SERUM CYSTATIN C IS A SUPERIOR MARKER IN ESTIMATING GFR TO ASSESS KIDNEYS DYSFUNCTION- A DESCRIPTIVE CONTROLLED COMPARATIVE STUDY

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ABSTRACT

BACKGROUND

Kidney function is accurately assessed by Glomerular Filtration Rate (GFR). GFR is estimated with various biomarkers like inulin, creatinine and Cystatin C. Inulin is not synthesised in the human body. Creatinine is a variable parameter. But, Cystatin C is removed completely from the blood stream by glomerular filtration. Hence, Cystatin C level in the blood can be used to estimate GFR.

MATERIALS AND METHODS

One study group of 50 patients with renal failure and another control group of 50 normal persons were selected for Cystatin C estimation. Cystatin C was measured in a random sample of serum of both control group and study group by using Quantitative Cystatin C immunoturbidimetric assay. Mean values of Cystatin C were statistically analysed by using "t" test. GFR from Cystatin C value was measured by using a prediction equation.

RESULTS

Cystatin C levels in blood were significantly increased in patients of renal failure. GFR was estimated by Cystatin C levels. The elevated Cystatin C level was correlated with estimated GFR.

CONCLUSION

Cystatin C level in patients of kidneys dysfunction was statistically elevated. Similarly, the GFR estimated using serum Cystatin C was also statistically elevated. Hence, Cystatin C was a good biological marker to assess kidneys dysfunction.

KEYWORDS

Cystatin C, Glomerular Filtration Rate, Kidneys Dysfunction, Turbidimetry.

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BACKGROUND

Chronic Kidney Disease (CKD) is a worldwide public health problem. There is rising incidence and prevalence of kidney failure. Early diagnosis of kidney diseases can be detected through laboratory testings. Accurate estimation of Glomerular Filtration Rate (GFR) is essential for the diagnosis, staging and management of CKD. Chronic Kidney Disease (CKD) is defined as the presence of persistent and usually progressive reduction in GFR (GFR <60 mL/min./1.73 m^2).[1]

Though Cystatin C levels have been altered in patients with varieties of cancer,[2] thyroid dysfunction,[3] cardiovascular disease[4] and neurologic disorders,[5] many studies found that Cystatin C is a best marker to assess chronic kidney dysfunction.

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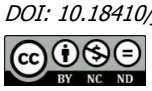

Creatinine as a Marker of GFR

Serum creatinine was tried as a marker of GFR. Creatinine is a by-product of muscle turnover. It is well established that a small amount of creatinine is also secreted by kidney tubules. Therefore, creatinine clearance will always over estimate GFR to some extent. Furthermore, muscle mass varies greatly between individuals depending on their age, gender and size. So, serum creatinine is inaccurate in estimating GFR.[6]

Cystatin C - A better Marker of GFR

Cystatin C, a polypeptide chain is made up of 120 amino acids. All tissues and body fluids contain Cystatin C. Also, Cystatin C is completely removed from the blood by glomerular filtration. Cystatin C has a stable production rate and is removed from the blood circulation by glomerular filtration. In healthy individuals, Cystatin C is completely reabsorbed and degraded in the tubules. Depending on the type of analytical method, normal values for Cystatin C in serum are between 0.52 and 0.98 mg/L and in patients with renal tubular disorders maybe raised as high as 2 to 5 times normal values. Normal Cystatin C serum levels are the same for men, women and children, unlike creatinine, which has varying normal levels for these groups.[7]

The serum concentration of Cystatin C remains unchanged with infections, inflammatory or neoplastic states and is not affected by body mass, diet or drugs. Thus, Cystatin C maybe more reliable marker of renal function (GFR) than creatinine.[8]

Monitoring of kidney function using creatinine based glomerular filtration rate is a routine part of clinical practice. Emerging evidence has shown that Cystatin C may improve classification of GFR in assessing CKD. Cystatin C has been available as a measure of kidneys function for many years. During the past decade, Cystatin C has been used extensively as a research tool for understanding kidney function.[9]

A new nephelometric immunoassay for determination of Cystatin C has made it more practical and clinically useful to estimate GFR. Serum Cystatin C measurement has been shown as better indicator of changes in GFR than serum creatinine.[10]

In clinical practice, Cystatin C is becoming more frequently known as the biomarker of choice for detecting renal failure and unlike creatinine is not dependent of age, sex, race, lean muscle mass or any inflammatory processes.[11]

Reference values differ in many populations and with sex and age. Across different studies, the mean reference interval was between 0.52 and 0.98 mg/L. For women, the average reference interval is 0.52 to 0.90 mg/L with a mean of 0.71 mg/L. For men, the average reference interval is 0.56 to 0.98 mg/L with a mean of 0.77 mg/L. Creatinine levels increase until puberty and differ according to gender from then on making their interpretation problematic for paediatric patients.[7]

Aims and Objectives

Glomerular filtration rate is inaccurate at detecting mild renal impairment and levels can vary with muscle mass and protein intake.[7] Cystatin C has a low molecular weight and it is removed from the blood stream by glomerular filtration in the kidneys. If kidney function and glomerular filtration rate decline, the blood levels of Cystatin C rise. The aim of the study is to show the serum levels of Cystatin C are a more precise test of kidney function than serum creatinine levels.

MATERIALS AND METHODS

Cystatin C can be measured in a random sample of serum using immunoassays such as nephelometry or particle-enhanced turbidimetry.[12]

Fifty renal failure patients of both sex with age more than 20 years were selected from the Registry of Nephrology Department of Kovai Medical Center and Hospital, Coimbatore, Tamilnadu, India. Renal failure was confirmed by estimating blood urea, serum creatinine and serum potassium. This study was made on renal failure patients before subjecting them for renal dialysis. Control group of fifty subjects of both sex with age more than 20 years were selected from Master Health Department. After getting consent from both subjects of control group and study group, venous blood samples were collected. Blood samples were centrifuged and clear serum samples were obtained.

Cystatin C was estimated in serum sample of both control group and study group by using quantitative Cystatin C immunoturbidimetric assay.[3] Estimated GFR was obtained by software using the formula, CKD-EPI creatinine and Cystatin C formula and simple Cystatin C formula (100/serum Cystatin C).[13]

Inclusion Criteria

Those who are confirmed renal failure patients of both sex with age more than 20 years are included in this study. Those who are free from other diseases like liver diseases, cardiovascular diseases, metabolic syndrome, etc. were included in this study. Control group of both sex with the same age group free of any kind of diseases were included in this study.

Exclusion Criteria

Those who are on chronic medications, congenital kidney diseases and those whose kidneys were affected by diseases like diabetes mellitus, hypertension, etc. were excluded from this study.

RESULTS

Mean values of Cystatin C were statistically analysed by using Student's t-test. The levels of Cystatin C in control group and study group were presented in Table 1.

Groups	Mean ± SD	Groups Compared	't' Value
Study Group (A) (50)	5.4 ± 1.44		
Control Group (B) (50)	0.8 ± 0.17	A and B	15.0

Table 1. Mean Values of Cystatin C in mg/L in Study Group Compared with Control Group

P <0.05 - Significant at 5% level.
P <0.01 - Significant at 1% level.

GFR from Cystatin C value was measured by using the chronic kidney disease epidemiology (CKD-EPI creatinine and Cystatin C formula) collaboration formula, a new GFR marker formula, modified as simple Cystatin C formula (100/Cystatin C).[13]

CKD- EPI Formula- GFR (mL/min./1.73 m^2) = 79.901/Cystatin C (mg/L).[1.4389]

Cystatin C Simple Formula- GFR (mL/min./1.73 m^2) = 100/Cystatin C mg/L.

Mean values of estimated GFR were statistically analysed by using Student's t-test. The levels of eGFR in control group and study group were statistically analysed by using Student's t-test were presented in table 2.

Groups	Mean ± SD (mL/min./1.73 m^2)	Groups Compared	't' Value
Study Group (A) (50) Control Group (B) (50)	7.7 ± 3.2 116 ± 32.13	A and B	16.7

Table 2. Glomerular Filtration Rate in mL/min./1.73 m^2 in Control and Study Group

P <0.05 - Significant at 5% level.
P <0.01 - Significant at 1% level.

DISCUSSION

Fifty renal failure patients with 20 years and above age group were selected as study subjects. Fifty normal persons with the same age group were selected as control group for comparison. The serum Cystatin C level in the study group was compared with serum Cystatin C level of the control group. GFR was estimated by using serum Cystatin C. GFR of study group was compared with control group.

Cystatin C has a low molecular weight (approximately 13.3 kilodaltons) and it is removed from the bloodstream by glomerular filtration in the kidneys. If kidney function and glomerular filtration rate decline, the blood levels of Cystatin C rise.[1,5]

The renal handling of Cystatin C differs from creatinine, while both are freely filtered by glomeruli, once it is filtered, Cystatin C, unlike creatinine is reabsorbed and metabolised by proximal renal tubules. Thus, under normal conditions, Cystatin C does not enter the final excreted urine to any significant degree.[14]

Cystatin C, a biomarker unlike creatinine is not dependent of age, sex, race, lean muscle mass and inflammation.

When the study group (5.4 mg/L ± 1.44) was compared with control group (0.8 mg/L ± 0.17), it is noted that serum Cystatin C is significantly increased in renal failure patients.

When the GFR in study group (7.7 ± 3.2 mL/min./1.73m^2) was compared with control group (116 ± 3.13 mL/min./1.73 m^2), it was observed that GFR was decreased significantly in renal failure patients.

The present study was very well correlated with the study of Dharnidharka et al and Roos J.F. et al.[15,16]

Cystatin C inversely correlates with the Glomerular Filtration Rate (GFR) that is elevated levels of Cystatin C indicate decreased GFR. Cystatin C may provide more accurate assessment of GFR for very obese, elderly or malnourished patients than creatinine. Cystatin C equation does not require patient ethnic data and can be used for those patients with this information unavailable.[7]

Normal GFR was estimated by using inulin, which was neither synthesised and nor utilised in the human body. Subsequently, creatinine level in the blood was used to measure GFR.

Since serum creatinine level varied with muscle mass and diet intake, accurate GFR could not be estimated and hence kidneys dysfunction could not be assessed.

Serum Cystatin C was proposed as a potential replacement for serum creatinine in Glomerular Filtration Rate (GFR) estimation. A high level of Cystatin C in blood corresponds to a decreased glomerular filtration rate and hence to kidney dysfunction. Serum Cystatin C is produced throughout the body at a constant rate and removed and broken down by the kidneys. It should remain at a steady level in the blood if the kidneys are working efficiently and the GFR is normal (>60 mL/min./1.73 m^2).

Serum levels of Cystatin C are more precise test of kidney function than serum creatinine level.

CONCLUSION

Serum Cystatin C has been proposed as a simple accurate and rapid endogenous marker of Glomerular Filtration Rate (GFR) and it is superior to serum creatinine. Hence, Cystatin C can be used to detect chronic kidneys dysfunction.

Cystatin C may help clinicians in diagnosing kidney damage more effectively than by measuring creatinine levels alone. Hence, Cystatin C is the potential marker to assess chronic kidneys dysfunction.

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