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# STUDYING THE RENAL ADVERSE EFFECTS IN SPONDYLOARTHRITIS SUBJECTS ON NON STEROIDAL ANTI STEROIDAL DRUGS

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## ABSTRACT

Background: NSAIDs are the primary treatment for spondyloarthritis, which is primarily diagnosed and treated by evaluating radiological findings, laboratory results, symptoms, and history. Subclinical renal damage, on the other hand, may result from them and go undetected on tests like creatinine.

**Aim**: Using serum cystatin-c and serum creatinine as benchmarks, investigate the relationship between the length of NSAID usage and the occurrence of subclinical renal damage in individuals with spondyloarthritis. **Methods**: This prospective observational research, which is hospital-based, was conducted on 36 individuals who suffer from spondyloarthritis. At baseline, 4 weeks, and 12 weeks, the blood creatinine and cystatin-c levels were measured. The gathered data were evaluated in order to formulate the results.

**Results**: After 12 weeks, there was no significant difference in the participants with spondyloarthritis who used various NSAIDs in terms of serum creatinine ($p=0.548$). However, there was a significant difference in the serum cystatin C levels ($p<0.001$) after 12 weeks.

**Conclusion**: There was no discernible change in the blood creatinine levels after taking NSAIDs. In contrast to serum creatinine, cystatin-c can be utilised as an early biomarker for subclinical renal impairment because there was a notable two- or three-fold rise in blood levels seen compared to the baseline value.

**Keywords**: Subclinical renal injury, NSAIDs, ankylosing spondylitis, and spondyloarthritis

## INTRODUCTION

Spondyloarthritis is a broad category of arthritis that is characterised by inflammation in the axial skeleton and enthesis. Spondylitis associated with inflammatory bowel disorders, psoriasis, reactive arthritis, ankylosing spondylitis, and/or arthritis are all included in spondyloarthritis.1. There are times when spondyloarthritis presents with nebulous symptoms that are difficult to diagnose. The symptoms of spondyloarthritis might include back discomfort and stiffness. The primary prototype of spondyloarthritis is ankylosing spondylitis.2. One of the most common conditions seen in the Outpatient Department of Medicine in young adult males is ankylosing spondylitis.

The most prevalent etiologic factor related with ankylosing spondylitis is a genetic predisposition with HLA B-27.3, and the most common presenting symptom in these people is back pain. Recent research indicates a correlation between TNF-α (tumour necrosis factor) and interleukins (IL-37, IL-23, IL-17, and IL-6) and

ankylosing spondylitis. Radiographic alterations, clinical characteristics, and genetic studies are often used to diagnose it.4

Biologicals and NSAIDs such as Etoricoxib, Naproxen, Indomethacin, and/or Aceclofenac are the mainstays of treatment for spondyloarthritis. Glucocorticoids and anti-rheumatic medications, which can function as disease-modifying agents, are additional therapeutic techniques. In western nations, biological therapy is widely used. Because biologicals are expensive, NSAIDs are often the primary line of therapy in impoverished nations like India. NSAID usage, however, is linked to a number of adverse consequences, including renal, cardiac, and gastrointestinal issues.5

Subclinical renal injuries are typically linked to NSAIDs, and these injuries are typically not detected by standard laboratory testing or renal function assessments. A small number of individuals with spondyloarthritis have reported clinical or overt renal adverse effects with NSAIDs (non-steroidal anti-inflammatory medicines), such as elevated blood creatinine levels.6

Therefore, by comparing serum cystatin-c with serum creatinine, the current study was conducted to investigate the relationship between the length of NSAID usage and the occurrence of subclinical renal damage in people with spondyloarthritis.

## MATERIALS AND METHODS

By comparing serum cystatin-c with serum creatinine, the current prospective hospital-based observational study aimed to investigate the relationship between the length of NSAID usage and the occurrence of subclinical kidney impairment in people with spondyloarthritis. The individuals who visited the Institute's Outpatient Department of Medicine made up the study population.

A total of 36 male patients with ages ranging from 19 to 56 and a mean age of 26.4±4.2 years were included in the research. A diagnosis of spondyloarthroplasty—either axial+peripheral, peripheral, or axial—was reached after considering several factors and radiological studies. Each clinical aspect received a score of 1 according to the Armour criteria, with values of 6 or above being considered spondyloarthroplasty. The typical clinical features that were taken into consideration were lumbar morning stiffness, lumbar night stiffness, non-gonococcal urethritis, cervicitis, and severe diarrhoea that occurred within a month of beginning.

The Buttock score received a score of 1. Inflammatory bowel disease (Crohn's or ulcerative colitis), balanitis, psoriasis, arthritis, well-defined enthesitis, arthritis, heel pain, sausage-like toe or digit(s), asymmetric oligoarthritic, bilateral alternating buttock pain, sacroiliitis (unilateral grade 3 and bilateral grade 2), human leukocyte antigen HLA-B27, and NSAIDs with a score of two were among the additional clinical features taken into consideration. The International Society for Axial Spondyloarthropathies provided additional criteria, such as sacroiliitis on radiographs with one HLA-B27 or spondyloarthrop¬athy feature, which included eye (uveitis), human leukocyte antigen (HLA-B27), elevated C-Reactive Protein (CRP) from Crohn's/colitis disease, arthritis, enthesitis (heel), good response to NSAIDs, inflammatory back pain, psoriasis-positive family history of spondyloarthropathies, and sausage digit (dactylitis).

According to the newly amended criteria, acute inflammation active on MRI was used to identify bilateral sacroiliitis, which was graded 2-4 on radiographs and 3-4 on unilateral radiographs. Every participant in the research had spondyloarthritis, with the exception of those with psoriasis, inflammatory bowel disease, prior renal disease, hypothyroidism, hypertension, or diabetes mellitus, as well as those using biologicals such as corticosteroids, methotrexate, and sulfasalazine. All subjects gave their written and verbal informed permission after being fully told about the study's concept.

Following each research subject's final inclusion, a thorough history was taken and a clinical examination was conducted. For the purpose of measuring serum cystatin-c and serum creatinine levels, blood samples from each of the 36 participants were taken under aseptic and sterile circumstances at baseline, 4 weeks, and 12 weeks, depending on the criteria.

ANOVA, Fischer's extract, Chi-square, and SPSS version 20 were the statistical tools used to assess the gathered data by Chicago Inc., USA. The data were presented as a mean, standard deviation, percentage, and number. At $p<0.05$, the significance threshold was maintained.

## RESULTS

By comparing serum cystatin-c with serum creatinine, the current prospective hospital-based observational study aimed to investigate the relationship between the length of NSAID usage and the occurrence of subclinical kidney impairment in people with spondyloarthritis. A total of 36 male patients with ages ranging from 19 to 56 and a mean age of 26.4±4.2 years were included in the research. Every research subject was a man. Of the participants, 41.66% (n=15) were HLA-B27 negative and 58.33% (n=21) were HLA positive. Axial spondyloarthritis accounted for the most prevalent diagnosis, occurring in 66.6% (n=24) of the participants,

followed by Axial+ peripheral spondyloarthritis in 19.44% (n=7) of the subjects, and peripheral spondyloarthritis in 13.8% (n=5) of the research subjects. The most often used NSAID was etoricoxib, which was taken in 52.7% (n=19) of the individuals, followed by indomethacin (19.4% (n=7), aceclofenac (16.6% (n=6)), and naproxen (11.1 %, n=4) of the research participants (Table 1).

With respect to the serum creatinine levels, there was no statistically significant difference between the four NSAIDs taken at baseline, 4 weeks, and 12 weeks, with corresponding p-values of 0.406, 0.623, and 0.548.

Between baseline (0.75±0.14) and 4 weeks and 12 weeks (0.81±0.15), the level of etoricoxib rose. The baseline values of aceclofenac were 0.71±0.15, which dropped to 0.70±0.14 at 4 weeks, and then rose to 0.73±0.07 after 12 weeks. The levels of indomethacin fell slightly from baseline (0.77±0.13) to 0.76±0.08 at 4 weeks, and then were constant at 12 weeks. Serum creatinine values for Naproxen dropped from baseline, ranging from 0.86±0.14 to 0.81±0.08 at 4 weeks, and then from 0.79±0.13 at 12 weeks (Table 2).

Cystatin C blood levels rose for etoricoxib from baseline to 4 weeks and 12 weeks, rising from 0.85±0.13 to 0.93±0.07 and 1.08±0.13, respectively, when the changes in levels were evaluated. Serum cystatin C levels with 4 NSAIDs administered did not change significantly at baseline or after 4 weeks (p=0.953). At four weeks, comparable outcomes with a p-value of 0.509 were seen. After a 12-week period, Naproxen had the highest blood cystatin C levels (1.14±0.16), whereas Etoricoxib, 1.08±0.13, Indomethacin, 1.06±0.09, and Aceclofenac had the lowest values (0.84±0.12 with p=0.01).

At baseline, aceclofenac had the highest blood eGFR cystatin C levels, followed by etoricoxib, naproxen, and indomethacin, which had the lowest values. With p=0.984, this was statistically not significant. Similar outcomes were observed after 4 weeks, with p=0.224. Serum eGFR cystatin c levels at 12 weeks were as follows: aceclofenac had the highest value at 115.22±14.84, followed by indomethacin at 83.02±11.73, etoricoxib at 81.86±19.54, and naproxen at 74.69±22.79. Table 4 indicates that this difference was statistically significant at p=0.006.

**DISCUSSION**

By comparing serum cystatin-c with serum creatinine, the current prospective hospital-based observational study aimed to investigate the relationship between the length of NSAID usage and the occurrence of subclinical kidney impairment in people with spondyloarthritis.

A total of 36 male patients with ages ranging from 19 to 56 and a mean age of 26.4±4.2 years were included in the research. Every research subject was a man. Of the participants, 41.66% (n=15) were HLA-B27 negative and 58.33% (n=21) were HLA positive. Axial spondyloarthritis accounted for the most prevalent diagnosis, occurring in 66.6% (n=24) of the participants, followed by Axial+ peripheral spondyloarthritis in 19.44% (n=7) of the subjects, and peripheral spondyloarthritis in 13.8% (n=5) of the research subjects. The most often used NSAID was etoricoxib, which was used in 52.7% (n=19) of the individuals, followed by indomethacin (19.4% (n=7), aceclofenac (16.6% (n=6)), and naproxen (11.1%) of the research subjects.

The present study's demographics and illness features were found to be similar to those evaluated by the authors of two previous investigations, namely Hoek FJ et al. (2003) and Hasse-Fielitz A et al. (2009), in which the individuals had similar characteristics. With corresponding p-values of 0.406, 0.623, and 0.548, the blood creatinine levels were not significantly different across the four NSAIDs administered at baseline, 4 weeks, or 12 weeks. Between baseline (0.75±0.14) and 4 weeks and 12 weeks (0.81±0.15), the level of etoricoxib rose. The baseline values of aceclofenac were 0.71±0.15, which dropped to 0.70±0.14 at 4 weeks, and then rose to 0.73±0.07 after 12 weeks.

The levels of indomethacin fell slightly from baseline (0.77±0.13) to 0.76±0.08 at 4 weeks, and then were constant at 12 weeks. Serum creatinine levels dropped from baseline, 0.86±0.14, to 0.81±0.08 at 4 weeks, and then to 0.79±0.13 at 12 weeks, after using naproxen. These outcomes were in line with those of studies conducted in 2010 by Briguori C et al. and in 2009 by Lafrance JP et al., who noted that NSAID use for spondyloarthritis was associated with similar changes in blood creatinine levels. Regarding the alterations in cystatin C blood levels, at baseline, 4 weeks, and 12 weeks, levels rose from 0.85±0.13 to 0.93±0.07 and 1.08±0.13, respectively, for etoricoxib.

Serum cystatin C levels with 4 NSAIDs administered did not change significantly at baseline or after 4 weeks (p=0.953). At four weeks, comparable outcomes with a p-value of 0.509 were seen. After a 12-week period, Naproxen had the highest blood cystatin C levels (1.14±0.16), whereas Etoricoxib, 1.08±0.13, Indomethacin, 1.06±0.09, and Aceclofenac had the lowest values (0.84±0.12 with p=0.01). These results corroborated those of Akgul O et al. (2011) and Chen B et al. (2015), who found that using naproxen in patients with spondyloarthritis resulted in considerably greater levels of cystatin C. The findings of this study were comparable to those of studies conducted by Shukla A et al. in 2017 and Terenzi R et al. in 2018, whose authors proposed that naproxen should be used to achieve the maximum levels of blood cystatin C.

When measuring the baseline serum eGFR cystatin C levels, aceclofenac had the highest levels, followed by etoricoxib, naproxen, and indomethacin, which had the lowest values. With p=0.984, this was statistically not significant. Similar outcomes were observed after 4 weeks, with p=0.224. Serum eGFR cystatin c levels at 12 weeks were as follows: aceclofenac had the highest value at 115.22±14.84, followed by indomethacin at 83.02±11.73, etoricoxib at 81.86±19.54, and naproxen at 74.69±22.79.

This difference was statistically significant with p=0.006. These results were in line with the results of Lipton S[13] in 2012 and Malakar A et al[14] in 2020 where authors reported serum eGFR cystatin c levels similar to the present study.

## CONCLUSION

Considering its limitations, the present study concludes that following intake of NSAIDs, no significant change was seen in the values of serum creatinine. However, a significant increase by 2 or 3-folds was seen in levels of serum cystatin-c compared to the initial value, and hence, cystatin-c can be used as an early biomarker for subclinical renal injury compared to serum creatinine. However, the present study had a few limitations including a small sample size, short monitoring time, and geographical area biases. Hence, more longitudinal studies with larger sample size and longer monitoring period will help reach a definitive conclusion.

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## TABLES

| S. No | Characteristics | Percentage (%) | Number (n=36) |
|---|---|---|---|
| **1.** | **Mean age (years)** | 26.4±4.2 | |
| **2.** | **Gender** | | |
| **a)** | Females | 0 | 0 |
| **b)** | Males | 100 | 36 |
| **3.** | **HLA-B27** | | |
| **a)** | Negative | 41.66 | 15 |
| **b)** | Positive | 58.33 | 21 |
| **4.** | **Diagnosis** | | |
| **a)** | Axial+ peripheral spondyloarthritis | 19.44 | 7 |
| **b)** | Peripheral spondyloarthritis | 13.8 | 5 |
| **c)** | Axial spondyloarthritis | 66.6 | 24 |
| **5.** | **NSAIDs used** | | |
| **a)** | Etoricoxib | 52.7 | 19 |
| **b)** | Naproxen | 11.1 | 4 |
| **c)** | Indomethacin | 19.4 | 7 |
| **d)** | Aceclofenac | 16.6 | 6 |

**Table 1: Demographic and disease characteristics of the study subjects**

| S. No | Time | Etoricoxib (Mean± S.D) | Naproxen (Mean± S.D) | Indomethacin (Mean± S.D) | Aceclofenac (Mean± S.D) | p-value |
|---|---|---|---|---|---|---|
| **1.** | **Baseline** | 0.75±0.14 | 0.86±0.14 | 0.77±0.13 | 0.71±0.15 | 0.406 |
| **2.** | **4 weeks** | 0.79±0.19 | 0.81±0.08 | 0.76±0.08 | 0.70±0.14 | 0.623 |
| **3.** | **12 weeks** | 0.81±0.15 | 0.79±0.13 | 0.76±0.06 | 0.73±0.07 | 0.548 |

**Table 2: Change in serum creatinine levels with different NSAIDs in the study subjects**

| S. No | Time | Etoricoxib (Mean± S.D) | Naproxen (Mean± S.D) | Indomethacin (Mean± S.D) | Aceclofenac (Mean± S.D) | p-value |
|---|---|---|---|---|---|---|
| **1.** | **Baseline** | 0.85±0.13 | 0.84±0.12 | 0.88±0.15 | 0.88±0.23 | 0.953 |
| **2.** | **4 weeks** | 0.93±0.07 | 0.94±0.07 | 0.91±0.05 | 0.86±0.13 | 0.509 |
| **3.** | **12 weeks** | 1.08±0.13 | 1.14±0.16 | 1.06±0.09 | 0.84±0.12 | **0.01** |

**Table 3: Change in serum cystatin c levels with different NSAIDs in the study subjects**

| S. No | Time | Etoricoxib (Mean± S.D) | Naproxen (Mean± S.D) | Indomethacin (Mean± S.D) | Aceclofenac (Mean± S.D) | p-value |
|---|---|---|---|---|---|---|
| **1.** | **Baseline** | 108.02±15.07 | 107.35±18.21 | 107.02±19.25 | 111.82±24.37 | 0.984 |
| **2.** | **4 weeks** | 97.73±14.28 | 95.35±19.64 | 101.85±9.56 | 113.22±19.25 | 0.224 |
| **3.** | **12 weeks** | 81.86±19.54 | 74.69±22.79 | 83.02±11.73 | 115.22±14.84 | **0.006** |

**Table 4: Change in serum eGFR cystatin c levels with different NSAIDs in the study subjects**