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Effect of Vitamin D and Calcium Supplementations on Reducing the Incidence of Hypocalcemia after Thyroidectomy

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Abstract: Hypocalcemia is a frequent complication after total thyroidectomy. Despite the different methods to evaluate and predict postoperative hypocalcemia, there is no consensus on the role of calcium and/or vitamin D supplementation following thyroidectomy. The objectives of this study was to evaluate the potential role of potential role of calcium and vitamin D supplementation for the prevention of post-thyroidectomy hypocalcemia and to draw therapy guidelines that may prevent this common complication. The study was done from March 2016 to May 2017, thirty consecutive patients who underwent total or hemi-thyroidectomy were included. They were received oral calcium carbonate (1300 mg/day) and vitamin D3 (600 IU/day) postoperative surgery, Symptoms and signs of hypocalcemia were monitored. The level of vitamin D3, calcium and other biomedical variables were measured pre- and post- operatively at 30 day and 90 days after thyroidectomy and compared statistically by a t-test, Chi-Square test and Mann-Whitney U test. Serum calcium level <2 mmol/L was considered as laboratory hypocalcemia. Results showed that, vitamin D3 and parathyroid hormone levels were increased significantly in postoperative follow-up (30 and 90 d after thyroidectomy). On the other side, thyroid-stimulating hormone (TSH), triiodothyronine and thyroglobulin were decreased significantly in postoperative (30 and 90 d after thyroidectomy). In conclusion calcium and vitamin D3 supplementation can significantly reduce postoperative thyroidectomy hypocalcemia.

Key words: Vitamin D-Hypocalcemia · Thyroidectomy · Calcium · Supplementations

INTRODUCTION

Vitamin D3 is a fat-soluble vitamin that is naturally present in very few foods and available as a dietary supplement. It promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic-tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D3 sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis [1]. Vitamin D3 (cholecalciferol) is synthesized in the human skin from 7-dehydrocholesterol upon exposure to ultraviolet (UV) radiation from sunlight. Vitamin D2 (ergocalciferol) is a vitamin D analog photosynthesized in plants, mushrooms and yeasts; it is also sometimes used in vitamin D food fortification. When vitamin D3 in skin is inadequate due to insufficient exposure to UV radiation, oral intake of vitamin D is necessary to meet vitamin D requirements [2].

Vitamin D can regulate cell differentiation and growth by binding to the vitamin D receptor found in most body cells. Observational study has reported associations between low sun exposure, poor vitamin D status and increased risk of developing colorectal and breast cancer [2]. Various observational studies have reported an association between vitamin D status and the susceptibility or severity of autoimmune diseases, including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus [3]. Hypocalcemia is the most common complication after thyroid surgery [4]. Low postoperative serum calcium has been attributed to transient hypo-parathyroidism due to intra-operative injury to the adjacent parathyroid tissue or its blood supply [5-8]. Hypocalcemia is a well-known complication and concern following thyroid surgery.

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Although in most cases it is only temporary, post-thyroidectomy hypocalcemia can lead to an increased cost by prolonging the length of stay and increasing the need for expensive medications, frequent biomedical tests and multiple outpatient visits [9]. The incidence of transient hypocalcemia has been estimated to occur between 3% to 30% of cases even after preservation of one or more parathyroids [10]. Permanent hypocalcaemia, although much less frequent, still occurs, with an incidence of around 2-4% reported in the literature.

Thyroidectomy is one of the most common head and neck surgical procedures performed worldwide [11]. Although trauma to the parathyroid glands during surgery is likely the most important factor in developing significant postoperative hypocalcemia. Recent evidence suggests that low pre-operative vitamin D status may also be a risk factor [12].

Study of patients undergoing hemi thyroidectomy revealed that changes in vitamin D metabolism could occur even in the absence of total thyroidectomy. Although hospital readmission is rare after thyroidectomy, hypocalcaemia remains the most common reason for readmission. The ability to predict which patients will develop hypocalcaemia has been challenging [13]. Traditionally, serum or ionized calcium levels are evaluated on the evening of surgery and again on postoperative day 1 to evaluate for low calcium. However, symptomatic hypocalcemia can frequently occur 48 to 72 hours after discharge. Discharging patients on calcium supplementation has been endorsed as a means to reduce symptomatic hypocalcemia [14]. Therefore, the aim of this study was to evaluate the clinical usefulness postoperative oral vitamin D and calcium supplements in the prevention of hypocalcemia after thyroidectomy.

MATERIAL AND METHODS

Subjects: Thirty consecutive patients from March 2016 to May 2017, recruited from KAU Hospital in Jeddah, Saudi Arabia were included. Comparable attributes to the study group was chosen, postoperative follow-up was up to 3 months. The patients who did not continue throughout the postoperative follow-up (90 d after thyroidectomy) were excluded from the this study. All participants had different indications of undergoing thyroidectomy (hemi- or total thyroidectomy).

Inclusion Criteria: Subjects must meet the following requirements to be selected for the current study. Initial screening subjects must be adult between the ages of 18 to 75 years of age at the time when the blood samples were taken, patients undergoing thyroidectomy, free from metabolic bone diseases, diabetes mellitus, cardiovascular disease, renal or hepatic disease, absence of chronic diseases that could affect vitamin D metabolism, endocrine and autoimmune disease.

Exclusion Criterion: Subjects less than 18 years, the presence of metabolic bone diseases, diabetes mellitus, cardiovascular disease, renal, hepatic, endocrine disease and autoimmune disease. The participants not willing to provide blood samples and presence of diseases that could affect vitamin D metabolism.

Anthropometric Measurements: Body weight and height were recorded using a calibrated Seca scale and cotton ruler, respectively. The BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Calcium and Vitamin D3 Supplementation: The study group was supplemented with calcium and vitamin D3. They received oral calcium carbonate (1300 mg/day) and vitamin D3 (600 IU/day) postoperative surgery, according to the management of medical supervision. The duration of calcium and vitamin D3 supplementation was estimated by the treating physician for 3 months.

Biomedical Measurements: Blood samples were obtained from patients who consented to enter the study. They were collected postoperatively (one and three months after thyroidectomy) to indicate the level of vitamin D3, calcium (Ca), parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), total triiodothyronine (T3), total thyroxine (T4), albumin (Alb) and thyroglobulin (Tg).

Statistical Analysis: Results were presented as Mean ± SD and comparisons were performed using the T-test, the Chi-Square (x^2) test and the Mann-Whitney U test, depending on the type of data included in the analysis. The p value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 20 statistical package.

RESULTS

Characteristics of the volunteered patients were illustrated in Table (1) Our patients participants were adults and categorized into 4 age groups with 30 % from participants located into group of 41 to 50 years old, while 26.7% from participants had 31 to 40 years old and as well

Table 1: Characteristics of the patients participants

Variable (n = 30)		Number	%
Age	18 to 30 years	5	16.7
	31 to 40 years	8	26.7
	41 to 50 years	9	30.0
	> 51 years	8	26.7
	Total	30	100
Gender	Male	5	16.7
	Female	25	83.3
Thyroidectomy type	Total thyroidectomy	25	83.3
	Hemithyroidectomy	5	16.7
Anthropometric measurements		Mean	SD
Weight, Kg		69.76	16.39
Height, m		160.96	8.63
BMI, Kg/m^2		26.91	5.77

BMI, body mass index. SD, standard deviation.

as 26.7% had more than 51 years old. Last age group had 18 to 30 years old with 16.7%. The data also showed that females were 83.3% from total participants and only 16.7% were males. Related to anthropometric measurements, the mean and SD for weight was 69.76 ± 16.39 and for height was 160.96 ± 8.63, therefore, BMI mean and SD was 26.91 ± 5.77.

Table (2) demonstrated the level of vitamin D3, regards to preoperative and postoperative follow-up (30 d and 90 d after thyroidectomy) measurements. There was a significant differences in vitamin D_3 level between pre- and postoperative (30 d) and between pre- and postoperative (90 d), where the concentration in postoperative (90 d) higher than postoperative (30 d).

The level of Ca regards to pre- and postoperative follow-up measurements. There was no difference between pre-and postoperative (30 d) in related to calcium level. However, postoperative (90 d) concentration was higher than postoperative (30 d), both of them were higher than preoperative. There was significant differences ($p <$ 0.003) between postoperative (90 d) and preoperative. Parathyroid hormone (PTH) was significantly higher in postoperative follow-up (30 and 90 d) than preoperative ($p < 0.000$) in patients. On the other side, TSH, T3 and Tg were significantly lower, while T4 and albumin were significantly higher in postoperative (30 and 90 d) compared to preoperative ($p < 0.05$).

The relation between thyroidectomy type and all tested biochemical parameters level were studied and illustrated according to pre- and postoperative follow-up (30 and 90 day) Table (3). The data were analyzed using Mann-Whitney U and illustrated no significant differences.

Table 2. Serum biochemical measurements level in pre-and postoperative patients

Biomedical measurements		Preoperative	Postoperative 30 D	Postoperative 90 D	*P*-value*	*P*-value**
Vit D_3 (pmol/L)	Mean	42.61	53.59	74.49	0.001	0.000
	SD	27.26	24.96	34.20		
Ca (mmol/L)	Mean	2.15	2.10	2.35	0.402	0.003
	SD	0.29	0.18	0.18		
PTH (ng/L)	Mean	8.53	14.16	20.93	0.000	0.000
	SD	1.23	2.19	2.45		
TSH (μU/L)	Mean	2.44	1.77	1.47	0.002	0.026
	SD	2.46	1.62	1.22		
T3 (nmol/L)	Mean	7.09	3.83	3.76	0.045	0.000
	SD	10.66	1.63	1.02		
T4 (nmol/L)	Mean	155.75	169.14	165.15	0.036	0.037
	SD	24.20	23.81	40.16		
Alb (g/L)	Mean	31.00	36.40	40.17	0.047	0.002
	SD	14.31	4.00	3.83		
Tg (μg/L)	Mean	16.71	2.03	1.75	0.000	0.000
	SD	2.97	4.52	4.68		

* Paired t-test between preoperative and postoperative (30 d after thyroidectomy)

** Paired t-test between preoperative and postoperative (90 d after thyroidectomy)

Table 3: Relationship between type of thyroidectomy and all biomedical measurements in pre- and postoperative patients

Parameter			Total thyroidectomy (n=25)	Hemi thyroidectomy (n=5)	Mann-Whitney U	*P*-value
Vit. D	Pre-		15.64	14.80	59.00	0.845
	Post-	30 d	15.58	15.10	60.50	0.911
		90 d	15.66	14.70	58.50	0.824
Ca	Pre-		15.84	13.80	54.00	0.636
	Post-	30 d	15.50	15.50	62.50	1.000
		90 d	15.48	15.60	62.00	0.978
PTH	Pre-		14.90	18.50	47.50	0.403
	Post-	30 d	15.50	15.50	62.50	1.000
		90 d	16.26	11.70	43.50	0.290
TSH	Pre-		16.22	11.90	44.50	0.316
	Post-	30 d	16.10	12.50	47.50	0.403
		90 d	15.52	15.40	62.00	0.978
T3	Pre-		15.82	13.90	54.50	0.656
	Post-	30 d	14.46	20.70	36.50	0.147
		90 d	14.88	18.60	47.00	0.387
T4	Pre-		15.88	13.60	53.00	0.596
	Post-	30 d	15.90	13.50	52.50	0.576
		90 d	16.38	11.10	40.50	0.220
Alb	Pre-		14.58	20.10	39.50	0.199
	Post-	30 d	15.38	16.10	59.50	0.867
		90 d	15.18	17.10	54.50	0.651
Tg	Pre-		15.10	17.50	52.50	0.578
	Post-	30 d	15.20	17.00	55.00	0.676
		90 d	15.04	17.80	51.00	0.521

DISCUSSION

Hypocalcemia is one of the most common postoperative complications following thyroid surgery in clinical practice. The occurrence of hypocalcemia is mainly attributed to hypoparathyroidism when parathyroid glands are devascularized, injured, or dissected during the surgery. The objectives of this study were to evaluate the potential role of calcium and vitamin D supplementation for the prevention of post-thyroidectomy hypocalcemia and to draw therapy guidelines that may prevent these common complications.

In our study the age of the patient (n = 30) calcified to 18 to > 51 years, patients > 30 years (83 %) and < 30 years (17 %). The present study showed highest incidence in adult, which is similar to the study conducted by Rosa *et al*. [15] and Kumar *et al.* [16]. This might be due to difference in presentation of benign Goitre, papillary and follicular Carcinoma. Male to female ratio in the present study, which was 1:5, similar to other studies where the male to female ratio was between 1:3.3 to 1:5.25 [17, 18], or higher as found by Kumar *et al*. [16] (1:6.5). This might be due to increased incidence of thyroid disease in women.

Our data illustrated that there were no significant differences by using Mann-Whitney U between the thyroidectomy type or gender and both of vit D, Ca, PTH, TSH, T3, T4, Alb and tg in relation to pre- and postoperative follow-up (30 and 90 d), that may be due to the small sample size and it would be constructive to include more patients in groups. The duration of calcium and vitamin D3 supplementations was estimated for 3 months, this is the minimal duration of treatment and the follow-up would be extended to six months, as recommended previously by Perros *et al.* [19], Bollerslev *et al.* [20], Terris *et al*. [21] and Stacks *et al.* [22].

Our results have shown that the early oral supplementations for asymptomatic hypocalcaemia with calcium and vitamin D supplements adjust the serum calcium and level above 2 mmol/L, in our postoperative patients (30 and 90 d), compared to laboratory reference values (2.2–2.6 mmol/liter) [23]. While vitamin D level varied significantly in comparison between pre- and postoperative to reach the normal level 60-108 pmol/L [23]. This may be explained by the adjustment of parathyroid hormone (PTH). The 3 main calcium-regulating hormones are PTH, vitamin D and calcitonin through their specific effects on the bowel, kidneys and skeleton [24,25].Inadequate vitamin D levels lead to a reduction in gastrointestinal calcium absorption up to 50%, resulting in only 10-15% of dietary intestinal calcium being absorbed [26]. It is likely that low normal calcium level was the result of vitamin D deficiency, which itself has been shown to be one of the factors associated with postoperative hypocalcemia [12].

Our results found that postoperative serum calcium level was associated with preoperative calcium level and nature of thyroid function. Nevertheless, preoperative vitamin D3 was low and increased significantly postoperative to reach the laboratory reference values 30 d after thyroidectomy. However, preoperative serum calcium was the only independent association of postoperative hypocalcemia. However, the effect of preoperative calcium and vitamin D has seldom been tested. Docimo *et al*. [27] supplemented fifty consecutive patients undergoing total thyroidectomy with pre and post-operative calcium and Vitamin D. The results showed that the incidence of symptomatic hypocalcemia had been 6% and that of laboratory hypocalcemia had been 10%.

In another prospective study, patients with Graves' disease managed over a 9 month period took 1 g of calcium carbonate three times a day for 2 weeks before total thyroidectomy. Postoperatively, patients with untreated Graves' disease had lower serum calcium levels than pretreated patients or control subjects without Graves' disease. This study had a disadvantage that population was limited to patients with Graves' disease only [28].

In our study, the dosage and duration of calcium and vitamin D intake were also of concern. Oral calcium 1300 mg/day and 600 IU/day vitamin D3 were given postoperatively. In the study by Moore [29], patients were given oral calcium on an empirical basis as 5 g/day for 2 weeks. On this dose, one elderly patient became lethargic and developed hypercalcemia. In the trial conducted by Bellantone *et al*. [30] the dosage of calcium was 3 g/day and vitamin D was 1 µg/day for 7 days after surgery and it did not lead to any complications.

Hence, our result suggests the role of postoperative oral calcium and vitamin D supplements in avoiding the incidence and severity of hypocalcemia after thyroidectomy. Our results are in agreement with Jaan *et al*. [31] results, who concluded that routine post total thyroidectomy calcium and vitamin D supplementation can significantly reduce postoperative hypocalcemia. The same authors also found that it does not completely eliminate the occurrence of postoperative hypocalcemia in one group of patients, they explained that by the small sample size and it would be constructive to include more patients.

Generally, our results were in agreement with Tartaglia *et al*. [32] who demonstrated that oral administration of calcitriol and calcium salts after total thyroidectomy significantly decreased the risk of severe postoperative hypocalcemia. Pisaniello *et al*. [33] and Alhefdhi *et al*. [34] concluded that early and combined oral administration of both calcium and vitamin D seemed to have major efficacy in preventing and treating postoperative hypocalcemia, demonstrating mean serum calcium levels higher than those of patients who received only oral calcium administration.

The PTH control calcium, phosphorus and vitamin D levels in the blood and regulate bone growth. In brief, PTH increases the calcium concentration in the blood by reducing the excretion of calcium though the kidneys and increasing the influx of calcium from the skeleton [35]. Our patients results indicated that PTH level was (8.53 ± 1.23 ng/liter) at preoperative stage, followed by significant increasing (14.16 ± 2.19 and 20.93 ± 2.45 ng/liter, postoperative 30 and 90 d, respectively) in comparison to the laboratory reference values (10–60 ng/liter).

In our study, the serum calcium and PTH levels at postoperative follow-up 30 d after thyroidectomy were in agreement with Roh and Park [36] (2.3 ± 0.32 mmol Ca /liter and 33.4 ± 30.2 ng PTH /liter, respectively) and (2.22 ±0.1 mmol Ca /liter and 30.2 ± 10.6 ng PTH /liter, respectively) who given oral calcium and vitamin D supplementation (calcium 3 g/day + vitamin D 1 g/day for 2 weeks and calcium 3 g/day + vitamin D 1µg/day, respectively), even though all values were within normal laboratory reference values limits [36]. The same authors stated that there was no significant statistical differences in serum calcium level on preoperative and postoperative follow-up (30 d after thyroidectomy). However, there was significant statistical differences for the serum PTH at postoperative follow-up 30 d after thyroidectomy.

Our results indicated that TSH level in preoperative was within the laboratory reference values range (2.44 ± 2.46 µU/L) and decreased to (1.77 ± 1.62 and 1.47 ± 1.22 µU/L postoperative follow-up (30 and 90 d after thyroidectomy), respectively) in comparison to the normal laboratory reference values range of TSH (0.35-5.5 µU/L). This finding was in the same line with Ravikumar *et al*. [37] who found that TSH level was 2.37 ± 1.16 µU/L.

In albumin level in preoperative patients was (31.00 ± 14.31 g/L) close to normal laboratory reference values range of albumin (35-55 g/L) and not significantly increased throughout follow-up 36.40 ± 4.00, 40.17 ± 3.83 g/L (postoperative follow-up (30 and 90 d after thyroidectomy), respectively). Our results are in agreed with Chisthi *et al*. [38].

In our study the results showed that, the highest level of Tg preoperative was (16.71 ± 2.97 µg/L). while it significantly decreased after thyroidectomy and throughout the follow periods to 2.03 ± 4.52 and 1.75 ±

4.68 µg/L (postoperative (30 and 90 d after thyroidectomy), respectively). In conclusion, early calcium and vitamin D supplementation had positive effects to treat hypocalcemia postoperative thyroidectomy.

REFERENCES

1. IMO, 2010. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press.
2. Cranney, C., T. Horsely, S. O'Donnell, H. Weiler, D. Ooi, S. Atkinson, L. Ward, D. Moher, D. Hanley, M. Fang, F. Yazdi, C. Garritty, M. Sampson, N. A.Tsertsvadz and V.Mamaladze, 2007. Effectiveness and safety of vitamin D in relation to bone health.. Evid. Rep. Technol. Assess., (158): 1-235.
3. Holick, M.F., 2006. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin. Proc., 81(3): 353-373. Make references like this style.
4. Cmilansky, P. and L. Mrozova, 2014. Hypocalcemia - the most common complication after total thyroidectomy. Bratisl LekListy, (3): 175-178.
5. Falk, S., 1990. Complications of Thyroid Surgery: hypocalemia, hypoparathyreoidism. New York, NY: Raven Press.
6. Reeve, T. and N.W. Thompson, 2000.Complications of thyroid surgery: how to avoid them, how to manage them and observations on their possible effect on the whole patient. World J. Surge., 24(8): 971-975.
7. Quiros, R.M., C.E. Pesce, S.M. Wilhelm, G. Djuricin and R.A. Prinz, 2005. Intraoperative parathyroid hormone levels in thyroid surgery are predictive of postoperative hypothyroidism and need for vitamin D supplementation. Am. J. Surg., 189(3): 306-309.
8. Demeester-Mirkine, N., L. Hooghe and J. Van Geertudyen, 1992. Hypocalcaemia after thyroidectomy. Arch. Surg., 127: 854.
9. Shahai, A., A. Symes and T. Jedd, 2005. Short stay thyroid surgery. Br. J. Surg., 92: 58-59.
10. Pappalardo, G., A. Guadalaxara, F.M. Frattaroli, G. Illomei and P. Falaschi, 1998. Total compared with subtotal thyroidectomy in benign nodular disease: personal series and review of published reports. Eur. J. Surg., 164(7): 501-506.
11. Jonathon O. Russell, Salem I. Noureldine, M.G. Al Khadem and R.P. Tufano, 2016. Minimally invasive and remote access thyroid surgery in the era of the American Thyroid Association guidelines Laryngoscope Investig tolaryngol, 1(6): 175-179.
12. Tripathi, M., R.K. Karwasra and S. Parshad, 2014. Effect of preoperative Vitamin D deficiency on postoperative hypocalcemia after thyroid surgery. Thyroid Res., 7: 8.
13. Puzziello, A., L. Rosato, N. Innaro, G. Orlando, N. Avenia, G. Perigli, P.G. Calò and M. De Palma, 2014. Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. Endocrine, 47(2): 537-42.
14. Tartaglia, F., A. Giuliani, S. Sorrenti, S. Tromba, A. Carbotta, G. Maturo, L. Carbotta, R. De anna, G. Merola, F. Livadoti, F. Pelle and S. Ulisse, 2016. Early discharge after total thyroidectomy: a retrospective feasibility study. G Chir, 37(6): 250-256.
15. Rosa, K.M., L.L. de Matos, C.R. Cernea, L.G. Brandao and V.J.F. de Araujo Filho, 2015. Postoperative calcium levels as a diagnostic measure for hypoparathyroidism after total thyroidectomy. Arch Endocrinal Metab., 59(5): 428-32.
16. Kumar, S., S.C. Kandhasamy, A. Sangwan, G. Gunasekaran, R. Ramasamy and S.K. Meena, 2016. Early prediction of hypocalcaemia following total thyroidectomy by serial parathyroid hormone and ionized calcium assay. International Surgery J., (3): 1611-1617.
17. Nair, C.G., M.J. Babu, R. Menon and P. Jacob, 2013. Hypocalcaemia following total thyroidectomy: an analysis of 806 patients. Indian J. Endocrinal Metab., 17(2): 298.
18. Islam, M.S., D. Paul, T. Sultana, M.Q. Rahman, Z. Rehana and A.N.N. Ahmed, 2011. Evaluation of serum calcium level measurement in total thyroidectomy patients - a prospective study in tertiary hospitals. Bangladesh J. Med. Biochem., 4(1): 4-9.
19. Perros, P., K. Boelaert, S. Colley, C. Evans, R.M. Evans and G.B.A. Gerrard, 2014. Guidelines for the management of thyroid cancer. Clinical Endocrinology, 81(Suppl;. 1): (1). 1-122.
20. Bollerslev, J., L. Rejnmark, C. Marcocci, D.M. Shoback, A. Sitges-Serra, W. van Biesen and. OM. Dekkers, 2015. European society of endocrinology clinical guideline: treatment of chronic hypoparathyroidism in adult. European J. of Surg., 173(2): 1-20.

21. Terris, D.J., S. Snyder, D. Carneiro-Pla, W.B. Inabnet, E. Kandil and L. Orloff, 2013. American Thyroid Association Surgical Affairs Committee Writing Task Force. American Thyroid Association statement on outpatient thyroidectomy. Thyroid, 23(10): 1193-1202.
22. Stacks, B.C. Jr, D.N. Bimston, D.L. Bodenner, E.M. Brett, H. Dralle, L.A. Orloff, J. Pallota, S.K. Snyder, R.J. Wong and G.W. Randolph, 2015. American Association of Clinical Endocrinologists and American College of Endocrinology Disease state clinical review: postoperative hypoparathyroidism - definitions and management. Endocrine Practice, 21(6): 674-85.
23. Kratz, A., M. Ferraro, P.M. Sluss and K.B. Lewandrowski, 2004. Normal reference laboratory values. New England J Med., 351(15): 1548-1563.
24. Cooper, M.S. and N.J. Gittoes, 2008. Diagnosis and management of hypocalcaemia. BMJ, 336: 1298-302.
25. Murphy, E. and G.R. Williams, 2009. Hypocalcaemia. Medicine, 37(9): 465-8.
26. Holick, M.F., 2007. Vitamin D deficiency. N. Engl. J. Med., 357(3): 266-81.
27. Docimo, G., S. Tolone, D. Pasquali, G. Conzo, A. D'Alessandro, G. Casalino, S. Gili, L. Brusciano, A. Gubitosi, G. Del Genio, R. Ruggiero and Docimo, 2012. Role of pre and postoperative oral calcium and Vitamin D supplements in prevention of hypocalcemia after total thyroidectomy. G. Chir., (33): 374-8.
28. Al Qahtani, A., A. Parsyan, R. Payne and R. Tabah, 2014. Parathyroid hormone levels 1 hour after thyroidectomy: An early predictor of postoperative hypocalcemia. Can. J. Surg., (57): 237-240.
29. Moore F.D. Jr, 1994. Oral calcium supplements to enhance early hospital discharge after bilateral surgical treatment of the thyroid gland or exploration of the parathyroid glands. J. Am. Coll. Surg., (178): 11-16.
30. Bellantone, R., C.P. Lombardi, M. Raffaelli, M. Boscherini, P.F. Alesina, C. De Crea, E. Traini and P. Princi, 2002. Is routine supplementation therapy (calcium and Vitamin D) useful after total thyroidectomy Surgery, 132: 1109-1112.
31. Jaan, S., A. Sehgal, R.A. Wani, M.A. Wani, K.A. Wani and B.A. Laway, 2017. Usefulness of pre and post-operative calcium and Vitamin D supplementation in prevention of hypocalcemia after total thyroidectomy: A randomized controlled trial. Indian J Endocr Metab, 21: 51-55.
32. Tartaglia, F., A. Giuliani, M. Sgueglia, F. Biancari, T. Juvonen and F.P. Campana, 2005. Randomized study on oral administration of calcitriol to prevent symptomatic hypocalcemia after total thyroidectomy. Am J Surg, 190(3): 424-429.
33. Pisaniello, D., D. Parmeggiani, A. Piatto, N. Avenia, M. d'Ajello, M. Monacelli, F. Calzolari, A.U. and P. Sperlongano, 2005. Which therapy to prevent post-thyroidectomy hypocalcemia?. Giornale di Chirurgia, 26(10): 357-361.
34. Alhefdhi, A., H. Mazeh and H. Chen, 2013. Role of Postoperative Vitamin D and/or Calcium Routine Supplementation in Preventing Hypocalcemia After Thyroidectomy: ASystematic Review and Meta-Analysis. The Oncologist, 18: 533-542.
35. Pagana, K. and T. Pagana., 2006. Mosby's Manual of Diagnostic and Laboratory Tests. 3rd ed., Publisher, St. Louis: Mosby Elsevier, pp: 409-412& 447-448. Make references like this style.
36. Roh, J.L. and C.I. Park, 2006. Routine oral calcium and vitamin D supplements for prevention of hypocalcemia after total thyroidectomy. Am. J. Surg., (192): 675-678.
37. Ravikumar, K., D. Sadacharan, S. Muthukumar, T. Sundarram, S. Periyasamy and R.V. Suresh, 2017. A Prospective Study on Role of Supplemental Oral Calcium and Vitamin D in Prevention of Post thyroidectomy Hypocalcemia. Indian J. Endocrinal Metal., 21(4): 498-503.
38. Chisthi, M.M., R.S. Nair, K.G. Kuttanchettiyar and I. Yadev, 2017. Mechanisms behind Post-Thyroidectomy Hypocalcemia: Interplay of Calcitonin, Parathormone and Albumin-A Prospective Study. J. Invest. Surgery, 30(4): 217-225.