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Serum Protein and Prolactin in Evaluation of Uterine Fibroids

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ABSTRACT

Background: uterine fibroid (leiomyoma) is the most common benign uterine tumors in women of reproductive age. The majority of leiomyomas are asymptomatic, however up to 20% cause menorrhagia, pelvic pain and genitourinary symptoms.

Objective: the aim of the study was to evaluate using of total protein or serum prolactin as a marker for evaluation and follow up of uterine leiomyomas.

Patients and Methods: a randomized, controlled clinical trial study design was utilized to prove the relation between uterine fibroid and serum prolactin and serum protein. The study was performed at Obstetrics and Gynecology Department in AL Hussein Hospital. 100 females have myoma of different sizes are included in this research.

Results: it was concluded that serum total protein and albumin levels in patients with elevated serum TNF levels were significantly lower ($p < 0.05$) than the corresponding values in patients with undetectable serum TNF levels. The study concluded that prolactin (PRL) levels are decreased following surgical therapy in patients with uterine fibroids. In addition, a slight increase in serum total protein was detected after surgery in uterine patients.

Conclusion: in conclusion, a highly significant correlation was found between serum PRL and its ratio with serum total protein. This result ensured and supported the relation between the patient's serum PRL and serum total protein with their fibroid number. This enables to suggest these variables as a simple biochemical marker supporting other clinical findings.

Keywords: Serum protein, Prolactin, Uterine fibroids.

INTRODUCTION

Uterine leiomyomas are benign tumors affecting up to 60% to 80% of reproductive aged women. The majority of leiomyomas are asymptomatic, however up to 20% cause menorrhagia, pelvic pain, and genitourinary symptoms [(1)]. Leiomyomas grow in the presence of gonadal steroids, disproportionally affect women of African descent and are associated with 10% of infertility cases. The diagnosis of uterine fibroids is usually achieved through radiographic modalities or surgical procedures [(2)]. The sensitivities and specificities of available diagnostic tools vary; currently, they range from 50% and 20% for hysterosalpingogram (HSG), 90% and 87% for transvaginal ultrasound, and approach 100% for magnetic resonance imaging (MRI)[(3)].

Biomarkers are biologic compounds that can be obtained from the serum or other easily accessible tissue. They are a reflection of normal physiology or a pathologic process. They are useful in a variety of clinical situations that involve detection of subclinical disease, risk stratification, preoperative planning, treatment monitoring, and diagnosis. Serum biomarkers for uterine leiomyomas that accurately diagnose, differentiate, or monitor response to therapy are currently absent from the clinician's arsenal [(4)].

Potential biomarkers

Prolactin

Prolactin is a protein hormone involved in a variety of mammalian physiologic actions such as lactogenesis. Prolactin mediates its function by interacting with type-1 cytokine receptors and signals through Janus kinase, signal transducers, and activators of transcription (JAK/STAT) pathways. Although, it is isolated as a pituitary hormone, prolactin is expressed in other tissues including uterine leiomyomas [(5)].

Total Protein:

Serum total protein test measures the total amount of albumin and globulin in the blood. Values below the normal threshold usually are associated with nutritional deficiency, liver and kidney disease or prolonged hemorrhage or anemia. Elevated total protein values can be a marker of chronic inflammation or malignancies such as multiple myeloma. In a prospective trial examining total protein as a biomarker for uterine leiomyomas, the serum total protein level was lower in patients with uterine fibroids before they underwent hysterectomy for leiomyomas or myomectomy [(6)].

AIM OF THE WORK

The aim of the study was to evaluate using of total protein or serum prolactin as a marker for evaluation and follow up of uterine leiomyomas.

PATIENTS and METHODS

Design of study: A randomized, controlled clinical trial study design was utilized to prove the relation between uterine fibroid and serum prolactin and serum protein.

Setting of study: The study was performed at Obstetrics and Gynecology Department in AL Hussein University Hospital.

Population of study: 100 females have myomas of different sizes are included in this research.

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Inclusion criteria: All cases were collected from Outpatient Clinic of Obstetrics and Gynecology Department at ALHussien University Hospital and diagnosed to have myoma and do not have causes of hyperprolactinemia.

Exclusion criteria

Other causes of hyperprolactinemia as:

1-Prolactinoma 2- Physiological - hypersecretion as pregnancy

3-Acromegaly 4-Hypothyroidism

5-Chronic renal failure 6-Cirrhosis

7-Epilepsy 8-Some drugs as Calcium channel blockers.

Steps of study

1-Consent: written consent was singed and **approval of the University Ethical Committee.**

2-Complete history taking include:

- Personal history (age, residence, job)
- Complain
- Menstrual history (age of menarche, type and duration of menstrual irregularity)
- Family history.

3-Clinical examination:

- general examination (body built, weight, blood pressure, pulse).
- abdominal examination.
- local examination.

4 –Ultrasound examination

- abdominal ultrasound
- vaginal ultrasound

5-Laboratory examination:

a –Preoperative total protein and prolactin

b –Investigations for preparation of patient for the operation

(C.B.C-liver function-kidney function- coagulation profile)

6-Making the operation (myomectomy or hysterectomy).

7-Examination of serum protein and prolactin after 2 weeks of the operation

8-Comparing the level of serum protein and prolactin before and after the operation.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)

- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

The mean standard error (mean ± SE) of the patient's serum PRL before surgery (n=48) was 169.64 ± 133.11 ng/ml, which was higher than after surgery (19.69 ± 9.54 ng/ml), and higher than in healthy normal women (18.6 ± 2.3 ng/ml) (n=48).

There was a decrease in the patient's total serum protein (5.56 ± 9.66) before surgery, compared to total serum protein in the controls (18.93 ± 5.16 ng/ml), and after surgery (19.69 ± 9.54ng/ml).

The mean ± SE size of fibroids harvested from different uterine patient's sites was 28.52 ± 27.64 cm3. Only 6 out of 48(12.5%) uterine fibroid patients had normal serum PRL levels although their fibroid sizes ranged from 1-100 cm3. The remaining 42 patients (87.5%) all had high levels of PRL in their serum and so were considered as nonpituitary hyperprolactinemic. Their fibroid sizes ranged from 0.09-280 cm3 (Table 1**).**

Table (1): Serum prolactin level among patients' group with their size of fibroids

Serum prolactin, ng/ml	n%	Range of fibroids size (cm^3)
35≤	6(12.5)	1-100
>35	42(87.5)	0.09-280
Total	48(100)	

As shown in **table (2),** the highest percentage of uterine fibroids is found in (30-39) years while the lowest percentage in (20-29) years.

Table (2): Relation between uterine fibroid and age of patients

Age (years)	Number of patients	Percentage (%)
20-29	2	3
30-39	23	48
40-49	19	41
50≤	4	8
Total	48	100

As shown in table (3), the patient's serum PRL gradually increased with the number of uterine fibroids. The lowest mean ± SE level of serum PRL was found in patients with one fibroid, while the highest mean ± SE was found in patients with 5 fibroids.

Table (3): Range of serum prolactin (PRL) level in patient group (n=48) according to their fibroid(s) number

Number of fibroids	N	%	Serum PRL standard error
1	21	43.7	141.78±14.39
2	13	27	160.48±13.2
3	6	12.5	189.8±34.53
4	5	10.4	512.34±38.85
5	3	6.4	554.4±41.75

Women with no pregnancy had high risk for uterine fibroids more than women having history of pregnancy as shown in table (4).

Table (4): Relation of parity and uterine fibroids

Parity	Number of patients	Percentage (%)
0	29	60.4
1	12	25
2	5	10.4
3	1	2.1
4≥	1	2.1

Table (5) illustrated the significance between serum PRL and total serum proteins before and after surgery.

Table (5): One-way analysis of variance for prolactin and total protein in patient serum before and after surgery.

Protein	Mean ± SE	95%CI	P-value
Before surgery			
Serum PRL	169.64 ± 13.11	123.82-183.34	0.0001
Total serum protein	5.56 ± 1.66	5.38-5.77	0.0001
After surgery			
Serum PRL	19.69 ± 1.54	17.50-21.76	0.0001
Total serum protien	6.83 ± 0.9	6.68-7.06	0.0001

CI: confidence interval.

A positive correlation with positive linear regression equations was found between serum PRL and total serum protein before and after surgery as shown in figures (1 and 2).

To ensure these correlations before and after surgery, a positive linear regression, and correlations also were found between serum prolactin and its ratios with serum total protein before and after surgery (figures 3 and 4).

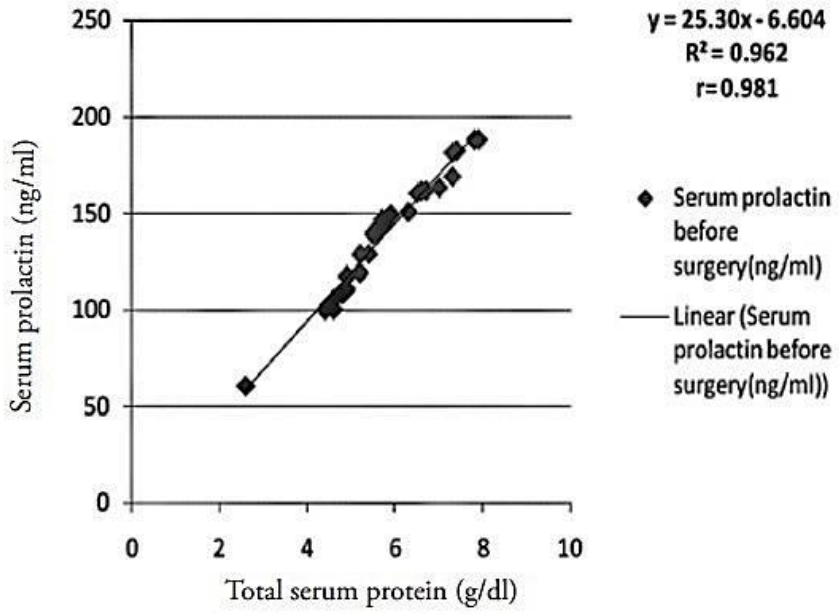

Figure (1): Linear regression between serum prolactin and total serum protein before surgery.

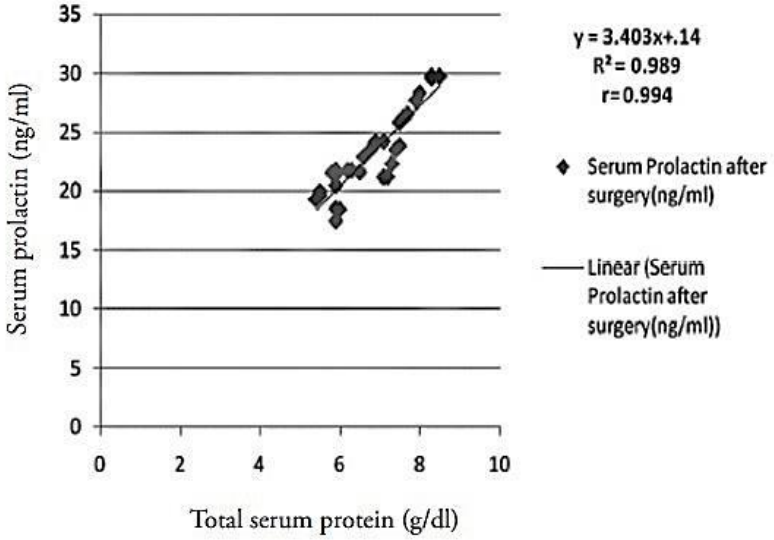

Figure (2): Linear regression between serum prolactin and total serum protein after surgery

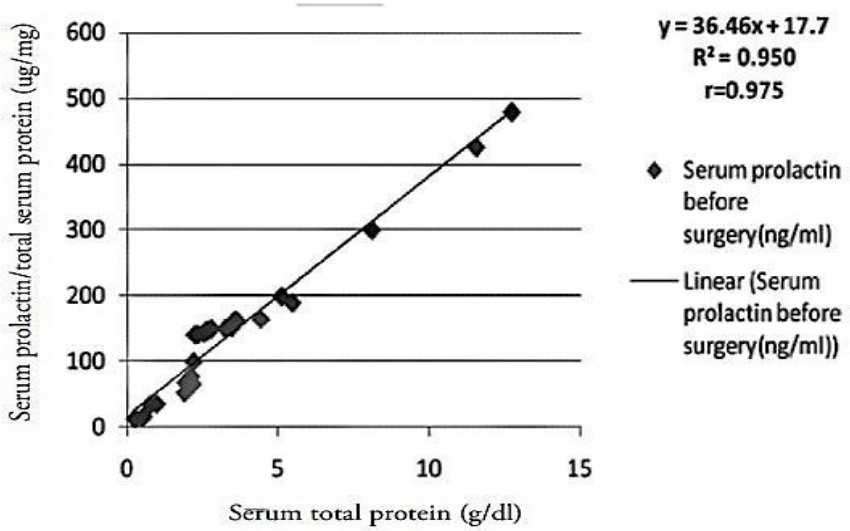

Figure (3): Linear regression between serum prolactin and its ratios with serum total protein before surgery

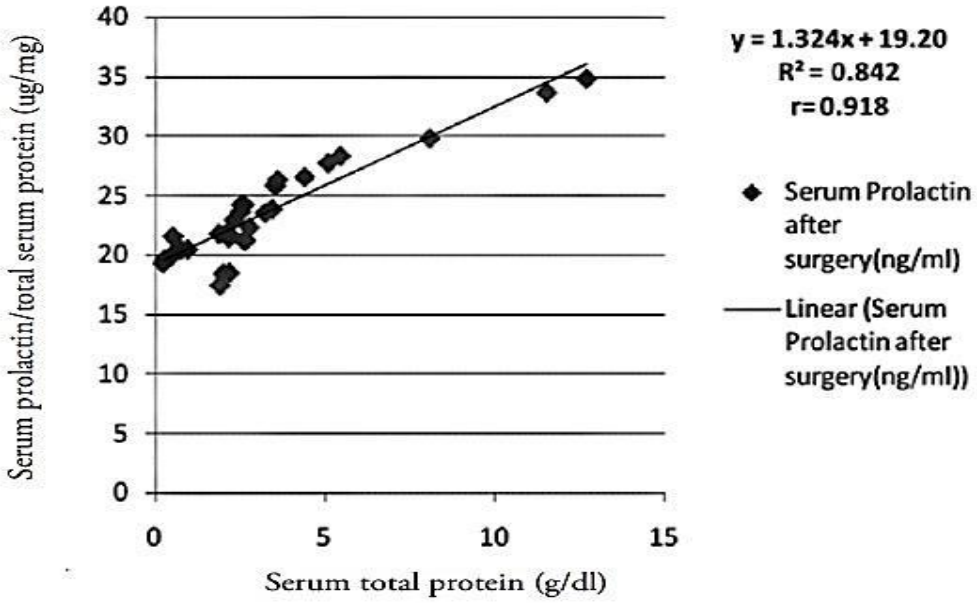

Figure (4): Linear regression between serum prolactin and its ratios with serum total protein after surgery.

DISCUSSION

In recent years, magnetic resonance imaging (MRI) has gained popularity. However, it does not add clinically relevant information in most cases. Ultrasonography appears to be as efficient as MRI in fibroid detection, and essentially as good for assessing their size and location, if the uteri have less than 5 lesions. Conversely, when the number of lesions is higher, the MRI exceeds the ultrasound's technical limitation in precise fibroid mapping and characterization [7].

Many studies revealed that the clinical accuracy of tumor markers could be increased by analyzing a panel of markers. Currently, no such panel for cancer exists. Monitoring assays that may increase the clinical accuracy of patients in panels include: tumor markers (currently used in diagnostics), hormones (indicators of patient health), heat shock proteins (indicators of general or systemic stress), and auto-antibodies (indicators of immune system activity or stress**) [8].**

Prolactin hormone is not secreted from anterior pituitary only, but there are different sites for its secretion as from hypothalamus, placenta, amnion, decidua and uterine muscle. Prolactin can be detected in epithelial cell of lactating mammary gland as well as milk itself **[9].** In addition to the decidualized endometrium of the late luteal phase and of pregnancy, the human myometrium has been proposed as a second source of uterine PRL, since immunoreactive PRL was found in supernatants from myometrial explant cultures.

The aim of this study was to investigate the possible relationship between circulating levels of PRL and total protein with uterine fibroid, and the possibility of these parameters to be used as a diagnostic marker.

First, it should be mentioned that the only limitation faced in this study was following up patients after surgery. The follow up is dependent basically upon patient cooperation, and so only such cooperative patients were included in this study.

Prolactin have been shown to be raised in certain group of patients with cancer **[10].** It also was concluded that surgical removal of cervical carcinoma resulted in normalization of serum PRL concentrations. This explains the increase of PRL concentration level in the patients, and the decline in their levels to a normal level after surgery. Prolactin can function as a circulating hormone and as a cytokine. The explanation of this function is based on PRL production and its distinct regulation in extrapituitary sites, its binding to membrane receptors of the cytokine receptor super family and activation of signaling pathways that promote cell growth and survival. Many studies showed an increasing evidence that PRL plays a role in several types of cancer in the reproductive and non-reproductive tissues via local production or accumulation. Considering PRL as an active participant in tumorigenesis should inspire and encourage the development of novel therapies aimed at reducing tumor growth by suppressing PRL production, or by blocking its receptors [11].

A case control study was carried out from March 2004 to October 2005 at Al-Kharch Hospital in Baghdad, Iraq. Thirty-two patients with uterine fibroid(s) and 30 healthy normal women were involved in the study. Blood was collected from uterine fibroid patients before and after surgery. The serum of patients with uterine fibroids before surgery showed an elevated prolactin level (169.64 ± 133.11 ng/ml) compared to their prolactin after surgery (19.69 ± 9.54 ng/ml) and to control group (18.93 ± 5.16 ng/ml). This also increased with increasing fibroid number independently of the site, or the size of the fibroid. Serum total protein was relatively low in the patient group before surgery (5.56 ± 9.66 g/dl), and returned to a healthy reference level after they underwent surgery (6.83 ± 0.9 g/dl), similar to the control group level (7.18 ± 0.75 g/dl**) [12].** Patients with elevated serum PRL levels were considered as non-pituitary hyperprolactinemic as shown in **(Table 1**). This elevated level of serum PRL was significantly decreased ($p < 0.0001$) after surgery **(Table 6)**.

The study concluded that PRL levels are decreased following surgical therapy in patients with uterine fibroids.

It was also concluded that serum total protein and albumin levels in patients with elevated serum TNF levels were significantly lower ($p < 0.05$) than the corresponding values in patients with undetectable serum TNF levels [13].

Uterine leiomyoma patients in this study showed a decrease in their total serum proteins compared to the same variable of normal healthy women (controls). An increase in serum total protein was detected after surgery in uterine patients with highly significant value ($p < 0.0001$) as shown in table (5).

Another study reported that changes in protein quantities or specific modifications could be discovered by comparing the complement of proteins expressed in a diseased state with proteins expressed in a normal state. The relevance of proteomics to disease biomarker discovery lies in the fact that proteins constitute the final form of gene expression and that the function or dysfunction of a protein and the pathways that it participates in are often dependent on post-translational modifications that are not reflected in changes in mRNA expression **[14].**

CONCLUSION

In conclusion, a highly significant correlation was found between serum PRL and its ratio with serum total protein. This result will ensure and support the relation between the patient's serum PRL, total serum protein with their fibroid number, enabling to suggest these variables as a simple biochemical marker supporting other clinical findings.

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