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ORIGINAL ARTICLE

Medicine Science 2021;10(2):374-9

Medicine Science International Medical Journal

Vitamin D status and post sternotomy bone healing; a prospective radiologic observational study

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Received 14 January 2021; Accepted 01 February 2021
Available online 25.03.2021 with doi: 10.5455/medscience.2021.01.010

Abstract

Sternotomy is the most common incision technique used in cardiac surgery. Some complications due to this method, which requires a large bone incision, increase morbidity and mortality. Vitamin D deficiency is an important health problem that can be observed in all age groups in the society. In this study, we aimed to radiologically examine the relationship between vitamin D level and bone healing after sternotomy.120 patients who underwent sternotomy for coronary artery bypass surgery under elective conditions between 2019-2020 were included in our study. The patients were divided into 3 groups according to their pre-operative 25-hydroxyvitamin D levels, with 40 patients in each group. Bone healing was evaluated with computed tomography at 3 and 6 months following the operation.Preoperative demographic data, laboratory and clinical results, except for vitamin D levels, were similar in all patients. There was no significant difference between the groups in terms of clinical bone healing in the first 3 months. However, it was observed that bone healing was weaker in patients with low vitamin D on radiological imaging. On the 6th month images, it was found that the differences in the level of bone tissue healing decreased in all patient groups.Vitamin D is a steroid-structured vitamin that plays important roles in many physiological mechanisms, especially bone healing. The results of our study showed that; In coronary bypass operations performed by sternotomy, there is a significant relationship between bone healing and vitamin D level, especially in the first 3 months. Pre-operative detection of vitamin D deficiency may help reduce sternotomy-related complications, especially in patient groups in which additional risk factors such as obesity and diabetes mellitus are identified.

Keywords: Vitamin D, sternotomy, osteotomy, coronary artery bypass, tomography

Introduction

The Median sternotomy technique was first used by Milton in 1897 [1]. Although minimally invasive surgical techniques are increasingly popular, it continues to be used as the preferred exploration method in major operations such as heart and aortic surgery. In addition to the surgical comfort this large incision method provides, it also brings in some complication risks. It provides a basis for many pathologies that increase morbidity and mortality in postoperative processes such as surgical site infections, mediastinitis, sternal dehiscence, and osteomyelitis.

The techniques and handicaps of this method, which has been used safely for many years, are well defined. However, despite all this enormous experience, these complications can still be encountered due to many reasons, especially comorbid diseases such as diabetes mellitus (DM), peripheral vascular diseases, chronic obstructive pulmonary disease (COPD), and some surgical procedures such as internal thoracic artery harvesting [2,3]. Preservation of tissue integrity is the basis of preventing these complications. In particular, the healing of bone tissue is a very difficult process that requires close observation [4].

Vitamin D, which is a steroid-structured vitamin, is either taken by digestion through foods or synthesized in the skin with the effect of ultraviolet sunlight. Five known forms of vitamin D have been identified. These; ergocalciferol with lumisterol (D1), ergocalciferol with ergosterol (D2), cholecalciferol (D3), 22 dihydrocalciferol (D4), and cytocalciferol (D5). Cholecalciferol

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and ergocalciferol are inactive biological precursors of vitamin D. Unless converted into active forms by hydroxylation in the liver and kidney, they have no efficacy. 25-hydroxyvitamin D [25(OH) D] is synthesized in the liver and 1.25 hydroxyvitamin D in the kidneys. The 25 (OH) D level in the blood is the parameter that best reflects the vitamin D level in the body. Vitamin D deficiency can be seen in the community due to reasons such as lack of sufficient sun exposure due to geographical reasons, insufficient food intake, or absorption disorders in the gastrointestinal system. It has recently been discovered that vitamin D deficiency has important roles in many metabolic events in the body, as well as its well-known effects on the musculoskeletal system [5,6]. In light of these studies, it has been understood that vitamin D deficiency and related pathologies are more common than expected in society [7].

Since vitamin D has an important role in calcium metabolism, it has been previously known that its deficiency causes negative consequences in bone healing. [8]. Median sternotomy healing processes should also be closely related to vitamin D in this context. In this current study, we aimed to investigate the role of vitamin D in bone healing after median sternotomy.

Material and Methods

120 adult patients who underwent CABG surgery with cardiopulmonary bypass via median sternotomy between 2019-2020 were included in this prospective observational cohort study. The 25-hydroxy vitamin D level in the blood was measured preoperatively in all patients. In light of the guidelines of the Endocrine Society (United States) [9] 40 patients with 25(OH)D levels of <20 ng/ml were studied in group 1 (Deficient vitamin D status), 40 patients with 21-29 ng/ml in group 2 (Insufficient vitamin D status), and 40 patients with >30 ng/ml in group 3 (Sufficient vitamin D status). Patients using vitamin D supplements before and after the procedure and patients who underwent combined valve or additional vascular surgery were not included in the study. Harvesting bilateral internal thoracic artery surgery, previous sternotomy, perioperative history of glucocorticoid drugs, perioperative history of immunosuppression therapy, hormone replacement use, autoimmune disease, history of parathyroid or thyroid disorders, history of bone metabolism- or bone development-related diseases, renal insufficiency (preoperative creatinine >200 μmol/L) post-operative low cardiac output syndrome (insertion of an intra-aortic balloon pump) and postoperative continuous renal replacement therapy were determined as exclusion criteria. The left internal thoracic artery was harvested in all patients. As a standard, 6-gauge stainless steel wire was used for sternum fixation. Two-wire sutures at the manubrium level and one at the xiphoid level were used, and the same surgeon (Ucak H.A.) performed all sternum closure procedures. Bone wax was not used in any patient. The local ethical committee approved our study protocol numbered 104, dated October 2, 2020. Informed consents were obtained from all subjects.

Physical examination findings of sternal recovery have been evaluated with previous studies [10]. In the study of Raman et al. comparing rigid fixation plates and conventional steel wires, a more objective healing criterion was revealed with a scoring system based on axial CT images that followed sternum healing. [11] Computed tomography (CT) imaging was performed in all patients included in our study at three and six months after the operation. 5 points were determined to be scored on these images. Axial imaging of the manubrium sterni, the upper level of the aortic arch, on the aorticopulmonary window, and part of the sternum just above the level of the main pulmonary artery was obtained. According to the CT images at these points, a rating between 0 and 5 points was made. (Table 1) The images that did not show any signs of healing and where the clearance between the bony plates was clearly observed got zero points. A score of 1 was given to images where two bone collars were seen in the same plane, but there was a weak healing and the bridging bone structure was not observed yet. 3 points were given to the immature bridging in the bone structure with a slight improvement. 4 points were given to the images showing regional union in the bone where the bridging bone structure was visible. The images in which the bone tissue fused completely together and the bridging bone structure was clearly observed were evaluated as 5 points. All images were evaluated using the described scoring system by a radiologist, an orthopaedist, and a cardiovascular surgeon without knowing which group the images belong to. An average sternum healing score was determined for each patient by taking the average of the observations of the evaluators at each point. 3 points where bridging started to be monitored was accepted as the threshold value of sternal healing. The kappa test was used to evaluate the interobserver agreement of the CT imaging method.

Table1. Sternal Healing Score

0 point	No signs of healing, no union in bone tissues, sternal separation is seen
1 point	Minimal improvement, sternal detachment, lack of bridging bone
2 points	mild healing (sternal separation with hazy, immature bone formation)
3 points	moderate healing (partial bridging bone indicative of sternal stability)
4 points	partial synthesis (significant bridging bone)
5 points	complete synthesis (complete bridging bone)

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 20.0 software (IBM SPSS Inc., Chicago, USA). Continuous variables shown to have abnormal distribution were log-transformed before deeper statistical analysis. Qualitative variables were expressed in numerical and percentage values. Continuous variables were expressed as mean and standard deviation values. The one-way ANOVA test was used when comparing the mean and standard deviation values of the continuous variables of the patients in all three groups. Mutual comparisons between groups were made using Tukey's post hoc analysis method. A significant P value was considered as <0.05.

Results

A total of 120 patients in three groups, including 40 patients in each group, were included in the study according to the serum 25(OH)D level in the samples taken preoperatively. All of the patients completed their clinical and radiological follow-ups for six months. Clinically significant sternal dehiscence and mediastinitis were not observed in any patient in any of the groups. When all patients were compared in terms of age, gender, body mass index (BMI), left ventricular ejection fraction, diabetes mellitus (DM), peripheral vascular disease, cerebrovascular disease, hypertension, and osteoporosis, no significant difference was observed between the groups. When the numbers of distal anastomoses performed during the operation, cross-clamp, total cardiopulmonary bypass, and total operation times were compared, there was no significant difference between the groups. Postoperative follow-up times in the mechanical ventilator, intensive care, and hospital stay were similar. None of the patients included in the study were re-operated for bleeding or any other reason during the 6-month follow-up period. No mortality was observed in any of the patients during this period. Demographic data, intraoperative data, and postoperative results of the subjects in all three groups are summarized in Table 2.

Some patients had serum 25(OH)D levels close to the breakpoints between groups. We also re-evaluated 25(OH)D levels at the time we performed imaging of the patients. At the third month follow-up, four patients from group 2 were found to have group 1 values. Similarly, it was found that three patients from group 3 decreased to group 2 values. At the sixth month control, it was observed that two patients from group 2 had group 1 values, while two patients from group 3 decreased to group 2 values. Although some of the patients had an increase in 25(OH)D levels, they did not fall within the value ranges of other groups. Even though we detected these transitions, we continued to evaluate the patients in the groups we determined before the operation.

Table 2. Baseline demographic-intraoperative data and postoperative results

		Group 1 Deficient Vitamin D Status (n = 40)	Group 2 Insufficient Vitamin D Status (n= 40)	Group 3 Sufficient Vitamin D Status (n = 40)	P Value
Demographic Data					
Age, Y		62.8 ± 4.1	63.1 ± 3.7	62.3 ± 2.9	0.482
Sex, n (%)	Male	25 (62.5 %)	22 (55 %)	26 (65 %)	0.754
	Female	15 (37.5 %)	18 (45 %)	14 (35 %)	0.354
Mean 25(OH)D level, ng/ml		14.7 (7.6-18.9)	26.1 (20.1-29.5)	39.8 (32-56)	<0.001
Body Mass Index, kg/m2		26.1 ± 2.1	25.8 ± 2.4	26.3 ± 2.4	0.812
LVEF, %		62.4 ± 12.8	64.2 ± 10.1	64 ± 11.6	0.741
Diabetes Mellitus		14(35 %)	17 (42.5 %)	13(32.5 %)	0.124
Smoking (Current)		10 (25 %)	9 (22.5 %)	11 (27.5 %)	0.602
Chronic Obstructive Pulmonary Disease		15 (37.5 %)	16 (40 %)	15 (37.5 %)	0.240
Peripheral Vascular Disease		5 (12.5 %)	7 (17.5 %)	7 (17.5 %)	0.138
Hypertension		21 (52.5 %)	24 (60 %)	23 (57.5 %)	0.961
Cerebrovascular Disease		2 (5 %)	0	1 (2.5 %)	0.275
Osteoporosis		10 (25 %)	7 (17.5 %)		0.413
Intraoperative Data					
Mean Number of Distal Anastomosis		2.7	2.9 ± 1.2	2.8± 1.1	0.358
Cross Clamp Time (Min)		34.1 ± 4.2	35.5± 3.9	34.8± 3.8	0.105
CPB Time (Min)		63.2 ± 8.3	64.8 ± 7.1	63.9 ± 7.7	0.098
Operation Time (H) (Skin to Skin)		3.7 ± 0.8	3.8 ± 0.7	3.7 ± 0.9	0.152
Postoperative Results					
Ventilation Time		5.1 ± 2.1	4.9 ± 1.9	5.7 ± 1.1	0.142
İCU Stay (h)		21.3 ± 4.4	23.5 ± 4.7	23.6 ± 4.2	0.570
Any Rhythm Disorder (In Hospital Stay)		16 (40 %)	17 (42.5 %)	16 (40 %)	0.628
Acute Renal Failure		1 (2.5 %)	0	1 (2.5 %)	0.179
Length of stay, d		4.9 ± 1.5	5.0 ± 1.3	4.9 ± 1.3	0.067
Mortality (6 months follow up)		0	0	0	-

Fleiss's kappa coefficient value was calculated as 0.832 for the congruence of the evaluations made by four observers at five points. This value was considered as a result indicating an almost perfect agreement among the observers. When the radiological sternal healing scores in CT imaging in the 3rd month are compared Mean CT Scanning Scores (mCTss) were similar between the groups. The mCTss in groups 1 and 2 were 0.8±0.4 and 1.1±0.4, respectively. However, in group 3, the mCTss was higher than in groups 1 and 2 (1.5±0.5, p=0.012). It was observed that there was no significant difference between the groups in terms of the number of patients whose MCTss value was above 3. The proportional distribution of the scoring values in sections taken from five points taken as reference in radiological imaging is also presented in Table 3. Accordingly, the ratio of sections scoring 0 points in the third month was similar between groups 1 and 2 and between groups 2 and 3, while a significant difference was observed between groups 1 and 3 (37.1% vs. 29.5%, p=0.024). The ratio of sections scoring 1 point was not significantly different between groups 1 and 2 and between groups 2 and 3, but there was a statistically significant difference between groups 1 and 3 (26.5% vs. 21.8 p=0.029). The ratio of sections scoring 2 points was similar in all three groups. The ratio of 3-point sections was 9.5% and 11.0% in groups 1 and 2, respectively, while a higher rate was observed in group 3 (12.3% p=0.046) compared to groups 1 and 2. The ratio of the sections scoring 4 points was observed to be significantly different among all groups. The values in groups 1, 2, and 3 were 6.2%, 7.4%, and 8.9%, respectively, while the p-value was 0.014. The ratio of 5-point sections in group 1 and group 2 is 2.4% vs. 2.8% respectively, while this value in group 3 was determined as 4.2% (p=0.036).

Comparing the radiological sternal healing scores on CT imaging performed in the sixth month, mCTss was significantly higher in patients in group 3 (3.5±0.8 p=0.026) compared to patients in groups 1 and 2 (2.8±0.6 and 3.1±0.4, respectively). The number of patients with MCTss value above 3 was 24 (60%), 28 (70%), and 34 (85%) respectively, and group 3 patients were found to be statistically significantly higher than the other two groups (p<0.001). The ratio of the sections with zero points in the imaging in the sixth month, i.e., the sections where the improvement was not seen, was 11.7%, 7.3%, and 4.5%, respectively, while it was significantly higher in group 1 patients with deficient vitamin D status (p<0.001). The distribution of the sections scoring 1, 2, 3, 4, and 5 points was observed similarly in all groups at six months.

Table 3. Sternal healing scores

			Group 1 DeficientVitamin D Status (N = 40)	Group 2 Insufficient Vitamin D Status (N = 40)	Group 3 Sufficient Vitamin D Status (N = 40)	P value
3 months CT scanning	Mean CT Scanning Score		0.8 ± 0.4[b]	1.1 ± 0.4	1.5 ± 0.5[b]	0.012
	Patients with Mean CT Scanning Score ≥ 3		7 (17.5 %)	8 (20 %)	9 (22.5 %)	0.151
	Sites with CT Scan Score (CTss) (%)	0	37.1[b]	33.8	29.5[b]	0.024
		1	26.5[b]	24.4	21.8[b]	0.029
		2	18.3	20.6	23.3	0.142
		3	9.5[b]	11.0[a]	12.3[b-c]	0.046
		4	6.2[a-b]	7.4[a-c]	8.9[b-c]	0.014
		5	2.4[b]	2.8	4.2[b]	0.036
6 months CT scanning	Mean CT Scanning Score		2.8 ± 0.6[b]	3.1 ± 0.4	3.5 ± 0.8[b]	0.026
	Patients with Mean CT Scanning Score ≥ 3		24 (60 %)[b]	28 (70 %)[c]	34 (85 %)[b-c]	<0.001
	Sites with CT Scan Score (CTss) (%)	0	11.7[a-b]	7.3[a]	4.5[b]	<0.001
		1	6.6	9.1	5.1	0.095
		2	3.8	5.2	6.9	0.153
		3	19.3	16.7	18.3	0.121
		4	27.2	29.6	30.5	0.351
		5	31.4	32.1	36.7	0.541

One-way analysis (ANOVA) of variances
a-The post hoc analysis revealed a difference between group 1 and group 2.
b-The post hoc analysis revealed a difference between group 1 and group 3.
c-The post hoc analysis revealed a difference between group 2 and group 3.
P value less than 0.05 is considered statistically significant

Discussion

The results of our study showed that there is a correlation between vitamin D level and sternum healing, especially in the first three months. To the best of our knowledge, our study is the first to demonstrate this relationship radiologically.

The metabolic role of vitamin D in bone healing, mineralization, and quality is essential. Bone tissue healing is classified into four basic processes. These are inflammation, soft callus formation, hard callus formation, and remodelling stages, respectively [12]. The healthy progress of these processes is as important as mechanical stabilization for bone healing. Some contradictory results have been reported in the literature regarding the relationship between inflammation and vitamin D [13,14]. The inflammation process takes place in the first 7-10 days period [15]. With the results of our study, it is not possible to make a healthy inference about the role of vitamin D in the inflammation phase of bone healing. This first stage of bone healing cannot be evaluated with any radiological findings, and more detailed studies are needed to examine these activities, which mostly occur at the cellular level.

In the next stage, the soft callus formation stage, chondrocytes produce a cartilaginous matrix until all granulation tissue is replaced by cartilage tissue. In areas where cartilage production is insufficient, fibrous tissue formation is provided by fibroblasts. As a result, a semi-rigid fibrotic matrix called soft callus is obtained. This period corresponds to 2-3 weeks of recovery. The proliferation and differentiation of costochondritis and fibroblasts responsible for the production of this fibrous tissue are triggered by some growth factors such as IGF-1 [16]. Ameri et al. showed the positive effect of vitamin D on the IGF-1 release in a study they conducted [17]. In another study, it was reported that vitamin D deficiency led to a decrease in the release of growth factors [18]. The results of our study showed that patients with sufficient vitamin D have a healthier healing process in these first two stages. Fault-free maintenance of inflammation and soft callus formation before the beginning of mineralization metabolism will create a basis for the healthy progress of the subsequent processes (hard callus formation and remodelling).

The role of mineralization is vital, especially in the hard callus formation and remodelling phases. Although vitamin D plays a role in all stages at the cellular level, its role in bone healing is observed even more in these two stages. The hard callus formation phase, the osteogenic differentiation of osteoblasts, osteopontin, osteocalcin (non-collagen matrix proteins), and collagen synthesis by osteoblasts are vitamin D-modulated processes [15]. Hard callus formation takes place between 4-16 weeks following fixation of the bone [19]. With the formation of hard callus, bridging bone is expected to be seen in the sternum [20].

In a study by Ghiasi et al., they showed that the remodelling phase continues for months or even years [21].

Median sternotomy is the largest controlled bone incision made to access a cavity among conventional surgical techniques. Similarly, the incidence of complications associated with sternotomy incision increases as a result of cardiac surgery operations being performed more and more, especially on elderly patients. Although many minimally invasive methods have been developed to avoid all these risks, sternotomy remains almost as standard in cardiac surgery. The fact that many of the mentioned complications can increase morbidity and mortality independently of the pathologies related to the coronary artery, heart valves, or aorta, which are the main purpose of the operation, is proof of how carefully the sternotomy must be managed. In a radiological study by Bitkover et al., although no complications were observed in the patients, they reported that complete recovery was almost not observed in the first three months and that complete recovery was observed only in 50% of the patients in the sixth-month imaging [22]. However, it is difficult to make a healthy comparison since this study was designed retrospectively and CT was performed only in patients who were considered to be dehisced. Nevertheless, in the results of our study, bridging bone formation, which is accepted as a sign of healing, was observed to be at most 22.5% in all patient groups in the first three months. When considered from this point of view, it was seen that there was no difference between the groups. The prospective design of our study was able to process the healing data of bone tissue in a more refined manner with different 5-point healing scores. The cut-off mCTss value of sternal healing was accepted as 3. This value is equivalent to monitoring the bridging structure at any point. The number of patients with mCTss ≥ 3 in all three groups in the third-month images was similar. However, it was observed that as the 25(OH)D level increased, the mCTss values of the patients were gradually better. The number of sections with CTss values of 2 or less in the third month was observed more in group 1 than in the other groups. The proportion of regions scored 4 and above was also observed to be significantly increased with the 25(OH)D level. By the sixth month, a more homogeneous distribution was observed between the recovery scores and it was observed that there was no clear difference between the groups. The reason for this can be accepted as the fact that bone healing has now passed to the hard callus phase. However, when mCTss values were compared in order to evaluate the whole sternum bone as a whole, a significant increase was observed from the first group to the third group. With these data, it can be concluded that this healing process is still continuing even in the sternum, which we now consider as a complete union. In addition, the number of patients with mCTss ≥ 3 was higher in groups 2 and 3, respectively, in parallel with the 25(OH)D level.

The results of this study showed that patients with pre-operative vitamin D deficiency had a radiologically detectable decrease in bone healing. In cases to be operated with a median sternotomy, vitamin D levels should be considered before and after the operation. In patients with vitamin d deficiency, vitamin D-rich foods should be intake and vitamin D supplements should be given. There is not yet a sufficient study in the literature examining the effect of vitamin D supplementation on bone healing after any cardiac surgery. Obesity, COPD, osteoporosis, advanced age and patient incompatibility play an important role in bone union, especially after sternotomy. Especially in this group of patients, careful evaluation should be made in terms of vitamin D levels. Patients with bone metabolism disorders such as osteoporosis were not included in our study. Evaluating the results of vitamin D supplementation in these risk groups with further studies will make important contributions to the literature. Therefore, further studies are required to clarify these assumptions.

Limitations of The Study

Our study had some limitations. This study has been carried out in a single center with a limited number of patients. The patients included in the study were grouped according to the vitamin d values before the operation and also assessed in this group during the follow-up. However, some patients had limit values for vitamin d levels. Some of these patients have a change in the status of vitamin d level during the follow-up period. These changes have overall been observed as a decrease in vitamin d level. We consider the main reason under this situation is the patient behaviour during recovery period. Since the patients have a habit to be insulated from the environment in this period, the lack of sun contact can explain this situation. Larger patient groups and multi-center studies are needed in the future to explore the relationship of vitamin d and bone healing after sternotomy.

Conclusion

Ultimately, the results of our study showed that sternal bone healing in the first three months had a positive relationship with vitamin D levels. This relationship continued in a weaker manner in the following months, without creating clinically significant negativity in the recovery processes of the patients. Although every stage of the healing process is critical, soft callus formation filling the sternal space and preparing the ground for bone mineralization is especially the most critical period. Passing this phase without any damage is essential for hard callus formation. In the bone that has developed hard callus formation and the sternal space is filled with calcium minerals, the remodelling phase will begin, which can last for years. At this point, in our patient group, the performance of patients without vitamin D deficiency was more successful in callus formation processes.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The local ethical committee approved our study protocol numbered 104, dated October 2, 2020.

References

1. Julian OC, Lopez-Belio M, Dye WS, et al. The median sternal incision in intracardiac surgery with extracorporeal circulation: A general evaluation of its use in heart surgery. Surgery. 1957;42:753–61.
2. Gatti G, Benussi B, Brunetti D, et al. The fate of patients having deep sternal infection after bilateral internal thoracic artery grafting in the negative pressure wound therapy era. Int J Cardiol. 2018;269:67–74.
3. Bonacchi M, Prifti E, Bugetti M, et al. Deep sternal infections after in situ bilateral internal thoracic artery grafting for left ventricular myocardial revascularization: Predictors and influence on 20-year outcomes. J Thoracic Dis. 2018;10:5208–21.
4. Reser D, Caliskan E, Tolboom H, et al. Median Sternotomy. Multimedia manual of cardiothoracic surgery. MMCTS. 2015;2015.
5. Brandenburg VM, Vervloet MG, Marx N. The role of vitamin D in cardiovascular disease: From present evidence to future perspectives. Vol. 225, Atherosclerosis. 2012. p. 253–63.
6. Skaaby T, Thuesen BH, Linneberg A. Vitamin D, cardiovascular disease and risk factors. Adv Exp Med Biol. 2017;996:221-30.
7. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: When to test and how to treat. Vol. 85, Mayo Clinic Proceedings. Elsevier Ltd. 2010. p.752–8.
8. Lips P, Bouillon R, van Schoor NM, et al. Reducing fracture risk with calcium and vitamin D. Clin Endocrinol (Oxf). 2010;73:277-85.
9. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metabol. (Oxf). 2011;7:1911–30.
10. Bejko J, Tarzia V, de Franceschi M, et al. Nitinol flexigrip sternal closure system and chest wound infections: Insight from a comparative analysis of complications and costs. Ann Thorac Surg. 2012;94:1848-53.
11. Raman J, Lehmann S, Zehr K, et al. Sternal closure with rigid plate fixation versus wire closure: A randomized controlled multicenter trial. Ann Thorac Surg. 2012;94:1854-61.
12. Schindeler A, McDonald MM, Bokko P, et al. Bone remodeling during fracture repair: The cellular picture. Vol. 19, Seminars in Cell and Developmental Biology. Elsevier Ltd. 2008. p. 459–66.
13. Lee BNR, Kim TH, Jun JB, et al. Upregulation of interleukin-1β production by 1,25-Dihydroxyvitamin D3 in activated human macrophages. Mol Bio Rep. 2011;38:2193–201.
14. Zarrabeitia MT, Riancho JA, Amado JA, et al. Effect of calcitriol on the secretion of prostaglandin E2, interleukin 1, and tumor necrosis factor α by human monocytes. Bone. 1992;13:185-9.
15. Gorter EA, Hamdy NAT, Appelman-Dijkstra NM, et al. The role of vitamin D in human fracture healing: A systematic review of the literature. Bone. Elsevier Inc. 2014;26:288–97.
16. Schindeler A, McDonald M, Bokko P, et al. Bone remodeling during fracture repair: The cellular picture. Elsevier. 2008;19:459-66.
17. Ameri P, Giusti A, Boschetti M, et al. Interactions between vitamin D and IGF-I: from physiology to clinical practice. Cli Endocrinol. 2013;79:457–63.
18. Bogazzi F, Rossi G, Lombardi M, et al. Vitamin D status may contribute to serum insulin-like growth factor I concentrations in healthy subjects. J Endocrinol Invest. 2011;34:200-3.
19. Anderson PH, Atkins GJ. The skeleton as an intracrine organ for vitamin D metabolism. Vol. 29. Molecular Aspects of Medicine. Pergamon. 2008. p. 397–406.
20. Wang B, He D, Wang M, et al. Analysis of sternal healing after median sternotomy in low risk patients at midterm follow-up: Retrospective cohort study from two centres. J Cardiothorac Surg. 2019;14:193.
21. Ghiasi MS, Chen J, Vaziri A, et al. Bone fracture healing in mechanobiological modeling: A review of principles and methods. Bone Rep. 2017:16;87-100.
22. Bitkover CY, Cederlund K, Åberg B, et al. Computed tomography of the sternum and mediastinum after median sternotomy. Ann Thorac Surg. 1999;68:858-63.