Prolactin Level In Women With Fibroadenoma Breast- A Cross Sectional Study

Saravanan. P.S.L1, Anu .S2

1Professor, Institute of Physiology, Madurai Medical College, Madurai.
2Professor & Head, Department of Physiology, Velammal Medical College and Hospital, Madurai.

ABSTRACT

Introduction: Prolactin has been proved to be involved in mammary cancer development in humans, but its role in fibroadenoma breast has long been controversial with conflicting reports. Hence this study was done to find out Prolactin level in women with fibroadenoma and if its role in development of tumor is proved, then a feasible drug treatment which could reduce the anxiety and cosmetic problems associated with surgical interventions can be identified.

Objectives:
1. To estimate serum prolactin level in patients with fibroadenoma breast.
2. To compare serum prolactin level of fibroadenoma patients with that of the controls
3. To consider whether prolactin level can be used as an indicator for fibroadenoma breast and has any relation to the disease progression

Materials and methods: A total of 20 female patients between the age group of 18-40 years attending Government Medical College Hospital, Madurai have been studied. Among them 13 patients had fibroadenoma of the breast and 7 normal women served as control. Prolactin level was measured by Immunoradiometric assay.

Results: No significant elevation of prolactin level is seen in women with fibroadenoma breast (mean=25.75ng/ml) when compared with the control and there is no significant association between increased prolactin level and breast fibroadenoma (X2 = 1.83; p = 0.1759).

Conclusion: Prolactin level is not significantly increased in fibroadenoma breast patients. A large scale study is required for a stronger confirmation. Studying the role of locally produced prolactin and mutation in prolactin receptors might help in proper therapeutic management.

Key Words: Fibroadenoma, Benign tumor, Females, Prolactin.

INTRODUCTION:

In recent times the incidence of tumors of breast is quite alarming all over the world. The most common benign tumor of the breast is fibroadenoma and its overall incidence is 2.2%.1,2 It is common in young women. It originates from the breast lobule and shows evidence of both connective tissue and epithelial proliferation. The exact etiology of a fibroadenoma is still unknown, while hypersensitivity to estrogen within a lobule has been suggested.

Fibroadenomas are characteristically mobile tumors, varying in size between 1 cm and 10 cm and frequently occur in the upper outer quadrant of the breasts. Women with fibroadenomas have 2.17 times risk for breast cancer.3

Address for correspondence:
S.Anu, Professor and Head, Department of Physiology, Vellammal Medical College and Hospital, Madurai.
Mobile : 98943 97527  Email id: anu.sengottaian@gmail.com
Development of breast involves coordinated action of many hormones including prolactin, estrogen, progesterone, gluocorticoids, insulin, growth hormone and thyroid hormone. Duct growth is promoted by estrogen, alveolar development is controlled by prolactin & progesterone and lactation is mediated by prolactin. The fact that Prolactin (PRL) is important in all phases of breast development and critical to breast control has been established by careful studies. Prolactin stimulates mammary epithelial cell proliferation in the presence of estrogen and quickens lobuloalveolar development in the presence of progesterone.

The circulating prolactin levels are lowest at midday and peak levels occur during middle to end of night. Prolactin level is found to increase during menarche as well as in the premenopausal women. Higher levels are also found during pregnancy both in the mother and the fetus. At term prolactin level is 10 times as in a non pregnant women. High levels of prolactin appear to be essential for the initiation of lactation. Once breast enzyme systems are activated, lactation can continue with even low levels of prolactin. Reduction in the prolactin level following menopause has been reported.

Role of prolactin in galactorrhea and infertility in women is largely known. Locally produced Prolactin acts as an autocrine / paracrine factor in breast tumor evolution. JAK2 is required for PRL mediated maintenance of differentiated alveolar cells. PRL may promote breast cancer via JAK 2/STAT 2 signaling pathway. Though little is produced in the mammary gland, due to local availability it plays an important role in tumor formation.

Breast tumor cells also express higher levels of PRL receptor when compared to healthy tissue. Estrogen stimulates PRL secretion and also up regulates human PRL receptor gene expression in the progress of the disease. Conflicting reports are found regarding the involvement of Prolactin in cases of tumors of breast. Hence this study is taken up to find whether the increasing incidence of fibroadenoma breast has any relation to the Prolactin level of the individual and also its relevance to the tumor.

MATERIALS & METHODS:

The Study was done at Government Rajaji Medical College Hospital, Madurai after getting clearance from the Institutional Ethical Committee.

Twenty subjects in the age group of 18-40yrs were chosen for the study by simple random sampling. 13 of them had benign tumor (fibroadenoma) of the breast. Patients were identified following histopathological examination of the tissue removed at surgery. All of them were in the premenopausal group. Seven premenopausal normal women having similar age and weight were selected and served as control.

After getting consent from the selected individuals, the Proforma was filled in eliciting the required data to find the possible risk factors. All patients included in this study were without any prior treatment. Women who were pregnant and / or lactating were excluded from the study. In all subjects blood samples were taken during the follicular phase of the menstrual cycle.

As far as could be ascertained, no patient was receiving phenothiazines, L-Dopa, monoamine
oxidase inhibitors, or other drugs known to affect the secretion of prolactin. Each patient had a blood sample taken between 11.00 am and 5.00 pm and blood was allowed to clot and the resulting serum was frozen at -20°C until assayed. Prolactin is estimated by Immuno Radio Metric Assay (IRMA).

**Principle of the test:**

This immunoradiometric assay is a non-competitive assay technique to quantitate prolactin in serum sample. In IRMA, two antibodies generated against different portions (epitopes) of the same antigen are used. The capture antibody is coupled to magnetic particles and used as the solid phase and the detection antibody is radiolabelled with $^{125}$I. When antigens (standards or sample) are incubated with the tracer and the solid phase, it simultaneously binds to both the antibodies in a bridge or sandwich fashion. Their entire complex remains bound to the magnetic particle. The bound radioactivity associated is then quantitated using a gamma counter calibrated for $^{125}$I. The concentration of prolactin in the sample is directly proportional to the radioactivity. The concentration of prolactin of unknown sample is read off by the interpolation from the curve.

**Statistical analysis:**

The quantitative data was checked for normality and summarized using mean/median and standard deviation / interquartile range as appropriate. Categorical data is summarized as frequencies and percentages. Prolactin level in fibroadenoma group and control group was compared using student t test & chi square test. P value < 0.05 is the cut off to determine statistical significance.

**RESULTS:**

**Table-1. Mean Prolactin level in Fibroadenoma patients.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects</th>
<th>Mean Prolactin level ng/ml</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroadenoma breast (all premenopausal)</td>
<td>13</td>
<td>25.75</td>
<td>24.77</td>
</tr>
</tbody>
</table>

**Table-2. Association of Prolactin level with fibroadenoma breast:**

**Chi-square test:**

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Increased Prolactin Level</th>
<th>Normal Prolactin Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroadenoma Breast</td>
<td>13</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

X$^2 = 1.83$  p = 0.1759

**Table-3. Student t Test:**

<table>
<thead>
<tr>
<th>Prolactin level</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroadenoma XControl</td>
<td>1.71</td>
<td>0.1041</td>
</tr>
</tbody>
</table>

**OBSERVATION:**

Among 07 controls, all were with normal Prolactin level < 20mg/ml.

Among 13 fibroadenoma breast cases,

5 i.e. 38.5% - were with increased prolactin level
8 i.e. 61.5% - were with normal prolactin level

**DISCUSSION:**

Evidence that Prolactin is a carcinogen in rat mammary cancer was presented in 1969.$^{11}$ Since then there are numerous reports in the literature of investigation of relationship between Prolactin and various aspects of breast tumors and many have found suggestive association between Prolactin and breast cancer. Studies for Prolactin level in...
fibroadenoma breast patients have also produced conflicting reports. Though few studies report that prolactin level is elevated in fibroadenoma breast patients, there are studies which had showed normal prolactin level in patients with benign breast tumors. In another study, only 27% & 5% of fibroadenoma patients had elevated prolactin. The present study results also showed increased prolactin levels only in 38.5% of fibroadenoma patients with normal prolactin level in the remaining 61.5% (as shown in table1). There is no significant increase in the level of prolactin in fibroadenoma patients when compared with the control (Table 2,3).

The interpretation of the result obtained in present study depends on the confidence with which a single prolactin estimate between 9.30 a.m to 5.00 p.m represents the prolactin status of the patient. The defined time period was chosen to avoid major variation due to the diurnal rhythm of prolactin. By 9.30 a.m the fall of prolactin levels from their nocturnal sleep induced peak has reached a plateau.

Though stress increases the prolactin level, a number of investigations have concluded that venepuncture rarely induces prolactin release.

Studies have shown that prolactin levels vary depending upon the phase of menstrual cycle. In the present study since blood samples are taken only in the follicular phase of the premenopausal subjects, the difference found in prolactin level cannot be attributed to the phase of menstrual cycle.

Similarly because the blood sample is taken prior to any treatment, the difference in the level cannot be attributed to surgery induced increased prolactin level or chemotherapy or Hormonal therapy induced suppression of prolactin level. Also studies show that routine breast examination does not alter serum prolactin level. Though artefactual high Prolactin levels may occur due to pulsatile release, number of investigations have concluded that frequent sampling does not improve the value of a result. These studies suggest that the result of the single estimate of prolactin level in the present study may be viewed with confidence.

Within the last few years however, with the advent in molecular biology several studies have supported the role of prolactin in fibroadenoma. Prolactin secretion, in the tumor initiation phase influences the metabolism of mammary epithelium by increasing its sensitivity to carcinogens and later directly acting as a promoter of transformed epithelium.

Prolactin alters progesterone and estrogen ratios and increases the expression of estrogen receptors in mammary gland. Estrogen replacement therapy increased the risk of fibroadenoma by potentiating the proliferation of mammary epithelial tissue by prolactin. Also increased estrogen increases plasma prolactin levels, which in turn interact with estradiol to cause mammary gland hypertrophy.

Recent studies have reported that prolactin is also synthesized and secreted by mammary epithelial cells. There is an autocrine / paracrine loop of action of prolactin to promote breast tumor. Hence another possible mechanism that can lead to tumor breast might include local over expression of prolactin inducing morphological and functional defects in mammary gland in the presence of normal serum prolactin. That might be the reason...
Dopamine agonists fail to show clinical improvement in patients with progressing tumor.

Also studies have shown that prolactin receptor antagonists inhibit the growth of breast cancer cell lines confirming the fact that prolactin receptors are up regulated in tumor breast cell lines and also functional mutation occurs in prolactin receptors.\(^{24,25,26}\)

Prolactin also promotes tumor growth by modulating cell cycle regulators in mammary tumor cells and by stimulating angiogenesis.\(^{27}\)

Another interesting observation made in mouse mammary glands is that prolactin promotes tumor growth by its anti apoptotic action via STAT 5.\(^{28}\)

At, genetic level it was shown that prolactin gene disruption arrests mammary gland development and retards tumor growth.\(^{29}\)

The role of prolactin in fibroadenoma is still controversial. A better understanding of genetic and molecular characteristics of prolactin is needed to aid treatment.

**CONCLUSION:**

In this study, there is no significant elevation of serum prolactin levels in fibroadenoma breast when compared to normal. As the number of cases are few to give an effective interpretation, a thorough investigation in future is required with more number of patients. This could open potential therapeutic approaches for fibroadenoma. A still thorough understanding of the role of prolactin and its receptor in tumorigenesis is needed. Parameters like the duration of hormone exposure, involved target tissue and genetic background should also be studied for understanding the tumorigenic effects of prolactin.

**REFERENCES**


