POST-OPERATIVE SERUM PARATHYROID HORMONE LEVELS AS A PREDICTOR OF HYPOCALCEMIA IN PATIENTS UNDERGOING TOTAL THYROIDECTOMY

By

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY
IN
OTORHINOLARYNGOLOGY

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LIST OF ABBREVIATIONS

ABBREVIATIONS	EXPANDED FORM
ADHH	Autosomal dominant hypocalcemia with hypercalciuria
AIRE	Auto Immune Regulator protein
AMP	Adenosine Mono Phosphate
APECED	Autoimmune Poly Endocrinopathy Candidiasis Ectodermal Dystrophy
APS1	Autoimmune Polyglandular Syndrome type 1
AR	Autosomal Recessive
BMD	Bone Mineral Density
BUN	Blood Urea Nitrogen
CASR	Calcium Sensing Receptor
DBP	Vitamin-D Binding Protein
FAM111A	Family with sequence similarity 111 member A gene
FGF23	Fibroblast Growth Factor 23
FHH	Familial Hypocalciuric Hypercalcemia
GCM2	Glial Cell Missing transcription factor 2
GFR	Glomerular Filtration Rate
GNAS1	Guanine Nucleotide binding protein, Alpha Stimulating polypeptide 1

HDR	hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome
HRD	Hypoparathyroidism, Retardation and Dysmorphism Syndrome
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
PHP	Pseudo Hypo Parathyroidism
PPI	Proton Pump Inhibitor
PTH	Parathyroid Hormone
RLN	Recurrent Laryngeal Nerve
TCBE	Tubulin Folding Co-factor Gene
TNF	Tumor Necrosis Factor
VDDR-1	Vitamin D-Dependent Rickets type 1
VDDR-2	Vitamin D-Dependent Rickets type 2
VDR	Vitamin D Receptor

ABSTRACT

BACKGROUND:

Postoperative hypocalcemia is a common complication of total thyroidectomy and the incidence varies from 1 - 50%. Post-thyroidectomy hypocalcemia is due to parathyroid gland dysfunction, caused by devascularization, stunning or accidental removal of the glands along with the thyroid gland. Since the onset and severity of post-operative hypocalcemia is unpredictable, various attempts have been made to identify predictors of hypocalcemia. There has been an increasing interest in measuring serum parathyroid hormone (PTH) levels as an early predictor for the development of hypocalcemia after total thyroidectomy. Early detection allows for prompt supplementation of patients at risk, thus minimizing long term periodic calcium testing during follow up. Focus is placed on the timing of PTH measurement and the ability to predict which patients will develop hypocalcemia requiring supplementation.

PTH levels drawn at differing time points, ranging from intraoperatively to postoperative day 1(POD1) have been taken into consideration in the various studies done regarding Hypocalcemia post thyroidectomy. It is because of the direct relation between PTH and calcium levels in blood. But despite the association, no specific guidelines regarding the use of PTH as a predictor of hypocalcemia is available.

OBJECTIVES:

1. To estimate serum PTH levels pre operatively and at 4th and 12th hour post operatively for patients undergoing total thyroidectomy.
2. To classify above patients as high risk (PTH < 12pg/ml) or low risk (PTH > 12pg/ml), based upon a cut-off level of serum PTH.
3. To monitor and document the onset and severity of hypocalcemia in high risk group after prophylactic treatment and in low risk group without prophylactic treatment.

MATERIALS AND METHODS:

It is a prospective study conducted on 33 patients undergoing total/completion thyroidectomy from December 2018 to May 2020. The serum total calcium, albumin and PTH levels were tested on three occasions (Pre-op and 4^{th} & 12^{th} hour Post-op). Based upon Post-op 4^{th} hour cut-off for PTH as 12pg/ml patients were further classified as High (<12pg/ml) and Low risk(>12pg/ml). Between both the Post-op levels of PTH, the one with better predictability of hypocalcemia was determined.

Statistical analysis: Chi-square test was used as test of significance for qualitative data.

Continuous data was represented as mean and SD. Independent t test was used as test of significance to identify the mean difference between two quantitative variables.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram and Scatter plots.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS:

Post-op 4th hour PTH is better predictor of hypocalcemia than the Post-op 12th hour PTH, (in the post-operative period) as the association of former with serum ionized calcium level has more statistical significance than the later, (p value – 0.005 and 0.021 respectively).

CONCLUSION:

The patients who are at high risk for hypocalcemia, should be started with intravenous calcium and calcitriol supplementation. Serum PTH determination after four hours of total thyroidectomy is a relatively better predictor of hypocalcemia. and can guide selective calcium supplementation for those at high risk in the post-operative period. However, to determine the risk of Hypocalcemia at the end of 1 month of follow-up, both Post-op 4th and Post-op 12th hour PTH have similar diagnostic accuracy.

Key words: PTH (Parathyroid hormone), Thyroidectomy, Post-thyroidectomy Hypocalcemia, Parathyroid gland dysfunction.

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INTRODUCTION

Total thyroidectomy is a frequently done surgery in the department of otorhinolaryngology in our hospital. Hypocalcemia is one of the complications of thyroid surgery which can be transient (3-30%) or permanent (0.5-10.6%).[1]

Clinically significant hypocalcemia may occur within 48 hours after thyroidectomy. However latent hypocalcemia may be delayed up to 4 days after the surgery.[2]

The onset and severity of hypocalcemia following total thyroidectomy is unpredictable. In order to monitor the serum calcium post operatively, patient may require multiple blood tests. Hypocalcemia can sometimes be life threatening. Various studies have been carried out to predict the onset and severity of hypocalcemia by estimating serum Parathyroid hormone (PTH) levels following total thyroidectomy.[3]

However, there is no consensus among these studies regarding the time intervals and cut-off levels of serum PTH to predict hypocalcemia.

In this study we intend to estimate the serum PTH levels at three-time intervals for patients undergoing total thyroidectomy. These include preoperative level and postoperative levels at 4^{th} and 12^{th} hour after surgery. An attempt will be made to classify these total thyroidectomy patients as high risk or low risk for postoperative hypocalcemia after documentation and analysis of PTH cut-off levels.

This study will therefore help in identifying patients developing hypocalcemia requiring calcium and vitamin-D supplementation following total thyroidectomy.

OBJECTIVES

OBJECTIVES OF THE STUDY

1. To estimate serum PTH levels pre operatively and at 4th and 12th hour post operatively for patients undergoing total thyroidectomy.

2. To classify above patients as high risk (PTH < 12pg/ml) or low risk (PTH > 12pg/ml), based upon a cut-off level of serum PTH.

3. To monitor and document the onset and severity of hypocalcemia in high risk group after prophylactic treatment and in low risk group without prophylactic treatment.

REVIEW OF LITERATURE

THYROID GLAND

EMBRYOLOGY

During the fourth week of development, the foramen cecum develops as an endodermal thickening in the floor of the primitive pharynx at the junction between the first and second pharyngeal pouches, immediately dorsal to the aortic sac. The medial thyroid primordium derives as a ventral diverticulum at the foramen cecum. During the fourth to seventh week of gestation, this primitive thyroid tissue penetrates the underlying mesenchymal tissue and descends anterior to the hyoid bone and the laryngeal cartilages to reach its final adult pre-tracheal position. During its descent, it is first spherical, and then enlarges and becomes bilobed as it grows caudally. The proximal portion of the diverticulum (connecting the gland and the foramen cecum) retracts and forms a solid fibrous stalk early in the fifth week. This thyroglossal duct ultimately atrophies, but any portion of it may persist to become the site of a thyroglossal duct cyst. The distal portion of this duct gives rise to the pyramidal lobe in adults. The lateral thyroid primordia (from the fourth and fifth pharyngeal pouches) descend to join the central component during the fifth week of gestation.

Calcitonin-secreting parafollicular C cells arise within the ultimobranchial bodies (recognized within the lateral thyroid primordia) from neural crest cells of the fourth pharyngeal pouch. They fuse to the medial thyroid anlage during the fifth week of gestation. These cells are therefore restricted to a zone deep within the middle to upper third of the lateral lobes.

The thyroid primordium initially consists of a solid mass of endodermal cells, which later break up into a network of cords with the invasion of the surrounding mesenchyme. The epithelial cords organize into clusters of cells with a central lumen.

Follicles begin to appear at the beginning of the second month, and most follicles have been formed by the end of the fourth prenatal month. Thereafter, additional growth is by enlargement of existing follicles. By the end of the third month the gland begins to function and is able to synthesize iodothyronines.

ANATOMY

The thyroid gland derives its name from its resemblance to a shield (In Greek "thyreos" means "shield" and "eidos" means "form"). The thyroid gland weighs between 15 and 25 g in adults and comprises two lateral lobes connected by a central isthmus. Each lobe is approximately 4 cm in length, 2 cm in width, and 2 to 3 cm in thickness. The isthmus measures about 2 cm in width, 2 cm in height, and 2 to 6 mm in thickness.

A pyramidal lobe may be present in about 50% of patients, arising from either lobe or the isthmus, and is directed upward, usually to the left side.

Location

The Thyroid gland lies on the anterolateral aspect of the cervical trachea, with the isthmus related to the second, third, and fourth tracheal rings posteriorly. The superior pole lies lateral to the inferior constrictor muscle, and posterior to the sternothyroid muscle. The inferior pole extends to the levels of the fifth or sixth tracheal ring. Posteriorly and laterally the gland overlaps the carotid sheath and its contents.

The gland is enveloped by the layers of the deep cervical fascia, and is covered by the strap muscles anteriorly and the sternocleidomastoid muscle more laterally.

The true thyroid capsule is tightly adherent to the gland, and continues into the parenchyma to form fibrous septae separating the gland into lobules.

Posteriorly, the middle layer of the deep cervical fascia condenses to form the posterior suspensory ligament of Berry, connecting the lobes of the thyroid to the cricoid cartilage and the first two tracheal rings.

Vascular supply:

The blood supply to the thyroid gland is derived from two pairs of arteries. The superior thyroid artery which is described as the first branch of the external carotid artery, travels along the inferior constrictor muscle with the superior thyroid vein to supply the upper pole of the gland. In this position, the artery lies superficial to the external branch of the superior laryngeal nerve as it courses to supply the cricothyroid muscle. In 16% of cases, the superior thyroid artery may be a branch of the common carotid artery.

The larger inferior thyroid artery is a branch of the thyrocervical trunk that arises from the subclavian artery. It courses along the anterior scalene muscle, turns medially behind the common carotid artery to descend on the posterior aspect of the lateral lobes before entering the inferior thyroid pole. In its course behind the common carotid artery, the artery can have a variable relationship to the sympathetic chain. This vessel may be absent in 6% of patients.

The thyroid ima artery is inconsistently present, and can arise from the innominate artery, subclavian artery, right common carotid artery, internal mammary, or aortic arch to supply the thyroid gland near the midline. It may occasionally replace the inferior thyroid artery as one of the principle vessels supplying the gland. It is more common on the right side. Because of its relation to the anterior aspect of the trachea, the thyroid ima artery is in danger of injury during a tracheostomy.

There is a dense network of connecting vessels within the thyroid capsule, with branches passing into the connective tissue between the lobules to form extensive capillary plexuses around individual follicles.

The veins draining the capillary plexuses give rise to the inferior, middle, and superior thyroid veins. These join the internal jugular or innominate veins. The paired inferior thyroid veins lie on the anterior aspect of the trachea and anastomose freely with each other before draining into the innominate veins. They represent a potential source of bleeding during thyroidectomy or tracheostomy.

Lymphatics:

Lymphatics traveling with the superior and middle thyroid vessels drain into the upper and middle deep cervical chain nodes respectively while the Lymphatics draining with the inferior thyroid vessels empty into the lower deep cervical chain nodes and the supraclavicular, pre-tracheal, and pre-laryngeal nodes.

Nerve supply:

The thyroid gland has a predominantly sympathetic innervation, from the superior, middle, and inferior cervical ganglia.[4,5]

BRIEF HISTORICAL REVIEW

ANATOMY

In 1852, the parathyroids were described by Sir Richard Owen in a rhinoceros at London. He discovered a small compact yellow glandular body, attached to thyroid gland in an Indian rhinoceros' cadaver, preserved in London.

Virchow identified one parathyroid gland in 1863, while demonstrating structures in the cervical region of a human cadaver, but did not emphasize on the finding. A Swedish anatomist Ivar Sandstrom is credited for the discovery of the human parathyroid glands made in the year 1877, when he was 25 years of age, while working as a medical student in the Department of Anatomy in Uppsala. His is also credited for the first thorough illustration based on the identification of parathyroid glands in 43 out of 50 autopsies, performed by him. His findings which included both gross and microscopic description of the human parathyroid glands, however could be published only in 1880, several years after his remarkable discovery. [4,6]

Though the anatomy of these newly discovered structures had been reasonably well described, their physiology was not understood until much later.

EARLY STUDIES ON PHYSIOLOGY

John Clarke in 1815 described Tetany in the pediatric age group, and carpopedal spasm and glottis spasm was described by George Kellie in 1816. Steinheim, working in Germany, described tetany as “acute rheumatism” in 1830. The clinical signs of hypocalcemia like Trousseau's sign, 1862; Erb's sign, 1873; and Chvostek's sign, 1876, were named after the surgeons who described them.

Eugene Gley studied the parathyroid glands in rabbits and performed parathyroidectomy in 1891 without any morbidity. He proposed that the parathyroids were potential thyroid tissue, as he found that these glands undergo hypertrophy after thyroidectomy. [5,7]

In 1895 and 1986 Giulio Vassale and Francesco Generali found results in contrast to Eugene Gley, as they demonstrated the occurrence of tetany and myxedema after thyroid and parathyroid removal, respectively. Though the studies regarding the anatomy and physiology of the parathyroid glands proceeded slowly, clinical medicine had recognized the symptoms of parathyroid disease quite early.

In 1909, Berkeley and Beebe described correction of tetany due to hypocalcemia, with parathyroid extract, in man.[8]

In the same year, Mac Callum and Vogetlin demonstrated a much simpler method of managing tetany with intravenous calcium chloride.[9]

SURGERY

Experimental parathyroidectomies were carried out by researchers in the nineteenth century, and the first parathyroid transplant was attempted by WS Halsted in 1909, in Baltimore. He transplanted canine parathyroids into thyroid tissue and under the skin, trying both iso- and auto- transplantation. Mandl was the first surgeon to include the parathyroid glands in the category of endocrine surgery. He successfully treated a case of osteitis fibrosa by surgical removal of a parathyroid adenoma in 1925.[8,10]

PARATHYROID GLAND

DEVELOPMENT

The parathyroid glands develop from the endoderm of the third and fourth pharyngeal pouches.

Both, the Inferior parathyroids and the thymus develop from the third pharyngeal pouch between the 5^{th} -6^{th} gestational weeks, with the dorsal wing developing into the inferior parathyroid glands while the ventral wing becoming the thymus. The thymus and parathyroids both lose their connections to the pharynx at the gestational age of 7^{th} week. During the migration of inferior parathyroid glands and the thymus towards the mediastinum, they separate and the inferior parathyroid glands become localized near the inferior poles of the thyroid, and the thymus continues to migrate towards the mediastinum.

The superior parathyroid glands and the ultimobranchial bodies are derived from the dorsal wing of fourth pharyngeal pouch between the 5^{th} - 6^{th} gestational weeks. During the fifth week of development the ultimobranchial bodies detach from the pharyngeal wall and fuse with the posterior aspect of the main body of the thyroid as it descends into the neck. Later on these cells differentiate into the parafollicular cells (C cells) that secrete calcitonin.

The superior parathyroid glands have to migrate a shorter distance than the inferior parathyroid glands, which results in a relatively more constant location in the neck.

At gestational week 7, the glands lose connections with the pharynx and migrate caudally along with the thyroid gland. Because the superior parathyroid glands travel with the ultimobranchial bodies, they remain in contact with the posterior part of the upper two-thirds of the thyroid lobes and thus they migrate far less than the thymus and the inferior parathyroids. Because of the shorter migration distance, the superior parathyroid glands are in a more constant location than the inferior parathyroids.

The superior parathyroids are generally located more posterior and medial than the inferior parathyroids, and the final resting point of both superior and inferior parathyroids is usually on the dorsal surface of the thyroid gland, outside the fibrous capsule of the thyroid gland. [11]

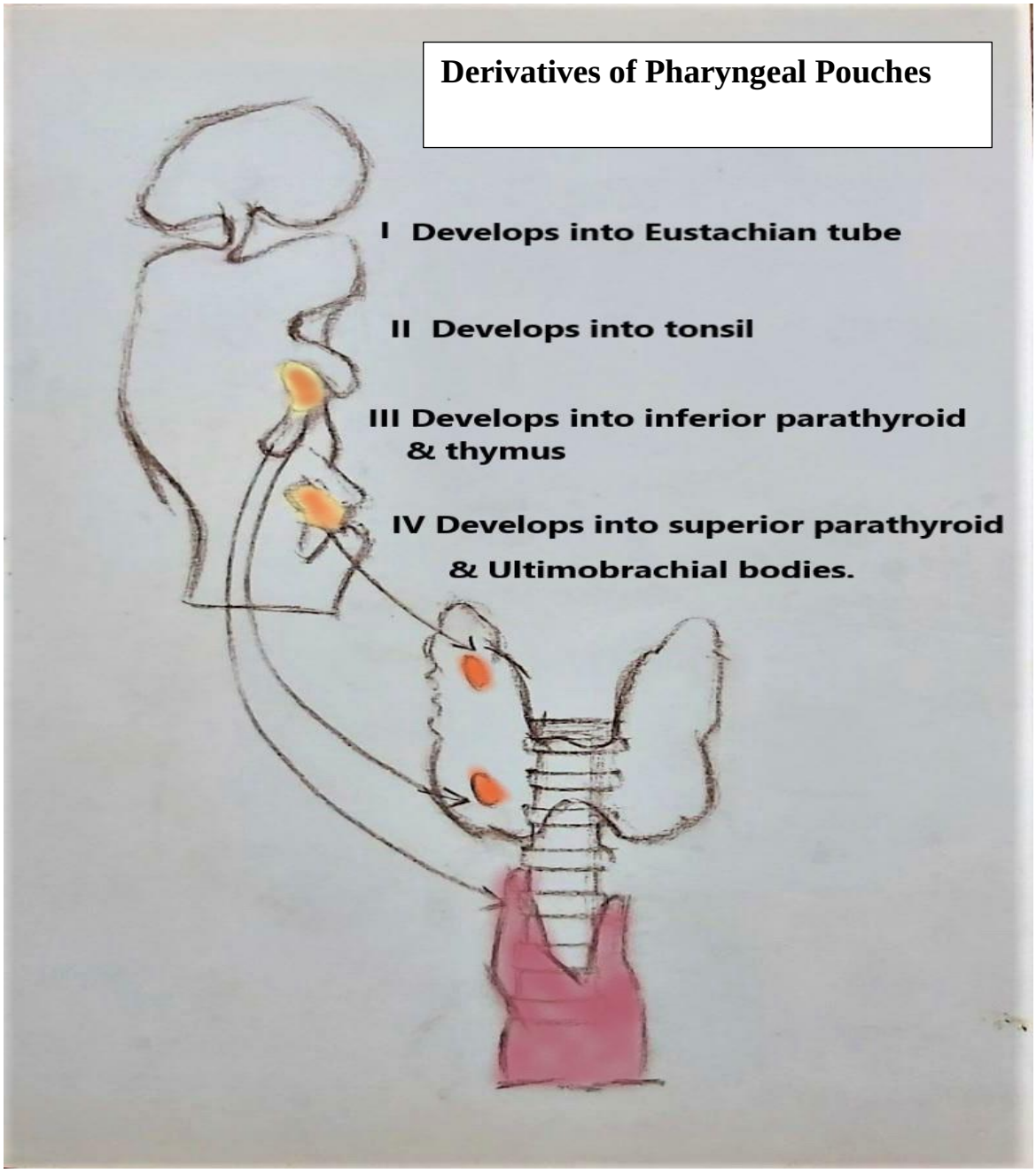


Figure 1: Development of Superior and Inferior parathyroid glands.

PARATHYROID EMBRYOLOGY- CLINICAL CORRELATIONS

There can be variation in the number and location of the parathyroid glands. 3% have less than 4 glands Accessory or supernumerary parathyroid glands are found in approximately 13% of individuals at autopsy. These glands most likely result due to tissue fragmentation that occurs during the migration of the glands rather than from an initial division of the primordia of the glands themselves.

Separation of cells from the main mass during the migratory process produces microscopic rests, or fragments, of ectopic tissue. 15-20% have ectopic glands (out of the usual locations). Rudimentary rests of parathyroid tissue can be differentiated from true supernumerary glands based on size. The former typically weighs less than 5 mg, while true supernumerary glands have an average weight of 24 mg. [12]

Primary and secondary hyperplasia may result in stimulation of embryologic fragments, resulting in the development of supernumerary glands proper.

Absence of parathyroids (i.e. < 4 glands) is noted in approximately 3% of individuals at autopsy. This absence may result from a failure of the primordia to differentiate into parathyroid glands or may be the result of parathyroid gland atrophy early in development.

Ectopic parathyroid glands occur in 15-20% of patients. The glands may be located near or even within the thyroid or thymus. If superior parathyroids do not descend entirely, they may be located as high as the bifurcation of the common carotid artery whereas, if they do not release from the thymus, they may be located intrathoracically, at the level of aortopulmonary window. Other common ectopic locations include the anterior mediastinum, posterior mediastinum, and retroesophageal and prevertebral regions.

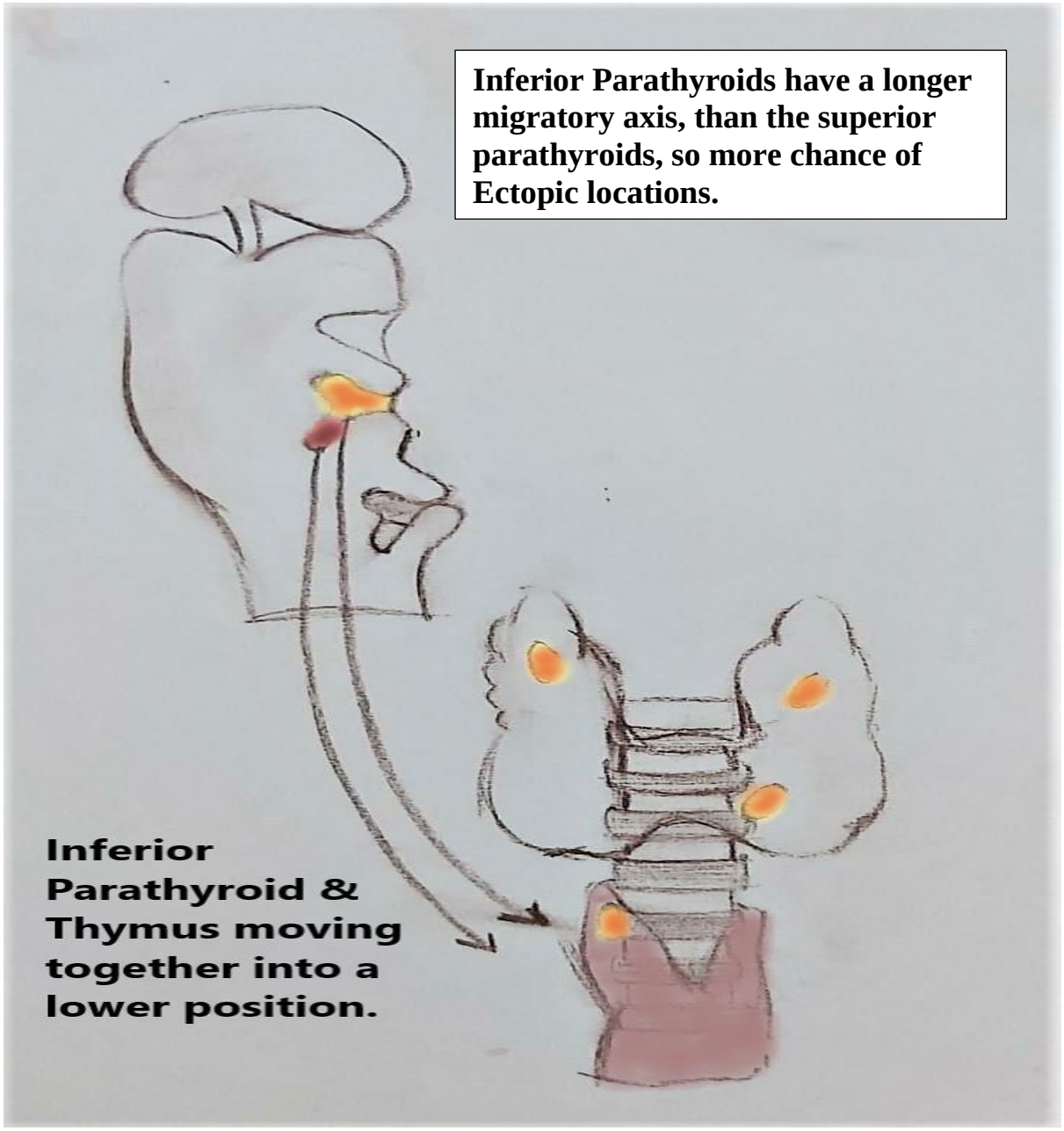


Figure 2: Descent of Inferior parathyroid gland

Ectopic location may also be acquired due to enlargement of a gland, with gravitational forces causing migration, or as a result of regional dynamics, such as laryngeal movement during swallowing or the influence of negative intrathoracic pressure. When the parathyroid glands are in an ectopic location, they are often symmetrical making localization of the glands easier.

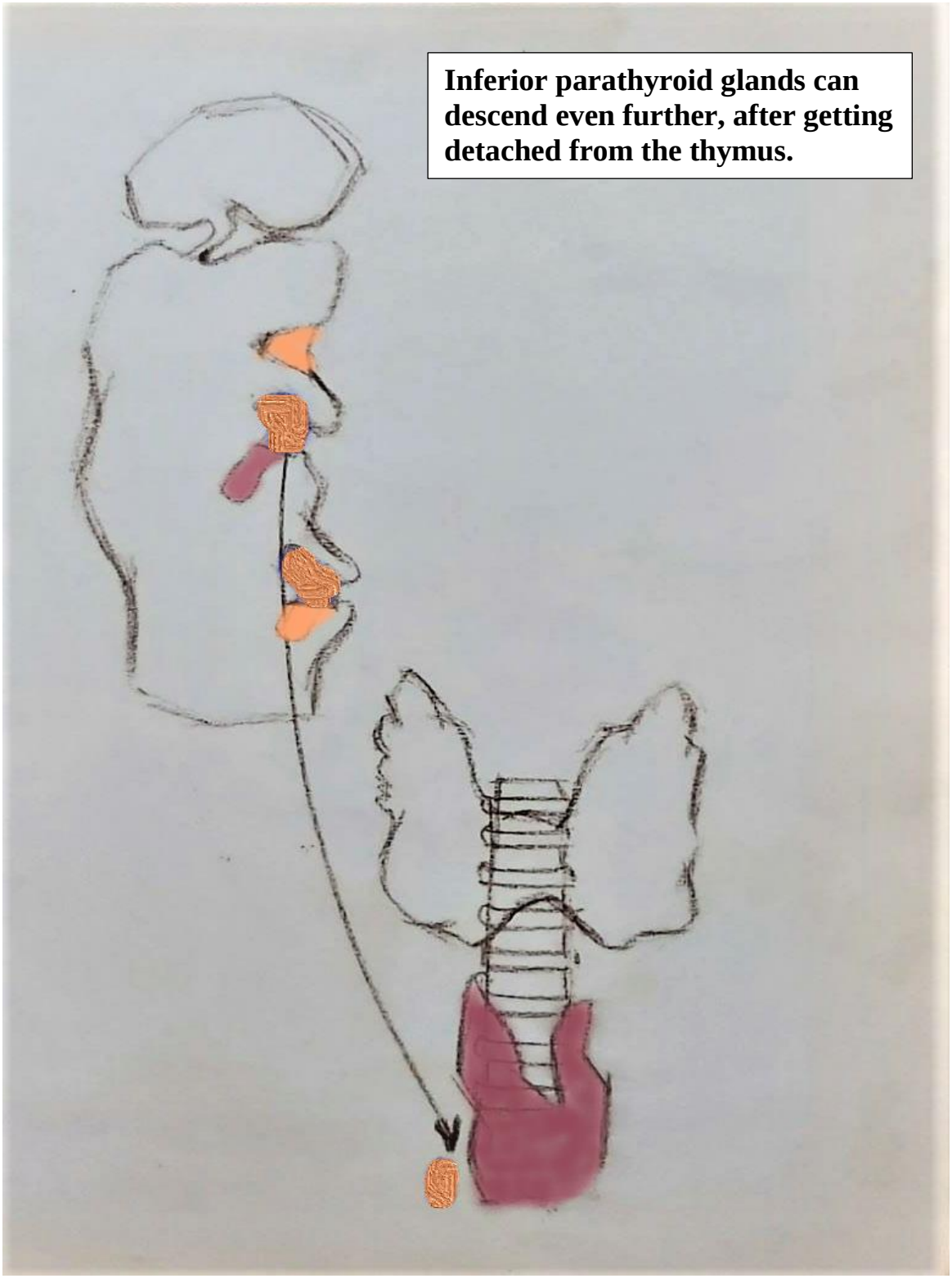


Figure 3: Ectopic location of Inferior parathyroid. This further descent of inferior parathyroid positions it in the upper mediastinum

Congenital ectopias are generally caused by anomalies in the migration of inferior parathyroids, whereas acquired ectopias usually affect superior parathyroids.

In some cases, after adhering to the thyroid capsule, the parathyroid gland can get embedded there, rather than being outside the gland. This situation results in an intrathyroidal parathyroid gland.

The underlying origin of this phenomenon has not yet been clearly defined. However, it has been concluded that superior and inferior glands and supernumerary glands can all be the source of intrathyroidal parathyroid glands.[13]

DiGeorge syndrome is the most frequent contiguous gene deletion syndrome in humans. It is an autosomal dominant condition caused by hemizygous microdeletion in the in chromosome 22q11.2, so the DiGeorge syndrome is also known as 22q11 deletion syndrome. The complete phenotype of DiGeorge syndrome includes usually asymptomatic hypocalcemia due to hypoparathyroidism (seen in 60% of cases), thymic aplasia or hypoplasia with immunodeficiency, congenital heart defects, cleft palate, dysmorphic facies, and renal abnormalities.[14]

ANATOMY

The parathyroid glands are small endocrine glands located on the posterior aspect of each thyroid lobe. These glands are caramel (golden yellow) colored and about 3-4mm in size. The shape of the glands varies from flattened to oval to bean like, and together they weigh about 20-40 mg. The parathyroids are responsible for the production of parathyroid hormone (PTH), which maintains the calcium homeostasis in the body.

Majority of people have four parathyroid glands; however, supernumerary glands and less than four glands have also been reported. Incidence of supernumerary glands in histopathology specimens can be 0.5% (6 glands), 25% (5 glands), 87% (4 glands), and 6.1% with only 3 glands. The majority of the supernumerary glands are either rudimentary or divided weighing as little as less than 5 mg and in close proximity of a normal gland.

The glands are classified into two pairs based upon their embryological development:

- Superior Parathyroids
- Inferior Parathyroids

Location:

These glands are situated, either within the fibrous capsule of the thyroid (intracapsular), or outside the capsule (extracapsular). If the parathyroids are intracapsular in location, then the tumor involving the parathyroid can expand locally within the thyroid capsule. While if it is extracapsular then the tumor growth is not constrained and may expand downwards into the mediastinum either anteriorly or posteriorly.

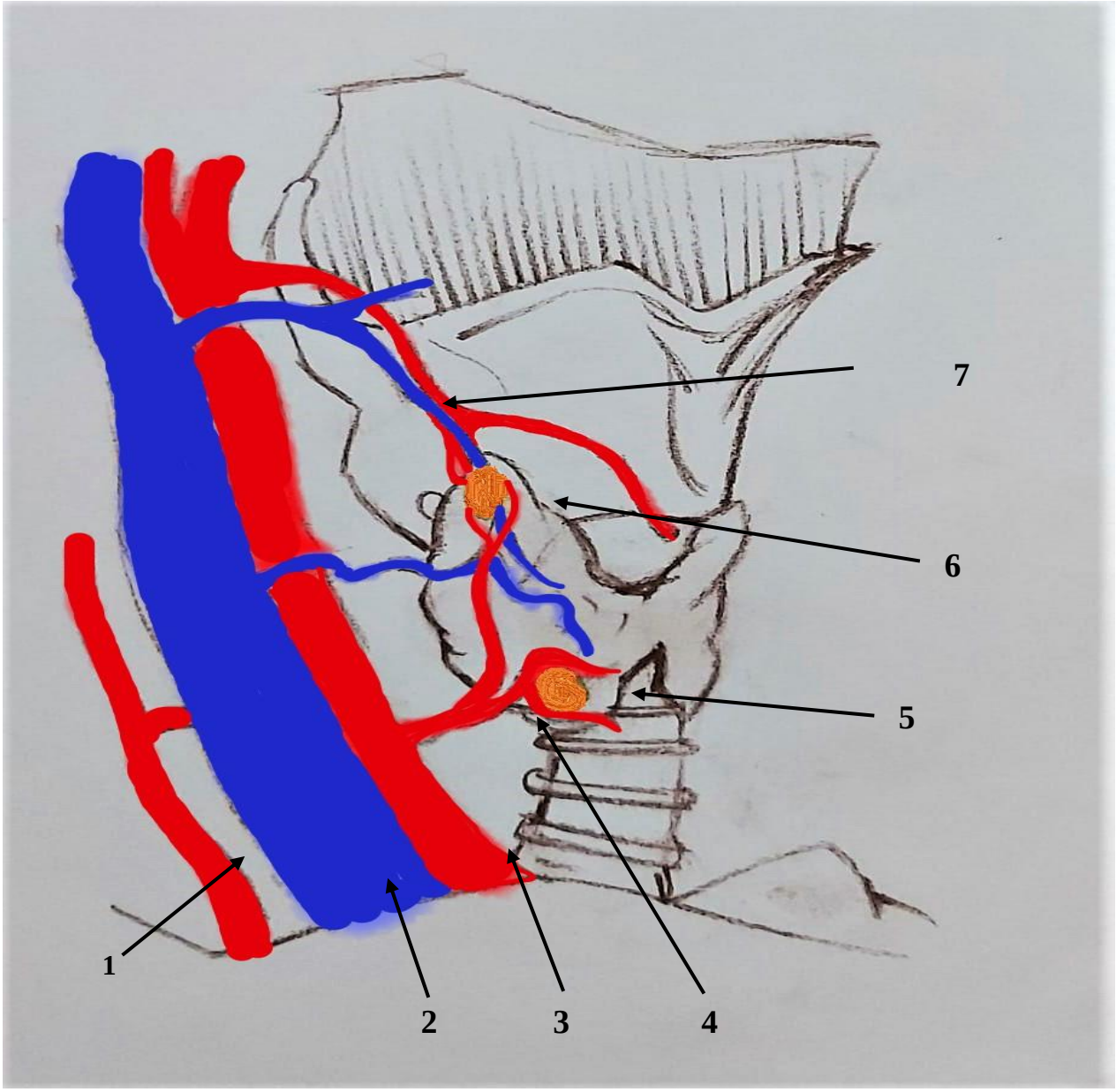


Figure 4: Anatomy of the Parathyroid glands. 1: Thyrocervical trunk;2: Internal Jugular vein; 3: Common carotid ; 4: Inferior thyroid artery; 5: Inferior parathyroid; 6: Superior Parathyroid; 7: Superior thyroid pedicle.

Superior Parathyroid Glands are generally found at the level of the upper two-thirds of the thyroid gland posterior to the Tubercle of Zuckerkandl (An enlargement of the lateral edge of the thyroid lobe formed by the fusion of the lateral and medial thyroid anlages). In about 80% of the people superior parathyroids are located on the posterior aspect of the thyroid gland within a circumscribed area of 2cm diameter and 1cm above the crossing point of the Recurrent Laryngeal Nerve (RLN) and inferior thyroid artery (ITA).

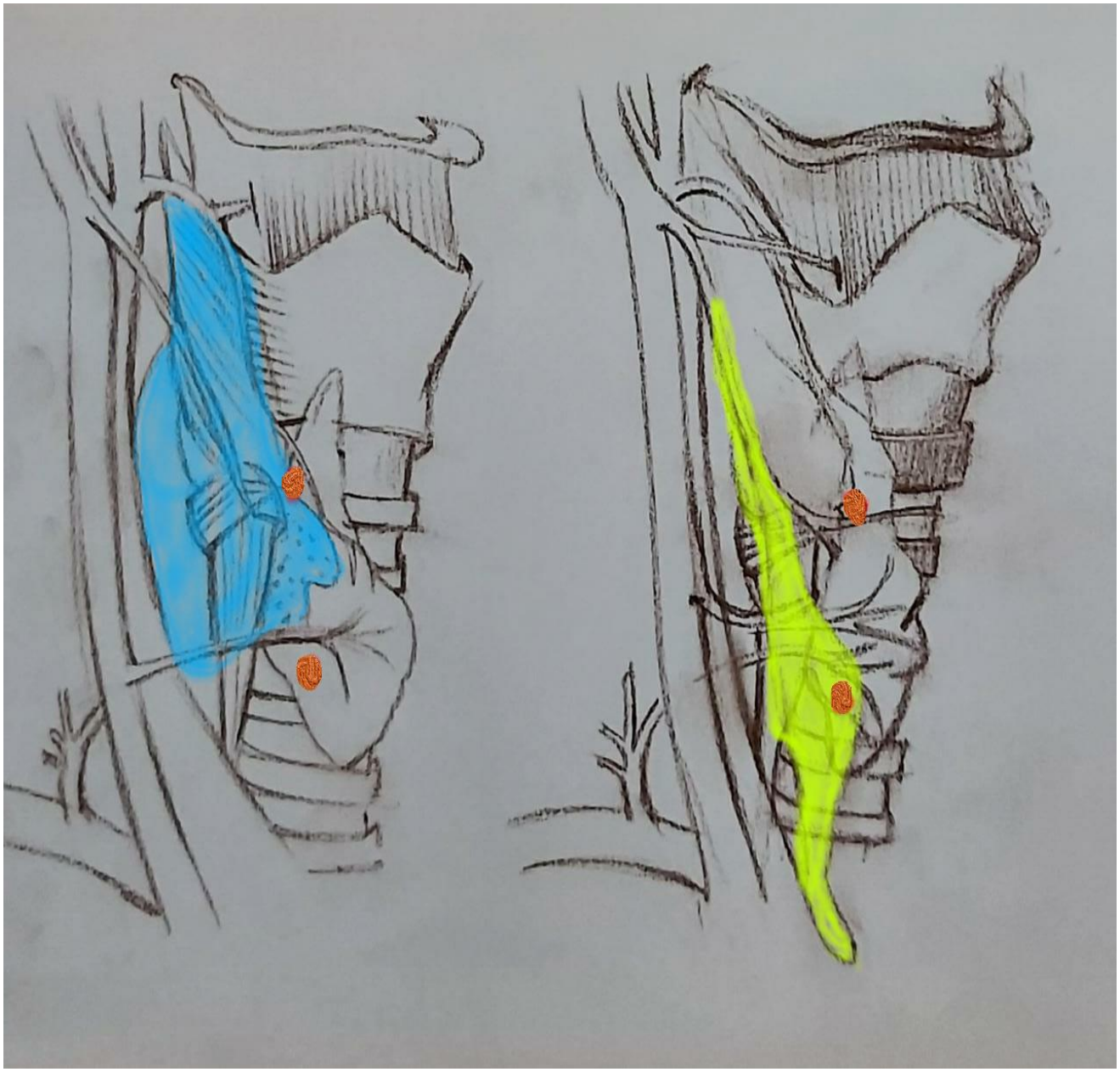


Figure 5:Probable locations of the ectopic parathyroid glands. Blue and Yellow shading denote the areas of probable distribution of Superior and Inferior Parathyroids, respectively.

Ectopic superior parathyroids are uncommon (1%), and can be found at the level of the upper pole of the thyroid gland in 2% of the subjects or above the pole in 0.8% of the subjects. The ectopic superior parathyroids may also be found in the posterior neck, retropharyngeal and retroesophageal spaces and within the thyroid stroma (intra-thyroid).[12,15]

Though location of Inferior parathyroid glands is inconsistent, these can be usually be found near the inferior poles of the thyroid gland. Their most common location is on the anterior or the posterolateral surfaces of the lower pole of the thyroid, which can be between the lower pole of thyroid and thyroid isthmus (44%); within the thyro-thymic ligament in the lower neck in proximity to the thymus (39%), within the carotid sheath (15%) or as far inferiorly as the superior mediastinum (2%).

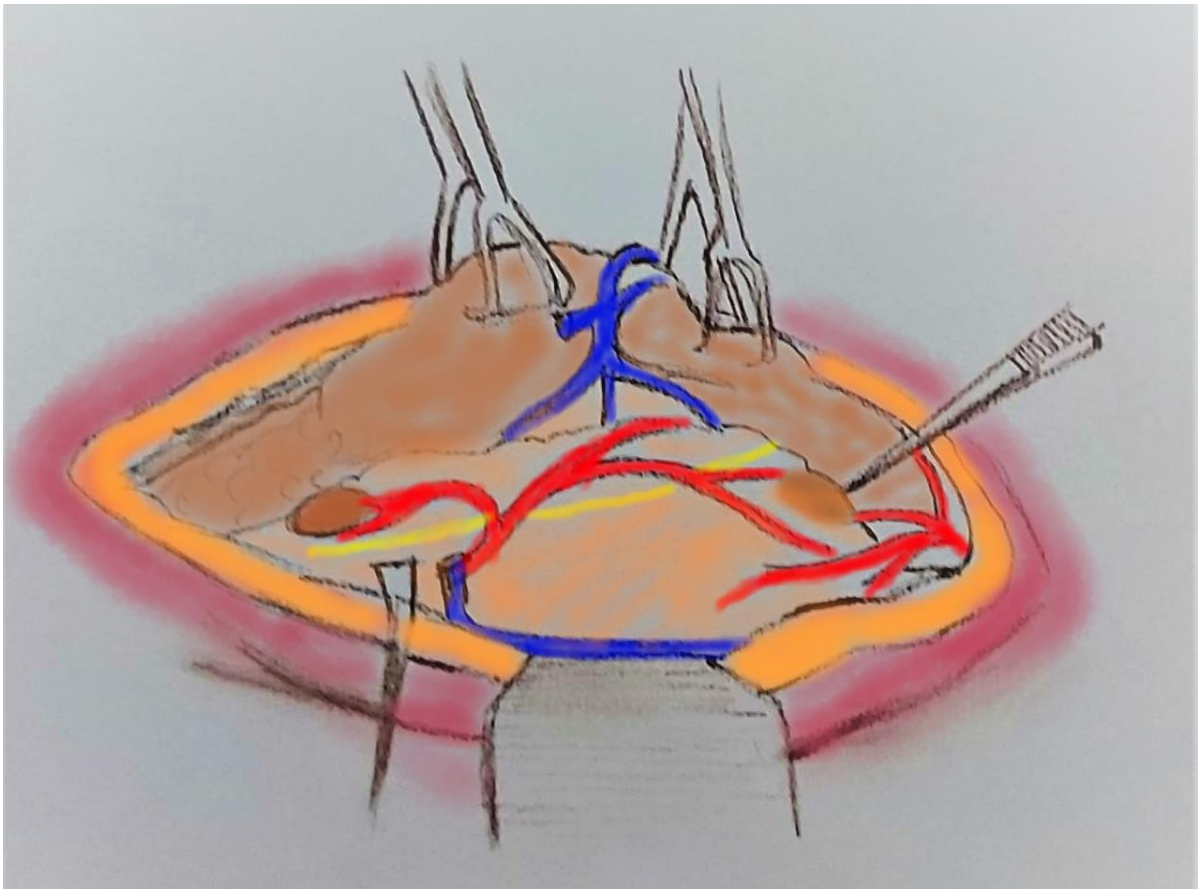


Figure 6: Relative position of parathyroids to Recurrent Laryngeal Nerve.

The relative position of the parathyroids in relation to the recurrent laryngeal nerve is of more importance than the relation of the glands to the inferior thyroid artery. The inferior parathyroids are usually found in a plane more ventral to that of the superior glands, i.e. the Superior parathyroids lie behind the plane of recurrent laryngeal nerve, while the Inferior parathyroids lie in front of this plane.

The parathyroids can be easily confused with Lymph nodes, surrounding fat and thyroid tissue, so during thyroid surgeries the following aspects are taken care of, like parathyroid glands have a distinct, encapsulated, smooth surface that differs from the thyroid gland, which has a more lobular surface, and the lymph nodes, which have pitted appearance. The color of the parathyroid glands is typically light brown to tan, which relates to their fat content, vascularity, and percentage of oxyphil cells within the glands.

The yellow color may be confused with surrounding fat. A distinct hilar vessel is also present that can be seen if the surrounding fat does not hide the glands' hila.

Lymphatics:

The Lymphatic vessels of the parathyroid glands drain along with those of the thyroid gland into the deep cervical lymph nodes and paratracheal lymph nodes.

Nerve Supply:

The parathyroid glands have an extensive supply of nerves, derived from thyroid branches of the cervical (sympathetic) ganglia. These nerves are vasomotor and not secretomotor as the endocrine secretion of parathyroid hormone is controlled hormonally.

Vascular Supply:

The inferior parathyroid gland is supplied by the inferior thyroid artery, a branch of the thyrocervical trunk. In approximately 10% of patients, the inferior thyroid artery is absent, most commonly on the left side. In these cases, a branch from the superior thyroid artery supplies the inferior parathyroid gland.

Inferior parathyroid glands that descend into the anterior mediastinum are usually vascularized by the inferior thyroid artery. If a parathyroid is positioned low in the mediastinum, it may be supplied by a thymic branch of the internal thoracic artery or even a direct branch of the aortic arch.

The superior parathyroid gland is also usually supplied by the inferior thyroid artery or by an anastomotic branch between the inferior thyroid and the superior thyroid artery.
Several studies have indicated that in 20-45% of cases, the superior parathyroid glands receive significant vascularity from the superior thyroid artery. This is usually in the form of a posterior branch of the superior thyroid artery which is formed at the level of the superior pole of the thyroid. The parathyroid veins drain into the thyroid plexus of veins.[16,17]

Histology of the parathyroids

The parathyroid glands are made up of two types of cell :

- **Chief cells** - These are the cells which secrete the parathyroid hormone (PTH)
- **Oxyphil cells** - These have a secretory function, and tend to become more common with age, but their precise role is not clear.

Rest of the gland is composed of adipose tissue which add bulk to the gland and increases with age and obesity; and fibrous tissue stroma which gives form to the gland as well as contains the capillaries to the glands.[13,18,19]

Histologically, differentiation of the chief cells occurs during the embryonic period, while that of the oxyphil cells takes place 5-7 years after birth.

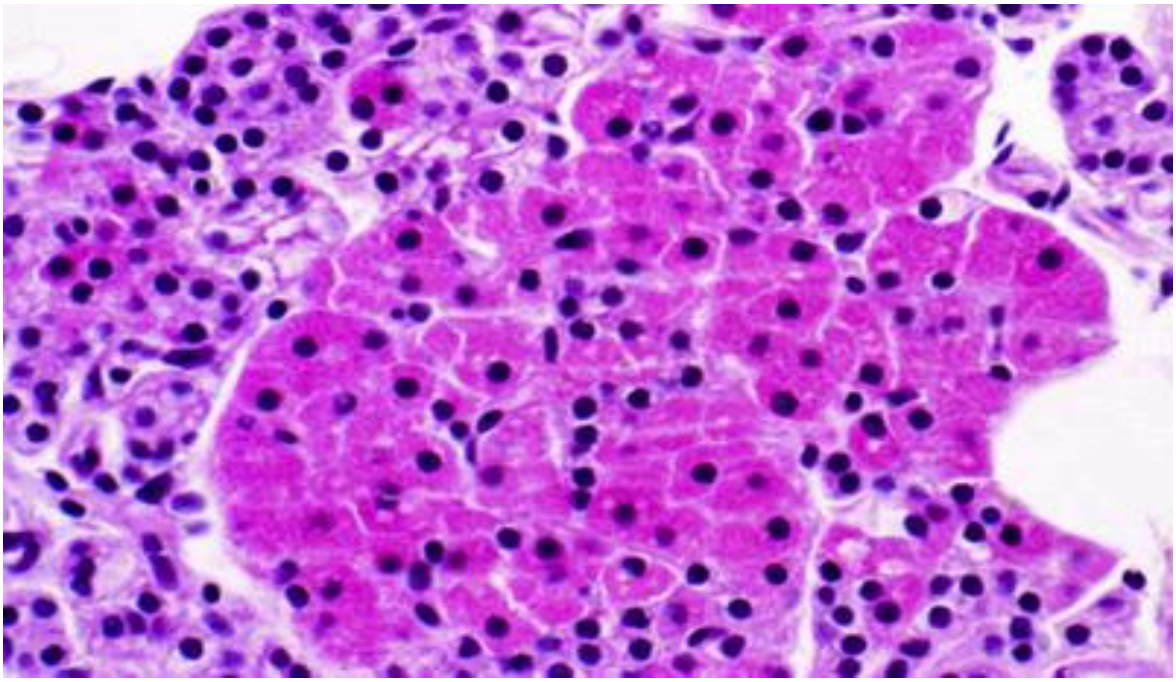


Figure 7: Histology slide of normal parathyroid showing Chief cells & Oxyphil cells.

Under the microscope the parenchymal cells (the specialized chief and oxyphil cells) are arranged in thick branching cords throughout the stroma (the adipose and vascular tissue). Sheet and tubular formations are also seen.

PARATHYROID HORMONE

Biosynthesis and Secretion:

Parathyroid hormone (PTH/ Parathormone) is a polypeptide containing 84 amino acids that is secreted by the parathyroid glands after cleavage from pre-pro-parathyroid hormone (115 amino acids) to pro-parathyroid hormone (90 amino acids) to the mature hormone. This polypeptide with 84 amino acids is the active form of PTH which is stored and secreted by the parathyroid chief cells. The process of synthesis, cleavage, and storage is estimated to take less than an hour. PTH secretion is an active process, which takes place in a matter of few seconds, when a decrease in serum calcium level is sensed by the Calcium sensing receptor (CaSR). The mechanism of secretion is by the process of exocytosis.

Metabolism:

The serum half-life of activated PTH is few minutes and is rapidly removed cleared from the serum by the kidney and liver.

Physiology:

Hypocalcemia is a potent stimulus for PTH synthesis and secretion. Other major factors affecting serum PTH levels include vitamin D, phosphate, magnesium, as well as fibroblast growth factor 23 [(FGF23), a peptide that suppresses 1-alpha-hydroxylase activity, decreases phosphate reabsorption in the kidney, and suppresses PTH release].

Parathyroid hormone is the main regulator of calcium physiology and the major target end organs for parathyroid hormone (PTH) action are the skeletal system, kidneys and intestine.

Action on bones:

Parathyroid hormone (PTH) acts directly on bone and induces bone resorption, causing an increase in serum calcium levels. It promotes absorption of calcium from the bone in 2 ways:

- Rapid phase
- Slow phase

The Rapid phase brings a rise in serum calcium within minutes and occurs at the level of the osteoblasts and osteocytes. These cells form an interconnected network known as the osteocytic membrane overlying the bone matrix, with a small layer of fluid between, called the bone fluid. When parathyroid hormone (PTH) binds to receptors on these cells, the osteocytic membrane pumps calcium ions from the bone fluid into the extracellular fluid.

The Slow phase of bone resorption occurs over several days and has 2 components, i.e. Osteoclasts activation (which cause resorption of the bone), and Osteoclasts proliferation.

Both the activation and proliferation of Osteoclasts are stimulated by cytokines released by activated osteoblasts and osteocytes and also by differentiation of immature osteoclast precursors that possess parathyroid hormone (PTH) and vitamin D receptors.

Action on Kidneys:

In the Kidneys the parathyroid hormone (PTH) causes increase in renal calcium resorption and phosphate excretion. It blocks reabsorption of phosphate in the proximal tubule while promoting calcium reabsorption in the ascending loop of Henle, distal tubule, and collecting tubule.

In addition, the final important function of parathyroid hormone (PTH) is conversion of 25-hydroxyvitamin D to its most active metabolite, 1,25-dihydroxyvitamin D-3 [1,25-(OH)2 D3], by activation of the enzyme 1-hydroxylase in the proximal tubules of the kidney.

Action on Intestine:

The active form of vitamin D acts directly on intestinal tissues, increasing the absorption of dietary calcium and phosphate.

Feedback inhibition of parathyroid hormone (PTH) release occurs primarily by direct effect of calcium at the level of the parathyroid gland. Also 1,25-(OH)2 D3 exerts a mild inhibitory effect on the parathyroid gland.[20,]

HYPOPARATHYROIDISM

Hypoparathyroidism is a relatively rare endocrine-deficiency disease characterized by absence or inadequately low circulating concentrations of parathyroid hormone (PTH) resulting in low serum calcium levels and elevated serum phosphorus levels in the blood. The most common cause of this condition is inadvertent removal of, or injury to, the parathyroid glands during neck surgery, followed by rarer etiologies such as genetic and autoimmune etiologies.

Hence based upon the cause hypoparathyroidism is broadly classified as:

- **PRIMARY,**
- **SECONDARY**

PRIMARY HYPOPARATHYROIDISM

Primary hypoparathyroidism occurs due to intrinsic defects of the parathyroid glands. It is also known as Congenital Hypoparathyroidism as the condition occurs due to inherited causes. This Inherited condition is due to various genetic defects which are also associated with complex syndromes involving defects of another organ or organ system.

The genetic causes of isolated hypoparathyroidism can be grouped into the following categories according to the mechanism by which they lead to hypoparathyroidism.

1. When parathyroid glands develop normally, but the secretion of parathyroid hormone at normal calcium concentrations is impaired like in autosomal-dominant hypocalcemic hypercalciuria (ADHH). ADHH is the most common genetic form of hypoparathyroidism.

This disorder is caused by activating (Gain- of-function) mutations of the calcium-sensing receptor characterized by depression of PTH secretion, hypocalcemia and hypercalciuria.

2. Absent or under-developed parathyroid glands, which can be the result of mutations mainly in transcription factor GCM2 (Glial Cells Missing 2) which is essential for parathyroid, differentiation and development.

3. Rare mutations of the PTH gene which causes incorrect processing and secretion of the hormone, leading to hypoparathyroidism.

4. When Hypoparathyroidism is a part of complex genetic syndromes such as:
   - Developmental abnormalities in the third and fourth pharyngeal pouches resulting in DiGeorge syndrome.
   - The hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome, caused by heterozygous mutations in the transcription factor GATA3
   - The hypoparathyroidism-retardation-dysmorphism syndromes (HRD) include the Kenny-Caffey, Sanjad-Sakati, and osteocraniostenosis syndromes. Mutations in the TCBE gene, a protein involved in microtubule assembly, and FAM111A have been implicated in HRD.

5. Hypoparathyroidism due to Parathyroid tissue destruction :

   Immune mediated destruction of the parathyroid glands leads to Autoimmune hypoparathyroidism, the second most common cause of the Hypoparathyroidism. It can occur sporadically, or as part of the inherited autoimmune polyglandular syndrome (APS-1), also known as Autoimmune-poly-endocrinopathy-candidiasis-ectodermal dystrophy (APECED). APS1 is an autosomal-recessive disorder resulting from a loss-of function of the AIRE (autoimmune regulator) gene.

The classical clinical triad of APS1 consists of Mucocutaneous candidiasis, Addison's disease, and Hypoparathyroidism. Other autoimmune diseases may appear, such as type 1 diabetes, Hashimoto's thyroiditis, or celiac disease. The target of the autoimmune attack of the parathyroid glands is not yet clearly understood.

Antibodies to the calcium-sensing receptor (CASR) have also been identified in a subgroup of patients with either APS1 or isolated autoimmune hypoparathyroidism.

- Neonatal hypoparathyroidism

  Neonatal Hypoparathyroidism develops mainly due to maternal hyperparathyroidism - An infant who is exposed in utero to maternal primary hyperparathyroidism (develops in 25% of women during childbearing years) is at risk of having suppressed parathyroid function and hypocalcemia during the first few weeks of life, which may persist up to 1 year of age. This condition is usually self-limiting. [21,22]

SECONDARY HYPOPARATHYROIDISM

Secondary hypoparathyroidism develops because of damage to the parathyroid glands, rendering them unable to secrete enough Parathyroid Hormone (PTH). The most common cause of secondary hypoparathyroidism is postoperative hypoparathyroidism (in about 75% of cases).

Postoperative hypoparathyroidism can occur after thyroid or parathyroid surgery, radical neck dissections or surgery for head and neck cancer, typically laryngeal cancer. It occurs more commonly with repeat or extensive surgeries.

Transient hypoparathyroidism after Total Thyroidectomy is relatively common (6.9% to 46%), often due to stunning of the glands whereas permanent hypoparathyroidism (0.9% to 1.6%) is less common. Most patients with postoperative hypoparathyroidism recover parathyroid gland function within several weeks to months after surgery and thus do not develop permanent disease. Persistent hypocalcemia beyond 6 months of surgery confirms the presence of permanent hypoparathyroidism.

The rates of postoperative hypoparathyroidism also depend on the surgeon's expertise, technique/ procedure of surgery, type of surgery and modality used for surgery.

Postoperative hypoparathyroidism, and the resulting hypocalcemia, may be permanent or transient.

The incidence of hypoparathyroidism is directly proportional to the extent of thyroidectomy and inversely proportional to the experience of the surgeon.

When types of thyroidectomies like, Sub-total, Near Total and Total Thyroidectomies are compared it is found that though the incidence of transient hypoparathyroidism increases with the extent of the resection, permanent complication rates are similar for all three surgical procedures.

Following total thyroidectomy, the incidence rates of temporary and permanent hypoparathyroidism are 14-60% and 4-11%.

In Patients undergoing total resection with central compartment clearance and unilateral neck dissection the incidence rates for temporary and permanent hypoparathyroidism are about 36.1% and 7.0%, while if bilateral neck dissection is performed the rates are around 51.9% and 16.2% respectively.

Thyroidectomies performed using energy devices like harmonic shears and Liga-Sure Precise have a lower rate of transient hypoparathyroidism, as the energy devices lead to shorter operative time and reduced overall systemic impact of surgery when compared with the conventional clamp and tie technique.

However, the rates of permanent hypoparathyroidism are similar to those of conventional procedures. [23,24,25]

The causes of Secondary Hypoparathyroidism are:

1. THYROIDECTOMY

It is the surgical removal of all or part of the thyroid gland done for various benign, malignant or cosmetic indications.

Thyroid surgery is one of the most frequently performed surgical procedures and also one of the safest. however, there are still many potential complications related to the surgery of thyroid gland like hypoparathyroidism (3 - 5%), recurrent laryngeal nerve palsy (0 - 2.1%), injury to superior laryngeal nerve (0 - 25%), hemorrhage (0.3 - 1%) and infections (1 - 2%).

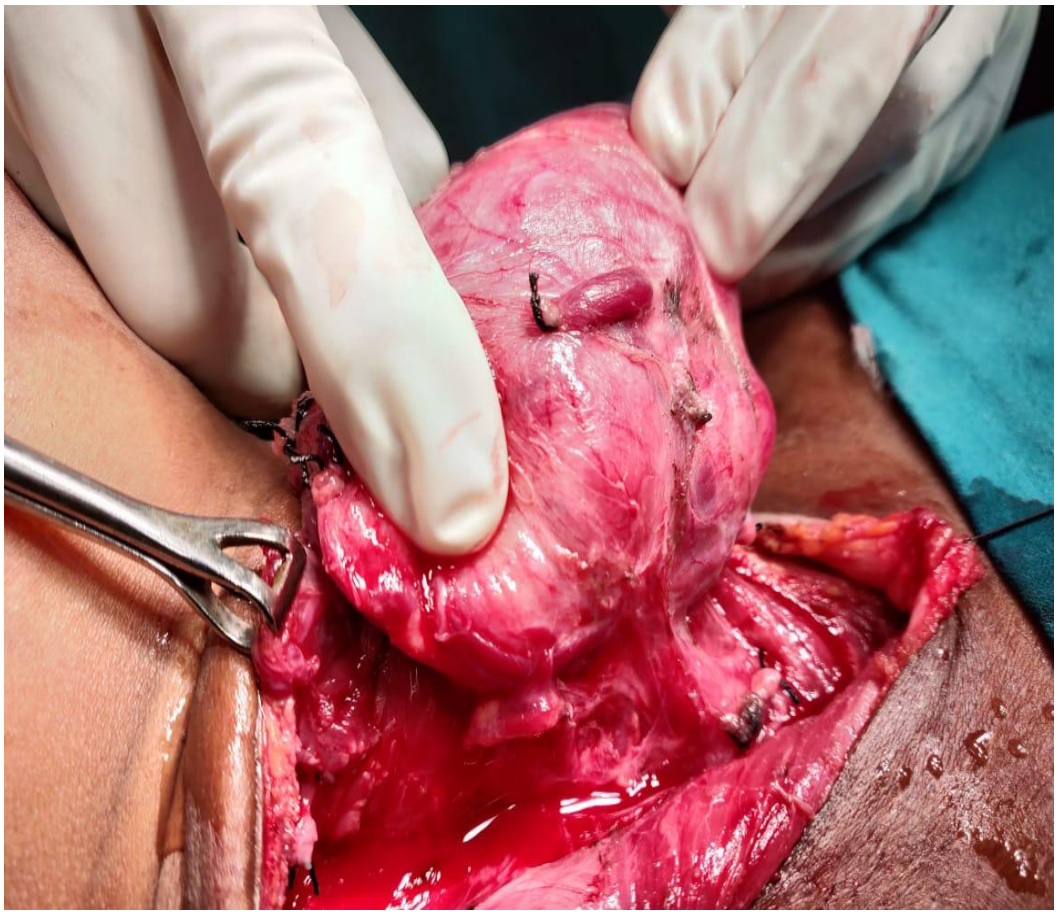


Image 1: Total Thyroidectomy

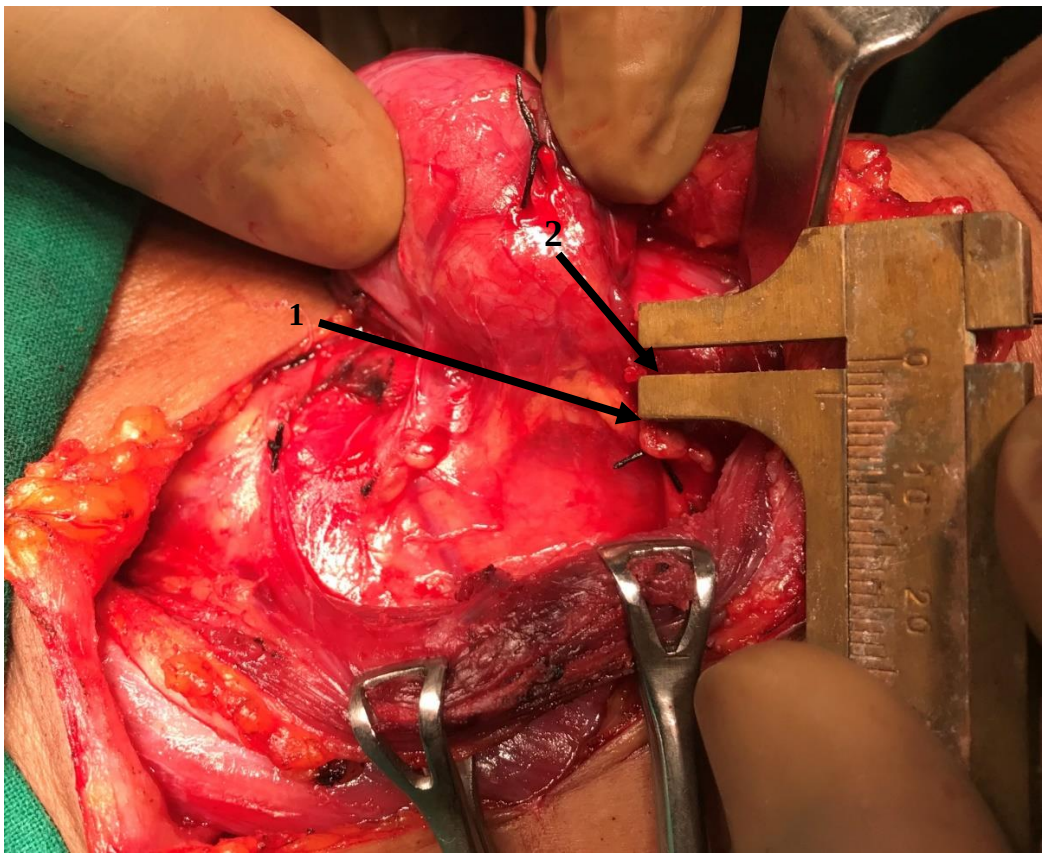


Image 2: Relation of, 1: RLN and 2: Superior Parathyroid gland. (left side)

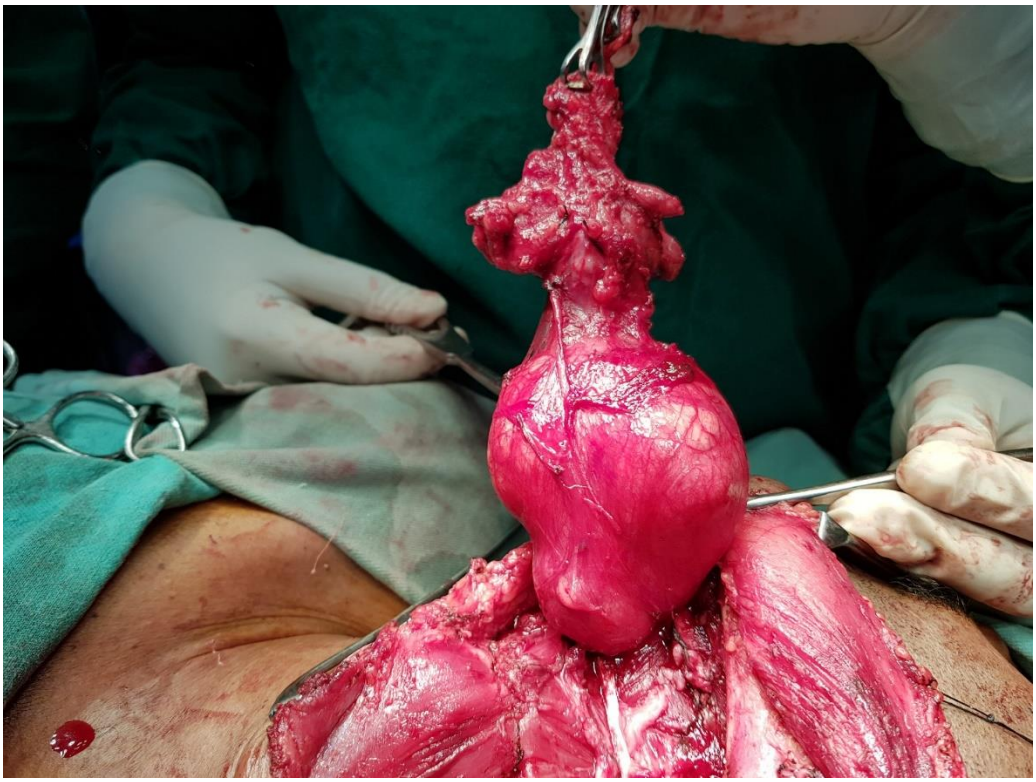


Image 3: Total thyroidectomy with Central Compartment Clearance

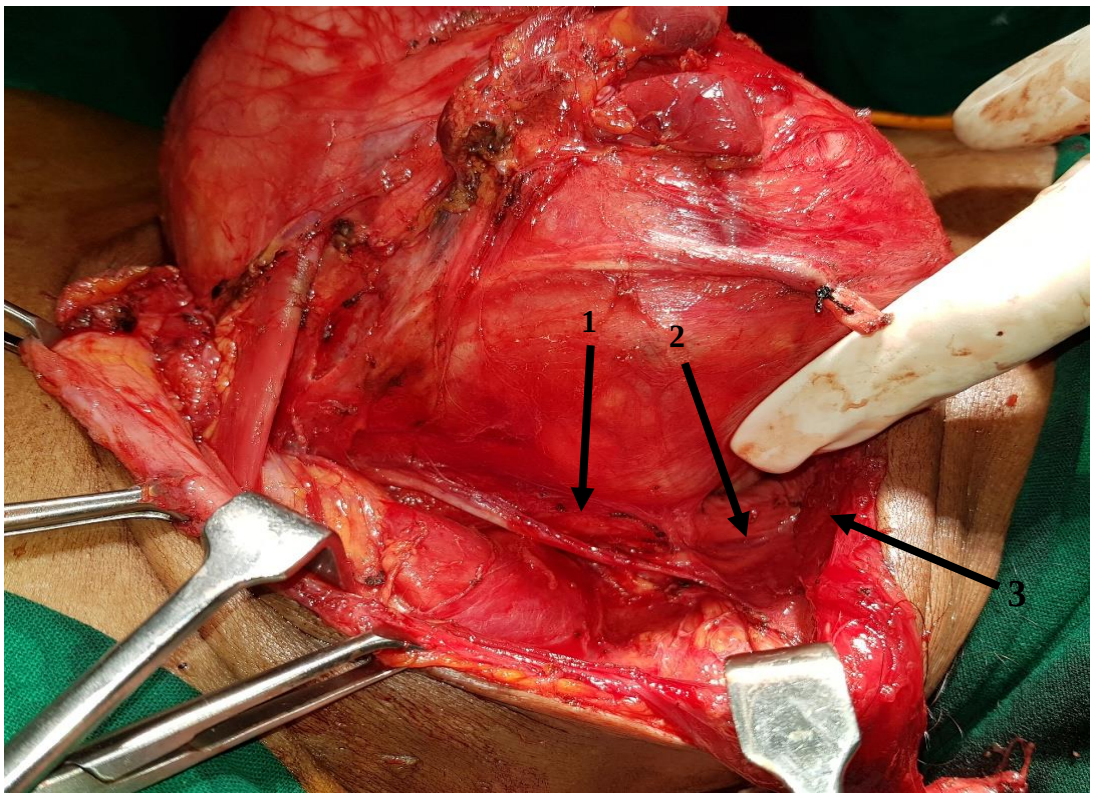


Image 4: Tumor being mobilized from carotid sheath. 1: Ansa cervicalis; 2: Middle thyroid vein ; 3: Internal carotid artery

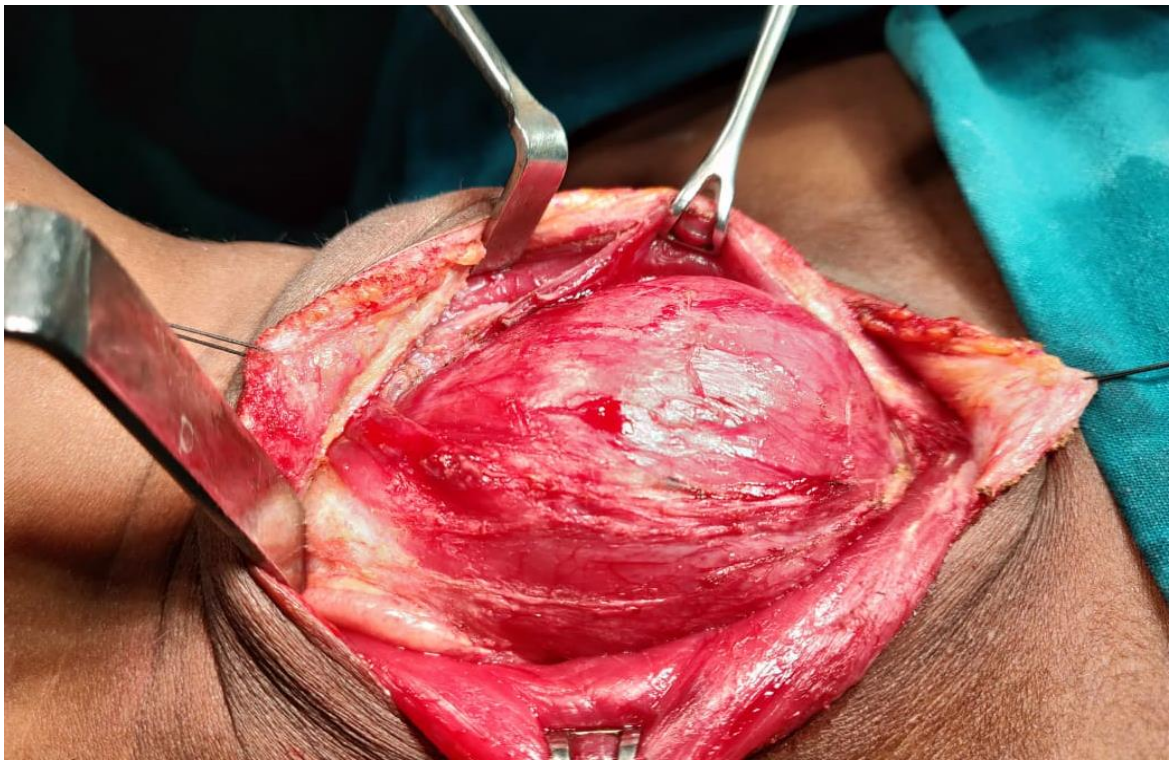


Image 5: Bulky multinodular goitre being mobilized from the strap muscles and sternocliedomastoid.

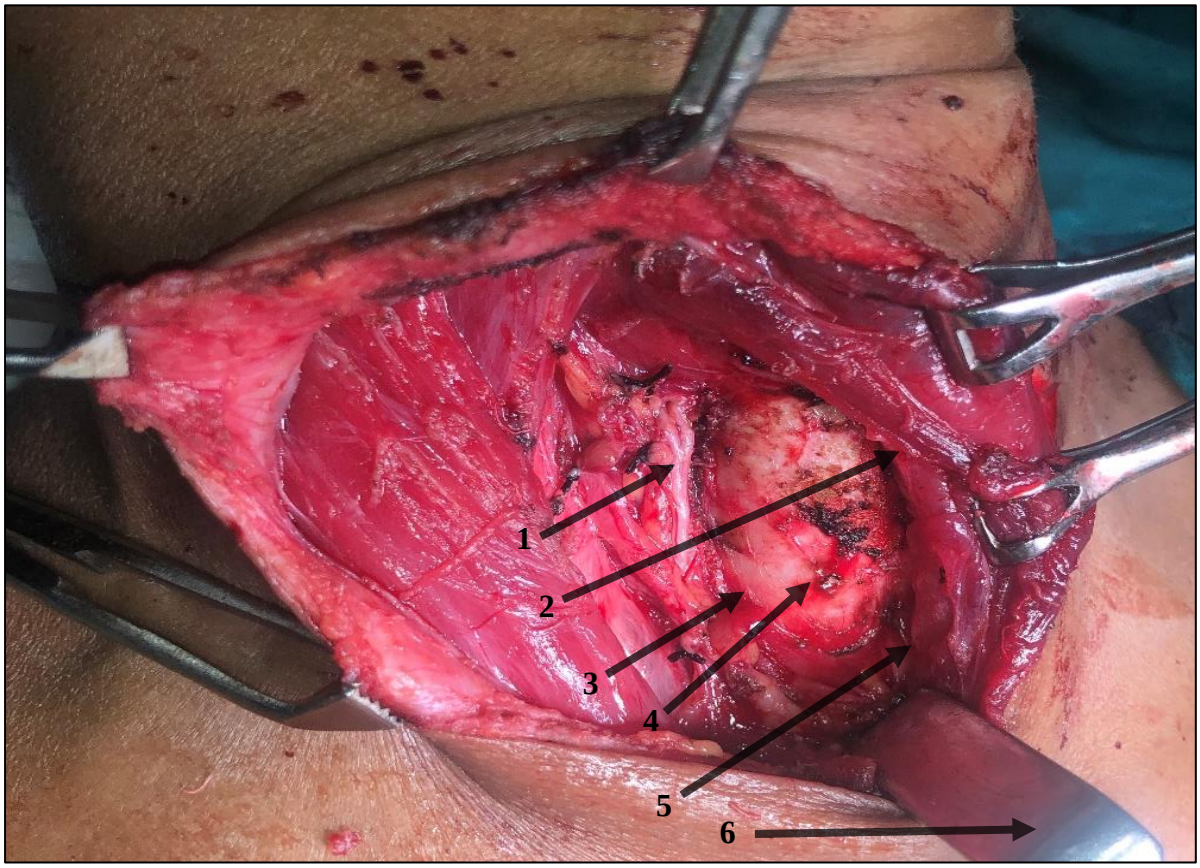


Image 6: Thyroid bed after total thyroidectomy showing, 1: Superior parathyroid;2: External br. Superior Laryngeal Nerve; 3: Inferior parathyroids; 4: RLN with bifurcation; 5: Trachea; 6: Central Compartment Nodes

Hypoparathyroidism is seen in 3-5 % of the patients undergoing total thyroidectomy and in most cases the patients are initially asymptomatic. During thyroidectomy, the various mechanisms leading to development of hypoparathyroidism are:

- Inadvertent removal of the glands (most common mechanism), which can happen due to the small size of the glands, resemblance of the parathyroids to lymph nodes, or similarity of the glands to surrounding fat tissue.
- Iatrogenic trauma to the glands while manipulation of the thyroid lobes can happen because of their restricted visualization due to the anatomic features like the intra-capsular location of the parathyroids or the location of the glands in the connective tissues.

- Inadvertent devascularization of the parathyroid glands due to ligation of the inferior thyroid artery away from the thyroid gland. also the vessels that feed the parathyroid glands are very small (< 1 mm in diameter), and variations in the pattern of blood supply can exist, which further predispose the glands to devascularization.

All the above factors can lead to state, called parathyroid gland "stunning." It persists for some days to weeks and results in transient Hypoparathyroidism. However, if it persists beyond 6 months, then it results in postoperative permanent hypoparathyroidism and this is a cause of significant morbidity to the patients.

Hence, parathyroid preservation during thyroidectomy is not only desirable, but essential for the effective management of diseases of the thyroid gland.

Other mechanisms which can cause transient post-operative hypocalcemia are

- Hungry bone syndrome in patients with hyperthyroidism and after removal of parathyroid adenoma. It is a state of low serum calcium levels resulting from rapid remineralization of the bone, when the stimulus for high bone turnover (e.g., high PTH or thyroid hormone levels) is removed.
- Increased urinary excretion due to surgical stress,
- Calcitonin release,
- Hemodilution

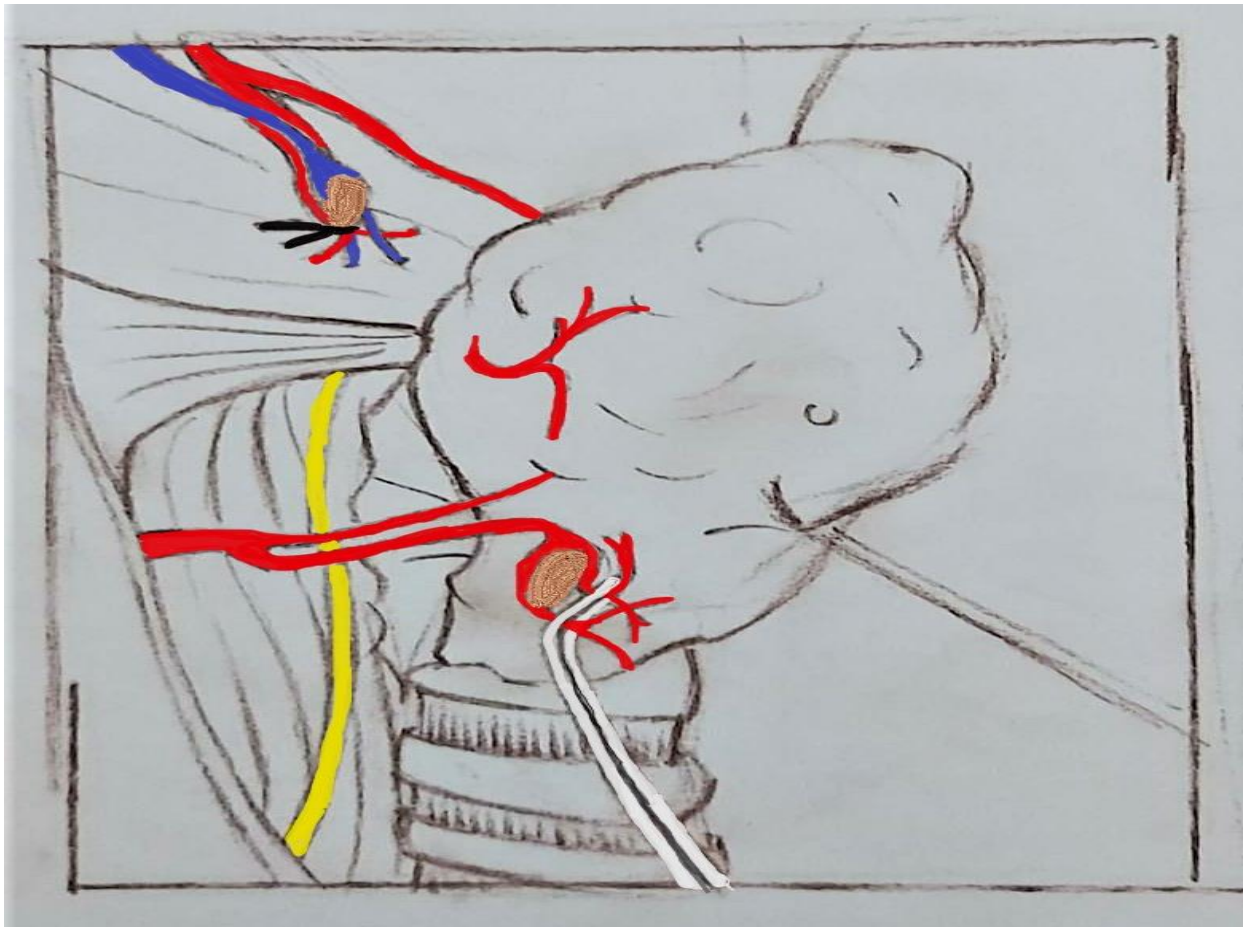


Figure 8: Distal ligation of the inferior thyroid artery after it has supplied the Inferior parathyroid.

2. PARATHYROID GLAND DESTRUCTION

Hypoparathyroidism can also develop due to parathyroid gland destruction. The destruction of the glands can be a result of extensive neck radiation therapy (due to accumulation of the radio-isotope in the vicinity of the glands, Inflammation or fibrosis of the glands), copper deposition in patients with Wilson's disease, Hemochromatosis (Due to iron deposition in parathyroids along with thyroid glands), granulomatous infiltration of the parathyroid glands (like in sarcoidosis), and metastatic cancer involving the parathyroid glands.[26,27,28]

CLINICAL FEATURES

The clinical picture of hypoparathyroidism can range from, a patient presenting with Acute medical emergency because of altered mental status/ seizures/ cardiac rhythm disturbances, refractory congestive heart failure/ laryngospasm, to a patient presenting with mild nonspecific neuromuscular symptoms or even patients in whom hypoparathyroidism is detected by incidental discovery of hypocalcemia by a routine biochemical test.[29]

Acute hypocalcemic states are potentially life-threatening and can be seen following anterior neck surgery or in individuals with known hypoparathyroidism whose needs for supplemental calcium and/or active vitamin D change or who has become noncompliant with the prescribed medications.

However, acute clinical presentation of hypoparathyroidism is rare and in most of the cases the clinical presentation of hypoparathyroidism is because of chronic hypocalcemia and hyperphosphatemia and, thus, not a medical emergency.

The acute symptoms of hypocalcemia are primarily due to neuromuscular irritability while the chronic manifestations of hypoparathyroidism may be due to the disease itself or to complications of therapy or both. The chronic complications of hypoparathyroidism can affect multiple organ systems, including the renal, neurologic, neuropsychiatric, skeletal, and immune systems.

ACUTE MANIFESTATIONS OF HYPOPARATHYROIDISM

Acute or severe hypocalcemia can cause well-recognized life-threatening manifestations which can lead to respiratory or cardiac arrest. Factors such as, rate of development of hypocalcemia, severity of hypocalcemia, hypomagnesemia or concomitant acidosis /alkalosis (Acidosis causes increase in ionized calcium in the plasma, whereas alkalosis decreases ionized calcium in the plasma) can influence the presentation of symptoms.

Neuromuscular Irritability

Neuromuscular irritability is the hallmark of acute hypocalcemia, presenting clinically with both sensory nerve and muscle dysfunction. Symptoms can be mild, with perioral numbness, tingling of the hands or feet, myalgias, or muscle cramping. Severe tetany can lead to generalized muscle contractions. Bronchospasm or laryngospasm can occur with severe hypocalcemia and can lead to respiratory arrest. In these severe cases the physical examination often reveals hyperreflexia and positive Chvostek's and/or Trousseau sign (carpal spasm due to latent tetany).

Cardiovascular

The cardiovascular manifestations can include hypotension, bradycardia, impaired cardiac contractility, and arrhythmias.

The underlying hypocalcemia can cause ECG changes like ST, QS, and T-wave changes suggestive of myocardial infarction.

CNS

Generalized tonic-clonic and focal motor seizures can be among the presenting symptoms because of hypocalcemia.

Miscellaneous Symptoms

- Psychiatric symptoms like delirium, cognitive impairment, irritability, depression, and anxiety can be present.
- Papilledema can be a finding in acute manifestation of hypoparathyroidism due to the severe hypocalcemia from any etiology.[30]

CHRONIC MANIFESTATIONS OF HYPOPARATHYROIDISM

The chronic manifestation of hypoparathyroidism may be due to the disease itself or due to complications of therapy, thus affecting multiple organ systems, like renal, neurologic, neuropsychiatric, skeletal, and immune systems. Low PTH concentrations, chronic hypocalcemia, relative hypercalcemia, hyperphosphatemia, an elevated calcium phosphate product, and hypercalciuria can all lead to development of chronic manifestations of hypoparathyroidism.

Renal Manifestations

Chronic hypoparathyroid subjects are prone to develop hypercalciuria due to intake of large amounts of calcium and/or active vitamin D supplements for maintaining the serum calcium levels.

The elevated calcium-phosphate product and hypercalciuria is associated to the risk of renal stones or nephrocalcinosis (incidence is12–57%)

Cardiac

In patients with surgical hypoparathyroidism the chronic hypocalcemia can cause cardiomyopathy and congestive heart failure, but it is reversible with treatment of hypocalcemia.

Neurologic

Seizures can occur in the setting of hypocalcemia due to chronic hypoparathyroidism.

Neuromotor abnormalities have been described in chronic hypoparathyroidism, in particular symptoms of parkinsonism, including bradykinesia, shuffling gait, and resting tremor. Other extrapyramidal symptoms (chorea, hemiballismus) and cerebellar findings (truncal ataxia, disordered coordination) have also been described.

Basal ganglia calcification are also noted in association with chronic hypoparathyroidism and the etiology is thought to be due to an elevated calcium phosphate product.

Miscellaneous

- Psychiatric: The risk of depression and bipolar disorders is two-folds in surgical hypoparathyroidism.
- Ophthalamic: Posterior subcapsular type of cataract is common in Post surgical hypoparathyroidism.
- Skeletal Manifestations: Bone remodeling is markedly reduced in patients with hypoparathyroidism, and bone mineral density values are typically greater than healthy, age-matched controls.
- Dermatologic: Chronic hypocalcemia is associated with dermatologic manifestations, like dry, rough, puffy, coarse skin; coarse and brittle hair with hair loss; and brittle nails with transverse grooves. The etiology for the nail disorders and dermatologic findings is believed to be Angiospasm. These findings can be reversed with treatment of hypocalcemia.
- Dental Enamel hypoplasia is the most common dental abnormality in patients with hypocalcemia. In the setting of hypocalcemia during early development before the teeth have entirely formed, dental aplasia or hypoplasia, failure of tooth eruption, defective root formation, and severe dental caries can occur. These dental abnormalities are much more common among those with autoimmune forms of hypoparathyroidism.
- Quality of Life: Patients with hypoparathyroidism have reduced quality of life in both physical and mental health domains as demonstrated by Studies using well-defined metrics. Quality of life is reduced even when patients are taking sufficient calcium and active vitamin D therapy to maintain serum calcium levels at goal.[31]

MANAGEMENT

The management involves, the diagnosis of hypoparathyroidism, evaluation to rule out the etiology, relevant investigations and the appropriate treatment.

DIAGNOSIS OF HYPOPARATHYROIDISM

The diagnostic hallmarks of hypoparathyroidism are decreased levels of PTH along with hypocalcemia. For diagnosis and adequate management of hypoparathyroidism, it should be distinguished from other underlying conditions having similar clinical presentation.

The biochemical diagnosis of hypoparathyroidism is based on the measurement of albumin-corrected total calcium or ionized serum calcium below the lower limits of the normal range and low, undetectable or inappropriate levels of PTH (measured by either a second- or third-generation immunoassay) on at least two occasions separated by at least 2 weeks, after hypomagnesemia has been ruled out.

For patients with history of anterior neck surgery and with persistence of hypocalcemia for more than 6 months postoperatively are diagnosed with Chronic hypoparathyroidism.

CLINICAL EVALUATION

A detailed medical and family history can help to point out the etiology in a patient with features of hypoparathyroidism. Any history of neck surgery suggests that parathyroid function may have been compromised by the surgical procedure.

A family history of hypocalcemia suggests a genetic cause while the presence of other autoimmune endocrinopathies like adrenal insufficiency or candidiasis points to autoimmune polyendocrine syndrome type -1 (APS-1). Immunodeficiency and other congenital defects point to the DiGeorge syndrome.

Physical examination should include an assessment of neuromuscular irritability by testing for Chvostek's and Trousseau's signs.

The skin should be examined carefully for a neck scar which suggests a postsurgical cause of hypocalcemia; for candidiasis and vitiligo (which are features of APS-1); and for generalized bronzing and signs of liver disease which are suggestive of hemochromatosis.

BIOCHEMICAL EVALUATION

The biochemical diagnosis of hypoparathyroidism is based on the measurement of :

- Serum Albumin estimation.
- Albumin-corrected Total calcium or ionized serum calcium level. Ionized calcium is more accurate to detect hypocalcemia. The sampling technique of ionized calcium has several limitations like, free-flowing venous blood should be obtained (not impeded by a tourniquet), strict anaerobic collection conditions, properly calibration of the instrument and immediate processing of the samples.
- Intact PTH - The intact PTH level can be normal or inappropriately low in a patient (measured by either a second- or third-generation immunoassay). The second-generation assay for PTH is more widely used and provides excellent discrimination between hypocalcemia due to hypoparathyroidism and the hypocalcemic states of secondary hyperparathyroidism.

- Serum Magnesium – In case of hypocalcemia Hypomagnesemia should always be ruled out as it indirectly leads to hypocalcemia by decreasing PTH secretion. If serum magnesium deficiency is detected, it is useful to measure the 24- hour urinary magnesium level to look for renal loss as the cause of magnesium depletion,
- Serum phosphorus - Serum phosphorus levels are usually high or at the high end of the normal range.
- Vitamin D assessment - Measurement of 25(OH) vitamin D levels is essential to rule out vitamin D deficiency as a contributor to or cause of hypocalcemia.

  However, measurement of 1,25(OH)2 vitamin D levels is generally not necessary in the initial evaluation of patients with hypoparathyroidism.
- 24 hour urinary calcium - Urinary calcium excretion varies as a function of calcium intake, but the fractional excretion of calcium is increased in hypoparathyroidism due to the lack of PTH. Low urinary calcium levels may be present in both severe hypocalcemia due to hypoparathyroidism and in vitamin D deficiency. Renal function is monitored annually by a 24-hour urine collection for calcium and creatinine excretion along with a measured creatinine clearance or eGFR.

For further evaluation referral to a pediatric or adult endocrinologist or geneticist should be done.

Also, the patient should undergo specialized testing, if genetic, auto-immune or other etiologies of hypoparathyroidism are contemplated. This testing may include gene sequencing for the extracellular calcium-sensing receptor, GATA3, or the autoimmune regulator protein; microarray studies or fluorescence in situ hybridization to diagnose the DiGeorge syndrome; and other hormone measurements to diagnose autoimmune polyendocrine syndrome type 1.

IMAGING STUDIES

Certain Imaging studies can be performed, especially in chronic cases such as

- CT Brain for basal ganglia and other intracerebral calcifications,
- Abdomen ultrasound for renal stones and calcifications, and
- Dual-energy x-ray absorptiometry for BMD measurement.[32]

TREATMENT

The intervention in an event of Hypoparathyroidism depends on presenting symptoms, and the severity and rapidity with which the hypocalcemia develops. This will be discussed in detail under the heading of management of Hypocalcemia.

CALCIUM

Calcium is a key intracellular messenger and cofactor for various enzymes. Ionized calcium, the physiologically active moiety, plays an essential role in many vital physiologic processes, including nerve impulse initiation and neurotransmission, cardiac conduction and contractility, blood coagulation, hormonal secretion, bone formation, skeletal and smooth muscle function, and a host of other crucial and diverse physiological functions. Therefore, normal ionized calcium levels are critical for the normal physiologic function of every cell.

Approximately 1.2 kg of calcium is present in the body of a 70-Kg human adult, more than 99% of which is stored as hydroxyapatite in bones. Less than 1% (5-6 g) is located in the intracellular and extracellular compartments, with only 1.3 g located extracellularly. Calcium accounts for 1 to 2 % of adult human body weight.

The total calcium concentration in the plasma is 4.5-5.1 mEq/L (9-10.2 mg/dL). Fifty percent of which is ionized, 40% is bound to proteins (90% of which binds to albumin), and 10% circulates in bound form to anions (eg, phosphate, carbonate, citrate, lactate, sulfate).[33]

At a plasma pH of 7.4, each gram of albumin binds 0.8 mg/dL of calcium. This bond is dependent on the carboxyl group of albumin and is highly dependent on pH. (Acidosis causes increase in ionized calcium in the plasma, whereas alkalosis decreases ionized calcium in the plasma)

ABSORPTION OF CALCIUM

Calcium requirement is fulfilled from the dietary sources containing calcium in the form of phosphate, carbonate, tartrate and oxalate. It is absorbed from the gastrointestinal tract in to the blood and distributed to various parts of the body by gut mucosa by Simple Diffusion and an active transport process, involving energy and calcium pump.

Factors controlling calcium absorption

- *Vitamin D* - It increases the absorption of Calcium & Phosphorus in the intestinal cells. Calcitriol binds with a cytosolic receptor to form a calcitriol-receptor complex. This complex approaches the nucleus and interacts with a specific DNA leading to synthesis of Calcium binding protein (CBP). This protein increases the Calcium uptake by the small intestine.
- *pH of the intestine:* Acidic pH in the upper intestine (duodenum) increases calcium absorption by keeping calcium salts in a soluble state. In lower intestine since pH is more alkaline, calcium salts undergoes precipitation.
- *Amount of dietary calcium and phosphates :* Increased level of calcium and phosphate in diet increases their absorption however up to a certain limit.

  This is because the active process of their absorption can bear with certain amounts of load beyond which the excess would pass out into faeces.
- *Phytic acid and Phytates :* They are present in oatmeal, meat and cereals and are considered anti-calcifying factors as they combine with calcium in the diet thus forming insoluble salts of calcium
- *Oxalates :* They are present in spinach and green leafy vegetables. They form oxalate precipitates with calcium present in the diet thus decreasing their availability.
- *Fats :* They combines with calcium and form insoluble calcium , thus decreasing calcium absorption.
- *Proteins and amino acids :* High protein diet increases calcium absorption as protein forms soluble complexes with calcium and keeps calcium in a form that is easily absorbable.

- *Carbohydrates :* Certain carbohydrates like lactose promotes calcium absorption by creating the acidity in the gut as they favors the growth of acid producing bacteria.
- *Bile salts :* They increases calcium absorption by promoting metabolism of lipids.[34]

REGULATION OF CALCIUM HOMEOSTASIS

The plasma calcium level is maintained within a narrow range which is essential for the normal physiologic function of each and every cell as the Calcium ion plays an important role in the numerous cellular functions including cell division, intracellular signaling, cell adhesion and plasma membrane integrity, protein secretion, muscle contraction, neuronal excitability, glycogen metabolism, and coagulation.

Parathyroid hormone (PTH) is the principal regulator of serum calcium and phosphate homeostasis, and acts with the other calcium-regulating hormones, including 1,25-dihydroxyvitamin D, and calcitonin, as well as the calcium sensor receptor (CaSR) to maintain serum calcium within the normal physiologic range that is required for optimal activity of the many extracellular and intracellular calcium-regulated processes.[35,36]

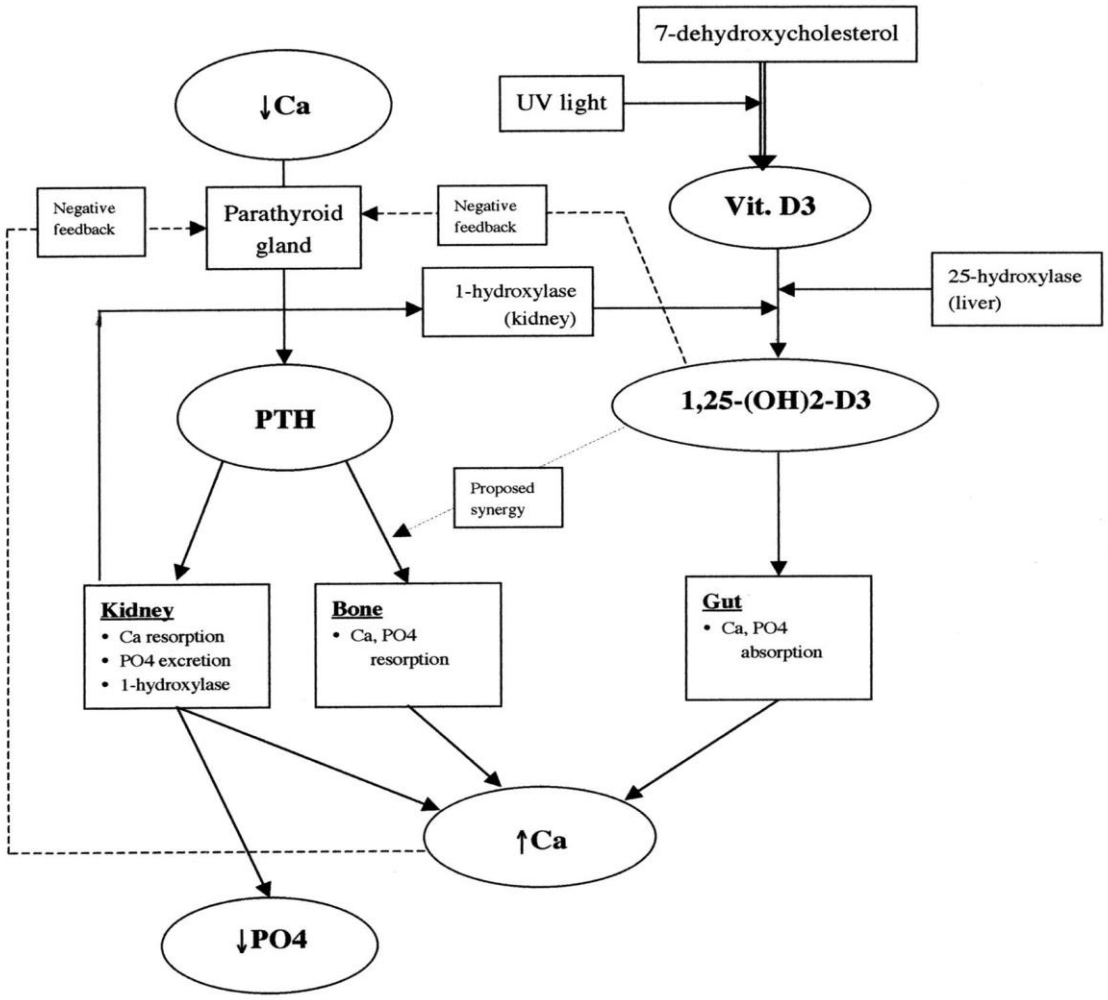


Figure 9: Schematic diagram showing Calcium Homeostasis.

Vitamin D

Vitamin D is a fat-soluble vitamin responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and has multiple other biological effects. For humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (ergocalciferol).

Vitamin D is transported in the blood by vitamin D-binding protein (DBP). Two hydroxylation reactions take place, the first one at the 25th carbon (C-25) and the second at carbon 1 (C-1), to produce the biologically active form of vitamin D i.e. the $1,25(OH)_2D_3$.
It is the major circulating form of vitamin D and the most reliable index of vitamin D status. The primary action of 1,25-(OH)2 D3 is to promote gut absorption of calcium by stimulating formation of calcium-binding protein within the intestinal epithelial cells.

In the intestine, $1,25(OH)_2D_3$ regulates every step of intestinal transcellular calcium transport process like calcium entry, calcium binding, and basolateral extrusion of calcium.

In bone, vitamin D may play a synergistic role with parathyroid hormone (PTH) in stimulating osteoclast proliferation and bone resorption. However, compared to parathyroid hormone (PTH), vitamin D exerts a much slower regulatory effect on calcium balance.[37]

Calcitonin

Calcitonin is also known as thyrocalcitonin. It is secreted by the parafollicular cells or C-cells of the thyroid gland. It is a minor regulator of calcium & phosphate metabolism. It is a single chain polypeptide with Molecular weight of 3400 and a Plasma concentration of – 10-20 ug/ml.

Calcitonin decreases Serum Calcium by decreasing the bone resorption which happens due to the *following changes* in Osteoclasts Cells: -

- Loss of ruffled borders
- Undergo cytoskeletal rearrangement
- Decreased mobility
- Detachment from bone.

Calcitonin is a Physiological Antagonist of PTH with respect to Calcium while with respect to Phosphate it has the same effect as PTH, i.e. ↓ Plasma Phosphate level.

CLINICAL PRESENTATION OF HYPOCALCEMIA

Hypocalcemia can present as an asymptomatic laboratory finding or as a severe, life-threatening condition. Distinguishing acute from chronic hypocalcemia and asymptomatic from severely symptomatic hypocalcemia is critical for determining appropriate therapy. In the setting of acute hypocalcemia, rapid treatment may be necessary. In contrast, chronic hypocalcemia may be well tolerated, but treatment is necessary to prevent long-term complications.

Table 1: Clinical Features Associated with Hypocalcemia

Neuromuscular irritability	Neurological signs and symptoms	Mental status	Skin Features	Smooth muscle involvement	Ophthalmic features	Cardiac manifestations
Chvostek's sign	Extrapyramidal signs due to calcification of basal ganglia	Confusion,	Delayed tooth eruption	Dysphagia,	Subcapsular cataracts	Prolonged QT interval on ECG
Trousseau's sign	Calcification of cerebral cortex or cerebellum	Disorientation	Increased dental caries	Abdominal pain	Papilledema	Congestive heart failure
Paresthesias	Impaired intellectual ability	Psychosis	Atopic eczema	Biliary colic		Cardiomyopathy
Tetany	Nonspecific EEG changes	Fatigue	Exfoliative dermatitis	Dyspnea		
Seizures (focal, petit mal, grand mal)	Increased intracranial pressure	Anxiety	Alopecia	Wheezing		
Muscle cramps	Parkinsonism, Choreoathetosis	Poor memory	Brittle nails			
Muscle weakness	Dystonic spasms	Reduced concentration	Dry skin			
Laryngospasm			Coarse hair			
Bronchospasm			Psoriasis			

The hallmark of acute hypocalcemia is neuromuscular irritability. Patients can have complains of numbness and tingling in their fingertips, toes, and the perioral region.

Paresthesia of the extremities may occur, along with fatigue and anxiety. Painful muscle cramps which can also progress to carpal spasm or tetany. In extreme cases of hypocalcemia, bronchospasm and laryngospasm with stridor may occur. Muscle symptoms can be so severe as to present with a polymyositis-like picture with elevated muscle isoenzymes. These symptoms are corrected by calcium replacement. Clinically, neuromuscular irritability can be demonstrated by eliciting *Chvostek's* or *Trousseau's* signs.[38]

Acute hypocalcemia may have cardiac manifestations. Prolongation of the QT-interval due to lengthening of the ST-segment on electrocardiogram is fairly common in hypocalcemic patients. T-waves are abnormal in approximately 50% of patients.

Hypomagnesemia if present with hypocalcemia may magnify the ECG abnormalities. Rarely, congestive heart failure may occur. Reversible cardiomyopathy due to hypocalcemia has been reported. In patients with mild, asymptomatic hypocalcemia, calcium replacement can result in improved cardiac output, and exercise tolerance.

On the other hand, chronic hypocalcemia has an entirely different presentation. Patients with idiopathic hypoparathyroidism or pseudohypoparathyroidism may develop neurological complications, including calcifications of the basal ganglia and other areas of the brain, and extrapyramidal symptoms. Grand mal, petit mal, or focal seizures can be seen in patients with hypocalcemia. Increased intracranial pressure and papilledema may be present. In patients with pre-existing subclinical epilepsy, hypocalcemia may lower the excitation threshold for seizures.

Electroencephalographic changes may be acute and nonspecific or present with distinct changes in the electroencephalogram (EEG). EEG changes may be present with or without symptoms of hypocalcemia.

Epidermal changes are frequently found in patients with chronic hypocalcemia. These include dry skin, coarse hair, and brittle nails. If hypocalcemia has occurred prior to the age of 5, dental abnormalities may be present. Dental abnormalities include enamel hypoplasia, defects in dentin, shortened premolar roots, thickened lamina dura, delayed tooth eruption, and an increase in the number of dental caries.

Alopecia has been noted following surgically-induced hypoparathyroidism and is also associated with autoimmune hypoparathyroidism. Other skin lesions reported in patients with hypoparathyroidism include atopic eczema, exfoliative dermatitis, impetigo herpetiformis, and psoriasis. Restoration of normal levels of calcium is reported to improve these skin disorders.

Changes in smooth muscle function with low serum levels of calcium may cause irritability of the autonomic ganglia and can result in dysphagia, abdominal pain, biliary colic, wheezing, and dyspnea. Subscapular cataracts occur in chronic, longstanding hypocalcemia.

Treatment of the hypocalcemia may improve mental functioning and personality, but of psychiatric symptoms is inconsistent. Delayed development, subnormal IQ, and poor cognitive function could also be a component of a syndrome that includes hypoparathyroidism as one of its features. This is critically important to consider in young patients being evaluated for the condition. In the elderly population, disorientation or confusion may be manifestations of hypocalcemia.[39]

ETIOLOGY OF HYPOCALCEMIA

Hypocalcemia can result from Hypoparathyroidism, disorders of vitamin D metabolism and action, resistance to parathyroid hormone (PTH), or a number of other conditions. These causes are described in the ***Table-2***. [40]

Table 2: Causes of Hypocalcemia

1. Hypoparathyroidism
2. Inadequate vitamin D production and action • *Nutritional deficiency* • *Lack of sunlight exposure* • *Malabsorption* • *Post-gastric bypass surgery* • *End-stage liver disease and cirrhosis* • *Chronic kidney disease* • *Vitamin D-dependent rickets type 1 and type 2*
3. PTH resistance – *Pseudohypoparathyroidism*
4. Functional hypoparathyroidism • *Hypoalbuminemia* • *Hypo/Hypermagnesemia*
5. **Miscellaneous etiologies** *Neonatal hypocalcemia* *Hyperphosphatemia* *Drugs* *Hungry Bone Syndrome* *Acute pancreatitis* *Acute critical illness* *Rapid transfusion of large volumes of citrate-containing blood* *Osteoblastic metastases* *Mitochondrial gene defects*

1. HYPOPARATHYROIDISM

This potentially severe complication seen following surgery of the Thyroid or the parathyroid glands presents with a broad range of signs and symptoms that may be either transient or permanent. The risk factors for development of hypoparathyroidism are listed in ***Table-3*** and the various etiologies of Hypoparathyroidism are mentioned in ***Table-4.*** [37,41]

Table 3: Risk Factors for Hypoparathyroidism

Bilateral central neck surgery
Surgery for thyroid malignancy with or without central
Neck dissection
Surgery for parathyroid hyperplasia
Female sex
Vitamin D deficiency
Pregnancy and Lactation
Autoimmune thyroid disease
Prior gastric bypass surgery

Table 4: Causes of Hypoparathyroidism

Acquired • Thyroidectomy • Destruction of Parathyroids
Neonatal • Maternal hyperparathyroidism
Autoimmune • Isolated • Autoimmune polyendocrine syndrome type 1 (APS-1)
Developmental disorders • DiGeorge Syndrome

2. VITAMIN D DISORDERS RESULTING IN HYPOCALCEMIA

Both inherited and acquired disorders of vitamin D and its metabolism may be associated with hypocalcemia.

Acquired Causes of Vitamin - D

- **Nutritional Vitamin D Deficiency**

Vitamin D deficiency has been recognized in children who have restricted diets or specialized diets. In countries that do not fortify foods, childhood vitamin D deficiency is more common. Vitamin D deficiency is recognized as a worldwide problem in older adults as well.

Exclusively breastfed infants are at high risk for vitamin D deficiency, as there is little vitamin D in human milk. The fortification of milk, cereals, breads, and other foods with vitamin D and the use of supplements are the reasons for few cases of vitamin D deficiency in children in the Developed countries.[42]

- **Lack of Sunlight Absorption**

Decreased synthesis of vitamin D in the skin is not uncommon and may be due to the lack of sun exposure due to excessive sunscreen usage, skin pigmentation, protective clothing, winter season, increased latitude or aging. Patients who are unable to be exposed to solar ultraviolet B radiation are at risk for vitamin D deficiency. In cultures where traditional dress includes long garments, hoods or veils, may result in reduced sun exposure and vitamin D deficiency.

- **Malabsorption** Fat malabsorption accompanying hepatic dysfunction, sprue, Whipple's disease, Crohn's disease, and gastric bypass surgery result in intestinal malabsorption of vitamin D and result in lower concentrations of circulating 25-hydroxy (25[OH]) vitamin D.

- **Liver Disease**

Liver disease is not a common cause of inadequate 25(OH) vitamin D levels, as over 90% of the liver has to be dysfunctional before the 25(OH) vitamin D drops to subnormal levels. However, intestinal fat malabsorption occurs in both parenchymal and cholestatic liver disease, and this may cause vitamin D deficiency. Certain anticonvulsant drugs can alter the kinetics and hepatic metabolism of 25(OH) vitamin D. Vitamin D deficiency is usually easily corrected by additional vitamin D administration.

- **Renal Disease**

Nephrotic syndrome with excretion of large amounts of protein has also been associated with lower levels of 25(OH) vitamin D and may be due to excretion of vitamin D binding protein. Chronic renal failure with a reduction in glomerular filtration rate to <30% of normal may present with decreased production of 1,25-(OH)2 vitamin D. In the setting of chronic renal failure, hyperphosphatemia and secondary hyperparathyroidism occur. Serum calcium tends to be in the low normal range.

Hypocalcemia is usually not observed in the presence of low levels of 25(OH) vitamin D due to the compensatory rise of PTH, which will mobilize the calcium from skeletal stores. Hypocalcemia only occurs when these stores are severely depleted.

Inherited Disorders of Vitamin D Metabolism and Action

Inherited disorders can result from the deficient renal production of 1,25-(OH)2 vitamin D (vitamin D-dependent rickets type 1,[VDDR-1]) or a defect in the vitamin D receptor (VDR) (vitamin D-dependent rickets type 2, [VDDR-2]). Patients with VDDR- Type 1 and VDDR-Type 2 have similar findings like rickets, hypocalcemia, hypophosphatemia, raised alkaline phosphatase, and secondary hyperparathyroidism. They only differ in serum levels of 1,25-(OH)2 vitamin D), in VDDR Type 1 it is decreased while in VDDR Type 2 it is elevated. [43,44]

3. PTH RESISTENCE – PSEUDOHYPOPARATHYROIDISM

Syndromes of PTH Resistance End-organ resistance to PTH, also known as pseudohypoparathyroidism (PHP), refers to a group of heterogeneous disorders characterized by target organ unresponsiveness to PTH. The biochemical findings in PTH resistance include hypocalcemia, hyperphosphatemia, and elevated PTH levels.

Table 5: The types of PHP and their characteristics

Defects	Serum PO4	PTH	25(OH)D	1,25(OH)2D	UcAMP*	UPO4*	Multiple Endocrine Defects
Hypoparathyroidism	↑	↓	-	↓	-	-	Yes/No**
Pseudohypoparathyroidism							
Type 1a	↑	↑	-	↓	↓	↓	Yes
Type 1b	↑	↑	-	↓	↓	↓	No/Yes#
Type 1c	↑	↑	-	↓	↓	↓	Yes
Type 2	↑	↑	-	↓	-	↓	No
↑, increased;↑, decreased; -, normal;							

PHP Type 1 - PHP type 1 is caused by mutations in GNAS , a gene encoding the alpha subunit of the stimulatory G protein coupled to the PTH receptor.

PHP Type 1a - PHP type 1a is characterized by distinct clinical findings known collectively as Albright's hereditary osteodystrophy, which include short stature, obesity, short neck, round face face, subcutaneous calcifications, short fourth and fifth metacarpal and metatarsal bones, and developmental delays. In addition, patients may have hyperparathyroid bone disease (osteitis fibrosa) as the resistance is not present in the skeleton.

PHP Type 1b - In this disorder, PTH resistance appears to be confined to the kidney. Thus, affected individuals have hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism without the phenotypic abnormalities of Albright's hereditary osteodystrophy.

PHP Type 1c - Patients with this disorder are phenotypically similar to those with PHP type 1a and have Albright's osteodystrophy.

PHP Type 2 - Patients with PHP type 2 do not have the features of Albright's hereditary osteodystrophy. They have normal or elevated urinary cyclic adenosine monophosphate concentrations without a concomitant increase in phosphate excretion in response to exogenous PTH administration.[45]

4. FUNCTIONAL HYPOPARATHYROIDISM

- **Hypoalbuminemia**

In patients with chronic illness, malnutrition, cirrhosis, or volume over-expansion, serum albumin may develop a reduction in the total, but generally not the ionized, fraction of serum calcium. This is referred to as "factitious" hypocalcemia. Patients do not have any signs or symptoms of hypocalcemia. If the serum albumin levels fall to <4.0 g/dL, for every 1.0 g/dL reduction in the serum albumin, 0.8 mg/dL is added to the measured total serum calcium.[46]

- **Hypo/Hypermagnesemia**

Magnesium is a cofactor for the adenylate cyclase enzyme complex. Thus, it is required for effective stimulus-secretion coupling in parathyroid cells. Magnesium deficiency may result in defective cyclic adenosine monophosphate generation in the parathyroid glands and in the PTH target organs.

This could be the principal mechanism resulting in both impaired PTH secretion and end-organ resistance to PTH, which together contribute to the development of hypocalcemia. The most common causes of hypomagnesemia include malabsorption, diarrhea, chronic alcoholism, pancreatitis, diuretic therapy, cisplatin therapy, proton pump inhibitor therapy, and treatment with aminoglycoside. Primary renal magnesium wasting states, such as Gittelman syndrome, are rare disorders that lead to chronic and persistent hypomagnesemia. Only after magnesium levels are restored can the PTH function return to normal and the hypocalcemia be corrected. Severe hypermagnesemia can also cause hypocalcemia, by activating parathyroid CaSRs, thereby suppressing the secretion of PTH. This may occur following high-dose magnesium administration in the treatment of preeclampsia.[47]

5. MISCELLANEOUS ETIOLOGIES

- **Neonatal Hypocalcemia**

A typically benign autosomal dominant disorder, familial hypocalciuric hypercalcemia (FHH), can paradoxically produce neonatal hypocalcemia. FHH is usually due to heterozygous inactivating mutations in the *CaSR*.

The hypoparathyroidism is thought to be due to fetal parathyroid suppression secondary to high maternal calcium levels in a mother with FHH due to a heterozygous *CaSR* mutation.[48]

- **Hyperphosphatemia**

Acute hyperphosphatemia occurs as a result of excessive phosphate intake (e.g., phosphate-containing enemas and supplements in patients with impaired renal function) or massive tissue breakdown (e.g., rhabdomyolysis and tumor lysis syndrome). The hyperphosphatemia may result in calcium-phosphate precipitation in skeletal and extraskeletal tissues, leading to symptomatic hypocalcemia. Hyperphosphatemia inhibits 1-alpha-hydroxylase activity in the kidney. The resulting lower circulating concentrations of 1,25(OH)2 vitamin D may further aggravate the hypocalcemia by impairing intestinal absorption of calcium, however low 1,25(OH)2 vitamin D levels may result in increased PTH secretion.

Hypocalcemia and tetany may occur if serum phosphate rises rapidly. Treatment should be directed towards reducing the hyperphosphatemia in order to correct the hypocalcemia.

- **Medications**

Categories of drugs are associated with hypocalcemia are; Agents inhibiting bone resorption like bisphosphonates, calcitonin, and denosumab; Anticonvulsants such as phenytoin or phenobarbital; Chemotherapeutic agents such as the combined use of 5-fluorouracil and leucovorin; Patients undergoing plasmapheresis with citrated blood; Proton pump inhibitors (PPIs) and histamine-2 receptor blockers (cimetidine); over-fluorinated public water supplies.[49]

- **"Hungry Bone Syndrome"**

Hypocalcemia can occur if the rate of skeletal mineralization exceeds the rate of osteoclast-mediated bone resorption. This syndrome can be associated with severe and diffuse bone pain and tetany. [50]

- **Acute Pancreatitis**

The mechanism of hypocalcemia acute pancreatitis involves sequestration of calcium by saponification with fatty acids, which are produced in the retroperitoneal area of the abdominal cavity by pancreatic lipases. In addition, decreased PTH may play a role. Hypocalcemia is an ominous prognostic sign in acute pancreatitis [51]

- Hypocalcemia Associated with Critical Illness

The incidence of hypocalcemia in critically ill patients approaches 80–90%. Multiple factors in the acute critical setting contribute to the development of hypocalcemia (low ionized calcium levels). These include poor nutrition, vitamin D insufficiency, reduced renal function, and acid-base disturbances. Sepsis and severe burns can be associated with hypocalcemia. The cause appears to be a combination of impaired PTH secretion, reduced calcitriol production, and endorgan resistance to the action of PTH [52]

In gram negative sepsis or in the "toxic shock syndrome", there is a reduction in both total and ionized serum calcium. The mechanism of action is unknown, but elevated levels of the cytokines IL-6 or TNF-alpha may be mediators of hypocalcemia. The level of hypocalcemia correlates with patient mortality.[53]

- **Transfusion-Related Causes of Hypocalcemia**

Infusion of citrate or lactate may decrease serum ionized calcium levels, by chelating calcium in the serum and increasing the incorporation of calcium into calcium-citrate or calcium-lactate complexes. This is usually seen following the transfusion of several units of packed red blood cells.[54]

- **Osteoblastic Metastases**

Metastatic bone lesions may cause hypocalcemia, particularly breast or prostate primary malignancies. The presumed pathophysiology is deposition of calcium in the newly formed bone around the osteoblastic tumor.

- **Mitochondrial Disease**

Several mitochondrial disorders have been associated with hypoparathyroidism. These syndromes are caused by deletions in mitochondrial DNA, and include the following:

• Kearns-Sayer syndrome, which is a mitochondrial cytopathy that is characterized by encephalopathy, ophthalmoplegia, retinitis pigmentosa, and cardiomyopathy.

• Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, which is a maternally inherited disorder caused by point mutations in mitochondrial tRNA, can occur. This syndrome usually manifests in childhood after a normal early development.[55]

MANAGEMENT OF HYPOCALCEMIA

Investigations for Hypocalcemia

Symptomatic patients with classic clinical findings of acute hypocalcemia require immediate resuscitation and evaluation. Most cases of hypocalcemia are discovered by clinical suspicion and appropriate laboratory testing.

The following lab investigations can be done:

- **Serum Ionized Calcium:**

  Ionized calcium is the definitive method for diagnosing hypocalcemia. A serum calcium level less than 8.5 mg/dL or an ionized calcium level less than 1.0 mmol/L is considered hypocalcemia. Analysis for the ionized calcium level must be performed rapidly with whole blood to avoid changes in pH and anion chelation. Blood should be drawn in an un-heparinized syringe for best results. Falsely elevated calcium levels may be seen with elevated acetaminophen levels, alcohol, hydralazine, and hemolysis while falsely depressed levels can be seen with heparin, oxalate, citrate, or hyperbilirubinemia.

- **Serum Phosphorus and Serum Magnesium:** In healthy kidneys, parathyroid hormone (PTH) stimulates phosphate excretion. The combination of hypocalcemia and elevated phosphorus levels typically suggests hypoparathyroidism or pseudohypoparathyroidism. Patients with renal failure and hypocalcemia usually present with hyperphosphatemia and high PTH levels. Hypophosphatemia develops in patients with vitamin D deficiency and hungry bone disease.

  The serum magnesium level should always be checked to determine its potential contribution to the hypocalcemia. Occasionally, inadequate dietary magnesium intake leads to hypomagnesemia, hypophosphatemia, and hypocalcemia.

- **Albumin -** In a patient with hypocalcemia, measurement of the serum albumin is essential to distinguish true hypocalcemia, which involves a reduction in ionized serum calcium, from factitious hypocalcemia, meaning decreased total, but not ionized, calcium.

- **Liver function tests**, and **Coagulation parameters**, to assess liver dysfunction and hypoalbuminemia.

- **Blood urea nitrogen (BUN) and serum creatinine** should be measured, as elevated levels may indicate renal dysfunction.

- **The parathyroid hormone (PTH)** level should also be evaluated.

- **Vitamin D** to be measured if deficiency is suspected.

- **Electrocardiogram** should be done at the earliest

- **Imaging studies** like plain radiography or computed tomography (CT) scans can be done. On radiographs, disorders associated with rickets or osteomalacia present with the pathognomonic Looser zones, which are seen in the pubic ramus, upper femoral bone, and ribs. Radiography can also indicate osteoblastic metastases from certain tumors (eg, breast, prostate, lung), which can cause hypocalcemia.

  CT scans of the head may show basal ganglia calcification and extrapyramidal neurologic symptoms (in idiopathic hypoparathyroidism).

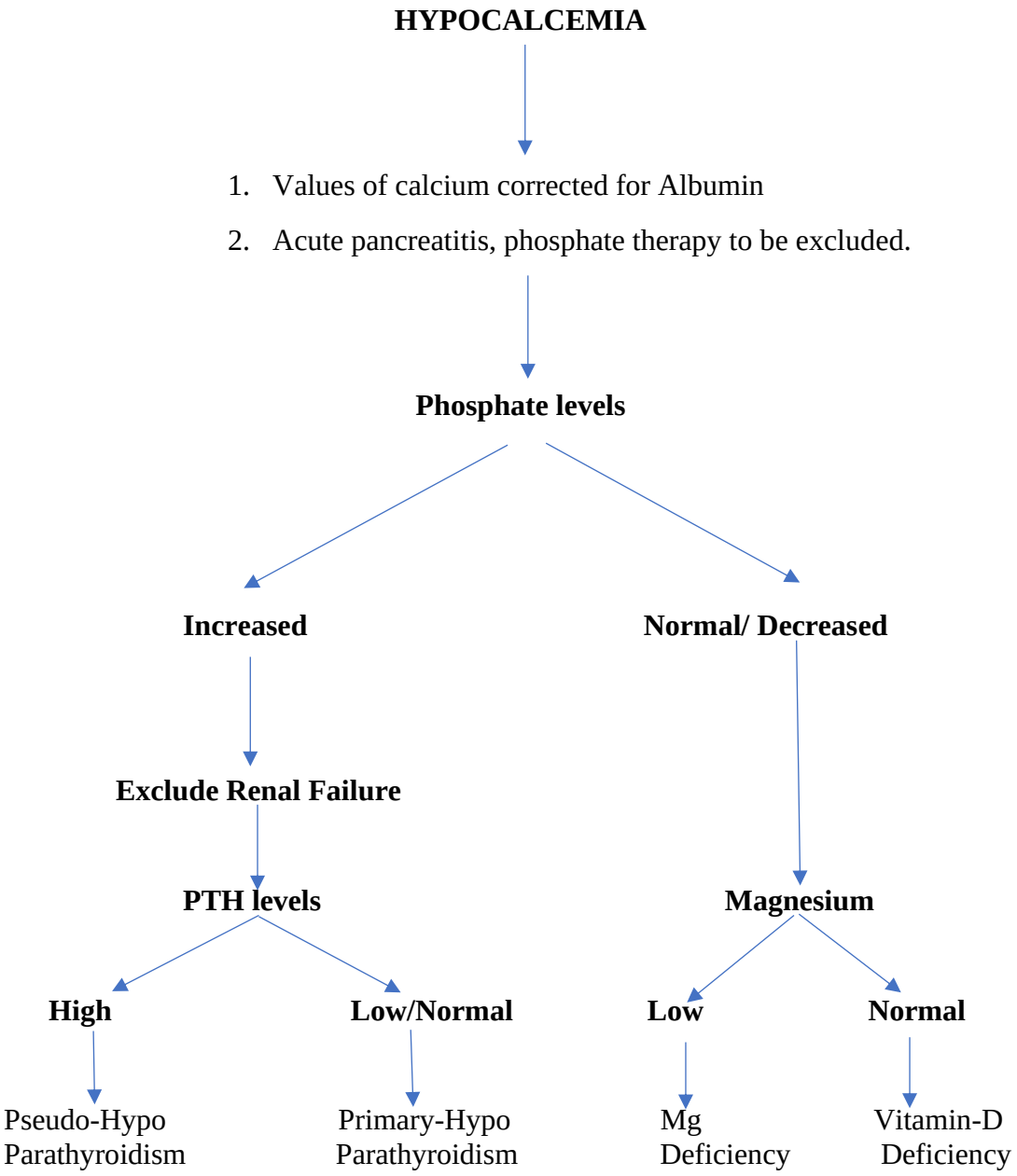


Figure 10: Flowchart showing evaluation of hypocalcemia

The intervention in an event of Hypocalcemia is dependent on presenting symptoms, and the severity and rapidity with which hypocalcemia develops.

The treatment depends on whether the hypocalcemia is Acute or Chronic. In any case, if intravenous infusions are required then it should be carried out under close monitoring in an intensive care unit or specialized unit with access to cardiac monitoring and rapid determinations of ionized calcium for evaluation.

Acute Hypocalcemia

Although hypoparathyroidism is a chronic disorder, patients can present with acute hypocalcemia in settings that reflect the early consequences of anterior neck surgery, unanticipated changes in requirements for calcium and vitamin D, or in patients who become noncompliant or are poorly compliant.

Acute hypocalcemia can be life-threatening, as patients may present with tetany, seizures, cardiac arrhythmias, laryngeal spasm, or altered mental status. After securing the Airway, 1 to 2 ampules (180 mg of elemental calcium) diluted in 50 to 100 mL of 5% dextrose is infused with a over 10 minutes, (Drip rates of 0.5-2.0 mg/kg/hour is recommended). Calcium gluconate is the preferred intravenous calcium salt as calcium chloride often causes local irritation. This can be repeated until the patient's symptoms have cleared. With persistent hypocalcemia, administration of a calcium gluconate drip over longer periods of time may be necessary.

Intravenous administration of calcium requires careful cardiac monitoring as rapid administration can result in arrhythmias. Local vein irritation can occur with solutions >200 mg/100 mL of elemental calcium. If there is local extravasation of the fluid into the soft tissues, then calcifications due to the precipitation of calcium phosphate crystals can occur.

As soon as possible, oral calcium supplementation should be initiated and, also vitamin D should be administered if required.

Calcium phosphate salt deposition can occur in any organ and is more likely if the calcium-phosphate product exceeds the value of 55. Calcium phosphate deposition in the lungs, kidney or other soft tissue may occur in patients receiving intravenous calcium especially in the presence of high serum phosphate levels.

Serum magnesium should be monitored in any patient who is hypocalcemic, and hypomagnesemia if any should be corrected prior to or along with correction of hypocalcemia.[56]

Chronic Hypocalcemia

Chronic hypocalcemia is commonly due to inadequate levels of parathyroid hormone or vitamin D, or due to resistance to these hormones. Treatment of chronic hypocalcemia involves administration of oral calcium and vitamin D supplements, as well as magnesium if deficiency is present. Treatment can be further intensified with thiazide diuretics, phosphate binders, and a low-salt and low-phosphorus diet when treating hypocalcemia secondary to hypoparathyroidism.

Oral doses calcium should be administered in the amount of 1 to 3 grams of elemental calcium in 3 to 4 divided doses with meals to ensure optimal absorption. In patients with achlorhydria, a solution of 10% calcium chloride (1- to 30 ml) every 8 hours can also effectively raise calcium levels.

One potential side effect of therapy in patients with hypoparathyroidism is hypercalciuria which can have sequalae like, nephrocalcinosis, nephrolithiasis, and or renal insufficiency.

An assessment of 24-hour urine calcium (target urinary calcium excretion is <4 mg/kg/24 hr) along with creatinine determination should be done at least annually once stable doses of supplements are established.

Vitamin D2 or D3 (ergocalciferol or cholecalciferol, respectively) or vitamin D metabolites [calcitriol]. Calcitriol, the active metabolite of vitamin D, is rapid-acting and physiologic and is often used for initial therapy. Most patients require 0.25 mcg twice daily and may require up to 0.5 mcg 4 times a day of calcitriol, however in case of growing children dose adjustment is necessary. Among other options, ergocalciferol is a less expensive choice and has a long duration of action. The usual dose is 50,000 to 100,000 IU/day. When therapy needs to be administered acutely, calcitriol is given for the first 3 weeks and then tapered off once the dose of ergocalciferol becomes effective.[57]

Serum 25 (OH) vitamin D level should be checked periodically to assure that serum 25 (OH) vitamin D levels of >20 ng/mL is maintained.

Estrogen increases calcium absorption at the level of the intestine and indirectly through stimulation of renal 1-alpha-hydroxylase activity. Dose adjustment may be required after changes in estrogen therapy due to alteration in calcium homeostasis.

Recombinant human rhPTH[1-84] and rhPTH[1-34] is being considered for the treatment of hypoparathyroidism in patients not responding to conventional therapy.

The international guidelines published in Journal of Clinical Endocrinology and Metabolism in 2016 recommended consideration of treatment with rhPTH(1-84) in patients with:

- Variable and inconstant control of the serum calcium with frequent episodes of hypo - and hypercalcemia
- Nephrolithiasis
- Nephrocalcinosis, reduced creatinine clearance or eGFR < 60 mL/min
- Hypercalciuria or other biochemical indices of renal stone risk or both
- Persistently increased serum phosphate or calcium x phosphate product or both (> 55 mg^2/dL^2 or 4.4 $mmol^2/L^2$)
- Excessive amounts of oral medications required to control symptoms, such as > 2.5 g of calcium or > 1.5 μg of active vitamin D or both
- A gastrointestinal tract disorder that might lead to variable calcium and vitamin D absorption.
- Reduced quality of life.

The six goals for management of patients with chronic hypoparathyroidism as per the International guidelines published in Journal of Clinical Endocrinology and Metabolism in 2016 include:

- Prevention of signs and symptoms of hypocalcemia
- Maintenance of serum calcium slightly below normal (no more than 0.5 mg/dL below normal) or in the low-normal range
- Maintenance of the calcium & phosphate product below 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)
- Avoidance of hypercalciuria, maintaining urinary calcium excretion within normal limits
- Avoidance of hypercalcemia.
- Avoidance of renal and other extra-skeletal calcifications.[58]

The contributions of several pioneers in thyroid surgery like Billroth, Halsted, and Kocher, along with the development of technical advances over the years, such as antisepsis and hemostatic clamps, have made thyroid surgery a relatively safe operative procedure. However, the complications associated with the surgery, although rare, are still observed. Symptomatic hypocalcemia is a particularly distressing complication and has been reported to occur in 1% to 30% of patients undergoing total thyroidectomy.

The large variation seen in incidence of postoperative hypoparathyroidism is attributed to factors such as operative technique, lymphatic dissection in the trachea-esophageal groove, extent of tumor in the central compartment, and previous thyroid surgery. Clinically, patients may present with transient or permanent hypoparathyroidism, characterized by signs and symptoms related to hypocalcemia.

By adhering to the anatomic principles and defined surgical guidelines, the incidence of iatrogenic hypoparathyroidism can be minimized to 1% to 3%. Hypoparathyroidism may result from direct injury, devascularization, and/or disruption of the parathyroid glands as discussed in above paragraphs. So familiarity with the regional anatomy is of prime importance in thyroid surgery in terms of number, location, blood supply and possible variations among each of them.

The superior parathyroids are fairly consistent in their location at the superior pole of the thyroid. The inferior parathyroids are more variable in position and, at times, are intrathymic. It is of paramount importance for the operating surgeon to understand the anatomy and blood supply of the parathyroid glands. The inferior parathyroid artery always arises from the inferior thyroid artery, which is a branch of the thyrocervical trunk.

The superior parathyroid usually receives its blood supply from the inferior thyroid artery, but occasionally the gland gets its blood supply either from the anastomotic loop between the superior and inferior thyroid arteries, or exclusively from a branch of the superior thyroid artery.

A few technical points are of paramount importance like, after ligating and dividing the middle thyroid vein, the upper pole is generally rotated medially to expose the superior parathyroid which is constant in position in the posterior aspect of the superior pole, and may be covered by the thyroid capsule. Then the superior thyroid vessels are meticulously dissected, individually ligated, and then divided. The parathyroid artery is preserved by leaving the most posterior branch of the superior thyroid artery intact until their relation to the parathyroid gland is established.

The inferior parathyroid glands are more difficult to locate because of their variable location which can be the lateral, anterolateral, or posterior aspects of the lower pole of the thyroid lobe or the gland can be intra-thymic;

Blunt dissection is used to isolate the parathyroid artery, and its origin from the inferior thyroid artery and the vessel is preserved. At this stage, the recurrent laryngeal nerve is exposed and traced carefully up to its entry into the larynx. The branches of the inferior thyroid artery are individually ligated medial to the point where they cross the recurrent laryngeal nerve. The older surgical practice to ligate the inferior thyroid artery away from the thyroid gland can probably lead to the devascularization of the parathyroid glands, so the current practice is to ligate the individual branches of the inferior thyroid artery close to the thyroid gland so that the parathyroid glands are preserved with their own blood supply.

The inferior parathyroid is frequently involved with the thymus gland, thus preservation of this tissue may maintain parathyroid function; Meticulous dissection is mandatory, and the inferior parathyroid artery must be ligated after it has given off the parathyroid branch.; Finally, the dissection in the trachea-esophageal groove should be limited without compromising excision of involved pathology.

The incidence of hypoparathyroidism is likely to be high in patients undergoing extensive trachea-esophageal groove dissection, central compartment clearance and also high in patients undergoing bilateral neck dissection. Every effort should be made to identify and carefully preserve the parathyroid with its blood supply in patients undergoing total thyroidectomy with neck dissection. If the blood supply to the glands is compromised, which can be evident by the change in colour of the glands or there is inadvertent excision of the parathyroids during surgery, it should be managed by auto transplantation, preferably in the sternocleidomastoid muscle.

Even with these techniques, occasionally the parathyroid may be difficult to preserve, especially if it is located in the anterior portion of the thyroid lobe receiving its blood supply exclusively from the thyroid gland. Under these circumstances, it may not be possible to preserve the parathyroid glands in situ, and thus parathyroid auto-transplantation should be considered.

It is also very important to confirm the diagnosis of normal parathyroid tissue before auto-transplantation so as not to auto-transplant fat pad, lymph node, or metastatic thyroid cancer. The preservation of parathyroid function is one of the requisites of thyroid surgery or surgery involving the anterior neck. Adhering to the strict surgical guidelines will minimize untoward morbidity related to thyroid surgery and prevents the sequelae of symptomatic hypoparathyroidism.

The practice followed in most hospitals requires serial measurement of serum calcium in patients undergoing Total or Completion thyroidectomy to monitor any hypocalcemia and to identify patients requiring calcium supplementation. Studies have shown that since the serum calcium levels do not undergo significant variation in the first few post-operative days, early identification of hypocalcemia is difficult and hence patients are subjected to multiple blood tests. Serum PTH can undergo a significant decrease in a short time following total thyroidectomy or any extensive neck dissection, by mechanisms like ischemia, edema or stunning of the glands. Hence the PTH levels are becoming the investigation of choice post thyroidectomy for early identification of patients who can develop hypocalcemia.

Various studies have been done regarding the appropriate timing for measuring the PTH levels, but there is no common consensus among them. PTH level estimation is expensive and many centers lack the technical feasibility to run this test, thereby limiting its widespread use.

Our study is based on estimation of post-op PTH levels at 4^{TH} and 12^{th} hour post thyroidectomy to correlate and predict the development of hypocalcemia.

MATERIALS AND METHODS

MATERIALS AND METHODS

SOURCE OF DATA:

33 patients who were planned for Total thyroidectomy in the Department of Otorhinolaryngology, R.L.J.H & R.C, Tamaka, Kolar, were taken up for the study after fulfilling the inclusion criteria and signing the informed consent.

The study took place during the period between December 2018 to May 2020.

Inclusion Criteria:

1. Patients requiring Total Thyroidectomy during the study period.

Exclusion Criteria:

1. Patients having parathyroid adenoma or hyperplasia.
2. Patients having chronic renal disease.
3. Lactating mothers.
4. Patients on calcium and vitamin –D supplementation.

STUDY DESIGN : An Cross-sectional Analytical study.

SAMPLING PROCEDURE:

SAMPLE COLLECTION - Venous blood sample will be collected under sterile precautions, 12 hours preoperatively and 4 hours and 12 hours post-operatively, 2ml Venous blood sample will be collected in red vacutainer tube taking aseptic precautions, centrifuged at 3000rpm for 10 minutes to separate serum from the clot.

The separated serum will be preserved at -20℃ until analysis. The serum sample separated will be assayed for Parathyroid hormone, total protein, albumin and total calcium levels.

SAMPLE ASSAY - Quantitative measurement of Parathyroid hormone in serum will be done by immunometric immunoassay technique using Vitros ECI Immunodiagnostic Systems. Parathyroid hormone present in the sample reacts with biotinylated antibody and horse-raddish peroxidase labelled antibody conjugate. The antigen antibody complex is captured by streptavidin on the wells. The bound HRP conjugate is measured by a Luminescent reaction. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of PTH present in the sample. The Quantitative estimation of total protein in the sample will be determined by the Biuret reagent method, serum albumin levels by bromocresol green method and total calcium by Arsenazo lll dye method using Vitros 5.1 FS dry chemistry analyzer in the central clinical biochemistry section, CDLS. THE IONISED CALCIUM levels in the sample will be determined by calculation using the formula – Ionized Calcium = [0.9 + (0.55 × total calcium - 0.3 × albumin)] .

Statistical methods :

Hypocalcemia, High risk, Low risk were considered as primary outcome variables. Post-op 4^{th} hour PTH and 12^{th} hour PTH were primary explanatory variables.

Descriptive analysis: Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables.

Data was also represented using appropriate diagrams like bar diagram, pie diagram.

All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as normal distribution.

The association between variables for non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Wilcoxon Signed Rank test, Mann Whitney U test and Kendall's W test.

X was considered as gold standard. Y was considered as screening test. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test along with their 95% CI were presented. Reliability of the screening test was assessed by kappa statistics along with its 95% CI and p Value.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram and Scatter plots.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

RESULTS

RESULTS

A total of 33 subjects were included in the final analysis.

Table 6: Descriptive analysis of age in study population (N=33)

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Age	45 ± 10.37	46.00	21.00	64.00	41.32	48.68

The mean age was 45 ± 10.37 in the study population, minimum was 21 and maximum was 64.

Table 7: Descriptive analysis of gender in the study population (N=33)

Gender	Frequency	Percentages
Male	6	18.18%
Female	27	81.82%

Among the study population, 6 (18.18%) were male and 27 (81.82%) were female.

Figure 10: Pie chart of gender in the study population (N=33)

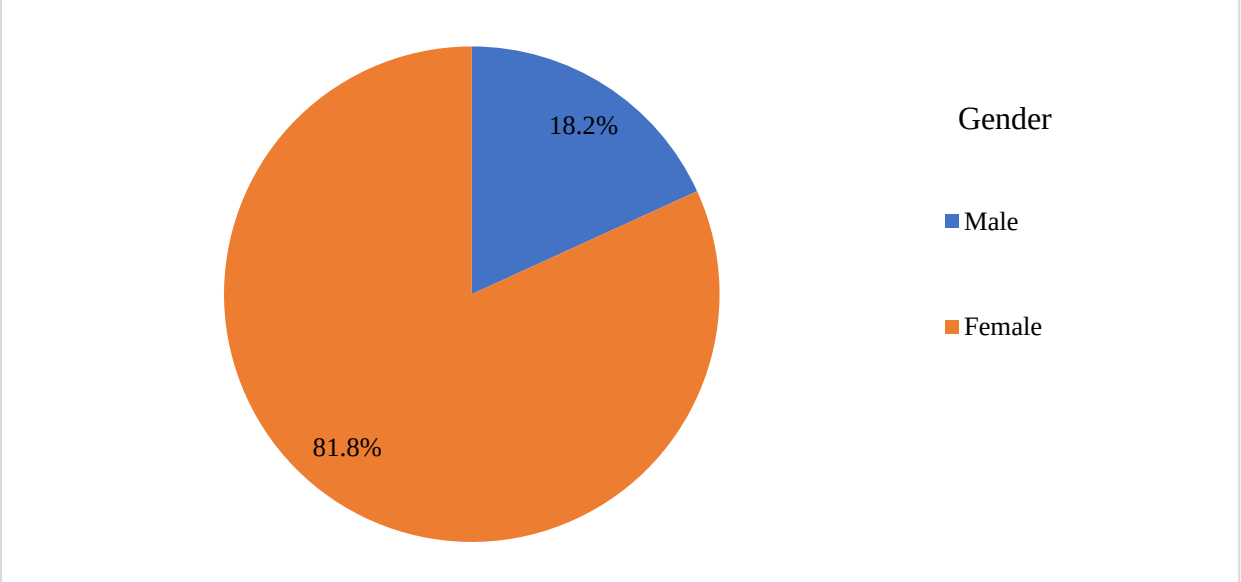


Table 8: Descriptive analysis of thyroid surgery in past in the study population (N=33)

Thyroid Surgery In Past	Frequency	Percentages
Yes	3	9.09%
No	30	90.91%

Among the study population, 3 (9.09%) had thyroid surgery in past.

Table 9: Descriptive analysis of thyroid medications in the study population (N=33)

Thyroid Medications	Frequency	Percentages
Taken	2	6.06%
Not taken	31	93.94%

Among the study population, only 2 patients (6.06%) had taken thyroid medications.

Figure 11: Pie chart of diagnosis in the study population (N=33)

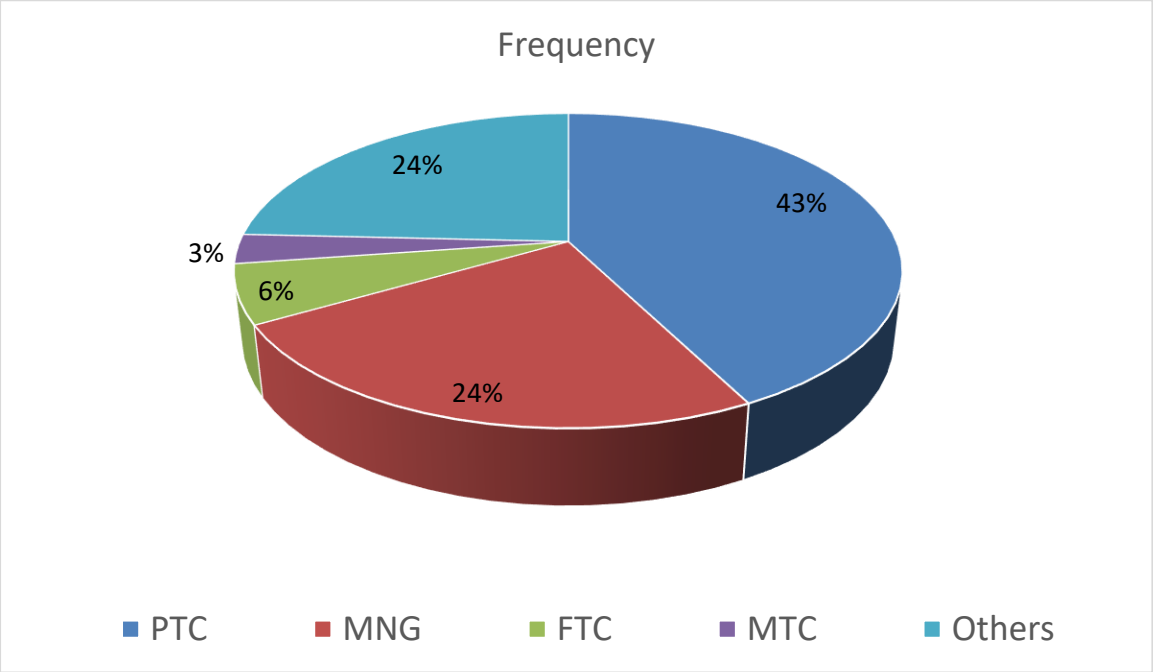


Figure 12: Bar chart of type of thyroidectomy in the study population (N=33)

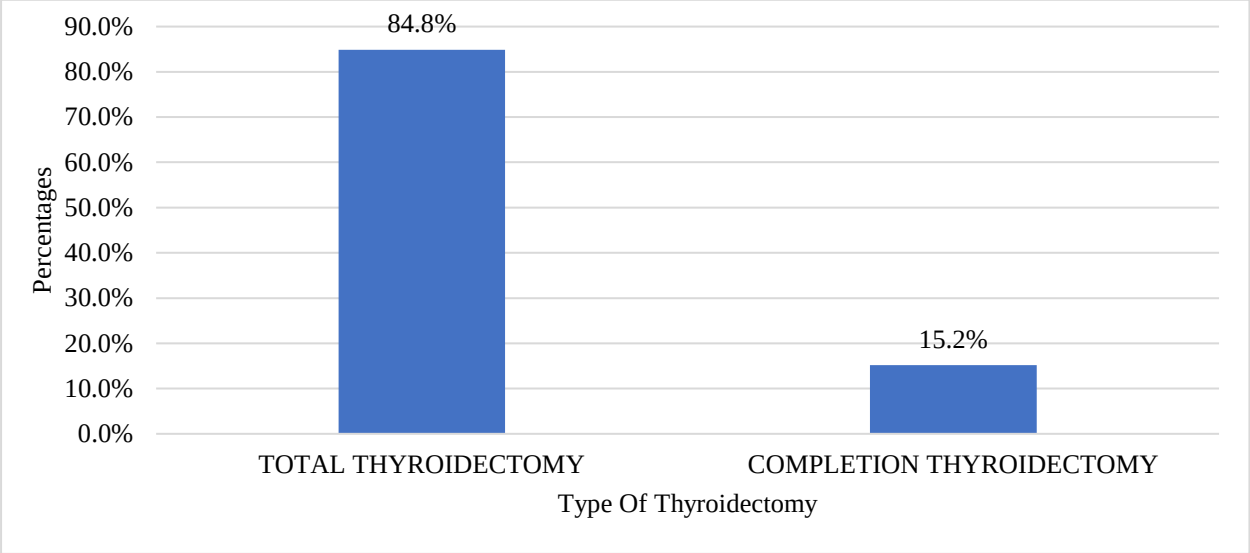


Figure 13: Bar chart of central compartment clearance in the study population (N=33)

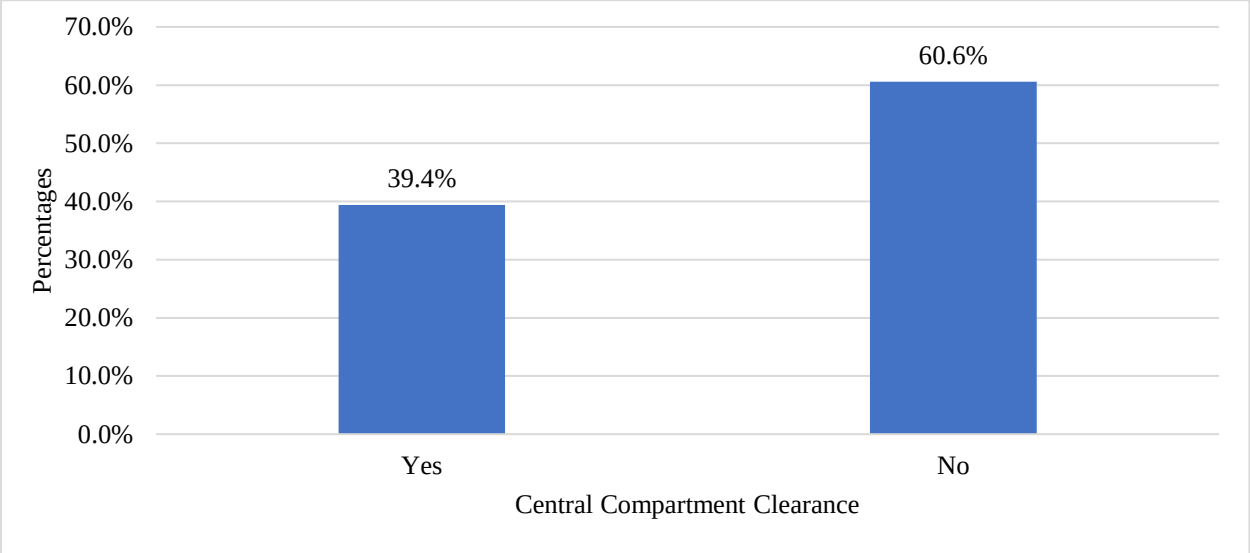


Table 10: Descriptive analysis of parathyroids visualized in the study population (N=33)

Parathyroids Visualized	Frequency	Percentages
2	9	27.27%
>2	24	72.73%

Among the study population, in 9 patients (27.27%) 2 parathyroids were visualized whereas in 24 (72.73%) > 2 parathyroid were visualized.

Table 11: Descriptive analysis of parathyroids saved in the study population (N=33)

Parathyroids Saved	Frequency	Percentages
2	25	75.76%
>2	8	24.24%

Among the study population, in 25 cases (75.76%) 2 parathyroids were saved while in 8 cases (24.24%) > 2 parathyroids were saved.

Table 12: Descriptive analysis of PTH, Total calcium, albumin and Ionized calcium in study population (N=33)

	Mean ± SD	**Median**	**Minimum**	**Maximum**	**95% C.I**	
					Lower	**Upper**
Pre-Op PTH	**18.16 ± 10.18**	**17**	**4.3**	**47.5**	**14.55**	**21.77**
Post-Op 4Th Hour	**12.77 ± 7.25**	**11**	**3.4**	**29.1**	**10.2**	**15.34**
Post-Op 12Th Hour	**9.71 ± 5.31**	**8.9**	**3.4**	**26.1**	**7.82**	**11.59**
Pre-Op Total calcium	**9.3 ± 0.84**	**9.5**	**7.2**	**10.8**	**9**	**9.6**
Post-Op 4Th Hour Total Calcium	**8.45 ± 0.96**	**8.4**	**6.2**	**10**	**8.1**	**8.79**
Post-Op 12Th Hour Total Calcium	**8.17 ± 1.17**	**8.3**	**4**	**9.8**	**7.75**	**8.58**
Serum. Albumin	**3.97 ± 0.3**	**3.9**	**3.5**	**4.5**	**3.87**	**4.08**
Post-Op 4Th Hour Ionized Ca2+	**4.35 ± 0.53**	**4.3**	**3.17**	**5.17**	**4.17**	**4.54**
Post-Op 12Th Hour Ionized Ca2+	**4.2 ± 0.65**	**4.22**	**1.9**	**5.1**	**3.97**	**4.43**

Figure 14: Bar chart of hypocalcemia symptoms in the study population (N=33)

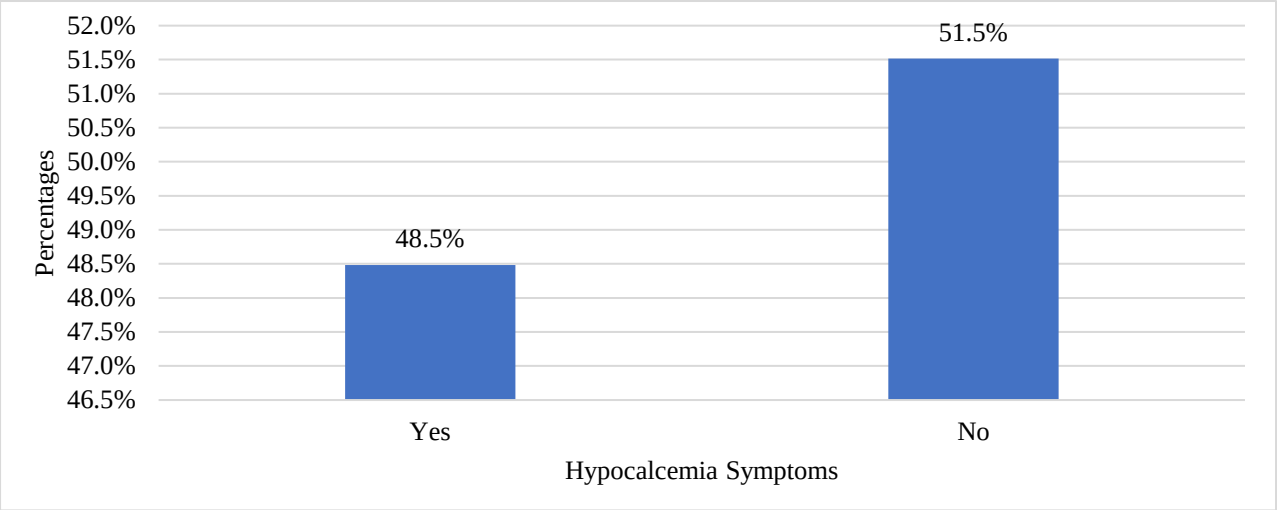


Figure 15: Bar chart of hypocalcemia signs in the study population (N=33)

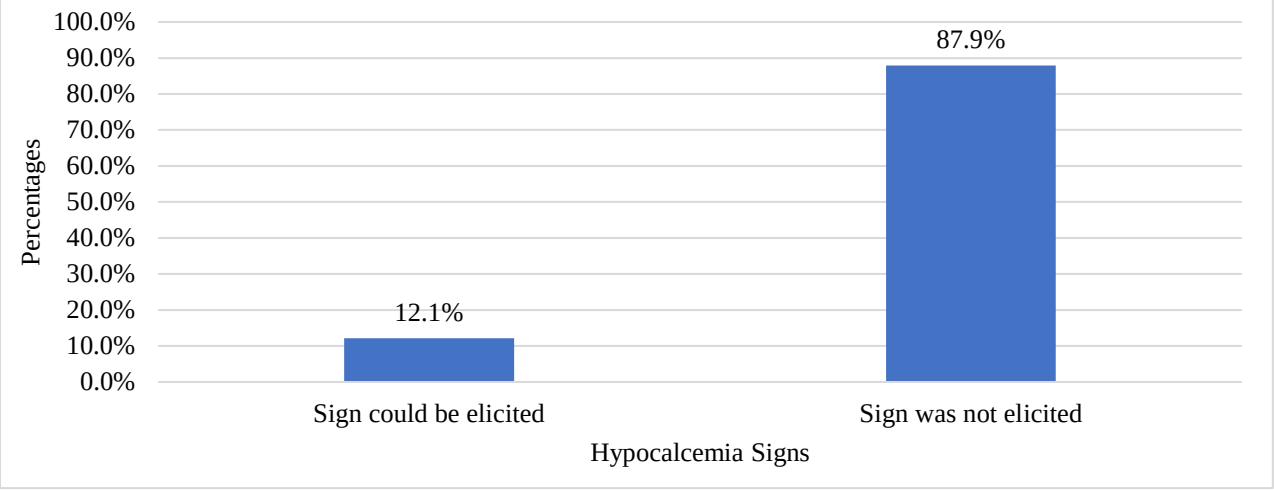


Table 13: Descriptive analysis of low risk cases in the study population (N=33)

Parameter	Frequency	Percentages
High Risk Cases (N=18)		
Normocalcemia	4	12.12%
Hypocalcemia	14	42.42%
Low Risk Cases (N=15)		
Normocalcemia	12	37.50%
Hypocalcemia	3	9.38%

Among the study population in high risk cases, 4 (12.12%) of the participants had Normocalcemia, 14 (42.42%) of the participants had Hypocalcemia.In the low risk cases, 12 (37.50%) of the participants had Normocalcemia, 3 (9.38%) of the participants had Hypocalcemia.

Figure 16: Pie chart of high risk cases in the study population (N=18)

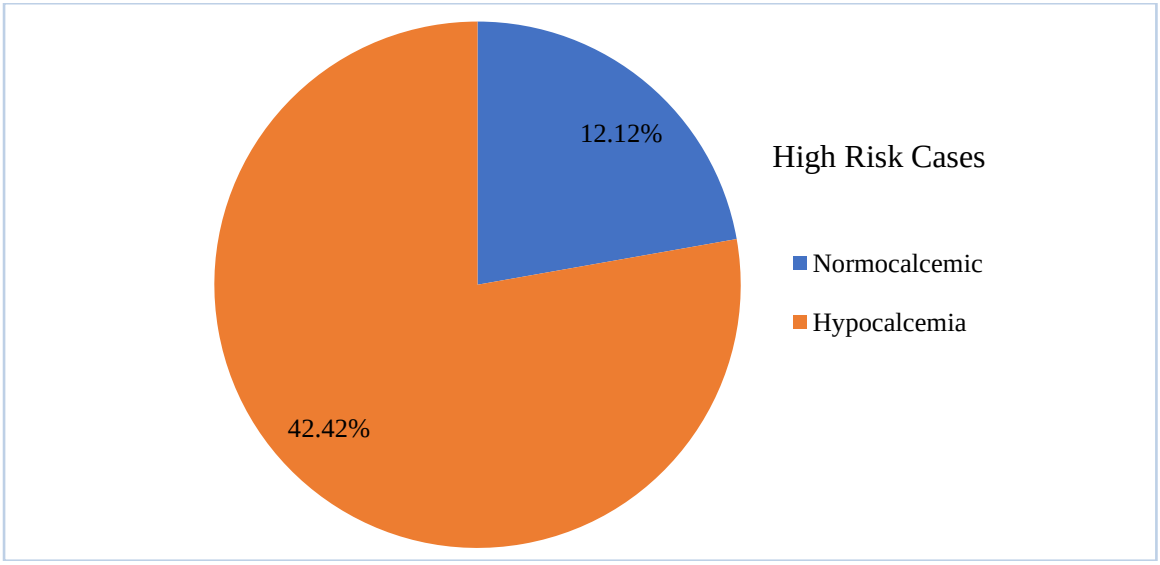


Figure 17: Pie chart of low risk cases in the study population (N=15)

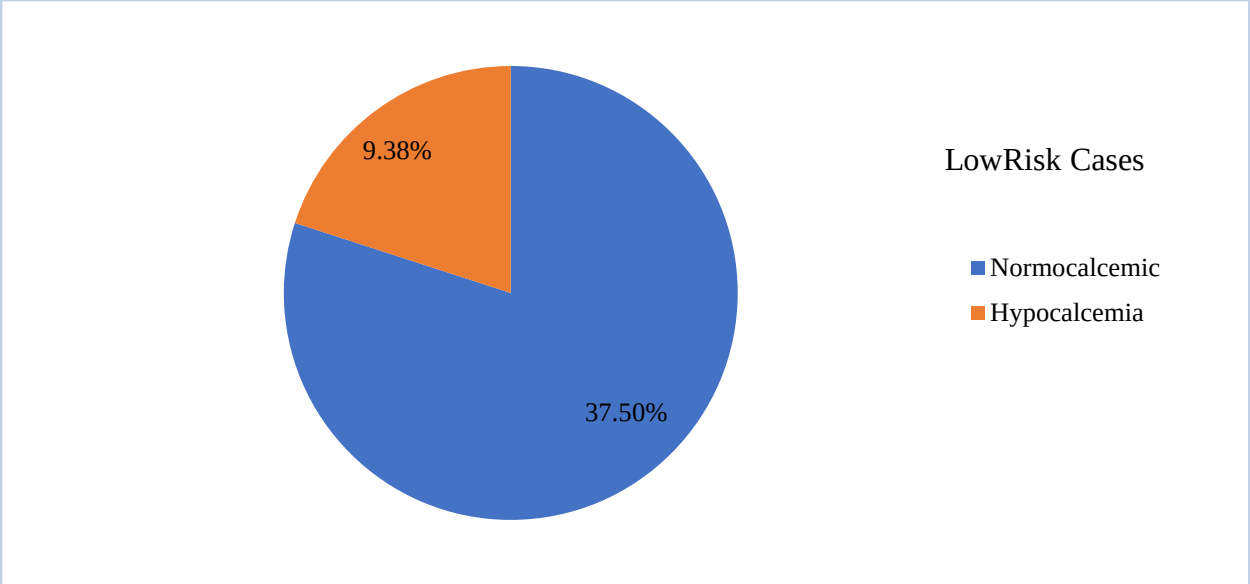


Table 14: Descriptive analysis of follow-up ionized calcium in the study population (N=32)

Follow-Up Ionized Calcium	Frequency	Percentages
Hypocalcemia	10	31.25%
Normocalcemic	22	68.75%

Among the study population, 10 (31.25%) of the participants had hypocalcemia after 1 month of follow-up while 22 (68.75%) of the participants were found to be Normocalcemic.

Figure 18: Bar chart of follow-up ionized calcium in the study population (N=32)

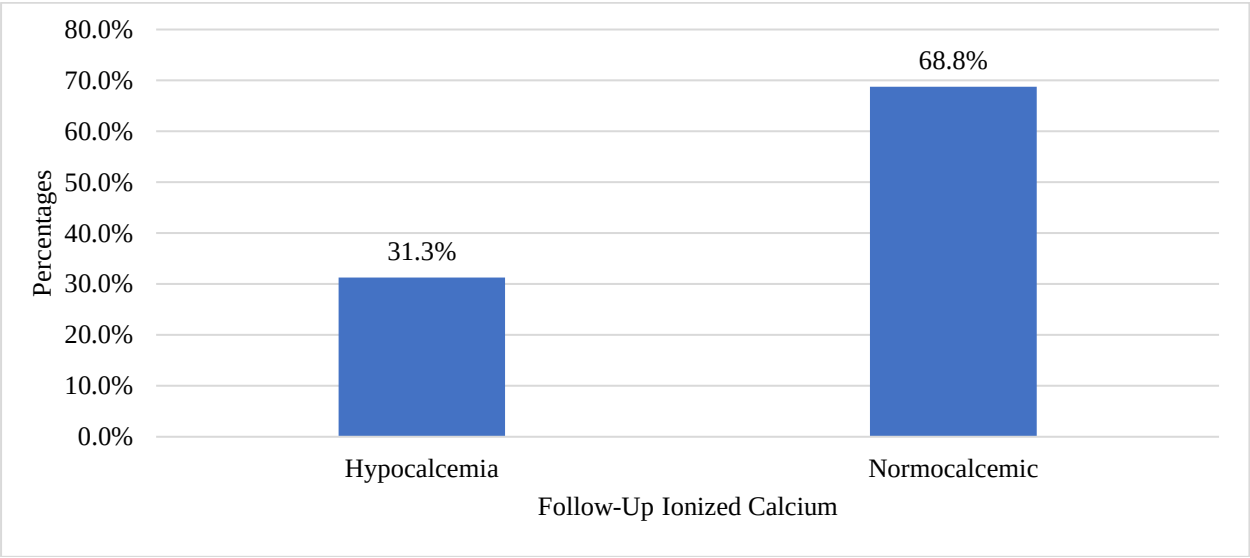


Table 15: Comparison of diagnosis between follow-up ionized calcium (N=32)

Diagnosis	Follow-Up Ionized Calcium	
	Hypocalcemia (N=10)	Normocalcemic (N=22)
PTC	6 (60%)	7 (31.82%)
MTC	0 (0%)	1 (4.55%)
FTC	2 (20%)	0 (0%)
MNG	1 (10%)	7 (31.82%)
Others (Inflammatory/Infectious Cause)	1 (10%)	7 (31.82%)

In hypocalcemic participants, 6 (60%) had PTC, 2 (20%) had FTC. For MNG and others each had 1 (10%). In normocalcemic participants, 7 (31.82%) had PTC, 1 (4.55%) had MTC, 7 (31.82%) had MNG, 7 (31.82%) had Others (Inflammatory Causes).

Figure 19: Cluster bar chart of comparison of diagnosis between follow-up ionized calcium (N=32)

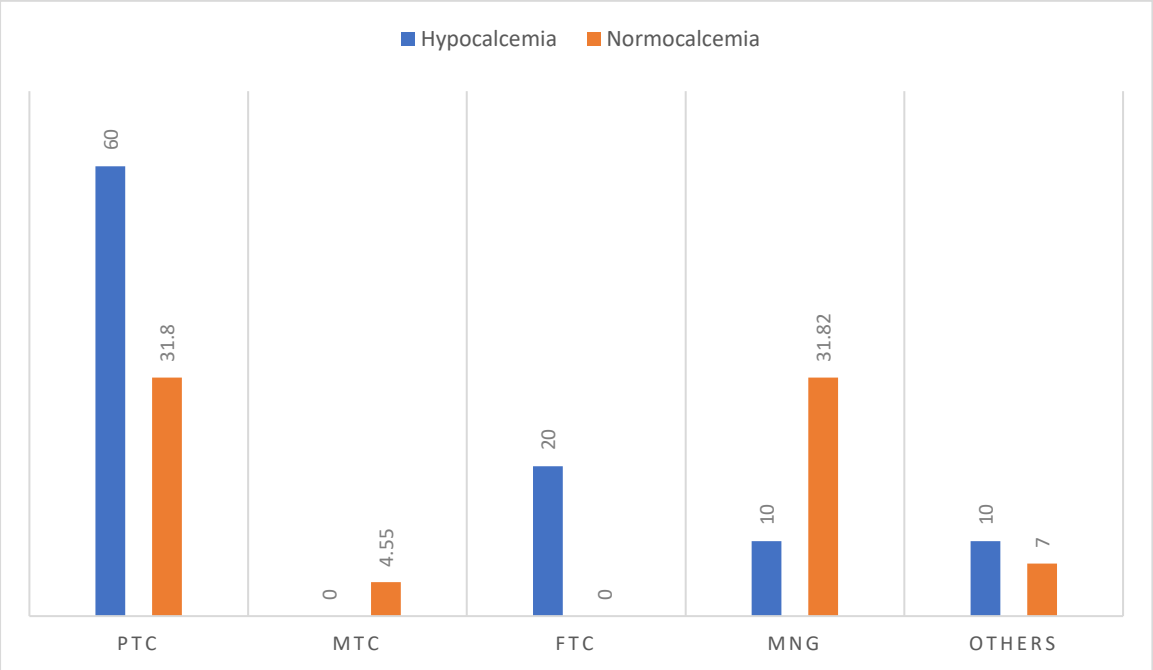


Table 16: Comparison of diagnosis between risk (N=33)

Diagnosis	Risk	
	High (N=18)	Low (N=15)
PTC	10 (55.5%)	4 (26.67%)
MTC	1 (5.56%)	0 (0%)
FTC	2 (11.11%)	0 (0%)
MNG	2 (11.11%)	6 (40%)
Others (Inflammatory/ Infectious Cause)	3 (16.67%)	5 (33.33%)

In high-risk participants, 10 (55.5%) had PTC, 1 (5.56%) had MTC, 2 (11.11%) had FTC, 2 (11.11%) had MNG and 3 (16.67%) had Others (Inflammatory). In low risk participants, 4 (26.67%) had PTC, 6 (40%) had MNG, 5 (33.33%) had Others (Inflammatory Cause).

Figure 20: Cluster bar chart of comparison of diagnosis between risk (N=33)

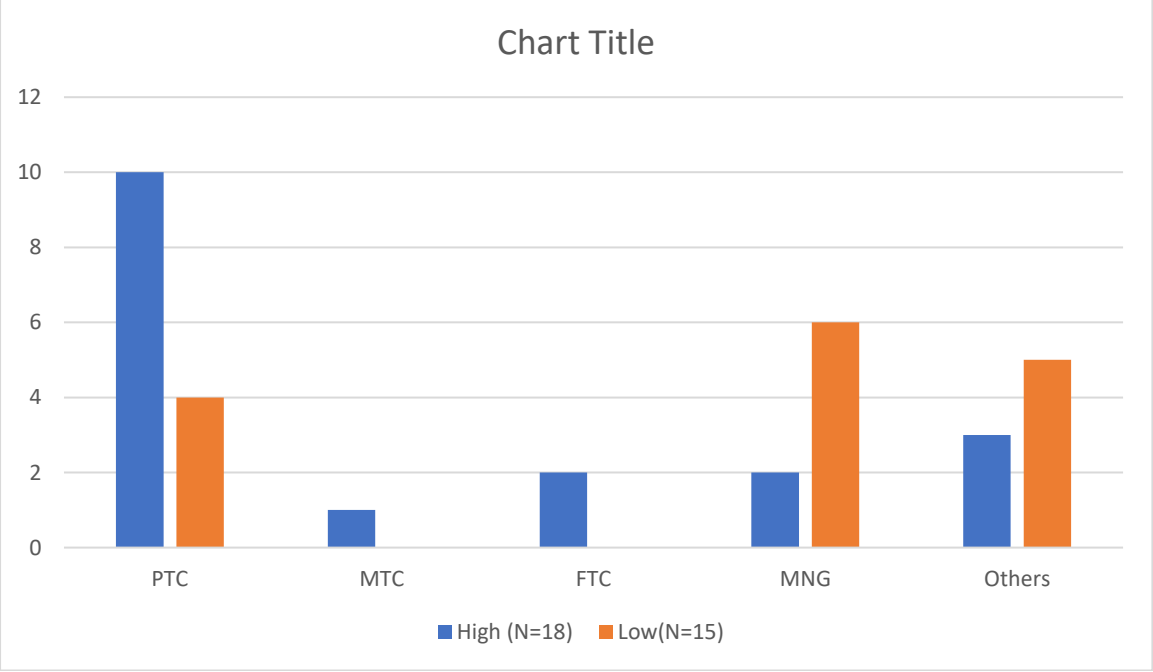


Table 17: Comparison of type of thyroidectomy between risk (N=33)

Type Of Thyroidectomy	Risk		Fisher exact P value
	High (N=18)	Low (N=15)	
Total Thyroidectomy	16 (88.89%)	12 (80%)	0.639
Completion Thyroidectomy	2 (11.11%)	3 (20%)	

In high-risk participants, 16 (88.89%) had Total Thyroidectomy and 2 (11.11%) had Completion Thyroidectomy. In low-risk participants, 12 (80%) had Total Thyroidectomy and 3 (20%) had Completion Thyroidectomy. There was no statistically significant difference between type of thyoidectomy and risk groups (P value 0.639).

Figure 21: Staked bar chart of comparison of type of thyroidectomy between risk (N=33)

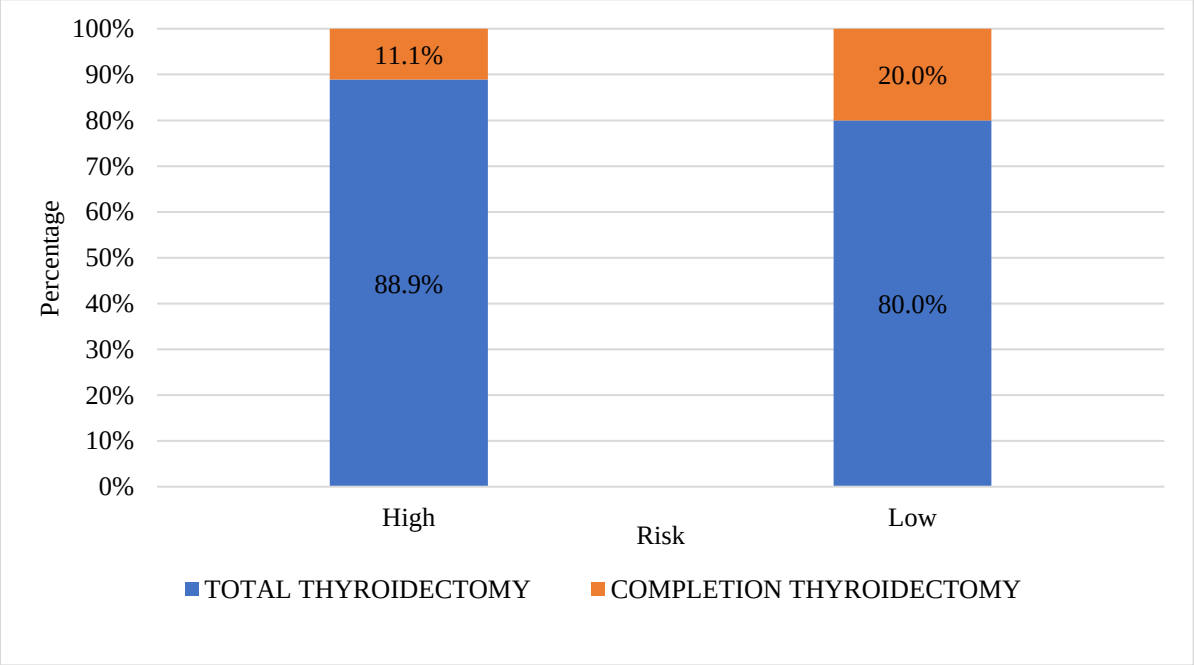
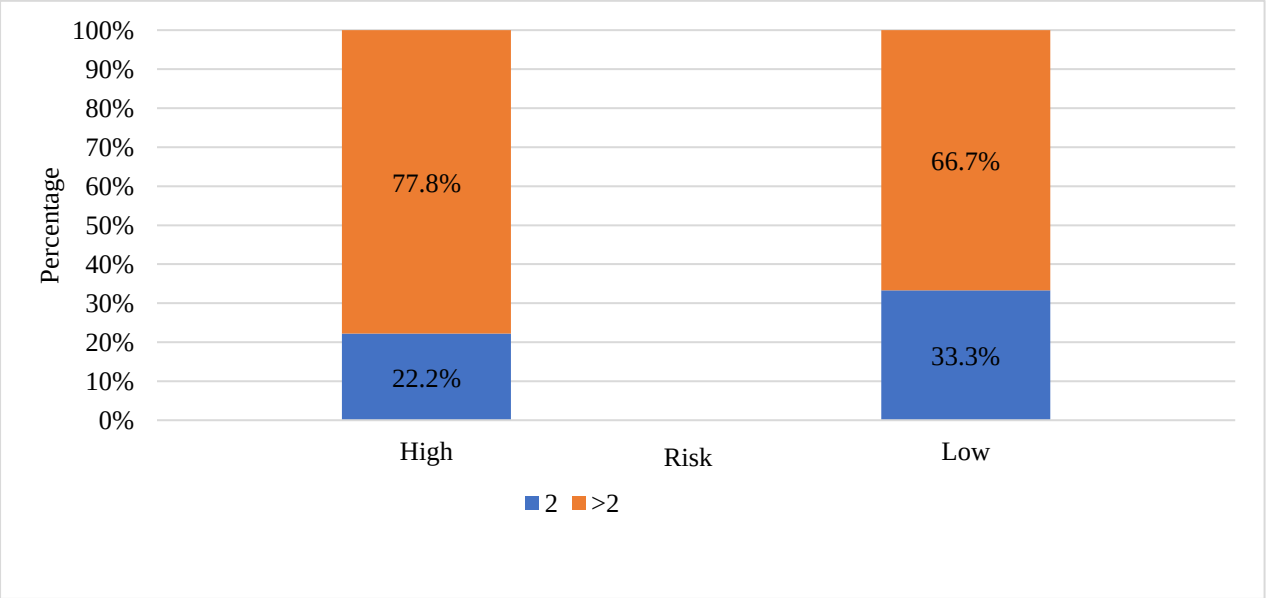


Table 18: Comparison of central compartment clearance between risk (N=33)

Central Compartment Clearance	Risk		Chi square	P value
	High (N=18)	Low (N=15)		
Yes	12 (66.67%)	1 (6.67%)	12.337	<0.001
No	6 (33.33%)	14 (93.33%)		

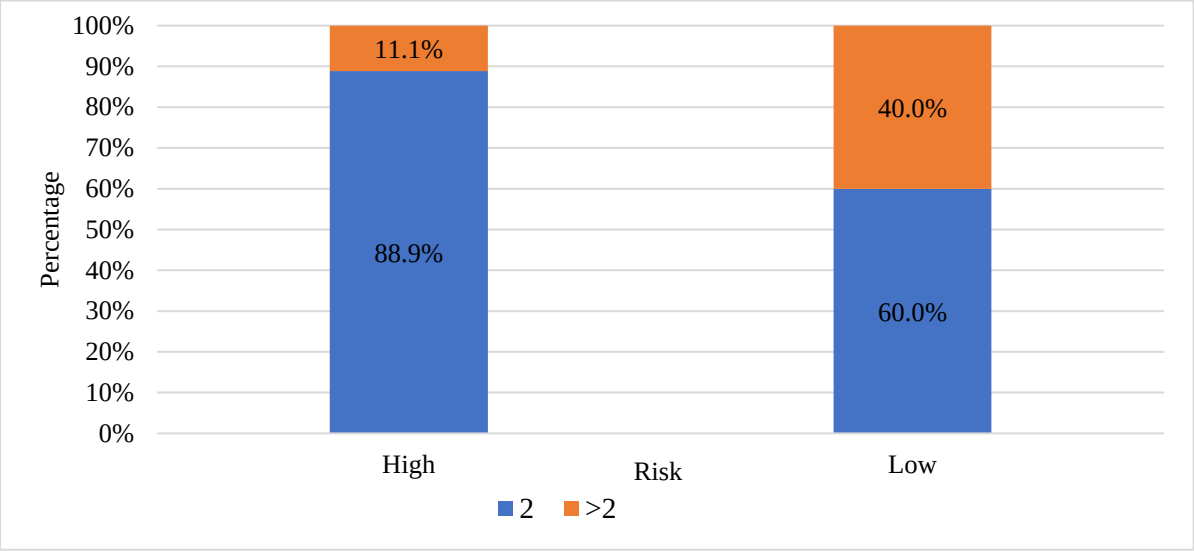
In high risk participants, 12 (66.67%) had Central Compartment Clearance and in low risk participants, 1 (6.67%) had Central Compartment Clearance. There was statistically significant difference in Central Compartment Clearance between risks. (P value <0.001)

Figure 22: Staked bar chart of comparison of parathyroids visualized between risk (N=33)



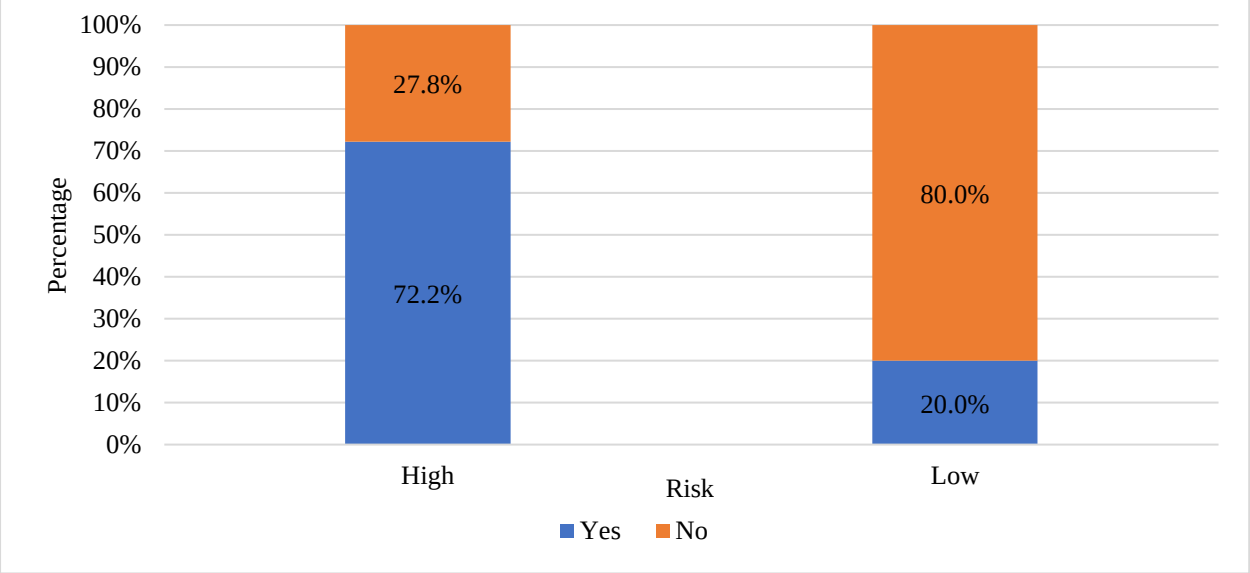
In high risk participants, 4 (22.22%) had 2 parathyroids visualized and 14 (77.78%) had >2 parathyroids visualized. In low risk participants, 5 (33.33%) had 2 parathyroids visualized and 10 (66.67%) had >2 parathyroids visualized. There was no statistically significant difference in parathyroids visualized between risk. (P value 0.697)

Figure 23: Staked bar chart of comparison of parathyroids saved between risk (N=33)



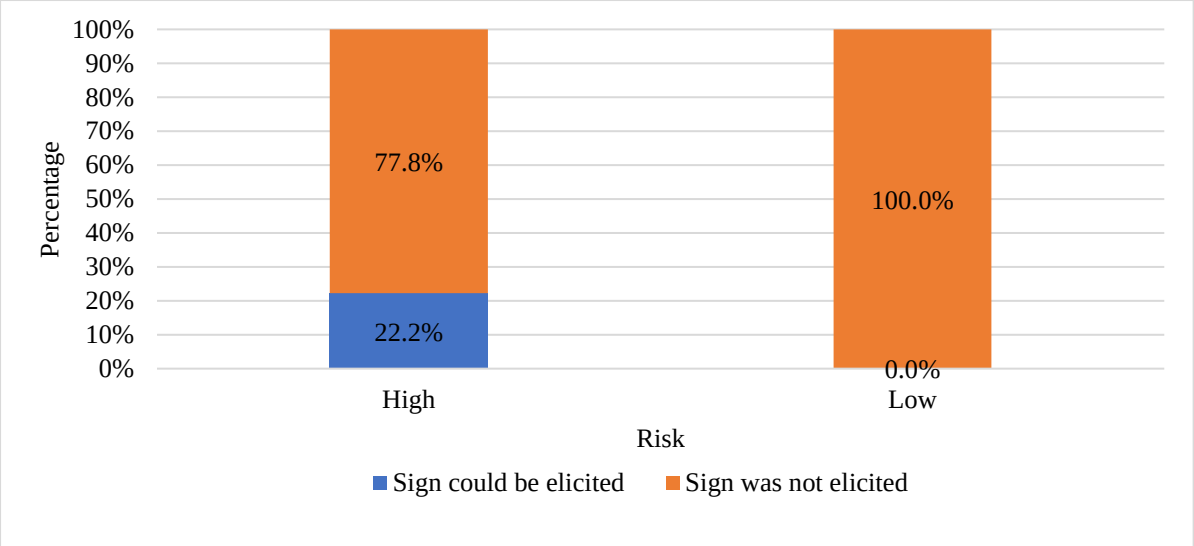
In high risk participants, 16 (88.89%) had 2 parathyroids saved and 2 (11.11%) had >2 parathyroids saved. In low risk participants, 9 (60%) had 2 parathyroids saved and 6 (40%) had >2 parathyroids saved. There was no statistically significant difference in parathyroids saved between risk. (P value 0.101).

Figure 24: Staked bar chart of comparison of hypocalcemia symptoms between risk (N=33)



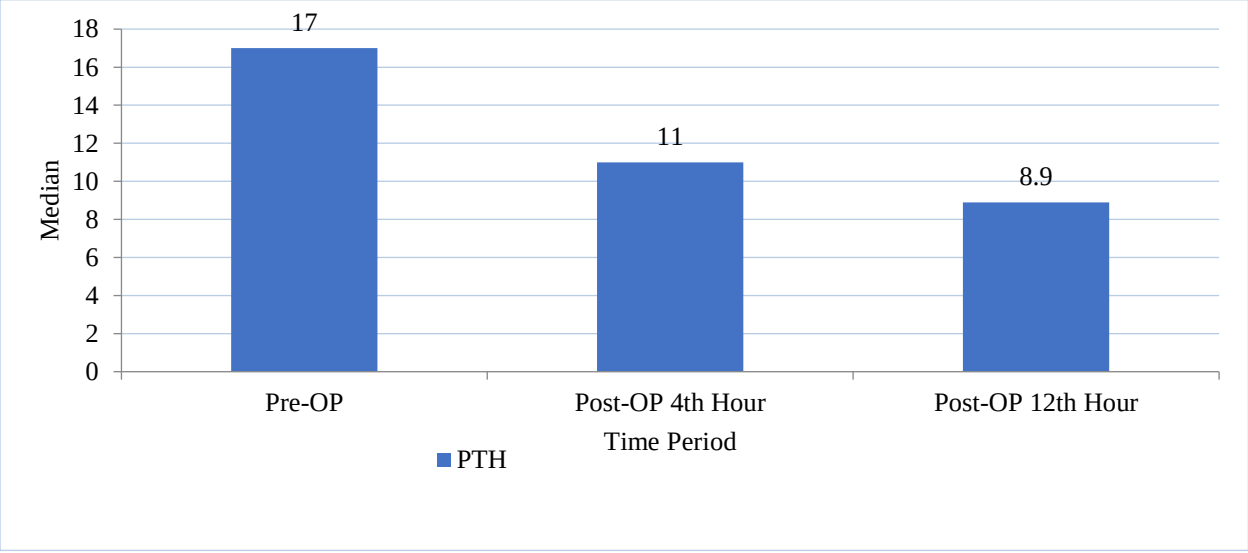
In high risk participants, 13 (72.22%) had hypocalcemia symptoms and in low risk participants 3 (20%) had hypocalcemia symptoms. There was statistically significant value in hypocalcemia symptoms between the risk. (P value 0.003)

Figure 25: Staked bar chart of comparison of hypocalcemia signs between risk (N=33)



In high participants, 4 (22.22%) had sign that elicited and in low risk participants none had sign that elicited.

Figure 26: Bar chart of PTH within each time period (N=33)



Among the study population, PTH median was 17 (IQR 9.75 to 26.25) of pre-operative, PTH median was 11 (IQR 7.05 to 16.60) of post-operative 4th Hour and PTH median was 8.9 (IQR 5.05 to 13.60) of post-operative 12thHour.There exists a statistically significant difference in PTH between different time periods of operation. (P Value <0.001).

Figure 27: Predictive validity of Post Op 4Th Hour PTH in predicting follow-up ionized calcium (ROC analysis)

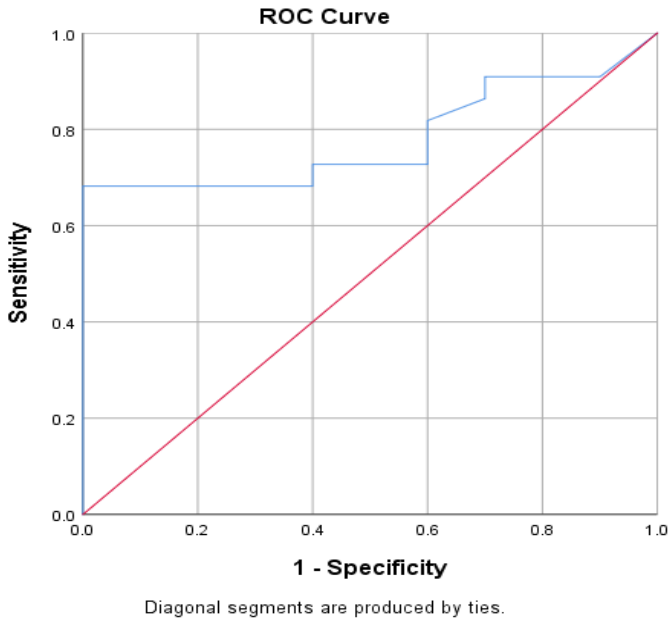


Table 19: Predictive validity of Post Op 4Th Hour PTH in predicting follow-up ionized calcium (ROC analysis) (N=32)

Test Result Variable(s): Post Op 4Th Hour PTH				
Area Under the Curve	Std. Error	95% Confidence Interval of AUC		P value
		Lower Bound	Upper Bound	0.012
0.780	0.081	0.621	0.938	

The Post Op 4Th Hour had fair predictive validity in predicting follow-up ionized calcium, as indicated by area under the curve of 0.780 (95% CI 0.621 to 0.938, P value 0.012).

Table 20: Predictive validity of Post Op 4Th Hour in predicting Follow-up ionized calcium (N=32)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	70.00%	34.75%	93.33%
Specificity	68.18%	45.13%	86.14%
False positive rate	31.82%	13.86%	54.87%
False negative rate	30.00%	6.67%	65.25%
Positive predictive value	50.00%	23.04%	76.96%
Negative predictive value	83.33%	58.58%	96.42%
Diagnostic accuracy	68.75%	49.99%	83.88%

Figure 28: Predictive validity of Post Op 12Th Hour PTH in predicting follow-up ionized calcium (ROC analysis)

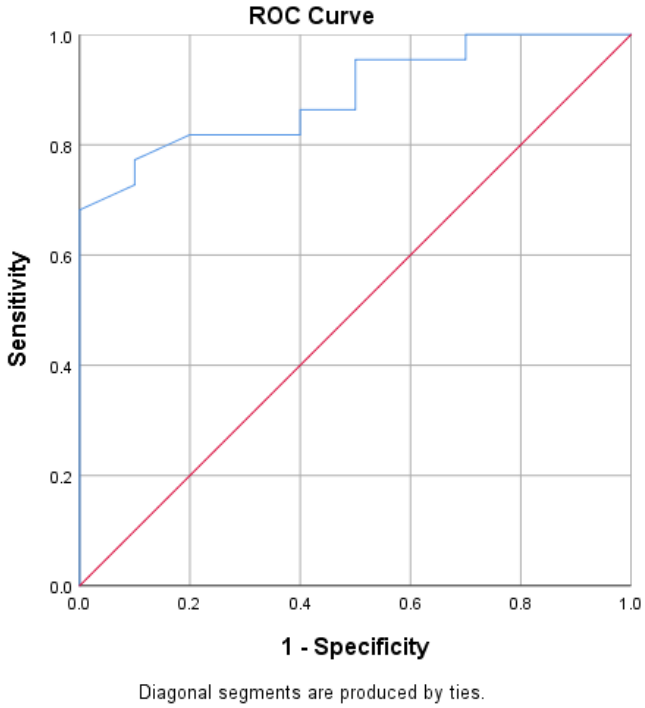


Table 21: Predictive validity of Post Op 12Th Hour in predicting follow-up ionized calcium (ROC analysis) (N=32)

Test Result Variable(s): Post Op 12Th Hour PTH				
Area Under the Curve	Std. Error	95% Confidence Interval of AUC		P value
		Lower Bound	Upper Bound	
0.891	0.056	0.782	1.000	<0.001

The Post Op 12Th Hour PTH had good predictive validity in predicting follow-up ionized calcium, as indicated by area under the curve of 0.891 (95% CI 0.782 to 1.000, P value <0.001)

Table 22: Predictive validity of Post Op 12Th PTH Hour in predicting Follow-up ionized calcium (N=32)

Parameter	**Value**	**95% CI**	
		Lower	**Upper**
Sensitivity	70.00%	34.75%	93.33%
Specificity	68.18%	45.13%	86.14%
False positive rate	31.82%	13.86%	54.87%
False negative rate	30.00%	6.67%	65.25%
Positive predictive value	50.00%	23.04%	76.96%
Negative predictive value	83.33%	58.58%	96.42%
Diagnostic accuracy	68.75%	49.99%	83.88%

Table 23: Correlation between Post Op 4th hour PTH and Post Op 4th hour Ionized calcium

Correlations			
		Post-Op 4th Hour PTH	Post-Op 4TH Hour Ionized Calcium
Post-Op 4th Hour PTH	Pearson Correlation	1	0.478**
	P value		0.005
	N	33	33
**. Correlation is significant at the 0.01 level (2-tailed).			

In the study there was significant correlation between Post Op PTH at 4th hour and Post Op 4th Hour Ionized Calcium i.e. with increase in PTH there was increase in Ionized calcium at post op 4th hour and vice versa.

Figure 29: Scatter Plot showing Correlation between Post Op 4th hour PTH and Post Op 4th hour Ionized calcium

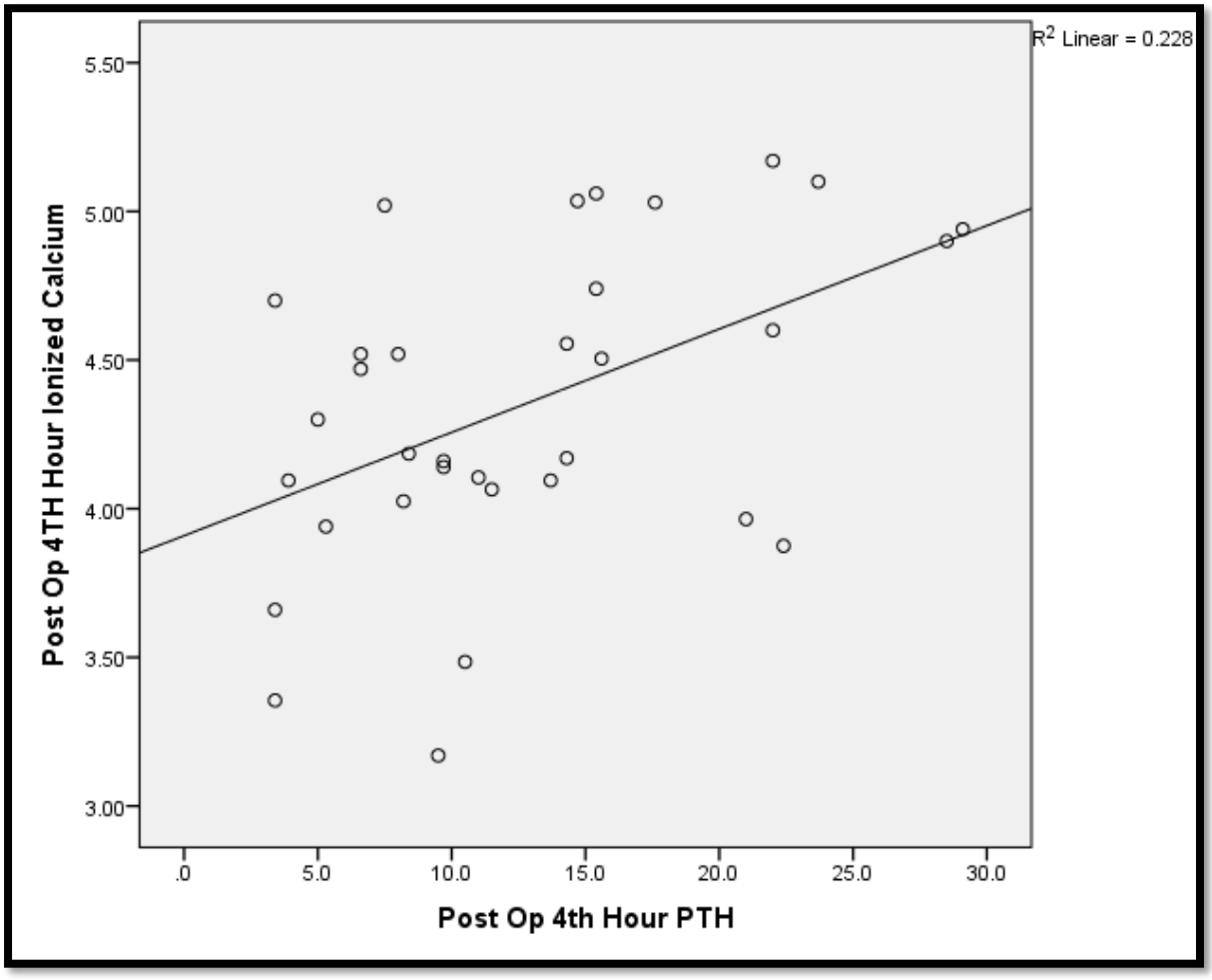


Table 24: Correlation between Post Op 12th hour PTH and Post Op 12th hour Ionized calcium

Correlations			
		Post-Op 12th Hour PTH	Post-Op 12TH Hour Ionized Calcium
Post-Op 12th Hour PTH	Pearson Correlation	1	0.399*
	P value		0.021*
	N	33	33
*. Correlation is significant at the 0.05 level (2-tailed).			

In the study there was significant correlation between Post Op PTH at 12th hour and Post Op 12th Hour Ionized Calcium i.e. with increase in PTH there was increase in Ionized calcium at post op 12th hour and vice versa.

Figure 30: Scatter Plot showing Correlation between Post Op 12th hour PTH and Post Op 12th hour Ionized calcium

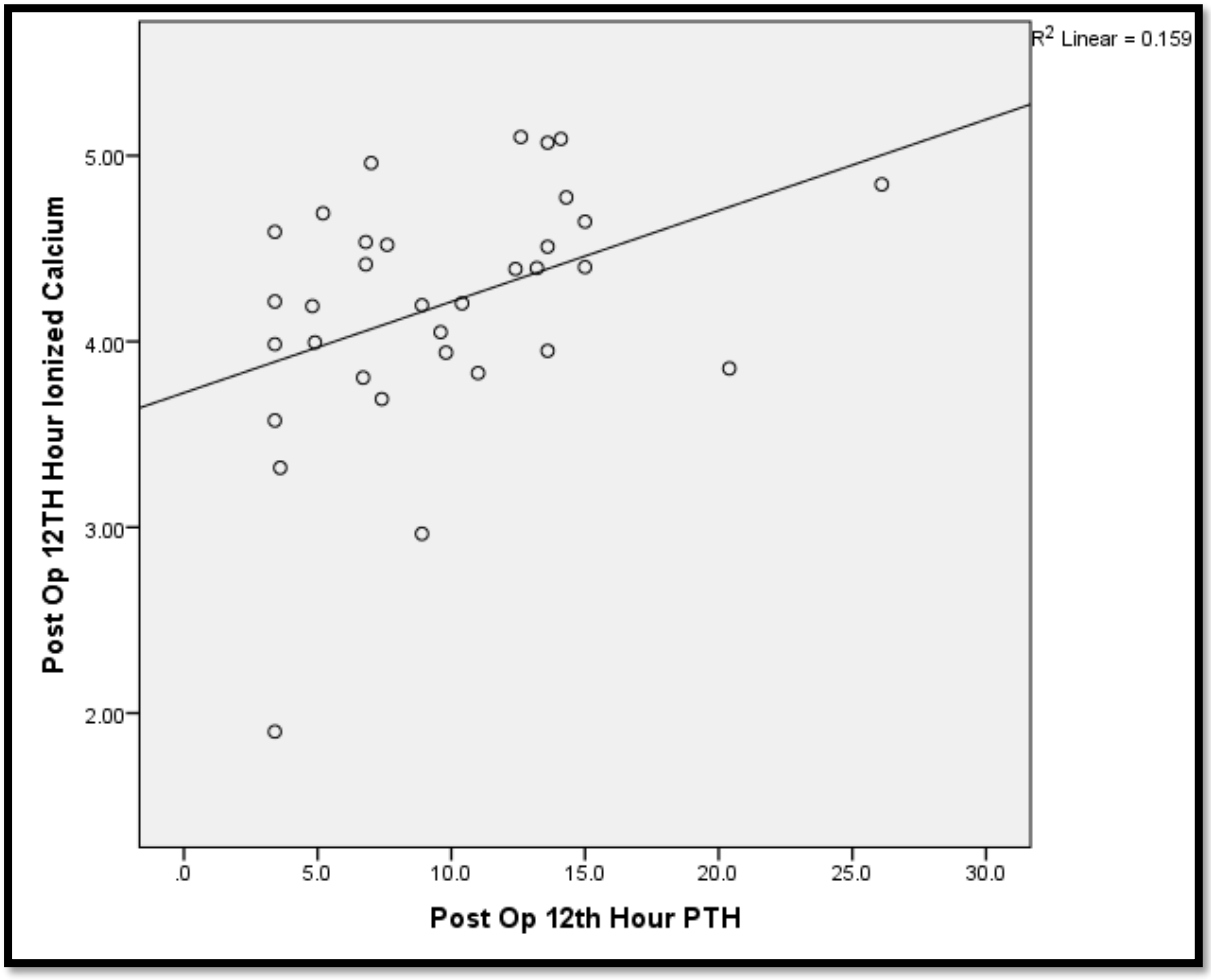


Table 25: Validity of PTH at 4th hour in predicting Hypocalcaemia at 4th Hour (ionized calcium)

Area under the ROC curve (AUC)	0.748
Standard Error	0.0946
95% Confidence interval	0.567 to 0.882
z statistic	2.624
Significance level P (Area=0.5)	0.0087

PTH value of ≤13.7 at 4th hour had highest sensitivity and specificity in predicting hypocalcaemia at post op 4th hour. Sensitivity was 83.3%, specificity was 73.33%, PPV was 78.9% and NPV was 78.6%.

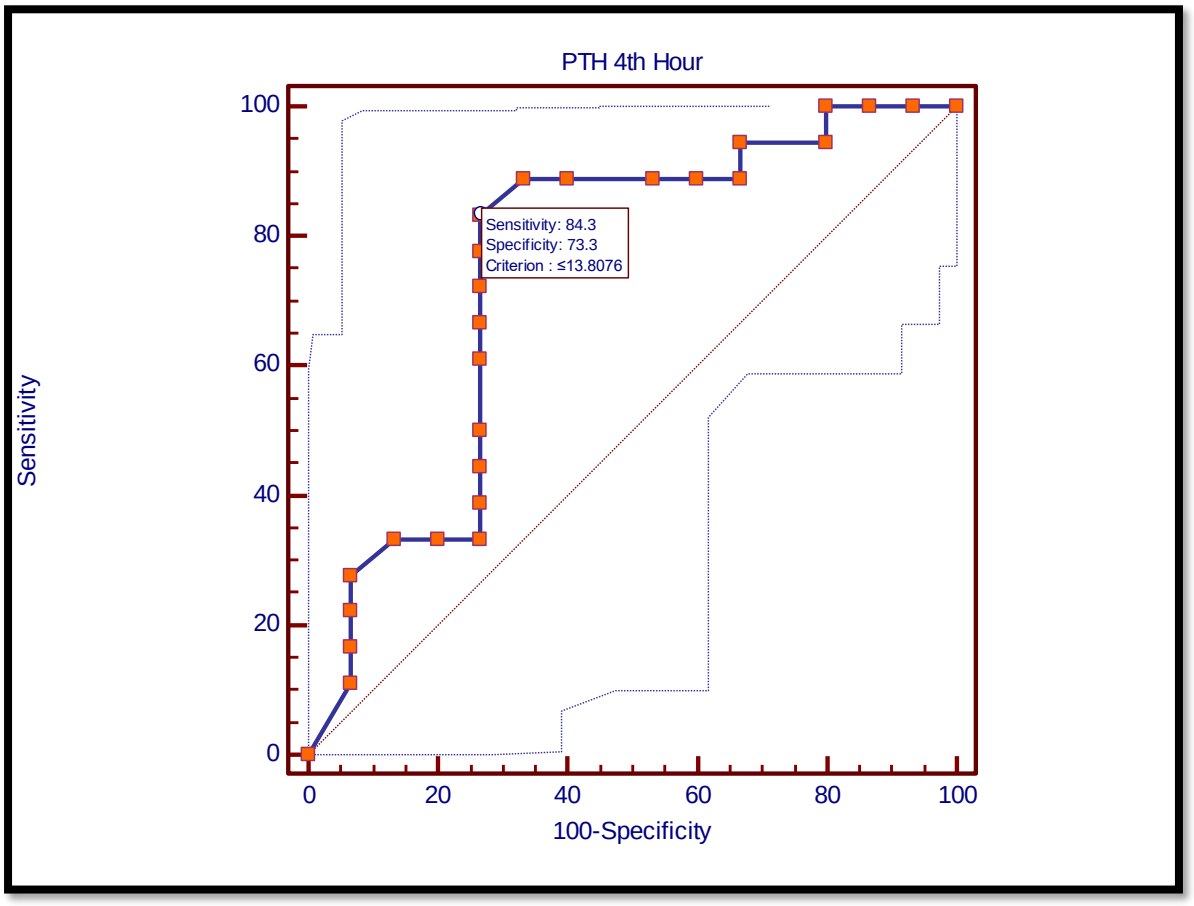
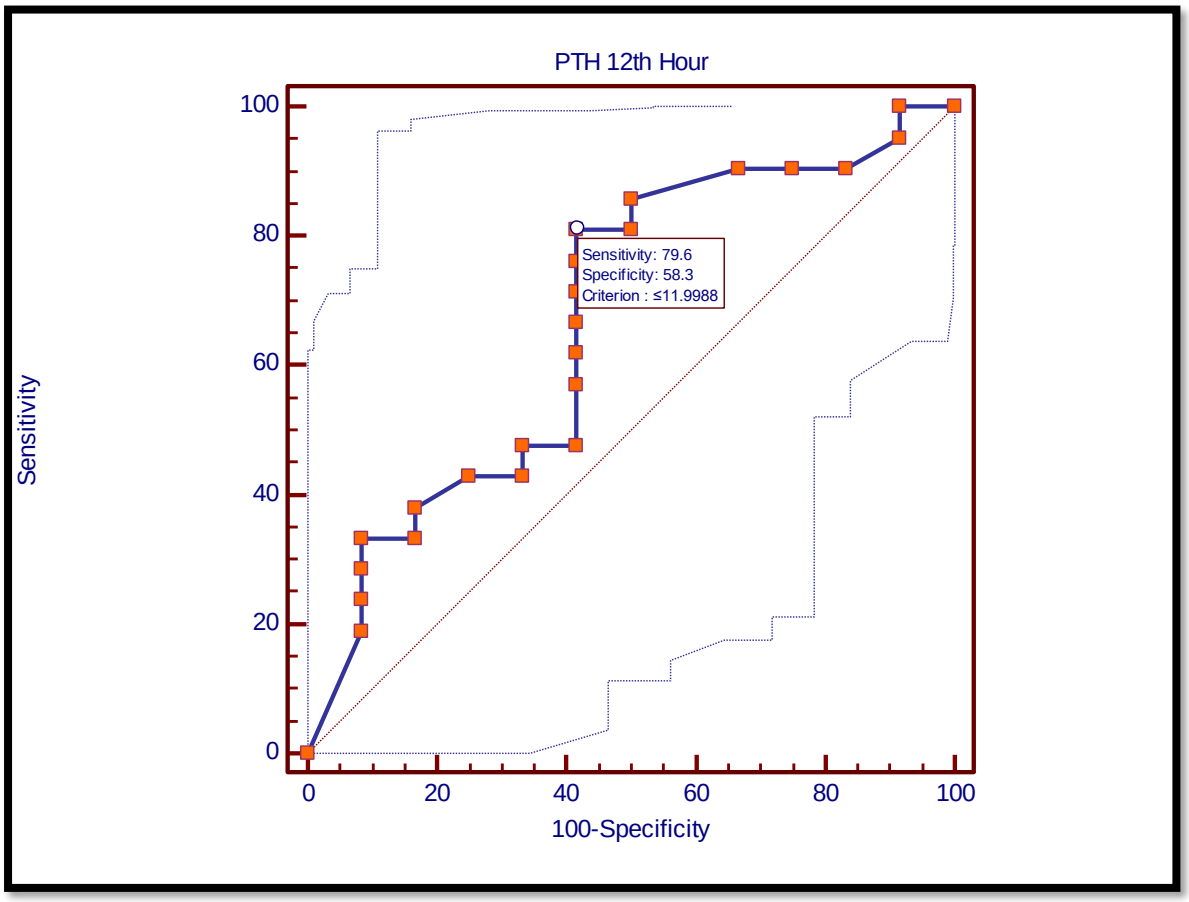


Table 26: Validity of PTH at 12th hour in predicting Hypocalcaemia at 12th Hour (ionized calcium)

Area under the ROC curve (AUC)	0.671
Standard Error	0.104
95% Confidence interval	0.486 to 0.824
z statistic	1.641
Significance level P (Area=0.5)	0.1007

PTH value of ≤12.4 at 12th hour had highest sensitivity and specificity in predicting hypocalcaemia at post op 12th hour. Sensitivity was **80.95**%, specificity was 58.33%, PPV was 77.3% and NPV was 63.6%.


PTH 12th Hour
Sensitivity
100
80
60
40
20
0
0
20
40
60
80
100
100-Specificity
Sensitivity: 79.6
Specificity: 58.3
Criterion : ≤11.9988

DISCUSSION

Thyroidectomy though considered safe carries risks especially, in terms of hypo-functioning of the parathyroid glands. Along with thyroid surgeries, any surgery of the anterior neck (central compartment) predisposes the parathyroid glands to the risk of being inadvertently removed along with the thyroid specimen, or having vascular compromise leading to a fall in the serum parathormone (PTH, Parathyroid hormone) levels.[59]

The fall in serum parathyroid hormone levels post thyroidectomy often manifests as hypocalcemia with an incidence of 1-50%.[60]

In our study, the estimated rate of transient hypocalcemia was 42%. This hyposecretion of PTH can be relatively transient [1.6% – 68%] or permanent [0.4% – 33%].[59,61]

Numerous theories have been described in the literature like, injury/removal or devascularization of the parathyroid glands, hemodilution secondary to intraoperative fluid administration, calcitonin release after manipulation of the thyroid or hungry bone syndrome, but the exact mechanism of transient hypocalcemia remains unclear.[62]

Some physicians follow routine administration of calcium and vitamin D supplementation to all total thyroidectomy patients, while others obtain serial calcium measurements in order to predict patients who can develop hypocalcemia. However, none are cost- -effective strategies since in former, all the patients are exposed to side effects of calcium (when less than half actually need the supplementation), and in the latter, there can be a delay in discharge and also the patient is subjected to the discomfort of multiple venipunctures. Some authors have suggested that protocols based on calcium slope are useful, but they still require serial blood sampling, can postpone treatment and may prolong hospital stay.[63]

Serum Calcium is not an accurate predictor for Hypocalcemia as levels do not undergo significant change until one to two days post thyroidectomy and also the hypocalcemia symptoms might not appear for 24 to 48 hours post-operatively.

Hence, post-operatively it is difficult to predict whether a patient is at a greater risk of developing hypocalcemia based upon only calcium levels or surgical events.[62,64]

So, as a common practice in our center, calcium and/or calcitriol are administered prophylactically to patients following total thyroidectomy surgery.[58,65]

Symptomatic hypocalcemia can be an emergency condition and therefore a cause for significant distress to the patient. Hence there is always a preferred need for a method that can reliably identify patients who are at risk for developing hypoparathyroidism in the post-operative period.

In order to reliably predict the risk of development of hypocalcemia in patients undergoing total thyroidectomy more specific biochemical tests can be done, like serum parathyroid hormone level estimation, as it has been shown by studies that the post-operative serum PTH levels can be a predictor of occurrence as well as severity of hypocalcemia after thyroidectomy.

Numerous studies have utilized either absolute values or relative percentage decrease of PTH for diagnosis and in addition, various timings for measurement of serum PTH levels have also been suggested by some studies, ranging from intraoperative measurements to measurements in the early postoperative period (generally 1-4 hours after surgery) and even up to 24 hours postoperatively. In almost all of these settings, PTH has been found to be a reliable early marker for postoperative hypocalcemia.

During the last several years, a number of researchers have measured PTH levels within minutes or hours of the thyroidectomy procedure in an attempt to predict postoperative hypocalcemia.

Most of these studies suggested that PTH assays performed within hours of the surgery may identify patients with hypocalcemia who require medical attention. Some of these studies showed that PTH levels had a predictive value of about 100%.

A large meta-analysis done in 2014, suggested that lower postoperative PTH levels 30 minutes to 5 days after surgery are associated with transient hypocalcaemia. It also showed that low postoperative PTH between 1 hour and 1 day after surgery had a sensitivity ranging from 69%-100% in predicting transient hypocalcaemia.

In a prospective study done in Canada, 42 patients were followed postoperatively with serial PTH and Calcium measurements and it was found that patients who exhibited a PTH level ≤ 9 pg/mL at post-op 1 hour, developed hypocalcemia requiring treatment with calcium and vitamin D whereas, none of the patients with PTH ≥ 9 developed hypocalcemia. Subsequent study conducted at same center (100 total and completion thyroidectomy patients), stated that more than half of the patients with 1-hour post-surgery PTH levels in the range of 9–12 pg/ml developed transient hypocalcemia.

Our study categorizes post-thyroidectomy patients as high risk for developing hypocalcemia based on Post-op 4^{th} hour PTH of less than 12 pg/ml. The high-risk group was started on prophylactic treatment with calcium and vitamin D whereas those with Post-op 4^{th} Hour PTH levels of 12 pg/ml or higher were classified as low risk, and were not given prophylactic treatment.

The outcomes of PTH determinations after a total thyroidectomy, led some investigators to evaluate its usefulness to predict hypocalcemia following thyroid surgery.

Studies have found that all patients with PTH level less than 8 pg/mL measured one hour after the surgery became hypocalcaemic, and all patients with PTH level greater than 9 pg/mL did not. Similarly, some have stated that, PTH less than 10 pg/mL measured four or six hours after surgery predicted hypocalcemia with an overall accuracy of 98%.

Few studies also state that a postoperative PTH level of 12 pg/mL or less was also a good predictor of hypocalcemia. The Australian Endocrine Guidelines has adopted the recommendations of Lombardi and colleagues to standardize obtaining a PTH level 4 hours after a thyroidectomy. The wide variability of the predictors for the development of hypocalcemia across centres suggests that the measurement of PTH at any time in the postoperative period may be a reliable predictor of hypocalcemia. Almost all studies define hypocalcemia as either low levels of serum calcium or development of symptoms of hypocalcemia. Our study was in accordance with these studies.[59,66,67,70]

Despite all favorable outcomes, however, no common guidelines regarding the use of PTH have been established, nor has its use been universally adopted in common practice, also the widespread application of PTH assay is expensive and many centers do not have access to the PTH assay kits or the technical feasibility to run the tests.

Studies have evaluated the possible risk factors that include patient characteristics, disease related factors or surgical procedures which can influence the development of post-thyroidectomy hypoparathyroidism. In literature, different opinions have been stated about the correlation between development of postoperative hypocalcemia and patient age.

A systematic review observed no correlation between patient's age and post-operative hypocalcemia. In most studies female gender has been identified as a significant risk factor for hypocalcemia. In fact, females have been found to be more prone for developing this complication. In our study, female patients developed transient hypocalcemia in 44% (12/27) of cases, which was significantly greater than that detected in men, 33% of the cases (2/6).[68,71,72]

There can be variations in the serum calcium levels in women due to hormonal changes during the time of menopause.

Hence evaluations of bone mineral density, menstruation status, and hormone levels (estrogen, progesterone) may be necessary. Almost all the previous studies, including ours, did not take into consideration, these possible confounding factors.[73]

In accordance with other studies, we did not find a relationship between patient demographic characteristics and development of hypocalcemia.

In our study we found that in both High and Low risk group there was significant decrease in mean Calcium levels at 4^{th} hour and 12^{th} hour compared to pre op Calcium levels and that the mean perioperative variation in serum calcium levels (difference between preoperative level and 4 h or 12 h postoperative level) was significantly higher in patients that developed transient hypocalcemia ($p < 0.001$) These findings clearly show that peri-operative variation of calcium levels plays an important role in development of transient hypocalcemia. This finding is also confirmed by other studies in which a larger decrease in post-operative calcium (measured within 6 hours of surgery) from preoperative levels was associated with transient hypocalcemia.

The extent of the thyroidectomy, and malignant neoplasm are commonly considered to be risk factors for post-thyroidectomy hypocalcemia. Multivariate analyses by various authors confirmed that extent of resection is a major risk factor for both transient and permanent hypoparathyroidism after thyroid surgery even when surgical technique and surgeon expertise are controlled for.

In our statistical analysis, the pathologic finding of malignancy was significantly associated with the development of hypocalcemia as can be shown by comparison of risk groups.[69,74]

The high risk group had majority of patients (75%) with thyroid malignancy, most of them had diagnosis of PTC (77%), 80 % of whom developed transient hypocalcemia, out of which 6 remained hypocalcemic at the end of 1 month.

Similarly, majority of the patients constituting the low risk group had benign pathology (73%) with Multinodular Goitre being the most common diagnosis. 3 patients, with MNG developed transient hypocalcemia. However all of them became normocalcemic by the end of 1 month.

The current study also demonstrates that extent of resection remains the strongest independent risk factor for postoperative hypoparathyroidism. In the study all patients who developed transient hypocalcemia and were hypocalcemic after 1 month of follow-up (i.e prolonged hypocalcemia) had undergone total thyroidectomy.

According to a meta-analysis, the incidence of transient and permanent hypocalcemia in a group that underwent prophylactic central compartment clearance were 26.0 and 2.0 %, respectively, when compared to 10.8 and 1.2 %, in the group that did not undergo prophylactic central compartment clearance.

Also, one of the largest series in the literature on complications of Central compartment clearance done in 1087 patients over a 30-year period, found that bilateral central compartment clearance had a significantly higher rate of transient (51.9% vs. 27.7%, respectively) and permanent hypoparathyroidism (16.2% vs. 6.3%, respectively) than total thyroidectomy alone.

In our study, patients undergoing TT with Central compartment clearance had a higher rate of Transient [69.2% vs. 20%, respectively] and Prolonged hypoparathyroidism [46% vs. 20%, respectively] than patients undergoing total thyroidectomy alone. However, central compartment clearance was found to be a significant risk factor for only transient hypoparathyroidism. (P value <0.001)

In our practice, 65% of patients with thyroid malignancy and 12.5% of patients with benign pathology (routine Central compartment clearance was done) underwent Central compartment clearance, out of which among the former, 91% had diagnosis as Papillary thyroid carcinoma whereas, in the later 1 had MNG while other patient Hashimoto's thyroiditis.[71,74,75,76]

Preservation of the parathyroid glands in situ by careful dissection and preservation of their blood supply is a recommended surgical strategy in thyroid surgery to decrease the rate of postoperative hypoparathyroidism. Removal of a single parathyroid gland is not associated with postoperative hypocalcemia whereas resection of at least 2 parathyroid glands increases the risk of transient and permanent hypoparathyroidism.[77,78]

Another study states that number of Parathyroid identified during surgery does not influence the occurrence of hypocalcemia.[2] Similar results were obtained in our study where, less than 2 parathyroids were visualized among 9 patients (27.27%) while in the rest 24 patients (72.73%) 2 or more parathyroids were visualized. In 25 (75.76%) patients less than or equal to 2 parathyroids were saved and in 8 (24.24%) of them more than 2 parathyroids were saved. There was no statistically significant difference in the occurrence of hypocalcemia with respect to the number of parathyroid visualized or saved within the risk groups. (P value 0.697) and (P value 0.101) respectively.

Additionally, we have also taken into account another time interval i.e. Post-op 12^{th} hour PTH, for evaluating its ability to predict hypocalcemia.

Based upon the ROC the Post Op 12Th Hour PTH had good predictive validity in predicting the risk, as indicated by area under the curve of 0.906 (95% CI 0.779 to 1.000, P value <0.001).

The Post Op 12Th Hour PTH had good predictive validity in predicting follow-up ionized calcium levels, as indicated by area under the curve of 0.891 (95% CI 0.782 to 1.000, P value <0.001). Hence utility of Post-op 12^{th} hour PTH as an additional time interval to predict hypocalcemia following total thyroidectomy can be considered.

Similarly, The Post Op 4Th Hour had fair predictive validity in predicting follow-up ionized calcium, as indicated by area under the curve of 0.780 (95% CI 0.621 to 0.938, P value 0.012).

In our study we found out that, in predicting the risk of development of hypocalcemia after 1 month of surgery, Post-op 4^{th} hour PTH and Post-op 12^{th} hour PTH have similar, sensitivity; specificity and Diagnostic accuracy (70%, 68.18%, and 68.75% each respectively) for predicting hypocalcemia at the end of 1month follow-up period.

While to predict the risk of development of transient hypocalcemia we found that post-op 4th hour PTH is a better predictor than the Post-op 12th hour PTH, as the association of former with development of hypocalcemia in the immediate post-operative period is statistically more significant than the latter.

Hence both post - op 4th and 12th hour PTH levels were found to have almost similar ability in predicting transient and prolonged hypocalcemia in the patients undergoing total thyroidectomy and either of them can be used as a predictor with similar results.

Additionally, with further analysis of our results, we suggest that PTH value of $\leq$ 13.7 at 4th hour and PTH value of $\leq$12.4 at 12th hour can be taken into consideration as cut-offs to predict hypocalcemia, however prospective studies with larger sample size are required to prove the reliability of each of these predictors of hypocalcemia.

Similar results have been observed in other studies with minimal variation of cut-off levels of serum parathyroid and serum calcium in the post-operative period.

SUMMARY

Total thyroidectomy is a frequently done surgery in the department of otorhinolaryngology in our hospital. Hypocalcemia is one of the complications of thyroid surgery which can be transient (3-30%) or permanent (0.5-10.6%). Clinically significant hypocalcemia may occur within 48 hours after thyroidectomy. However latent hypocalcemia may be delayed up to 4 days after the surgery. So, the onset and severity of hypocalcemia following total thyroidectomy is unpredictable and in order to monitor the serum calcium post operatively, patient may require multiple blood tests. Hypocalcemia can sometimes be life threatening. Various studies have been carried out to predict the onset and severity of hypocalcemia by estimating serum Parathyroid hormone (PTH) levels following total thyroidectomy but no definitive guidelines exist so far. In the present study we aimed to estimate serum PTH levels pre operatively and at 4^{th} and 12^{th} hour post operatively for patients undergoing total thyroidectomy. A lot of studies have utilized either relative percentage decrease of PTH or absolute values for diagnosis. In addition, various timings for measurement of serum PTH levels have been suggested by some studies, ranging from intraoperative measurements to measurements in the early postoperative period (generally 1-4 hours after surgery) and even up to 24 hours postoperatively. In almost all of these settings, PTH has been found to be a reliable early marker for postoperative hypocalcemia. However, there is no consensus among these studies regarding the time intervals and cut-off levels of serum PTH to predict hypocalcemia. In our study we found that post-op 4^{th} hour PTH is better predictor of transient hypocalcemia than the Post-op 12^{th} hour PTH.

After total thyroidectomy a PTH value of $\leq$13.7 at 4^{th} hour or a PTH value of $\leq$12.4 at 12^{th} hour can be considered as cut-off for predicting transient hypocalcaemia, however prospective studies with larger sample size are required to prove the reliability of each of these predictors of hypocalcemia.

Hence, both post - op 4^{th} and 12^{th} hour PTH levels were found to have similar ability in predicting transient and prolonged hypocalcemia in the patients undergoing total thyroidectomy and either of them can be used as a predictor with similar results.

CONCLUSIONS

- Hypocalcemia is a relatively common complication following total thyroidectomy and its risk increases following Central compartment clearance done for thyroid malignancies. Overall, hypocalcemia develops in about 50% of the patients undergoing total thyroidectomy.
- The patients were classified into high and low risk groups based upon the cut-off value of PTH as 12pg/ml, 4 hours following surgery.
- Risk factors for hypoparathyroidism after total thyroidectomy, include, female gender, malignancy, Total thyroidectomy and clearance of the central compartment nodes. Total thyroidectomy combined with central compartment clearance predisposes to development of both transient and prolonged hypocalcemia.
- Factors not contributory in predicting the risk of development of hypocalcemia are Age, Previous thyroid medications, and Number of parathyroid visualized.
- We could also confirm that perioperative changes in serum calcium levels can significantly predict the development of transient hypocalcemia.
- Post-operative 4^{th} and 12^{th} hour PTH estimation improves the predictability for hypocalcemia.
- Post-op 4^{th} hour PTH is a better predictor of transient hypocalcemia than the Post-op 12^{th} hour PTH, as the association of former with serum ionized calcium level has more statistical significance than the later.
- In our study, Post-op 4^{th} hour PTH and Post-op 12^{th} hour PTH had similar, sensitivity; specificity and Diagnostic accuracy (70%, 68.18%, and 68.75% each respectively) for predicting prolonged hypocalcemia.
- Based upon the analysis of ROC curves, we recommend a PTH value of ≤ 13.7 at 4^{th} hour and a PTH value of ≤ 12.4 at 12^{th} hour for predicting individuals at high risk of transient hypocalcaemia.

- Findings from our study can be incorporated in the management of patients undergoing total thyroidectomy, for early identification and initiation of prophylactic treatment to reduce the risk of development of hypocalcemia.
- PTH value of ≤ 13.7 at 4^{th} hour and PTH value of ≤12.4 at 12^{th} hour can be taken into consideration as cut-offs to predict hypocalcemia, however prospective studies with larger sample size are required to prove the reliability of each of these predictors of hypocalcemia.

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ANNEXURES

ANNEXURES

PROFORMA

Particulars of the patients
Name
Age
Gender
Occupation
Date of admission
Date of surgery
Date of discharge

Complaints

PREVIOUS HISTORY

Any thyroid surgery in past
Thyroid medications / drugs
History of intake of calcium or vitamin-D supplements

PERSONAL HISTORY

Diet
Appetite
Smoking
Alcohol
Bowel habits
Menstrual history

GENERAL PHYSICAL EXAMINATION

Appearance
Attitude
Build and Nourishment
Level of consciousness
Dehydration
Temperature
Pulse
Blood pressure
Respiration

EXAMINATION of THYROID GLAND

Inspection :

Palpation :

SYSTEMIC EXAMINATION

CVS/CNS/RS

INVESTIGATIONS –

USG scan -
FNAC -

	Preoperative Level (12 Hrs pre-op)	Post thyroidectomy 4th hour level	Post thyroidectomy 12th hour level
SERUM CALCIUM (mg/dl)			
PARATHYROID HORMONE (pg/ml)			

SURGERY PERFORMED :

- **Type of Thyroidectomy –**
- **Parathyroids visualized –**
- **Parathyroids saved –**

Signs / Symptoms in Post- Operative period

a. Circumoral numbness : Yes/No
b. Circumoral tingling : Yes/No
c. Chvostek's sign : Yes/No
d. Trousseau's sign : Yes/No
e. Latent tetany : Yes/No

Course in the hospital: -

Condition of the patient on discharge: -

Advice on discharge: -

PATIENT INFORMATION SHEET

STUDY TITLE: "POST-OPERATIVE SERUM PARATHYROID HORMONE LEVELS AS A PREDICTOR OF POST-THYROIDECTOMY HYPOCALCEMIA".

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

This is to inform you that, you require Total thyroidectomy
(complete removal of thyroid gland) for the treatment of your condition. The most common complication of this surgery is reduced calcium and vitamin-D levels in the blood which can cause muscle cramps, tingling sensation and difficulty in breathing. This can be treated by calcium and vitamin-D supplements either orally or i.v. injections depending on the severity. There is no consensus to predict the onset and severity of this complication. Various studies have used PTH levels in the blood to predict the severity of this condition, so that high risk patients can be started early on calcium and vitamin-D supplement and will require longer hospitalization and monitoring.

However there is no consensus regarding the exact time intervals in estimating serum PTH levels to predict this condition. We are conducting this study to predict the onset and severity of this condition.
If you are willing you will be enrolled in this study and we will estimate your blood levels [2ml of blood each] of serum PTH, calcium and serum proteins just before surgery and 4^{th} & 12^{th} hours after surgery.
You will receive the standard care for total thyroidectomy and you will be monitored for hypocalcemia (reduced calcium in blood).

This will facilitate identifying early hypocalcemia (if any) in you and treating it. It will also benefit other patients undergoing total thyroidectomy in future. You are free to opt-out of the study at anytime if you are not satisfied or apprehensive to be a part of the study. Your treatment and care will not be compromised if you refuse to be a part of the study. The study will not add any risk or financial burden to you if you are part of the study.
Your identity and clinical details will be confidential. You will not receive any financial benefit for being part of the study. You are free to contact DR KUNAL THAKUR or any other member of the above research team for any doubt or clarification you have.

Dr. KUNAL THAKUR
Mobile no: 9934161483
E-mail id: kunal1291scorpio@gmail.com

INFORMED CONSENT FORM

I Mr./Mrs. _____ have been explained in my own understandable language, that I will be included in a study which is **"POST-OPERATIVE SERUM PARATHYROID HORMONE LEVELS AS A PREDICTOR OF POST-THYROIDECTOMY HYPOCALCEMIA"**.

I have been explained that my clinical findings, investigations, intraoperative findings, post-operative course, will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary, and I can withdraw from the study any time and this will not affect my relation with my doctor or the treatment for my ailment.

I have been explained about the follow up details and possible benefits and adversities due to interventions, in my own understandable language.

I have understood that all my details found during the study are kept confidential and while publishing or sharing of the findings, my details will be masked.

I have principal investigator mobile number for enquiries.

I in my sound mind give full consent to be added in the part of this study.

Signature of the patient:

Name:

Signature of the witness:

Name:

Relation to patient:

Date:

Place: