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MORPHOMETRIC STUDY OF PITUITARY GLAND WITH MAGNETIC RESONANCE IMAGING

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BACKGROUND

Pituitary gland is a master gland of the body in which significant variation can be found among normal individuals in its size and volume. This study is aimed to evaluate pituitary morphometry and its correlation with sex and age with 3D MRI sequence.

METHODOLOGY

A cross-sectional study was performed in Radiology Department of Bir Hospital with 178 patients. The study included patients over 18 years with normal findings of sellar and parasellar region in MRI. Pituitary measurement was done on MPR images of 1 mm thin section in coronal and sagittal plain generated from 3D FLAIR sequence. Data was analyzed using SPSS program. Descriptive statistics and parametric test were used to evaluate the association between different parameters. Level of significance was kept at $p < 0.05$.

RESULTS

This study showed mean pituitary height in female 5.25±0.83mm, in male 5.16±0.85mm, mean pituitary length in female 11.04±1.05mm, in male 11.10±1.17mm, mean pituitary width in female 13.12±1.48 mm and in male 12.89±1.39mm, mean pituitary volume in female 392.66±73.73mm^3 and in male 384.07±89.77mm^3 respectively. There was weak linear correlation between age with pituitary height and volume. No statistical significant variation was found among male and female pituitary morphometry.

CONCLUSION

This study provides data regarding pituitary morphometry and its variation with respect to sex and age using 3D volumetric FLAIR sequences in MRI. Further larger study is advisable to establish a standard morphometry of pituitary gland in Nepali population.

Key words: Magnetic Resonance Imaging, 3 D FLAIR sequence, Pituitary, Morphometry

INTRODUCTION

The pituitary gland is a tiny, pea sized gland which is also called hypophysis cerebri. It lies within hypophyseal fossa or sella turcica (an indentation found in the sphenoid bone at the base of the skull).[1,2] Pituitary gland has two parts, smaller posterior region (neurohypophysis) and larger anterior region (adenohypophysis).[3] This gland controls functioning of all other glands and their hormonal secretions of the human body. Thus, it is called the master endocrine gland.[4, 5] The fully developed pituitary gland weighs approximately 0.5 gm and measures about 6 mm height, 12 mm width and 8 mm in antero-posterior dimension in normal population.[6] The gland is enveloped in the superior aspect by diaphragma sellae, a fold of duramater that separates the CSF filled sub arachnoid space from the pituitary gland. [7]

The sella region has significant differences among normal individuals, including sphenoid sinus and depth of sella which may bring variation in size, shape and volume of pituitary gland.[8] Frequently, borderline abnormalities such as increased lobulated margins, physiological hypertrophy, inflammatory diseases, microadenoma and empty sella are encountered in pituitary.[9] Pituitary adenomas particularly the micro-adenomas are diagnosed essentially with the information of pituitary size and its shape.[10] Therefore, a systematic pituitary measurement is very essential because sometimes findings are very subtle.

For comprehensive evaluation of pituitary gland, we need to be well known of its normal anatomy with the physiological disparities in its size, shape and volume in various age groups in both sexes.[11] Thus, to suggest what might be an abnormal pituitary gland, it is important to know the range of normal size.[10]

MRI is an advance imaging modality which gives information of protons at molecular level and has great influence on medical applications.[12, 13, 14] MRI has been established as an accurate diagnostic tool for the assessment of intracranial structures including pituitary gland.[15, 16, 17] Being non-invasive, multiplanar imaging and having better soft-tissue contrast, MRI has been proven to be efficient in assessing pituitary gland with higher precision.[18], [19] The size of pituitary gland can simply be measured in sectional MRI images.[8] Several author have testified pituitary volume measurement using indirect method using thin section 2D images.[16] Whereas, advanced 3D volumetric MRI imaging has revealed more accurate morphometric measurement.[20]

The study was performed in Bir hospital which is the oldest and one of the busiest central government university hospitals providing MRI service. Being a central referral hospital, there are ample no. of patients coming from different areas of Nepal with diverse geographical and ethnic background. Hence data can be used for the approximation of pituitary morphometry in Nepali population.[21]

The previous study conducted in Nepal for evaluation of pituitary gland was done with low strength 0.35 Tesla MRI scanner and thicker slices of 6 mm - 10 mm.[22] The goal of this study is to explore the quantitative analysis of pituitary gland morphometric with higher strength 1.5 Tesla MRI scanner and thinner slices reformatted from 3 Dimensional advance sequences. Necessity of this study arises from the lack of previous illustrations of pituitary morphometry with higher strength MRI scanner and thin slice acquisition precisely for Nepali population. This study provides reference standards of morphometry for pituitary gland and helps enhance the diagnosis and clinical management of pituitary pathologies in local population.

LITERATURE REVIEW

Anatomy of Pituitary Gland

Pituitary gland is a ductless gland that secretes hormones directly into the bloodstream and is called hypophysis cerebri. The term hypophysis is taken from the Greek word which means “lying under” because of the gland’s location underneath the brain. The pituitary gland is contained in a bony structure called the sella turcica which is present at the mid-base of the skull and immediately below the hypothalamus.[23] The gland weight about 500 to 900 mg in normal adults which is connected by a stalk formed by neuronal axons to the hypothalamus and also consist of hypophyseal portal veins.[24]

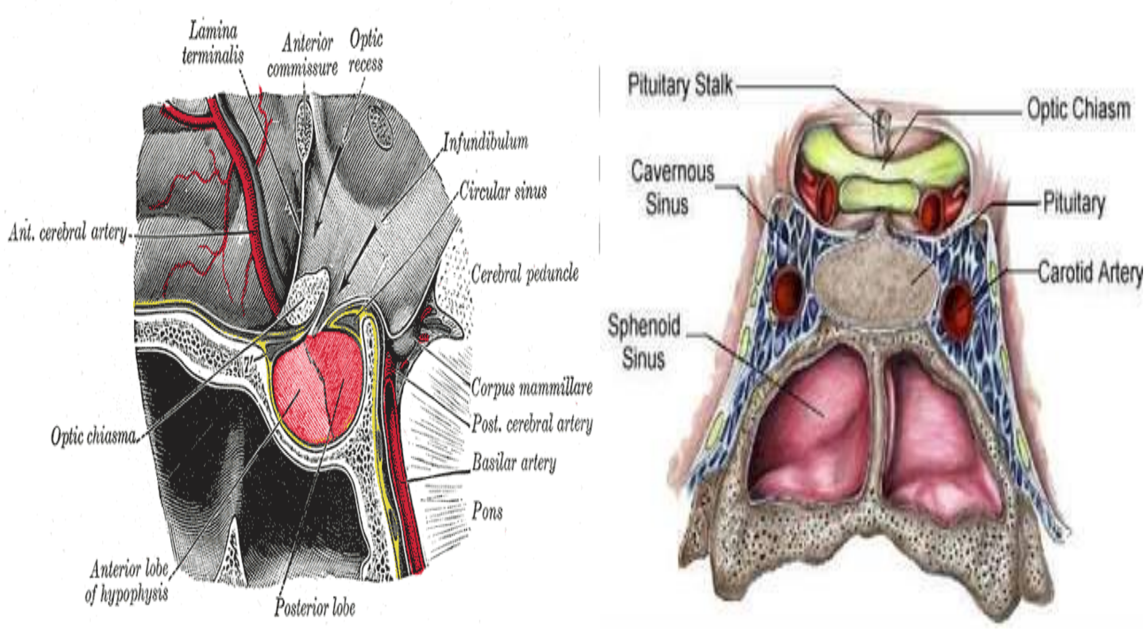

Figure 1 and 2: Sagittal and coronal sectional anatomy of pituitary gland

Embryology

The pituitary gland is developed entirely from ectodermal origin in which an oral ectoderm called Rathke's pouch develops anterior adenohypophysis and neural ectoderm develops the posterior neurohypophysis. [7] The oral ectoderm and the neural ectoderm are in close contact during early embryogenesis. Later Rathke's pouch undergoes constriction at its base until it completely separates from the oral epithelium.[25]

Parts of Pituitary Gland

Human pituitary have two main lobes, anterior and posterior lobe which are different developmentally, anatomically and functionally, and an indistinct intermediate lobe present between these two lobes. The anterior pituitary lobe is also called adenohypophysis that regulates several physiological processes like stress, growth, reproduction, and lactation etc. The intermediate lobe produces melanocyte-stimulating hormone whereas the posterior pituitary secrets oxytocin and ADH hormones which is also called neurohypophysis. It is functionally connected to the hypothalamus by the median eminence via a small tube called the pituitary stalk or infundibulum. [26,27]

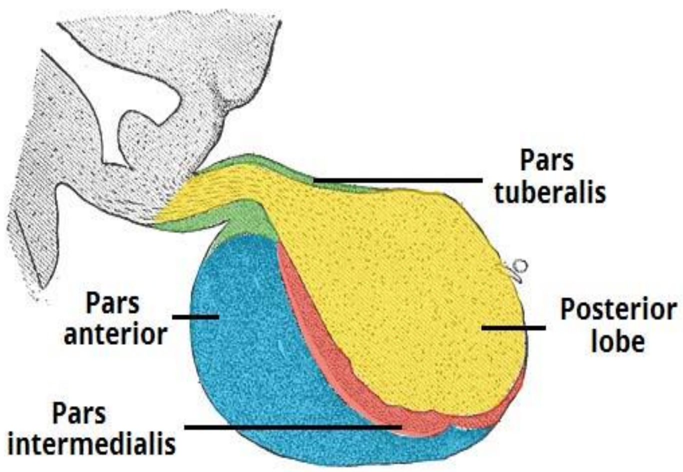

Figure 3: Pituitary gland parts and its lobes

Again, the anterior pituitary is composed of three regions: pars distalis, pars intermediate and pars tuberalis. The pars intermediate are a small and indistinct part present between the pars distalis and the posterior pituitary gland and makes the boundary between the anterior and posterior pituitaries. The pars tuberalis, whose function is poorly understood, makes a sheath that extends upwards from the pars distalis and connects with the pituitary stalk. The pars distalis contains the majority of anterior pituitary.[28] The posterior lobe of pituitary gland is not functionally glandular as of the anterior pituitary. Instead, it is largely a collection of axonal projections from the hypothalamus that terminate behind the anterior pituitary.[29]

Hormonal Controls of Pituitary

Pituitary gland being the "master gland" of the body controls other vital endocrine glands including the adrenal, thyroid and reproductive glands (e.g. ovaries and testes). Also pituitary gland has direct governing effects in major tissues, such as those of the musculoskeletal system. The anterior pituitary gland produces most of important pituitary hormone that controls various physiology and metabolism of the body whereas posterior lobe of pituitary serve as a site for the secretion of neurohypophysial hormones like oxytocin and vasopressin directly into the blood. [30]

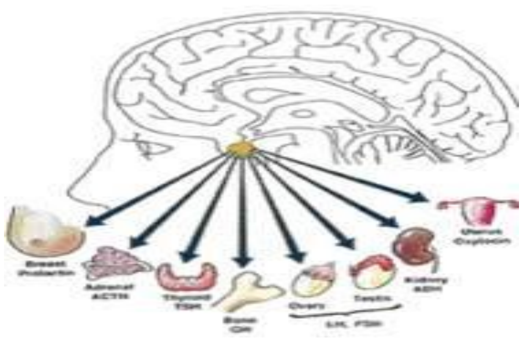

Figure 4: Pituitary gland and its hormonal controls

Hormones Released by the Pituitary Gland		
Hormone Site of Action		**Effects**
Oxytocin	uterus	stimulates contraction during labor
	breast	stimulates contraction to express milk
Antidiuretic hormone (ADH)	kidney	stimulates retention of water
Anterior Pituitary		
Corticotrophin (adrenocorticotrophic		
hormone, ACTH)	adrenal cortex	stimulates release of cortisol
Thyroid-stimulating hormone (TSH)	thyroid	stimulates release of thyroxine
Growth hormone (GH)	bone	stimulates growth
Follicle-stimulating hormone (FSH)	female ovaries	stimulates follicle to mature an egg, estrogen
		production
	male testes stimulates	sperm production
Luteinizing hormone (LH)	female ovaries	stimulates ovulation, progesterone production
	male testes stimulates	testosterone production
beta-Endorphin	brain	reduces pain

Figure 5: Various hormones secreted by pituitary gland and their function

Blood Supply of Pituitary Gland

Arterial blood supply to the neural hypophyseal stalk and ventromedial region is from ascending and descending infundibular branches imminent from arteries of the superior hypophyseal artery.[31] Also, some small vessels arising from the anastomoses joining the upper and the lower hypophyseal arteries supply blood to hypophyseal vessels. In the same way, many of these branches are continuous between the proximal arcuate nucleus and anterior pituitary, allowing rapid hormonal exchange.[32] Hormonal communications between systemic blood and the ventral hypothalamus is facilitated by capillary perivascular spaces of the median eminence and arcuate nucleus.[33]

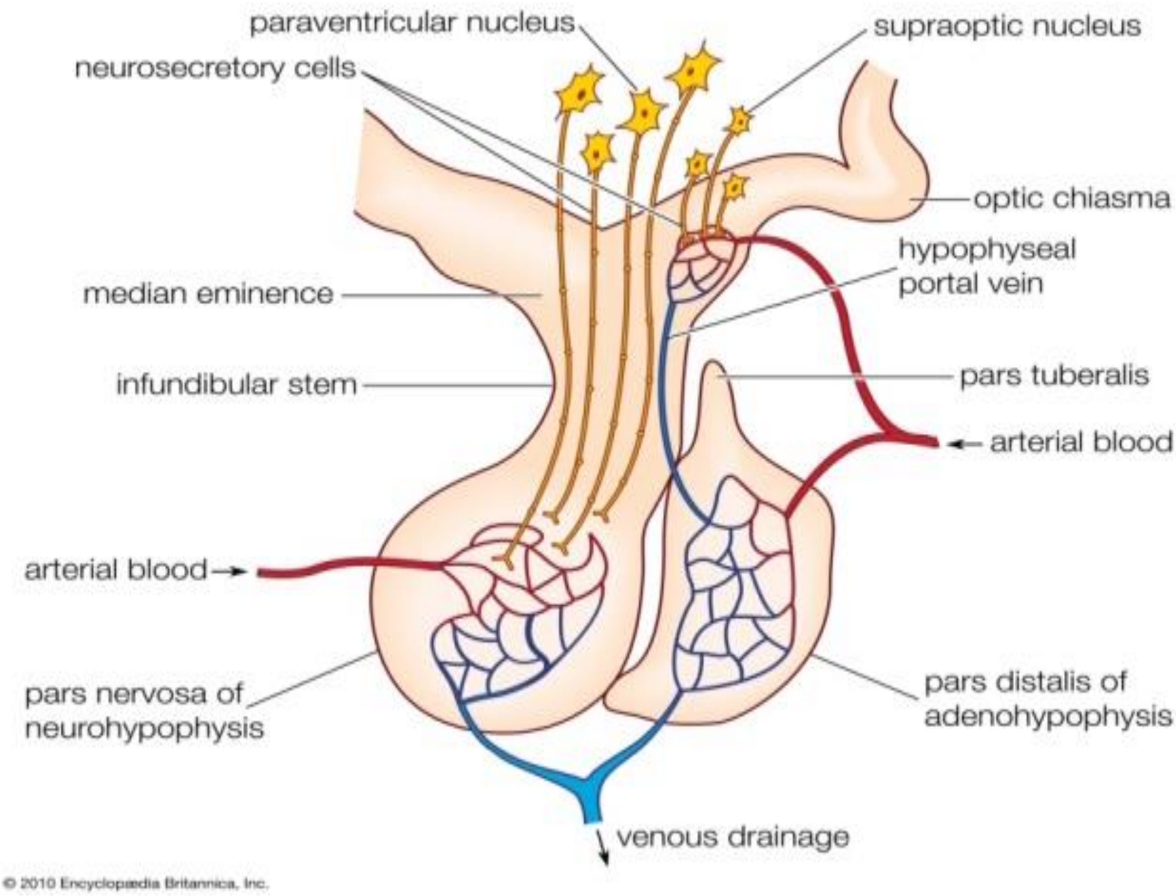

Figure 6: Pituitary blood circulations

Conditions of Pituitary Gland

Empty sella syndrome

It is a condition in which the pituitary gland gets reduced in size making it look like an empty sella. Empty sella syndrome doesn't truly mean the sella turcica is completely empty but is either partly or entirely occupied with cerebrospinal fluid (CSF). People with empty sella syndrome may have diminished pituitary glands size and may not even show up on imaging tests.[34] Total empty sella syndrome is considered when more than half of your sella is filled with CSF, and your pituitary gland height measures about 2 mm or less.[35]

Partial Empty Sella

It is a condition when some of the pituitary gland is remaining and is evident on imaging[7]. The partial empty sella can be characterized in to two groups, primary and secondary. Primary empty sella is called when a hole in diaphragmatic sella permits CSF fluid descends in the sella turcica and compresses pituitary gland. Whereas, secondary empty sella syndrome, is when the pituitary gland is damaged by a tumor, surgery or radiation therapy. Partial empty sella is considered when pituitary height measures 3 mm or less.[36]

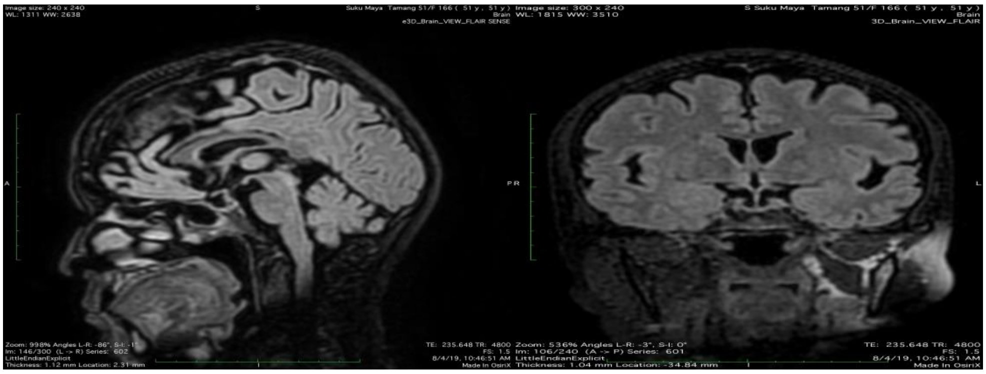

Figure 7: Partial empty sella syndrome of pituitary gland

Pituitary Adenomas

These are the common pituitary conditions which are mostly benign in almost 99% cases, and can be divided into two categories; hormone secreting tumors and non-functional tumors. Most pituitary adenomas do not yield excessive hormones thus known as non-functional adenomas. Some pituitary adenomas can result in increased production of hormone, causing severe endocrine problems like Acromegaly (GH excess), Cushing's syndrome (ACTH excess) or prolactinoma (prolactin excess). Pituitary adenomas smaller in size less than 1 cm diameter is called microadenoma and larger in size than microadenoma are called macroadenoma. Other disorders can also result in pituitary problems like tumors in the pituitary region, infections, autoimmune conditions etc. [37]

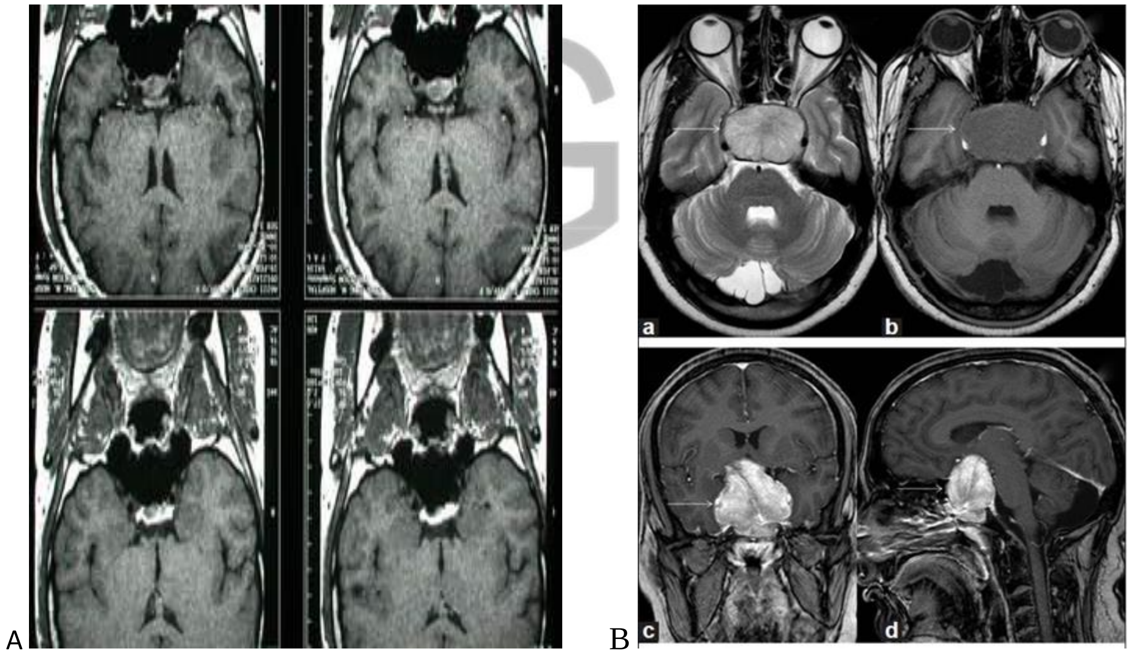

Figure 8: Pituitary gland A. Microadenoma, B. Macroadenoma.

Hypopituitarism and Panhypopituitarism

The condition when pituitary is not producing one or more of its hormones sufficiently are called hypopituitarism. If all the pituitary hormones produced by the anterior pituitary are reduced, then the condition is called Panhypopituitarism. Pituitary gland can be compressed as pituitary tumors grow and cause reduced hormonal production resulting in pituitary insufficiency, or hypopituitarism. Craniopharingiomas, cysts and meningiomas are examples of tumors that initiate in the vicinity of the pituitary gland and may cause hypopituitarism, headaches, visual and neurological difficulties.[3]

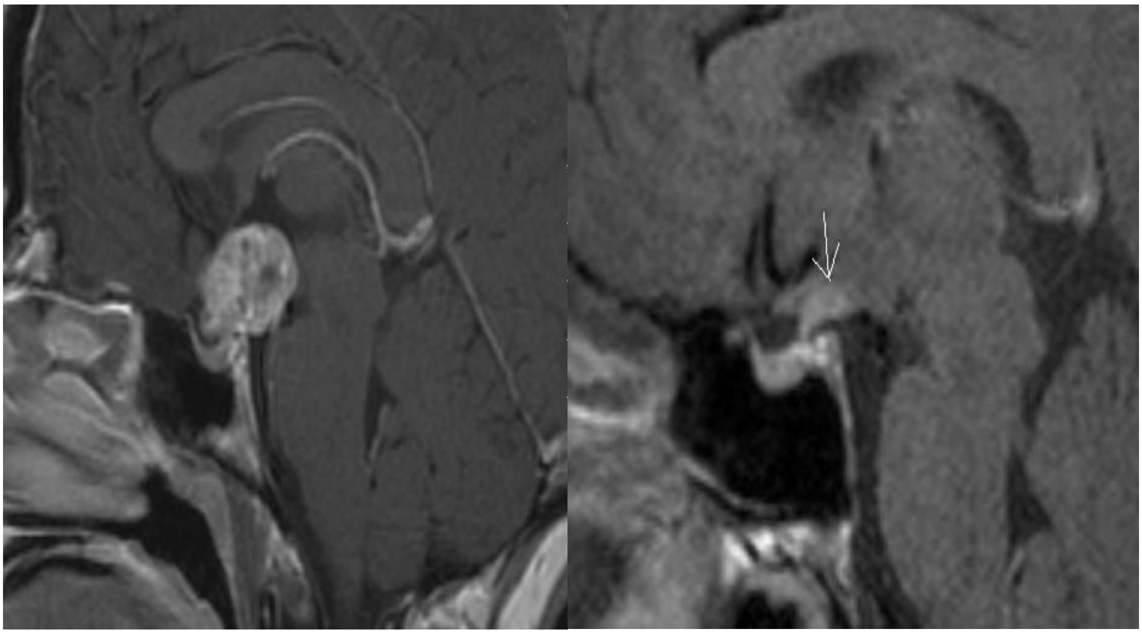

Figure 9: Pituitary gland a. Craniopharingiomas, b. Germinoma

Magnetic Resonance Imaging

MRI is a medical imaging technique that utilizes a magnetic field, radiofrequency waves and computer to generate comprehensive information of the body organs and acquire images of the internal organs noninvasively. Most MRI machines are large donut shaped magnets having accessories to accommodate patient positioned in it. Certain atomic nuclei such as hydrogen proton can absorb radio frequency energy and from a signal when employed in an external magnetic field. Thus these hydrogen atoms are maximally used to produce a measurable signal that is received by MR coils placed close to the body anatomy being examined. MRI scans essentially map the location of water and fat because hydrogen atoms are naturally plentiful in the body, particularly in water and fat.[14]

First the patient is placed inside an MRI machine; the magnetic field temporarily realigns hydrogen molecules inside the body. Then a radio frequency wave is sent which cause these aligned atoms to produce signal which generates MRI images after being detected by receiver coil with the help of computer. The MRI machine can produce 2D as well as 3D images that can be viewed from different angles in different planes.[38]

By changing the parameters of the pulse sequence, different contrasts can be created between tissues based on the relaxation properties of the hydrogen atoms therein. MRI scans are capable of producing a variety of chemical and physical data, in addition to detailed spatial images. Thus MRI is often used for imaging brain pathologies such as tumors, infection, stroke, injuries and trauma, disorders of the eye and inner ear, multiple sclerosis and aneurysms of cerebral vessels etc.[13] Similarly, MRI has very important role in imaging pituitary morphology as well as physiology with help of dynamic MR scanning.[39]

3D FLAIR Sequence

Three-dimensional (3D) acquisitions in MRI are being increasingly important in clinical application because of the inherent signal-to-noise ratio (SNR) benefits, high resolution, and isotropic voxels. The advantages of 3D imaging have been well accepted and comprise of volumetric measurements, coregistration, displays of surface anatomy, and others.[40] Volumetric isotropic imaging data can be reformatted to produce high quality, high spatial resolution thin slice image in multiple planes.[41]

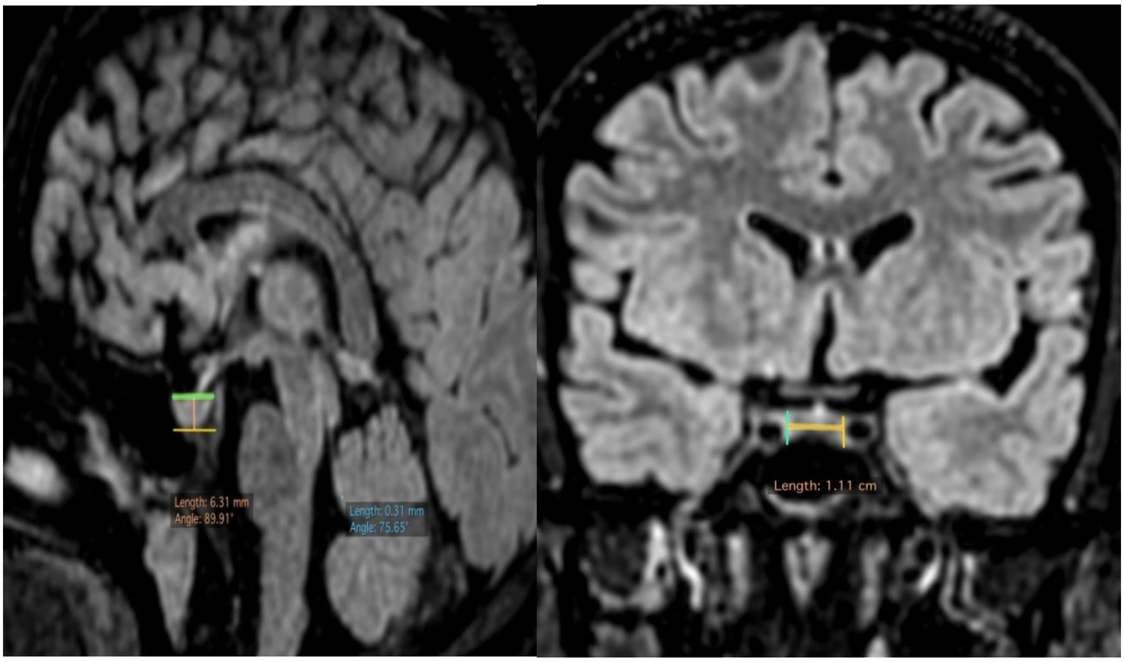

Figure 10: a. Sagittal and b. coronal FLAIR images showing pituitary detail

In addition, FLAIR imaging offers unsettled lesion conspicuity in various central nervous system disorders with high CNR for long T2 lesions.[42, 43] FLAIR images are superior to FSE images for its ability to distinguish T2 abnormalities because of suppressing high signal from CSF which results in an enhanced gray-scale dynamic range.[44]

In a latest report, the detection of multiple sclerosis (MS) lesions by 2D versus 3D single-slab FLAIR sequences at 3 T was compared. The authors testified that considerably higher CNR was attained and more MS lesions were spotted with the 3D FLAIR sequence when compared with 2D FLAIR sequence.[45] Thus, 3D FLAIR can be reflected as a promising technique for quantifying the degree of cerebral pathology in MS. Three-dimensional FLAIR data are nearly ideal for image guided radiotherapy and surgery as well.[46] 3D FLAIR is thus considered a very effective sequence to image and assess pituitary gland and its morphometry.[47]

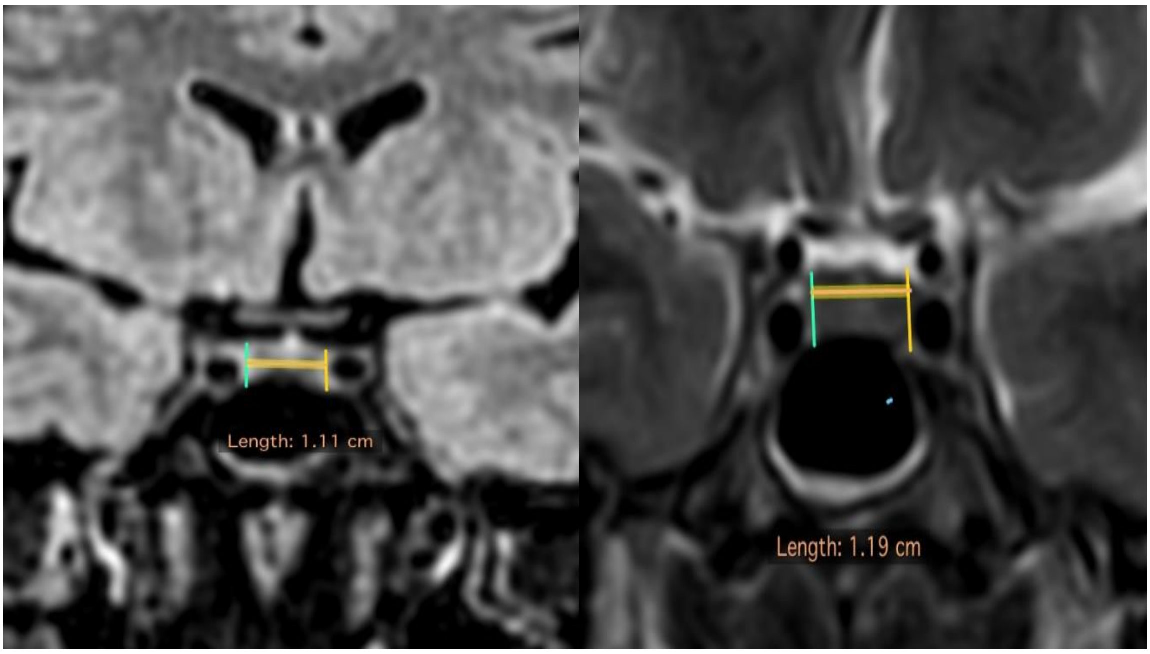

Figure 11: 3D FLAIR coronal and T2 coronal image differences

Özandaçat S et al[48] (2019) performed a research on title "The determination of the pituitary gland, optic chiasm and intercavernous distance measurements in healthy subjects according to age and gender" in Turkish population aged between 18-60 years in which 292 subjects were included (187 females and 105 males). It was a retrospective observational study done in Department of Radiology at Medline Hospital in Turkey. Patients were scanned for brain MRI protocol including coronal T2-weighted turbo spin echo and sagittal T2-weighted spin echo with 1.5 T MRI systems (Siemens; Essenza, Erlangen, Germany). The study results showed the overall means and standard deviations of the measurements were: pituitary gland width, 13.09±1.99 mm; pituitary gland height, 4.91±1.10 mm. No significant difference ($p>0.05$) was found in the corresponding mean values in both gender. The mean of the pituitary gland height in the age group 18-20 years was the highest value (5.45±1.25 mm). The same measurement was 5.08±1.02 mm in the age group 21-30 years; 4.81±1.01 mm in the age group 31-40 years; 4.58±1.06 mm in the age group 41-50 years and, 4.49±0.94 mm in the age group 51-60 years. The same value was observed to be 4.87±1.05 mm in both subjects. There were obtained negative moderate degree correlation in pituitary gland height and age.

Yadav p et al[11] (2017) studied in the title "MRI Evaluation of Size and Shape of Normal Pituitary Gland: Age and Sex Related Changes" included 500 Indian patients (261 males and 239 females, ranging from one year up to 80 years of age). The observation was divided into six groups according to age. The results showed mean height of pituitary gland in female patients of each age group was more than that of male patients in the same age group. Height of pituitary gland extended a maximum in the 21 to 30 years of age group in both males and females. The overall mean pituitary height in the age group 1-10 years came out to be 5.3±1.4 mm. In the age group 11- 20 years, mean pituitary height was 6.2±1.1 mm. In the age group 21-30 years 6.8±1.9 mm, 31-40 years age group

6.3±1.8 mm, in 41-50 years age group 6.5±1.5 mm and individuals above 50 years of age, mean pituitary height was witnessed as 7±2.1 mm. The mean pituitary volume in the age group 1-10 years came out to be males 210±0.73 mm^3 and in females 200±0.75 mm^3. In the age group 11-20 years mean pituitary volume in males was 340±127 mm^3 and in female's 280±123 mm^3. In the age group 21-30 years, mean pituitary volume in males was 430±116 mm3 and in females 440±180 mm^3. In the age group 31-40 years, mean pituitary volume in males was 380±140 mm^3 and in females was 440±111 mm^3. In 41-50 age groups mean pituitary volume in males was 400±159 mm^3 and in females it was 420±116 mm^3. In individuals above 50 years of age the mean pituitary volume was observed in males as 410±168 mm3 and 420±174 mm3 in females.[11]

Pecina HI et al[49] (2017) investigated the influence of age and sex on the volumes of the pituitary fossa and gland in 91 males and 108 females from Croatia who underwent magnetic resonance imaging of the endo-cranium for complaints not related to the pituitary gland. Isometric 3D T1 MPRAGE and 3D T1 MPR sequences were obtained on 1.5. Tesla and analyzed on ISSA software. The volumes were obtained from the sum of all the areas multiplied by the thickness of the section. The mean volume of the pituitary fossa for males was 1111.1.4 mm3, for female 1354.4.2 mm3. Correlation analysis showed a significant negative correlation between age of the patient, and pituitary volume.

Sinclair J et al[10] (2017) performed a retrospective study using 3D fluid-attenuated inversion recovery (3D FLAIR) sequences at Nine wells Hospital Dundee, Scotland. The purpose of the study was to compare the pituitary gland sizes of different categories of patients in which patients were grouped into 6 different age categories 16-25, 25-35, 35-45, 45-55, 55-65 and >65. The study showed linear decrease in average pituitary gland height with increasing age groups. No male patients had a pituitary height less than

4.36mm or greater than 7.10mm; a width less than 7.75mm or greater than 14.42mm and a depth less than 8.55mm or greater than 13.50mm. Whereas no female patients had a pituitary height less than 4.02mm or greater than 9.10mm; a width less than 8.87mm or greater than 16.19mm and a depth less than 9.35mm or greater than 12.95mm.

Mascalchi M et al[49] (2016) in the study titled " Effectiveness of 3D T2-Weighted FLAIR FSE Sequences with Fat Suppression for Detection of Brain MR Imaging Signal Changes in Children" the researcher concluded that T2-weighted FLAIR can be combined with 3D-FSE sequences with isotropic voxels, yielding higher signal-to noise ratio than 2D-FLAIR. The study was conducted one week after a joint training session with 2D 3T MR imaging examinations (8 under sedation) where 3 radiologists independently evaluated the presence and conspicuity of abnormal areas of T2 hyperintensities of the brain in FLAIR-VISTA with fat suppression (sagittal source and axial and coronal reformatted images) and in axial 2D-FLAIR without fat suppression in a test set of 100 3T MR imaging examinations (34 under sedation) of patients 2–18 years of age performed for several clinical indications. The study results indicated that 21 of 23 examinations in which the 3 radiologists agreed on the presence of abnormal T2 hyperintensities, FLAIR-VISTA with fat suppression images were viewed to show hyperintensities with better conspicuity than 2D-FLAIR. In 2 cases, conspicuity was equal, and in no case was conspicuity better in 2D-FLAIR. And the researcher concluded that FLAIR-VISTA with fat suppression can replace the 2D-FLAIR sequence in brain MR imaging protocols for children.

Naik D et al[2] (2015) performed the study aimed to analyze the shapes and volumes of the pituitary gland as seen on magnetic resonance imaging using two different methods in the adolescent age group (10 to 19 years). The study was intended as a retrospective review. MRI brain of 99 patients was done and pituitary volumes were calculated using voxel counting method and the ellipsoid formula. The average pituitary height was 5.8 mm ± 1.5 mm in both sexes, 5.5 mm ± 1.6 mm in males and 6.0 mm ± 1.5 mm in females. The volume, height and shape of the pituitary in male and female patients were analyzed. The average pituitary volume by voxel counting method was found to be 5.4 mm ± 1.6 mm in sexes, 5.1 ± 1.3 mm in males and 5.6 ± 1.9 mm in females. The average pituitary volume by ROI was found to be 4.2m ± 0.16 cc in both sexes, 0.40cc ± 0.15 cc in males and 0.43 cc ± 0.17 cc in females. The average volume of the pituitary gland was 6% greater in females. This study shows gradual increase in volume and height of pituitary gland with age. The two methods showed positive correlation which was statistically significant.

Aruna P et al[7] (2014) on title "Partial Empty Sella Syndrome: A Case Report and Review" an author described partial sella syndrome as a damaged pituitary gland where the gland has either shrunk or has been crushed and flattened making it look like an empty sella on MRI scan. The reported prevalence of primary empty sella in general population was concluded to be 8–35 %. The incidence was found to be more in females, the ratio being 5:1. It was generally found in middle aged women who were obese and hypertensive. There was a rare presentation of empty sella syndrome with both anterior and posterior pituitary involvement. The study revealed MRI–brain and sella plain showing most of the sella occupied with CSF and pituitary gland seemed to be thinned out with upper borders concavity. The enlarged sella turcica can either be caused due to intrasellar herniation of the suprasellar subarachnoid space with compression of the pituitary gland or due to previous enlargement of pituitary gland from primary hypothyroidism.

Sanjay S C et al[18] (2014) carried out a study in Indian population on the title ‘Variation in size and shape of normal adult female pituitary gland’. The study observed mean height of pituitary gland was 6.27 mm ± 0.56, the mean length was 9.10 mm± 0.78 and mean width was 11.22 mm±0.82. The size of pituitary gland also changed with age. The height was observed to decrease significantly as age progressed. However there was a mild increase in the height noted in the age group C (40-49). The length initially increased up to 40 years and later decreased. Maximum width was noted in the third decade and older age group. The researcher observed extremely wide variation in the morphology of the pituitary gland on high resolution MRI regardless of subject age.

Lamichhane T R et al[22] (2014) studied to obtain standard reference values for the height, transverse, anterior-posterior (AP) dimensions and volume of pituitary gland of healthy population. These dimensions were measured using standard spin echo sequences with 6 mm thickness in 0.3T permanent magnet MRI. A group of 170 subjects were taken as sample at Institute of Medicine, Radiology and Imaging Department, Tribhuvan University Teaching Hospital (TUTH) during April 23, 2014 to June 20, 2014. These individuals demonstrated no evidence of abnormalities to the central nervous or endocrine systems prior to the study. The anterior – posterior, height, transverse dimension and volume of pituitary were observed to be 10.3 mm, 6.1 mm, 13.6 mm and 466.8 mm^3 respectively. In this study, the researcher found that the size of the pituitary gland of the Nepali people reflected the normal values as expected in healthy people.

Sari S et al[50] **(**2014) conducted the study aimed to provide normative data about pituitary diameters in a pediatric population. Pituitary imaging is imperative for the assessment of the hypothalamo-pituitary axis defect. However, data about normal pituitary gland diameters and stalk are only limited, especially in children. Structure and the measurements of pituitary gland and pituitary stalk may vary due to infection, inflammation, or neoplasia. the study included 14,854 cranial/pituitary gland magnetic resonance imaging scans performed from 2011 to 2013, 2755 images of Turkish children aged between 0 and 18 were acquired. After exclusions, 517 images were left. Four radiologists were educated by an experienced pediatric radiologist for the measurement and assessment of the pituitary gland and pituitary stalk. Twenty cases were measured by all radiologists for a pilot study and there was no interobserver variability. There were 10–22 children in each age group. The maximum median height of the pituitary gland was 8.48±1.08 and 6.19±0.88 mm for girls and boys, respectively. Volumes were also correlated with gender similar to height. Minimum median height was 3.91±0.75 mm for girls and 3.81±0.68 mm for boys. The maximum and minimum pituitary stalk basilar artery ratios for girls were 0.73±0.12 and 0.59±0.10 mm. The ratios for boys were 0.70±0.12 and 0.56±0.11 mm. Our study demonstrated the pituitary gland and stalk size data of children in various age groups from.

Keanninsiri C et al [51](2012) performed a retrospective study in Thai people to find out the size and shape of the pituitary gland in normal puberty groups of both genders of age 1-30 years at Siriraj Hospital. Two planar vie0ws of the MRI sagittal and coronal images were used for measurement of the height, width of pituitary gland. The sample size (299 cases, 149 male and 150 female) were included. All cases have medical record and MRI brain scan, without pathology history related to the pituitary gland or hormonal disorders, surgery and treated by hormone therapy. The study result showed the mean and standard deviation of the height of pituitary gland in group 1 (1-10years) were 5.4 ± 1.2mm in male, n = 50, 5.1 ±1.3mm in female, n = 50, group 2 (11-20 years) were 6.8 ± 1.7mm in male, n = 50, 5.8 ±1.3mm.in female, n = 50 and group 3 (21-30 years) were 5.4 ± 1.3mm in male, n = 50, 5.9 ±1.5mm in female, n = 50 and significantly different in female ($p<0.001$) but no significantly different in male ($p = 0.181$). The mean and standard deviation of the width of pituitary gland of group 1 (1-10 years) were 10.8 ± 1.9mm in male, n = 50, 10.2 ±2.2mm.in female, n = 50, group 2(11-20 years) were 12.9 ± 2.0mm in male, n = 50, 13.5 ±1.5mm in female, n = 50 and group 3 (21-30 years) were 13.4 ±

1.7mm in male, n = 49 and 13.8 ± 1.7mm in female, n = 50 and significant different for both sexes ($p<0.001$).

Kyo-Sung J et al[52] (2010) studied "Morphometric Study of the Korean Adult Pituitary Glands and the Diaphragma Sellae" where researcher used 33 formaline fixed adult cadavers (23 male, 10 female) and measured the diaphragma sellae and pituitary gland. The authors explored the relationship between Dura and structures surrounding pituitary gland, morphometric aspect of central opening of diaphragma sellae and morphometric aspects of pituitary gland and stalk. The study result concluded that thin dural layer and pituitary capsule forms the boundary between the lateral surface of pituitary gland and the medial wall of cavernous sinus. The pituitary capsule was a continuation from the diaphragma sellae. Mean width, length, and height of the pituitary gland were noted to be 14.3 ± 2.1, 7.9 ± 1.3, and 6.0 ± 0.9 mm in anterior lobes, and 8.7 ± 1.7, 2.9 ± 1.1, and 5.8 ± 1.0 mm in posterior lobes, respectively. The diaphragmal opening was 5 mm or more in 26 (78.8%) of 33 specimen. The opening was round in 60.6% of the specimen and elliptical oriented in an anterior-posterior or transverse direction in 39.4%. Although all dimensions of anterior lobe in female were slightly greater than those in male, statistical significance was illustrious in only longitudinal dimension. The ratio of posterior lobe to the length of pituitary was about 27%.

Ikram MF et al[53] (2008) conducted a study in Karachi to establish measurements of selected pituitary parameters in cases with normal pituitary gland in population < 30 year old. The study taken total of 220 subjects with normal pituitary morphology using T2 weighted Magnetic Resonance (MR) Imaging. Pituitary height (PH) and shape of the superior surface of the gland was observed on midsaggital sections. Data was stratified into six groups on the basis of age and sex to observe the differences. The results showed that after the second month of life, the pituitary height increased gradually to achieve its peak in the second decade of life in the females (6.3 ± 1.4 mm, n = 43) and the third decade of life in the males (5.9 ± 1 mm, n = 41) Significant difference was observed in Pituitary height in different age groups in both genders. Gland was significantly higher in females than males in the second decade. Higher frequencies of convex superior surface followed the same pattern. Conclusion: This study provided the reference values for the Pituitary height and the shape of the superior surface of the pituitary gland.

Fink AM et al[54] (2005) conducted a research on title "Age-Related Pituitary Volumes in Prepubertal Children with Normal Endocrine Function: Volumetric Magnetic Resonance Data " where children under the age of 10 years were studied. The children who had no endocrine abnormality were recruited for brain MRI prospectively over 2 yr. Three-dimensional sequence were performed for all MRI scans consisting of 139 children with mean age, 5.2 yr. Contiguous 1-mm thick reconstructed coronal and sagittal images were used for direct pituitary volumes measurements. Estimated pituitary volumes were calculated using pituitary height, width, and length. The study results indicated the volumes obtained from reconstructions in either plane were essentially matching. There was a linear increase in log-transformed pituitary volume with age, but relatively weak correlations with height or body mass index. There was no gender difference and only weak correlations between pituitary height and pituitary volume and between estimated pituitary volume calculation and measured pituitary volume.

Kato K et al[55] (2002) studied in 300 individuals under the title 'Morphological changes on MR imaging of the normal pituitary gland related to age and sex: main emphasis on pubescent females' in Japan using a 1.5 Tesla (1.5T) MRI unit in Chiba Japan. The pituitary gland of individuals (ages: 3–85 years; 101 males and 199 females) with no pituitary gland related pathologies were studied. The aim of the study was to evaluate morphological changes at puberty in females. Among three parameters related to pituitary size, height changed the most remarkably in relation to age and sex, reaching to greatest values towards the first half of the third decade of a women's life. However, the convex shaped upper pituitary surface was most often documented in the first half of the second decade. Moreover, in children and adolescents, this shape was predominantly presented in females. A coronal deviation of the stalk attachment to the pituitary gland, which might be indicative of pituitary tumor, was most frequently observed in individuals less than 20 years of age and those over 50. The pituitary size and shape varied, especially with respect to height, likely in response to changes in the hormonal environment. Hence, care must be taken when evaluating the size of the pituitary gland by MRI, especially in the diagnosis of pituitary tumourThe study result showed the mean height of the pituitary gland to be 5.1±2.0mm, with a non-significant difference breakdown of 4.9±1.9mm (mean±SD) for males and 5.2±2.0mm for females. They also demonstrated that the height was significantly higher in the 20-49 age groups than in the older age groups.

Chanson P et al [56] (2001) performed a study to offer thorough clinical and hormonal data and long-term endocrinological and imaging follow-up data on subjects with incidentally revealed pituitary hypertrophy (height > 9 mm). Seven eugonadal nulliparous women, 15–27 year old, referred between 1989 and 1998 with incidentally diagnosed pituitary gland enlargement (height > 9 mm) and a suspected pituitary tumor, were considered in the study. Pituitary measurements and signal on magnetic resonance imaging (MRI) before and after IV contrast injection were evaluated. The study results suggest that careful examination of MRI results may help to differentiate physiologic pituitary hypertrophy from pituitary tumors and infiltrating lesions.

Denk CC et al[57] **(**1999) studied to measure heights of the pituitary glands by magnetic resonance imaging (MRI) technique in 201 individuals. There was no sellar or parasellar region pathology in the study group. The data were evaluated according to age and sex groups. In all cases the coronal and sagittal heights of the pituitary glands were equal. The mean values of the coronal and sagittal heights in females (6.1 +/- 0.1 mm, 6.1 +/- 0.1 mm respectively) were higher than in males (5.7 +/- 0.2 mm, 5.6 +/- 0.2 mm respectively). The highest values for the coronal and sagittal heights were in the 11-20 years age group in both sexes. A gradual increase in the coronal and sagittal heights of the pituitary glands in the 0-10, 11-20 age groups was present in both sexes. Decrease in the heights of the pituitary glands was noted after 20 years of age onwards. Nevertheless there was a conspicuous increase in the mean value of the pituitary glands' heights in the 51-60 years age group in males. In females, a minimal increase in the mean value of the pituitary glands' heights was observed in the 61 years and over age group.

Janssen YJ et al [58](1999) in the study published in The Journal of Clinical Endocrinology & Metabolism, the researcher concluded that the pituitary gland size and volume changes depending on hormonal status. Generally, younger adults have larger glands. Hormonally active individuals (puberty / pregnancy) have the largest glands. Younger has convex upper border with completely filled pituitary fossa, whereas older individuals will have a largely empty pituitary fossa. Reliable maximal figures for the height of the pituitary gland : children (less than 12 years) - 6mm (upper surface flat or slightly concave), puberty-10mm (upper surface convex, more in females), young adults male- 8mm and female-9mm, and pregnancy-12mm.

Tsunoda A et al [5] (1997) conducted a study on the title ‘MR height of the pituitary gland as a function of age and sex: especially physiological hypertrophy in adolescence and in climacterium’. The researcher reviewed sagittal T1-weighted MR images in 1020 individuals and observed the pituitary height in female (mean, 5.35 mm; SD, 1.2) which was significantly greater than that in male (mean, 4.93 mm; SD, 1.0). When the data were analyzed for different age ranges, sex-related variations were statistically significant only in the 10-19, 20-29, and 50- 59year-old age groups. The pituitary height peaked in the 20-29 age groups and tended to decline with age. In female subjects, however, there was a inclination for pituitary height to increase again in the 50-59 age group.

Elster AD et al [59] (1991) in the study titled "Size and shape of the pituitary gland during pregnancy and post-partum: measurement with MR imaging" brain magnetic resonance imaging was performed in 38 pregnant and postpartum women and 30 nonpregnant age-matched control subjects to evaluate pituitary gland size and shape during this period. A midline T1-weighted sagittal image was used for gland height and infundibulum width measurement. Throughout pregnancy, gland height was observed to increase linearly by approximately 0.08 mm/wk. No gland exceeded 10 mm in height during pregnancy. The maximum glands measurement was seen in the immediate postpartum period; during this period, five of 12 glands measured 10.0-11.8 mm. The researcher suggested that the pituitary gland enlarges throughout pregnancy but should not exceed 10 mm during most of this period and size of up to 12 mm is tolerable immediately postpartum.

OBJECTIVES

General Objective

- To evaluate size and volume of pituitary gland with MRI.

Specific Objectives

- To measure the height, length and width of pituitary gland in 1 mm thin mid sagittal and 1 mm thin coronal plane
- To estimate the volume of pituitary gland by multiplying length x height x width x 0.52 (volume of oval structure)
- To find out the association between pituitary gland height, width, length and volume with socio-demographic variables(age and sex)

METHODOLOGY

The descriptive, cross-sectional study was carried out with 1.5 T MRI machine in the Department of Radiology and Imaging, National Academy of Medical Science, Bir Hospital from May 2019 to November 2019. The study population consisted of 231 patients who underwent MRI brain scanning for clinical suspicion of brain pathology. Among these patients total of 178 patients were selected for data collection whose MRI showed normal sella and parasellar region and 53 patients were excluded from study due to various reasons.

Inclusion Criteria

The study sample included patient coming;

- For routine MRI brain scanning
- Either sex over 18 years of age
- With normal sellar and parasellar region verified in routine brain MRI scan

Exclusion Criteria

The candidates were excluded as the study sample on the following basis;

- Having pituitary and endocrinal abnormalities
- Under hormonal therapy
- Patient under 18 years
- Lactating and Pregnant women,
- Contrast studies
- Patient with ferromagnetic metal implants,
- Patient with sellar and parasellar abnormalities,
- Unstable and uncooperative patients
- Non Nepali patients

Sample Size

Considering pituitary height standard deviation of 2mm, reliability coefficient at 95% confidence interval (Z) of 1.96 and maximum tolerable error (D) to be 0.3 the sample size was calculated to be minimum of n= 171. The sample size was derived from the given formula; [22] **Sample size** $n = z^2.\sigma^2 / d^2$

From total of 231 study populations, only 178 candidates were selected as the sample, whereas 53 patients were not taken for pituitary measurement because of various reasons such as 15 partial empty sella, 3 lactating, 3 uncooperative, 4 under-age, 28 contrast cases having pathologies related to brain 18 and sella 10 such as macroadenoma, microadenoma, hyperprolactinating, SOL in brain stem, brain tumor in parasellar region etc.

Study Detail

All study population was scanned with MRI scanner of 1.5 T, Philips Achieva which is a superconducting magnet. Scanning was performed with routine brain protocol used in the Department of Radiology, Bir Hospital. An advanced sequence 'sagittal 3D FLAIR' was used in addition to the routine protocol which took approximately 3 minutes extra time for examination with no harm to the patient as well as the operator. Multi-Planer Reconstruction was done in coronal and sagittal thin 1 mm section for all 3D FLAIR acquisitions. The images were analyzed by consultant radiologist at Bir hospital. The determination of the case for inclusion or exclusion as a sample was done under supervision of the Radiologist. Any doubtful or conformed case of sellar and parasellar abnormality of brain by the consultant radiologist were not taken into consideration for measurement of pituitary.

Patient Preparation and Positioning

Patient were asked to remove all metal objects including keys, coins, wallets, cards with magnetic strips, jewelries, hearing aids and hairpins. Proper history about the clinical indications was taken and the weight of the patient was noted. A satisfactory written consent form was taken from all patients before entering the scanner room. Headphones and earplugs were offered during examination. Then the procedure was explained to patient in detail and instruction given to stay still during scanning. After that, the patients were positioned in supine position with head positioned within head coil (quadrature or phased array type) and centered over nasion. Immobilization pads and straps were used if necessary for immobilization. Then scanning was proceeded with departmental protocol for routine brain MRI taking 3 plain localizer first and various pulse sequences as following;

Protocol

The sequences for routine MRI Brain Protocol includes.

- Axial: T1, T2, Diffusion and T2* weighted,
- Sagittal: T1 weighted,
- Coronal T2 weighted.

Additional sequence-

- Sagittal 3D FLAIR

The sagittal 3D FLAIR was done including the entire brain which took approximately 3-3.5 minutes for scanning. The planning was done in coronal localizer image making the positioning block parallel to the third ventricle and in axial image parallel to falx cerebri.

Parameters

While performing FLAIR sequence following scanning parameters were used. Most of which are auto selected by the machine itself.

TE- 268, TR-4800,

TI -1660

Rel. SNR- 1.05, NSA- 1

FOV- 250 x 250 x 168 mm

Voxel- 1.1 x 1.1 x 1.2 mm

Matrix- 228 x 228

Slices- 300

Gap- -0.56

Fat saturation- SPIR

SENSE- yes

Stacks – 1,

Slice orientation - Sagittal

Bandwidth - 877.2 HZ

TSE es/ shot (ms) - 3.2/507

TSE- Turbo Spin Echo

Head SAR- < 6% (0.1 W/ kg),

SED- 0.2 kJ/ kg,

PNS- 35%

Coil type - SENSE- NV- 16 and Q- Body inbuilt coil.

Acquisition time- 3-3.5 minutes

Operational Definition

- Pituitary Morphometry: Measurement of pituitary height, length, width and volume

- Pituitary Height: The greatest distance between the superior and inferior borders of the gland in midline sagittal image or in coronal mid pituitary image at the level of pituitary stalk from base of pituitary stalk to lower border of pituitary.

- Pituitary Width: The greatest distance between the right to left borders of the gland in midline pituitary coronal images at the level of pituitary stalk

- Pituitary Length: The maximum anterior-posterior diameter as the longitudinal distance defined by a line connecting two corners of pituitary gland in mid sagittal image.
- Pituitary Volume: Volume is given by length x height x width x 0.52. Mathematically, the configuration of pituitary gland can be treated as scalene ellipsoid.[22]

Measurement

The measurement was done in the workstation using electronic calipers in the reconstructed thin slice sagittal and coronal images. The data were obtained through measuring the height and length in sagittal thin 1 mm section, and width of the pituitary gland in coronal thin 1 mm section. Measurement was done by using "ISP MR Software", already installed on MR console. Measurement values were measured in millimeters (mm). The measurement was conformed to the help of consultant radiologist.

Maximal pituitary height was determined from midline sagittal images by measuring the greatest distance between the superior and inferior borders of the gland. A criterion for midline image was visualization of the pituitary stalk, Sylvain aqueduct and mid brain stem.

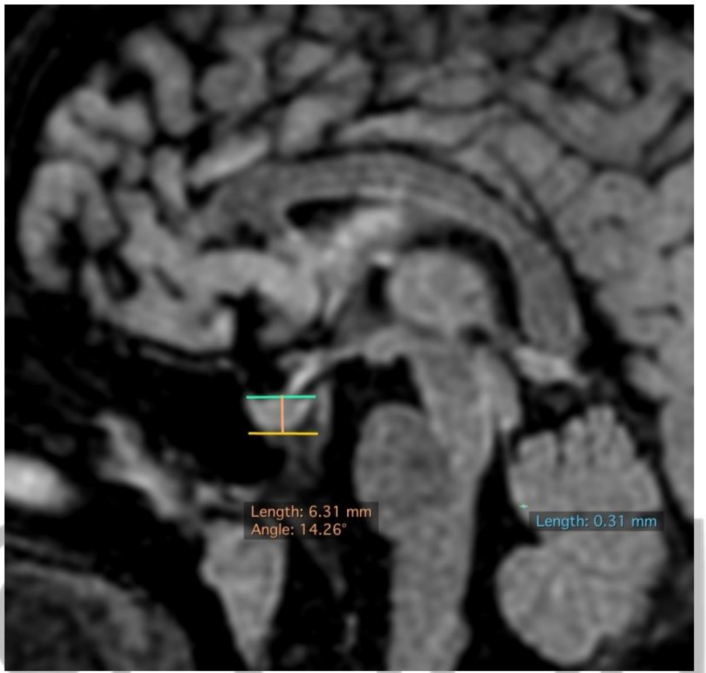

Figure 12: FLAIR sagittal reconstructed image showing measurement technique for pituitary height

Similarly length was determined by measuring the greatest dimensions between anterior to posterior border of the pituitary gland on mid sagittal images. The mid sagittal image was selected with the visual evidence of mid pituitary stalk and mid brain stem. The anterior and posterior border was determined by drawing two parallel lines along anterior and posterior pituitary ends where MR signal intensity changes abruptly. The hyper intense posterior pituitary was included in all measurements of the entire gland.

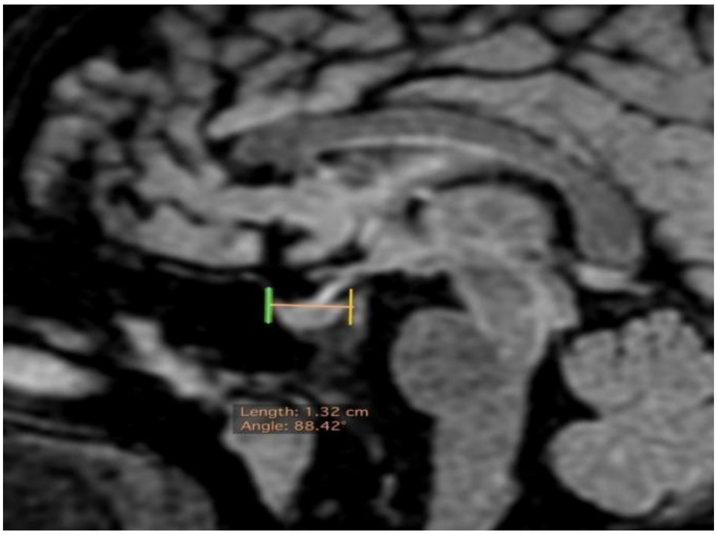

Figure 13: FLAIR sequence in sagittal reconstructed image showing measurement technique for pituitary length.

Right to left dimension or the width of pituitary gland was determined by measuring the greatest dimensions between right and left border of the pituitary gland on mid pituitary coronal images. The mid pituitary coronal image was selected with the visual evidence of mid pituitary stalk. The right and left border of pituitary gland was determined by drawing two parallel lines just medial to visible internal carotid vessel where pituitary gland ends showing signal intensity change abruptly.

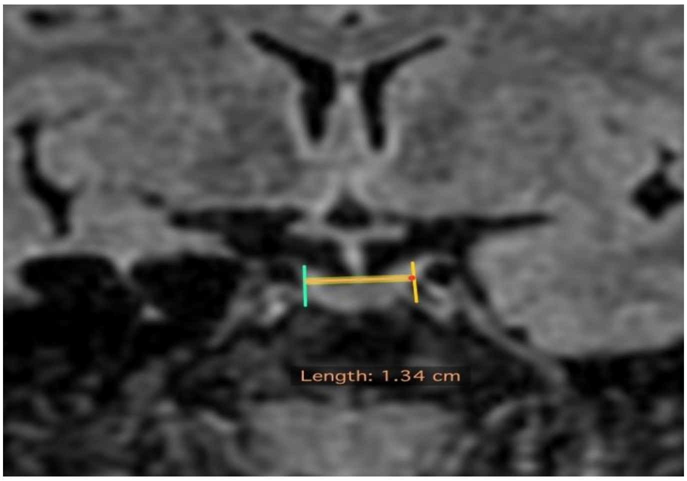

Figure 14: FLAIR sequence in Coronal reconstructed image showing measurement technique for pituitary width.

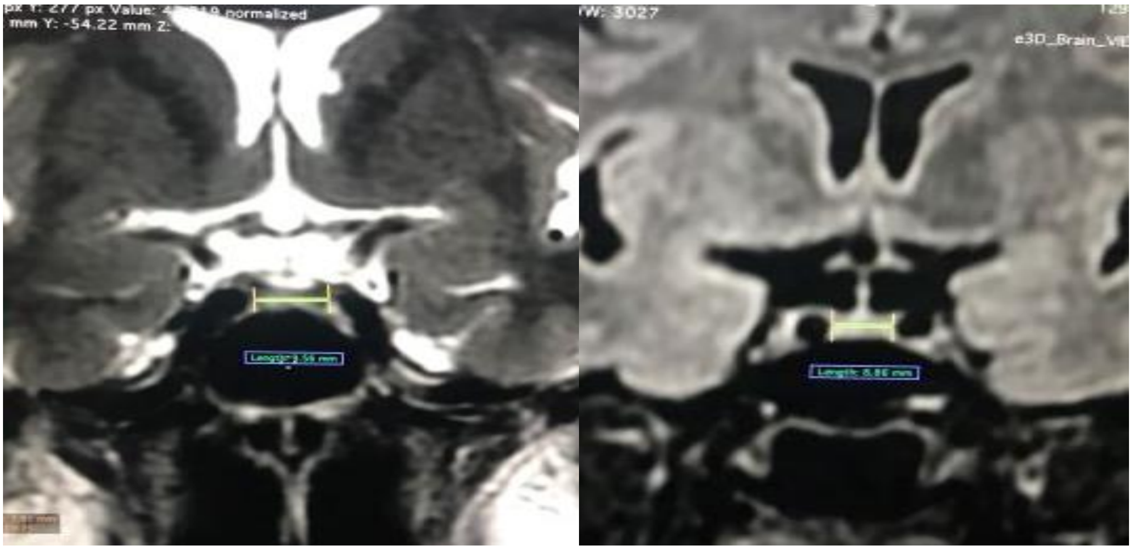

Figure 15: FLAIR sequence in coronal reconstructed image showing measurement variation in width among TSE T2 and FLAIR sequences .

Pituitary gland volume is calculated by the formula V = Antero-posterior dimension x Craniocaudal dimension x Transverse dimension x 0.52. The factor 0.52 is obtained from the sphere volume equation coefficient and cubic volume calculation given by formula: $(4/3\pi)\ (r3)/(2r)3=3.1416/6=0.52)$.[10]

Statistical Analysis

Data was analyzed using IBM Statistical Package for Social Sciences (SPSS) Windows Version 25.0 and Microsoft Excel 2016 software. Results were presented in tables, graphs and diagrams. And both descriptive and inferential statistics were performed. For descriptive statistics, central tendency and dispersion measures like mean and standard deviation were used. For inferential statistics Independent **t-** test, Person's correlation and ANOVA test were used to assess the association between pituitary parameters and demographic factors. A p-value of < 0.05 was considered to be statistically significant.

ETHICAL CONSIDERATION

Before commencing this study, thesis proposal was submitted to the Institutisonal Review Board (IRB) of NAMS and ethical clearance was taken. A written informed consent was taken from each participant after explaining the relevant details of the study. Those who did not give consent for participation were excluded from the study. Confidentiality was maintained to the utmost. No names, documents or results were disclosed or circulated anywhere other than the hospital doctors or research guide and co-guide. There was no extra cost to be bared by the patient as well as the hospital for the research.

RESULTS

A total of 178 cases were taken as a study sample out of 231 patients who came to perform routine MRI brain scan in the Radiology Department of Bir Hospital.

Gender Distribution

Out of 178 total patients there were 88(48.4%) female and 90(50.6%) males. This indicates that the study population was evenly distributed among both genders as shown in Table 1 and Figure 16.

Table 1: Gender Distribution

Gender	**Frequency**	**Percent (%)**
Female	88	49.4
Male	90	50.6
Total	178	100.0

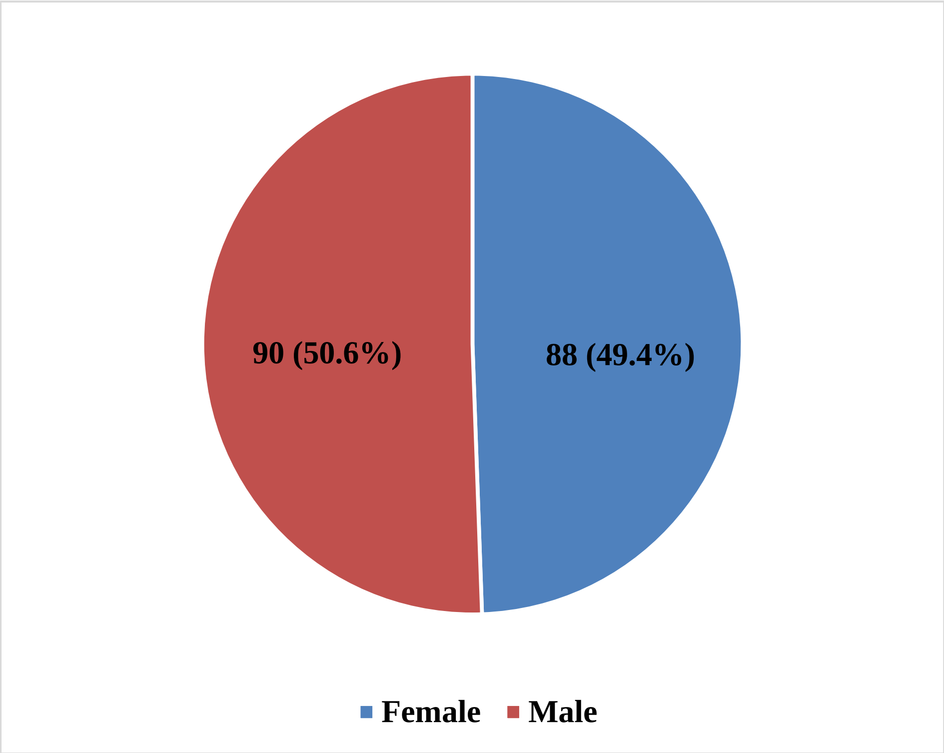

Figure 16: Pie chart showing gender distribution

Age Distribution

Table 2 shows the minimum, maximum, mean and standard deviation of age. Here the minimum age was 18 year and maximum was 86 year giving mean and SD to be 41.1 year and 17.02 year respectively.

Table 2: Distribution of age

Descriptive Statistics				
Parameter	**Minimum**	**Maximum**	**Mean**	**SD**
Age (years)	18	86	41.10	17.02

Descriptive Statistics of Pituitary Morphometric

Descriptive statistics of pituitary parameter like height, width, length and volume are given in the Table 3. Pituitary height was noted that the minimum height was 4mm; maximum height was 7.3mm with mean 5.20mm and SD±0.84mm, minimum length of pituitary was 7.95mm, maximum length was 13.9mm with mean 11.07mm and SD±1.11mm. The value of width was minimum 9.58mm, maximum 16.7mm with mean 13mm ±1.44mm SD. Finally, pituitary volume was found minimum to be 233.16 mm^3, maximum 651.12 mm^3, with mean 442.14 ±82.11 SD mm^3 as shown in Table 3.

Table 3: Pituitary morphometric analysis

Parameter	Minimum	Maximum	Mean	SD
Height (mm)	4	7.3	5.20	0.84
Length(mm)	7.95	13.9	11.07	1.11
Width(mm)	9.58	16.7	13.00	1.44
Volume$(mm)^3$	233.16	651.12	442.14	82.11

Gender variation of pituitary morphometry

The Table 4 shows the variation of pituitary morphometry among male and female patients. It was noted that the mean pituitary height in female was 5.25±0.83mm and in male 5.16±0.85mm. Similarly, volume of the pituitary gland in female was also found to be 392.66±73.73mm^3 and in male 384.07±89.77mm^3. There was no statistical significant variation (P<0.05) among male and female pituitary morphometry.

Table 4: Gender variation of pituitary morphometry

Parameter	Sex	Mean	SD	T	P
Height (mm)	**Female**	5.25	0.83	0.696	0.488
	Male	5.16	0.85		
Length (mm)	**Female**	11.04	1.05	-0.398	0.691
	Male	11.10	1.17		
Width (mm)	**Female**	13.12	1.48	1.043	0.298
	Male	12.89	1.39		
Volume (mm^3)	**Female**	392.66	73.73	0.697	0.487
	M	384.07	89.77		

Distribution of various age groups

The frequency of patients in various age groups were shown in Table 5 and Figure 17 where the total sample was divided into five groups with class intervals as ≤27, 28-37, 38-47, 48-57 and ≥58 years.

Table 5: Distribution of various age groups

Age (years)	Frequency	Percent (%)
≤27	47	26.4
28-37	40	22.5
38-47	27	15.2
48-57	26	14.6
≥58	38	21.3
Total	178	100

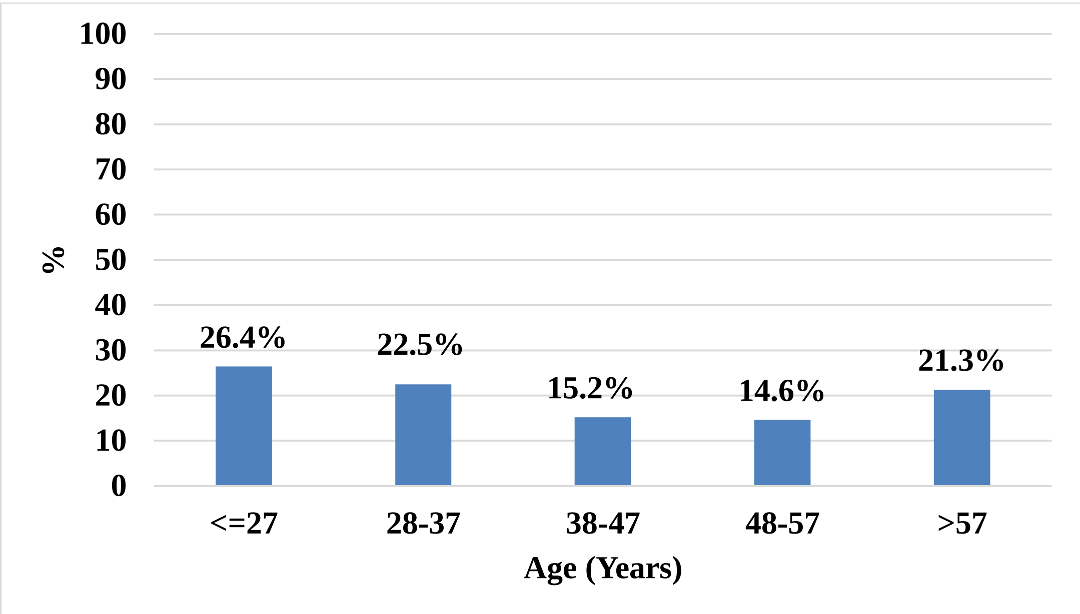

Figure 17: Distribution of various age groups

Comparing two means of pituitary height

On performing independent t-test, there was no significant difference in mean height of pituitary between male and female. The mean of pituitary height of various age groups are shown in Table 6. The mean height of pituitary gland seem to be decreasing as the age advances from group ≤27 to 38-47 and then increases in the age 48-57 year in male. In female, the pituitary height mean decreases gradually as the age advance but there is slight increase in pituitary mean height in age group 38-47.

Table 6: Independent t-test for comparing two means of pituitary height

	Male		**Female**			
Age(year)	**Mean (mm)**	**SD**	**Mean (mm)**	**SD**	**t**	**P**
≤27	5.62	0.92	5.81	0.65	-0.814	0.420
28-37	5.28	0.67	5.17	0.80	0.456	0.651
38-47	4.74	0.67	5.32	0.76	-1.938	0.064
48-57	5.22	0.92	5.12	0.84	0.285	0.778
≥58	4.72	0.70	4.44	0.50	1.321	0.195

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Scatter Diagram

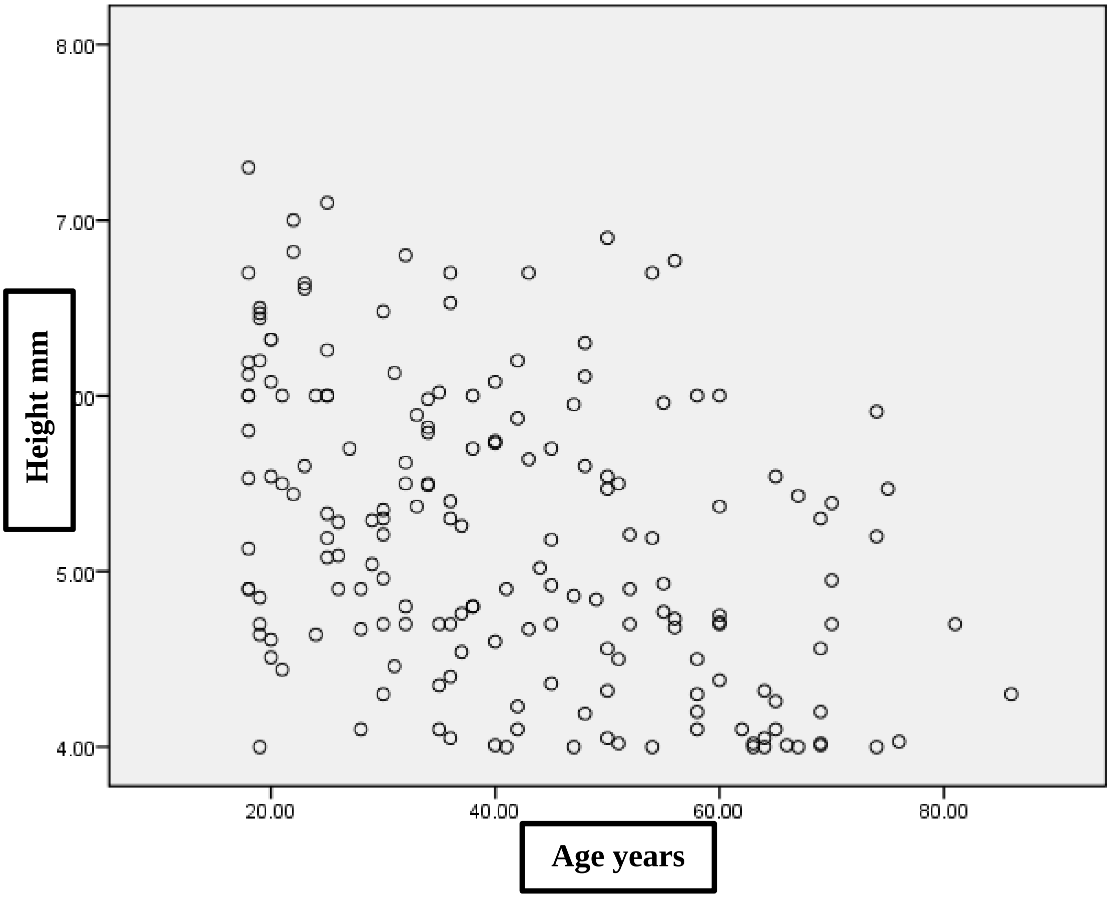

Figure 18: Scatter diagram plotted between pituitary height and age

Comparing two means of pituitary length

The mean of pituitary length of various age groups in male and t-test are shown in the Table 7. The result of t-test shows no significant difference in mean length of pituitary between male and female.

Table 7: Independent t- test for comparing two means of pituitary length

	Male		Female			
Age(years)	**Mean (mm)**	**SD**	**Mean (mm)**	**SD**	**T**	**P**
≤27	11.04	1.51	10.51	1.01	1.402	0.169
28-37	11.13	1.00	11.18	1.16	-0.151	0.881
38-47	11.40	1.15	11.22	0.92	0.437	0.666
48-57	11.31	1.01	11.06	0.90	0.661	0.515
≥58	10.92	1.05	11.42	1.00	-1.453	0.155

Scatter Diagrams

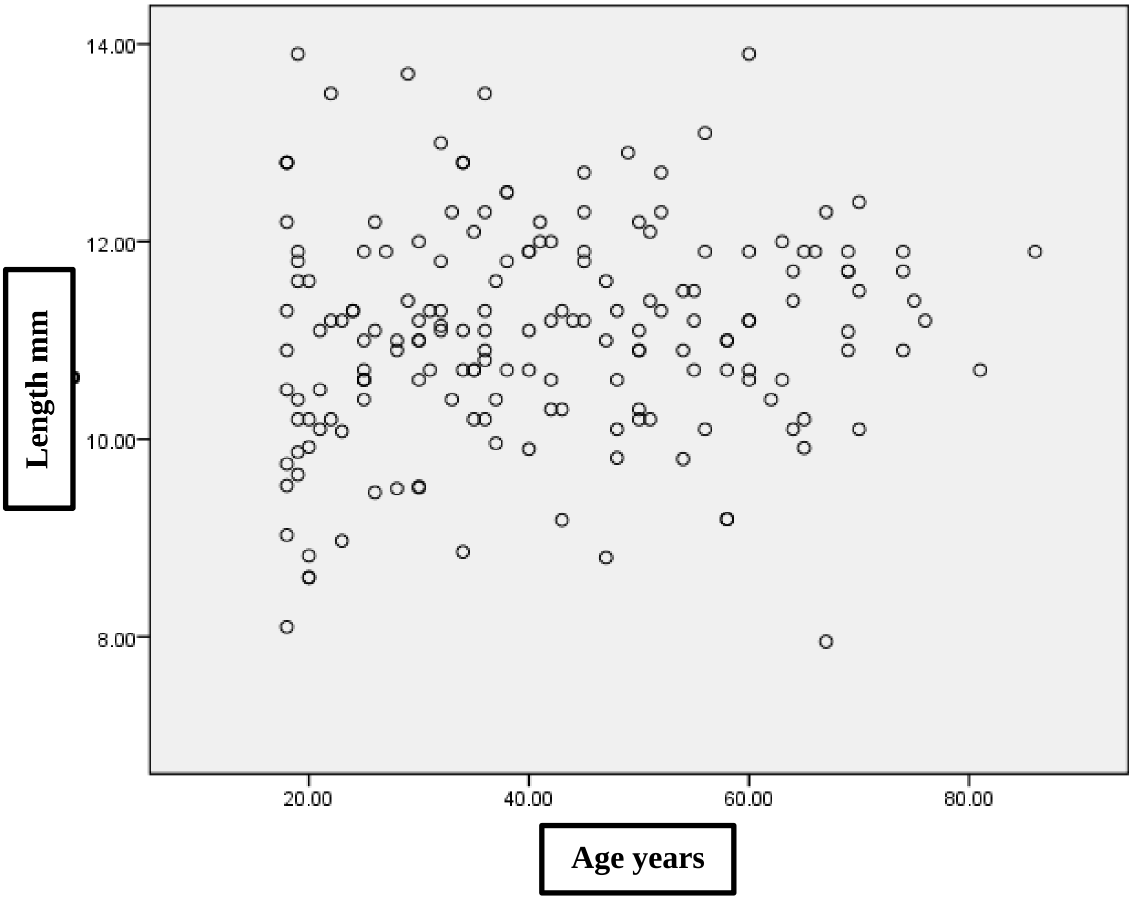

Figure 19: Scatter diagram plotted between pituitary length and age

Comparing two means of pituitary width

The means of pituitary width of various age groups in male and female are shown in the Table 8. On performing independent t-test there was no significant difference in mean width of pituitary gland between male and female in all age groups except the age group ≥58 with p value 0.02 as shown in Table 8.

Table 8: Independent t-test for comparing two means of pituitary width

	Male		**Female**			
Age(years)	**Mean (mm)**	**SD**	**Mean (mm)**	**SD**	**T**	**P**
≤27	13.21	1.61	13.13	1.91	0.158	0.875
28-37	12.86	1.19	12.51	1.39	0.846	0.403
38-47	12.73	1.70	13.11	1.48	-0.587	0.563
48-57	12.72	1.29	13.48	0.93	-1.681	0.106
≥58	12.75	1.30	13.70	0.89	-2.415	0.021

Scatter Diagram

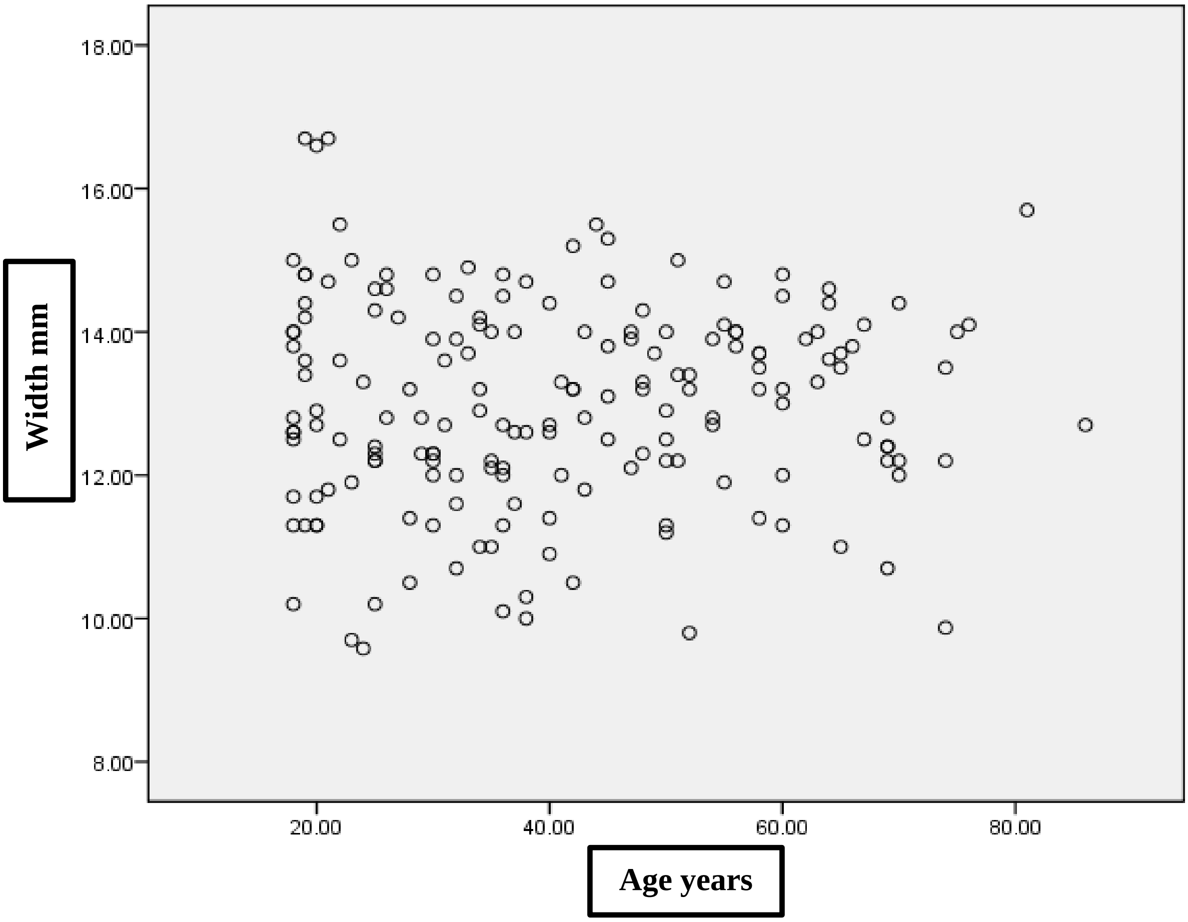

Figure 20: Scatter diagram plotted between pituitary width with age

Bar diagram Figures 21 and 23, and scatter diagrams Figures 18, 19, 20, 22 illustrating a visual difference in the different dimensions of the pituitary gland with respect to different age groups. Trend lines have also been added to this bar graph to further illustrate the trends in the different dimensions through the age groups.

Bar diagram

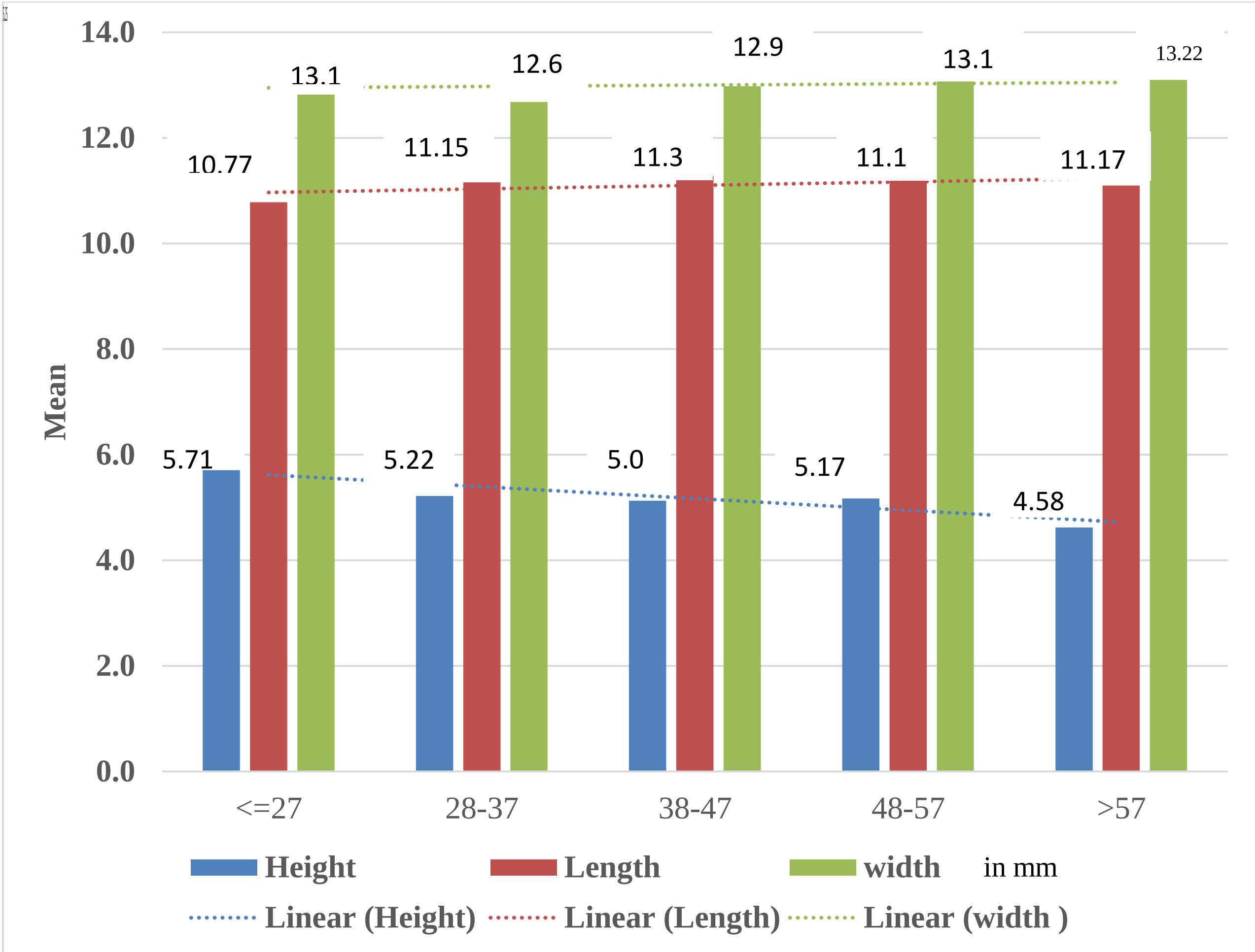

Figure 21: Distribution of pituitary morphometry in various age groups

Comparing two means of pituitary volume

The means of pituitary volume of various age groups are shown in the Table 9. On performing independent t-test, there was no significant difference in mean volume between male and female. The difference between mean of pituitary volume between male and female was found to be significant only in the age group 38-47 year with P value 0.097 (male 354.76±60.74 mm^3 and female 406.77±79.25 mm^3). The maximum mean pituitary volume was noted in age group ≤27 and the minimum mean pituitary volume was noted in age group ≥58 in both genders.

Table 9: Independent t-test for comparing two means of pituitary volume

	Male (n=90)		**Female (n=88)**			
Age(years)	**Mean** (mm^3)	**SD**	**Mean** (mm^3)	**SD**	**t**	**P**
≤27	425.81	106.54	414.09	70.36	0.443	0.660
28-37	395.83	85.48	374.77	71.72	0.847	0.402
38-47	354.76	60.74	406.77	79.25	-1.725	0.097
48-57	392.74	101.50	396.54	76.36	-0.106	0.916
≥58	338.95	50.69	362.82	66.10	-1.251	0.219

Scatter Diagram

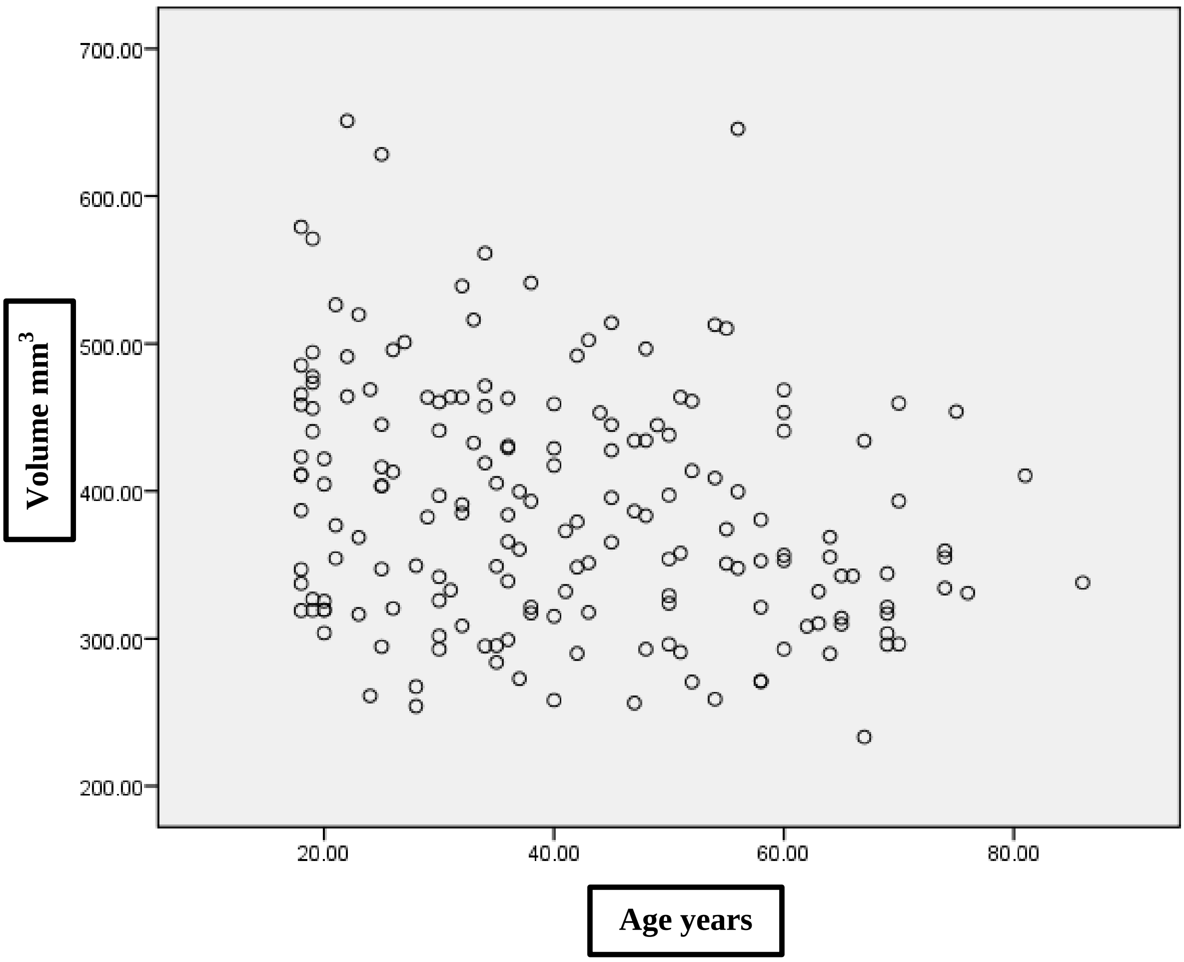

Figure 22: Scatter diagram plotted between pituitary volume and age

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Bar diagram illustrating a visual difference in the different dimensions of the pituitary gland volume with respect to different age groups. Trend lines have also been added to this bar graph to further illustrate the trends in the different dimensions through the age groups.

Bar diagram

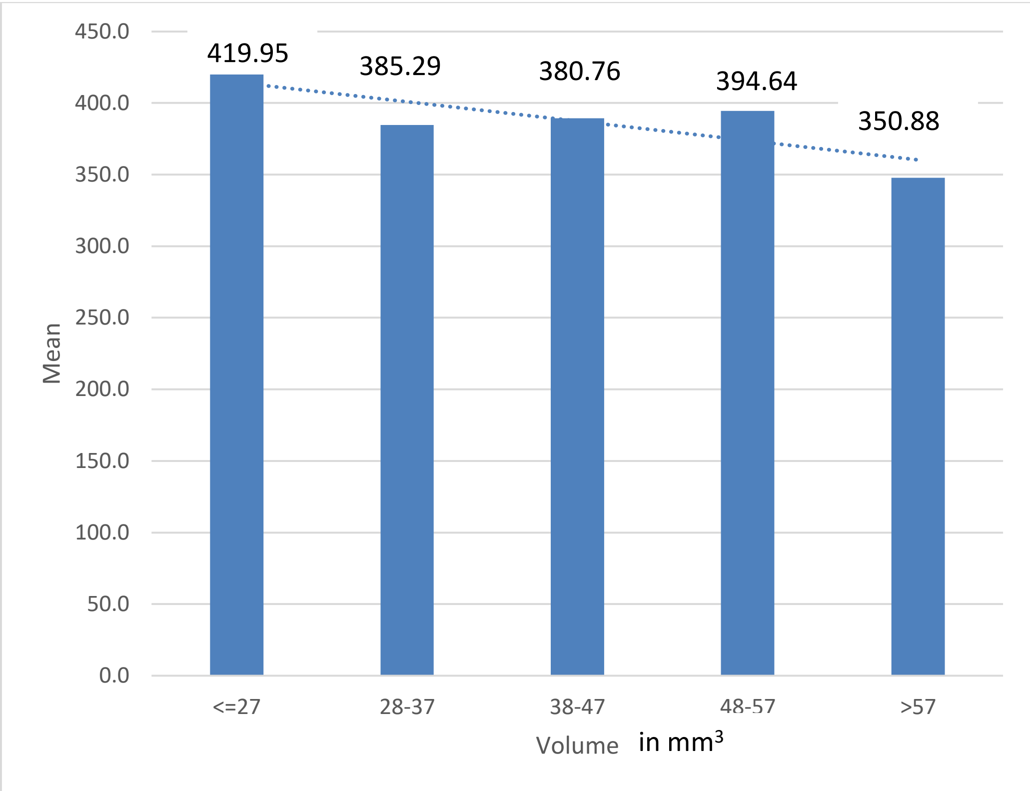

Figure 23: Distribution of pituitary volumes in various age groups

Correlation between age and pituitary morphometry

Correlation of pituitary parameters with age of the patient is indicated in Table 10 and Figures 18, 19, 20 and 22. On performing Pearson's correlation coefficient, it was indicated that there is a weak linear correlation between age with pituitary height and volume.

Table 10: Karl Pearson's correlation for pituitary parameters and age

		Height	Length	Width	Volume
Age	**Pearson's Correlation**	-.415	.113	.027	-.249
	P	<0.001	.133	.721	.001

Correlation of age and sex with pituitary parameters

On performing, ANOVA to show the correlation of age and sex with pituitary parameters the result showed that height and volume are significantly different across various group of age having p values <0.001 and 0.002 whereas pituitary width and length seemed to be not significantly correlated with different age groups , as shown in Table 11. A two-way ANOVA was conducted that examined the effect of gender and age on height, length, width and volume. There was no statistically significant interaction between the effects of gender and age on height (p=0.226), length (p=0.325), width (p=0.262) and volume (p=0.381).

Table 11: ANOVA for pituitary parameters and age

Age(year)	**18-27**		**28-37**		**38-47**		**48-57**		**≥58**			
Parameters	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**P**
Height (mm)	5.71	0.80	5.22	0.73	5.13	0.77	5.17	0.86	4.62	0.64	10.958	<0.001
Length (mm)	10.78	1.30	11.16	1.07	11.28	0.99	11.19	0.95	11.10	1.05	1.211	0.308
Width(mm)	13.17	1.74	12.68	1.30	12.98	1.53	13.07	1.18	13.10	1.24	0.741	0.565
Volume (mm^3)	420.08	89.88	384.77	78.25	389.43	76.59	394.49	89.03	347.75	57.17	4.456	0.002

Multiple comparisons for pituitary parameters and age

Mean height is significantly different in age 18-27 as compared to all other age groups. Mean height for age 28-37 is significantly different as compared to age ≥ 58 with p value .005, but not significantly different as compared to other age groups. Height in age group 38-47 and 48-57 is significantly different from height in age group ≥58 with p value 0.063 and 0.038. Mean length and width are not significantly different in different age group. Mean volume is significantly different in age 18-27 and age ≥ 58 with p≤0.001. For other age groups, volume is not significantly different as shown in Table 12.

Table 12: Multiple comparison of height, length, width and volume in different age groups

Parameter		Height (mm)	Length (mm)	Width (mm)	Volume (mm^3)
Age (years)	**Age**	**P**	**P**	**P**	**P**
18-27	28-37	.026	.500	.492	.237
	38-47	.015	.334	.982	.498
	48-57	.032	.546	.998	.678
	≥58	<0.001	.666	.999	<0.001
28-37	18-27				
	38-47	.986	.992	.911	.999
	48-57	.999	1.000	.810	.988
	≥58	.005	.999	.681	.241
38-47	18-27				
	28-37				
	48-57	1.000	.998	.999	.999
	≥58	.063	.969	.997	.229
48-57	18-27				
	28-37				
	38-47				
	≥58	.038	.998	1.000	.144

DISCUSSION

One of the most commonly performed MRI examinations is MRI brain in which all radiologists wisely evaluate the pituitary gland to decide if it is normal. It is crucial to define what constitutes “normal” so that abnormal is differentiated and steps are taken for further specialist referral. This study was aimed to generate concise data for ‘normal’ pituitary measurements from a healthy population using higher tesla MRI scanner and advance imaging pulse sequence 3D FLAIR.

MRI is an important diagnostic modality useful for detailed examinations of pituitary gland. Many conditions such as inflammatory disease, empty sella, embryonic abnormalities, physiological hypertrophy, neoplasia (microadenoma or macroadenomas) and increased lobulated margin can be assessed with MRI.[5, 11] It can also substitute CT for pituitary measurements due to its lesser potential risk, no use of ionizing radiation and greater facility to the patient. Additionally, it helps for surgical approach to be practical through preoperative imaging of the tumors.[60, 61]

Although there have been multiple studies done internationally to gain understanding of the size of the pituitary gland in the recent years, this study is the first of its kind in Nepal. Similar population study was done in 2014 in Nepal using the MRI scanner of 0.35 tesla, 2D sequence and thicker (10mm) slice. This study helps update data using currently used advanced scanning technique with 3D FLAIR sequence and 3 tesla MRI machine in order to increase validity of the previously established data.[22]

A study performed by Özandaç S et al in Turkish population resulted that the overall means and standard deviations of the measurements were: pituitary gland width, 13.09±1.99 mm; pituitary gland height, 4.91±1.10 mm which is very much similar to the results of this study where the pituitary width 13±1.44mm and height 5.2±0.84. This shows the pituitary height in Nepali population is slightly greater than that in Turkish population. Again, Özandaç study showed no significant difference ($p>0.05$) found in the corresponding mean values in both gender and a negative moderate degree correlation in pituitary gland height and age as in this study.[48]

This study showed no significant correlation of pituitary morphometry and gender which is in contrary to the result of study done by Yadav P et al in Indian population where the results showed mean height of pituitary gland in female patients of each age group was more than that of male patients in the same age group. Yadav P et al further concluded the height of pituitary gland extended a maximum in the 21 to 30 years of age group in both males and females which matches the result of this study where it was concluded that the maximum height was measured in the age group < 27 years. [11]

The study by John Sinclair in Scottish population showed remarkably similar results with this study showing mean pituitary gland height of 5.52±0.73 in male and 5.66±0.96 in female. In John's study, patients were grouped into 6 different age categories 16-25, 25-35, 35- 45, 45-55, 55-65 and >65, similarly to this study. John's study showed linear decrease in average pituitary gland height and volume with increasing age groups, as this study also showed similar results. [10]

Naik D et al studied the shape and size of pituitary gland which showed matching results to this study. The average pituitary height was 5.8 mm ± 1.5 mm in both sexes, 5.5 mm ± 0.16 mm in males and 6.0 mm ± 0.15 mm in females comparable to this study where the mean height was 5.20±0.84mm. In contrary to this study, D. Naik concluded that the height and volume of pituitary gland increases with the age showing positive correlation with statistical significance. Whereas in this study, it was shown that there is a weak negative correlation.[2]

Suzuki M et al have also described that height of pituitary gland reaches a maximum in the 10-19-year-old age group of both sexes. In 20-29 years old age group, which was also consistent with the finding of this study where pituitary height reaches to its maximum in the age group ≤27 years.[62]

Sanjay SC et al established that mean height of pituitary gland was 6.27±0.56 in Indian population which is slightly higher than the measurement data of this study. On the other hand, the width and length of pituitary gland was found to be more in the population of this study in comparison to Indian population. They also observed that the height decreased as the age advanced, however there was mild increase in height in 40-49 years age group just like this study where there is increase of height in age group 38-47 year age group.[18]

Furthermore, Ikram M F et al in the study done in Pakistan showed a different type of result than in this study. The study concluded that after the second month of life, the pituitary height increased gradually to achieve its peak in the second decade of life in the female (6.3 ± 1.4 mm, n = 43) and the third decade of life in the male (5.9 ± 1 mm, n = 41). Significant difference was observed in pituitary height in different age groups in both genders and gland was significantly higher in females than males in the second decade unlike this study where there was no significant difference in pituitary morphometry with respect to gender.[63]

JU KS et al studied by performing autopsy of human cadaver in Korean which result showed that, there was some degree of compression in pituitary width by the carotid artery in 22% of study population and gland had a superior-to-inferior dimension at least 2 mm less than the depth of the pituitary fossa in 23% with the dimension of some glands being less than half this depth. The researcher further advocates that the adult hypophysis measures approximately 10 mm in length, 10 to 15 mm in width, and about 5 mm in height which comply with the result of this study where it is concluded that mean height

5.20±0.84mm, length 11.07±1.11mm, width 13±1.44mm and volume 442.14 ±82.11mm^3.[52] The researcher further suggested that a dynamic contrast MRI scan of pituitary gland should be done for further assessment in cases where there is abnormality suspected in the size of pituitary gland.[22]

Various studies done in different population such as Thai, Indian, Korean, Japanese, Pakistani Turkish and Scottish population showed differences in the period of peak height of the pituitary gland than the population data of this study. Pituitary mean height was found as 5.52 mm and 5.66 mm in Scottish male and female 5.0 mm and 5.2 mm in Japanese male and female, 5.60 mm and 5.80 mm in Pakistani male and female and 5.37 mm and 6.27 mm in Indian male and female respectively.[10, 11, 55, 53] Mean pituitary height was found to be 5.16 mm and 5.25 mm in male and female respectively in this study.

According to the result of this study, measurement data of pituitary height were lower than the population data of Scottish, Pakistani, Thai, and Indian population. Whereas, the measurement data of pituitary height in this study population were greater than the measurement data of Turkish, Japanese and Korean population. At the same time, the result of this study was closest to the study results of Scottish, Turkish and Pakistani population. In the contrary to the previous study of pituitary morphometry done in Nepali population, the pituitary height and volume showed diminished measurement values.

Some of the previous studies stated the peak height of the pituitary gland was observed in 1^{st} decade.[15, 11, 18, 52, 57, 59] In the contrary, other studies showed peak height of the pituitary gland in 2^{nd} decade.[53, 55, 61] In this study, the peak height of pituitary was found in the age group 18-27 years (late 2^{nd} up to late 3^{rd} decade) in both female and male population.

We consider that these differences could be a result of such factors like genetic variables, race, demographic variables (age, gender), method of measurement, thickness of the slice acquired, strength of the MRI scanner, ratio of females in the study, mean age of participants, stress, hormonal changes, and menstrual cycle etc. Moreover, pituitary gland diseases like prolactinoma, gigantism, and hyperthyroidism or diseases including acromegaly, hypothyroidism, and Addison's or Graves diseases can cause variation in the morphometry of pituitary gland.[22]

Although, variation in the size of pituitary gland is principally due to the changes in pituitary height, this study has tried to expand further insight into the width and length of the gland as well. As there was no significant age related effects found in gland length or width. Lurie SN et al suggested that upcoming studies might reasonably use pituitary height alone serving as the single measure of pituitary size.[16] It was the width of pituitary gland which was found greatest among the dimensions of pituitary on average.

Just like any other scientific studies, this study also had one of the major issues about the reproducibility of measurement data. The smallest variation in measurement may establish to a gross miscalculation of gland dimension resulting in error of data, particularly when the superior aspect of pituitary gland was concave. In such shape, the height measurement was found to be difficult and the consistency of measurement technique was questionable. Thus, in this study for achieving scientific consistency, measurement of the pituitary gland dimensions were done with only one technique as stated in the methodology. Furthermore, a radiological standard for measurement of the pituitary gland size is necessary and is highlighted throughout this study.

Yadav P et al in her study mentioned that the pituitary gland is often concave in its superior aspect, and this would not be reflected in a single, thick sagittal image, which may show only the higher lateral margins of the gland.[11]This can cause errors in measurements of the pituitary gland height. This can lead to decreased gland even though the pituitary height is increased (as it was measured from the lateral margins of the gland). The same problem is also seen in partially empty sellae where we can see the gland tissue extending up to the full height along its lateral margins. To correct this problem measurement was taken in thinnest slice (1mm) possible in both sagittal and coronal section and mean was taken for more accurate data measurement.[11, 27, 54]

One of the unavoidable limitations to this study is that the study population did not include patient below the age of 18 years. Due to lack of anesthesia service and sedation in Bir hospital, negligible number of pediatric patient was referred for MRI brain. Hence they were excluded from the data. In addition, WHO has defined the adult population as the population above the age of 18 years and the aim of the study is to establish pituitary morphometry for normal adult population.

As previously stated, fifteen patients with partial empty sella were excluded from this study. We took an upper limit of 4mm to define partial empty sella and 2 mm to define complete empty sella. The finding of this study is coherent with other study reports stating approximately 6.4% incidence of partial empty sella in the given population where previous studies says that the empty sella is found in approximately 5-15% of patients.[7]

Similarly, pituitary adenoma is a common incidental finding within the population approximating that 10% of the adult population have an asymptomatic pituitary adenoma.[64] In this study, the suspected pituitary adenoma was approximately 5.6%. This could be due to either the small population size or an underestimation of the number of pituitary adenomas within this population.

Furthermore, this study indicated a reduction in pituitary height with relation to advancing age but the pituitary width and length seems unaffected. This can be explained in such way that the diaphragm sella becomes weak as aging progresses and CSF descends downwards due to gravitational force. Meanwhile the bony cavity (sella turcica) remains unchanged with aging thus the width and length of the pituitary gland also doesn't change.[10]

Earlier studies done in similar topic advised that changes in the hormonal levels may result such variation in the pituitary morphometry. Increase in pituitary height can be related with the increased production of LH during puberty. Moderately bigger pituitary height in young males and females than older patients may be caused due to physiological alterations in the neuro-endocrinal hormones such as gonadotropic hormones decreases after puberty up to the fifth decade of life. However, in females there is an increase of concentration of these hormones in their fifth and sixth decades because of age-related decrease in circulating gonadal steroid hormones and an increase in gonadotropin releasing hormones.[56]

Earlier studies have shown the considerable increase in the pituitary height in females of post-menopausal age. As per the results in this study there is a greater pituitary height in females of 48-57 years. Former studies have also shown that the growth in the pituitary height is noted in the elderly subjects possibly due to compensatory hypertrophy after a significant decrease in gonadal steroid feedback effect.[52, 11]

Pregnancy and lactation is one of the major causes which may have a substantial impact on the size of pituitary glands. Many studies have already testified clearly that the pituitary gland increases in size during pregnancy.[59] In Bir hospital, we rarely perform MRI in pregnant patients. None of the females included in this study had known pregnancy. However, there were three patients lactating who were excluded from the study. This can be taken as one limitation of this study. So, we can study the pituitary dimensions and its variation in pregnant and lactating females in the future studies.

No studies have been done till date considering the alteration in the size of the pituitary gland within closed ethnic groups. This study also did not take ethnic background of the patients into account and did not study variation on the pituitary dimension due to ethnicity. Future study can be done considering the variation in pituitary morphometry in relation to different ethnic groups.

CONCLUSION

This study provides data regarding pituitary morphometry and its variation with respect to sex and age using 3D volumetric FLAIR sequences in MRI. There was weak linear correlation between age with pituitary height and volume. No statistical significant variation was found among male and female pituitary morphometry. This information will help to know whether the pituitary under study is within or out of normal limits. The morphometric information provided by this study will enhance in differentiation and diagnosis of pituitary pathologies. Further larger study is advisable to establish a standard morphometry of pituitary gland in Nepali population.

LIMITATIONS

Limitations of this study are as follows;

- Selection bias- as expensive MRI test prohibited the normal volunteers for the study
- Small sample size for the population study
- Volume measurement was done by applying the formula of an oval structure, i e. length x width x height x 0.52 but all pituitary were not oval in shape. Also there was no volume measurement software installed in MR scanner at research site
- Morphometric study of pituitary gland in pediatric was not considered in this study because of unavailability of sedation or anesthesia facility and pediatric ward too.
- Most of the old age patients were excluded from the study because of having partial empty sella features.

RECOMENDATIONS

- Larger sample size would provide larger margin of error and yield more accurate measurement so sample size can be increased in future studies.
- The volume measurement could be done more accurately with the advance volume measurement software instead of using volume estimation formula of an oval shape
- Further study can be done with extension of age groups including pediatric patients.
- Alteration in the size of the pituitary gland within closed ethnic groups can be a good consideration to study variation on the pituitary dimension due to ethnicity in future studies of same kind.

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Name of the candidate/ researcher: Mrs. Maheswori Shrestha
Registration No.: M.Sc. MIT-1-2017
Program and year: Master of Science in Medical Imaging Technology, 2017
Department: Department of Radiology and Imaging

Title of the Proposal: "MORPHOMETRIC STUDY OF PITUITARY GLAND WITH MAGNETIC RESONANCE IMAGING"
Name of Guide: Prof. Dr. Swoyam Prakash Pandit
Name of Co-guide: Consultant Dr. Bikash Raj Thapa
Study design: Descriptive cross-sectional.
Sample size: Considering Margin of error: 5%, Confidence Interval: 95%, Population size: 226 and Sample proportion: 50% and standard deviation of pituitary size 2 mm, the Sample size is calculated to be 171 from following formula.

Specific Objectives:

- To measure the width, height and anterior-posterior dimension of pituitary gland in 1 mm thin coronal and 1 mm thin sagittal plane.
- To estimate the volume of pituitary gland by multiplying Length X Height X Width X 0.52 (volume of oval structure).
- To find out the association between pituitary gland height, width and length with socio-demographic variables (age and sex).

Ethical clearance: Ethical clearance given

Date of proposal submission: 2075/11/27 (March 11, 2019)

Date of IRB approval: 2076/2/1 (May 15, 2019)

The following thesis proposal has been accepted by Institutional Review Board (IRB) of National Academy of Medical Sciences, Bir Hospital, Kathmandu.

You are advised to conduct the study according to the technical and ethical standards and rules and regulation laid down by concerned institute /NAMS/ IRC and required to submit a copy of your final report/ publication to IRB, NAMS.

Prof. Aarati Shah
Chairman, IRB, NAMS

E-mail: admin@nams.org.np Website: www.nams.org.np P.O.Box No. 13606

Annex. 2

Consent form

I am Mrs. Maheswori Shrestha, studying as a student of M.Sc. MIT 2nd yr. in National Academy of Medical Sciences, Bir Hospital. I am undertaking the research on the topic **'MORPHOMETRIC STUDY OF PITUITARY GLAND WITH MRI'**. For this purpose, I request you to participate in the research. The privacy of your information will be maintained.

I ………………………………..…would like participate in this research. I am fully informed about the procedures and the effect of the research.

Patients name...................... Patient's signature............................

Visitors name.......................... Visitor's signature..........................

Date.................. Relation with the patient................

Annex. 3

<u>मन्जुरीनामा</u>

म/मेरो ....लाई यस **"MORPHOMETRIC STUDY OF PITUITARY GLAND WITH MRI."** नामको अनुसन्धानात्मक अध्ययनमा संलघ्न गराईएको कुरा मलाई जानकारी छ। उक्त अनुसन्धानको बारेमा मैले राम्रोसंग बुझेको छु र यसमा भाग लिन म राजीखुशी छु। अनुसन्धानको प्रकृति तथा अनुसन्धानको क्रममा यसका सम्भावित जोखिमहरूको बारेमा पनि मलाई जानकारी गराउनु भएको छ। यस अनुसन्धानबाट, ईच्छा नलागेको खण्डमा कुनैपनि बेला बाहिरिन सकिने कुरा पनि मलाई जानकारी गराईएको छ।

बिरामीको नाम: सही

मिति:

नाता :

Annex. 4

Proforma

S. N	Name	Age	Sex		Pituitary			
			Male	Female	Height (mm)	Length (mm)	Width (mm)	Volume (mm^3)
Total								

Annex. 5

Budget:

S.N	Items	Price	Remarks
1	Statistician Consultation	8000	
2	Stationary	8000	
3	Printing price	5000	
4	Hard copy binding	2500	
5	Miscellaneous	2500	
6	Total	26,000	