

## THE EFFECT OF BROMOCRIPTINE ON C-REACTIVE PROTEIN IN WOMEN WITH HYPERPROLACTINEMIC AMENORRHEA

Isam Hamo Mahmood

### ABSTRACT

C-reactive protein has become the subject of avid interest in recent years. Increased concentrations of C-reactive protein (CRP) became widely accepted as a risk factor of many inflammatory diseases including atherosclerosis, ischemic vascular diseases, type 2 diabetes mellitus, hypertension and colon cancer. Data evaluating the concentration of CRP in hyperprolactinemic condition and the effect of bromocriptine on CRP concentration are not available. Thus the present study was designed to measure the concentration of CRP in a number of women with hyperprolactinemic amenorrhea and to evaluate the effect of bromocriptine on CRP concentration. The study tackled sixty women, who had amenorrhea for at least three months and serum prolactin concentration at least twice the upper limit of normal values. Bromocriptine is administered in a daily dose of 2 (2.5 mg) tablets. Serum prolactin and serum CRP were assessed before and after bromocriptine administration, using commercial kits. Mean CRP concentration of the control group was  $1.38 \pm 1.85$  mg/L which is statistically lower than value of  $6.35 \pm 4.62$  mg/L of the patients before bromocriptine therapy ( $P < 0.001$ ). A significant drop of CRP (from a mean of  $6.35 \pm 4.62$  mg/L to a mean of  $2.73 \pm 3.14$  mg/L) was obtained after treatment with bromocriptine ( $P < 0.001$ ). The correlation between serum prolactin level and serum CRP level before and after bromocriptine administration was not statistically significant:  $r = 0.24$ ,  $P > 0.05$  and  $r = 0.12$ ,  $P > 0.2$ , respectively. The present study showed that women with hyperprolactinemic amenorrhea is associated with increased level of CRP and therapy with bromocriptine significantly reduced CRP, suggesting a possible anti-inflammatory action of bromocriptine in addition to prolactin lowering effects.

### INTRODUCTION

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis, with a prevalence of 0.4% in an unselected adult population to 9-17% in women with reproductive disorders.<sup>[1]</sup> It is characterized by elevated serum levels of the hormone prolactin. It occurs in both genders, although it is the most prevalent disorder among reproductive aged women.<sup>[2]</sup> It was demonstrated that patients with hyperprolactinemia have low-grade inflammation.<sup>[3]</sup> The interrelationship between prolactin and the immune system have been elucidated in the last decade, opening new important horizons in the field of the immunoendocrinology.<sup>[4]</sup> Prolactin is secreted not only by anterior pituitary gland but also by many extrapituitary sites including the immune cells, whether endocrine or autocrine. Prolactin exerts profound effects on a wide range of tissues, with over 300 effects described in vertebrates.<sup>[5]</sup> Multiple lines of evidence support the concept that the high levels of prolactin has a pathogenic role in rheumatic and autoimmune diseases including, rheumatoid arthritis,<sup>[6]</sup>

systemic lupus erythematosus,<sup>[7]</sup> Reiter's syndrome,<sup>[8]</sup> psoriatic arthritis,<sup>[9]</sup> celiac disease, type 1 diabetes mellitus, experimental allergic encephalomyelitis, uveitis, and thyroid disease.<sup>[10,11]</sup> In vitro<sup>[12]</sup> and in vivo<sup>[13]</sup> studies demonstrated that prolactin exhibits immunostimulatory properties and can modulate inflammatory responses. Based on these data patients with hyperprolactinemia might present increased markers of systemic inflammation such as C-reactive protein. C-reactive protein (CRP) is a plasma protein; an acute phase protein produced by the liver. It is a member of the pentraxin family of proteins. It should not be confused with C-peptides or protein C.<sup>[14]</sup> It is present in the sera of acutely ill patients and that is able to bind the C-polysaccharide on the cell wall of streptococcus pneumonia was first described in 1930.<sup>[15]</sup> CRP rapidly increases within hours after tissue injury, and it is suggested that it is part of the innate immune system and contributes to host defense.<sup>[16]</sup> CRP has become the subject of avid interest in recent years. Increased concentrations of C-reactive protein (CRP) became widely accepted as a risk

factor of many inflammatory diseases including atherosclerosis,<sup>[17,18]</sup> myocardial infarction, ischemic stroke, peripheral vascular disease and sudden cardiac death<sup>[19-21]</sup> and metabolic syndrome.<sup>[22,23]</sup> Several studies demonstrate that CRP can be used to predict the development of type 2 diabetes mellitus.<sup>[24,25]</sup> C-reactive protein levels are associated with future development of hypertension, which suggests that hypertension is in part an inflammatory disorder.<sup>[26]</sup> CRP is elevated in patients with colon cancer indicating that anti-inflammatory drugs could lower colon cancer risk.<sup>[27,28]</sup> Bromocriptine, introduced in 1971, is a dopamine agonist,<sup>[29]</sup> the original preparation against which newer dopamine agonists are compared. It is effective in suppressing prolactin hypersecretion, reducing prolactinoma size, and restoring gonadal function.<sup>[30]</sup> Because of its short half life (3.3 hours), bromocriptine may require multiple dosing throughout the day.<sup>[31]</sup> Several trials demonstrated that the dopaminergic agonist bromocriptine appears to have therapeutic effects in rheumatic and autoimmune diseases which are associated with hyperprolactinemia including, rheumatoid arthritis,<sup>[32]</sup> systemic lupus erythematosus,<sup>[33]</sup> Reiter's syndrome, psoriatic arthritis and uveitis.<sup>[6]</sup> Trial data evaluating the concentration of CRP in hyperprolactinemic conditions and the effect of bromocriptine on CRP concentration are not available. Thus the present study was designed to measure the concentration of CRP in a number of women with hyperprolactinemic amenorrhea and to evaluate the effect of bromocriptine on CRP concentration.

#### PATIENTS AND METHODS

The study was an open, 8-week period trial conducted to measure the concentration of C-reactive protein and to evaluate the effect of bromocriptine (Parlodel, 2.5 mg tablets, manufactured by NOVARTIS PHARMA S.A.E., Cairo, under licence from Novartis pharma AG., Basle, Switzerland) on the concentration of CRP in women with hyperprolactinemia, who were collected from Al-Batool Teaching Hospital for Gynaecology and Obstetrics in Mosul city. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation of Nineveh Health

Administration and with the Helsinki Declaration. The study tackled sixty women, 21 to 39 years of age who had amenorrhea for at least three months and serum prolactin concentration at least twice the upper limit of normal values, at least four weeks after the discontinuation of any previous therapy. Women were excluded from the study that shows the presence of a pituitary macroadenoma, any disorder that could prevent normal menstruation, hyperprolactinemia related to polycystic ovary disease, thyroid or adrenal disorders, renal or hepatic disease and a history of allergy to ergot derivatives. Women were also excluded who had used any drugs that affect secretion of prolactin from the pituitary such as neuroleptics. Bromocriptine is administered in a daily dose of 2 (2.5 mg) tablets. Another forty apparently healthy women whose age ranged from 21 to 38 years were included in the study as a control group. Serum prolactin was measured at baseline and at the end of 8-week of bromocriptine administration (at the end of the trial) with commercially available Kit (immunoradiometric assay) (IRMA), Kit, Beckman Coulter Company-Czech Republic. The upper range of normal serum prolactin level was considered 16 µg/L. Serum CRP was assessed by using Chemelex, S.A. kit (Pol.Ind.Can Castells. C / industria 113.Nau J) before and after bromocriptine administration. The upper range of normal serum CRP level was considered up to 6 mg/L. Serum Prolactin and CRP were also measured in the control subjects. All values were quoted as the mean±SD. Paired t-test was used to compare serum prolactin and CRP level at baseline and after treatment. Unpaired t-test was used to compare between serum CRP concentration and serum prolactin concentration of the patient group before treatment and those of the control group. Pearson correlation coefficient was performed to find the relationship between prolactin levels and CRP before and after treatment with bromocriptine.

#### RESULTS

A significant reduction of serum prolactin level was demonstrated after treatment with bromocriptine ( $P < 0.001$ ) (Table-1).

**Table 1. Serum prolactin levels before and after treatment with bromocriptine**

Parameter	No. Patients	Before treatment	After treatment	P-value
Serum Prolactin Concentration (µg/L).	60	Range: 31.2-171.9 Mean: 48.04±24.12	Range: 1.77-69.42 Mean: 12.61±11.79	P < 0.001

Normalization of serum prolactin levels was achieved in 52 of 60 (86.7%) patients. A significant drop of CRP was obtained after treatment with bromocriptine (P<0.001) (Table-2).

**Table 2. Serum CRP concentration before and after treatment with bromocriptine**

Parameter	No. Patients	Before treatment	After treatment	P-value
CRP Concentration mg/L	60	Range: 0-17 Mean: 6.35± 4.62	Range: 0-8 Mean: 2.73± 3.14	P<0.001

Mean CRP concentration of the control group was 1.38±1.85 mg/L which is statistically significantly lower than value of 6.35±4.62/L of the patients before bromocriptine therapy (P<0.001) and mean serum prolactin levels of the control group was 6.46±4.12 µg/L which is statistically significantly lower than value of 48.04±24.12 µg/L of the patients before bromocriptine therapy (P<0.001).

The correlation between serum prolactin level and serum CRP level before and after bromocriptine administration were: r= 0.24, P > 0.05 and r = 0.12, P>0.2, respectively (Table-3).

**Table 3. The Correlation Coefficient between Prolactin and C - reactive protein before and after bromocriptine therapy**

Parameter No. Patients	Prolactin (µg/l)	CRP (mg/l)	The correlation coefficient (r)
60			
Before treatment	48.04±24.12	6.35± 4.62	r= 0.24, P>0.05
After treatment	12.61±11.79	2.73± 3.14	r = 0.12, P>0.2,

**DISCUSSION**

The data obtained from the present study revealed a reduction or normalization of serum prolactin level in the majority of patients, such findings confirms results obtained from previous studies which demonstrated the benefit of bromocriptine in lowering serum prolactin level.<sup>[34-36]</sup> The present study demonstrated that hyperprolactinemic amenorrhea condition is associated with an inflammatory state, as represented by elevated serum CRP level, an important marker of inflammation. Treatment with bromocriptine reduced significantly the level of CRP. Recent research has focused on the use of CRP, a marker of inflammation, in the detection of patients at increased risk for cardiovascular disease,<sup>[37]</sup> and the addition of CRP to current strategies for global risk assessment, such as the Framingham Risk Score, may have the potential to increase the accuracy of cardiovascular risk prediction.<sup>[38-40]</sup>

Thus, the findings in the present study may be an of clinical importance as CRP is thought to be independent risk factor for cardiovascular disease.<sup>[41]</sup> The mean CRP reported in the present study is 6.35 mg/L is in the range of increased risk for cardiovascular disease whereas the mean value of CRP of 1.38 mg/L in the control group is in the range of low cardiovascular risk. The risk of serum CRP levels for cardiovascular disease is as follows: low risk <1mg/L, average risk 1-3 mg/L and high risk > 3mg/L.<sup>[42]</sup> Bromocriptine in the present study significantly reduced the level of CRP after 8 week interval. Bromocriptine is dopamine agonists that suppress pituitary secretion of prolactin. The mechanism by which bromocriptine reduce CRP concentration is not clear, it may be due to suppressing circulatory prolactin, and through this mechanism, has the potential to suppress inflammatory reaction caused by prolactin, and through this mechanism, the stimulating effect of prolactin on the hepatocytes to synthesized CRP is suppressed resulting in the reduction of CRP level. But the present study demonstrated a very weak, non significant relation between serum prolactin and serum CRP level before and after bromocriptine administration. This may indicate that another mechanism may be involved in the reduction of CRP by bromocriptine other than its effect on prolactin secretion, suggesting an

anti-inflammatory effect for bromocriptine in addition to prolactin lowering effect. The anterior pituitary hormone prolactin has a pathogenic role in rheumatic and autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, Reiter's syndrome, psoriatic arthritis and uveitis. Conversely, the dopaminergic agonist bromocriptine appears to have therapeutic effects through suppression of pituitary prolactin secretion and perhaps through actions on peripheral dopamine receptors.<sup>[6]</sup> The reduction of the elevated CRP in the present study may explain the beneficial therapeutic effect of bromocriptine reported in the above diseases in part by its effect on CRP a marker of inflammation. In addition to bromocriptine which is reported in the present study to reduce the concentration of CRP in women with hyperprolactinemic amenorrhea. A number of other agents have been reported by other studies to reduce the concentration of CRP in other diseases. Reduction in CRP levels has been seen following treatment with statins; a group of hypolipidemic agents including pravastatin, simvastatin, and atorvastatin.<sup>[43]</sup> In addition many other drugs have been found to affect the concentration of CRP including azetimibe,<sup>[44]</sup> aspirin and clopidogrel,<sup>[45]</sup> and the antihypertensive drug valsartan.<sup>[46]</sup>

**In conclusion:** The present study showed that women with hyperprolactinemic amenorrhea are associated with increased level of CRP and therapy with bromocriptine significantly reduced CRP, suggesting a possible anti-inflammatory action of bromocriptine in addition to prolactin lowering effects.

## REFERENCES

1. Josimovich JB, Lavenhar MA, Devanesan MM, Sesta HJ, Wilchins SA, Smith AC. Heterogenous distribution of serum prolactin values in apparently healthy young women, and the effects of oral contraceptives. *Fertility and Sterility* 1987; 47: 785-791.
2. Biller BM, Luciano A. Guidelines for the diagnosis and treatment of hyperprolactinemia. *J Reprod Med* 1999; 44: 1075-1084.
3. Yavuz D, Deyneli O, Akpınar I, Yildiz E, Gozu H, Sezgin O, et al. Endothelial dysfunction, reduced insulin sensitivity and inflammatory markers in hyperprolactinemic pre-menopausal women. *European J Endocrinol* 2003; 149: 187-193.
4. De Bellis A, Bizzarro A, Pivonello R, Lombardi G, Bellastella A. Prolactin and autoimmunity. *Pituitary* 2005; 8: 25-30.

5. Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor Knockout mice. *Endocr Rev* 1998; 19: 225-268.
6. Zautra AJ, Burleson MH, Matt KS, Roth S, Burrows L. Interpersonal stress, depression and disease activity in rheumatoid arthritis and osteoarthritis patients. *Health Psychol* 1994; 13: 139-148.
7. Walker SE, Mc Murray RW, Houry JM, Allen SH, Keisler D, Sharp GC, et al. Effects of prolactin in stimulating disease activity in systemic lupus erythematosus. *Ann N Y Acad Sci* 1998; 840: 762-772.
8. Gutierrez MA, Anaya JM, Cabrera GE, Vindrola O, Espinoza LR. Prolactin, a link between the neuroendocrine and immune systems. *Rev Rhum Ed Fr* 1994; 61: 278-285.
9. Mc Murray RW. Bromocriptine in rheumatic and autoimmune diseases. *Semin Arthritis Rheum* 2001; 31: 21-32.
10. Reber PM. Prolactin and immunomodulation. *Am J Med* 1993; 95: 637-644.
11. Neidhart M. Prolactin in autoimmune diseases. *Proc Soc Exp Biol Med* 1998; 217: 408-419.
12. Yu Lee LY. Prolactin modulation of immune and inflammatory responses. *Recent progress in hormone research* 2002; 57: 435-455.
13. Serri O, Li L, Manputu JC, Beauchamp MC, Maingrette F, Renier G. The influence of hyperprolactinemia and obesity on cardiovascular risk markers: effects of cabergoline therapy. *Clin Endocrinol* 2006; 64: 366-370.
14. Wikipedia. C-reactive protein. 12 January 2007. Available at: [http://en.wikipedia.org/wiki/C-reactive\\_protein](http://en.wikipedia.org/wiki/C-reactive_protein).
15. Pepys MB. C-reactive protein: Fifty years on. *Lancet* 1981; 1: 653-657.
16. Pflutzner A, Forst T. High-sensitivity C-reactive protein as cardiovascular risk marker in patients with diabetes mellitus. *Diabetes Technol Ther* 2006; 8: 28-36.
17. Ridker PM, Bassuk SS, Toth PP. C-reactive protein and risk of cardiovascular disease: Evidence and clinical application. *Curr Atheroscler Rep* 2003; 5: 341-349.
18. Blake GJ, ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. *J Am Coll Cardiol* 2003; 41: 37 S- 42 S.
19. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003; 107: 363-369.
20. Ridker PM. High - sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001; 103: 1813-1818.
21. Crea F, Monaco C, Lanza GA, Maggi E, Ginnett F, Cianflone D, et al. Inflammatory predictors of mortality in the Scandinavian Simvastatin Survival Study. *Clin Cardiol* 2002; 25: 461-466.
22. Ridker PM, Buring JE, Cook NR, Rifai. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 2003; 107: 391-397.

23. Lemieux I, Pascot A, Prudhomme D, Almeras N, Bogaty P, Nadeau A, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 2001; 21: 961-967.
24. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; 286: 327-334.
25. Pradhan AD, Cook NR, Buring JE, Manson JE, Ridker PM. C-reactive protein is independently associated with fasting insulin in nondiabetic women. *Arterioscler Thromb Vasc Biol* 2003; 23: 650-655.
26. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003; 290: 2945-2951.
27. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. *JAMA* 2004; 291: 585-590.
28. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003; 348: 891-899.
29. Mah PM, Webster J. Hyperprolactinemia: etiology, diagnosis and Management. *Semin Reprod Med* 2002; 20: 365-374.
30. Verhelst J, Roger ABS, Maiter D, Bruel AVD, Vandeweghe M, Velkeniers B, et al. Cabergoline in the treatment of Hyperprolactinemia: a study in 455 patients. *J Clin Endocrin Metab* 1999; 84: 2518-2522.
31. Jones TH. The management of hyperprolactinemia. *Br J. Hosp Med* 1995; 53: 374-378.
32. Mader R. Bromocriptine for refractory rheumatoid arthritis. *Harefuah* 1997; 133: 527-529.
33. Walker SE. Treatment of systemic lupus erythematosus with Bromocriptine. *Lupus* 2001; 10: 197-202.
34. Buvant J, Buvat-Herbaut M (1982) Prolactin, bromocriptine and gonadal function in women: recent advances. 11. Treatment of female hyperprolactinemia and other indications for the use of bromocriptine. *J Gynecol Obstet Biol Reprod (Paris)* 1982; 11:509-524.
35. Al-Suleiman SA, Najashi S, Rahman J, Rahman MS. Outcome of treatment with bromocriptine in patients with hyperprolactinemia. *Aus NZJ Obstet Gynecol* 1989; 29: 176-179.
36. Lamberts SW, Quik RF (1991) A comparison of the efficacy and Safety of pergolide and bromocriptine in the treatment of Hyperprolactinemia. *J Clin Endocrinol Metab* 1991; 72: 635-641.
37. Verma S, Szmitka PE, Ridker PM. C-reactive protein comes of age. *Nature clinical practice cardiovascular Medicine* 2005; 2: 29-36.
38. Albert MA, Glynn RJ, Ridker PM. Plasma concentration of C-reactive protein and the calculated Framingham coronary heart disease risk score. *Circulation* 2003; 108: 161-165.
39. Koenig W, Lowel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the Framingham score: implications for future risk assessment: results from a large cohort study in southern Germany. *Circulation* 2004; 109: 1349-1353.
40. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham risk scores. *Circulation* 2004; 109: 1955-1959.
41. Gotto AM. Statins and C-reactive protein considering a novel marker of cardiovascular risk. *Prev Cardiol* 2002; 5: 200-203.
42. Pearson TA, Mensah GA, Honey Y, Smith SC. The centers for disease control and prevention and the American heart workshop on markers of inflammation and cardiovascular disease. CDC/AHA workshop on markers of inflammation and cardiovascular disease: application to clinical and public health practice: overview. *Circulation* 2004; 110: 543-544.
43. Devaraj S, Rogers J, Jialal I. statins and biomarkers of inflammation. *Curr Atheroscler Rep* 2007; 9: 33-41.
44. Sager PT, capece R, Lipka L, Strny J, yang B, Suresh R, et al. Effects of azetimibe coadministered with simvastatin on C-reactive protein in a large cohort of hypercholesterolemic patients. *Atherosclerosis* 2005; 179: 362-367.
45. Woodward M, Lowe GD, Francis LM, Rumley A, Cobbe SM. A randomized comparison of the effects of aspirin and clopidogrel on thrombotic risk factors and C-reactive protein following myocardial infarction: the CADET trial. *J Thromb Haemost* 2004; 2: 1934-1940.
46. Novartis. Diovan (valsartan) the first blood pressure medication in a large scale clinical trial to lower C-reactive protein, an important marker of inflammation. New York, May 19, 2006. At internet: <http://www.novartis.com/>.