of 59.50±11.881 years. The controls were equal in number to the patients and were

relatives of them; they were healthy in respect for cardiac or pulmonary morbidity; and were matched by age and gender.

The diagnosis of pulmonary hypertension was accomplished by transthoracic echocardiography by measuring right ventricular systolic pressure (RVSP) and tricuspid annular plane systolic excursion (TAPSE) to evaluate right ventricular systolic function . Echocardiographic evaluations employed colored Doppler and two-dimensional transthoracic studies with a cardiac ultrasound machine GE-Medical Systems XDclear E9 USA 2014 equipped with 2.5 MHz multifrequency array transducer. Applying continuous wave doppler of the Tricusped valve by the apical four chambers view to measure the maximal tricuspid regurgitation velocity to estimste RVSP . Patient with right ventricular systolic pressure of more than 40 mmhg (correspond to mean pulmonary artery pressure of 25 mmhg) were diagnosed as pulmonary hypertension. Patient with Tricuspid annular plane systolic excursion of 1.5 cm or less were diagnosed with right ventricular systolic dysfunction. Exclusion criteria were liver or renal impairments; presence of congenital heart disease, ischemic heart disease, moderate to severe valvular heart disease or heart failure (ejection fraction less than 55%), presence of chronic pulmonary diseases, thyroid or parathyroid diseases, hypertension , diabetes mellitus and those patient with poor image quality by by transthoracic echocardiography. Baseline data, including age and gender and laboratory data including estimation of vitamin D level were all collected from both patients and controls.

Blood samples for the estimation of vitamin D level were collected into an EDTA tubes and were analyzed by the use of vitamin D total kit utilizing ELISA technology [14] .

3-Ethical approval:

Written and verbal consent agreement were obtained from each subject participated in this work .Moreover, this work was approved by a research ethical committee in College of medicine –Babylon University /Iraq.

4-Statistical analysis

Numeric data (age, vitamin D level, RVSP and TAPSE) were stated as mean ± standard deviation (SD), while the other string data (gender) were stated as percentages. Patients and controls were compared using independent-samples t-test for the numeric data and chi-square test for the string data. All tests were established by the use of SPSS ver-sion 18.0 software (SPSS Inc., Chicago, IL, USA). $p<0.05$ was encountered statistically significant.

5-Results

Age and gender distributions are stated in tables (1) and (2) which showed no significant difference between study groups regarding them (*p* values=0.991 and 0.571, respectively).

Groups / Age	Patients (n=25)	Controls (n=25)	*P*-value
Years (Mean ± SD)	59.52±11.973	59.48±12.035	0.991

FIGURE 1: Agedistribution of patients with pulmonaryhypertension and control group.

Groups / Gender	Patients (n=25)	Controls (n=25)	Total No. (%)	*P*-value
Males No. (%)	13 (52)	11 (44)	24 (48)	0.571
Females No. (%)	12 (48)	14 (56)	26 (52)	
Total No. (%)	25 (50)	25 (50)	50 (100)	

FIGURE 2: Gender distribution Of patients with pulmonaryhypertension and control group

Groups / Vitamin D	Patients (n=25)	Controls (n=25)	*P*-value
ng/ml (Mean ± SD)	20.66±6.27	39.07±10.07	0.000

FIGURE 3: Vitamin Dlevel for patients with pulmonary hypertension and control group.

Groups / RVSP	Patients (n=25)	Controls (n=25)	*P*-value
mmHg (Mean ± SD)	47.52±12.69	29.64±7.03	0.000

FIGURE 4: Rightventricular systolic pressure (RVSP) for patients with pulmonary hypertensionand control group.

Groups / TAPSE	Patients (n=25)	Controls (n=25)	*P*-value
mmHg (Mean ± SD)	13.52±2.64	20.56±2.67	0.000

FIGURE 5: Tricuspid annular plane systolic excursion (TAPSE)for patients with pulmonary hypertension and control group.lin

6-Discussion

Pulmonary hypertension is a serious illness that is associated with an increase in pul- monary vascular resistance which ensues to cardiac failure, and also lowering cardiac output ending in mortality [15]. Multiple ways are found to manage this condition, how- ever, the affected patients may be complicated by other illnesses, as deficiency in vitamin D during the progress of the disease [16].a link between vitamin D and cardiovascular illness was proposed by several other evidences, such as clinical trials detecting vitamin D receptors in endothelial cells and vascular smooth muscle cells in addition to cardiac cells [17] .

In this study, it was clearly obvious that there is a strong connection between lack of vitamin D and pulmonary hypertension in affected patients compared to control group; this could suggest that vitamin D is playing a crucial role in maintaining pulmonary arterial pressure within normal values and its deficiency has a potential promoting effect on increasing the prevalence of pulmonary hypertension in affected patients.

Several studies had consistent outcomes to the findings of this study; Demir *et al.* 2013 stated that vitamin D deficiency triggers renin-angiotensin-aldosterone system that affects cardiovascular system and the stimulation of this pathway is linked to pulmonary hypertension. Moreover, Mirdamadi *et al.* [18] concluded that replacement therapy of vitamin D in patients affected by pulmonary hypertension carries a beneficial outcome on improving the dimensions of the right ventricle and that the value of pulmonary artery pressure showed some improvement after the course of treatment.

Furthermore, a systematic review and meta-analysis established by Norma *et al. [19]* pointed out that information from several prospective studies predict an inverse relation-

ship between vitamin D and cardiovascular hazard. In contrast to this; another meta-analysis done by Mohamed *et al. [20]*concluded that records offered to date cannot establish a statistically significant decrement in mortality and cardiac risk related to vitamin D.

A study by Luke *et al. [21]* stated that elevated values of RVSP and low values of TAPSE are linked to a high and significant mortality risk among patients with pulmonary hypertension, and these findings supports those of the current study. A consistent findings were pointed out by Stefano *et al*. [22] in that a base line normal RVSP and TAPSE values in pulmonary hypertensive patients were associated with a lower risk of death.

Other study parameters that showed no statistical significant difference like age and gender distributions could be allied to the small number of the study's participants, or may be connected to genetic, environmental, demographic or other unreachable factors.

7-Conclusions and Recommendations

This study brings about an outcome that Vitamin D deficiency is more frequent and preva- lent among patients with Pulmonary hypertension and right ventricular systolic dysfunc- tion compared to control group of subjects, and this may also be linked to other car- diovascular risk factors. Additional future studies with a bigger sample size are strongly recommended to address other related factors that could not be accomplished in this study and to validate benefit of supplementing vitamin D in patients at risk for pulmonary hy- pertension who are likely to be vitamin D deficient

Acknowledgements

Author would like to express grateful thanks to Dr Fadhel Al-sultani manager of Merjan Teaching Hospital for his continuous support during the study time, also sincere gratitude to statisticians for their helpful participation in the statistical aspects in this study.

References

[1] H. F. DeLuca, "Overview of general physiologic features and functions of vitamin d." Am. J. Clin. Nutr, (2004, pp. 80:1689–1696.

[2] G. Rawal, S. Yadav, and P. Shokeen, "Health and the vitamin," *D. Int. J. Health Sci. Res*, vol. 2015, pp. 5–416.

[3] J. L. Anderson, H. T. May, B. D. Horne, H. T. Anderson, J. L.; May, and B. D. Horne, "Relation of vitamin d deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population." Am. J. Cardiol, 2010, pp. 963–968.

[4] T. Entezari-Maleki, A. Talasaz, M. Salarifar, A. Entezari-Maleki, T.; Talasaz, and M. Salarifar, "Plasma vitamin d status and its correlation with risk factors of throm-

bosis, p-selectin and hs-crp level in patients with venous thromboembolism; the first study of iranian population." Iran: J. Pharm. Res, 2014, pp. 13: 319–327.

[5] J. H. Lee, J. H. O'Keefe, D. Bell, D. D. Hensrud, M. F. Holick, J. H. B. D. H. D. D. Lee, J. H.; O'Keefe, and M. F. Holick, "Vitamin d deficiency: an important, common, and easily treatable cardiovascular risk factor?" J. Am. Coll. Cardiol, 2008, pp. 52: 1949–1956.

[6] S. M. Hashemi, S. M. Mokhtari, M. Sadeghi, R. Foroozan, M. Safari, S. M. S. M. F. R. Hashemi, S. M.; Mokhtari, and M. Safari, "Effect of vitamin d therapy on endothelial function in ischemic heart disease female patients with vitamin d deficiency or insufficiency: A primary report. arya atheroscler," 2015, pp. 11: 54–59.

[7] M. Rahman, H. Galal, and A. Omar, "Correlation between serum vitamin d level and cardiac function: Echocardiographic assessment," *Egyp. Heart J*, vol. 2015, pp. 67–299.

[8] S. Ulrich, M. Hersberger, M. Fischler, L. C. Huber, O. Senn, and U. Treder, "Bone mineral density and secondary hyperparathyroidism in pulmonary hypertension," *Open*, pp. 3–53, 2009.

[9] M. Rabinovitch, C. Guignabert, M. Humbert, and M. R. Nicolls, "Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension," *Circ. Res*, vol. 2014, pp. 115–165.

[10] B. Heidari, Y. Javadian, M. Monadi, Y. Dankob, A. Firouzjahi, Y. M. M. D. Y. Heidari, B.; Javadian, and A. Firouzjahi, "Vitamin d status and distribution in patients with chronic obstructive pulmonary disease versus healthy controls." Caspian J. Intern. Med., 2015, pp. 6: 93–97.

[11] L. Mosekilde, "Vitamin d and elderly. clin. endocrine (oxf.)," 2005, pp. 62(3): 265–281.

[12] S. Pilz, H. Dobnig, and J. E. Fischer, "Low vitamin d levels predict stroke in patients referred to coronary angiography," *Stroke*, pp. 39–2611, 2008.

[13] N. K. A., D. X. Tishkoff, and S. D. Hershey, "D3 actions on cell proliferation, size, gene expression, and receptor localization, in the hl-1 cardiac myocyte," *J. Steroid Biochem. Mol. Biol(2007)*, vol. 1, no. 25, pp. 533–537.

[14] A. C. Heijboer, M. A. Blankenstein, I. P. Kema, M. A. Heijboer, A. C.; Blankenstein, and I. P. Kema, "Accuracy of 6 routine 25-hydroxyvitamin d assays: influence of vitamin d binding protein concentration." Clin. Chem, 2012, pp. 58: 543–548.

[15] G. Simonneau, N. Galie, and L. J. Rubin, "Clinical classification of pulmonary hypertension," *J. Am. Coll. Cardiol*, vol. 2004, pp. 43–5.

[16] M. Demir, U. Uyan, S. Keceoclu, and C. Demir, "The relationship between vitamin d deficiency and pulmonary hypertension." Prague Med. Rep, 2013, pp. 114: 154–161.

[17] R. Thadhani, E. Appelbaum, and Y. Pritchett, "Vitamin d therapy and cardiac structure and function in patients with chronic kidney disease: the primo randomized controlled trial," pp. 307–674.

[18] A. Mirdamadi and P. Moshkdar, "Benefits from the correction of vitamin d deficiency in patients with pulmonary hypertension." Caspian J. Intern. Med., 2016, pp.2012. 7(4): 253–259.

[19] C. Norma, P. Grandi-Lutz, and B. V. Hermann, "D and cardiovascular disease: Systematic review and meta-analysis of prospective studies," *Prev. Med. J*, vol. 2010, pp. 51–228.

[20] B. Mohamed, O. Nisrin, B. Khalid, M. Mitra, A. Aziz, P. Jaime, O. K. B. M. M. A. A. Mohamed, B.; Nisrin, and P. Jaime, "Vitamin d and cardiovascular outcomes: A systematic review and meta-analysis." J. Clin. Endocrinol. Metab., 2011, pp. 96: 1931–1942.

[21] S. Luke, G. Julia, D. David, B. Michael, J. B., G. D. D. M. B. Luke, S.; Julia, and J. B., "Echocardiographic assessment of pulmonary hypertension: standard operating procedure." Eur. Respir. Rev., 2012, pp. 21: 239–248.

[22] G. Stefano, P. Silvia, K. Catherine, G. Eleonora, and S. Laura, "Prognostic value of tapse after therapy optimization in patients with pulmonary arterial hypertension is independent of the hemodynamic effects of therapy," *Open Heart*, vol. 2016, no. 3.