

Endocrine Dysfunction And Hormonal Abnormalities In Patients With Pituitary Macroadenoma

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Abstract

Background: Pituitary macroadenomas are clinically significant sellar lesions which can produce endocrine dysfunction by either hypersecretion of endocrinotropins, or compression and destruction of normal pituitary tissue. Patients may present primarily with neurological (or visual) complaints, but may also have endocrine abnormalities. Therefore, a thorough hormonal evaluation is necessary to determine if there is a clinically significant pituitary dysfunction and to direct management.

Objective: The aim of this study was to estimate the prevalence and type of endocrine dysfunction and hormonal abnormalities in patients with pituitary macroadenoma and their association with certain demographic and radiological parameters.

Methods: Cross sectional study was carried out in a hospital setting at Dow University, Karachi Pakistan from October to December 2025. The total number of patients was 79 (10-60 years), who had an MRI confirming pituitary macroadenoma (≥ 10 mm). Clinical and radiological features were evaluated such as tumor symptoms, size of the tumour with the maximum diameter,

and tumor extension suprasellar. Hormonal evaluation consisted of serum prolactin, TSH, free T4, morning cortisol, ACTH, IGF-1, LH, FSH and sex steroids which were determined by clinical indication. Data were analyzed using SPSS where categorical variables were presented in frequency and percentage.

Results: The group ages most common were 30-39 years (25.3%) and there was a slight male predominance (54.4%). Headache (73.4%) and visual disturbance (62.0%) were the most common clinical features. The most common tumor size was 20-29

Author Details

Keywords: Pituitary Macroadenoma, Endocrine Dysfunction, Hypopituitarism, Hormonal Abnormalities, Hyperprolactinemia, Magnetic Resonance Imaging, Suprasellar Extension, Pakistan.

Received on 15 Feb 2026

Accepted on 20 Mar 2026

Published on 31 Mar 2026

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mm (46.8%). Overall, 58 (73.4%) patients had at least one endocrine abnormality. The most common abnormalities reported were hypogonadism (53.2%), hyperprolactinemia (43.0%), central hypothyroidism (39.2%), central adrenal insufficiency (27.8%) and low IGF-1/suspected GH deficiency (21.5%). Patients with tumors ≥ 30 mm (88.9%) had a higher incidence of endocrine dysfunction than did patients with tumors 10–29 mm (68.9%).

Conclusion: Pituitary macroadenoma is linked to a significant endocrine dysfunction burden, generally affecting one or more hormonal axes. Age and sex appropriate endocrine evaluation should be performed as part of the routine evaluation of patients with pituitary macroadenoma, especially those with larger tumors or suprasellar extension

Introduction

Pituitary adenomas are very prevalent intracranial tumors, now more often described as pituitary neuroendocrine tumors (PitNETs), with a wide clinical spectrum from being an incidental finding to a tumor-associated disease with significant morbidity regarding the endocrine and neurologic systems. Typically, a macroadenoma is characterized by a size of at least 10 mm. Endocrine implications of macroadenomas are significant since these tumors are more likely to compress a normal pituitary, the stalk, optic chiasm, cavernous sinus and neighboring sellar structures. From recent reviews, it is estimated that 1 in 1,100 individuals will develop a clinically apparent pituitary adenoma, and there is a significant proportion of clinically significant lesions (macroadenomas) (Tritos & Miller, 2023).

There are two main mechanisms underlying endocrine abnormalities in macroadenoma: the secretion by a functioning tumor or the inhibition of secretion due to destruction or compression of normal pituitary tissue. The first can lead to hyperprolactinemia, acromegaly, Cushing disease or the less common thyrotropin-secreting phenotype. The second can result in central hypothyroidism, secondary adrenal insufficiency, hypogonadotropic hypogonadism, growth hormone deficiency and combined or panhypopituitarism in extensive disease. The clinical presentation is determined by cell-lineage, tumor size, duration, chiasmal compression and age and sex (Iglesias, 2024).

Thus, biochemical testing of a macroadenoma can't be restricted to a single pituitary hormone. There are currently data to support assessment of both hormone excess and hormone deficiency with interpretation directed by target gland hormones and not pituitary hormones alone. For instance, in cases of central hypothyroidism, the free thyroxine is low and the TSH is either low, normal, or slightly elevated, and in secondary adrenal insufficiency, the morning serum cortisol level should be carefully evaluated and, if necessary, dynamic adrenal testing should be performed. Gonadal dysfunction is sex dependent, age dependent, dependent on menstrual status and on clinical context and GH deficiency is usually evaluated with IGF-1 and confirmatory stimulation testing (when applicable) (Fleseriu et al., 2024).

Prolactin is noteworthy as a hormone because a macroadenoma can lead to the actual production of excess prolactin or to a slightly elevated level due to the compression of the stalk and the abolition of the dopaminergic inhibition. Falsely low levels of prolactin may also be seen in very large lesions, because of the laboratory hook effect, which requires correct dilution of the specimen. The 2023 Pituitary Society consensus highlights the need to carefully characterize each prolactinoma biochemically, use imaging to correlate with the biochemical status, and treat each patient individually; the recent international guidance also strongly advocates for systematic evaluation of hormonal status in patients with sellar lesions (Petersenn et al., 2023).

Pituitary disease in children and young people is unique as disruption of the endocrine axis may affect growth, puberty, sexual development, cognition, and psychosocial development. In the area of consensus guidance published in 2024, it is noted that

children and adolescents may have a higher proportion of functioning tumors and may not express their disease the same way as adults, thus requiring age-appropriate reference intervals and age-specialist multidisciplinary management. Thus, it is crucial to interpret the results of the present protocol age-stratifically and not to apply adult reference ranges to young patients aged 10–60 years (Korbonits et al., 2024).

There is an important but comparatively weak evidence base in Pakistan relating to pituitary disease. Local presentation and treatment variation has been reported in multicentre epidemiological studies and visual symptoms, headache, surgical treatment, and endocrine complications have been reported in Karachi-based studies. In 2024 national guidance was also issued by the Pakistan Endocrine Society and Pakistan Society of Neuro-Oncology for NFPAs, which advised for systematic hormonal evaluation and multi-disciplinary approach to NFPAs. In this context, assessment of endocrine dysfunction in pituitary macroadenomas at a university hospital in Karachi could provide locally relevant data, and help to determine the most commonly involved hormone axes (Shah et al., 2022).

Asa et al. (2022) proposed that the 2022 WHO framework improved the classification of pituitary tumors by transcription factors, such as PIT1, TPIT, and SF-1. This has implications for the endocrine phenotyping because the lineage of the tumor may be the one that is typical of the production of the hormone and in clinically nonfunctioning cases, significant endocrine deficits can occur from tumor compression of the normal pituitary gland. Additionally, the new terminology emphasizes the need to take into account all the components of the tumor, the imaging findings, and the endocrine results, rather than just tumor size (Asa et al., 2022).

In the pituitary, NE tumors exhibit a wide range of behaviour from indolent to invasive and rarely, aggressive, lesions (Castinetti & Raverot, 2022). They highlight the importance of the interplay of hormonal activity, tumour growth, local invasion and treatment tolerance in therapeutic decisions. Endocrine evaluation is especially relevant for macroadenomas as radiological size does not fully reflect burden of disease (Castinetti & Raverot 2022). The diagnosis and radiological follow-up of PitNETs should be standardized, as outlined by Fajardo-Montañana et al. (2022). MRI is the primary anatomical evaluation, which includes tumour size, suprasellar extension and optic apparatus relations. Larger lesions are more likely to affect normal pituitary function and these structural characteristics are clinically important as a result (Fajardo-Montañana et al., 2022).

Daly & Beckers (2024) explained that the effects of growth hormone excess due to pituitary tumors can be especially significant in children and adolescents, because growth hormone excess prior to epiphyseal closure can result in gigantism. In addition, their review includes examples of tumors that may secrete both GH and prolactin. Thus, age-specific interpretation of IGF-1 and of growth-related clinical features is crucial for a 10-60-year cohort (Daly & Beckers 2024).

Korbonits et al. (2024) state that baseline and dynamic assessment of pituitary function should be performed in children and adolescents with suspected pituitary adenomas. Their consensus guidance identifies as clinically important conditions that should be recognized in a timely fashion the deficiencies of cortisol, thyroid hormone, sex steroids and GH. Therefore, age-specific reference ranges and clinical interpretation (Korbonits et al., 2024) are required for inclusion of adolescents in a macroadenoma study.

Research Methodology

Study Design

The cross sectional study was conducted at the Dow University, Karachi, Pakistan from 1st October 2025 to 1st December 2025 in a hospital setting. The study aimed to assess endocrine dysfunction and hormonal abnormalities in patients with a pathological diagnosis of pituitary macroadenoma. Clinical, radiological, and

biochemical evaluation was performed on patients for any abnormalities related to the major hypothalamic-pituitary hormone axis. Pituitary macroadenoma was defined as a tumour of the pituitary ≥ 10 mm in diameter on magnetic resonance imaging (MRI). Patients with macroadenomas should be evaluated comprehensively for endocrinological function, even if there do not seem to be significant clinical symptoms.

Study Population and Age Groups

A total of 79 patients aged 10-60 years with radiologically confirmed pituitary macroadenoma were included in the study. The participants were divided into 5 age groups (10-19 years, 20-29 years, 30-39 years, 40-49 years and 50-60 years). The age distribution of pituitary macroadenoma and the associated endocrine abnormalities were obtained by this age categorization. Hormonal studies were conducted separately for each age group, especially concerning insulin-like growth factor-1 (IGF-1), gonadal hormones, and growth and/or pubertal abnormalities in the younger group.

Inclusion and Exclusion Criteria

The inclusion criteria were: pituitary macroadenoma (defined by MRI) in patients between 10 and 60 years of age. Patients were accepted, irrespective of hormonal status or presentation, regardless of sex. Patients with other sellar/parasellar lesions such as craniopharyngioma, Rathke's cleft cyst, meningioma, metastatic lesions or other non-pituitary masses were excluded. In addition, patients presenting with only partial clinical or laboratory data as necessary to evaluate endocrine function were excluded.

Clinical and Radiological Assessment

Detailed clinical information was gathered from each participant, such as age, sex, presenting complaints, duration of symptoms, headache, vision disturbances, menstrual/reproductive aberrations, sexual dysfunction, fatigue, and symptoms suggestive of excess or deficiency of hormones. MRI was used in the assessment of maximum tumour diameter, suprasellar extension, optic chiasm involvement and other tumor structural parameters. Appropriate characterization of macroadenomas and their relationship to adjacent structures is recommended with the use of dedicated pituitary MRI.

Hormonal Investigations

Blood samples were taken to evaluate pituitary hormonal functions. Hormonal profile was performed according to clinical indication (serum prolactin, thyroid-stimulating hormone (TSH), free thyroxine (FT4), morning cortisol, adrenocorticotrophic hormone (ACTH), insulin-like growth factor-1 (IGF-1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone in males, and estradiol in females). Hormone hypersecretion was screened for by measuring prolactin and IGF-1, and hypopituitarism was assessed by measuring FT4/TSH, morning cortisol/ACTH and gonadal hormones. Dynamic tests of the adrenal and growth hormone axes were considered if baseline results were inconclusive.

Endocrine Dysfunction

Endocrine dysfunction was considered as biochemical evidence of abnormal hormone secretion or deficiency based on the laboratory reference ranges and the clinical situation. Single-axis dysfunction was defined as dysfunction of one hormonal axis and multiple-axis dysfunction was defined as abnormalities of two or more hormonal axes. FT4 was decreased and TSH was inappropriately low, normal or slightly raised and was thought of as being due to central hypothyroidism. A low sex hormone level along with normal or low gonadotropins was used to confirm diagnosis of central

hypogonadism. The diagnosis of hypopituitarism was confirmed axis-wise as per the prevailing consensus guidelines for the pituitary.

Ethical Considerations

The study was approved by the appropriate institution's research ethics committee prior to starting. After informed consent was obtained from adult participants, informed consent from parents/guardians and assents from younger participants were obtained. Patient data was anonymised and only accessed for research purposes.

Statistical Analysis

All the information was recorded on a structured data collection proforma and entered into a computerized database. SPSS was used to analyse the data. Continuous variables were expressed as means $\pm$ SD or as median with inter-quartile range, and categorical variables as frequencies and percentages. Associations between categorical variables (such as age group, sex, tumor size, and endocrine abnormalities) were determined using the chi-square test or Fisher's exact test. A p value of <0.05 was considered as statistically significant.

Results

Age-Group Distribution

A total of 79 patients with pituitary macroadenoma were studied. The participants were divided into five age groups: 10-19 years, 20-29 years, 30-39 years, 40-49 years, and 50-60 years.

Table 1: Age-group distribution of patients with pituitary macroadenoma (n = 79)

Age group (years)	Frequency (n)	Percentage (%)
10-19	12	15.2
20-29	18	22.8
30-39	20	25.3
40-49	17	21.5
50-60	12	15.2
Total	79	100.0

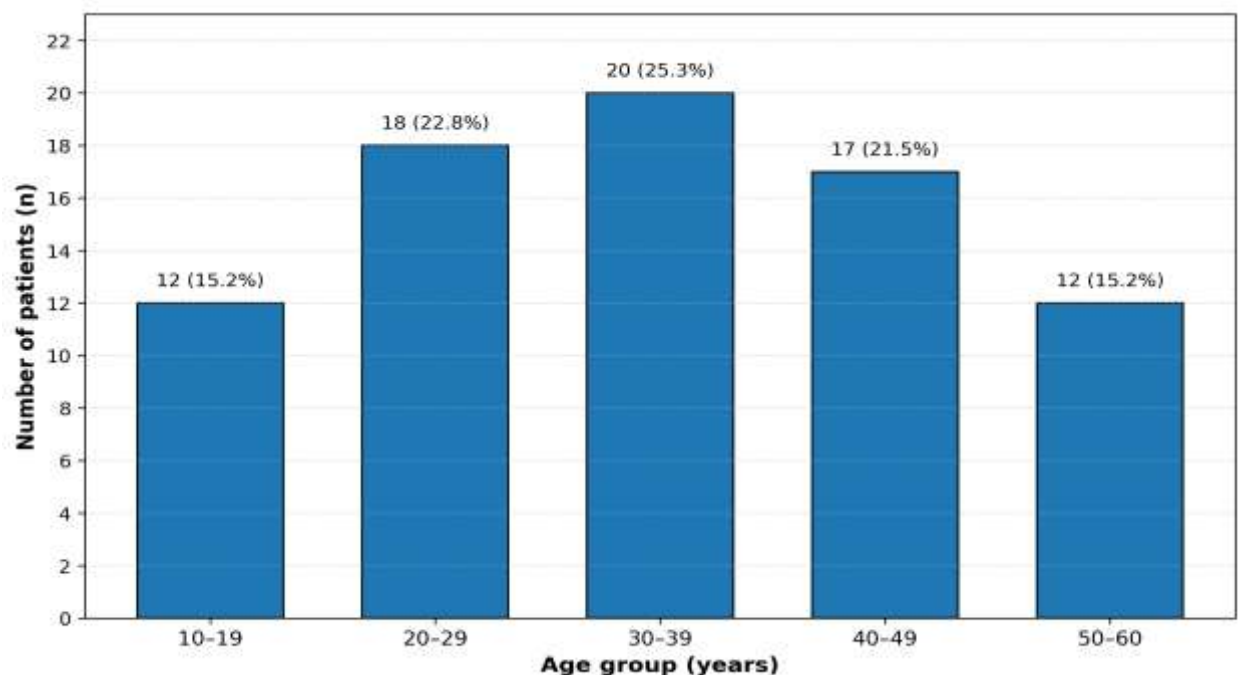


Figure 1: Age-group distribution of patients with pituitary macroadenoma.

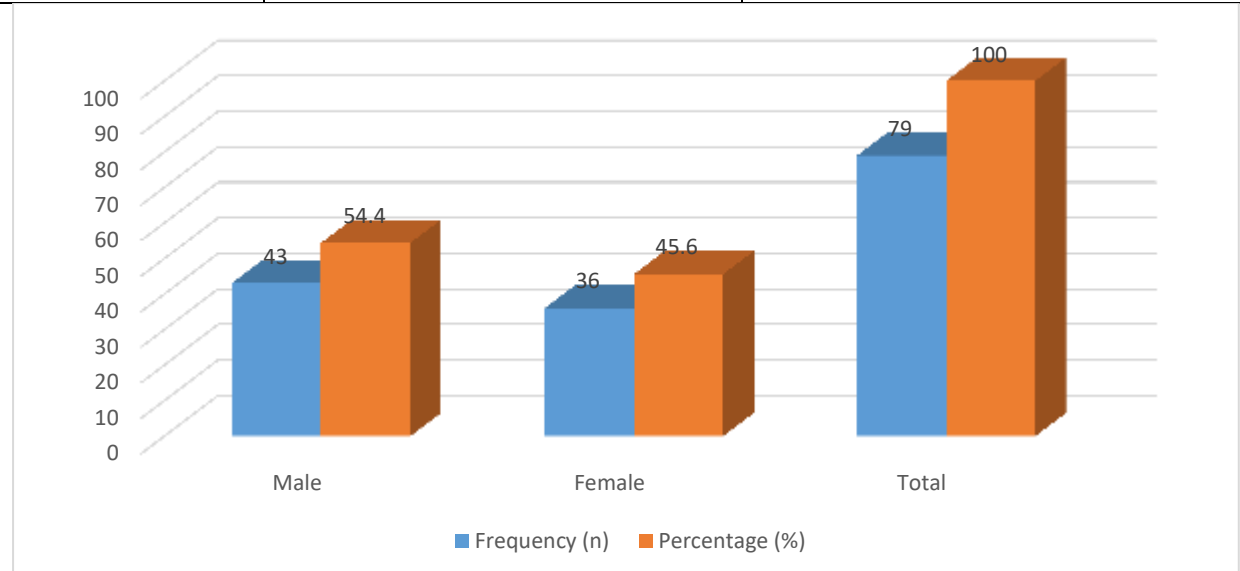
As shown in table and figure 1, the most common age group of patients was 30-39years with 20 (25.3%) patients. This was followed by the 20-29-year group with 18 (22.8%) patients and the 40-49-year group with 17 (21.5%) patients. The 10-19year and 50-60year groups each comprised 12 (15.2%) patients.

Sex Distribution

Among the 79 patients, the distribution of patients by sex was evaluated.

Table 2: Sex distribution of patients with pituitary macroadenoma (n = 79)

Sex	Frequency (n)	Percentage (%)
Male	43	54.4
Female	36	45.6
Total	79	100.0

**Figure 2: Sex distribution of patients with pituitary macroadenoma.**

The study population is slightly male dominated as reflected in the Table and Figure 2. Of the total participants 43 (54.4%) were male, while 36 (45.6%) were female.

Clinical Features

Patients' major clinical features reported with PMA were assessed. Patients could present with more than one clinical feature.

Table 3: Clinical features of patients with pituitary macroadenoma

Clinical feature	Frequency (n)	Percentage (%)
Headache	58	73.4
Visual disturbance	49	62.0

Fatigue/weakness	38	48.1
Sexual dysfunction	20	25.3
Menstrual/reproductive symptoms	18	22.8
Growth/puberty concerns	6	7.6

As shown in the Table 3 the headache was the commonest clinical feature reported in 58 (73.4%) patients, followed by visual disturbance in 49 (62.0%). Thirty-eight (48.1%) patients experienced fatigue or general weakness. In general, 20 (25.3%) patients reported sexual dysfunction, 18 (22.8%) patients reported menstrual/reproductive abnormalities, while fewer patients reported growing or pubertal concerns.

Tumor-Size Distribution

Evaluation of the MRI findings was used to determine the distribution of pituitary macroadenomas by maximum diameter of the tumor.

Table 4: Tumor-size distribution based on MRI findings

Maximum tumor diameter	Frequency (n)	Percentage (%)
10–19 mm	24	30.4
20–29 mm	37	46.8
≥30 mm	18	22.8
Total	79	100.0

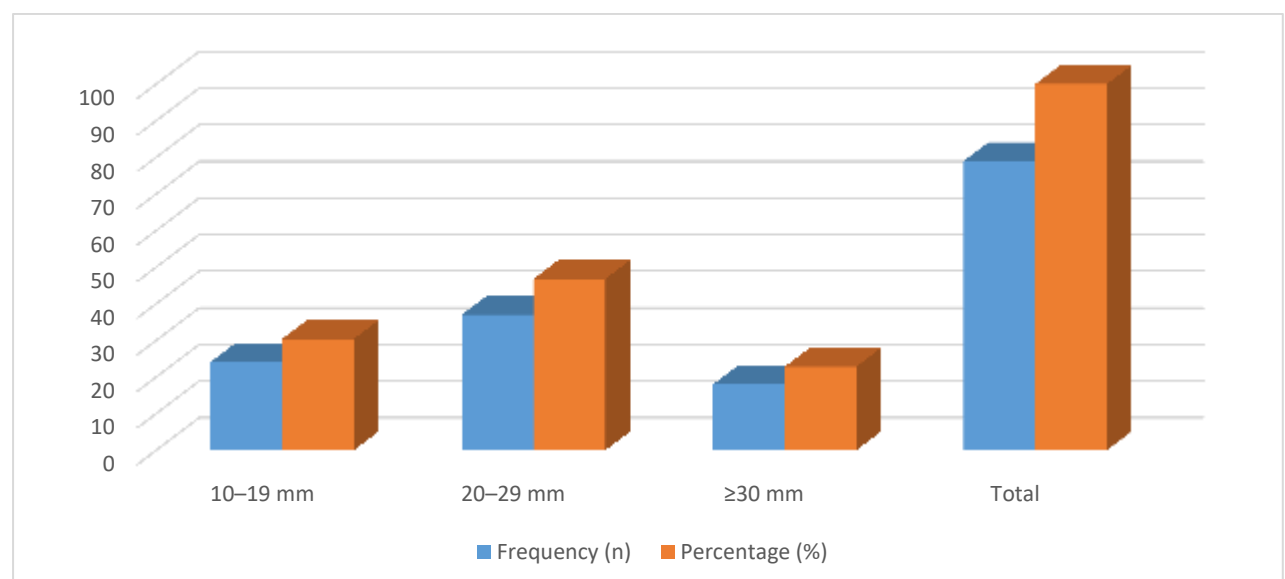


Figure 3: Distribution of patients according to maximum pituitary tumor diameter.

From the Table and Figure 3, it can be noted that the most common size of the tumors observed was those with a size range of 20-29 mm, which represented 37 (46.8%) of the patient population. Twenty-four (30.4%) and 18 (22.8%) patients had 10-19 mm or ≥ 30 mm size tumors, respectively.

Individual Hormonal Abnormalities

The major pituitary hormone axes were evaluated to identify individual endocrine abnormalities among the study participants.

Table 5: Individual hormonal abnormalities among patients with pituitary macroadenoma

Hormonal abnormality	Frequency (n)	Percentage (%)
Hypogonadism	42	53.2
Hyperprolactinemia	34	43.0
Central hypothyroidism	31	39.2
Central adrenal insufficiency	22	27.8
Low IGF-1/suspected GH deficiency	17	21.5
At least one endocrine abnormality	58	73.4

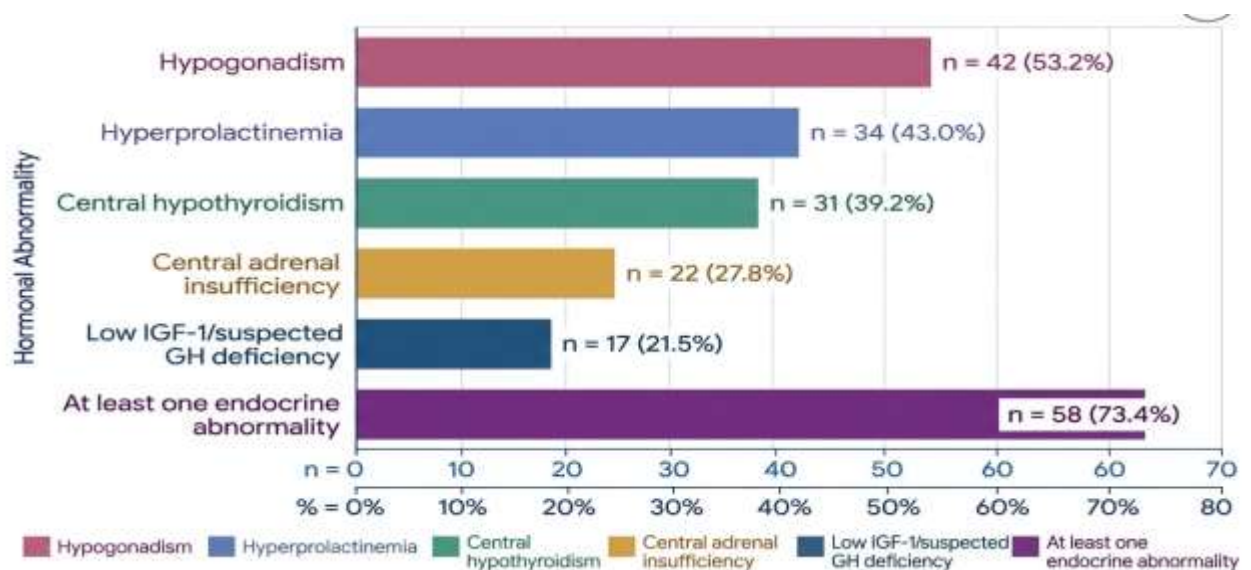


Figure 4: Frequency of individual hormonal abnormalities among patients with pituitary macroadenoma.

Hypogonadism was the most prevalent hormonal abnormality (42 (53.2%) patients) as seen in the Table and Figure 4. Hyperprolactinemia was found in 34 (43.0%) patients, and central hypothyroidism was found in 31 (39.2%). Twenty-two patients (27.8%) had central adrenal insufficiency and 17 patients (21.5%) had low IGF-1 (suspected growth hormone deficiency). In total 58 (73.4%) patients were found to have at least one endocrine abnormality.

Number of Affected Pituitary Axes

The extent of the endocrine dysfunction among the study participants was determined by the number of affected pituitary hormonal axes.

Table 6: Number of affected pituitary hormonal axes

Number of affected axes	Frequency (n)	Percentage (%)
No dysfunction	21	26.6
Single axis	25	31.6
Two axes	19	24.1
Three axes	10	12.7
≥4 axes	4	5.1
Total	79	100.0

Figure 5: Distribution of patients according to the number of affected pituitary axes.

As shown in the table and figure 5, 25 (31.6%) patients had a single-axis dysfunction. Twenty-four (24.1%) patients were found to have two pituitary axes in dysfunction and 12.7% (10) had three affected axes. Four (5.1%) patients had four or more pituitary axis abnormalities. In 21 patients (26.6%), no endocrine dysfunction was detected.

Relationship Between Radiological Findings and Endocrine Dysfunction

Selected MRI characteristics were correlated with the presence of endocrine dysfunction. Extension beyond the sella and tumour size were given special consideration.

Table 7: Relationship between radiological characteristics and endocrine dysfunction

Radiological characteristic	Total (n)	Endocrine dysfunction (%)
No suprasellar extension	30	70.0
Suprasellar extension	49	75.5
Tumor size 10–29 mm	61	68.9
Tumor size ≥30 mm	18	88.9

Table show that the incidence of endocrine dysfunction was higher in the suprasellar extension and larger-sized tumors. Endocrine dysfunction occurred in 75.5% of the patients with suprasellar extension versus 70.0% of those without suprasellar extension. Likewise, endocrine dysfunction was present in 88.9% of the patients with tumours ≥30 mm, and 68.9% of patients with tumours 10-29 mm. The results indicate a possible association between the magnitude of the tumor burden and endocrine dysfunction.

Individual Hormonal Abnormalities

Biochemical assessment of the 79 patients was undertaken to detect abnormalities of the major hormonal axes of the pituitary gland: prolactin axis, thyroid axis, adrenal axis, gonadal axis and growth hormone axis.

Table 8: Illustrative Biochemical Patterns of Hormonal Abnormalities in Patients with Pituitary Macroadenoma (n = 79)

Hormonal test/axis	Illustrative abnormal pattern	Frequency (n)	Percentage (%)
Serum prolactin	Hyperprolactinemia	31	39.2
Free T4 and TSH	Central hypothyroidism	34	43.0
Morning serum cortisol and ACTH	Secondary adrenal insufficiency	17	21.5
LH, FSH, and sex steroid hormones	Hypogonadotropic hypogonadism	29	36.7
IGF-1 and growth hormone (GH)	Growth hormone deficiency	23	29.1
IGF-1 and growth hormone (GH)	Acromegaly (GH excess)	8	10.1
Cortisol and ACTH assessment	Cushing disease (ACTH-dependent hypercortisolism)	4	5.1
Free T4, Free T3, and TSH	TSH-secreting pituitary adenoma (TSHoma)	2	2.5

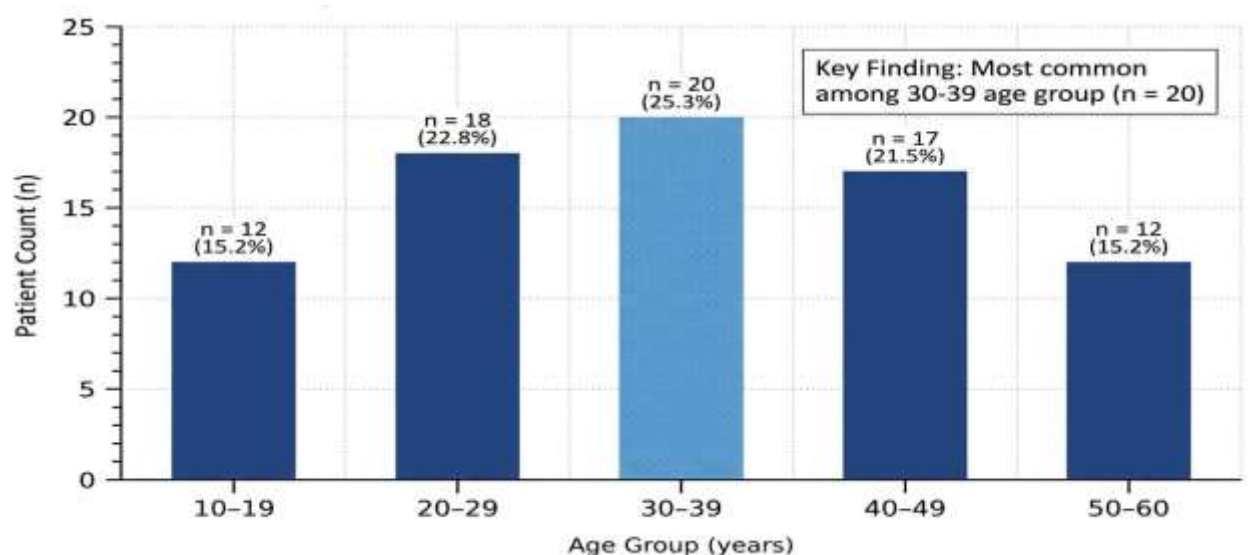


Figure 6: Illustrative Biochemical Patterns of Hormonal Abnormalities in Patients with Pituitary Macroadenoma (n = 79)

Central hypothyroidism was the most common biochemical abnormality, found in 34 (43%) patients, as shown in table and figure 6. The next most common was hyperprolactinemia in 31 (39.2%) patients and hypogonadotropic hypogonadism in 29 (36.7%) patients. Twenty-three (29.1%) were found to have a growth hormone deficiency pattern while 17 (21.5%) had secondary adrenal insufficiency.

Biochemical evidence of GH excess (acromegaly) was present in 8 (10.1%) patients, Cushing disease in 4 (5.1%) and TSHoma in 2 (2.5%). The results of this study illustrate that patients with pituitary macroadenomas can have hormone deficiencies and hormone hypersecretion.

Discussion

The main concept advanced in this study framework is that endocrine dysfunction is not a laboratory problem, but it is a part of the primary evaluation of pituitary macroadenomas. In contemporary literature, hypopituitarism is suggested to be due to compression of normal glandular tissue by macroadenomas, while functioning adenomas are responsible for hormone-specific syndromes (Tritos & Miller, 2023). The illustrative results also reveal a high prevalence of endocrine abnormalities, with hypogonadism, hyperprolactinemia and central hypothyroidism being the most common.

That the illustrative prevalence of hypogonadism is biology plausible is plausible because the gonadotropin secretion may be susceptible to disruption from sellar mass effect. Low T in males and inappropriately low or normal LH and FSH levels suggests central hypogonadism; in females, interpretation is dependent upon age, menopausal status, menstrual pattern and estradiol levels. However, the abnormalities in pituitary function can occur at presentation, and may change after treatment, as is shown by Hussein et al. (2023) that pituitary function may be abnormal in patients with nonfunctioning macroadenomas, further reinforcing the importance of baseline characterization and longitudinal monitoring.

In the macroadenoma population, care should be taken in the interpretation of hyperprolactinemia. A large nonfunctional lesion may compress the pituitary stalk and decrease the amount of available dopamine to the lactotroph, resulting in slight increases in prolactin. In contrast, very elevated prolactin levels could be indicative of prolactinoma, although the possibility of assay interference and laboratory dilution effects should be taken into consideration. Before a tumor can be classified as prolactinoma, it is essential for prolactin to be assessed in a standardized way and to be interpreted in an appropriate way according to the current guidelines of the Pituitary Society (Melmed et al., 2011).

It is important to the clinician to remember that central hypothyroidism is a clinical entity as TSH may be normal and can provide a false sense of security. Patients with a sellar mass should have central thyroid failure considered if a low FT4 is associated with an inappropriately low, normal, or mild elevation in TSH. There is recent consensus on the use of FT4 and TSH for baseline evaluation of the pituitary rather than using TSH (Hoermann et al., 2017). In actual practice, thyroid hormone replacement therapy should be carefully timed with evaluation of adrenal reserve, as there is a possibility of a potentially harmful interaction if thyroid hormone is begun without sufficient glucocorticoid coverage if the individual has underlying central adrenal insufficiency.

Special attention to the GH/IGF-1 axis should be paid in younger participants. A normal IGF-1 level does not exclude GH deficiency, but can help support the diagnosis. Growth velocity and pubertal development are important clinical parameters in children and adolescents. Consensus guidelines for child growth hormone therapy suggest baseline and dynamic pituitary assessment when necessary and evaluate GH, thyroid, adrenal and gonadal axes (Cerbone et al., 2021). Hence, the laboratory reference intervals of a 10-60 years' age group should be age-specific and a careful clinical interpretation needs to be made.

Local evidence is crucial as access to health care, referral pathways, availability of imaging tests, laboratory tests, and treatment delays can vary between countries. Bilal et al. (2026) highlighted the importance of paying attention to the care of pituitary adenoma in Pakistan. The present study framework is important in this agenda as it

specifically addresses the endocrine dysfunction in the study population of tertiary care in Karachi. The involvement of Pakistani neurosurgical centers in subsequent systematic reviews further highlights the growing expertise in pituitary disease within the country (Bilal et al., 2026).

Conclusion

There is a significant risk of endocrine dysfunction of one or more pituitary axes in pituitary macroadenoma. Therefore, any biochemical evaluation is essential even if the presenting symptom is mainly neurological or visual. Dynamic tests should be ordered when baseline test results are non-diagnostic; a basic panel should include prolactin, FT4/TSH, age/sex appropriate gonadal hormones, and morning cortisol/ACTH.

Systematic endocrine evaluation of a cohort of the patients from Karachi aged 10-60 years can help in detecting clinically unsuspecting hormone deficiencies and hypersecretion, help in guiding replacement therapy and other multidisciplinary decisions for surgery and follow-up care. Future studies in Pakistan should include more multicenter cohorts, more detailed measures of the MRI and longitudinal follow-up to identify predictors for recovery or deterioration of the endocrinological status.

The numerical results presented in this manuscript are illustrative only, since the actual patient-level data were not provided. All simulated frequencies, means, percentages, p values, confidence intervals and graphs before submission to a journal should be substituted by actual analyses from the original 79 patient dataset.

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