Plasma cGMP Level as a Marker of the Hydration State in Haemodialysis Patients

Thesis

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Master Degree in Internal Medicine

By

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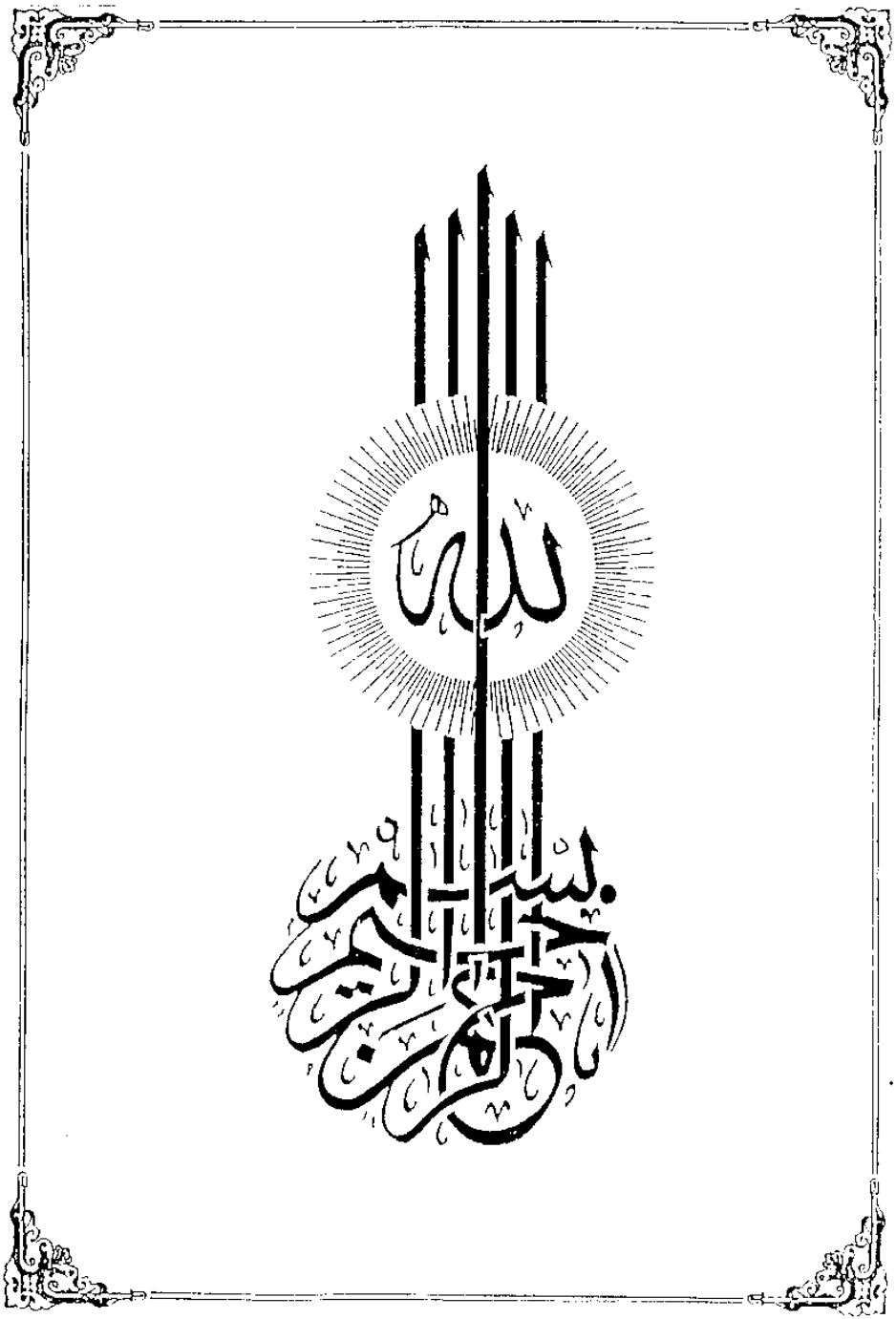
بسم الله الرحمن الرحيم

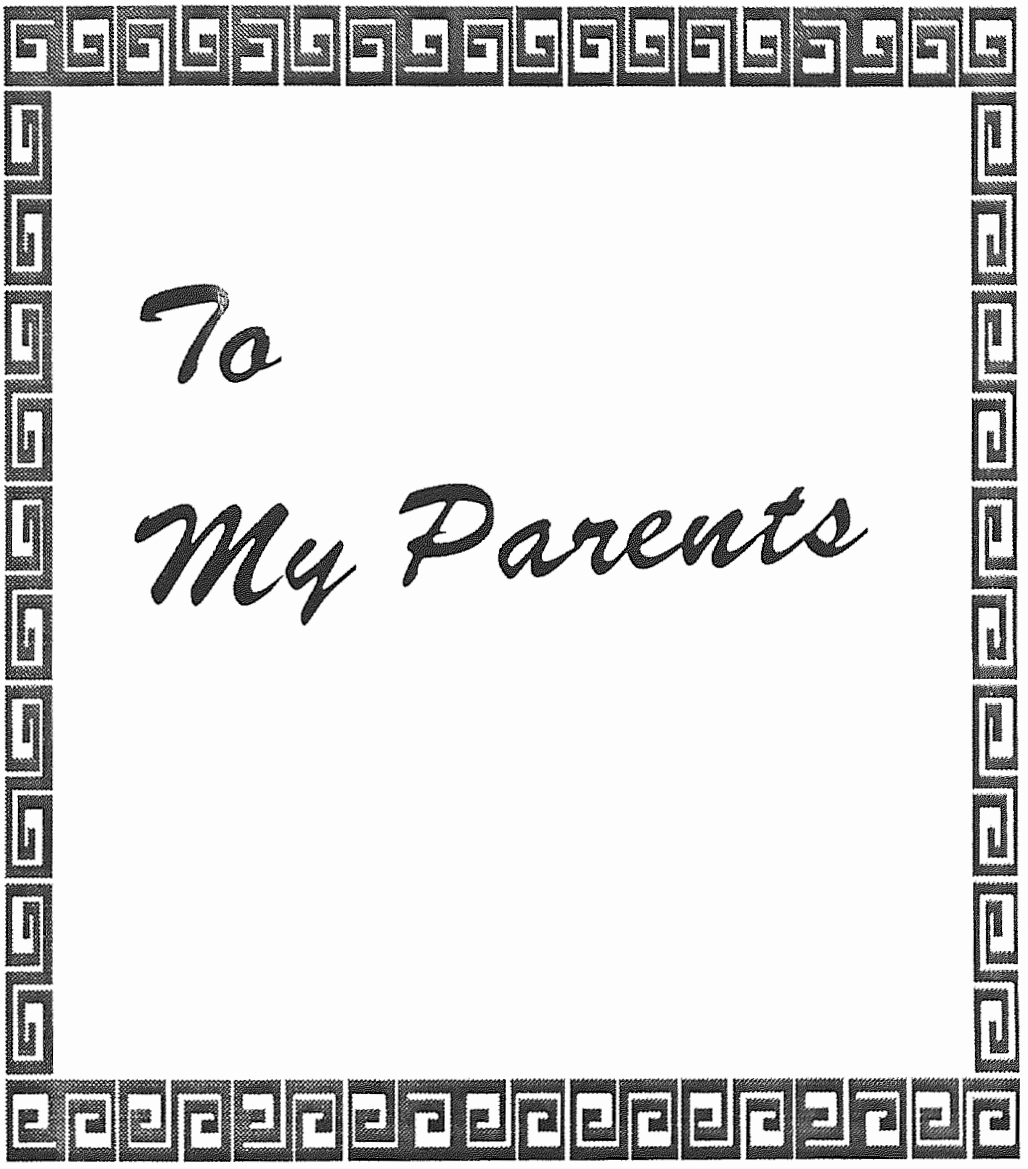
وعلمك ما لم تكن تعلم وكان

فضل الله عليك عظيما

صدق الله العظيم

(سورة النساء آيه : ١١٣)




To
My Parents

Acknowledgment

Thanks forever for God who helped me through this work.

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CONTENTS

INTRODUCTION

Introduction:

Patients with end stage renal failure maintained on non transplant renal replacement therapy usually require reduction of their body fluid volume in conjunction with dialysis. The determination of the amount of fluid over load in patients with terminal renal failure still represents one of the central issues of chronic renal replacement therapy. **(Weidmann et al., 1988).**

The usual procedures for the assessment of "dry body weight" in dialysis patients are the observation of clinical symptoms such as blood pressure, dyspnea or peripheral oedema and the evaluation of a chest x-ray. These methods , however, lack specificity and sensitivity. Thus, dry body weight estimation may be inaccurate in many patients with end stage renal disease. Expansion of the plasma volume is an important determinant for the secretion of the atrial natriuretic peptide ANP. **(Weidmann et al., 1988).**

Cyclic GMP (cGMP) is considered a reliable marker for ANP action in humans and its plasma level seems to reflect volume expansion at least as accurately as ANP itself **(Weil et al., 1985).** Plasma levels of ANP and cGMP are elevated in diseases with expanded extracellular fluid volume such as heart failure or chronic renal falilure **(Weidmann et al., 1988).**

It has repeatedly been demonstrated that plasma ANP and cGMP levels fall significantly during fluid removal by hemodialysis or hemofilteration (**Saxenhofer et al., 1987**).

Using Duplex Scanning and color flow mapping, **Natori et al., 1979,** showed that the antero-posterior diameter and the amount of inspiratory decrease of the inferior vena cava (I.V.C), measured just below the diamphragm in the hepatic segment, in patients lying in supine position, correlated well with central venous pressure. Because Duplex Scanning and color flow mapping investigation of I.V.C can easily be performed in most patients, it might be valuable as a potential tool in guiding optimal fluid balance during hemodialysis treatment. (**Moreno et al., 1984**).

Aim of the Study :

The aim of this study is :

1) To assess the reliability of measuring plasma level of cGMP as a marker of fluid overload in hemodialysis patients.
2) Find out an accurate non invasive measure for the hydration state and dry body weight in patients receiving hemodialysis.

REVIEW OF LITERATURE

CHRONIC RENAL FAILURE

Definition:

Chronic renal failure results from progressive loss of nephrons which causes a permanent impaired renal functions.

Diminished renal reserve is the first stage of chronic renal failure. Plasma biochemistry is normal and the abnormality in renal functions is detected only as a decrease in the glomerular filtration rate (GFR). Diminished renal reserve progresses to early renal failure when the GFR is about 30 ml/min. Late renal failure occurs when the GFR is about 10 ml/min.

End stage renal failure (ESRF) occurs when GFR is only 5 ml/min.

The term **azotemia** is used to indicate that the measured products of nitrogen metabolism usually urea and creatinine, exceed the normal blood levels. **Uremia** is the illness which results from renal failure. It presents as a spectrum of symptoms resulting from the metabolic poisoning of different body organs and systems. Many diseases causing progressive loss of renal function do so slowely and the symptoms of uremia may therefore develop insidiously **(Drukker et al., 1983).**

Approximately one third of patients presenting with ESRD do so as relative emergencies, their kidney failure being diagnosed only days or weeks before some form of renal replacement therapy (RRT) is necessary for their survival. **(Klaht et al., 1981).**

Pathophysiology of chronic renal failure:

In chronic renal failure many compensatory and adaptive mechanisms work together to maintain acceptable health until GFR is about 10-15 ml/minute. Life sustained renal excretory and hemostatic functions may continue until GFR is less than 5 ml/min. The relation-ship between the blood urea and GFR is shown in Fig. (1):

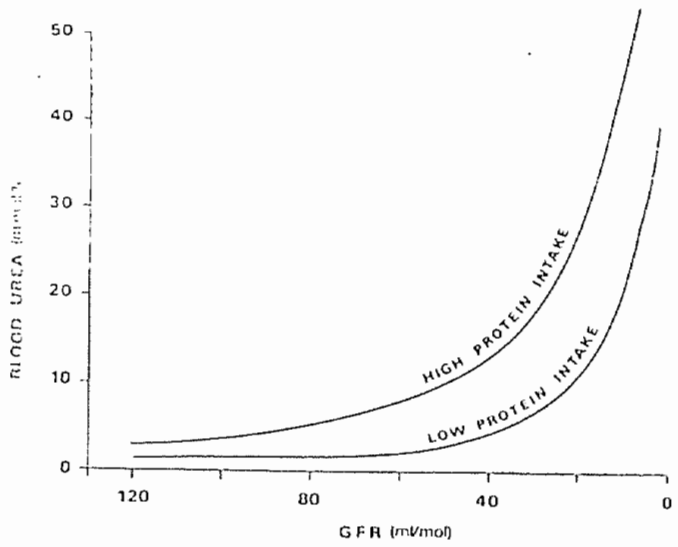

Fig. (1) : Relationship between GFR (measured by creatinine clearance) and blood urea.

The popular explanation for continuing function in remaining nephrons is the "**Intact nephron hypothesis**", i.e. that most nephrons are non functioning, while the remaining few function normally. **(Bricker and Fine., 1981).**

These functioning nephrons produce an increased volume of filtrate and their tubules respond appropriately by excreting fluid and

solutes in amounts which maintain external balance. For sodium and potassium some balance exists at GFR 5 ml/min. and plasma values are commonly normal (**Bricker and Fine., 1981**)

For water and phosphate, adaptation is less precise and plasma concentrations are increased in many patients at GFR 20 ml/min., and in almost all at 5-10 ml/min. (**Mitch et al., 1986**).

The "**trade off**" hypothesis is to be considered together with the intact nephron hypothesis, i.e. the concept that adaptations arising in chronic renal failure may control one abnormality, but only in such a way as to produce other changes characteristic of the uremic syndrome. Although the mechanisms involved are largely unknown, examples are parathormone in phosphorus balance, vasopressin in free water clearance and atrial natriuretic peptide in the control of sodium excretion. (**Olson et al., 1988**).

The established example of "**trade off**" is excess parathormone essential for phosphate excretion, as GFR falls plasma phosphate rises, PTH secretion increases, and plasma phosphate is lowered by decreased tubular reabsorption. The cost of normal plasma phosphate is elevated PTH, secondary hyperparathyroidism, and metastatic calcification. Other abnormalities attributed to excess PTH include central and peripheral nervous diseases, impotence, myopathy, carbohydrate intolerance and lipid disorders (**Kraus et al., 1985; Feinfeld et al. 1988**).

It is also suggested that there are "trade offs" associated with the homeostasis of sodium, potassium and others solutes. **(Olson et al., 1988).**

Loss of nephrons from any cause initiates a process of progressive nephron destruction which continues independently of the original cause(s) of the renal disease. It appears that hyperperfusion of the remaining intact nephrons causes hyperfiltration and damage which reveals itself first as mesangial thickening. This subsequently evolves into glomerulosclerosis. **(Ischikawa et al., 1988).**

Hypertension and phosphate retention may also play a part in this process. This leads to consideration of a third hypothesis which is related to the pathogenesis of chronic renal failure, it states that hyperfiltration in residual nephrons is increased by a high load of protein metabolites, resulting in the more rapid exhaustion of nephrons. Work in experimental animals with diminished renal mass indicates that low protein diets permit increased survival with remnant kidneys. Evaluation of this hypothesis in clinical practice is difficult but early evidence suggests that the rate of progression of renal failure in some diseases can be slowed by the institution of low protein diets. **(Miller et al., 1988).**

CONTROL OF EXTRA CELLULAR FLUID VOLUME

Extra cellular fluid volume is maintained within narrow limits in normal human subjects despiete day-to-day variations in the dietary intake of salt and water over a very wide range. **(Luft et al., 1979).**

The opertion of a system for sodium homeostasis requires:

1. Sensors that detect changes in extracellular fluid volume.
2. Effector mechanisms that ultimately modify the rate of sodium excretion by the kidney to meet the demands of volume homeostasis. **(Bonventre and Leaf., 1982).**

Afferent limb: The sensors for fluid volume homeostasis:

The afferent sensing sites are composed of cardiopulmonary and arterial baroreceptors as well as renal, central nervous system and hepatic sensors.

I. Cardiopulmonary volume sensors:

1. Atrial sensors:

The cardiac atria possess the distensibility and the complaince necessary to effectively monitor changes in intra thoracic venous volume. **Henry and colleagues (1956)**, demonstrated that left atrial distention induced diuresis. Since that time, diuresis and natriuresis as consequences of increasing atrial wall tension have been clearly established. **[Reinhardt et al., (1980), Kaczmarczyk et al., (1981)].**