VOLUME 39 NUMBER 6 NOVEMBER - DECEMBER 2024

Academic Journal of Health Sciences

MEDICINA BALEAR

PUBLICATION OF THE ROYAL ACADEMY OF MEDICINE OF THE BALEARIC ISLANDS

www.medicinabalear.org

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VOLUME 39 NUM. 6
NOVEMBER - DECEMBER 2024

ORIGINALS ARTICLES

eISSN 2255-0569

ORIGINAL

Prolactin levels measyred in females for five years period in Bitola, North Macedonia

Niveles de prolactina reducidos en mujeres durante cinco años en Bitola, Macedonia del Norte

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Received: 15 - VI - 2024
Accepted: 8 - VII - 2024

doi: 10.3306/AJHS.2024.39.06.40

Abstract

Introduction: Hyperprolactinemia is a very common condition in endocrine practice worldwide. The aim of the study is to determine the presence of hyperprolactinemia in patients who had irregular menstrual cycles and infertility and who sought help from family or hospital gynecologists.

Materials and Methods: We made a retrospective study in the Department of Medical Biochemistry in PHO Clinical Hospital Dr. Trifun Panovski, in Bitola city in Macedonia for the period of January 2019 to December 2023. We measured prolactin concentrations in 9710 participants. The patients were referred by gynecologists from our hospital or family gynecologists from private clinics in our city. For healthy subjects, prolactin reference range was lower than 530 mIU/L.

Results: We measured circulating prolactin concentrations in 9710 subjects, 8549 of them have normal values of prolactin and 1161 patients have increased prolactin values.The highest percentage of patients with hyperprolactinemia (19%) was observed in patients aged 26-30 years, followed by the age groups of 16-20 and 20-25 years with 17% representation, and the age group 31-35 years with 16%, the rest of the older groups have almost twice as much lower representation compared to younger patients.

Conclusions: Hyperprolactinemia is a worrying condition in our municipality. It affects women from a young age, affects their offspring, and has a wide variety of etiologies. A detailed history and clinical assessment are important first steps in differential diagnosis and verification of pathological causes. Exclusion of macroprolactinoma is an important point in the diagnostic approach.

Key words: prolactin, hyperprolactinemia, Bitola, Macedonia.

Resumen

Introducción: La hiperprolactinemia es una condición muy común en la práctica endocrina en todo el mundo. El objetivo del estudio es determinar la presencia de hiperprolactinemia en pacientes que presentaban ciclos menstruales irregulares e infertilidad y que acudieron a consulta con ginecólogos familiares u hospitalarios.

Material y métodos: Realizamos un estudio retrospectivo en el Departamento de Bioquímica Médica del Hospital Clínico Dr. Trifun Panovski de PHO, en la ciudad de Bitola, Macedonia, durante el período comprendido entre enero de 2019 y diciembre de 2023. Medimos las concentraciones de prolactina en 9710 participantes. Las pacientes fueron remitidas por ginecólogos de nuestro hospital o ginecólogos de familia de clínicas privadas de nuestra ciudad. Para sujetos sanos, el rango de referencia de prolactina fue inferior a 530 mUI/L.

Resultados: Medimos las concentraciones circulantes de prolactina en 9710 sujetos, 8549 de ellos tenían valores normales de prolactina y 1161 pacientes tenían valores elevados de prolactina. El mayor porcentaje de pacientes con hiperprolactinemia (19%) se observó en pacientes de 26 a 30 años, seguido por la edad. Los grupos de 16-20 y 20-25 años con un 17% de representación, y el grupo de edad de 31-35 años con un 16%, el resto de grupos de mayor edad tienen casi el doble de representación que los pacientes más jóvenes.

Conclusiones. La hiperprolactinemia es un padecimiento preocupante en nuestro municipio. Afecta a mujeres desde edades tempranas, afecta a su descendencia y tiene una amplia variedad de etiologías. Una historia clínica detallada y una evaluación clínica son primeros pasos importantes en el diagnóstico diferencial y la verificación de las causas patológicas. La exclusión del macroprolactinoma es un punto importante en el abordaje diagnóstico.

Palabras clave: prolactina, hiperprolactinemia, Bitola, Macedonia.

Cite as: Ilkovska B, Kotevska Trifunova B, Avramovski P. Prolactin levels measyred in females for five years period in Bitola, North Macedonia. *Academic Journal of Health Sciences 2024*;39 (6): 40-44 doi: 10.3306/AJHS.2024.39.06.40

Introduction

Hyperprolactinemia is a very common condition in endocrine practice worldwide[1]. Elevated serum prolactin is a common finding when testing women with irregular menstrual cycles and infertility[2]. Prolactin is a pituitary peptide hormone secreted by lactotrophic acidophilic cells of the anterior lobe. Secretion of prolactin has also been observed from the endometrium, breasts, placenta, cells of the reticuloendothelial system, and sometimes neoplasm's. Chemically, prolactin is a protein, with a molecular mass of 23.4 kDa, composed of 199 amino acids and three bisulfide bonds[3,4]. Prolactin has a role in increasing the mass of the mammary glands and stimulating and maintaining lactation after childbirth. Thus, it shows mammotrophic, galactopoietics and lactogenic effect[5]. The causes of hyperprolactinemia are physiological, iatrogenic, pathological, idiopathic, non-physiological (disorders of the pituitary gland, drugs, hypothyroidism)[6]. Physiological reasons for increased prolactin are circadian rhythm with increased value during REM sleep[7]. The highest concentration of prolactin was measured between 02:00 and 05:00 in the morning[8]. The highest level of prolactin is during pregnancy, childbirth and lactation. An increased level of prolactin has been observed during intake of a high-protein diet, stress, and physical exertion[9]. An increased concentration of prolactin in the blood causes many disorders in the function of the sexual organs, leads to an imbalance in the secretion of gonadotropic hormones and luteotropic hormones and hypoestrogenism. In this way, it indirectly disrupts lipid metabolism, leads to osteoporosis, increases the secretion of adenocorticotropin hormone and adrenal androgens, disrupts insulin secretion and decreases globulin synthesis in the liver[10]. Androgenic hormones disrupt oocyte development[11]. Hyperprolactinemia reduces the secretion of follicle-stimulating hormone and luteotropic hormone, which leads to inhibition of estradiol production. A decrease in the concentration of follicle-stimulating hormone in the blood leads to impaired maturation of the Graffian follicle, therefore anovulatory cycles are observed. On the other hand, reduced levels of luteotropic hormone cause lutein insufficiency, which results in reduced activity of enzymes that participate in steroidogenesis[5]. High concentrations of androgens have been observed during oocyte development[12]. Elevated levels of prolactin lead to the destruction of ovarian follicles, and the corresponding premature death of ovarian activity[13]. All these disorders give a plethora of clinical manifestations: menstrual disorders (irregular cycles every six weeks and up to six months, oligomenorrhea amenorrhea,hypermenorrhea, hypomenorrhea,), shortened menstrual cycles (polymenorrhea), galactorrhea, premature regression of the premenstrual syndrome of the corpus luteum, hirsutism, acne, headaches and visual disturbances (with the presence of prolactinoma, mainly macroprolactinoma)[10]. The aim of the study is to determine the presence of hyperprolactinemia in patients who had irregular menstrual cycles and infertility and who sought help from family or hospital gynecologists.

Materials and methods

We made a retrospective study in the Department of Medical Biochemistry in PHO Clinical Hospital Dr. Trifun Panovski, in Bitola city in Macedonia for the period of January 2019 to December 2023. We measured prolactin concentrations in 9710 participants. The patients were referred by gynecologists from our hospital or family gynecologists from private clinics in our city. For each patient in whom prolactin was examined, a history of the disease was taken by the family gynecologist, in order to determine primary or secondary amenorrhea. When taking the history, it was determined which drugs the patient was taking - whether they affect the secretion of prolactin. Women reported the presence or absence of galactorrhea. Pregnancy was excluded in all subjects, so as not to get false positive results. In order to diagnose the disease, a blood sample is taken from the patient's basilic vein or from another easily accessible place. The examination was carried out in the morning, 2-3 hours after waking up. Before analysis, samples were centrifuged at 3000 relative centrifugal force for 15 min. We measured prolactin using Immulte 2000 hpi analyzer. We divided total patients in 10 age groups i.e. 16-20, 21-25, 26-30, 31- 35, 36-40, 41-45, 46-50, 51-55, 56-60, and older than 60 years. For healthy subjects, prolactin reference range was lower than 530 mIU/L. The data are presented as mean± standard deviation (SD). The results were done with the SPSS version 13.

Results

We measured circulating prolactin concentrations in 9710 subjects, 8549 of them have normal values of prolactin and 1161 patients have increased prolactin values. Mean age of all patients with hyperprolactinaemia was 35 years, and the age-range was 16-96 years. The highest incidence rates of hyperprolactinaemia were found in women aged 16-35.

From what is shown in **table I** and **figure 1**, it can be concluded that the largest number of healthy subjects are aged 41-45 years, followed by the age group of 36-40 years, then 31-35 years and so on.

The highest percentage of patients with hyperprolactinemia (19%) was observed in patients aged 26-30 years, followed by the age groups of 16-20 and 20-25 years with 17% representation, and the age group 31-35 years with 16%, the rest of the older groups have almost twice as much lower representation compared to younger patients.

When we observe the mediana of prolactin **table II** in all age groups, it can be noted that its values range from 918 mIU/L in the age group 56-60 years, to 687 mIU/L in the age group 51-55 years. In the rest of the age groups, a constant can be observed in the value of prolactin, which is close to the value of 750 mIU/L.

Table I: Patient characteristics (n=9710).

Age of diagnosis (years)	Healthy subjects	Patients with Increased Prolactin
16-20	185	39 (17%)
21-25	739	148 (17%)
26-30	938	225 (19%)
31-35	1275	239 (16%)
36-40	1532	178 (10%)
41-45	1598	123 (7%)
46-50	1240	113 (8%)
51-55	555	57 (9%)
56-60	284	21 (7%)
>60	203	18 (8%)

Figure 1: Present number of cases in different age groups.

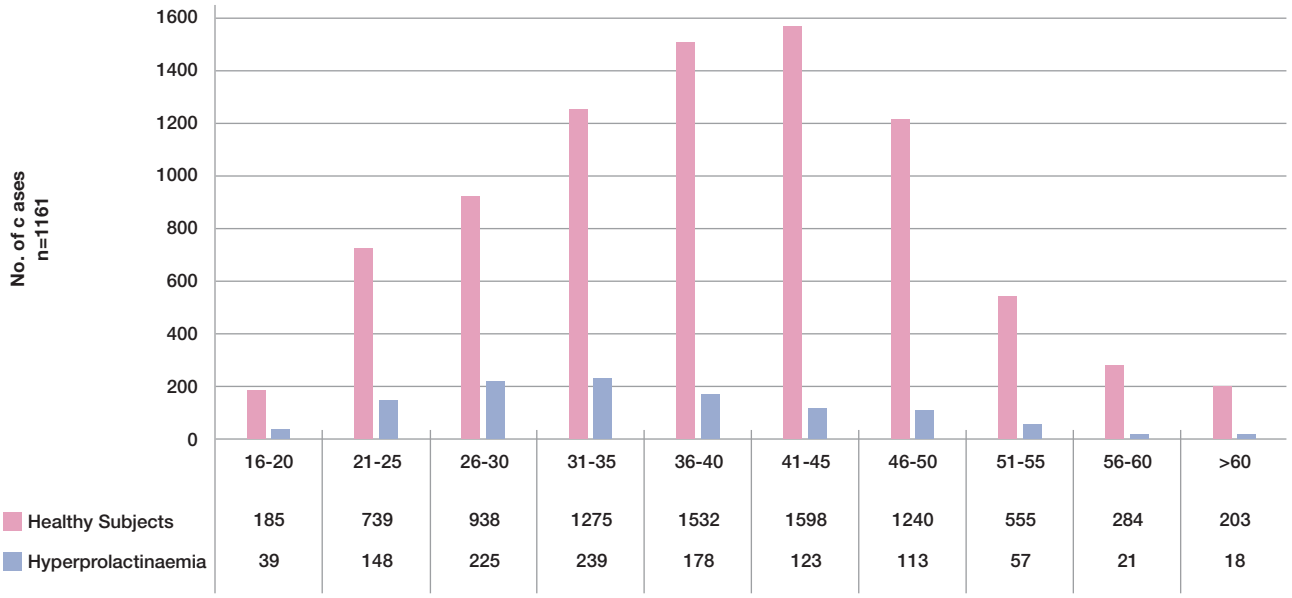

Table II: Mediana of prolactin values in all age groups.

Age in years	No. of cases n=1161	Mediana of prolactin	Standard deviation
16-20	39	700	435.7
21-25	148	808	801.9
26-30	225	738	512.9
31-35	239	765	686.2
36-40	178	783.5	879
41-45	123	765	498
46-50	113	723	495
51-55	57	687	1181
55-60	21	918	419
>60	18	744	700

Discusion

Hyperprolactinaemia is not usually a disease in itself. It is just a symptom that makes us think, to discover the disturbed function of another organ. Treatment of hyperprolactinaemia and, indirectly, of infertility should begin with thorough diagnostics of the causes of the condition[14]. Our study was retrospective and included an analysis of more than 11,000 patient outcomes. A large number of patients were excluded from the study due to unfulfilled criteria regarding pregnancy, medication use (cholinergic receptor agonists, dopaminergic receptor blockers, oral contraceptives containing oestrogens, dopamine synthesis inhibitors, anti-hypertensive drugs, antidepressants, antihistamines, antipsychotics, antiemetics (metoclopramide), anaesthetics, drugs

inhibiting the action of catecholamines, neuroleptics, neuropeptides, opioids, and their antagonists) and improper preparation for the examination. More than 1000 results were obtained from multiple testing of patients with hyperprolactinemia. In the end, the number of 9710 respondents was reached in five years period, of which 1161 patients have hyperprolactinemia (12%). At the global level, the rate of hyperprolactinemia is 23.9 per 100,000 person years. Our study showed that in our city this rate is ten times higher because Bitola is a municipality with less than 80,000 inhabitants. On average, if we divide the total number of patients with hyperprolactinemia, we get about 230 patients per year. That is an enormously higher rate compared to world statistics. Study of Soto-Pedre showed an overall prevalence of hyperprolactinaemia (i.e. prolactin greater than 1000 U/L) over a period of 20 years of 1 per 1000 of the population and the age–sex-adjusted incidence rates were 21.5 per 100,000 person-years for women[15]. In Shlomo Melmed, study in women aged 25-34 yr, the annual incidence of hyperprolactinemia was reported to be 23.9 per 100,000 person years[16]. The highest percentage of patients with hyperprolactinemia (19%) was observed in patients aged 26-30 years, similar to the study of numerous other authors[16]. Soto - Pedre reported the highest incidence rates were found in women aged 25-44 years[15]. We prove hyperprolactinaemia when at least two test results of blood prolactin concentration are abnormal or a single incidental measurement exceeds the upper limit of the norm at least five times. In patients with long-term, persistent hyperprolactinemia, when other etiologies are excluded, we recommended performing Magnetic Resonance for a visual examination of the sella turcica, to exclude diseases that cause damage to pituitary cells or other structures of the central nervous system, neoplastic tumors on the brain. We recommend other examination were made for inflammatory conditions of the pituitary gland, operations, injuries, radiation of the pituitary gland, meningitis[9], septicemia, chronic uremia or idiopathic factors. Also we recommend analyses for systemic diseases: chronic renal failure, liver cirrhosis, epilepsy, chest injuries and operations, polycystic ovary syndrome, pseudo pregnancy, Cushing's disease and Addison's disease. In recent years, a number of studies have investigated the association of prolactin with other diseases. Recent studies show an association of high prolactin concentrations with cardiovascular disease, osteoporosis, autoimmune conditions, and mortality from these causes[1]. The association of hyperprolactinemia with valvular heart disease (from the use of dopamine agonist therapy), cardiovascular risk factors, or cardiovascular mortality is controversial[17-19].

Numerous studies talk about the connection between prolactin and breast cancer[20], ovarian[21], colon[22,23] and hepatocellular carcinoma[24]. Basic science studies have implicated the role of prolactin and its receptor in the pathogenesis of various malignancies[25-27], but a clear causal relationship between prolactin and cancer is controversial[20]. There are quite a few epidemiological studies on this topic, but the results are conflicting[20]. The relationship between hyperprolactinemia and cancer should be interpreted with caution, because some studies include people with normal prolactin values or studies are done with a single measurement of prolactin[20]. Dekkers did a study of 1342 women with hyperprolactinemia and found no increased risk of breast cancer compared to the general population[28]. Further epidemiological and clinical studies investigating this issue are needed. Our goal in the future is to follow the disease evaluation of patients with hyperprolactinemia and find out the exact cause of it. This will reduce infertility and improve the quality of life for our patients.

Conclusions

Hyperprolactinemia is a worrying condition in our municipality. It affects women from a young age, affects their offspring, and has a wide variety of etiologies. A detailed history and clinical assessment are important first steps in differential diagnosis and verification of pathological causes. Exclusion of macroprolactinoma is an important point in the diagnostic approach.

Competing Interests

The authors declared that there were no conflicts of interest.

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