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THE RELATION OF PROLACTINE HORMONE AND ZINC IN THE HYPERPROLACTINEMIC INFERTILE WOMEN IN MOSUL.

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ABSTRACT

Background: Hyperprolactinemia is the commonest endocrine disorder of hypothalamic pituitary gland axis occurring most commonly in women but it can occur also in men. The relationship of serum level of Zn with PRL in human was a matter of controversy. Some authors found that there was no correlation between Zn and PRL in both sexes. However, the weight of evidence points to the existence of inverse relationship. **Aim of the study:** To examine the relationship of serum PRL and serum Zn in the control women and in hyperprolactinemic infertile women before and after treatment with dopamine agonist drug (bromocriptine). **Subjects Materials and Methods** Serum levels of PRL and Zn were measured in 90 women aged 18-45 years selected from the relatives and patients attending the Infertility Unit at Al-Batool Hospital in Mosul during the period of five months from March 2001 so the end of July 2001. Thirty normal fertile women were allocated as controls and 60 women who were complaining from infertility and hyperprolactinemia for more than 1 year allocated as cases group before treatment. Then those women treated by bromocriptine and followed up for 3 months and allocated as cases group after treatment. Serum PRL and Zn concentrations were estimated using MINI VIDAS instrument and Atomic Absorption Spectrophotometer respectively. **Results:** The serum level of PRL in cases group before treatment (38.98 ng/ml) was significantly higher than in control group (10.75 ng/ml) at ($p<0.005$) and the mean value of serum level of Zn in cases group before treatment (66.49 µg/dl) was significantly lower than in controls group (97.83µg/dl) at ($p<0.005$). The mean values of serum level of PRL among group before treatment was (38.98 ng/ml) and among cases after treatment was (20.66 ng/ml); the difference was statistically significant ($p < 0.005$). On the other hand, the mean values of serum level of Zn between cases group before treatment (66.49 µg/dl) and cases group after treatment (82.45 µg/dl) shows that Zn increases significantly ($p < 0.005$). Additionally, the differences of PRL and Zn between cases after treatment and controls were statistically significant at ($p<0.005$). The correlation between PRL and Zn in each study group was significant in the cases group before treatment only. **Conclusion:** The results of this work may suggest that there is a sort of reciprocal relationship between PRL and Zn.

KEYWORDS: Hyperprolactinemia, Infertility, Prolactine hormone, Zinc.

INTRODUCTION

Hyperprolactinemia is the commonest endocrine disorder of hypothalamic pituitary axis occurring most commonly in women but it can occur also in men.[1,2] In an unselected group of healthy adults, the prevalence of hyperprolactinemia ranges from 0.4% to as high as 9-17% in females with reproductive problems.[2] Hyperprolactinemia in women presents most commonly with secondary amenorrhea, Galacatorrhea, oligomenorrhea, menorrhagia and anovulation with infertility.[3] Men may present with decreased libido, abnormal spermiogram, infertility, gynaecomastia and impotence.[1] Subjects with hyperprolactinemia of unknown etiology may harbor a pituitary macroadenoma too small to be detected radiologically.[4]

Treatment of hyperprolactinemia has become effective and simple depending on the reason of raised serum PRL. Regardless of etiology, treatment is aimed at normalizing PRI level to improve gonadal function and halt the Galacatorrhea. Oral medical drugs like oral dopamine agonists (e.g bromocriptine cabergoline or pergolide) are the mainstay of therapy.[3, 5]

PRL is a glycoprotein of single polypeptide chain. In human, PRL consists of 199 amino acid residues and three intermolecular disulfide bridges.[6,7] The normal serum level of PRL is between 1.3-25 ng/ml in female and 1.5-19 ng/ml in male.[7,8] The relatively higher concentration in female compared to male is due to presence of estrogen.[9] PRL level does not change significantly during menstrual cycle.[10] In pregnancy the basal PRL level gradually increases and it reaches up to 200 ng/ml at term. Some say that PRL is low in serum during mid pregnancy, so it may have no role in the maintenance of mid-term pregnancy.[9,22], PRL level returns to non pregnant level within several weeks after birth. The practice of lactation causes transient tenfold increase in PRL secretion that lasts approximately one hour each time suckling occurred. These reported PRL surges provide the stimulus for continued lactogenesis. If PRL surges were blocked, they disappear within few days and lactogenesis disappears also.[11]

One of the crucial trace elements that was found in minute levels in biological systems was zinc (Zn), a divalent cation. It played a very important role in human and animal metabolism and in normal functions of the body.[12, 13]

Zn is a constituent of several hundred enzymes and hence a deficiency of this element can entail a functional decrease or loss of essential biochemical mechanisms "Zn is important in hormonal homeostasis since it can interact with almost all hormones. Zn promotes baseline hGH secretion in healthy persons as it was intimately associated to thyroid, steroid, insulin, parathormone, and pituitary hormones, particularly PRL.[14, 15] It was a component of insulin and was found in the pancreatic islet cells responsible for producing insulin. The combination of insulin with Zn increases the duration of insulin action.[16] Zn increases insulin binding to hepatocytes and adipocytes.[17]

The relationship between serum level of Zn and PRL in human was a matter of controversy. Some authors found that there was no correlation between Zn and PRL in both sexes.[18,19] However, the weight of evidence points to the existence of inverse relationship.[20,21]

The inhibitory activity of Zn on PRL synthesis, secretion and release was first described by Labella-Dular in 1973.[22] The mechanism of Zn inhibition on PRL release was not clear yet. It has been found that suppression of PRL release by Zn in vitro was dose dependent over a range of physiological Zn concentration. The physiological concentration of Zn inhibits secretion to a greater extent than synthesis, while pharmacological concentration inhibits both synthesis and secretion.[23,24] Both basal and TRH stimulated secretions are reversibly inhibited by Zn and the process is specific for PRL. Zn can inhibit PRL secretion within a range of physiologically and pharmacologically relevant concentrations. This property has raised the possibility of clinical application of Zn in the treatment of hyperprolactinemia.[25] Lorenson *et al*[26] investigated the hypothesis that Zn contributes to the stability of intragranular PRL due to its inhibitory effect on PRL release from isolated granules and its effect on the particular stuffing of PRL inside granules. They proposed that binding of Zn stabilizes the intermolecularly bonded storage form of PRL.[26]

The possible site of action of Zn is unknown. At pituitary level, the functional integrity of lactotropic cells depends on several processes which may be influenced by Zn. Zn may interact with membrane proteins containing the sulfhydryl group and this modify the activity of many enzymes or directly inhibits lipid peroxidation of the membrane. Zn modifies the structure and function of PRL secreting granules or it is known to interact with calcium channels.[24.25] Zinc also might act on dopaminergic receptors by increasing the affinity and activity of dopamine for lactotropic cells.[24]

The available recent literature gives contradictory results about the relationship between the ante for pituitary hormone PRL and the trace element Zn. Therefore a local study is needed to clarify this relationship and to see if there is a correlation in normal women when the values of PRL and Zn are within physiological range. In addition to find out the relation between PRL and Zn when PRL is high as inhyperprolactinemic infertile women and when PRL is lowered bydopamine agonist drugs.

SUBJECTS MATERIALS AND METHODS

This case-control study involved 90 married women in the reproductive age. Their age ranged between 18-45 years with a mean of 27.98± 0.55 years. The women included in this study were allocated into three groups as follows.

1. Controls group: this includes 30 normal, married and fertile women who accompanied the infertile patients attending the infertility unit. Complete history and clinical examination were carried out according to a special form designed for this purpose. Serum level of PRL and Zn were determined in this group. The blood samples were drawn in the mid follicular phase of the cycle.
2. Cases group before treatment: this group involved 60 women complaining of infertility for more than 1 year with signs and symptoms of hyperprolactinemia such as galactorrhea with or without menstrual disturbances. These women attending the infertility unit at Al-Batool hospital in Mosul from March 2001 to the end of July 2001. This infertility must be associated with galactorrhea or other signs and symptoms of hyperprolactinemia. Some patients were complaining only from mastodenia with menstrual irregularity or amenorrhea.

All the above women were free from medications affecting the level of PRL in serum for at least one month before the start of the study.

The patients were examined first by a gynecologist who conducted a clinical examination to rule out any abnormality and to refer suitable patients for this study. Complete history was obtained, questions concerning menstrual cycle, venereal diseases, sexual habits, post pubertal mump oophoritis, smoking and drugs which are thought to affect fertility according to a special form designed for this purpose. The serum level of PRI and Zn were determined in this group also blood samples were drawn in the mid follicular phase of the cycle.

3. Cases group after treatment: This was the same 60 women in cases group were followed after treatment with bromocriptine (Dopamine agonist) in a dose of 2.5 mg twice daily for 3 months. The serum level of PRL and Zn were determined afterwards. The blood samples were drawn in the mid follicular phase of the cycle also.

Collection of blood samples

Blood samples were obtained from the controls and the patients. All women were invited to a quiet room. Disposable syringes and plain plastic tubes were prepared and labeled. Each woman has a special form written on it the name, date, serial number and history. Blood samples of 5ml in volume were taken by an antecubital venipuncture in the morning between 9.00 am-12.00 am to avoid diurnal variation. Then blood was allowed to clot in plain plastic tubes in an incubator at temperature of 37 °C for about 10 minutes. After that centrifugation was done at 3000 RPM speed to separate the serum. Then the serum was transferred by Gilson pipette and divided into 2 plastic tubes; the first one for PRL assay and the second one for zinc measurements. Both samples of sera are aliquoted and stored at -18 °C until the assay was done after 1-4 months of storage. PRL assay was done by a MINI VIDAS instrument which is an automated computerized quantitative test analyzer for the enzyme immunoassay determination of human serum or plasma using ELFA techniques (Enzyme Linked Fluorescent Assay).

Statistical analysis

Standard statistical methods were used to determine the mean (x). standard deviation (SD) and standard error (SE) in all groups, the Unpaired t-test was used in the comparison of each PRL level and Zn level between controls group with and cases group before treatment and between controls group and cases group after treatment. While the paired t-test was used in the comparison between cases group before treatment and cases group after treatment for both PRL and Zn levels. Pearson correlation coefficient (*r*) was used to determine if there is any correlation between PRL and Zn levels inside each group. The p-value≤0.05wasconsidered significant.

RESULTS

The mean value± SE of serum level of PRL among the controls group was 10.75 ± 0.92 ng/ml and the mean value ± SE of serum level of Zn was 97.83± 3.44 µg/dl. Among the cases group before treatment the mean value ± SE of serum level of PRL in hyperprolactinemic untreated women was 38.98 4.01 ng/ml. The mean value of serum level ± SE of Zn was 66.49+2.69 µg/dl. The cases group after treatment with bromocriptine for 3 months showed that the mean ±SE of serum level of PRL decreased from 38.98 ng/ml to 20.66±2.02 ng/ml but it did not reach the mean control level of 10.75 ng/ml. The mean value of serum level S.E. of Zn in this cases group after treatment increased from 66.49+ 2.69 µg/dl to 82.45+ 2.13 µg/dl but it did not reach the mean control level of 97.83+ 3.44 µg/dl.

Table (1): The mean ± SE of serum level of PRL and Zn in the study groups.

Groups	N	parameters	
		PRL (Mean ± S.E.)	Zn (Mean ±S.E.)
Controls	30	10.57 ± 0.92	97.83 = 3.44
Cases before treatment	60	38.98 ± 4.41	66.49 = 2.13
Cases after treatment	60	20.66 ± 2.02	82.45 2.13

The comparison of serum level of PRL and Zn between controls and cases groups was demonstrated in table (2) which revealed that serum level of PRL in cases group before treatment (38.98 ng/ml) was significantly higher than that in control group (10.75 ng/ml) at (p<0.005). On the other hand, the mean value of serum level of Zn in cases group before treatment (66.49 µg/dl) was significantly lower than that in controls group (97.83µg/dl) at (p<0.005).

Table (2): Comparison of serum level of PRL and Zn between study groups.

Statistical Values		X± S.E	t-value	p-value*
Parameter	Group			
PRL Ng/ml	Controls	10.75 ± 0.92	7.08	<0.005
	Cases before treatment	38.98 ± 4.01		
Zn (µg/dl)	Controls	97.83 ± 3.44	5.82	<0.005
	Cases before treatment	66.49±2.69		

* paired t-test

The comparison of serum level of PRL and Zn between cases group before treatment and cases groups after treatment was demonstrated in table (3). The mean values of serum level of PRL among group before treatment was (38.98 ng/ml) and among cases after treatment was (20.66 ng/ml); the difference was statistically significant (p < 0.005). On the other hand, the mean values of serum level of Zn between cases group before treatment (66.49 µg/dl) and cases group after treatment (82.45 µg/dl) shows that Zn increases significantly (p < 0.005).

Table (3): Comparison of serum level of PRL and Zn between study groups.

Statistical Values		X±S.E	t-value	p-value*
Parameter	**Group**			
PRL Ng/ml	Cases before treatment	38.98± 4.01	6.17	<0.005
	Cases after treatment	20.66 ± 2.02		
Zn (µg/dl)	Cases before treatment	66.49 2.69	4.06	<0.005
	Cases after treatment	82.45 ±2.13		

* paired t-test

The comparison of serum level of PRL and Zn between cases group after treatment and controls group was demonstrated in table (4) and revealed that the bromocriptine treatment decreased the level of PRL and increased level of Zn towards normal range However, this decrease in PRL and increase in Zn towards normal physiological range as a result of bromocriptine treatment did not reach the mean value of serum level of the control group; the differences of PRL and Zn between cases after treatment and controls were statistically significant at (p<0.005).

Table (4): Comparison of serum level of PRL and Zn between study groups.

Statistical Values		X±S.E	t-value	p-value*
Parameter	**Group**			
PRL Ng/ml	Controls	10.75 ± 092	4.94	<0.005
	Cases after treatment	20.66 ± 2.02		
Zn (µg/dl)	Controls	97.83 ± 3.44	3.68	<0.005
	Cases after treatment	82.45 ±2.13		

*t-test for independent two means

The correlation between PRL and Zn in each study group was demonstrated in table (5). In the controls group there is a negative and very weak correlation between PRL, and Zn (*r*= -0.049), and this inverse relationship between PRL and Zn was not statistically significance (p>0.1). In cases group before treatment, there was negative and weak correlation (*r*= -0.297) but statistically significant (p<0.025). In cases group after treatment, there was negative and very weak correlation (*r*= -0.196) but statistically not significant (p>0.1).

Table (5): The correlation between PRL and Zn in each study group.

Groups	Parameters	Statistical values		
		n	***(r)***	**p-value***
Controls	PRL and Zn	30	-0.049	> 0.1 N.S.
Cases before treatment	PRL and Zn	60	-0.297	<0.025
Cases after treatment	PRL and Zn	60	-0.196	> 0.1 N.S.

*Pearson correlation

DISCUSSION

The serum level of PRL in the control group was within the normal physiological range of healthy fertile women not suffering from any sign or symptom of hyperprolactinemia.[27.28] Equally so, the serum level of Zn in the controls group was within the normal physiological range of healthy individuals who were not suffering from any sign or symptom of hypozincemia or hyperprolactinemia.[17]

In hyperprolactinemic women (cases group before treatment) the serum level of PRL is nearly four times as much as the control level. The difference in PRL level between the control group and hyperprolactinemics is highly significant. This is expected since all women in this group are suffering from signs and symptoms of hyperprolactinemia such as galactorrhea, irregular cycle, amenorrhea, mastodenia and infertility.[29, 30] therefore these women were referred to the infertility unit for investigations. The biochemical results of high PRL levels reflect the clinical condition of women in this group. This high serum level of PRL is associated with low level of Zn. The value of Zn is nearly two thirds of the control value. The decrease in Zn level in hyperprolactinemics in comparison with the control is highly significant.

As a result of three months treatment of women in cases group (before treatment) with bromocriptine (now they became cases group after treatment), the serum level of PRL, decreased to nearly half its pretreatment level. Contrariwise Zn level increased 25% of its pretreatment level. Here it was clearly that when PRL is high, Zn is low (cases group before treatment) and when PRL decreases, Zn increases (cases group after treatment), as if there is a reciprocal relation between them. It remains to be seen whether there is a cause and effect relationship between PRL and Zn, or at least whether there is a sort of negative correlation between these two parameters or not.

The result of the bromocriptine's action in cases group after treatment is confirmatory to already known knowledge about the inhibitory action of dopamine agonist drugs on the synthesis, secretion and release of PRL from lactotrops of the pituitary gland.[3-5.29]

The mechanism of the inhibitory action of copamine or dopamine agonist drugs on PRL level is believed to be a pituitary gland.[9,31] Dopamine binds directly to D_2 -receptors which are located at the plasmatic membrane of the lactotrops and it is likely that dopamine exerts its major inhibitory action on the lactotrops through a mechanism which is triggered by this initial interaction.[32] Dopamine suppresses all aspects of PRL secretion. It inhibits the biosynthesis and release of PRL. It also inhibits cell division and DNA synthesis and brings about the loss of stored PRI in granules by stimulating crinophagy (autodigestion of secretory product).[31] Dopamine inhibits secretion of PRL through inhibiting the formation of cyclic AMP (a stimulator of PRL secretion) and inhibits synthesis of phosphoinositol, an important step in post receptor regulation of PRL secretion.[1] Some authors say that the action of dopamine as inhibitor of PRI occurs independent of zinc. Both dopamine and Zn cause inhibition of PRL, each acts by its own mechanism.[33] Others say that Zn might act on dopaminergic receptors by increasing the affinity and activity of dopamine for lactotropic cells.[21]

Although the action of bromocriptine brought down the level of PRL to a value near the normal range, and brought up Zn to a value which is within the normal range also, yet both levels did not reach the pretreatment levels. This finding can be explained on the basis of the dose and/or duration of treatment. Some cases of hyperprolactinemia need higher dose and/or longer duration of treatment.[29, 34]

Looking at the level of Zn in cases group before treatment and cases group after treatment we see that Zn behaves in a reciprocal manner with PRL level. Its level is normal in controls group, low in group cases group before treatment when PRL is high and increases when PRL decreases in cases group after treatment.

The nature of the relationship between PRL and Zn in each group was assessed in the present study. Statistical correlation study has been done for each group separately. In the control group it is found that there was no obvious correlation (r= -0.049) between PRI and Zn. This finding agrees with the work of Al-Janabi *et al*[35] when they determined serum Zn and PRL in 21 unmarried young healthy male volunteers. They found that the correlation between serum levels of PRL versus Zn in male is negative but fails to reach a significant level and they attributed it to close serum level of PRL and Zn to normal values. Probably in the physiological range of PRL and Zn, the inverse relationship though it is existing but it is not so prominent. The evidence which support this ideas was the finding of negative and significant correlation (r=-0.297, $p<0.025$) in cases group before treatment of the current study. This inverse relationship between PRL and Zn also exists in cases group after treatment, and it is highly significant ($p<0.025$).

It seems that when the level of PRL and Zn are beyond their physiological range such as pathological or pharmacological levels, the inverse relationship showed itself clearly. While when the levels are physiological, this inverse relationship is just apparent. This agrees with the work of Caticha *et al*[36] who investigated the interrelationship between plasma Zn and PRL level in patients with chronic renal failure presented with hyperprolactinemia and found that depletion of total body Zn may represent one of the major mechanisms that leads to uremic hyperprolactinemia. However, other researchers were unable to find an inverse relation between PRL and Zn in chronic renal failure. For example Rodger *et al*[18] in 1989 on studying a selective group of males on dialysis complaining of sexual dysfunction found that patients with normal serum PRL concentrations had significantly lower serum Zn values.

There are few references denying the existence of inverse relationship between PRL and Zn[37,38] and that Zn administration does not inhibit PRL level.[18,19,33] However evidence is accumulating from tremendous research works going on in different parts of the world supporting the doubtless existence of inverse relationship between PRL and Zn.[20,22.35,39,40] Al-Mallah *et al.*[39] showed the significant negative correlation between Zn and PRI in subfertile hyperprolactinemic men irrespective of the state of semen analysis. They suggested the possibility of treating hyperprolactinemic subfertile men with Zn supplement in the din before using dopamine agonist drugs. Also Al-Janabi *et al*[35] determined serum Zn and PRL in 21 females and 21 males who were healthy and unmarried. They found that serum Zn level influences inversely the level of PRL in females while in males the pattern of correlation was also negative but statistically not significant. Whether PRL hormone influences the metabolism of Zn or Zn influences PRL synthesis and secretion[33] is still a matter of discussion. But the evidence is pointing to the lowering effect of Zn on PRL and not vice versa.[21, 23, 24, 33, 40] Judd *et al*[41] in 1984 showed that Zn inhibits pituitary PRL secretion in selective and reversible way and the magnitude of inhibition was non sustained during Zn exposure. Upon Zn withdrawal, PRL secretion rapidly rebounded to reach the basal level. This agrees with the results of Michele et al in 1989 and Allan *et al.*[40] Labella-Dular *et al*[22] were the first who described the inhibitory activity of the trace element Zn on PRL synthesis and secretion by incubating purified fraction of Zn-containing hypothalamic tissue with bovine pituitary extracts in vitro. This finding was later confirmed by in vitro researche of Cooper[42] which determined the effect of metal cation Zn on PRL level in vitro on studying the anterior pituitary glands of adult male rats. They found that baseline PRL release was decreased by Zn.

In vivo, Mahajan *et al*[43] showed the consequence of Zn supplementation on hyperprolactinemia in uremic men. They found that Zn treated patients had significantly higher plasma Zn levels and lower PRL level than untreated patients. This is consistent with Brands *et al* study[21] in which they examined the plasma PRL response to oral intake of escalating doses of Zn in vivo in 17 healthy adult men and women and discovered that the PRL level dramatically decreased in response to rising plasma Zn levels. According to the findings, normal people's basal PRL secretion is inhibited by acute hyperzicemia. A later work by Koppleman *et al*[19] that discovered that PRL release suppression is reliant on a range of physiological Zn values further corroborated this result. Some authors are so convinced about the inhibitory role of the trace element Zn on PRL to such an extent that they recommend the use of Zn in the treatment of hyperprolactinemia either alone in the form of Zn sulphate drugs[20, 33, 40, 44], or Zn acetate[18, 20, 33] or together with dopamine agonist. If look at the results in group 2a and cases group after treatment notice that in cases group before treatment when PRL level is high, Zn level is low and this biochemical result is reversed in cases group after treatment where the high PRL level has been lowered and the Zn level has become higher. This agrees with the work of Travailing *et al.*[33] They used bromocriptine in a dose of 2.5-5mg daily in patients with prolactinoma and they noticed that bromocriptine decreased PRI level and increased Zn level significantly. The fall in PRL was more obvious when those patients received bromocriptine than when they received Zn sulphate alone, while Zn level increases significantly in both conditions. Mahajan *et al*[43] studied the effect of Zn acetate supplementation on hyperprolactinemia in uremic men. They found that Zn treated patients had significantly higher plasma Zn levels and lower serum PRL levels than untreated patients, but the plasma Zn and serum PRL were inversely related in Zn-treated patients. Salih study[24] showed that Zn sulphate administration potentiates the effect of bromocriptine in lowering PRL level in hyperprolactinemic women. The fall in PRL level was greater in women receiving both bromocriptine and Zn sulphate when compared with those women receiving bromocriptine alone or Zn sulphate alone.

The actionable location of Zn is still unknown. Labella-Dular *et al*[22] demonstrated that bovine hypothalamus is rich in peptides complexed with metals which may be hypothalamic factors. At pituitary level, the functional integrity of lactotropic cells depends on several physiological processes, many of which may be influenced by Zn. Among them are stabilization and protection of cell membrane since Zn may interact with membrane proteins containing the sulfhydryl group and thus modify the activity of many enzymes, Directly Zn inhibits lipid peroxidation of the membrane[45] Zn is also known to interact with calcium channels or to modify the structure and function of PRL secretory granules[22,24] Another possibility is a direct influence of Zn on the calcium calmodulin complex inactivity. It may also be proposed that Zn might act on dopaminergic receptors by increasing the affinity and activity of dopamine for lactotropic cells so Zn inhibits PRL either in the way of its synthesis[22], or in the way of its secretion.[24, 40]

Finally, finding the existence of inverse relationship between PRL and Zn which is supported by other research workers opens a new horizon in the treatment of hyperprolactinemia.

CONCLUSION

There is no correlation between serum level of PRL and Zn in normal fertile women. While in hyperprolactinemic infertile women, the mean Zn level is decreased and the negative correlation between PRL and Zn is prominent and it is statistically significant. When hyperprolactinemic women are treated with bromocriptine, PRL level decreases and Zn level increases, but this inverse relationship is statistically not significant. The results of this work may suggest that there is a sort of reciprocal relationship between PRL and Zn.

Recommendations

Further research is recommended to study the optimum response of the treatment of hyperprolactinemic cases in females by comparing three lines of treatment.

A) Giving dopamine agonist drugs alone for different doses and durations.

B) Giving Zn compounds alone for different doses and durations.

C) Combined treatment of dopamine agonist drugs with Zn compounds for different doses and durations.

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