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Testosterone: A Modifiable Risk Factor to Prevent Cognitive Impairment in Indian Pre Dialysis Chronic Kidney Disease Patients

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Abstract
Background: *cognitive and executive function impairment is common in predialysis CKD patients and occurs in even young patients. It is a major cause of morbidity. It impairs quality of life, hampers decision making and self-management of patients. Although initially subtle but may herald future and increase the burden on caregivers. Hence modifiable risk factors for cognitive impairment needs to be identified.*
Objective: *To identify modifiable risk factors to prevent cognitive impairment in predialysis CKD patients. This will help to device a simple, reliable and non-invasive bedside marker to predict and prevent cognitive and executive functional impairment in patients of CKD.*
Methods: *70 CKD patients as defined by K/DOQI guidelines (kidney disease outcome quality initiative group) having an estimated GFR (eGFR)<60ml/min/1.73sq.mrtre, who had not undergone renal replacement therapy at the time of presentation were chosen as subjects of the study. They were compared with equal number of age and sex matched controls. Cognitive and executive functions of all cases and controls were assessed by using 6-item cognitive impairment test, MMSE, Trail making test-A and Trial making Test-B. All subjects underwent extensive blood and urine investigations. Testosterone level (samples were taken at 9 Am after overnight fasting) was done by a solid-phase enzyme immune assay by XEMA kit.*
Results: *Serum testosterone mean value among cases was 1.94±1.17 and among control was 6.04 ±3.16 (p= 0.0005). Serum Testosterone levels was found to be significantly correlating with the impairment of cognitive function statistically (p value<0.005). Similarly, hyperuricemia also correlated with cognitive impairment in patients of CKD. (MMSE p =0.0001, 6CIT p =0.043 & TRAIL A &B p =0.0001). Impairment of cognitive function did not correlate statistically with any other parameter in this study. Multivariate regression analysis revealed that hyperuricemia correlated inversely and was the most important factor affecting cognitive function in predialysis CKD patients (r = - 0.4259, p =0.0002) followed by serum testosterone (r = 0.282, p=0.0181).*
Conclusion: *Early treatment of hyperuricemia and testosterone replacement therapy may go a long way in preventing the cognitive impairment in CKD patients.*
Keywords: *Cognitive impairment, Testosterone, Hyperuricemia,Predialysis CKD.*

Introduction

Chronic kidney disease (CKD) is a worldwide growing health problem that is found in 23-35% of adults above 64 years [1]. The overall prevalence has been estimated as 8-16% across the world.

The term "cognition" covers aspects of brain function related to various domains such as attention, language, memory, learning, reasoning, decision making, and problem solving. Cognitive impairment can be understood as a decline in patient baseline functions possibly at a level severe enough to interfere with the performance of activities of daily living by the individual.

Cognitive impairment is a frequent finding in patients with chronic kidney disease with being reported to vary between 17-50% in CKD patients and >85% in patients of ESRD [1]. This is an understatement and represents only the tip of the iceberg as many cases of mild cognitive dysfunction are not reported/ evaluated. The emergence of new evidence indicating that cognitive and executive function are more common in CKD patients [2-4] than in general population has paved way to research of newer factors that may help in early diagnosis and intervention for improving the worsening cognitive decline in CKD patients.

CKD per say associated with a wide range of metabolic alteration, including disorders in secretion of hormone and response of target tissue, causing a number of endocrine dysfunctions that may contribute to worse outcomes [6-7]. Among those, male hypogonadism (i.e. testosterone deficiency) is most common gonadal alteration in men; mainly due to reduced prolactin clearance [8] and uremic inhibition of luteinizing hormone signaling at the level of leydig cells.

Several endocrine abnormalities that arise as direct consequences of CKD traditionally have been considered 'innocent' consequences of uremia and received scare attention. Dysfunction of hypothalamic-pituitary-testicular axis exists, and decreased synthesis and secretion of testosterone follow with progressive CKD [9-11].

Testosterone deficiency has been associated with anemia and erythropoiesis stimulating agent hypo responsiveness, arterial stiffness, low muscle mass, poor quality of life and death (cardiovascular). [5]

Numerous studies have attempted to describe the relationship between serum testosterone levels and cognitive ability in younger adults and older patients. No conclusion was apparent in few studies while few studies showed positive results.

Any association between serum testosterone, and cognitive impairment in the Indian population would allow us for early intervention to prevent cognitive decline.

Material and Methods

This was a case-control and cross sectional prospective study on 140 participants (70 were CKD patients and 70 were normal GFR healthy volunteer), with CKD as defined by K/DOQI guidelines (kidney disease outcome quality initiative group) having an estimated GFR (eGFR) <60ml/min/1.73sq.mrtre, who had not undergone renal replacement therapy at the time of presentation (called as predialysis CKD patients). These were the patients attended the nephrology clinic, general medicine outpatient and wards. Staging of these patients was done according to the eGFR using MDRD formula (modification of diet in renal disease formula). They were subjected to detailed history and physical examination with emphasis on cognitive function.Cognitive and executive functions of all cases and controls were assessed by using 6-item cognitive impairment test, MMSE, Trail making test-A and Trial making Test-B. All subjects were investigated extensively (complete hemogram, KFT, LFT, serum calcium and phosphate, Blood sugar, Uric Acid, Lipid Profile, Serum Testosterone level, Urine routine microscopy, 24 hr Urinary protein, USG abdomen and ECG. Testosterone level (samples were taken at 9 Am after overnight fasting) was done by a solid-phase enzyme immune assay by XEMA kit.

Inclusion Criteria- CKD patients were included in the study only when satisfied the following criteria –

1) Age>18 years old males,

(2)eGFR<60ml/min/1.73sq.metre. (stage 3,4&5).

Exclusion Criteria – The exclusion criteria for the study included –

1) Patients with known neurodegenerative or psychiatric disease,
2) Evidence of acute infection,
3) Patients with known testicular tumor or on testosterone therapy and
4) Patients who cannot read or write in any language or do counting,
5) Patient on renal replacement therapy.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then non parametric test was used.

Statistical tests were applied as follows-

1) Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2) Qualitative variables were correlated using Chi-Square test /Fisher's exact test. A p value of <0.05 was considered statistically significant.
3) Multivariate regression analysis were applied to assess cognitive impairment with variable factors

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Present case control study of 70 male chronic kidney disease predialysis patients (cases) and 70 healthy volunteers (controls) was conducted in Medicine department, VMMC and Safdarjung hospital, Delhi, which is tertiary care teaching institute. Patients with eGFR <60ml/min/1.73m^2 who were not on dialysis were included in the present study group. Out of 70 cases, 8(11.43%) of the cases belonged to stage 3 of CKD, 22(31.43%) belonged to stage 4 of CKD and rest 40(57.57%) belonged to stage 5 of CKD. The mean eGFR among cases was 17.71 (SD=10.33).

Age distribution of study subjects were uniform in both cases and control groups. (p = 0.553).

Cognitive impairment was assessed using 4 parameters- i.MMSE; ii.6CIT; iii.TRAIL A; iv.TRAIL B

In this study there were 91.4% CKD patients with cognitive impairment and 8.6% with normal cognition (p=<0.005). However, no statistical significance was seen between cognitive impairment and amongst stage3,4 and 5 CKD patients (p=0.099). Thus no difference in the level of cognitive impairment was seen in different stages of CKD.

Mean value of MMSE among cases was 20.51(SD=2.95) and among controls was 29.11 (SD=1.71). There was a statistically significant difference in MMSE between CKD patients and healthy volunteers. (p<0.0005).

Mean value of 6 CIT was 11.4 (SD=3.36) among cases and 1.69 (SD=2.17) among controls. There was a statistically significant difference in 6 CIT between CKD patients and healthy volunteers (p<0.0005).

Mean value for TRAIL A was 87.86 (SD=17.13) seconds among cases and 30.77 (SD=12.68) seconds among controls. There was a statistically significant difference in TRAIL A between CKD patients and healthy volunteers (p=0.0005).Mean value for TRAIL B was 273 (SD=37.49) seconds among cases and 68.03 (SD=11.25) seconds among controls. There was a statistically significant difference in TRAIL B between CKD patients and healthy volunteers (p<0.0005).

Among 70 CKD patients there were 62 (88.57%) patients having abnormally low s. testosterone levels. Serum testosterone mean value among cases was 1.94 (SD=1.17) and among control was 6.04 (SD=3.16). There was a statistically significant difference in S. testosterone between CKD patients and healthy volunteers (p<0.0005). Thus it proved that serum testosterone levels decline in CKD patients. However, on further evaluation it was seen that no association was found between the

testosterone decline and the various stages of CKD (p=0.361).

The association between cognitive impairment (MMSE, 6 CIT, TRAIL A and TRAIL B) and testosterone among the CKD cases was found to be statistically significant (p = 0.029, 0.045, 0.012, 0.022 respectively).

There was statistical significant correlation between age and cognitive impairment in CKD patients (p value of MMSE=0.008, 6CIT=.017, TRAIL A =0.045 and TRAIL B=0.001).The serum uric acid and cognitive impairment are highly significant as correlation (p value for MMSE=0.0001, 6CIT= 0.043, TRAIL A=0.0001 and TRAIL B=0.0001).

In determining the association of serum calcium and cognitive impairment, only 6CIT showed association (p =0.026). All other 3 tests of cognitive impairment were statistically insignificant (p value for MMSE=0.491, TRAIL A=0.396 and TRAIL B =0.308). No statistical significance between phosphate levels, Hb, cholesterol with cognitive impairment in pre dialysis CKD patients. (p= 0.415, 0.507,0.286 respectively)

Multivariate regression analysis revealed that serum testosterone correlated best with cognitive impairment by all methods of assessment i.e. MMSE (p= 0.02, r = 0.23), 6CIT (p= 0.045, r = 0.12), TRAIL A (p =0.016, r =0.25), TRAIL B (p=0.025, r = 0.18)

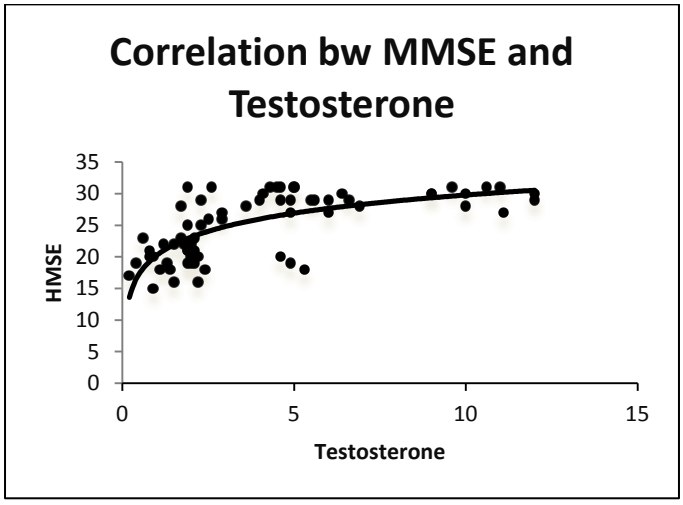

Figure 1: correlation between cognitive impairment (measured by MMSE) and serum testosterone in predialysis CKD patients.

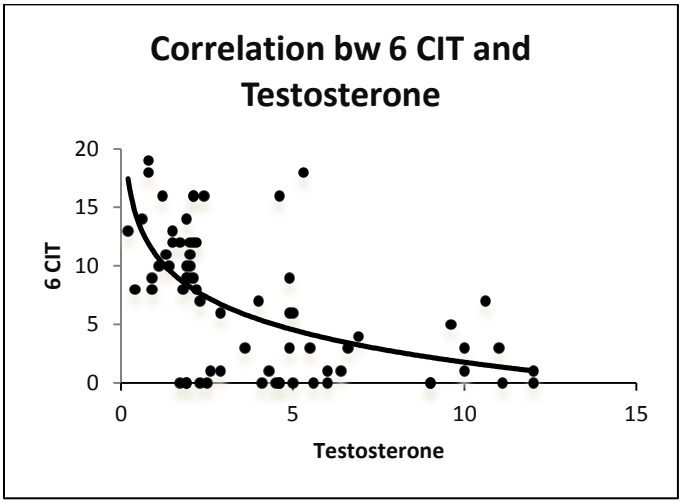

Figure 2: correlation between cognitive impairment (measured by 6CIT) and serum testosterone in predialysis CKD patients.

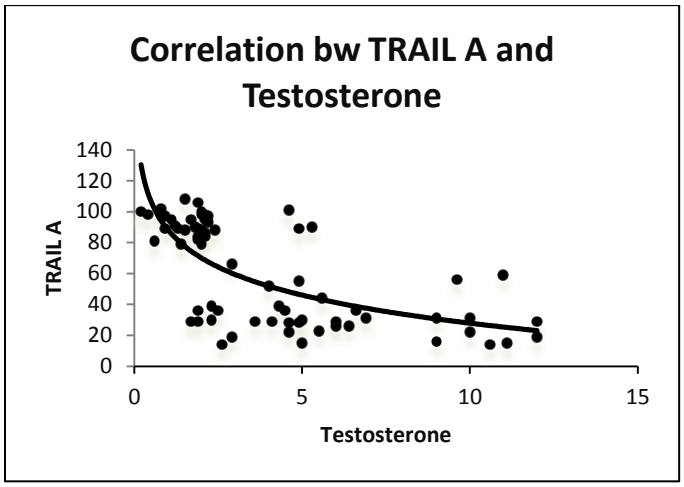

Figure 3: correlation between cognitive impairment (measured by TRAIL A) and serum testosterone in predialysis CKD patients.

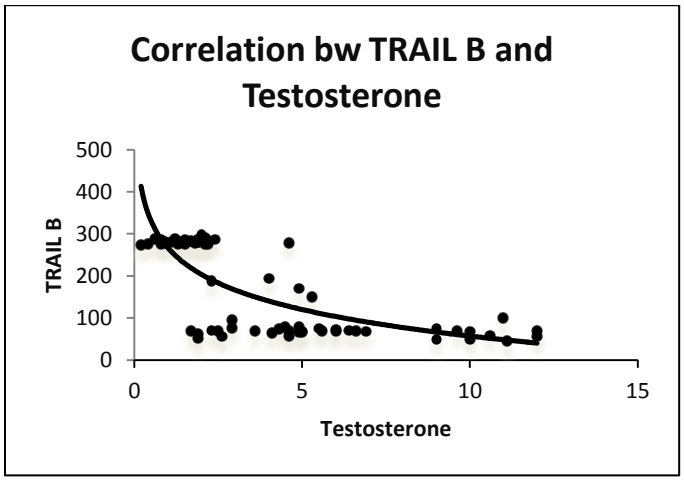

Figure 4: correlation between cognitive impairment (measured by TRAIL B) and serum testosterone in predialysis CKD patients.

Discussion

Evidence is emerging that cognitive and executive function are common in CKD patients [2-4]. Cognitive impairment is a well-recognized manifestation of uraemia. This is characterized by quiet stupor, dullness of intellect, sluggishness of manner and drowsiness. (12)

Few studies in the literature suggest a possible link between CKD and cognitive impairment. It is not known whether cognitive impairment is mediated by direct effect of uraemia per say or it attributed to high prevalence of predisposing risk factors among the individual with CKD.

Cognitive impairment and its negative outcome in CKD patients have been largely neglected by the clinicians. Significant association between falling kidney function and cognitive dysfunction and its association of low testosterone and is shown by recently published literature although there are studies refuting the same. Studies which are relevant to Indian population are still lacking

Possible mechanisms to explain the relationship between testosterone and cognitive ability in older adults are based on preclinical observations of the neurotropic and neuroprotective effects of testosterone (14, 15). In the brain, testosterone can be metabolized to dihydro-testosterone and bind to androgen receptors, or it can be converted to oestradiol by the enzyme aromatase. Both aromatase and androgen receptors are found in key regions in the brain involved in memory and learning, including the hippocampus and amygdala (14). Testosterone has been shown to increase concentrations of nerve growth factor (NGF) in the hippocampus and up regulate NGF receptors in the forebrain(16). Androgens can prevent N-Methyl-D-aspartate receptor excitation in hippocampal neurons and promote fibre outgrowth and sprouting, which may help neurons recover after injury (17, 18). Neuroprotective effects against oxidative stress (19) and apoptosis(20) could also help protect the brain against accelerated age-related cognitive decline.

Hypogonadism is a very common finding in men with CKD, with a reported prevalence of approximately 50%-70% among contemporary dialysis cohorts.

This study showed that the occurrence of cognitive impairment was much more common in CKD group that the general population control group. This was in concordance with the REGARDS study(13). However, on further evaluation it was inferred that despite cognitive impairment in all stage of CKD, no significant difference was found in stages 3,4 and 5.

Testosterone levels were found to be lower in CKD patients than in healthy volunteers, thus proving that serum testosterone levels declines in CKD patients. However, on further evaluation it was seen that no association was found between the testosterone decline and the various stages of CKD. These were in contrast with study by Baris Afsar et al, in which Total testosterone level were different between stages 3 and 5 and stage 4 and 5 CKD patients but not between 3 and 4 CKD patients. It is conceivable that correction of falling testosterone levels at early stages of CKD, will likely affect the cognition. Positively studies are required in this direction.

The association was found to exist between age, uric acid levels, serum calcium and serum testosterone with cognitive impairment (assessed by MMSE, 6 CIT, TRAIL A and TRAIL B) among the CKD patients. No association was found between Haemoglobin, cholesterol and phosphate with cognitive impairment. Serum testosterone was found to be the single most important variable affecting cognitive impairment. Also TRAIL A was found to be the most reliable test for cognitive function amongst CKD patients. The limitation of our study involved a small sample size and was cross sectional in nature.

Conclusion

It was concluded from our study that serum testosterone correlated with cognitive impairment in pre dialysis CKD patients. Early intervention in this regard may herald the progression of cognitive decline and may be a future prospect.

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