Prolactin and adequacy of dialysis

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Abstract: Hyperprolactinemia is a common endocrinal alteration in chronic renal failure, Several investigators examined the serum concentration of prolactin in patients with chronic renal failure and found it to be elevated. The aim of the study: is to evaluate the relation between adequacy of dialysis and levels of serum Prolactin in long term hemodialysis patients, in order to clarify if adequate dialysis adds a benefit in lowering Prolactin levels. Method: Thirty Patients with chronic renal failure (males aged 35 to 70) who participated in this study were maintained on hemodialysis 3 times/week, 4 hours each session. Dialyser membranes were 1.4 m^2 low flux Baxter. Duration of dialysis was more than 5 years for all patients Results: Our study revealed a statistically significant negative correlation between serum prolactin level and URR, i.e. the better the dialysis adequacy the less the serum prolactin level. Conclusion: As increasing dialysis adequacy would improve hyperparathyroidism, erythropoietin sensitivity and clearance of uremic toxins, this could all contribute to improved prolactin profile.
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1. Introduction

Hyperprolactinemia is a common endocrinal alteration in chronic renal failure. Its prevalence ranges from 30% to 65% being mainly the consequence of reduced renal clearance but also increased production due to altered dopaminergic activity [1]. Prolactin (PRL) levels predicted major cardiovascular events and gynecomastia in men, therefore uremia-induced hyperprolactinemia may relate to the increased CVD risk of this patient population[2, 3].

Several investigators examined the serum concentration of prolactin in patients with chronic renal failure and found it to be elevated [4, 5]. Prolactin secretion is regulated by the hypothalamus[6, 7], and hypothalamic abnormalities have recently been demonstrated in patients on chronic hemodialysis [8, 9].

Also, in the presence of chronic renal failure, the physiological oscillations of serum PRL levels diminish, and the circadian rhythm of PRL secretion progressively disappears[10]. In addition to the abnormal regulation of PRL secretion, PRL has a longer half-life and a lower metabolic clearance rate in the circulation of patients with CKD [11, 12]. The latter may be due to impaired renal degradation, which is significant in the healthy kidney as the PRL concentration in the renal vein is approximately 16% lower than in the renal artery[13].

Hypogonadism (testosterone deficiency) is the most common gonadal alteration in men with renal failure, mainly because of uremic inhibition of luteinizing hormone signaling at the level of the Leyding cells and hyperprolactinemia [14].

Aim of study:

The aim of the present study is to evaluate the relation between adequacy of dialysis and levels of serum Prolactin in long term hemodialysis patients, in order to clarify if adequate dialysis adds a benefit in lowering Prolactin levels.

Material and methods:

Thirty Patients with chronic renal failure (males aged 35 to 70) who participated in this study were maintained on hemodialysis 3 times/week, 4 hours each session. Dialyser membranes were 1.4 m^2 low flux Baxter. Duration of dialysis was more than 5 years for all patients. All the patients were not receiving medications known to affect prolactin levels.

All patients were subjected to the following:

1- Complete history and physical examination.

2- Routine laboratory investigations complete blood count,, serum urea, serum creatinine, serum calcium and serum Phosphorus.

3- Urea reduction ratio (URR):

U_{post} subtracted from U_{pre} devided by U_{pre} X 100.

Where:

- U_{pre} is the pre-dialysis urea level
- U_{post} is the post-dialysis urea level

4- Prolactin**:** serum level of prolactin was measured by using (TOSOH Bioscience automated immunoassay analyzer AIA-360). Principle the ST AIA-PACK PRL is a two site immunoenzymometric assay which was performed entirely in the ST AIA-PACK PRL test cups, prolactin present in the test sample was bound with monoclonal antibody

immobilized on a magnetic solid phase and enzyme labeled monoclonal antibody in the test cups, the magnetic beads were washed to remove unbound enzyme labeled monoclonal antibody and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP) the amount of enzyme labeled monoclonal antibody that binds to the beads is directly proportional to the prolactin concentration in the test sample then absorbance measured at 450 nm. Concentration of the prolactin was calculated by standard curve.

3. Results

Table 1: Correlation between serum prolactin and Urr % and different parameters in the studied group.

	Urr%		**Prolactin**	
	r	***p value***	***r***	***p value***
Urr%	---	---	-0.875	0.001*
Prolactin	-0.875	0.001*	---	---
Age	0.006	0.975	0.027	0.888
Duration	-0.159	0.401	0.051	0.789
BMI	-0.153	0.421	0.116	0.541
Ca	0.197	0.297	-0.194	0.304
Ph	-0.113	0.552	0.116	0.543
Creatinine	0.123	0.516	-0.160	0.397
Hb	0.171	0.367	-0.247	0.188

r= Spearman's Rank correlation coefficient.
*p< 0.05= significant.

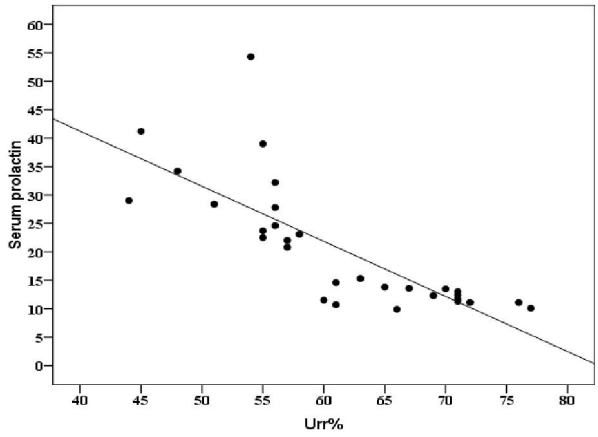

Figure 1: Correlation between serum prolactin and Urr % in the studied patients (-0.875; p= 0.001).

The participants were all male patients (n=30) (aged 35-70). They were maintained on hemodialysis 3 times/week, 4 hours each session. Dialyser membranes were 1.4 m^2 low flux Gambro. Duration of dialysis was more than 5 years for all patients. All the patients were not receiving medications known to affect prolactin level.

There was a statistically significant negative correlation between serum prolactin level and URR.

Statistical analysis

Correlation between serum prolactin and Urr % and different parameters in patient group was performed using Spearman's Rank correlation coefficient. SPSS computer program (version 19 windows) was used for data analysis. P value ≤ 0.05 was considered significant.

4. Discussion

Abnormalities of the hypothalamo-pituitary-gonadal axis are a common finding in end stage renal disease. Males have decreased testosterone (total and free) levels, due to lack of its production by Leyding cells, which is caused by uremic toxins. LH hormone is increased due to lack of negative feedback by testosterone. FSH hormone is increased due to lack of negative feedback by inhibin (a hormone produced by Sertoli cells in seminiferous tubules). The LH/FSH ratio is increased [15]. Elevated prolactin hormone levels have long been documented in chronic kidney disease (CKD).

Theories exist for this finding. Palmer BF (1999) stated that this is primarily caused by an increase in its production rather than by decreased clearance. Furthermore he explained that PRL production in CKD is autonomous, resistant to maneuvers which would normally cause its stimulation or inhibition. This is proved by the fact that PRL in CKD patients is neither inhibited by a dopamine infusion, nor is it stimulated by e.g. insulin-induced hypoglycemia, both being measures which would have caused significant decrease or increase in PRL levels in normal subjects respectively. Suggested explanations for increased prolacrin production in CKD include hyperparathyroidism and zinc stores depletion.[16] Another explanation for the increased PRL levels in CKD patients is the decreased renal clearance, which was supported by Yavuz, Dilek (2005)[17]

Our study revealed a statistically significant negative correlation between serum prolactin level and URR, i.e. the better the dialysis adequacy the less the serum prolactin level.

Since prolactin is a 23000D hormone, it is considered a middle molecule, not cleared by low flux membranes used in our study. It could only be cleared by high flux membranes. We found however a significant negative correlation between serum prolactin level and URR of our patients, which we could explain by the fact that improvement of uremic milieu is associated with decreased prolactin production.

Since prolactin has been associated with endothelial dysfunction and increased risk of cardiovascular events [1], it is important to study

mechanisms by which hyperprolactinemia can be improved. Using high flux hemodialysis membranes in online-HDF is one method, even shifting to daily online-HDF instead of standard three times weekly [18], however using low flux membranes in economically challenged countries like our own, could still affect the prolactin hormone clearance, if dialysis adequacy could be improved. As increasing dialysis adequacy would improve hyperparathyroidism, erythropoietin sensitivity and clearance of uremic toxins, this could all contribute to improved prolactin profile.

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