# ESTIMATION OF BRAIN NATRIURETIC PEPTIDE HORMONE AS PREDICTOR OF BRAIN STROKE AND NEUROCOGNITIVE IMPAIRMENT IN CHRONIC KIDNEY DISEASE PATIENTS IN BAGHDAD PROVINCE/IRAQ

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**ABSTRACT**

Present investigation aimed to study plasma BNP hormone estimation as predictor of brain stroke and neurocognitive in relative with other limitations in CKD patient. The case control experimental study was conducted on CKD patient at Yarmuk Hospital at Baghdad Province, Iraq from February to April 2020. The results showed that there were significant variances ($P \leq 0.05$) between CKD patients and control group, there was significant increase in BNP hormone and cystatin-C levels at patient, while ihematological parameters were significantly decreased. The parameters of lipid profile were significantly increased ($P \leq 0.05$). The result revealed that there was relationship between BNP hormone level and CKD. This support that BNP level is related with the renal stage progression in disease. B type natriuretic peptide (BNP) is a beneficial biomarker in the management the failure of heart and brain strokes. The secreted peptides into the circulation after degradation of its originator proBNP and excrete from the kidneys in the active forms or as metabolites.

***Key words*:** Chronic kidney disease, brain natriuretic peptide (BNP) hormone, brain stroke

## Introduction

The chronic kidney disease (CKD diagnosis depend on starting chronic decline in the function and structural loss of kidney. The glomerular filtration rate (GFR), is known as the best existing indicator of general kidney function, where the total amount of fluids filtered by functioning nephrons per unit of time equals to GFR (Webster *et al.,* 2017). The management of renal disease are classified agreeing to stages of disease severity, which are measured from albuminuria, glomerular filtration rate (GFR) and clinical diagnosis (Levey and Coresh, 2012). Stroke that results from disorders are one of the greatest common causes of disability. With nurological impairment almost 600 million aging human are affected (Sousa *et al.,* 2009). Due to the lack of exact task-oriented rehabilitation treatment, the motor impairment related with stroke and physical incapacity affects the quality of patient's life. Numerous rehabilitative treatments have remained used to restore motor functions of upper and lower limb. These lines comprise: alternative movements, passive facilitation, aerobic exercises, movement therapy of constraint, bilateral arm training, training of direct intense task and treadmill training. The therapy of Intra-venous fibrinolytic and endovascular clot disturbance being two of the only treatments with proven advantage (Ciccone *et al.,* 2013) group of Researchers investigative the results of rehabilitative efforts in physiotherapy, occupational treatment, and speech and language treatment are promising, but the intervention lead to full recovery of function (Langhorne *et al.,* 2011). The serum biomarkers that used in prediction of consequences after acute ischemic stroke is limited, because of the data are mainly based on analysis of short-range (about 3 months) outcomes and mortality after-stroke (Whiteley *et al.,* 2009). Additionally, no currently confirmed serum biomarkers are obtainable to assist prediction in acute ischemic stroke. The exact influence of chronic kidney disease on the B-type natriuretic peptide (BNP) levels and NT-pro BNP, the two commonly used natriuretic peptide (NPs) in clinical practice (Tagore *et al.,* 2008; Jalil and Karevskiy*,* 2019). BNP is mainly secreted from cardiomyocytes after volume expansion or pressure overload. It has been linked to cardiac affection before appearance of symptoms. Lately, it has been linked to many noncardiac diseases such as rheumatic diseases, pulmonary diseases, and atherosclerosis, kidney diseases, it is found to be elevated in general population with peripheral arterial diseases (Fahmy *et al.,* 2017). The BNP physiologic functions respond many detrimental neurohormonal, these functions include natriuretic, diuresis, vasodilation, sympathetic tone inhibition and the renin-angiotensin-aldosterone inhibition. Chronic renal Stages effect on BNP Concentrations. The National Kidney Foundation recommends (NKFR) reported that CKD be divided into 5 stages established on glomerular filtration rate (GFR) levels: stage I, CKD risk factors (GFR 90 or more); stage II, mild renal insufficiency (GFR 60 to 89); stage III, moderate renal insufficiency (GFR 30 to 59); stage IV, severe renal insufficiency (GFR 15 to 29); and stage V, end-stage renal disease (GFR less than 15). The Cystatin-C is very low-molecular weight protein, non-glycosylated, produced and secreted by all human nucleated cells. Cystatin-C is a sensitive biomarker in regard GFR and not secreted through the kidney tubules or reabsorbed back into the serum. In the diagnosis of renal function impairment, it is better than creatinine clearance, as it is not affected by diet, sex, height, and muscle mass (Behairy *et al.,*2017).

## Materials and Methods

Enrolled chronic kidney diseases patients were exposed to:

· Full history taking with tension on age at first stage for renal

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disease, therapy type.

· Clinical examination, including the characteristics for the illness that is causal chronic kidney disease (CKD) (*eg*., arteriosclerosis, lupus, pressure) or its complications (*eg*, anemia, bleeding).

**The laboratory examinations**

The blood samples: Five mL of venous blood was drained with full aseptic conditions as follows:

1. Two mL EDTA whole blood with gently mixing for complete blood count (CBC). Use the automated hematology apparatus (Sysmex XE 5000, USA). The EDTA whole blood also centrifuged to obtain clear blood plasma for estimation BNP.
2. Four ml of blood were taken without anticoagulant in gel test tube. The allowed samples for coagulation about 30 minutes in room temperatures, after that centrifuged about10 minutes for 3000/rpm. serum that is separated was used for the following tests:

- Urea and serum creatinine and ALB: by use Beckman coulter Au400 automated analyzer /USA, by appropriate chemical principles.
- The levels of Cystatin C were measured using immunofluorescence Fincare system with test range (7.8-550 ng/ml)
- Estimation of lipid profile: TG, CHOL, HDL, LDL using automated chemistry BECKMAN COULTER AU400/USA.

**Statistical Analysis**

The biostatistical analysis was achieved by use SPSS 18 version software. The data were expressed as mean and standard division SD values for parametric results, Student t-test was used for value mean. The level of significance for all analyses, was at P<0.05.

**Results and Discussion**

A case - control study was completed to access certain parameters between patients group (25) have chronic kidney disease CKD.CKD is conditions affecting renal structures and functions, cardiovascular diseases is common problems of CKD. Chronic kidney disease stimulates pressure and lipid disorders, which in go can contributes to the development of kidney failure. Also, nephropathy caused by diabetes is the chief cause of kidney dysfunction.

**Host information on chronic kidney disease (CKD)**

Table 1 show the demographic characters where there is no biostatistics important differences had been found at age, family history and BMI (age, P-value: 0.361, family history, P-value: 0.82, BMI,. P-value: 0.79), while the hypertension, gender, Smoking and cardiovascular disease parameters of the studied group show there is significance, at all comparisons at (P<0.05). The study showed that chronic kidney disease was most common in the advanced age groups this in agree with (Glassock *et al*., 2015). Which conduct that the disease become more complex in these age groups. There is association between sex and CKD, where the occurrence of CKD tends to be greater in women, the CKD is also having higher progress rate and mortality risk at males in compare with females, excepting in post-menopausal women and diabetic patients (Goldberg and Krause, 2016). The present study showed low significance between healthy group and patient group at ($P \leq 0.05$) in relation to gender. Hypertension is known to have progression rate with CKD and lead to increase the risk rate for cardiovascular occurrence, the associations between hypertension, cardiovascular risk, and development of CKD are well established, hypertension is the major changeable risk for heart diseases, kidney renal and stroke. Chronic kidney diseases (CKD) are a common reason of hypertension and it is also a complication of uncontrolled hypertension. Hypertension uses harmful actions on the brain and its blood circulation. (Dickinson, 2001). The brain is one of the dominant target organs at which high blood pressure (HBP) is mainly harmful (Moser and Roccella, 2013). Hypertension is the major risk aspect for stroke, the second reason of death internationally and a major cause of long-term disability. Hypertension is also a important risk cause for vascular cognitive impairment (VCI), in addition to Alzheimer disease (AD), the greatest common reason of dementia in the ageing (Gorelick *et al.,* 2011). In our study showed there is significance between healthy group and patient group at ($P \leq 0.05$) in relation to hypertension.

**Biochemical parameters of study groups**

Table 1: The demographics features at the study population.

| Parameter | Control (Means ± SD) | | Patients (Means ± SD) | P-Values |
|---|---|---|---|---|
| Numbers | 25 | | 25 | - |
| Age | 35.17± 7.27 | | 53.33 ± 9.21 | 0.36 |
| Gender(F/M) | 9 / 16 | | 13 / 12 | 0.055 |
| BMI | 26.3 | | 27.7 | 0.79 |
| Family history | Yes | NO. 2 | NO. 5 | 0.82 |
| | No | NO. 23 | NO. 20 | |
| Smoking | Yes | NO. 9 | NO. 14 | 0.05 |
| | No | NO. 16 | NO. 11 | |
| Hypertension | Yes | NO. 3 | NO. 15 | 0.038 |
| | No | NO.22 | NO. 10 | |
| History of cardiovascular disease | Yes | NO. 1 | NO. 11 | 0.04 |
| | No | NO.24 | NO. 14 | |

SD: standard deviation. NO: number

Table 2: the mean BNP concentrations distribution between male and female for each of patients and control.

| Groups / Gender | BNP pg/ml (Means ± SD) Female | BNP pg/ml (Means ± SD) male |
|---|---|---|
| CKD | 437 ± 66.4 (n=13) | 467 ± 58.72 (n=12) |
| Control | 149.5± 82.6 (n=9) | 158.21± 71.33 (n=16) |
| P-Value | 0.067 | 0.079 |

Fig. 1 show that the renal functions of the patients were in increase as compare with healthy group. The urea, serum creatinine and cystatin-C. In this study we also compared between chronic kidney disease stages, where these parameters at high concentrations (P= 0.001) in stage 4 and 5 in comparison with renal stage 1-3 and control group. Cystatin-

C show start to variation for unusual line levels on stages 1-3 and it became has abnormal levels in CKD stages 4-5 (Fig. 2) this in compare with other investigations that used s.Cr, s.Ur and ALB which may be more useful, serum cystatin-C has been suggested as a perfect biomarker for evaluating the GFR. A numerous of studies have shown that serum cystatin-C is a highly sensitive and specific marker of a primary and slight reduction in kidney functions than serum creatinine (Fan *et al.,* 2014; Kukla *et al.,* 2014). These results look logically precision as serum cystatin-C levels have stability and nondependent of body tallness, weight, and muscles mass. Cystatin-C is produced in stability degree, that is non-effected by human age, gender and nutrition.

The concentration of different serum lipid component from CKD patients compared to healthy control results are shown in Fig. 3. A profound increase in serum TG, CHOL, LDL and VLDL concentration (P<0.002). In addition, the levels of HDL-C are significantly lower in cases (P<0.024). The present study shows significant changes in lipid profile of ESRD patients when compared with that of healthy matched controls. These results show comparable to the results showed in other studies by Saland *et al.* (2019), Mohamed Ragab and Amany Ragab (2007) found that dyslipidemia is common among Chronic kidney disease patients. In the dialysis patients, the lipid metabolism disorders are more than a dys-lipidemia and hyper-lipidemia. The levels of Triglyceride (TG) are increased while the levels of cholesterol are slightly increased. Very low-densities lipoproteins (VLDL) and chylomicron (CM) Lipolysis is reduced in part as a results of declined lipoprotein lipase and as a result of increase in level of apolipoprotein (apo) C III. Apolipoprotein C III is thoroughly related with reduced catabolism of Triglyceride-rich lipoprotein in MS and is associated with TG levels increase in CKD.

**Consequences of CKD on the haematological parameters**

Effect of chronic kidney disease on haematological parameters show in Fig. 4, where the RBC count, haemoglobin levels and MCV and MCH are significantly reduced (p<0.05) at the patients of CKD, erythropoietin production decrease and other causes which suppress bone marrow production of cell is consider the main cause of decreased RBC counts and resulting decrease in the Hb concentration and haematocrit (HCT) in CKD (Habib *et al.,* 2017). Anaemia is the more common, constant and severe factor of the numerous haematological defects (Dorgalaleh *et al.,* 2013). Although anaemia may be found at different CKD stages, a high correlation found among the anaemia incidence and the degree of CKD severity. In addition to chronic renal failure patients with anaemia are disposed to progress infections and haemorrhage diathesis (Dogara *et al.,* 2018). It is well known that haematological parameters are reduced in CKD. The most affected ones are erythrocyte indices. This is because majority of erythropoietin is synthesized in the juxta glomerular apparatus except 10% in liver and other organs. Apart from decreased erythropoietin, changes in red blood cells (RBCs) indices may be caused by iron, vitamin B-12 and folic acid deficiencies, which are result from dietary deficiency or blood less or by decreased erythrocytes' life span. Other causes of anemia in CKD may include gastrointestinal bleeding; severe hyperparathyroidism and systemic inflammation (Locatelli *et al.,* 2007).

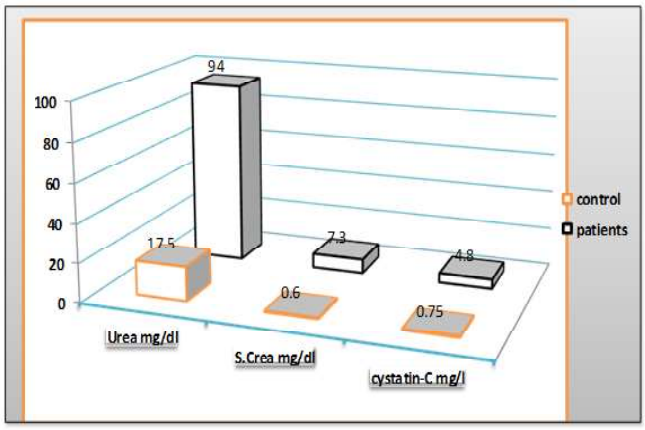


Fig.1: The concentration of renal functions parameters between patients and control.

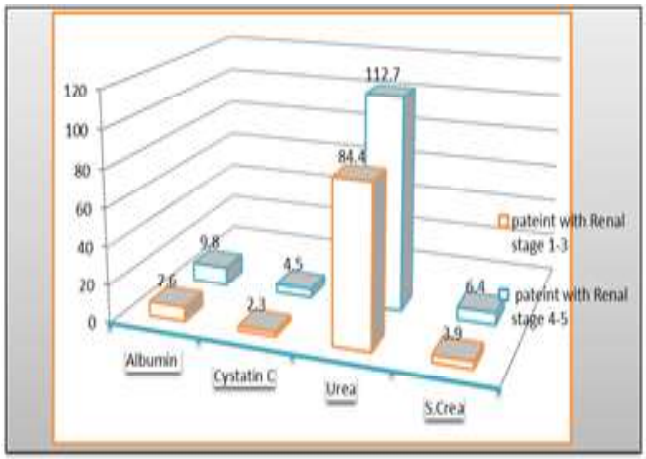


Fig.2: The concentration of renal functions parameters between patients with renal stage 1-3 and renal stage 4-5 CKD.

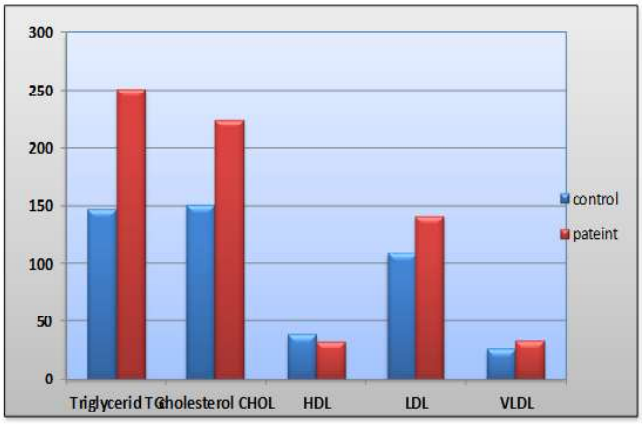


Fig. 3: Distribution of the cases according to the concentration of serum lipid profile in CKD.

**Brain natriuretic peptide hormone (BNP) and CKD**

Fig. 5 display that plasma N-BNP concentration was

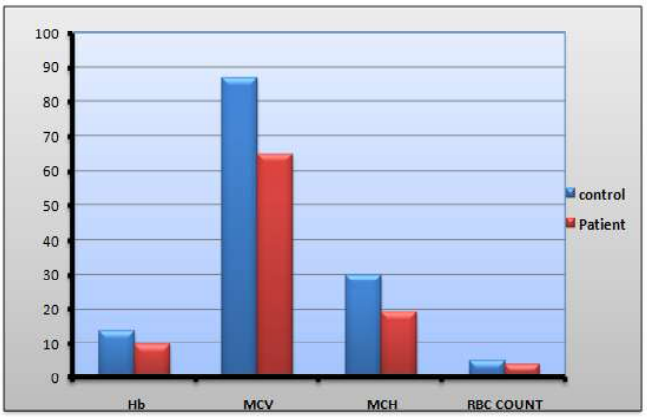


Fig. 4: Distribution of the cases according to the concentration of Hb, MCV and MCH in CKD.

significantly greater in patients of chronic kidney disease than control group (p<0.001). The plasma median level of BNP for patients through high increase of serum creatinine or serum urea is 474.9 pg/ml compared with 149 pg/ml in control subjects (P< 0.001). The numerous studies reported that plasma levels of N-BNP seem to expect risk of cardiovascular event and mortality in a CKD patient. Some Studies demonstrate the advantage of BNP as a possible biomarker in together

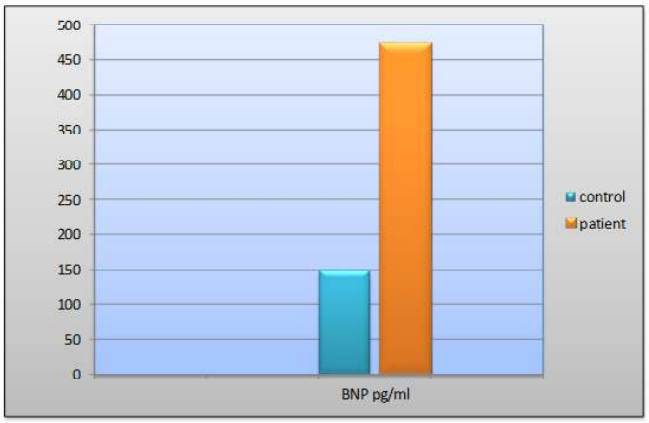


Fig. 5: The mean BNP concentrations CKD.

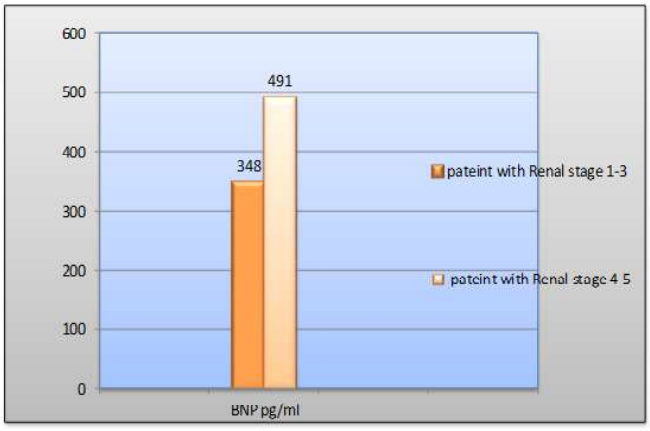


Fig. 6: The mean BNP concentrations in patient with renal stage 1-3 and stage 4-5 in CKD.

non-uraemic and uraemic population. plasma BNP Clearance, the biologically active part of pro-BNP, happens through endocytosis and lysosome degradation next binding to natriuretic peptides clearance and secondarily *via* proteolysis by endo- peptidase 24-11 (Vanderheyden *et al.,* 2004). NT-proBNP Peripheral receptors are not recognized and its clearances less well recognized, but also kidney excretion may play role (Tagore *et al.,* 2008).

Fig. 6 display that plasma N-BNP concentration was significantly greater in patients with renal stage (1-3) with high increase of serum creatinine or urea was 491.3 pg/ml in compare with 348 pg/ml in patients with renal stages (4-5) (P-value<0.01). This study revealed that the BNP increased with the renal disease advance and this make the BNP act as early or predictor marker for the chronic renal disease (CKD). The BNP reported as marker for cardiovascular disease and stroke in brain and other sites, other studies mentioned complications of CKD and their effects on brain (Yang *et al*., 2018).

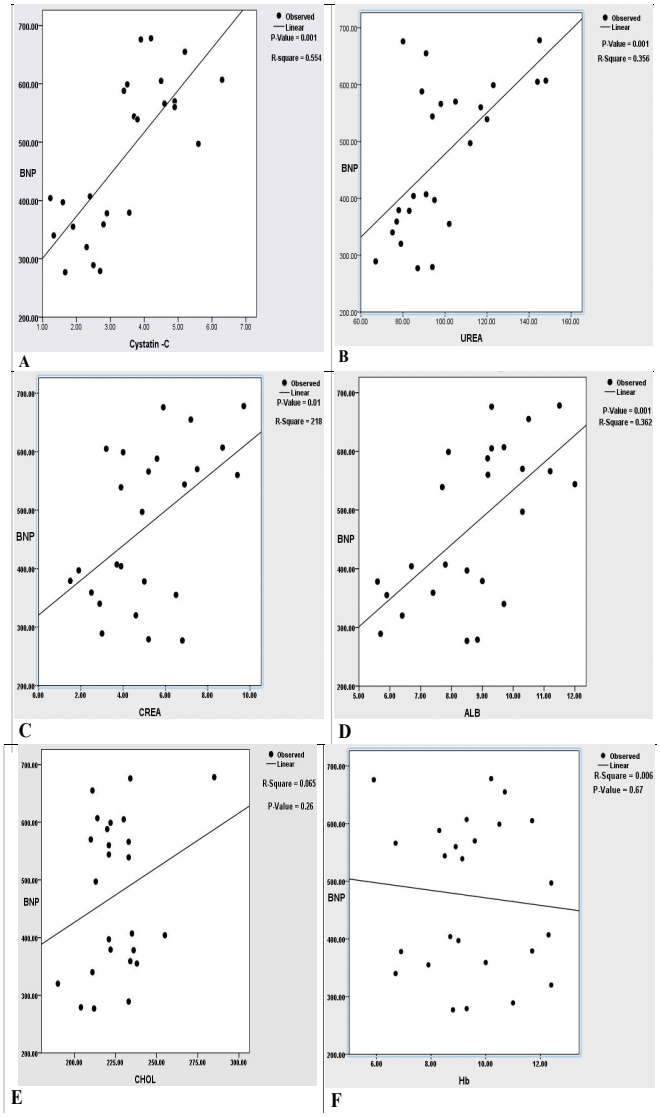


Fig. 7: The mean BNP concentrations in correlation with other CKD parameters.

Fig. 7 show the mean BNP concentrations in correlation with other CKD parameters, where the results showed there is high correlation between BNP and Cystatin - C and Urea, creatinine, cholesterol, Hb and ALB as shown in A, B, C, D, E and F. A significantly relationship was observed among BNP and other markers in all renal stages.

**Conclusion**

Our study conducted there is a main relationship between BNPhormone level and CKD. This support that BNP level is related with the renal stage progression in disease.

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