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Study on Effect of Imatinib Therapy on Pituitary Hormones (LH, FSH and Prolactin) In Newly Diagnosed CML Patients

Prakash G[1], Dokwal S[2], Bansal P[3], Prashant P[3], Ghalaut VS[2], Bala M[2], Ghalaut PS[4]

[1]Department of Biochemistry, SHKM Medical College, Mewat, Nalhar, Haryana 122107, India
[2]Department of Biochemistry, PGIMS Rohtak, SH 16A, Haryana 124514, India
[3]Department of Biochemistry, Bhagat Phool Singh Medical College (BPSGMC), Ganaur - Gohana Rd, Khanpur Kalan, Haryana 131305, India
[4]Department of Medicine, PGIMS Rohtak, SH 16A, Haryana 124514, India

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***Corresponding author:** Dr. Sumit Dokwal

Abstract **Original Research Article**

Chronic myelogenous leukemia is characterized by the fusion gene BCR-ABL, encoding a constitutively active tyrosine kinase and treated by the tyrosine kinase inhibitor imatinib. Some case reports in literature suggest imatinib therapy may alter the pituitary hormones LH, FSH and prolactin levels affecting various functions of reproductive system. The study was designed to prospectively study serum LH, FSH and prolactin levels at baseline and at 6 months of imatinib treatment in 30 newly diagnosed BCR-ABL positive CML patients. The hormones were measured a highly accurate two-site sandwich immunoassay using chemiluminisence method on ADVIA Centaur system from Siemens. Of the 30 CML patients (17M & 13F), 2 patients presented in accelerated phase and 26 achieved haematological remission by 6 months. Baseline levels of LH, FSH and prolactin were similar in patients and controls. S. LH levels increased significantly after 6 months of imatinib therapy in male patients (13.82±4.25mIU/mL vs. 7.32±3.84mIU/mL, p =0.001) and in female patients (12.67±4.74mIU/mL vs.7.16±3.94mIU/mL, p =0.002). S. FSH levels increased significantly after 6 months of imatinib therapy in male patients (22.30±8.74mIU/mL vs. 11.77±7.23mIU/mL, p =0.003) and also in female patients (12.57±4.94mIU/mL vs. 5.51±1.82mIU/mL, p=0.005). Serum prolactin levels decreased significantly after 6 months of imatinib therapy in male patients (10.93±7.77ng/mL vs. 14.21±12.68ng/mL, p=0.039). Baseline levels of LH, FSH and prolactin were similar in patients and controls. The findings of significantly increased LH and FSH levels after imatinib therapy the present study are consistent with the previous reports that document the effect of imatinib on testicular function in adult male patients. The findings of significant increase in LH and FSH levels in pre-menopausal females in present study suggests that further studies on lager number of female patients are required to fully assess the effects of imatinib on multiple female reproductive hormones and their clinical significance.

Keywords: CML, Imatinib, LH, FSH, Prolactin.

INTRODUCTION

CML: Chronic myelogenous leukemia is characterized by the fusion gene BCR-ABL, encoding a constitutively active tyrosine kinase [1, 2]. CML usually is diagnosed in the chronic phase (CP) but patients may also present in accelrataed phase (AP) or blast crisis (BC) which mimics acute leukemia where the percentage of blasts in peripheral blood is increased to more than 10% and 20 % respectively. Untreated chronic phase patients can evolve into BC in a median time of 4 years [3]. CML is treated by the tyrosine kinase inhibitor, Imatinib mesylate, which competitively inhibits ABL kinase at the ATP binding site. This stops the signal transduction of BCR-ABL leading to apoptosis of the malignant cells [4, 5]. The goal of imatinib therapy is to decrease the cells bearing the t(9;22) translocation (leukemic cells) to the lowest levels possible (BCR-ABL/ABL expression ratio <0.05% by 18 months of therapy), under which conditions normal (polyclonal) haematopoiesis is restored [1]. However imatinib has been shown to inhibit other tyrosine kinases like platelet derived growth factor receptor-α (PDGFR-α), PDGFR-β, c-Fms, Arg and c-kit (stem cell factor receptor) also. This may be responsible for some of the side effects and endocrine disturbances. Effects of imatinib on multiple endocrine hormones are now being recognized and may affect quality of life in the CML patients [6].

LH and FSH in Females

LH and FSH are pituitary hormones responsible for normal reproductive and menstrual function. Theoretically it can be postulated that as the kinases that are inhibited by imatinib (c-kit, c-abl, and platelet-derived growth factor receptor) are expressed in mammalian ovaries and appear to be important in multiple aspects of the growth and development of oocytes and follicles, imatinib therapy may have multiple effects on these hormones and ovarian function [7]. Yaghmaei et al., described in female Wistar rats, that after imatinib exposure FSH concentrations were decreased significantly, and LH concentration decreased but was not statistically significant [8]. Christopoulos et al., reported the development of ovarian insufficiency in a 28 year old woman who was treated with imatinib for CML [7]. Though ovarian failure is not a recognized complication of imatinib treatment, and successful conception and pregnancy have occurred in women receiving the drug, conflicting reports in literature suggest lack of clarity on effect of imatinib therapy on LH and FSH levels.

LH and FSH in Males

Yaghmaei *et al*., investigating the effects of Imatinib on male fertility in Wistar rats described that LH and FSH increased significantly, and the number of sperm in both the epididymis and sertoli cells decreased [9]. Nurmio *et al*., investigated the effect of short postnatal imatinib exposure on fertility of the male rats and offspring of these animals and found that the plasma levels of LH and FSH were also elevated in these animals, suggesting the action of compensatory mechanisms designed to maintain normal testicular function [6]. Mariani *et al.*, reported increased FSH levels during long-term treatment with imatinib started before the onset of puberty in an 18-year-old man along with severe oligozoospermia [10]. These reports suggest LH and FSH levels worth investigating in patients on imatinib therapy.

Prolactin

Normal leukocytes and bone marrow stromal cells express variable levels of prolactin depending on the differentiation and activation stage [11, 12]. Prolactin has been considered as haemopoietic growth factors and exert immunomodulatory functions at physiological concentrations [11]. Prolactin is also known to have number of redundant effects on the immune system. Mavoungou et al., demonstrated that prolactin up-regulates and cortisol down-regulates the surface expression of NKp46 and NKp30 (triggering receptors responsible for natural killer (NK) cell-mediated cytotoxicity) on K562, a human chronic myelogenous leukaemia cell line. Prolactin dramatically increased the NK-mediated killing of the K562 cell line, whereas cortisol abolished this activity [13]. Expression of prolactin has been demonstrated in several transformed hematopoietic cell lines. Scarce data exist regarding the production of PRL by myeloid leukaemia cells [12]. A moderate increase in serum PRL levels has been reported in 16 patients with AML out of 28 in one study [14]. Mulashi et al., reported occurrence of hyper-prolactinemia as a paraneoplastic phenomenon in AML [15]. There is a lack of reports on serum level of prolactin in CML patients and effect of imatinib on it.

METHODOLOGY

The study was a prospective, nonrandomized, observational study conducted on 30 newly diagnosed patients of CML (17 males and 13 females) in chronic phase. Thirty age and sex matched healthy controls (17 males and 13 females) were also taken. Patients were recruited from the Haematology clinic in Post Graduate Institute of Medical Sciences, Rohtak, Haryana after taking informed consent. Ethical approval was obtained from the institutional board of studies. Diagnosis was made by history, clinical examination, total and differential leukocyte count, and bone marrow examination and further confirmed by real-time PCR for BCR-ABL fusion transcript. Exclusion criteria: patients with other acute or chronic co-morbidities like liver and kidney diseases, reproductive system disorders, endocrine disorders, other malignancies, CML-blast crisis, chronic infections like tuberculosis, etc. and those taking any other medication besides imatinib and haematinics (folic acid, vitamin B12, vitamin B6, iron, etc.) were excluded. Imatinib therapy was given initially in a dosage of 400 mg/day and increased to 600 mg/day or to 800 mg/day (400 mg every 12 h), if required and tolerated [2, 4]. Haematological remission criteria were used for evaluation of response and were defined as total leukocyte count<$10X10^9$/l, platelet count < $450X10^9$/l, no immature myeloid cells in the blood, disappearance of all signs and symptoms related to leukaemia (including palpable splenomegaly) lasting for at least 4 weeks [4, 5]. Serum LH, FSH, prolactin, routine biochemical investigations and other relevant investigations were done at the time of diagnosis (baseline) and in controls. LH, FSH and prolactin levels and other tests were repeated at 6 months or first complete remission (whichever is earlier) in CML patients.

LH, FSH and Prolactin Estimation

For estimation of LH and FSH in pre-menopausal females samples were taken in the follicular phase (day 2-5 of menstrual cycle) [16]. For biochemical testing fasting early morning venous blood sample was taken in a plain red capped evacuated blood collection tube under all aseptic precautions. Samples were processed within one hour of collection. Serum was separated by centrifugation at 3000 rpm X 10 minutes after clotting. Levels were estimated on same day of sample collection as far as possible. Sample was stored at -20^0C in a deep freezer if analysis was not possible on same day. Levels were estimated by a chemiluminisence method on ADVIA Centaur system from Siemens. All three hormones are measured by

highly accurate two-site sandwich immunoassay using direct chemiluminometric technology [17-19]. Appropriate quality controls were also used.

Statistical Analysis

The data were compiled and subject to statistical analysis using SPSS v20. Baseline and post-therapy values were compared using Wilcoxon signed rank test. Comparison of data between groups was done using Mann Whitney Test for quantitative data and Chi-square test for qualitative data. Correlations and regression between groups were analyzed using suitable models. Spearman's correlation coefficient (r) formula was used to assess correlations.

OBSERVATIONS

Patient Characteristics

During the study 33 patients enrolled of which 3 were excluded due to diagnosis of blast crisis. Mean age at diagnosis was 39.5±12.7 years and was comparable with mean age of controls (37.2±11.1 years). Median duration of history of presenting illness was 6 weeks in CML patients. 10% patients were asymptomatic and diagnosed incidentally on routine lab examination. 2 (6.7%) patients presented with accelerated phase of disease (blast count 10-20%). 26 patients (87.7%) achieved remission at 6 month of imatinib therapy while 4 (13.3%) patients were not in haematological remission. None of the patients had any significant side effect form imatinib therapy to warrant dose reduction or discontinuation. Clinical and hematological features at diagnosis are summarized in Table-1.

Table-1: Clinical and hematological features at diagnosis in CML patients

	CML (n=30)
Median Duration	6 weeks (asymptomatic – 3)
Fever	21 (70%)
Weakness	27 (90%)
H/o Bleeding	3 (10%)
Spleenomegaly	22 (73.3%)
Hepatomegaly	18 (60%)
Lymphadenopathy	1 (3.3%)
Median Hb	8.5 g/dL
Median TLC	75,000 / cu.mm
Median Platelet count	3,00,000 / cu.mm
Median Blast%	5.5 %

Table-2: Comparison of mean ±SD S. LH, FSH and Prolactin levels in CML patients with controls

		CML PATIENTS	**CONTROLS**	**p value**
LH# (mIU/mL)	**M(17)**	7.32 ± 3.84	6.85 ± 3.80	0.838
	F(10)	7.16 ± 3.94	7.08 ± 4.48	0.973
FSH# (mIU/mL)	**M(17)**	11.77 ± 7.23	10.72 ± 6.65	0.734
	F(10)	5.51 ± 1.82	6.91 ± 3.65	0.426
PROLACTIN (ng/mL)	**M(17)**	14.21 ± 12.68	10.50 ± 6.19	0.658
	F(13)	21.70 ± 27.43	18.42 ± 9.17	0.264

LH & FSH were compared in premenopausal females (patients:10, Controls: 11).

S. LH levels were 7.32±3.84 mIU/mL in male and 7.16±3.94 mIU/mL in premenopausal female patients. Levels were 6.85±3.80 mIU/mL and 7.08±4.48 mIU/mL in respective controls. The difference was not statistically significant (Table-2 & Figure-1). S. FSH levels were 11.77±7.23 mIU/mL in male and 5.51±1.82 mIU/mL in premenopausal female patients. Levels were 10.72±6.65 mIU/mL and 6.91±3.65 mIU/mL in respective controls. The difference was not statistically significant (Table-2 & Figure-2). LH & FSH Levels in post-menopausal female patients (n=3) were 37.41±15.43 mIU/mL and 39.15±24.76 mIU/mL. Levels were in controls (n=2) were 38.56±10.4 and 55.35±14.18 mIU/mL respectively (LH: p = 1.0, FSH: p = 0.400). Serum prolactin levels were 14.21±12.68 ng/mL in male patients as compared to 10.50± 6.19 ng/mL in controls. The difference was not significant. Serum prolactin levels were 21.70±27.43 ng/mL in female patients as compared to 18.41± 9.17 ng/mL in controls. The difference was not significant (Table-2 & Figure-3).

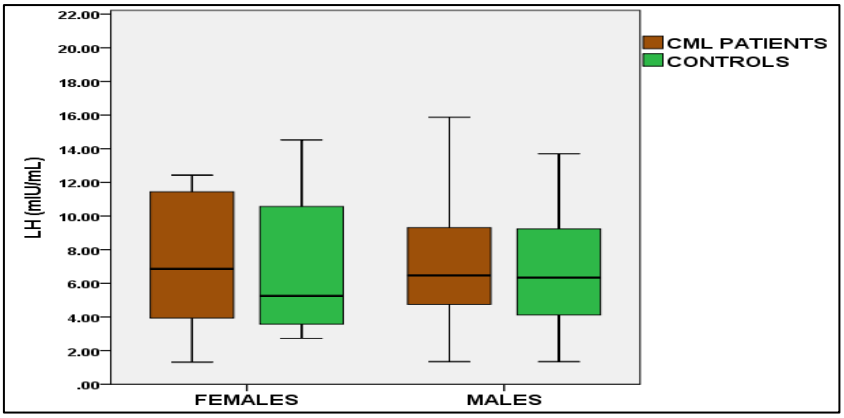

Fig-1: Serum LH levels in CML patients and controls

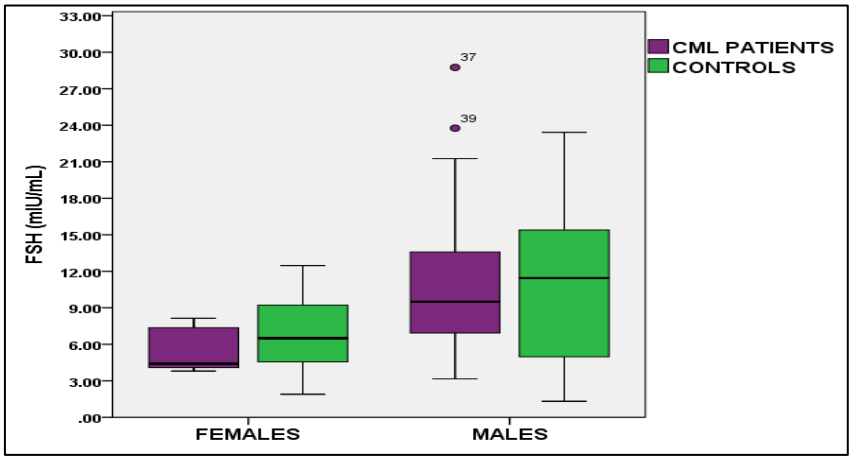

Fig-2: Serum FSH levels in CML patients and controls

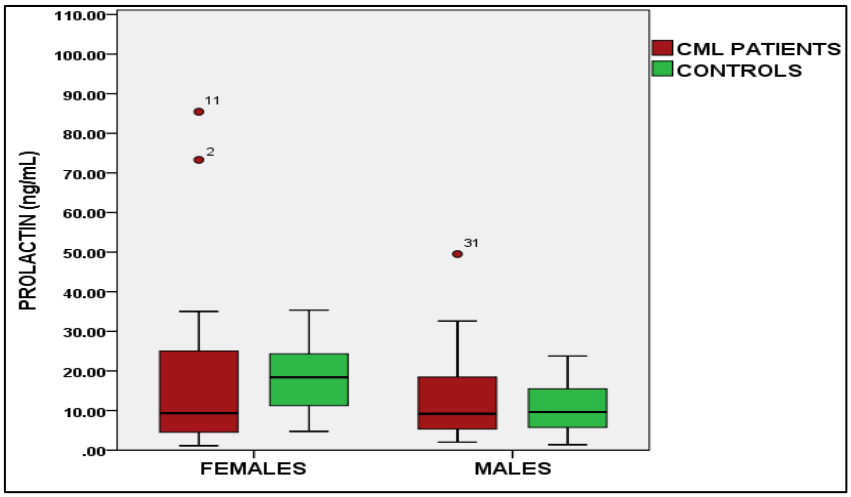

Fig-3: Serum Prolactin levels in CML patients and controls

Table-3: Comparison of S. LH, FSH & Prolactin levels in CML patients before and after therapy

			BEFORE	AFTER	p value
LH# (mIU/mL)	**M(17)**	Mean	7.32 ± 3.84	13.82 ± 4.25	0.001
	F(10)	Mean	7.16 ± 3.94	12.67 ± 4.74	0.022
FSH# (mIU/mL)	**M(17)**	Mean	11.77 ± 7.23	22.30 ± 8.74	0.003
	F(10)	Mean	5.51 ± 1.82	12.57 ± 4.94	0.005
PROLACTIN (ng/mL)	**M(17)**	Mean	14.21 ± 12.68	10.93 ± 7.77	0.039
	F(13)	Mean	21.70 ± 27.43	12.95 ± 11.57	0.087

LH & FSH were compared in premenopausal females (n= 10).

S. LH levels increased significantly after 6 months of imatinib therapy in male patients (13.82±4.25 mIU/mL vs. 7.32±3.84 mIU/mL, p =0.001) and in female patients (12.67±4.74 mIU/mL vs.7.16±3.94 mIU/mL, p =0.002) (table 3 and figure 4). S. FSH levels increased significantly after 6 months of imatinib therapy in male patients (22.30±8.74 mIU/mL vs. 11.77±7.23 mIU/mL, p =0.003) and also in female patients (12.57±4.94 mIU/mL vs. 5.51±1.82 mIU/mL, p =0.005) (table 3 and figure 5). S. LH and FSH levelss in post-menopausal females (n= 3) were 37.41±15.43 mIU/mL and 39.15±24.76 mIU/mL before therapy and 36.43±9.54 and 28.49±9.93 mIU/mL after therapy (p = 1.00 and 0.285). Serum prolactin levels decreased significantly after 6 months of imatinib therapy in male patients (10.93±7.77 ng/mL vs. 14.21±12.68 ng/mL, p =0.039). Serum prolactin levels decreased after 6 months of imatinib therapy in female patients (12.95±11.57 ng/mL vs. 21.70±27.43 ng/mL, p =0.087) though the difference was not significant statistically (Table-3 and Figure-6).

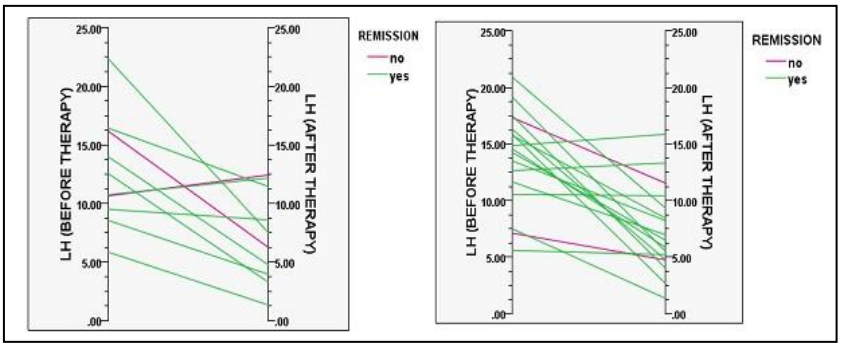

Fig-4: Comparison of S. LH before and after therapy in female (left) and male (right) CML patients

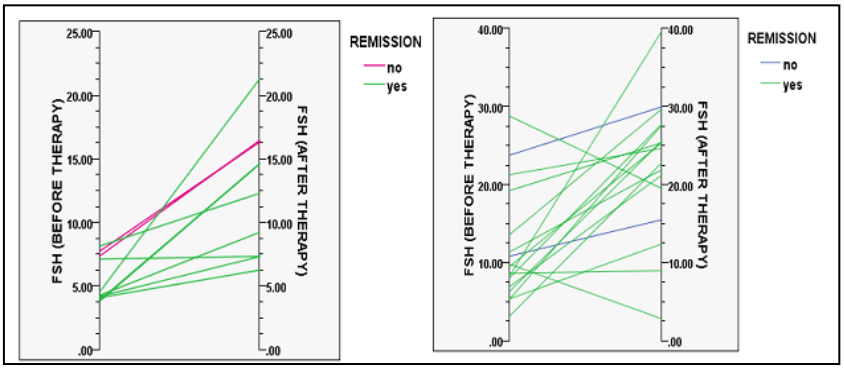

Fig-5: Comparison of S. FSH before and after therapy in female (left) and male (right) CML patients

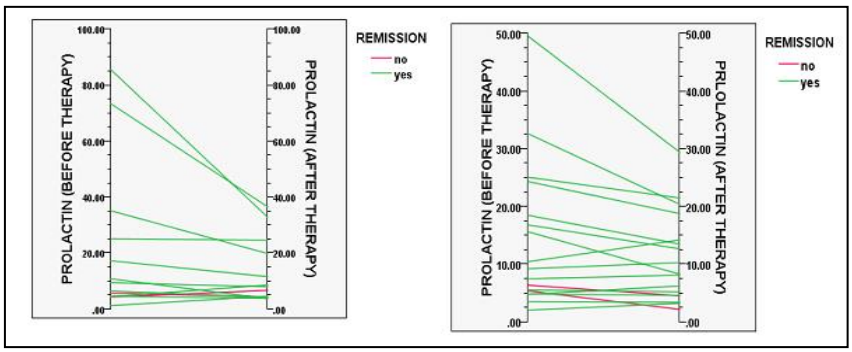

Fig-6: Comparison of S. Prolactin before and after therapy in female (left) and male (right) CML patients

DISCUSSION

In the present study there were 17 (56.7%) male and 13 (43.3%) female patients (1.3:1) (Table-1 & Fig-1). Mean age at diagnosis was 39.5±12.7 years and was comparable with mean age of controls (37.2±11.1 years). CML is more common in males and though peak ince=idence has been described at 55-74 years of age hospital based studies have reported peak age of incidence at much younger age as in present study [20]. Median duration of history of presenting illness was 6 weeks. Three out of 30 patients were asymptomatic and diagnosed incidentally on routine lab examination. The clinical onset of the chronic phase is generally

insidious. Accordingly, some patients are diagnosed, while still asymptomatic, during health-screening tests [3]. 26 patients (87.7%) achieved remission at 6 month of imatinib therapy while 4 (13.3%) patients were not in hematological remission. The hematologic remission rate of patients treated with imatinib has been reported to be 95% [4,20].

LH, FSH IN FEMALES

Pre-therapy levels of LH and FSH were not significantly different from levels in control subjects (Table-2 & Figures 1 & 2). At 6 months of treatment with imatinib serum LH levels increased significantly (12.67 ± 4.74 mIU/mL vs. 7.16 ± 3.94 mIU/mL, p =0.002). Serum FSH levels also increased significantly (12.57 ± 4.94 mIU/mL vs. 5.51 ± 1.82 mIU/mL, p =0.005) (Table-3 & Figure 4 & 5). Changes in post-menopausal women were not significant. Thus there was significant increase in LH and FSH levels in pre-menopausal females. Ault *et al*., reported the experience on 19 pregnancies involving 18 patients (10 females and 8 males) who conceived while receiving imatinib for the treatment of CML. All female patients discontinued therapy immediately on recognition of pregnancy. Three pregnancies (involving two female patients and one male patient) ended in spontaneous abortion, and one patient had an elective abortion. All other pregnancies were uneventful. Two of the 16 babies had minor abnormalities at or shortly after birth (hypospadias in one baby and rotation of small intestine in one baby) that were surgically repaired. All babies have continued normal growth and development. Among female patients who interrupted therapy, five of nine in complete hematologic remission (CHR) at the time of treatment interruption eventually lost CHR, and six experienced an increase in Philadelphia chromosome–positive metaphases. At a median of 18 months after resuming therapy with imatinib, eight patients had a cytogenetic response (complete in three patients). They concluded that although there is no evidence that a brief exposure to imatinib during conception and pregnancy adversely affects the developing fetus, most patients lose their response after treatment interruption [21]. Christopoulos *et al*., reported the development of ovarian insufficiency in a 28 year old woman who was treated with imatinib for CML [7]. Griffith *et al*., and Jensen *et al*., also described the potential application of imatinib in endometriosis treatment showing that it inhibits endometrial stromal cell (ESC) attachment, proliferation, and invasion possibly by altering interaction) between colony-stimulating factor 1 (CSF-1) and its receptor, c-fms [22, 23]. The present study and reports in literature suggest a variable effect of imatinib therapy on female reproductive hormones. While pregnancy in CML therapy is discouraged, with chronic life-long administration of imatinib effect on menstrual health also becomes a quality of life issue. As LH and FSH levels are disturbed in the present study, this suggests a need for evaluating in a larger sample size and for a longer follow up period the effect of imatinib on reproductive hormones and its clinical effects on menstrual health in pre-menopausal females.

LH, FSH IN MALES

Pre-therapy levels of LH and FSH were not significantly different from levels in control subjects (Table-2 & Figure 1 & 2). Serum LH levels increased significantly after 6 months of imatinib therapy (13.82±4.25 mIU/mL vs. 7.32±3.84 mIU/mL, p =0.001). Serum FSH levels increased significantly after 6 months of imatinib therapy (22.30±8.74 mIU/mL vs. 11.77±7.23 mIU/mL, p =0.003) (Table-3 & Figure 4 & 5). Kim *et al*., reported a 42 year old gastrointestinal stromal tumor (GIST) patient with male gyenecomastia and testicular hydrocele after treatment with imatinib mesylate. He developed high LH and FSH levels and his serum testosterone concentration had decreased to 2.3 ng/mL (7.9nmol/L). His gyenecomastia improved after androgen support [24]. Mariani *et al*., reported the effect of long-term treatment with the tyrosine kinase inhibitor imatinib started before the onset of puberty on semen parameters, and hormone values in an 18-year-old man given treatment for chronic myeloid leukemia. Semen analyses showed severe oligozoospermia after long-term administration of imatinib started before puberty. The inhibin-B/FSH ratio was reduced [10]. Seshadri *et al*., also described the occurrence of Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome [25]. Yaghmaei *et al*., Nurmio *et al.*, and Prasad *et al.*, described in animal studies that imatinib exposure led to significantly higher LH and FSH levels [6, 9, 26]. Thus the findings of significantly increased LH and FSH levels in the present study are consistent with the previous reports and document the effect of imatinib. It has been suggested that Imatinib reduces testosterone production through the block of PDGFR and c-kit in the testis [10, 24, 27]. Decreased feedback inhibition leads to elevation of LH and FSH levels [28]. PDGF signaling is important in testes organogenesis and Leydig cell differentiation. Also, PDGF-A is obligatory for adult Leydig cell recruitment and spermatogenesis. c-Kit activity is modulated by stem cell factor which had effect on luteinizing hormone receptor and increased the expression of Steroidogenic Acute Regulatory Protien (StAR), CYP11A, CYP17, and 3 – hydroxysteroid dehydrogenase mRNA expression [10, 24, 27]. As LH and FSH levels are disturbed in the present study, this suggests a need for comprehensive evaluation of male reproductive hormones and functions in a larger sample size and for a longer follow up period to study the effect of the effect of imatinib.

PROLACTIN

Serum prolactin levels in male and female patients were not significantly different from levels in control subjects (Table-2 and Figure-3). Serum prolactin levels decreased significantly after 6 months

of imatinib therapy in male patients (10.93±7.77 ng/mL vs. 14.21±12.68 ng/mL, p =0.039, Table-3 & Figure-6). Serum prolactin levels decreased after 6 months of imatinib therapy in female patients (12.95±11.57 ng/mL vs. 21.70±27.43 ng/mL, p =0.087) though the difference was not significant statistically (Table-3 & Figure-6). Welniak *et al.*, demonstrated use of prolactin and growth hormone in preclinical models for promotion of hematopoietic recovery and immune function [11]. However its effects on the hemopoietic and immune system have been considered redundant [11]. Scarce data exist regarding the production of PRL by myeloid leukaemia cells [12]. A moderate increase in serum PRL levels has been reported in 16 patients with AML out of 28 in one study [14]. Mulashi *et al*., reported occurrence of hyper-prolactinemia as a paraneoplastic phenomenon in AML [15]. However the present study did not find any significant alterations in the serum levels of prolactin in CML patients or its association with any prognostic factor. Prolactin levels were significantly decreased in males with imatinib therapy in the present study. This suggests a need for comprehensive evaluation of male reproductive hormones and functions in a larger sample size and for a longer follow up period to study the effect of the effect of imatinib.

CONCLUSIONS

Baseline levels of LH, FSH and prolactin were similar in patients and controls. The present study did not find any significant alterations in the serum levels of prolactin in CML patients or its association with any prognostic factor. The findings of significantly increased LH and FSH levels after imatinib therapy the present study are consistent with the previous reports and document the effect of imatinib on testicular function in adult male patients. The findings of significant increase in LH and FSH levels in pre-menopausal females in present study suggests that further studies on lager number of female patients are required to fully assess the effects of imatinib on multiple female reproductive hormones and their clinical significance.

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