

# Atrial natriuretic peptide in chronic renal failure on maintenance hemodialysis : effect of heart failure

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## ABSTRACT

**Objective:** To examine the plasma level of atrial natriuretic peptide (ANP) in patients with chronic renal failure (CRF) undergoing maintenance hemodialysis (HD) and to evaluate the effect of superimposed cardiac functional impairment on the plasma level of this hormone.

**Design:** A case- series study

**Setting:** Artificial Kidney and Dialysis Unit of Ibn-Sena Teaching Hospital, Mosul; during the period from June 2003 to August 2004.

**Participants:** Forty patients with CRF undergoing maintenance HD, were divided into 2 groups depending on presence or absence of heart failure. Group I, includes 20 patients with CRF who did not have heart failure and group II, includes 20 patients with CRF who had heart failure. The study also includes 20 healthy volunteers as a control group.

**Methods:** Plasma ANP, serum creatinine, urea and body weights were measured in CRF patients before and after HD. The same parameters were also measured in the control group. The paired-t-test was used to examine the difference in the mean of the studied parameters in patients with CRF before and after HD. The Unpaired -t- test was used to assess the difference in the mean of the above-mentioned parameters between patients and control group. Pearson correlation coefficient was used to study the relation of the means of differences between pre and post dialysis values of the studied parameters within each patient group.

**Results:** The mean of plasma ANP level was significantly higher in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) than that in the control group before and after HD. Furthermore, the plasma ANP in group II was significantly higher ( $p < 0.0001$ ) than that in group I. There was a significant decrease in the plasma ANP in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) after HD. A significant positive correlation was found between the mean of decrease in plasma ANP level and body weight loss after HD in group I ( $r = 0.83$ ,  $p < 0.0001$ ) and group II ( $r = 0.93$ ,  $p < 0.0001$ ). A similar positive correlation was found between the mean of decrease in plasma ANP and the mean of decrease in serum creatinine in group II ( $r = 0.95$ ,  $p < 0.0001$ ), and between the mean of decrease in plasma ANP and the mean of decrease in serum concentration of urea in group I ( $r = 0.48$ ,  $p < 0.05$ ).

**Conclusion:** Periodic measurement of plasma ANP level in patients with CRF may be of great value in evaluating the actual fluid status in patients having CRF and in determination of frequency and duration of dialysis sessions. It also may be of value in predicting cardiac dysfunction in patients with CRF.

**Key words:** Atrial natriuretic peptide, chronic renal failure, haemodialysis.

## الخلاصة

**الهدف:** دراسة مستوى هورمون البيبتيد الاذيني المدر للصبوديوم في البلازما لدى المرضى المصابين بعجز الكلية المزمن والمعالجين بطريقة التنقية الدموية المستمرة ولمعرفة مدى تأثير قصور وظيفة القلب على مستوى هذا الهرمون.

**التصميم:** دراسة الحالات المتسلسلة.

**المكان:** وحدة الكلية الاصطناعية في مستشفى ابن سينا التعليمي - الموصل.

**الزمان:** حزيران 2003 الى آب 2004

**المشاركون:** أجريت الدراسة على 40 مريضا مصابا بعجز الكلية المزمن، تم تقسيمهم إلى مجموعتين بالاعتماد على وظيفة القلب. المجموعة الأولى ضمت 20 مريضا ممن ليس لديهم قصور في وظيفة القلب والمجموعة الثانية وضمت 20 مريضا ممن لديهم قصور في وظيفة القلب. وعينة ضابطة مكونة من 20 شخص من الأصحاء.

**الطريقة:** تم قياس مستوى هرمون البيبتيد الاذني المدر للصوديوم في البلازما، والمستوى المصلي للكرياتينين، اليوريا (جوه البول) ووزن الجسم لدى المرضى المصابين بعجز الكلية المزمن قبل وبعد عملية التنقية الدموية. كما تم إجراء نفس القياسات لأفراد العينة الضابطة. تمت مقارنة التغيرات الحاصلة في القياسات المذكورة اعلاه باستعمال اختبار -ت- كما تمت دراسة العلاقة بين هذه المتغيرات باستخدام معامل ارتباط بيرسون.

**النتائج:** أظهرت الدراسة وجود زيادة إحصائية معنوية في قيم مستوى هرمون البيبتيد الاذني المدر للصوديوم في البلازما لدى مرضى المجموعة الأولى ( $P < 0.0001$ ) و مرضى المجموعة الثانية ( $P < 0.0001$ ) بالمقارنة مع العينة الضابطة قبل وبعد إجراء عملية التنقية الدموية. إضافة على ذلك لوحظ أن مستوى هذا الهرمون لدى المرضى المصابين بعجز الكلية المزمن والذين يعانون من عجز القلب (المجموعة الثانية) اعلى مما هو عليه لدى المرضى الذين ليست لديهم تلك المضاعفات (المجموعة الأولى) وبقيمة إحصائية مقدارها ( $P < 0.0001$ ). كما أظهرت الدراسة انخفاضاً معنوياً في مستوى هرمون البيبتيد الاذني المدر للصوديوم لدى مرضى المجموعة الأولى ( $P < 0.0001$ ) و مرضى المجموعة الثانية ( $P < 0.0001$ ) بعد إجراء عملية التنقية الدموية المستمرة. وتشير نتائج الدراسة إلى وجود علاقة معنوية موجبة بين معدل النقص الحاصل في مستوى هرمون البيبتيد الاذني المدر للصوديوم في البلازما ومعدل النقصان في وزن الجسم بعد إجراء عملية التنقية الدموية لدى مرضى المجموعة الأولى ( $r = 0.83, P < 0.0001$ ) و مرضى المجموعة الثانية ( $r = 0.93, P < 0.0001$ ). كما تبين من نتائج الدراسة وجود زيادة إحصائية معنوية في تركيز الكرياتينين واليوريا لدى مرضى المجموعة الأولى ( $P < 0.0001$ ,  $P < 0.0001$ ) و مرضى المجموعة الثانية ( $P < 0.0001$ ,  $P < 0.0001$ ) بالمقارنة مع العينة الضابطة قبل وبعد إجراء عملية التنقية الدموية.

**الاستنتاج:** يستدل من نتائج الدراسة أن ارتفاع مستوى هرمون البيبتيد الاذني المدر للصوديوم في البلازما هي حالة مألوفة لدى المرضى المصابين بعجز الكلية المزمن وخاصة أولئك الذين يعانون من قصور القلب وعلى هذا الأساس يمكن القول إن قياس المستوى المصلي لهرمون البيبتيد الاذني المدر للصوديوم لدى المرضى المصابين بعجز الكلية المزمن يعتبر ذو أهمية كبيرة في تحديد مدى الزيادة في حجم السوائل لدى هؤلاء المرضى وبذلك يمكن أن يساعد في تقدير فترة و معدل عملية التنقية الدموية لدى هؤلاء المرضى، وكذلك من الممكن اعتباره مؤشراً على اعتلال وظيفة القلب لديهم.

**A**trial natriuretic peptide (ANP) is a cardiac peptide released in response to increase of intravascular volume or any other factor which leads to stretching of the cardiac atrial wall<sup>(1)</sup>. ANP plays a key role in the regulation of fluids and electrolytes balance, as well as blood pressure homeostasis<sup>(2)</sup>. The natriuretic and diuretic action of the hormone is mediated through its effect on renal hemodynamics and renal tubular function<sup>(3)</sup>. CRF is a circumstance where disease presents the opportunity to dissect apart renal regulatory mechanisms. Such patients tend to accumulate salt and water between dialysis sessions; this accumulation provides a strong and sustained stimulus to the release of the ANP hormone<sup>(4)</sup>. It is well documented that patients with CRF have a high incidence of cardiovascular disease<sup>(5)</sup>. Approximately 80% of patients with CRF start dialysis with left ventricular hypertrophy, left ventricular dilation or frank heart failure<sup>(6)</sup>. The poor prognosis of patients with CRF is mainly due to the frequent occurrence of cardiovascular events specially myocardial infarction and heart failure<sup>(7)</sup>, and since ANP is released in response to increased intravascular volume<sup>(1)</sup>, therefore, its estimation may be of value in the follow up of these patients. Accordingly this study was designed to achieve this goal.

## PATIENTS AND METHODS

Forty patients with CRF (24 males and 16 females) who were attending the Dialysis Unit at Ibn-Sena teaching hospital for maintenance HD during the period from June 2003 to August 2004 were included in this study. The patients were divided into two groups according to the presence or absence of heart failure. Group I includes 20 patients (13 males and 7 females) with CRF who did not have heart failure. Their age ranged from 24 to 71 years with a mean  $\pm$  SD of (47.3  $\pm$  14.5). Group II includes 20 patients (11 males and 9 females) with CRF who have heart failure. Their age ranged from 28 to 73 years (49.6  $\pm$  14.0). All patients included in the study were dialyzed 4 hours twice weekly. The study also includes 20 apparently healthy volunteers (10 males and 10 females), their age ranged from 26 to 73 years (46.9  $\pm$  16.2) as a control group.

Ten ml of venous blood were obtained from a suitable forearm vein. Five ml of the sample was collected in heparinized tube and immediately placed in ice for the measurement of the ANP level. The other 5 ml was placed in a plain tube for the measurement of serum creatinine and urea level. Both tubes were centrifuged within 30 minutes, the plasma and serum were then separated and kept in capped plastic tubes

in deep freeze (-20C) until analysis. Plasma ANP concentration was determined by Enzyme Linked ImmunoSorbent Assay (ELISA)<sup>(8)</sup> utilising kits provided by DRG International Inc., USA.(Cat.No.:Eia-1524). Serum creatinine is measured manually by Jaffe end point method<sup>(9)</sup> using kit from Rando colorimetric (with deproteinization). Serum urea concentration was determined enzymatically using kit from Bicon, W. Germany<sup>(10)</sup>. The body weight of patients before and after dialysis, as well as that of the control group was accurately measured.

Statistical analysis was performed using the paired  $t$ -test to examine the difference in the mean of the studied parameters in patients with CRF before and after dialysis. The unpaired  $t$ -test was used to assess the difference in the mean of the above mentioned parameters between patients and control group. Pearson correlation coefficient was used to study the relation of the means of differences between pre and post dialysis values of the studied parameters within each patient group. All values are expressed as mean  $\pm$  SD.

## RESULTS

The plasma levels of ANP, serum creatinine, serum urea and body weights of group I, group II and control group are shown in Table 1. The mean of plasma ANP was significantly higher in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) than that in control group before and after HD. Furthermore, the plasma ANP in group II

was significantly higher ( $p < 0.0001$ ) than that in group I. There was a significant decrease in the plasma level of ANP in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) after HD, Figure(1). The mean of serum creatinine before HD was found to be significantly higher in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) than that in control group. After HD the serum creatinine was significantly decreased in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ), but it was still significantly higher than that in control group ( $p < 0.0001$ ,  $p < 0.0001$  respectively). The mean of serum urea before HD was found to be significantly higher in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) than that in control group. After HD the serum urea was significantly decreased in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ), but it was still significantly higher than that in control group ( $p < 0.0001$ ,  $p < 0.0001$  respectively). There was a significant reduction in the mean of the body weight after HD in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ). There was a significant positive correlation between the mean of reduction in plasma ANP level and the mean of body weight loss in group I ( $r = 0.83$ ,  $p < 0.0001$ ) and group II ( $r = 0.94$ ,  $p < 0.0001$ ). A similar correlation was also observed between the mean of reduction in plasma ANP level and the mean of reduction in the serum creatinine in group II ( $r = 0.95$ ,  $p < 0.0001$ ), and between the mean of reduction in plasma ANP and the mean of reduction in the serum urea in group I ( $r = 0.48$ ,  $p < 0.05$ ).

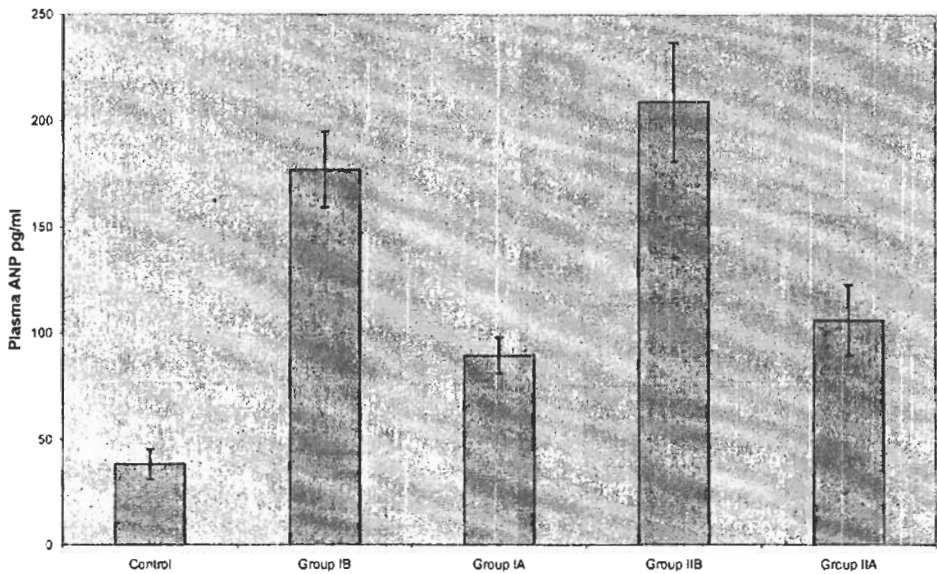
**Table (1):** The mean  $\pm$  SD of plasma ANP, serum creatinine and urea and body weight in group I, group II and control group.

Parameters	Group I		Group II		Control group
	Before dialysis	After dialysis	Before dialysis	After dialysis	
Plasma ANP Pg/ml	177.2 $\pm$ 17.8	89.5 $\pm$ 8.5	209.1 $\pm$ 28.1 <sup>A</sup>	105.8 $\pm$ 16.8	38.1 $\pm$ 7.3
	P < 0.0001		P < 0.0001		B,C
S. creatinine $\mu$ mol/L	798.6 $\pm$ 56.8	625.1 $\pm$ 57.1	850.4 $\pm$ 81.4	647.7 $\pm$ 64.9	69.7 $\pm$ 7.1
	P < 0.0001		P < 0.0001		B,C
S. urea mmol/L	35.6 $\pm$ 3.6	17.1 $\pm$ 2.4	37.8 $\pm$ 4.3	18.4 $\pm$ 3.5	3.3 $\pm$ 0.57
	P < 0.0001		P < 0.0001		B,C
Body weight Kg.	69.5 $\pm$ 8.9	67.5 $\pm$ 8.9	68.9 $\pm$ 7.1	66.9 $\pm$ 7.2	66.9 $\pm$ 10.2
	P < 0.0001		P < 0.0001		

A : significantly higher in groupII from respective values in group I ( $p < 0.0001$ ).

B : significantly higher in groupI from respective values in control group ( $p < 0.0001$ ).

C : significantly higher in groupII from respective values in control group ( $p < 0.0001$ ).



**Figure (1):** Mean  $\pm$  SD of plasma ANP level in control group, group I before (IB) and after (IA) hemodialysis and group II before (IIB) and after (IIA) hemodialysis.

## DISCUSSION

It is well known that plasma level of ANP is elevated by several folds in patients with CRF when compared to values obtained in normal subjects<sup>(11)</sup>. The primary stimulus for the release of the ANP is increased stretch of the atrial myocyte as a consequence of increased circulating blood volume and increased intra-atrial pressure<sup>(12)</sup>. Patients with CRF tend to retain water and salts between dialysis sessions; this accumulation should provide a potent stimulus to the release of this hormone. The present study showed that the mean of plasma ANP in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) were significantly higher than that in control group. Moreover, the results also showed a significantly higher level of plasma ANP in group II ( $p < 0.0001$ ) in comparison with that of group I. In fact, this finding appears to be logical since patients with CRF who had heart failure tend to have an extra water and salt retention in comparison with patients with CRF who did not have such complication. Accordingly, they had an additional increment in atrial pressure and more stimulus to release ANP by atrial myocyte<sup>(13)</sup>.

After HD the plasma ANP was significantly reduced in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ), but the level remained above the normal range. The reduction in plasma ANP level observed after dialysis is probably due to volume depletion with subsequent decrease in plasma volume and atrial pressure<sup>(14)</sup>. The present study revealed a significant loss in

body weights after dialysis in group I ( $p < 0.0001$ ) and group II ( $p < 0.0001$ ) in comparison to the pre dialysis values. Furthermore, the study showed a significant positive correlation between the mean reduction in body weights and mean decrease in plasma ANP levels in group I ( $r = 0.83$ ,  $p < 0.0001$ ) and group II ( $r = 0.94$ ,  $p < 0.0001$ ). A second factor that may contribute to the reduction in plasma ANP is the clearance of the hormone during the process of HD. Indeed many investigators have reported the presence of considerable amount of ANP in the dialyser filtrate, and they also observed a significant positive correlation between plasma level of the ANP and the ANP content of the filtered solution<sup>(15)</sup>.

In conclusion the present study revealed a significant increase in the plasma ANP level in patients with CRF in comparison to normal subjects. The study also showed that plasma ANP level tends to be significantly higher in patients with CRF who had heart failure in comparison to those patients who did not have such complication. Therefore, periodic measurement of plasma ANP level in patients with CRF may be of great value in evaluating the actual fluid status in these patients and in determination of frequency and duration of dialysis sessions. It also may be of value in predicting cardiac dysfunction in patients with CRF.

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