Cystatin C and its Twin Position in Estimating Renal and Cardiovascular Fame; An Overview

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Abstract

In this Review of the location of cystatin C in clinical remedy emphasizes, and discuss the proof, that cystatin C-based totally GFR-estimating equations do not require the usage of vague terms like race and sex, that cystatin C-based totally GFR-estimating equations are useful for each youngsters and adults, together with the aged, that the high-quality GFR-estimation calls for simultaneous use of both cystatin C- and creatinine-based equations, that cystatin C-primarily based GFR-estimating equations are advanced to creatinine-based totally equations in predicting end-stage renal sickness, cardiovascular manifestations, hospitalisation and dying eventually that cystatin C is needed to diagnose the brand new syndrome “Shrunken Pore Syndrome” with its excessive mortality and morbidity, even within the absence of decreased GFR. when automatic laboratory gadget is to be had, the value of cystatin C is comparable to that of enzymatically decided creatinine. The realization is that cystatin C have to be used at least as regularly as creatinine in scientific medication.

Keywords: Cystatin C; Renal; Twin Position; World Health Organization

Introduction

Continual Kidney ailment (CKD) refers to a pathological situation, in which the kidneys get broken past reversal, ensuing in compromised blood filtering, in comparison to generally functioning kidneys. As an end result, excess fluid and waste from the blood stay inside the body rather of having filtered, leading to more than one fitness troubles. According to country wide persistent Kidney fact Sheet of 2017, 30 million human beings or 15% people adults are predicted to have CKD, and 48% of these with considerably compromised kidney feature but not on dialysis are oblivious of having CKD, that is a compelling count number of problem [1]. A drastic upward thrust inside the incidence of CKD has been observed global. In 2010, CKD turned into ranked as 18th a few of the major causes of mortality global, in preference to twenty seventh in 1990 [2]. In western international locations, Diabetes Mellitus (DM) and high blood pressure (HTN) make a contribution to over -thirds of the instances of CKD. In India, DM and HTN currently account for 40 - 60% instances of CKD. With the superiority of DM and HTN at the upward push, prevalence of CKD in India is anticipated to upward thrust on an alarming stage [3].

in the latest many years, high incidence of continual Kidney ailment of Unknown etiology (CKDu) has been suggested a few of the working-age populations of agricultural groups of tropical/subtropical areas, notably in primary America and Sri Lanka. In international locations like Nicaragua and El Salvador, the predicted prevalence of eGFR (predicted glomerular filtration rate), without DM and HTN as comorbidities, went as low as 60 ml/min according to 1.73m2 in 10 - 20% inside the affected populations [4]. Financial improvement, together with altering lifestyle behavior increasingly more have an impact on public health, consisting of in growing nations like India, wherein danger elements like DM, HTN and obesity predispose patients to expand CKD. CKD increases patient morbidity and mortality, thanks to development to ESRD (give up-degree renal sickness) and more dangers of cardiovascular headaches sub served [5].

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many nations, the prevalence of persistent kidney disease approximates to 15% of the person population, ordinarily due to diabetic and hypertensive nephropathy, culminating in heightened clinical and monetary burden. Kidney disease and loss of life from renal failure, although giant, yet is poorly documented for both low income and center-income countries. In low-profits countries, infectious reasons, environmental pollution, and publicity to pollutants are taken into consideration to be the main participants to each acute kidney harm (AKI) and CKD. Considering center-earnings international locations such as India, persisting excessive occurrence of infectious causes, hovering rates of HTN in addition to upward thrust in instances of untreated diabetes, make susceptibility to CKD easier; for that reason impeding speedy monetary and epidemiological transitions. Because the improvement of CKD is distinctly dangerous, underdiagnosis of threat elements like DM and HTN is directly proportional to the staging and severity of CKD [6]. Persistent kidney sickness (CKD) is related to age-associated renal function deterioration, similarly sped up in comorbid hypertension, diabetes, weight problems and primary renal disorders. Cardiovascular disease (CVD) constitutes the number one purpose of morbidity and mortality, wherein CKD is taken into consideration as an accelerator of CVD risk and an impartial chance issue for CVD activities. There’s a graded inverse relationship among CVD danger and glomerular filtration price (GFR), no matter age, intercourse and different danger elements. Decreased renal characteristic leads to heightened length of hospitalization, improved threat of cognitive dysfunction and negative first-rate of lifestyles [7]. When you consider that 2015, Kidney studies united kingdom has spearheaded a national venture entitled “assist and treatment of people with revolutionary continual Kidney sickness” (assist-CKD), with the objective of figuring out humans at the best susceptibility of developing persistent kidney sickness (CKD). The venture, that’s being performed through pilot studies across the UK, uses software to map statistics from ordinary blood checks and perceive human beings with chance elements as early as feasible. This helps sufferers to obtain well timed assist and hospital therapy, required to hold their kidney functionality for longer period in their existence-span, and in a few instances, to even postpone or prevent the want for dialysis or renal transplantation. Kidney research UK, via this venture, strives to lessen the quantity of human beings whose lives are rendered brief by means of kidney ailment and to assist people stay higher fitness-related great of life. The charity also focusses in utilising extra investment in studies to discover better remedies and treatment plans for renal diseases. Considering that 1985, Kidney studies united kingdom has invested about £sixty five million into renal studies and related conditions [8].

Biomarkers

Biomarkers are defined as measurable biological parameters, that function indicators for health-and body structure-related tests, inclusive of sickness threat, psychiatric problems, environmental publicity and its consequences, sickness diagnosis, metabolic tactics, substance abuse, being pregnant, cellular line improvement, epidemiologic research, etc. In 2001, a countrywide institute of health (NIH) operating institution standardized the definition of a biomarker as “a feature this is objectively measured and evaluated as a hallmark of regular organic tactics, pathogenic tactics, or pharmacologic responses to a healing intervention”. Measurable organic parameters may additionally include particular enzyme awareness, specific hormone attention, specific gene phenotype distribution in a population, presence of organic materials, and so forth [9].

Biomarkers used to diagnose renal disorder

Serum Creatinine-Creatinine is a breakdown fabricated from creatinine phosphate in muscle. Stimulated through muscles concentration, creatinine is generally produced at a reasonably regular price by means of the body. Creatinine is typically used as degree of kidney function. The normal creatinine clearance check fee is a hundred and ten-a hundred and fifty ml/min in men, whereas in girls it’s far 100-a hundred thirty ml/min. The creatinine clearance take a look at is used to evaluate quantity and severity of renal ailment. Renal disease is commonly suspected when serum creatinine levels exceed the higher restrict of the normal stage. In CKD and uremia, glomeruli and kidney tubules are not able to eliminate creatinine from frame. Creatinine values may vary from person to man or woman, on the idea of muscle function, muscle composition, hobby, weight loss plan, health popularity, ethnicity, gender, and many others. In patients with kidney dysfunction, fake terrible values of creatinine can be acquired because of multiplied tubular secretion of creatinine [10]. Consider-
ing creatinine is produced due to non-enzymatic degradation of muscle creatinine, the previous is at once proportional to muscle tissues. Even though creatinine is freely filtered by using the glomerulus and not reabsorbed via renal tubules, it could be secreted at variable quotes. Tubular secretion of creatinine can be hindered by tablets like cimetidine and trimethoprim [11]. Consistent with the Kidney disorder enhancing global effects (KDIGO) (2012) clinical practice tenet for AKI (Acute Kidney damage), AKI is taken into consideration as a common scientific trouble, defined by means of a sudden (< 48h) increase in serum creatinine (SCr), as a result of an injury or insult, resulting in an extraordinary kidney structure and function, related to blood, urine and tissue check or imaging markers of renal harm in terms of exception, persisting for extra than 6 hours [12].

GFR can be anticipated the use of Cockcroft-Gault equation, that is as follows:

\[
\text{Estimated GFR} = \frac{(140 - \text{Age(years)}) \times \text{Body weight(kg)}}{72 \times \text{serum creatinine (mg per dl)}}
\]

Multiply result by 0.85 if calculating for a female patient.

**Figure 1:** Definition of AKI: risk, injury, failure, loss, end-stage renal disease (RIFLE) criteria [11].

**Figure 2:** Definition of acute kidney injury: Acute kidney injury network (AKIN) criteria [11].

**Connective tissue growth factor**

Connective tissue increase aspect (CTGF, CCN2) is a key mediator of tissue fibrosis. CCN2 has a widespread role to play in the incidence of glomerular and tubule interstitial fibrosis in modern kidney illnesses [13]. CCN proteins are worried in mitosis, adhesion, apoptosis, extracellular matrix manufacturing, angiogenesis, increase arrest, wound healing and migration of more than one cell types [14]. CCN3
is overexpressed in prostate and renal carcinomas [15]. Inside the kidney, CTGF is expressed at low levels in everyday situation and at high ranges, in kidney fibrosis. CTGF overexpression is known to occur drastically inside the extra-capillary and mesangial lesions of glomerulonephritis in human kidney biopsy samples. Similarly, to involvement in fibrosis, CTGF additionally regulates the expression of inflammatory mediators, consisting of cytokines and chemokines, via wonderful signaling pathways, in numerous mobile systems [16].

**Figure 3: Schematic representation of the CTGF structure and interaction with the molecules.** IGFBP, insulin-like growth factor binding protein domain; vWC, von Willebrand factor C domain; TSP-1, thrombospondin type 1 repeat domain; CT, C-terminal domain. Integrins were shown in each α and β sub-units [16].

**Insulin**

The renal clearance of inulin has been considered because the gold standard for evaluating glomerular filtration rate (GFR). Inulin refers to an uncharged poly fructose molecule with a mean molecular weight of approximately 5,000. Inulin is unbound to plasma proteins, freely filtered in glomeruli, and is neither reabsorbed nor secreted by using the renal tubules [17]. Inulin is a physiologically inert substance and is considered a really perfect diagnostic parameter for GFR. Although inulin clearance is taken into consideration the gold-fashionable for determining GFR, numerous drawbacks make it a less ultimate alternative for GFR estimation, which include want for non-stop infusion, multiple blood and urine sampling [18]. Inulin reduces the electricity density of meals and are therefore used to enhance food with nutritional fiber or to replace sugar and fats. The need of continuous infusion or bolus administration of the marker (subcutaneous or intravenous) inulin, substantially limits their application in medical practice and epidemiological research, rendering the marker neither value nor time-effective [18].

**Blood urea nitrogen (BUN)**

Blood Urea Nitrogen (BUN) quantifies urea nitrogen in the blood. BUN is a nitrogen-containing compound formed within the liver as the end made from protein metabolism and urea cycle. About 85% of urea is excreted thru kidneys, while the rest, via the gastrointestinal (GI) tract. Serum urea is improved in conditions where renal clearance is compromised, as in acute and chronic renal failure/impairment. Urea levels may also be expanded in non-renal sicknesses/conditions, along with higher GI bleeding, dehydration, catabolic states and high protein diets [19]. BUN attention is measured in mg/dL. Urea is likewise expressed because the complete molecule (no longer simply the nitrogen a part of the molecule) in SI units (mmol/L). Seeing that BUN displays simplest the nitrogen content of urea (MW 28) and urea size displays the whole of the molecule (MW 60), urea is about two times (60/28 = 2.14) to that of BUN. For that reason, BUN measurement of 10 mg/dL is equivalent to urea 21.4 mg/dL [20].

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β 2 micro-globulin

β 2 micro-globulin (B2-M) is filtered by means of the glomeruli and reabsorbed with the aid of the proximal tubular cells where it is metabolized, its normal value being 0 - 0.3 µg/m [21]. β 2-microglobulin (B2-M) is a small molecule of 11.8 kDa and constitutes a class-I HLA. B2-M is present in all nucleated cells of the frame, inclusive of better quantities of immune cells like lymphocytes and monocytes [18]. The renal proximal tubular feature in neonates is evaluated by means of measuring urinary β 2-microglobulin concentrations. In sick neonates, the urinary β 2-microglobulin and N-acetyl-β-D-glucosaminidase have been taken into consideration to be the early markers of renal tubular disorder. It’s also assumed that excessive levels of urinary β 2-microglobulin and N-acetyl-β-D-glucosaminidase in neonates born with meconium-stained amniotic fluid signified renal tubular dysfunction, of which a likely explanation might be prenatal distress [10].

Proteinuria

The presence of albuminuria or proteinuria suggests renal damage and together with the estimation of glomerular filtration price is primarily based at the assessment of persistent kidney ailment, its normal value being 0 - 20 mg/dl. Proteinuria is a robust marker for both progression of continual kidney sickness and also of cardiovascular morbimortality [22]. However, it’s miles unsure whether outcomes of proteinuria on predicted GFR is drastically prompted by means of baseline level of kidney characteristic [23]. An boom in intra-glomerular pressures should set off leakage and harm to the glomerular membrane, thereby main to excretion of significant amounts and sorts of proteins via urine. In contrary, thinking about coronary heart failure, intra-glomerular pressures are commonly low [24].

N-Acetyl-β-D-glucosaminidase

Urinary N-acetyl-β-D-glucosaminidase (uNAG) prognosticates diabetic kidney ailment (DKD) progression, a great deal earlier than improvement of albuminuria in diabetics. Being an indicator or renal proximal tubule harm, Urinary N-acetyl-β-D-glucosaminidase (uNAG) commonly will increase with elevated blood glucose levels (regardless of albuminuria) and decreases with strict glycemic manipulate in diabetics [25].

Cysteine-rich 61 (Cyr 61)

Cyr 61 is a heparin-binding, extracellular matrix associated protein of the Cyr61/CTGF family. It has a molecular weight of 42,000 Da [12]. Cysteine-rich protein 61 (Cyr61) consists of Cyr61 (CCN1), connective tissue growth factor (CTGF, CCN2), nephroblastoma overexpressed (NOV, CCN3), WNT 1-inducible signaling pathway proteins (WISP)-1 (CCN4), WISP-2 (CCN5), and WISP-3 (CCN6). Cyr61 is involved in modulation of a large number of biological and cellular activities. Cyr61 is known to control the cell cycle, stimulate chemostasis and agrandize growth factor-induced effects. By promoting endothelial cell survival and stimulating pro-angiogenic factors, Cyr61 also has a significant role to play in angiogenesis. Cyr61 also attunes biological mechanisms with respect to cutaneous wound healing. It also coordinates gene expression involved in matrix remodeling and stimulating senescence and apoptosis in fibroblasts. Of late, it was discovered that Cyr61 promotes inflammation and modifies the effects of cytokines on cell death. All of the aforesaid mentioned mechanisms of Cyr61 are crucial aspects, as far as renal fibrosis progression is concerned [26].

Need for an ideal GFR marker

In spite of the uses of aforesaid explained markers, blood urea nitrogen (BUN), serum creatinine (SCr), proteinuria, β-2 microglobulin (B2M), N-acetyl β-glucosaminidase, inulin, Cyr-61 have limitations as renal markers, resulting in a persisting search for an ideal endogenous marker of GFR [27]. These markers are greatly influenced with body mass index (BMI), age, gender, dietary protein intake, race, ethnicity [28]. Thus, here, we review recent studies examining methods, reference intervals, and the diagnostic accuracy of another endogenous substance, Cystatin C (CysC), as a marker of GFR.
Cystatin C

Cystatin C belongs to the cystatin superfamily of cysteine protease inhibitors. There are actually eleven contributors of this circle of relatives, of which cystatin C is taken into consideration the maximum physiologically vital inhibitor of endogenous cysteine proteases [29]. Despite the fact that Cystatin C is freely filtered with the aid of the glomerulus, reabsorbed and catabolized, it isn’t secreted by means of the tubules [30]. A key criteria that Cystatin C should fulfill that allows you to be a good sized substitute for creatinine is that its manufacturing rate need to be regular, or much less influenced in comparison to creatinine. There may be tremendous proof in support of the truth that all nucleated cells produce Cystatin C [29]. Cystatin C stages is effective as a marker in detecting ARF. What is thrilling approximately Cystatin C is the fact that it is able to assist in detecting development of impending ARF, one or days before serum creatinine (SCr) can [30]. Cystatin C is cleared approximately six instances more rapidly than b2-microglobulin at some stage in hemodialysis and about 1 to 2-fold instances extra in peritoneal dialysis [29]. Cystatin C monomer is found in all human frame fluids; in higher concentrations in cerebrospinal fluid, seminal plasma and milk. Cystatins are also believed to have a protecting position towards microbial infections: 54 the cystatin remote from horseshoe crab hemocytes has antimicrobial activity against Gram-bad bacteria, which includes Salmonella typhimurium, Escherichia coli and Klebsiella pneumoniae. Immuno histochemical research have proven cystatin C-unique staining of cells of the adeno hypophysis and the adrenal medulla, the A-cells of the pancreatic islets, the C-cells of the thyroid gland, and a few brain cortical neurons, thereby proving the reality that a few cells of the neuroendocrine gadget also are synthesizing cystatin C. Cystatin C-encoding mRNA has been found in heart, kidney, lung, liver; intestine, pancreas, uterus, and seminal vesicles. Kidney serves as the important catabolic web page of Cystatin C, clearing it from flow thru glomerular ultrafiltration. The features of cystatin C, in addition to those of other type 2 cystatins, may be grouped into 4 preferred categories: (a) direct inhibition of endogenous or exogenous cysteine peptidases; (b) immune machine modulation; (c) antibacterial and antiviral activities, no matter inhibition of cysteine peptidases; and (d) response to injury within the brain. The reference range of cystatin C in adults is 0.6 - 1 mg/L in adults and in newborns is 1.36 - 2.23 mg/L. Cystatin C serum attention remain static for at least three reasons: a) due to the fact that Cystatin C is produced by way of all nucleated human cells, the marker’s secretion price could be unhindered; b) negligible greater-renal catabolism; and c) now not influenced by way of diet, muscular tissues etc. In patients with gestational hypertension, twin pregnancy, and preeclampsia, Cystatin C levels were discovered to be higher as compared to wholesome pregnant girls [31]. Cystatin C levels stay static, irrespective of infection, infections or by dietary and constitutional elements [32]. Cystatin C degrees may be stimulated by factors that determine Cystatin C charge of synthesis, consisting of thyroid status, use of steroids, and so forth.

Cystatin C is an important renal function biomarker, in that it’s far a diagnostic parameter of preference in a variety of medical scenarios, ranging from GFR tracking in diabetics to assessment of AKI in seriously ill sufferers. Cystatin C performs a function in inflammatory reactions and turned into even weakly correlated with a number of inflammatory markers, together with CRP (C-reactive protein). Cystatin C is a better predictor of the chance of all-cause mortality and cardiovascular events than creatinine. The involvement of the proximal convoluted tubule in the re-uptake method suggests that the estimation of urinary cystatin C may supply an insight into tubular feature. The measurement of cystatin C may also permit detection of tubular disorder inside the presence of pure and blended nephropathies [33]. It has additionally been determined that sufferers with higher circulating cystatin C concentrations seem to have an multiplied cardiovascular risk profile, i.e. they’re older and feature a higher incidence of systemic hypertension, dyslipidemia, documented cardiovascular ailment, multiplied body mass index and elevated concentrations of C-reactive protein. Excessive concentrations of cystatin C were independently associated with cardiovascular threat factors including age, girl intercourse, BMI, low HDL cholesterol and smoking, even in individuals without CKD or microalbuminuria. The superiority of threat factors including cigarette smoking, high blood pressure and low HDL, LDL cholesterol become higher in people with better cystatin C concentrations. Moreover, the prevalence of CVD, myocardial infarction (MI), angina pectoris and stroke elevated with increasing concentrations of cystatin C. Regardless of adjustment for age, intercourse, race and predominant cardiovascular threat elements, cystatin C become nevertheless independently associated with CVD. Cystatin C concentrations were predictors of incident peripheral arterial ailment inside the aged, whereas creatinine and eGFR had been now not, thereby organising the twin position of cystatin C within the estimation of cardiovascular ailment, in addition to renal function.

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Inflammation owing to atherogenic changes, may be one mechanism associated with cystatin C and cardiovascular risk, and high cystatin C concentrations have been found to be associated with high concentrations of CRP [34-36].

Figure 4: Proposed mechanisms linking renal dysfunction, inflammation, atherogenesis, and cardiovascular events [36].

Figure 5: Schematic overview of sources of renal biomarkers [26].
Conclusion

This evaluate aimed to consciousness on the numerous varieties of renal biomarkers used inside the assessment of kidney feature and the merits of Cystatin C over they all. Salient merits of Cystatin C over other traditional biomarkers encompass:

1. Cystatin C is less variable than serum creatinine, BUN, proteinuria, inulin since it does not vary with age, gender, muscle groups, race, ethnicity, nutritional consumption of protein.

2. Its efficacy as a biomarker is regardless of physiological states of frame.

3. It helps to access tubular feature.

4. It’s far a dependable marker for early estimation of acute and persistent renal failure than creatinine.

5. It receives unexpectedly cleared in hemodialysis than β-2 microglobulin, thereby supporting in estimation of renal status.

6. If the cost of Cystatin C will increase, the danger for cardiovascular illnesses additionally increases, therefore being a promising marker to identify each the renal and cardiovascular repute.

Consequently, we finish with the commentary that Cystatin C has an higher hand, both in renal disorder identity, and also in cardiovascular sickness chance estimation.

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