Cystatin C vs Creatinine to Assess Glomerular Filtration Rate on Kidneys

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Abstract
Accurate glomerular filtration rate estimation informs drug dosing and risk stratification. Creatinine estimation will be unreliable in patients with low or high muscle mass. Cystatin C provides an alternative estimation of glomerular filtration rate that is independent on muscle mass. We compare here the cystatin C and creatinine based glomerular filtration rate of kidney function.

Key Words: Glomerular filtration rate, Creatinine, Cystatin C

I. Introduction:
Glomerular filtration rate is a marker of kidney health and measured by injecting compounds such as inulin, radioisotopes, chromium -EDTA, i-ithalamate and radio contrast agents. These methods are complicating, time consuming and have potential side effects. So to estimate GFR the above procedures are monotonous[1]. Because of that to estimate GFR rate cystatin C and creatinine levels are maneuvered in 1999 to assess the condition of the kidneys through endogenous methods.

To estimate the GFR some equations are used like cockcroft-gault, modification of diet in renal disease (MDRD), chronic kidney disease (CKD-ETI) epidemiology collaboration are regarded as measures of serum creatinine or cystatin based on the age, gender, race then factored to produce a numerical quantity similar to measured GFR[2]

Cockcroft and gault GFR ml/min (male) = (140-age) × weight (kg) ÷ 7.2 × Scr (mg/dl)
Cockcroft and gault GFR ml/min (female) = (140-age) × weight (kg) ÷ 7.2 × Scr (mg/dl) × 0.85

MDRD GFR (male)= 175×Scr (mg/dl) ÷ 1.154 × age -0.203
MDRD GFR (female)= 175×Scr (mg/dl) ÷ 1.154 × age -0.203 × 0.7442
GFR Normal level male = 125ml/min/1.73m²
GFR Normal level female = 105ml/min/1.73m²

Some of the reports say that thyroid function has impact on both cystatin and creatinine levels[3]. Serum creatinine levels have shown to be elevated in hypothyroidism, and lower in Hyperthyroidism. For cystatin C levels the contrary is that it is due to the change in synthesis of the cystatin C but also could be due to the changes in the clearance.

Cystatin C is a low molecular weight (approximately 13.3 kilodaltons) serum protein secreted out of the blood by the kidneys and serves as a measure of kidney function. Cystatin C is formerly a gamma trace found in 1961 and it is also called as post gamma globulin and Neuroendocrine basic polypeptide[4]. This protein is encoded by CST3 gene which is used as a biomarker for the kidney function. So it is called as cystatin 3 or CST3 gene.

It is produced steadily by all types of nucleated cells in the body and act as a chain of 120 amino acids. Cystatin C is virtually seen in different fluids including blood, spinal fluid and breast milk. Cystatin C is a cysteine protease inhibitor produced by nucleated cells and encoded by housekeeping gene. It is freely filtered by glomerulus and then reabsorbed by proximal tubules where it is metabolized. Its concentration in the blood correlates with the glomerular filtration rate. The level of cystatin is independent on weight, muscle mass, sex and age.
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It is potent inhibitor of lysosomal proteases and most probably one of the most important cysteine proteases. CST3 leads to the prediction of new onset or deteriorating cardiovascular disease [5]. The blood levels of cystatin C predicts the survival of one type of heart attack. A high level of cystatin C after heart attack is ominous sign because it reflects the failure of the kidney to clear the cystatin from blood into the urine [6]. A mutation of the gene is responsible for an amyloidosis when it gets deposited in brain leads to premature stroke, intracranial hemorrhage and dementia [7]. This disease is called amyloidosis or cerebrovascular amyloidosis. It is inherited in an autosomal dominant manner. Mutations in this gene due to Icelandic type of hereditary cerebral amyloid angiopathy, a condition predisposing to intracerebral hemorrhage, stroke and dementia. Condition is inherited in a dominant fashion [8].

Since cystatin 3 binds amyloid beta and reduces its aggregation and deposition, it is a potential target in Alzheimer's disease. A role of cystatin C in multiple sclerosis and other demyelinating disease remains controversial. Cystatin C decreases in atherosclerosis and aneurysmal lesions of aorta. Break down of parts of the vessel wall in these conditions is thought to result from an imbalance between proteases matrix and their inhibitors.

Cystatin C gene role in age relates as macular degradation and even as prognostic marker in cancer [9].

Cystatin levels are aggravated by cigarette smoking and levels of reactive protein and HIV infections altered in patients with cancer, thyroid dysfunction and glucocorticoid therapy in some but not in all situations. Normal levels of cystatin C is 0.6-1mg/l.

Creatinine is widely available, rapidly measured, relatively inexpensive and reliable indicator of kidney function that is related to change in GFR. It is the universal test to monitor both acute and chronic kidney diseases. It is a chemical waste molecule that is generated from muscle metabolism [10]. Approximately 2% is transported to blood stream through kidneys.

Kidneys seep out the at most of the creatinine and discard it in the urine. Creatinine itself is a product via a biological system involving creatinine phosphate creatine and ATP. It is primarily synthesized in liver from the methylation of glycocyanin by serum adenosyl methionine [11,12].

Young age children will have more creatinine clearance than normal and elderly people will have less creatinine clearance when compared to normal people. Infants normal levels is about 0.2 or more depend on the muscle mass [13]. To assess the good kidney function GFR should be observed like below 60ml/min/1.73m² for 3 months and above 60ml/min/1.73m² with signs of kidney damage having protein in urine as sign of kidney damage [14].

**Creatinine normal level** -0.6 to 1mg/l
Creatinine clearance normal value (male) = 110 to 150 mL/min
Creatinine clearance normal value (female) = 100 to 130 mL/min

II. Case Presentation:

A report of hyperthyroid with a discrepancy between the GFR estimates from cystatin C and creatinine. The results show that cystatin C concentration (1.36 mg/L) was higher and cystatin-estimated GFR was lower (51mL/min/1.73m²), while the creatinine concentration was lower (36 µmol/L) and creatinine-estimated GFR was higher (145 mL/min/1.79 m²) than the iohexol-estimated GFR (121 mL/min/1.73 m²) during the hyperthyroid period. After thyroidectomy, the creatinine concentration was 36µmol/L and creatinine-calculated GFR was 73mL/min/1.73 m², while the cystatin C concentration was 0.78mg/L and 114 mL/min/1.73 m², respectively.

III. Discussion:

As hypotheypothyroid and hyperthyroid diseases occur frequently, it is important to be aware of spurious results due to these conditions. The cystatin C-estimated GFR (51mL/min/1.73m²) during the hypothyroid was lower than the iohexol-estimated GFR (121mL/min/1.73m²). Contrarily the cystatin C-estimated GFR value postoperatively (114mL/min/1.73m²) was close to the iohexol-estimated GFR during the hyperthyroid period [15]. Thus, this indicates that subsequent changes in cystatin C (increase) and cystatin C-estimated GFR (decrease) is not due to a change in glomerular clearance, but rather due to increased secretions in hyperthyroid state. Here iohexol clearance was performed only during hyperthyroid state to evaluate whether the patient had a decreased GFR or not and it is not performed in the euthyroid state (after surgery).

During euthyroid state (normal), the cystatin C-estimated GFR was 114mL/min/1.73m² and the creatinine-estimated GFR was 73mL/min/1.73m². According to previous reports, the MDRD equations used to report the results below 60 mL/min/1.73m². Thus both GFR estimates in the euthyroid period were considered normal. Hence, it is therefore not considered obligatory to perform an additional iohexol clearance during euthyroid period. On the other hand, the creatinine values (36 µmol/L) were reduced during the hyperthyroid period with an ensuring catabolic state resulting in an overestimation of the creatinine-estimated GFR (145 mL/min/1.73m²). Thus, both cystatin C and creatinine gave erroneous GFRs in comparison to iohexol clearance, which is used as a reference method in hyperthyroid state.
INTERPRETATION:-

Here, in contrast to creatinine, the cystatin C levels rose in the hyperthyroid state compared to the euthyroid state, and the cystatin C-estimated GFR was reduced compared to iohexol-estimated GFR. Hence, in this case, the alterations in the cystatin C level is not due to change in the GFR in connection with hyperthyroidism. Thus, when both cystatin C and creatinine are used as markers for kidney functioning, the altered thyroid functions must be considered.

MEDICATION:

Serum creatinine levels can increase without reflecting a change in the actual GFR. The antibiotic trimethoprim sulfamethoxazole and H2 blocker cimeditine are commonly used drugs that decrease the secretion of creatinine. Famotidine and Ranitidine causes increase in creatinine but to a lesser degree. Cephalosporin antibiotics causes elevated levels of creatinine. Fenofibrate increases creatinine levels[16]. Ketosteril reduces the concentrations of creatinine in blood. Chitosan supplements also reduce creatinine in body. Corticosteroids increases concentrations of cystatin in tissues. Larger doses of glucocorticoids also increase the production of cystatinC.

For patients whose GFR is below 60ml/min/1.73m2, the proper use of analgesics remains an important issues. NSAIDS such as diclofenac, ibuprofen and indomethacin, selective cox-2 inhibitors should only be given with monitoring serum creatinine level. Several drugs such as Trimethoprim, salicylates, cimetidine have been reported to increase plasma creatinine without influencing its GFR.

COMPARITIVE GRAPH STUDY

Fig.1 Plot of serum creatinine vs diminishing GFR

It illustrates that serum creatinine changes minimally as GFR clearly declines from around 120ml/min/1.73m2 to 60mL/min/1.73m2.

Fig.2 Graph illustrating creatinine levels.
Cystatin concentrations were much more stable in individuals without renal disease than GFR measured by creatinine clearance. The cystatin can easily accumulate in the blood compared to the creatinine. The prevalence of an estimated GFR less than 60 ml per minute per 1.73 m² of body surface area was higher with cystatin C based GFR than with creatinine based eGFR.

Cystatin c has received much attention as an alternative filtration marker with stronger and more linear risk relationships than creatinine. The use of cystatin c alone or in combination with creatinine strengthens the association between eGFR and risk of deaths and end stage renal disease. Serum creatinine is widely available, rapidly measured, inexpensive, and reliable indicator of kidney function that is related to changes in GFR.

### References


[5]. Toffaletti, John G. "Clarifying the confusion of GFRs, creatinine, and cystatin C." (2018).


