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Research Article

Cystatin levels in a rural South Indian population

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ABSTRACT

Aim: Our aim was to study the potential role of Cystatin C as a marker for renal function and cardiovascular disease in a rural South Indian population.

Methods: Local Ethics Committee approval and informed consent was obtained from all participants. Inclusion criterion was that participants had to be ≥20 and ≤85 years of age. All participants were administered a detailed questionnaire, and had their anthropometric measurements taken including height, weight, and waist circumference. Blood was drawn for determining random glucose, glycosylated hemoglobin, nonfasting lipid profile, Cystatin C, uric acid, and hemoglobin. Urine samples were collected for urine protein creatinine ratio. All participants had their carotid intima thickness determined by high-resolution B-mode carotid ultrasound.

Results: A total of 865 participants were screened in this study. Cystatin C value of >1 mg/l and creatinine of >1.1 mg/dl in females and 1.3 mg/dl in males were defined as "elevated levels." Nearly a third of this population had elevated Cystatin C levels. Higher levels of Cystatin C, even within the normal creatinine range, was associated with cardiovascular risk markers like age, blood pressures, uric acid, and carotid intima thickness.

Conclusions: Cystatin C in a rural South Indian population correlates well with creatinine and cardiovascular markers. Long-term follow-up of this cohort stratified on the basis of Cystatin C will be extremely helpful in augmenting the utility of Cystatin C as an atherosclerotic risk marker in an Indian population.

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1. Background

Cystatin C is a member of the family of cysteine proteinase inhibitors, which are produced by all nucleated cells at a constant rate.[1–3] The history of Cystatin C began more than 50 years ago with a multitude of clinical data over the past decade on its utility as a marker for kidney (dys) function and atherosclerotic cardiovascular disease. Owing to its free filtration in the glomerulus, complete reabsorption, and lack of tubular secretion, the plasma concentration of Cystatin C is thought to depend mainly on the glomerular filtration rate. Several studies have also shown that Cystatin C has a stronger association with cardiovascular outcomes than serum creatinine.[4–9] Despite such exciting prospects, Cystatin C still widely remains a research tool rather than an important investigation in clinical practice. The reasons include lack of standardization of available kits, lack of familiarity with the test that has not proven to affect clinical decision-making in a significant manner, and costs of Cystatin C measurement as opposed to creatinine measurements.[10] There have been very few Indian studies evaluating the utility of Cystatin C as a marker for renal function and cardiovascular disease.[11,12] Our aim, therefore, was to evaluate the utility of Cystatin C in a larger rural South Indian population and follow-up this cohort long-term to assess the implications of doing this test.

2. Study design

Nallampatti is a typical rural farming village in South India with a population of around 3500. This village was selected due to the ease of logistics and contacts with the local village heads. All participants >20 years of age were invited to participate in this study through pamphlets and word of mouth. The study was conducted over a 4-week period from March 15th to April 15th, 2015. Ethical Committee approval and informed consent were obtained.

A detailed questionnaire was administered followed by anthropometry, blood pressure recordings, and blood investigations including random glucose, glycosylated hemoglobin, nonfasting lipids, Cystatin C, hemoglobin, uric acid, urine protein creatinine ratio (PCR), and carotid intima thickness using carotid ultrasound.

Cystatin C results were classified into the following three groups: **Group A**: normal Cystatin C and normal creatinine, **Group B**: elevated Cystatin C and normal creatinine, and **Group C**: elevated Cystatin C and elevated creatinine. Cystatin C levels were analyzed using the nephlometric method (BN Prospec Instrument, Seimens).

All results were tabulated on Microsoft Excel and transposed to SPSS 20 for further analysis. Discrete values were analyzed for mean and standard deviation. Categorical variables were analyzed using Pearson's chi-square test. Linear regression was also performed at certain instances to measure the strength of association between the testing variables. Student *t*-test was employed to calculate the absolute difference in mean between Groups A and B. $p < 0.05$ was considered statistically significant. The participants were grouped to have abnormal creatinine level based on National Institute of Health's guidelines, in which cutoff value of creatinine for men is fixed at 1.3 mg/dl and that of women is fixed at 1.1 mg/dl. People were considered to have abnormal Cystatin C if their value is more than 1 mg/dl.

3. Outcomes

A total of 865 participants participated in this study. Cystatin C levels were elevated in 28.4% of the study population. Mean Cystatin C level was 0.95 mg/l (SD 0.29, range 0.23–3.4 mg/l). We observed an exponential increase in Cystatin C levels with increasing age groups. The percentage of participants with elevated Cystatin C in the age groups 20–40, 41–60, and >60 years were 7.7%, 31.8%, and 54.2%, respectively (Pearson's chi-square p value <0.001). Linear regression was performed to analyze the strength of association between Cystatin C and various covariates. For every unit increase in age, the Cystatin C increases by 0.009 units (95% CI 0.007–0.010, $p < 0.001$). Women had lower Cystatin C levels, i.e. 0.131 units, compared to men (95% CI, 0.093–0.17, $p < 0.001$).

Participants were classified into three groups, as detailed in the methods section. Baseline characteristics of the three groups are outlined in Table 1. We compared the means between Group A (normal Cystatin C and normal creatinine) and Group B (elevated Cystatin C and normal creatinine). Participants in Group B were older, and had significantly higher systolic and diastolic blood pressures, creatinine level, uric acid level, urine PCR, and carotid intima media thickness. HDL-C levels were significantly lower in Group B compared to Group A (Table 2).

There was a positive correlation between Cystatin C and various cardiovascular risk markers including age, blood pressures, creatinine, uric acid, and carotid intima media

Table 1 – Baseline characteristics of three cystatin groups.

Variable	Group A	Group B	Group C
Total (*n*)	632	216	17
Mean age (years)	44.9 (13.1)	56.2 (11.1)	64.5 (8.08)
Weight (kg)	58.7 (12.6)	60.2 (13.2)	50.6 (7.9)
SBP (mmHg)	129.4 (21.4)	135.4 (20.7)	141.6 (21.3)
DBP (mmHg)	81.3 (11.6)	84.9 (12.4)	84.2 (13.8)
Cystatin C (mg/l)	0.83 (0.10)	1.15 (0.16)	2.36 (0.5)
Creatinine (mg/dl)	0.70 (0.11)	0.80 (0.13)	1.67 (0.3)
Uric acid (mg/dl)	4.5 (1.3)	5.19 (1.2)	7.52 (1.3)
HbA1c (%)	5.9 (1.0)	6.1 (1.1)	6.1 (0.5)
Total cholesterol (mg/dl)	184.4 (37.6)	188 (42.3)	189 (38.9)
LDL-C (mg/dl)	109 (30.3)	112 (34.6)	110.3 (26.7)
HDL-C (mg/dl)	45 (9.3)	41.5 (9.9)	46.9 (26.7)
Urine PCR	0.06 (0.09)	0.11 (0.1)	0.37 (0.3)
CIMT right (cm)	0.06 (0.01)	0.07 (0.02)	0.08 (0.01)
CIMT left (cm)	0.06 (0.01)	0.07 (0.02)	0.08 (0.01)

Group A: normal Cystatin C and normal creatinine.
Group B: elevated Cystatin C and normal creatinine.
Group C: elevated Cystatin C and elevated creatinine.

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