Cystatin C and its diagnostic ability in various clinical conditions

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ABSTRACT

The diagnosis of acute renal failure is usually based on serum creatinine and urea nitrogen. Although these markers are widely used to assess renal function, they do not perform optimally in certain clinical settings. Cystatin C might be a better marker for glomerular filtration rate (GFR) than serum creatinine. Cystain C offers an advantage over creatinine because of its age and gender independence, but it has certain limitation in various clinical conditions. We conducted a review of publications that evaluated biomarkers for acute renal failure. Two reviewers independently searched MEDLINE and EMBASE database from September 2011 to November 2011 for studies related to biomarkers of acute renal failure. Twenty studies were relevant and related with our subject of interest. Multiple new biomarkers have great potential to advance in the fields of nephrology and critical care only when they are used in combination. These include a plasma panel [neutrophil gelatinase-associated lipocalin (NGAL) and Cystatin C] and a urinary panel [NGAL, interleukin 18 (IL-18), and kidney injury molecule 1 (KIM-1)]. Our objective was to evaluate the accuracy and reliability of new biomarkers for the diagnosis of acute renal failure.

Key words: cystatin c, plasma biomarkers, acute renal failure, urinary biomarkers

INTRODUCTION

Renal failure is a silent epidemic of the 21st century. Its occurrence is universal; not confined to the developed countries. The numbers afflicted with renal failure are going to rise sharply because of the rising incidence of diabetes mellitus and hypertension (two of the major causes of renal failure). World Kidney Day, observed on March 9, is a significant milestone in pushing forward the agenda of bringing into focus a rapidly advancing disease- kidney failure. The lack of early biomarkers for acute renal failure has crippled our ability to launch potentially effective therapeutic measures. The best way to improve outcomes of acute renal failure is prevention; the definition should have a high diagnostic accuracy and allow early detection of acute kidney injury. Quantifying the extent of injury will also prove valuable to guide therapeutic recommendations and allow reasonable comparisons of outcomes between various treatment strategies.

Glomerular Filtration Rate (GFR) is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in a unit of time[1]. GFR is routinely assessed by measuring the serum markers such as urea nitrogen and serum creatinine. Although these markers are widely used to assess renal function, they do not perform optimally in certain clinical settings. Cystatin C might be a better marker for GFR than serum creatinine.[2] Cystain C offers an advantage over creatinine because of its age and gender independence. Human Cystatin C is a 13 Kda basic (PI = 9.3) non-glycosylated protein produced by all nucleated cells.[3] It contains 122 amino acids and it is a member of the family of cystein proteinase inhibitors. It is the product of a "housekeeping" gene expressed in all nucleated cells and is produced at constant rate.[4] Because of its small size and basic PI, Cystatin C is freely filtered by the glomerulus. It is not secreted, but is reabsorbed by tubular epithelial cells and subsequently catabolized so that it does not return to the blood flow.[5] This property negates calculations of its clearance using urine concentrations of Cystatin C. The use of serum Cystatin C to estimate GFR is based on the same logic as the use of blood urea nitrogen and creatinine, but because it does not return to the blood stream and is not secreted by

renal tubules, it has been suggested to be closer to the "ideal" endogenous marker. Gender and external disease did not alter serum Cystatin C concentrations. This is in accordance with two previous studies;[6,9] however, others found higher levels in males. It was found that Cystatin C is higher before the age of 3 months and after the age of 70 years.[7,8] The decrease in GFR and increased Cystatin C value above the age of 70 years was found in some studies.[8] This property made it attractive to further examine Cystatin C in certain groups of patients. This review mainly focuses on the diagnostic performance of Cystatin C in various clinical conditions.

METHODS

We performed a review of recent publications that evaluated new biomarkers for the detection of acute renal failure. Two reviewers independently searched the Medline and Embase databases (September 2011- November 2011) for studies related to biomarkers for acute renal failure. A total of 20 studies were evaluated. It was noted that Cystatin C has limitations in various clinical conditions but when used in combination, very good result were demonstrated. The recent publications indicated that the biomarkers can maximize diagnostic ability when used in combination.

RESULT

It was noted that Cystatin C has limitation in the following clinical conditions:

Impact of thyroid disease on Cystatin C

It has been observed that thyroid dysfunction may alter creatinine, which has been found to be increased in hypothyroidism and decreased in hyperthyroidism. Fuicker M, et al., in their study concluded that thyroid dysfunction has a major impact on Cystatin C levels. Therefore, thyroid function needs to be considered when Cystatin C is used as a marker of kidney function. In contrast to creatinine concentrations, Cystatin C levels are lower in the hypothyroid and higher in the hyperthyroid state as compared with the euthyroid state.[10]

Knight and colleagues found that Cystatin C concentrations were significantly associated with increased age, male sex, increased weight, tall individuals, current smoking and higher C-reactive protein (CRP) levels, even after adjustment for creatinine clearance. They concluded that the above characteristics must bias Cystatin C concentrations as a measure of GFR.[11] The above studies suggested that the serum concentrations of Cystatin C may increase in settings of increased metabolic rate, perhaps as a result of increased cell turnover. The use of glucocorticoids has also been associated with higher concentrations of Cystatin C.[12,13]

Impact of dialysis on Cystatin C

The process of dialysis leads to a significant fall in mean serum creatinine concentration. In contrast to this, the serum Cystatin C levels were significantly higher in the post-dialysis samples as compared with the pre-dialysis ones. The rise in serum Cystatin C following hemodialysis was observed in all the patients taken up for the study. This was in spite of the concomitant fall in serum creatinine, which is an accepted index for the adequacy of dialysis. The rise in the serum Cystatin C following dialysis could be attributed to several factors such as the nature of the dialyzing membrane and the composition of the dialyzing fluid.[14] When dialysis is carried out using low flux membrane, the pore size is smaller than 1.5 nm which does not permit the removal of low molecular weight proteins such as Cystatin C. Another factor to be considered is the electro-static interaction between micro-proteins and other plasma proteins adsorbed onto the dialyzer membranes. Cystatin C is strongly cationic and the charged nature of the molecule might hinder its filtration.[14] The rise in serum Cystatin C could also be attributed to the effect of hemoconcentration which occurs during dialysis.

The fall in serum creatinine despite such changes is

because of the magnitude of reduction of this metabolite during dialysis. These studies have concluded that serum Cystatin C cannot be used to monitor adequacy of hemodialysis.

Impact of Jaundice on Cystatin C

A study conducted by Lofberg and Grubb revealed that hyperbilirrubinea is associated with higher Cystatin C levels. However, it has been shown that bilirubin concentrations upto 700 m mol/l do not interfere with the immunoturbidometric assay for Cystatin C.[15] Despite normalization of bilirubin levels after the first weeks of life, higher Cystatin C concentration persisted for several months, further excluding assay interference by hyperbilirubinemia.

DISCUSSION

The published data from studies of serum and urinary biomarkers suggested that the biomarkers such as Neutrophil gelatinase-associated lipocalin (NGAL), Cystatin C, interleukin 18 (IL-18), and kidney injury molecule -1 (KIM-1) may influence the diagnosis of acute renal failure significantly. Normally NGAL is produced and secreted by kidney tubule cells at low levels, but the amount produced and secreted into the urine increases dramatically after ischemic, septic, or nephrotoxic injury of the kidneys. Urine and blood NGAL concentrations rapidly increase after acute injury; elevations occur 2 hours after injury. Kidney injury molecule-1 (Kim-1) is a type 1 membrane protein with extracellular immunoglobulin and mucin domains. The mRNA and protein for Kim-1 are expressed at very low levels in normal kidney, but expression increases dramatically after injury in proximal tubule epithelial cells in post-ischemic kidney during ischemic acute renal failure. There is evidence that urinary interleukin-18 (IL-18) – a pro-inflammatory cytokine released in response to injury to renal tubular epithelial cells and demonstrated in activated macrophages – might act as an earlier biomarker along with Cystatin C, kidney injury molecule 1 (KIM)-1 and NGAL.[16]

Therefore, the emerging biomarkers of acute renal failure in combination, similar to troponins, can increase the sensitivity of diagnosis of the renal disease. These include a plasma panel [neutrophil gelatinase-associated lipocalin (NGAL) and Cystatin C] and a urinary panel [neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), and kidney injury molecule 1 (KIM)-1]. Based on the differential expression of the biomarkers, it is also likely that the acute renal failure panels will distinguish between the various types and etiologies of acute renal failure

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