

# Epidemiological and clinical profiles of Saudi patients with hyperprolactinemia in a single tertiary care center

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**BACKGROUND:** Prolactin is a hormone of the pituitary gland whose main function is the production of milk. Hyperprolactinemia is defined as an increase in prolactin levels above 25 µg/L in women and 20 µg/L in men. Causes of hyperprolactinemia include pituitary tumors, especially prolactinomas. Hyperprolactinemia can manifest clinically with a variety of symptoms, including galactorrhea and menstrual irregularities in women and erectile dysfunction in men. There are limited data on the epidemiology of hyperprolactinemia in the Middle East region.

**OBJECTIVES:** Description of the epidemiology and clinical features of hyperprolactinemia in a cohort from Saudi Arabia.

**DESIGN:** Medical record review

**SETTING:** Tertiary medical center in Riyadh

**PATIENTS AND METHODS:** The study included adult patients with hyperprolactinemia in King Abdulaziz Medical City in Riyadh. The patients were treated in endocrinology clinics from 2015 to 2019. Patients of both sexes older than 14 years were enrolled in the study. Patients with insufficient follow-up were excluded. Data were collected on demographic characteristics, symptoms, prolactin level, cause of high prolactin level, and treatment.

**MAIN OUTCOME MEASURES:** The frequency of different etiologies and symptoms in patients with hyperprolactinemia.

**SAMPLE SIZE:** 295 patients

**RESULTS:** The majority of patients with hyperprolactinemia were female 256 (86.8%). Hyperprolactinemia was diagnosed more frequently in patients in the age groups 21-30 years (42.6%) and 31-40 years (24.1%). The majority of the study population was obese or overweight: 136 (46.3%) and 74 (25.2%), respectively. Most of the cases were symptomatic (192, 65.1%). In women, the most common symptom was oligomenorrhea (35%). In men, infertility and erectile dysfunction were the most common clinical symptoms (50% and 44.7%, respectively). Idiopathic causes were the most common etiology (108, 36.6%), followed by pituitary adenomas (81, 27.5%). The majority of patients were treated (184, 62.4%), with cabergoline being the most commonly used medication (173, 94.0%).

**CONCLUSION:** The demographic and clinical presentations and causes of hyperprolactinemia in male and female Saudi patients were similar to that in studies in other populations.

**LIMITATIONS:** Single-center retrospective chart review study.

**CONFLICT OF INTEREST:** None.

**P**rolactin is a hormone of the pituitary gland whose main function is the development of the mammary glands and production of milk. It also regulates sex hormones in males and females. Prolactin levels are mainly controlled by dopamine inhibition of lactotrophs. The normal range of prolactin is between 10 and 25 µg/L in females and between 10 and 20 µg/L in males.<sup>1</sup> Hyperprolactinemia is defined as a prolactin level that is above the normal range. The prevalence of hyperprolactinemia is approximately 0.4% in an unselected adult population and is more common in women.<sup>2</sup> However, a prevalence of up to 9-17% has been reported.<sup>1</sup> Blood prolactin levels may be physiologically or pathologically elevated. Elevated prolactin levels may result from disruption of dopamine suppression of lactotroph cells, such as in the peduncle effect of Sellar tumors, or from medications such as antipsychotics.<sup>3</sup> In addition, hyperprolactinemia is often the result of increased lactotroph cell mass, such as in prolactinomas. In addition, elevated levels of hormones that stimulate lactotroph cells, such as thyroid-stimulating hormone (TRH) in primary hypothyroidism, lead to hyperprolactinemia.<sup>4</sup> Increased estradiol levels during pregnancy also lead to a physiological increase in prolactin due to the stimulatory effect of estradiol on lactotroph cells. Impaired excretion of prolactin from the circulation, as in chronic kidney disease, is another mechanism of hyperprolactinemia.

Other pathological causes of hyperprolactinemia include polycystic ovary syndrome, the mechanism of which is largely unexplained.<sup>1,4</sup> Overall, there are many causes of hyperprolactinemia in the literature that clinicians should be aware of.<sup>4</sup> Worldwide, the most common cause of hyperprolactinemia is pituitary adenoma. Prolactin-secreting adenomas account for an estimated 20% to 30% of all functioning pituitary adenomas.<sup>2</sup> Furthermore, the correlation between prolactinoma size and prolactin amount is well established.<sup>4,5</sup>

Macroprolactin is an asymptomatic condition characterized by an aggregated form of prolactin hormone that can cause a false increase in prolactin levels without any symptoms. Macroprolactin has been reported to occur in 3.6% of healthy individuals without clinical sequelae.<sup>6</sup>

Hyperprolactinemia can be clinically manifested by a variety of symptoms related to dysregulation of prolactin functions, such as galactorrhea, erectile dysfunction, and menstrual abnormalities.<sup>4,7</sup> Treatment of hyperprolactinemia relies on stimulation of dopamine receptors, a known prolactin inhibitor. The two most commonly used drugs are bromocriptine and cabergoline. Bromocriptine is effective in up to 78% of patients,

while with cabergoline up to 86% of patients will respond.<sup>8,9</sup> In Saudi Arabia, there is limited research and limited knowledge of the epidemiological features of hyperprolactinemia. The aim of this study was to provide information about the epidemiology of hyperprolactinemia in a Saudi population. This study focused on determining the prevalence of causes, symptoms, and treatment of hyperprolactinemia, as well as the clinical and biochemical profiles of patients with this condition.

## PATIENTS AND METHODS

A retrospective chart review study was conducted of adult patients diagnosed with hyperprolactinemia who were treated at King Abdulaziz Medical City-Riyadh endocrinology clinics from 2015 to 2019. We included patients of either sex who were older than 14 years and diagnosed with hyperprolactinemia during the study period. Patients with insufficient data were excluded from the study.

Data were collected from electronic medical records. Excel was used to enter demographic data, clinical symptoms and signs, age of diagnosis, and laboratory data. Imaging results, medication history (e.g., antipsychotic medications), and treatment were also recorded. Prolactin levels after sample dilution and macroprolactin measurement were collected when available. Ethical approval was obtained from the institutional review board of King Abdullah International Medical Research Center under study number SP19/361/R.

Statistical analysis was performed using IBM SPSS (Armonk, New York, United States: IBM Corp) version 27. Categorical variables were described as frequencies and percentages, and numerical variables were described as means and standard deviations. The chi-square test was used to assess the association between categorical variables. The test was considered significant if the *P* value was less than .05.

## RESULTS

Of 295 patients, most were female 256 (86.8%). Fifty-nine (20.3%) patients were 20 years old or younger (**Table 1**). The majority of the study population was obese or overweight. The median prolactin level at diagnosis was 1185 mIU/L. Only one patient had dilatational studies to exclude hook effect with no change in the prolactin level after dilution.

Idiopathic hyperprolactinemia was most common in both sexes (36.7% of females and 35.9% of males) (**Figure 1**). Pituitary adenoma was the second most common cause of hyperprolactinemia in female and male patients (27.0% and 30.8%, respectively). The majority of patients with pituitary adenoma had microprolactino-

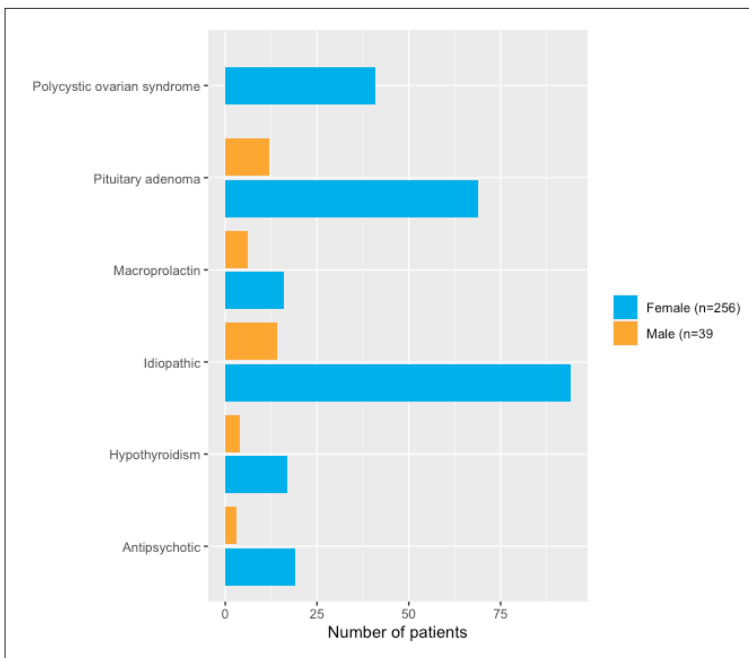


Figure 1. Causes of hyperprolactinemia.

ma (adenoma size <10 mm), but macroprolactinomas (adenoma size ≥10 mm) were more common in male, elderly and obese patients (Table 2). Other etiologies of hyperprolactinemia in female patients were polycystic ovary syndrome in 16%, antipsychotics in 7.4%, hypothyroidism in 6.6%, and macroprolactin in 6.3%. In male patients, other causes of hyperprolactinemia were macroprolactin in 15.4%, hypothyroidism in 10.3%, and antipsychotics in 7.7%. Of note, macroprolactin testing was performed in 83 (28.2%) of the patients, and 33 (39.8%) tested positive for macroprolactin.

Most patients 192 (65.1%) were symptomatic (63.7% of females and 74.4% of males). The most common symptom and clinical presentation in female patients was oligomenorrhea (35%), followed by infertility, headache, amenorrhea, hirsutism, breast milk discharge, and visual disturbances (Figure 2). On the other hand, the most common symptom and clinical presentation for male was infertility (50%), followed by erectile dysfunction, headache, gynecomastia, visual disturbances, and breast discharge (Figure 3).

Most patients, 184 (62.4%) were treated, most com-

Table 1. Patient characteristics (n=250).

Sex	
Male	39 (13.2)
Female	256 (86.8)
Age of diagnosis (years)	
<20	59 (20.3)
21-30	124 (42.6)
31-40	70 (24.1)
>40	38 (13.1)
Marital status	
Single	131 (44.6)
Married	163 (55.4)
Have children	
No	173 (62.7)
Yes	103 (37.3)
Body mass index	
Underweight	14 (4.8)
Normal weight	70 (23.8)
Overweight	74 (25.2)
Obese	136 (46.3)

Data are n (%). BMI: underweight, <18.5, normal, ≥18.5-<25, overweight, 25-≤30, >30 obese.

Table 2. Microprolactinoma versus macroprolactinoma in relation to age, sex and weight.

	Adenoma size		Fisher exact test
	<10 mm	≥10 mm	
Sex			
Female	48 (84.2)	9 (15.8)	.026
Male	7 (53.8)	6 (46.2)	
Age (years)			
≤20	11 (91.7)	1 (8.3)	<.001
21-30	24 (92.3)	2 (7.7)	
31-40	17 (77.3)	5 (22.7)	
>40	2 (22.2)	7 (77.8)	
Body mass index			
Underweight	1 (100.0)	0	.018
Normal	14 (100.0)	0	
Overweight	15 (88.2)	2 (11.8)	
Obese	24 (64.9)	13 (35.1)	

Data are n (%). BMI: underweight, <18.5, normal, ≥18.5-<25, overweight, 25-≤30, >30 obese.

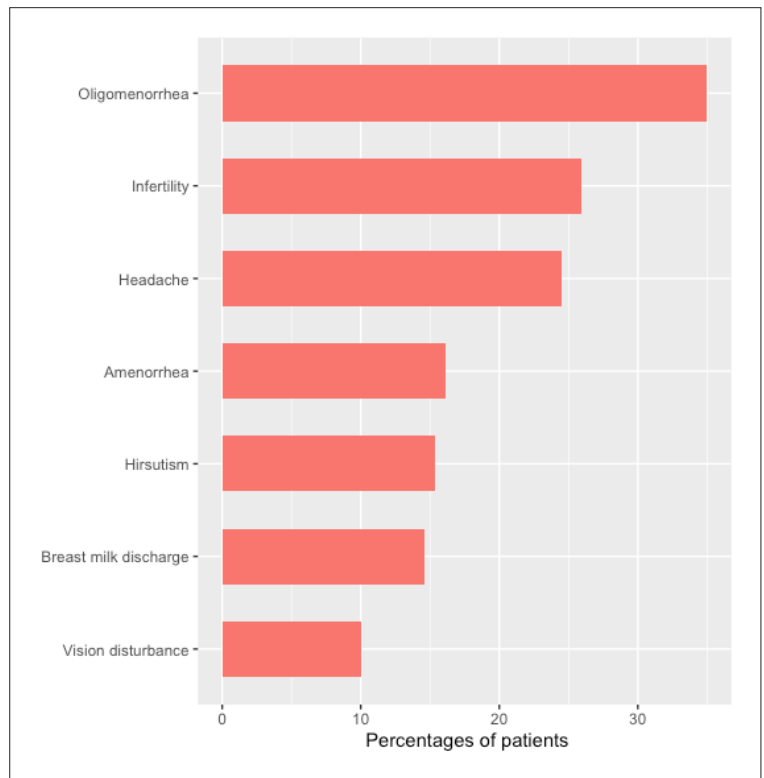
monly with cabergoline (173 patients, 94.0%) of whom 124 (71.7%) experienced improvement in symptoms. Bromocriptine was used in 11 patients (6.0%) of whom 6 (54.5%) experienced improvement in their symptoms (**Figure 4**).

Follow-up data in terms of pituitary adenoma evolution was available in 42 patients with microadenoma. Five patients (11.9%) were not treated with dopamine agonists since they had no symptoms. In one patient, the adenoma increased in size from 4 mm at maximum diameter to 11 mm while the rest had no change in the size of the microadenoma. Thirty-four patients (80.9%) were treated with cabergoline while 3 patients (7.1%) received bromocriptine. Seven patients out of the 37 patients treated with dopamine agonists (20.5%) had complete resolution of the pituitary microadenoma on follow-up MRI (6 were treated with cabergoline and 1 patient was treated with bromocriptine). Sixteen patients (43.2%) had no significant change in the adenoma size. Three patients (8.1%) had a marginal increase in the microadenoma size (1-3 mm). Eleven patients (29.7%) showed a reduction of the microadenoma size with mean reduction of 1.8 mm±1.3 mm in the maximum diameter. None of the patients with microadenoma underwent surgery (**Supplementary Table 1**).

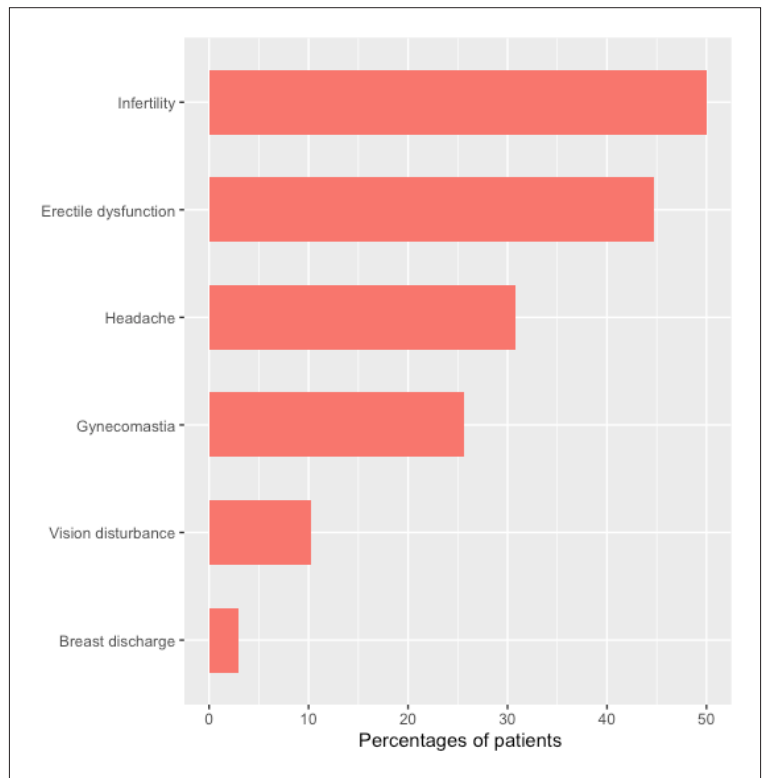
For patients with macroadenoma, only one patient underwent trans-sphenoidal surgery for apoplexy causing visual field defects, which was then followed by cabergoline with subsequent development of empty cells. All other patients were treated with dopamine agonists; cabergoline in 11 patients and bromocriptine in 1 patient. One patient who received cabergoline had complete resolution of the pituitary macroadenoma. Two patients had no change in the adenoma size. One patient had marginal growth of the adenoma size (3 mm). The remaining patients had reduction of the macroadenoma size with mean reduction of 8.55 mm±9.7 mm in the maximum diameter (**Supplementary Table 2**).

**DISCUSSION**

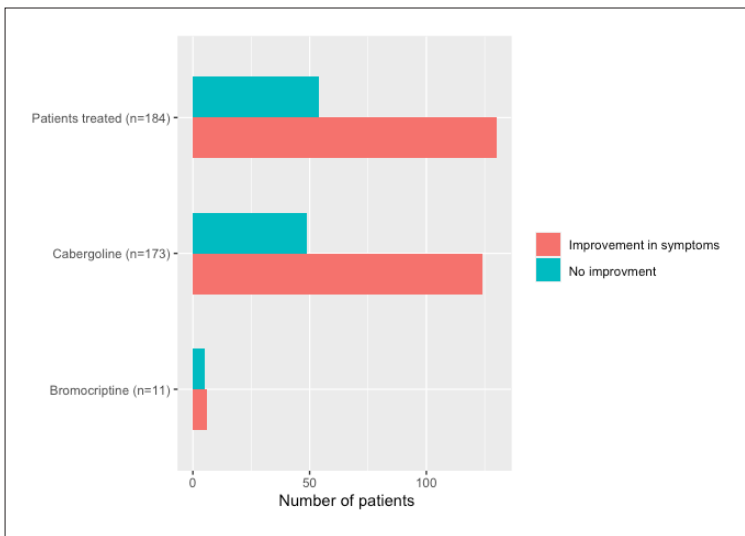
Although hyperprolactinemia is a relatively common clinical condition, there is scarce data on its epidemiology in Saudi Arabia. In our study, we evaluated patients who were diagnosed with hyperprolactinemia to characterize demographic and clinical presentation, causes of hyperprolactinemia and management. More female than male patients had hyperprolactinemia, which is consistent with other studies.<sup>4,5</sup> The majority of patients with hyperprolactinemia were between 20 and 40 years old, which is comparable to other studies.<sup>5</sup> It is common that hyperprolactinemia is often diagnosed in young female patients because the symptoms of hyper-



**Figure 2.** Frequency of symptoms in female patients (n=256).



**Figure 3.** Frequency of symptoms in male patients (n=39).



**Figure 4.** Response to treatment.

prolactinemia are easily recognizable in young women, such as oligomenorrhea. The majority of patients in the study were either obese or overweight, which is consistent with the reported association between high prolactin and excessive body weight.<sup>10,11</sup> The exact mechanism of weight gain in hyperprolactinemia is not yet fully understood, but prolactin-induced lipogenesis and dysregulation of dopaminergic tone are possible explanations.<sup>12</sup>

Overall, the majority of patients were symptomatic. The most common symptoms were oligomenorrhea and infertility in female patients, which is similar to other population groups.<sup>13</sup> Menstrual irregularities and hyperprolactinemia are closely related because prolactin-induced suppression of gonadotropin hormone-releasing hormone leads to low estradiol levels in female patients.<sup>14</sup> Similarly, elevated prolactin levels in male patients leads to hypogonadism with low gonadotropins and testosterone. Infertility was the most common symptom in male patients, followed by erectile dysfunction. These findings are consistent with studies in other populations.<sup>15,16</sup> Overall, hyperprolactinemia is known to be highly associated with sexual dysfunction in both male and female patients.<sup>4</sup> The cause of a high prolactin level has been associated with various diagnoses. An idiopathic cause was the main diagnosis of hyperprolactinemia in our study, which seemed to be higher than the other reported diagnoses seemed higher than that reported in other studies.<sup>16</sup> Idiopathic hyperprolactinemia is diagnosed when a thorough clinical examination and search for a cause of hyperprolactinemia reveals no cause. However, in many of these patients, a tiny prolactinoma below the limit of

detection on MRI is a possible cause.<sup>17</sup> In agreement with our study, Soto-Pedre et al reported that a pituitary adenoma was the cause of hyperprolactinemia in 25.6% of cases.<sup>16</sup> However, in a radiological study, Aljabri et al reported that of 399 patients with hyperprolactinemia, MRI showed an abnormality (mainly a pituitary adenoma) in 62%.<sup>5</sup> This discrepant reporting of pituitary adenoma in association with hyperprolactinemia is likely due to variability in MRI reporting by radiologists. The majority of patients with pituitary adenomas in the study had microadenomas (size <10 mm). However, in male patients, almost half had macroprolactinomas (size  $\geq 10$  mm), while in female patients about 15% had macroprolactinomas only. These results are consistent with the literature that macroprolactinomas are more common in male patients.<sup>4,18</sup> In addition, we found that older and obese patients were more frequently diagnosed with macroadenomas than microadenomas. The association between adenoma size and age is well established.<sup>4,18</sup> However, the association between adenoma size and weight is a unique finding. In fact, the linear positive correlation between prolactin level and prolactinoma size is well known.<sup>4</sup> Moreover, a correlation between prolactin level and BMI has been documented.<sup>19</sup> Therefore, the finding that macroadenomas were diagnosed more frequently in obese patients may be indirectly related to the fact that the higher prolactin level in these patients leads to greater weight gain. Further studies are needed to confirm this finding.

The distribution of other causes of hyperprolactinemia among the study sample was similar to other studies. For example, Soto-Pedre et al found that drug-induced hyperprolactinemia was the most common cause of hyperprolactinemia in the Tayside Scottish population<sup>16</sup> whereas in our study, drug-induced hyperprolactinemia was relatively rare. In a study of psychiatric patients, Alosaimi et al found that 44% had hyperprolactinemia,<sup>20</sup> which is expected since dopamine antagonists are commonly used in patients with psychiatric disorders. Therefore, it is important to note that the prevalence of different etiologies may vary depending on the population studied.

Other causes of hyperprolactinemia in the study included polycystic ovary syndrome and hypothyroidism. These causes often lead to an increase in prolactin. If hypothyroidism and polycystic ovary syndrome are properly treated, the prolactin increase is likely to regress.<sup>4</sup> Macroprolactin is an important differential diagnosis for hyperprolactinemia in the study because a high percentage of patients who had a macroprolactin measurement tested positive

(approximately 40%). Previous studies showed a similar prevalence of macroprolactinemia.<sup>21,22</sup> This highlights the need to measure macroprolactin in all patients with hyperprolactinemia to avoid unnecessary interventions.<sup>23</sup> Although patients with macroprolactinemia are usually asymptomatic, some patients may present with symptoms that need to be managed.<sup>23-25</sup> Another important diagnostic pitfall of hyperprolactinemia is the "high dose hook effect", which is usually suspected when there is a mismatch between the clinical presentation and the prolactin level. The term is from the hook appearance on a graph of immune complex concentrations when the apparent response signal declines when antigen concentrations are high.<sup>26</sup> The hook effect is commonly encountered in patients with large prolactinomas and florid clinical symptoms and signs of hyperprolactinemia while the prolactin level is normal or only mildly elevated. The hook effect occurs in some immunoassays due to excess antigens preventing the formation of antigen-antibody complexes. Re-measurement of prolactin level after dilution of the sample is sufficient to exclude the hook effect.<sup>4,26</sup> In our study, all patients had hyperprolactinemia at a level consistent with their clinical presentation. A prolactin dilution study was done only in one patient with macroadenoma and the prolactin level was the same after the sample dilution.

If no secondary cause of hyperprolactinemia is found, dopamine agonists are usually used to normalize prolactin levels to improve symptoms associated with hyperprolactinemia. Cabergoline and bromocriptine are the most commonly used dopamine agonists, with cabergoline being the most widely used.

Surgery is rarely needed as the first line of treatment in patients with prolactinomas. Surgery is indicated in patients with resistant prolactinomas or in patients who are intolerant to dopamine agonists. Moreover, patients with prolactinomas who develop an acute apoplexy with mass effect are candidates for surgical intervention.<sup>4,27</sup> The majority of patients in the study received cabergoline, which improved their symptoms regardless of the cause of hyperprolactinemia. The superiority of cabergoline over bromocriptine is well established and is recommended as first-line treatment, except in a few patients, such as in early pregnancy.<sup>8,28</sup> Patients with pituitary adenomas are mostly managed with dopamine agonists as well. One patient in the study required surgery due to apoplexy. The adenoma size improved in most of our patients after use of a dopamine agonist as has been reported in other studies.<sup>4,27</sup> Limitations of our study include that it was retrospective and conducted at a single center. Nevertheless, this study provides important insights into the epidemiology of hyperprolactinemia in terms of clinical presentation and etiology in Saudi patients.

In conclusion, the majority of patients were female, with idiopathic hyperprolactinemia being the most common diagnosis. The majority of patients were symptomatic. Oligamenorrhea and infertility were most common in female patients, while infertility and erectile dysfunction were seen in male patients. The majority of patients were treated with cabergoline and symptoms improved. The demographic and clinical presentations and causes of hyperprolactinemia in male and female Saudi patients were similar to that in studies in other populations.



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**Supplementary Table 1.** Adenoma size change in patients with microprolactinomas.

	Age of diagnosis	Gender	Baseline adenoma maximum diameter (mm)	Follow-up adenoma maximum diameter (mm)	Maximum diameter change (mm)	Treatment
Patient 1	34	Female	3	3	0	None
Patient 2	23	Female	6	6	0	Cabergoline
Patient 3	28	Female	7	7	0	Cabergoline
Patient 4	32	Female	4.5	4.5	0	Cabergoline
Patient 5	16	Female	6	6	0	Bromocriptine
Patient 6	25	Female	6	6	0	Cabergoline
Patient 7	16	Male	4	No adenoma	Complete resolution	Cabergoline
Patient 8	20	Female	3	3	0	Cabergoline
Patient 9	33	Male	6	No adenoma	Complete resolution	Cabergoline
Patient 10	21	Female	7	7	0	Cabergoline
Patient 11	37	Female	3	2	-1	Cabergoline
Patient 12	39	Female	7	No adenoma	Complete resolution	Cabergoline
Patient 13	45	Male	5	5	0	Cabergoline
Patient 14	35	Female	7	3	-4	Cabergoline
Patient 15	32	Female	9	9	0	Cabergoline
Patient 16	26	Male	4	5	+1	Cabergoline
Patient 17	25	Female	4	3	-1	Cabergoline
Patient 18	16	Female	4	11	7	None
Patient 19	29	Female	9	7	-2	Bromocriptine
Patient 20	29	Female	4	4	0	Cabergoline
Patient 21	35	Female	6	3	-3	Cabergoline
Patient 22	33	Female	5	7	+2	Cabergoline
Patient 23	18	Female	3	3	0	None
Patient 24	26	Female	6.2	4	-2.2	Cabergoline
Patient 25	38	Female	6	6	0	Cabergoline
Patient 26	26	Female	6	4	-2	Cabergoline
Patient 27	26	Female	6	6	0	None
Patient 28	30	Female	3	3	0	Cabergoline
Patient 29	54	Female	4	6	+2	Cabergoline
Patient 30	25	Female	3	6	+3	Cabergoline
Patient 31	25	Female	9	9	0	Cabergoline
Patient 32	22	Female	3	3	0	None
Patient 33	27	Female	8	5	-3	Cabergoline
Patient 34	35	Male	3	3	0	Cabergoline
Patient 35	25	Female	6	No adenoma	Complete resolution	Cabergoline
Patient 36	22	Female	7	No adenoma	Complete resolution	Bromocriptine



**Supplementary Table 1 (cont.).** Adenoma size change in patients with microprolactinomas.

	Age of diagnosis	Gender	Baseline adenoma maximum diameter (mm)	Follow-up adenoma maximum diameter (mm)	Maximum diameter change (mm)	Treatment
Patient 37	36	Female	9	No adenoma	Complete resolution	Cabergoline
Patient 38	53	Female	6	3.5	-1.5	Cabergoline
Patient 39	18	Female	5.7	5.7	0	Cabergoline
Patient 40	33	Female	5	No adenoma	Complete resolution	Cabergoline
Patient 41	29	Female	8	7	-1	Cabergoline
Patient 42	17	Female	5	5	0	Cabergoline

**Supplementary Table 2.** Adenoma size change in patients with macroprolactinomas.

	Gender	Age of diagnosis	Baseline adenoma maximum diameter (mm)	Follow-up adenoma maximum diameter (mm)	Maximum diameter change (mm)	Treatment
Patient 1	Male	46	25	14	-11	Cabergoline
Patient 2	Female	47	29	26	-3	Cabergoline
Patient 3	Male	27	18	9	-9	Cabergoline
Patient 4	Male	75	37	30	-7	Cabergoline
Patient 5	Male	49	60	29	-31	Cabergoline
Patient 6	Female	31	10	No adenoma	Complete resolution	Cabergoline
Patient 7	Female	29	11	9	-2	Bromocriptine
Patient 8	Female	43	11	13	3	Cabergoline
Patient 9	Female	32	13	13	0	Cabergoline
Patient 10	Female	38	10	5.6	-4.4	Cabergoline
Patient 11	Female	34	12	11	-1	Cabergoline
Patient 12	Male	45	30	30	0	Cabergoline
Patient 13	Female	23	60	Empty Sella	Complete resolution	Trans-sphenoidal Surgery done due to apoplexy and visual field impairment followed by cabergoline