C-reactive protein (CRP) and its predictive role in rapid progression of renal failure: a retrospective assessment

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A. Study purpose and rationale

C-reactive protein (CRP) is an acute phase reactant that is produced by the liver under the cytokine influence. Its levels tend to rise sharply in acute inflammation, and its duration is short-lived, making its use as a marker of acute inflammation very valuable. On the other hand, in chronic inflammation, its levels can be elevated to very high levels, and for indefinite periods of time. As such, it has been implicated as a maker of inflammation in a number of chronic conditions such as coronary artery disease[i,ii], and chronic renal disease [iii,iv,v]. This relationship has been most well characterized in cardiovascular disease (CVD), particularly in atherosclerosis, where there is ongoing, chronic inflammation. Some studies have gone beyond showing an association, to showing a direct predictive role in CVD[vi], both in event occurrence, as well as in mortality from CVD. More recent studies are suggestive of possible predictive value for other conditions such as cerebrovascular disease[vii].

In regards to renal failure, some studies have demonstrated a relationship between elevated CRP and mortality in patients with end-stage renal disease[viii], however this has been most well characterized in terms of mortality from CVD in this patient population. Many questions still remain unanswered regarding the role of CRP in renal disease. As renal failure contributes to significant morbidity and mortality, increasing the body of knowledge to predict its development can help to stem this tide. Few studies have evaluated the predictive value of CRP in the progression of renal disease. As such, the purpose of this study is to evaluate if elevated CRP is predictive of a rapid decline in renal function, as measured by a decrease in glomerular filtration rate (GFR) over time.

B. Study design and statistical analysis

This is a retrospective, observational study that will evaluate if elevated CRP is predictive of a rapid decline in renal function. The data will be analyzed from the MESA (Multi-Ethnic Study of Atherosclerosis) trial database. This study is a multi-center, prospective cohort, on which there is a collection of predictive variables of subclinical cardiovascular disease. Participants in this study were obtained from responders recruited through random digit dial. The data collection is ongoing for duration of 10 years, but the data to be used for the current study will be from collected data of 3 years ago, spanning 2001 to 2004. The number of participants in the database is approximately 1200. The variables of interest are CRP levels, and those required to calculate the GFR: creatinine, age, weight, and sex.

The participants will be selected for inclusion based on a baseline GFR of 50% to reflect some baseline level of renal dysfunction. Change in GFR over the 3 year period will be assessed, and group assignment will be based on this observed change. Those patients where the GFR has decreased by at least 25% (resultant GFR of 25% or less) will be assigned to the cases group (characterized as rapid progressors); those where the GFR remains within a range of +/-5% (45% to 55%) will be assigned to the control group. Those patients where the change in GFR is >5%, but <25% will be excluded from the study.

CRP levels will then be assessed at year 1. Normal range for CRP is 0-3mg/L. An elevation in CRP will be characterized as any level above 3. It is anticipated that in patients with some level of renal dysfunction, there will be a low incidence of elevation in CRP levels, and this is approximated at 20% of the controls. A difference of approximately 20% is anticipated between the cases and controls, with elevation in CRP in cases present in approximately 40%. As such, 100 cases will be needed for the study

to be 80% powered to detect a statistically significant difference with $p<0.05$. Controls will be matched with cases at ratio of 3:1, resulting in 300 controls and 100 cases.

It is estimated that approximately 20% of patients in the database will have the level of decrease in renal dysfunction to fit inclusion criteria (GFR 50%). This result is based on comparisons with population data on chronic renal insufficiency. It is then anticipated that it would be feasible to obtain sufficient subjects for analysis, as approximately 15% of these patients are expected to be rapid progressors (and thus be assigned to the cases group).

Chi-square analysis will be peformed on categorical variables. Logistic regression will be performed to assess for confounders. The following variables will be included in the model: age, sex, BMI, and diabetes. Other variables of interest which may be entered as well, or considered for subgroup analyses are hypercholesterolemia, albumin, alcohol use, tobacco use, and education level.

C. Study procedure

Not applicable

D. Study drugs

Not applicable

E. Medical Device

Not applicable

F. Study questionnaires

Not applicable

G. Study subjects

As indicated above, subjects will be participants in the MESA study who are part of a cohort, aged 45-84, being followed prospectively to identify risk factors for subclinical CVD. Variables of interest are collected on all subjects, and is available for the 3-year time period of interest: 2001 to 2004. Subjects included in the study will meet an inclusion criteria of baseline GFR of approximately 50%. Cases will be patients with decrease in GFR over 3 years to 25% or less. Controls will be patients with stable GFR, in range of 45-55%.

H. Recruitment of subjects

No subject recruitment is needed in this study.

I. Confidentiality of study data

Participant information is coded to preserve confidentiality, and is stored in location that is secure and accessible only to study investigators.

J. Potential conflict of interest

There is no potential conflict of interest for this study.

K. Location of study

This study will be conducted at Columbia Presbyterian Hospital.

L. Potential risks

There are no potential risks.

M. Potential benefits

Information obtained through this study may help to broaden the body of knowledge in regards to renal disease. As this condition contributes to significant morbidity and mortality, improving its recognition, and potentially its management could have significant, far-reaching benefits.

N. Alternative therapies

Not applicable

O. Compensation to subjects

Not applicable

P. Cost to subjects

There is no cost to subjects.

Q. Minors as subjects

Not applicable

R. Radiation or radioactive substances

Not applicable

S. References

[i] Miller M, Shan M, & Havas S. (2005). High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors. *Archives of Internal Medicine*, (165): 2063-2068.

[ii] De Servi S, Mariani M, Mariani G, and Mazzone AC. (2005). C-Reactive protein increase in unstable coronary disease. *Journal of the American College of Cardiology*, (46): 1496-1502.

[iii] Arici, M & Walls, J. (2001). End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? *Kidney International*, (59): 407-414.

[iv] Menon V, Greene T, Wang X, Pereira A, Marcovina S, Beck G, Kusek J, Collins A, Levey A, & Sarnak M. (2005). C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney* International, (68): 766-772.

[v] Stigant C, Djurdjev O, & Levin A. (2005). C-reactive protein levels in patients on maintenance hemodialysis: reliability and reflection on the utility of single measurements. *International urology and nephrology*, (37): 133-140.

[vi] Clearfield M. (2005). C-reactive protein: a new risk assessment tool for cardiovascular disease. *JAOA*, (105): 9: 409-416.

[vii] Kocer A, Canbulat C, Gozke E & Ilhan A. (2005). C-reactive protein is an indicator for fatal outcomes in first-time stroke patients. *Medical Science Monitor*, (11): CR540-544.

[viii] Iseki K, Tozawa M, Yoshi S, & Fukiyama K. (1999). Serum C-reactive protein and the risk of death in chronic dialysis patients. *Nephrology Dialysis Transplant*, (14): 1956-1960.