

Serum Prolidase Levels in Ankylosing Spondylitis: Correlation with Disease Activity and Inflammatory Markers

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ABSTRACT

Background: Prolidase is a multifunctional enzyme involved in the final stages of collagen degradation and plays an important role in collagen turnover, inflammation, wound healing, and angiogenesis. Alterations in prolidase activity may reflect changes in collagen metabolism associated with inflammatory and musculoskeletal disorders. Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by inflammation of the axial skeleton and alterations in bone and collagen metabolism. The potential role of serum prolidase as a biomarker of disease activity in AS remains insufficiently established.

Aim: To estimate serum prolidase levels in patients with ankylosing spondylitis and evaluate their association with disease severity and inflammatory markers.

Methods: A prospective, observational, cross-sectional study was conducted from July 2016 to September 2017 in the Departments of Biochemistry, SCB Medical College and Hospital and SVP PG Institute of Pediatrics, Cuttack. Sixty patients with AS fulfilling the modified New York criteria (1984) and 30 age- and sex-matched healthy controls were enrolled. Disease activity and functional status were assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). Serum prolidase was estimated using a human Prolidase/Peptidase D (PEPD) sandwich ELISA. ESR and CRP were assessed as inflammatory markers. Statistical analysis was performed using Student's t-test, Pearson's correlation and ANOVA, with $p < 0.05$ considered statistically significant.

Results: The mean serum prolidase level was significantly higher in AS patients than controls (13.65 ± 5.32 vs. 9.48 ± 2.81 ng/mL; $p < 0.0001$). ESR and CRP were also significantly elevated in patients compared with controls (69.64 ± 38.45 vs. 18.93 ± 5.36 mm/hr and 78.09 ± 61.37 vs. 2.47 ± 1.08 mg/L, respectively; $p < 0.0001$). Serum prolidase showed a weak positive correlation with BASDAI ($r = 0.05$), ESR ($r = 0.19$), and CRP ($r = 0.01$), although these correlations were not statistically significant. A weak negative correlation was observed with BASFI ($r = -0.03$).

Conclusion: Serum prolidase levels were significantly elevated in patients with AS compared with healthy controls. The findings suggest a potential role for prolidase as a biomarker reflecting altered collagen metabolism in active AS; however, its relationship with established disease activity and inflammatory parameters requires validation in larger prospective studies.

Keywords: NA

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Introduction

Imidodipeptides containing proline or hydroxyproline at the C-terminal position are specifically hydrolysed by the multifunctional intracellular and extracellular enzyme prolidase. It is extensively dispersed throughout the body and takes involved in the last phases of dietary and endogenous protein breakdown. Because collagen contains a significant amount of proline and hydroxyproline residues, its function in collagen metabolism is very crucial. As a result, variations in serum prolidase activity have been studied in a number of illness states and may indicate changes in collagen turnover. Prolidase is also involved in physiological and pathological processes such as inflammation, wound healing, and angiogenesis. It also helps regulate growth hormones and transcription factors (1, 2).

A chronic, progressive inflammatory musculoskeletal condition that mostly affects the axial skeleton, ankylosing spondylitis (AS) can cause significant functional impairment. Significant changes in bone turnover and persistent systemic inflammation are linked to the condition, which often strikes people at a young age. Investigating collagen-related enzymes like prolidase in AS is justified since these inflammatory and structural processes may be accompanied by changes in collagen metabolism. Serum prolidase and disease activity in chronic inflammatory musculoskeletal illnesses may be related, according to earlier research (3). It has been suggested that altered collagen turnover and fibrosis are reflected in lower prolidase activity, while a faster collagen cycle may result in higher activity. Serum prolidase may be helpful for evaluating disease activity in AS, according to Turkish studies, and it may perform similarly to well-known clinical indices like the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Prolidase has, however, seldom been studied in rheumatic conditions, and there is still little data especially pertaining to AS (4, 5).

Therefore, prolidase's usefulness as a biomarker in AS remained unclear. As a result, the study looked at blood prolidase levels in AS patients and how they related to BASDAI, BASFI, ESR, and CRP (6).

Aim

To measure serum prolidase levels in patients with ankylosing spondylitis and evaluate their relationship with disease severity and inflammatory activity.

Objectives

1. To measure serum prolidase levels in patients with ankylosing spondylitis.
2. To correlate serum prolidase levels with disease severity indices, namely BASDAI and BASFI.
3. To correlate serum prolidase levels with inflammatory markers, namely ESR and CRP.

Materials and Methods**Study Design and Setting**

A prospective, observational, cross-sectional study was conducted in the Department of Biochemistry, SCB Medical College and Hospital, Cuttack from July 2016 to September 2017. The study included 60 patients with ankylosing spondylitis and 30 healthy controls.

Study Population

Patients aged 20–65 years, irrespective of sex, diagnosed with ankylosing spondylitis and admitted to the Clinical Immunology and Rheumatology unit of the Department of Medicine, SCB Medical College, were enrolled. All patients fulfilled the modified New York criteria (1984). Age- and sex-matched healthy individuals constituted the control group. Written informed consent was obtained from all participants, and the study protocol was approved by the institutional ethics committee.

Exclusion Criteria

Participants with malignant cancer, other inflammatory or rheumatic diseases, endocrine disorders, chronic renal or hepatic disease, acute or chronic infections, heart failure, cerebrovascular disease, alcohol abuse, infectious or endocrine-related arthropathy, pregnancy, or lactation were excluded.

Clinical Assessment

Detailed clinical and systemic examination was performed, and demographic and clinical information including age, sex, disease duration, family history, past medical history, and current medications were recorded. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), while functional status was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI).

BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX (BASDAI)

Please tick the box which represents your answer (for example, ☒ 10).
All questions refer to **last week**.

1. How would you describe the overall level of fatigue/tiredness you have experienced?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

2. How would you describe the overall level of AS **neck, back or hip** pain you have had?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

3. How would you describe the overall level of pain/swelling in joints **other than** neck, back or hips you have had?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

6. How long does your morning stiffness last from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10
0 hrs					1 hr					2 hrs or more

BATH ANKYLOSING SPONDYLITIS FUNCTIONAL INDEX (BASFI)

Please indicate your level of ability with each of the following activities during the **last week**.
Tick a box to indicate your answer (for example, ☒ 10).

- Putting on your socks or tights without help or aids (e.g., sock aid).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Bending forward from the waist to pick up a pen from the floor without an aid.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Reaching up to a high shelf without help or aids (e.g., helping hand).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Getting up out of an armless dining room chair without using your hands or any other help.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Getting up off the floor without help from lying on your back.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Standing unsupported for 10 minutes without discomfort.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Climbing 12-15 steps without using a handrail or walking aid. **One foot at each step.**

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Looking over your shoulder without turning your body.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Doing physically demanding activities (e.g., physiotherapy exercises, gardening or sports).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible
- Doing a full day's activities, whether it be at home or at work.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

Sample Collection and Laboratory Investigations

Five millilitres of fasting venous blood was collected from each participant. Samples were appropriately distributed for hematological, biochemical, inflammatory, and special investigations. ESR was measured by the Westergren method, while routine biochemical investigations included fasting blood glucose, liver function tests, renal function tests, and lipid profile. HLA-B27 was assessed by flow cytometry and quantitative CRP was estimated by immunoturbidimetry.

Estimation of Serum Prolidase

Serum samples for prolidase estimation were stored at -20°C . Serum human Prolidase/Peptidase D (PEPD) was estimated using a 96-well ELISA kit by the sandwich ELISA technique. Following sample incubation, HRP-conjugated antibody and TMB substrate were added, and

the reaction was terminated using stop solution. Optical density was measured at 450 nm using an ELISA reader. Prolidase concentration was derived from the standard curve and expressed in ng/mL. The assay range was 0.78–50 ng/mL.

Statistical Analysis

Data were entered into an Excel spreadsheet and analyzed using GraphPad Prism 7. Results were expressed as mean $\pm$ standard deviation. Student's t-test was used for comparison of means, Pearson's correlation test was used to assess relationships between variables, and ANOVA was applied where appropriate. Scatter plots were generated for correlation analysis. A p-value <0.05 was considered statistically significant, while $p<0.001$ was considered highly significant.

Results

DEMOGRAPHIC PROFILE

Table 1. Demographic characteristics of study participants

Variable	AS patients (n=60)	Healthy controls (n=30)	p-value
Age (years), mean $\pm$ SD	33.73 $\pm$ 10.26	30.43 $\pm$ 5.56	0.10
Male, n (%)	58 (96.7)	30 (100.0)	0.57
Female, n (%)	2 (3.3)	0 (0.0)	0.57

The mean age was comparable in both the groups and was statistically non-significant.

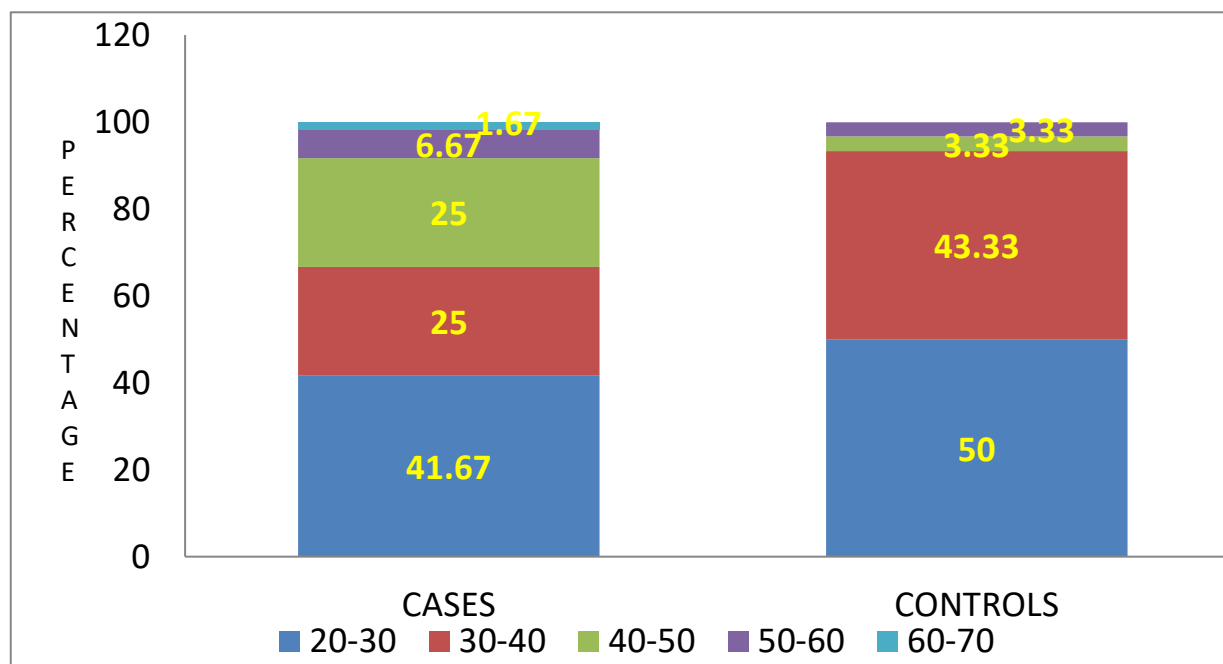


FIG 1: COMPARISON OF AGE (%) IN CASE AND CONTROL GROUP

Table 2. Comparison of inflammatory markers between AS patients and healthy controls

Inflammatory marker	AS patients (n=60), Mean $\pm$ SD	Healthy controls (n=30), Mean $\pm$ SD	p-value
ESR (mm/hr)	69.64 $\pm$ 38.45	18.93 $\pm$ 5.36	<0.0001
CRP (mg/L)	78.09 $\pm$ 61.37	2.47 $\pm$ 1.08	<0.0001

Cases included 58 male patients and 2 female patients. Controls included 30 healthy male volunteers.

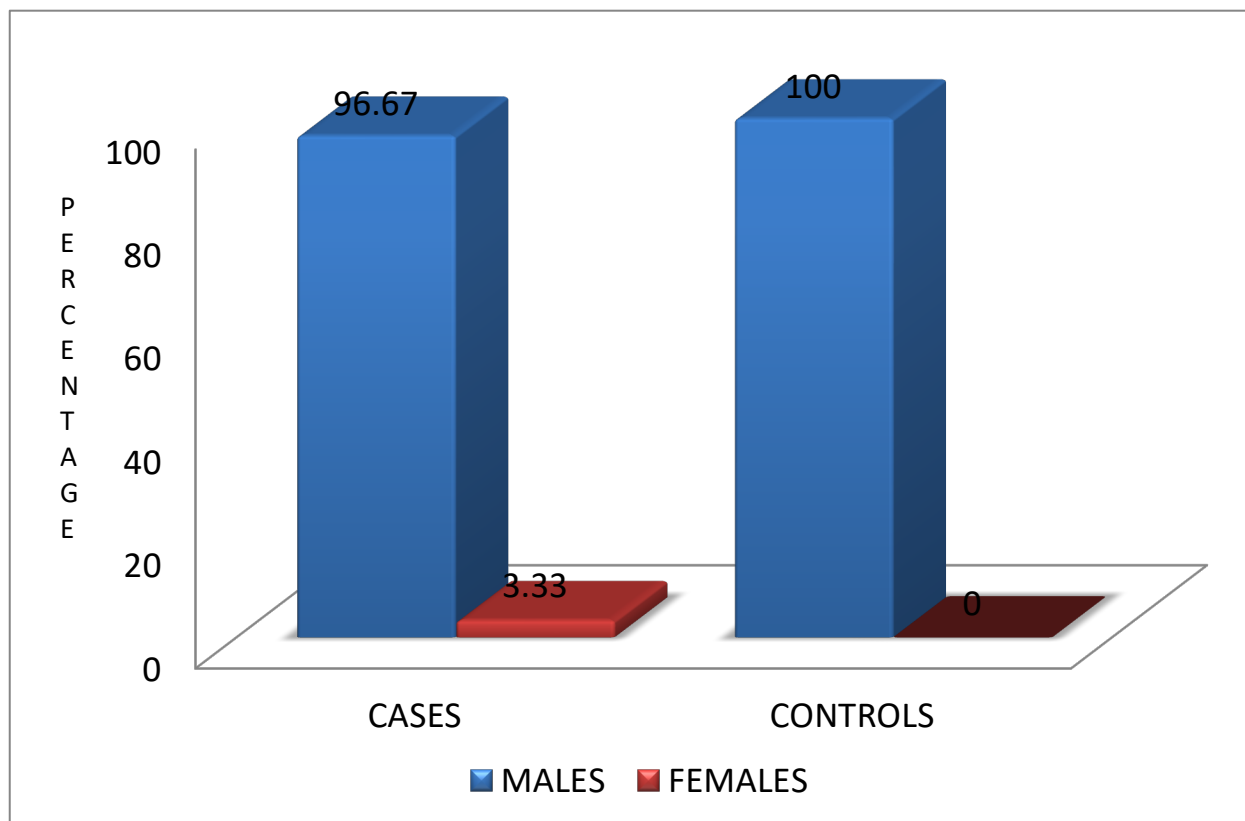


FIG 2: COMPARISON OF GENDER WISE DISTRIBUTION OF CASES AND CONTROLS

Table 3. Comparison of serum prolidase (PEPD) levels between AS patients and controls

Variable	AS patients (n=60)	Healthy controls (n=30)	p-value
Serum prolidase/PEPD (ng/mL), mean $\pm$ SD	13.65 $\pm$ 5.32	9.48 $\pm$ 2.81	<0.0001

P < 0.05; statistically significant

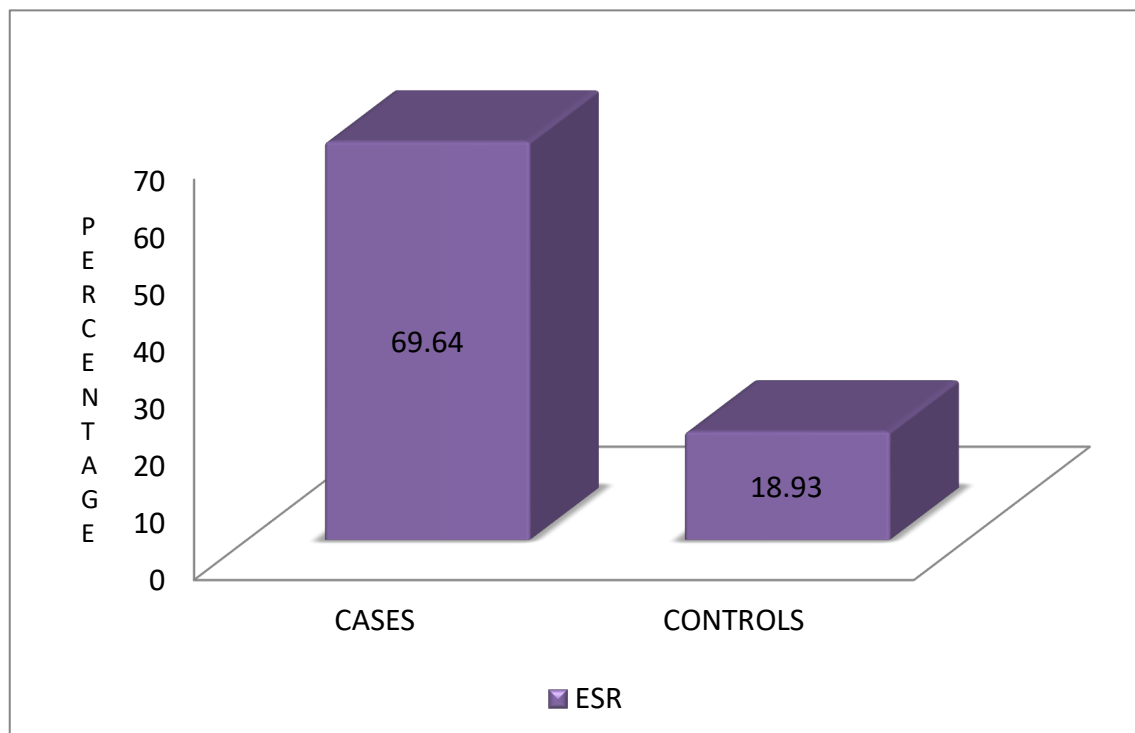


FIG 3: COMPARISON OF ESR IN CASE AND CONTROL GROUP

Table 4. Disease activity and functional status among AS patients

Clinical index	AS patients (n=60), Mean $\pm$ SD
BASDAI	5.82 $\pm$ 1.09
BASFI	6.02 $\pm$ 1.40

P < 0.05; statistically significant

The mean CRP in cases was 78.09 ± 61.37 mg/l, which was higher than that of controls, 2.47 ± 1.08 mg/l, with a statistically significant difference of p value <0.0001.

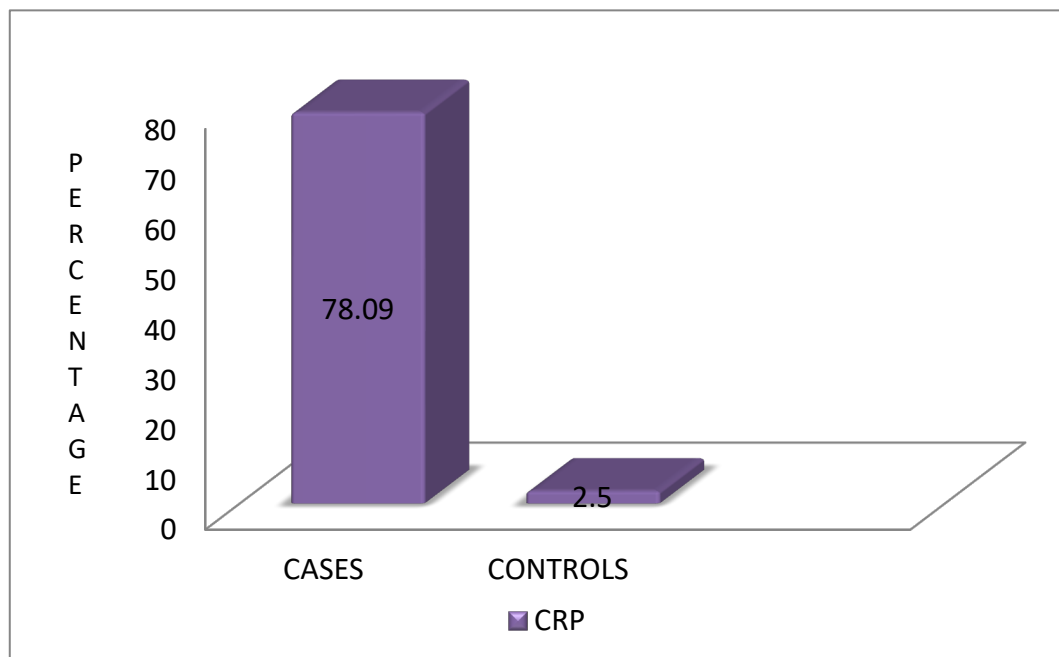


FIG 4: COMPARISON OF CRP IN CASE AND CONTROL GROUP

Table 5. Correlation of serum prolidase/PEPD with disease activity, functional status and inflammatory markers

Variable correlated with serum prolidase	Pearson's correlation coefficient (r)	p-value	Interpretation
BASDAI	0.05	0.67	Non-significant
BASFI	-0.03	0.80	Non-significant
ESR	0.19	0.13	Non-significant
CRP	0.01	0.91	Non-significant

Serum prolidase showed weak positive correlations with BASDAI and ESR and a negligible positive correlation with CRP, while a weak negative correlation was observed with BASFI. None of these associations reached statistical significance.

$P < 0.05$; statistically significant

The mean serum prolidase level in cases was 13.65 ± 5.32 ng/ml, which was higher than that of controls, 9.479 ± 2.81 ng/ml, and the difference was statistically highly significant with p value < 0.0001 .

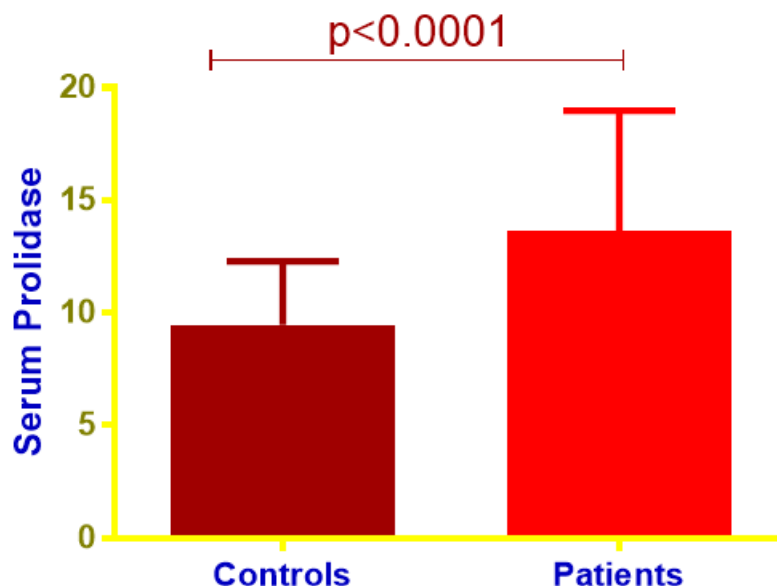


FIG 5: COMPARISON OF SERUM PROLIDASE LEVEL IN CASE AND CONTROL GROUP

Table 6. Serum prolidase/PEPD according to pattern of disease involvement

Type of AS	Mean serum prolidase (ng/mL)	SD	SEM
Axial AS	13.14	3.13	1.04
Axial + peripheral AS	13.18	5.04	0.73

The mean BASDAI score of patients was found out to be 5.82 ± 1.09 , i.e., > 4 .

The mean BASFI score was found out to be 6.02 ± 1.4 .

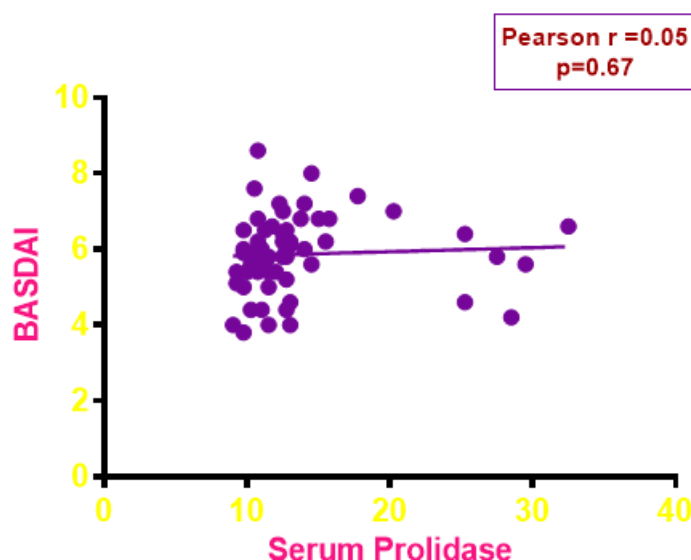


FIG 6: CORRELATION OF SERUM PROLIDASE WITH BASDAI

Serum prolidase and BASDAI were positively correlated ($r=0.05$). p value $=0.67$; non-significant association.

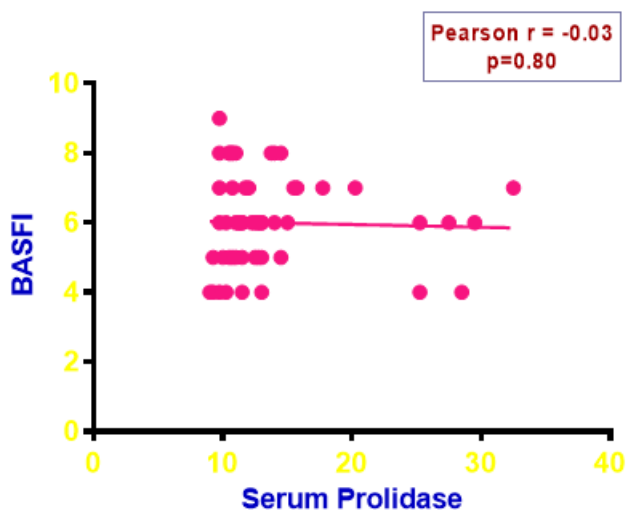


FIG 7: CORRELATION OF SERUM PROLIDASE WITH BASFI

Serum prolidase and BASFI were negatively correlated ($r = -0.03$). p value= 0.80; non-significant association.

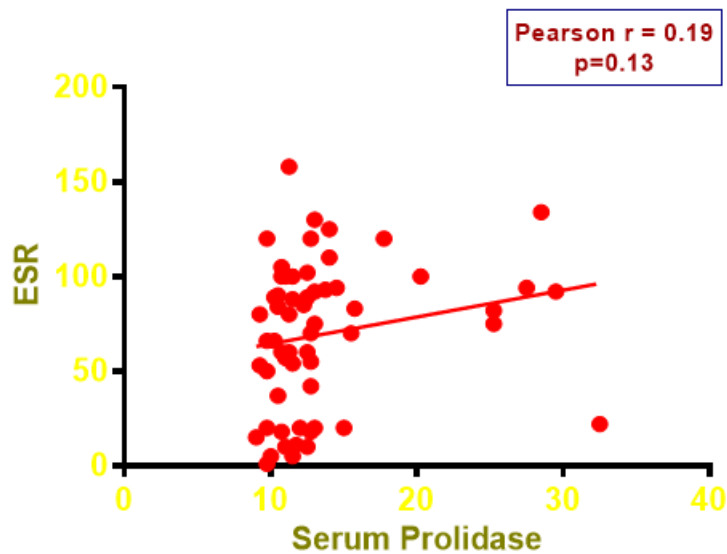


FIG 8: CORRELATION OF SERUM PROLIDASE WITH ESR

Serum prolidase and ESR were correlated positively ($r=0.19$). p value=0.13; non-significant association.

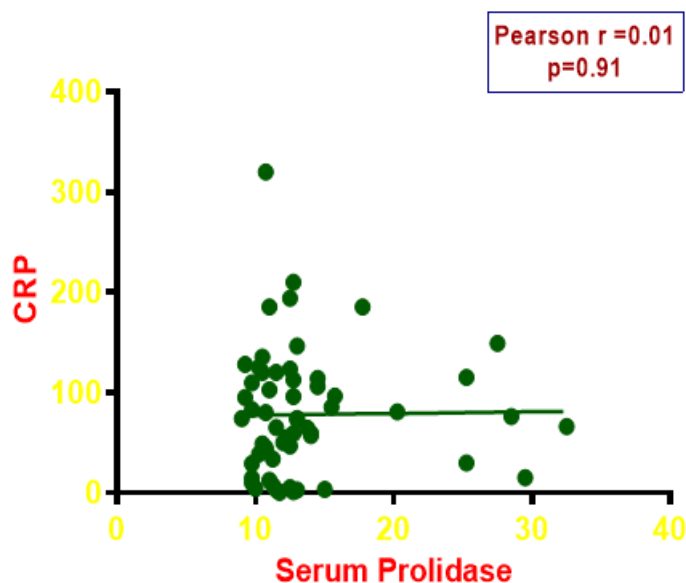


FIG 9: CORRELATION OF SERUM PROLIDASE WITH CRP

Serum prolidase and CRP were correlated positively ($r=0.01$). p value= 0.91 ; non-significant association.

Table 7. Serum prolidase/PEPD according to disease duration

Disease duration	Mean serum prolidase (ng/mL)	SD	SEM
<5 years	13.36	5.44	0.95
5–10 years	13.75	4.93	1.27
>10 years	14.33	5.86	1.69

There was a gradual numerical increase in serum prolidase concentration with increasing disease duration, from 13.36 ng/mL in patients with disease duration <5 years to 14.33 ng/mL in those with disease duration >10 years.

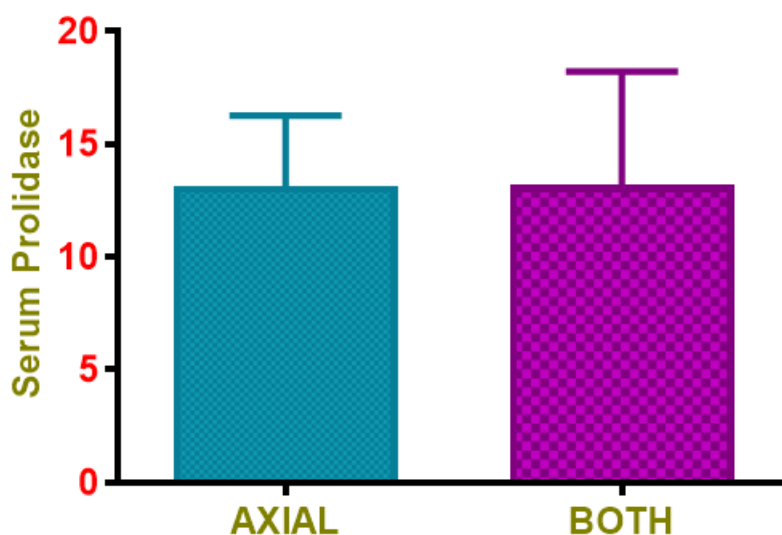


FIG 10: CORRELATION OF SERUM PROLIDASE WITH TYPE OF DISEASE

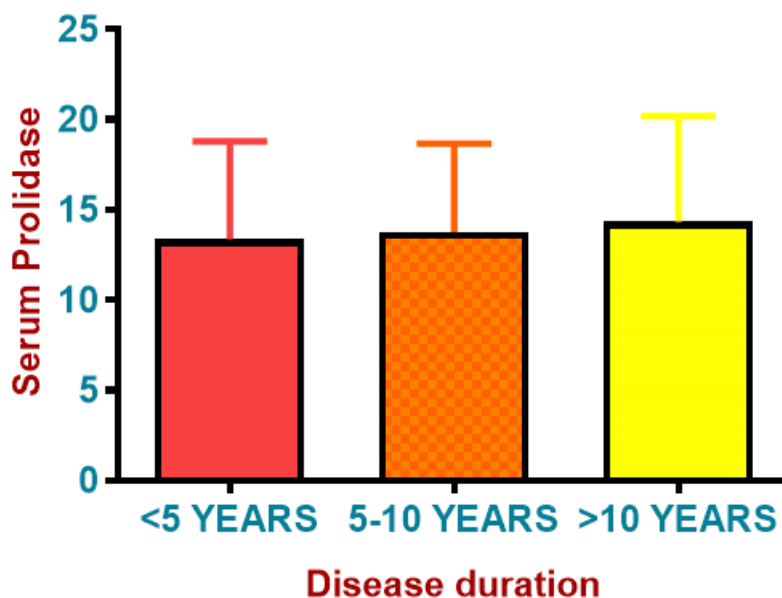


FIG 11: CORRELATION OF SERUM PROLIDASE LEVEL WITH DISEASE DURATION

Discussion

The current study assessed serum prolidase levels in ankylosing spondylitis (AS) patients and looked at how these levels related to systemic inflammatory markers, disease activity, and functional impairment. The main discovery was that patients with AS had significantly higher serum prolidase levels than healthy controls. Patients' mean serum prolidase was 13.65 ± 5.32 ng/mL, while controls' was 9.48 ± 2.81 ng/mL ($p < 0.0001$) (7). This

result lends credence to the hypothesis that AS is associated with altered collagen metabolism and extracellular matrix remodelling, and that prolidase may serve as an additional biochemical diagnostic of the illness. Because AS is characterised by complicated structural remodelling, including pathological new bone production and ankylosis, in addition to persistent inflammation, the current findings are especially pertinent (8, 9).

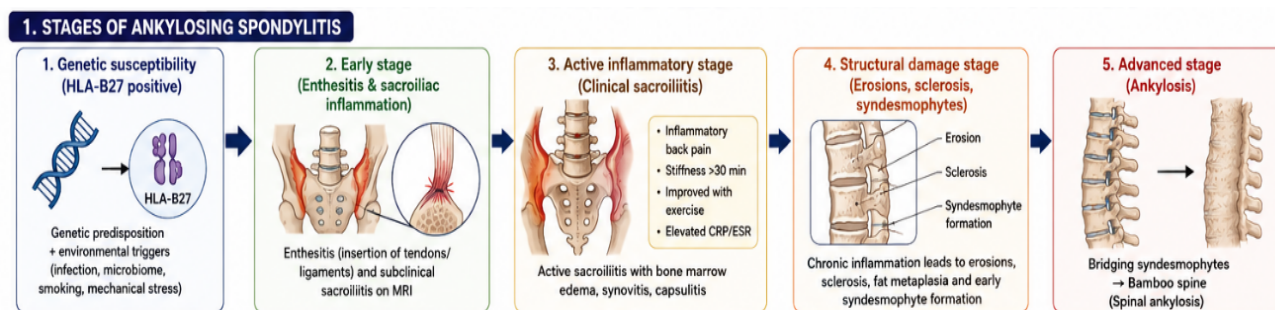


Fig 1: Stages of Ankylosing Spondylitis

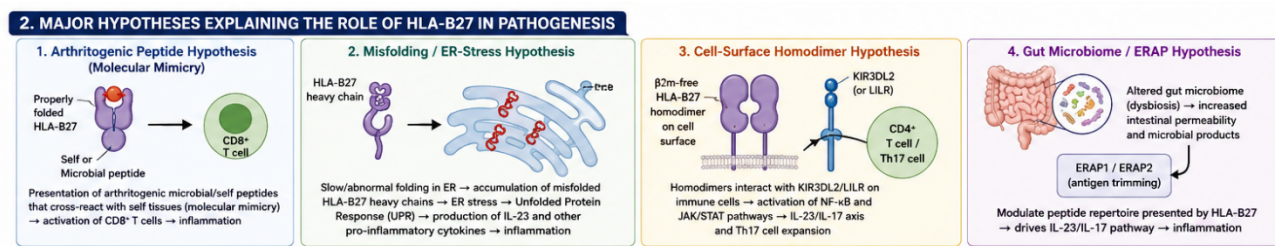


Fig 2: Various hypothesis explaining the role of HLA-B27 in pathogenesis of AS

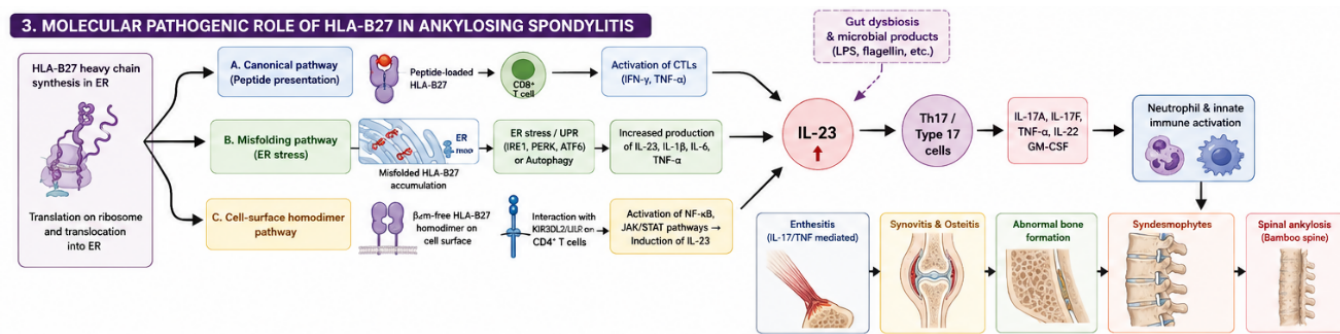
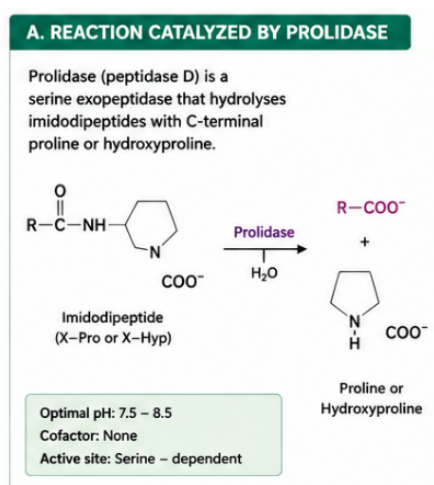


Fig 3: The molecular pathogenic role of HLA-B27 in AS



ig 4: Reaction catalyzed by prolidase

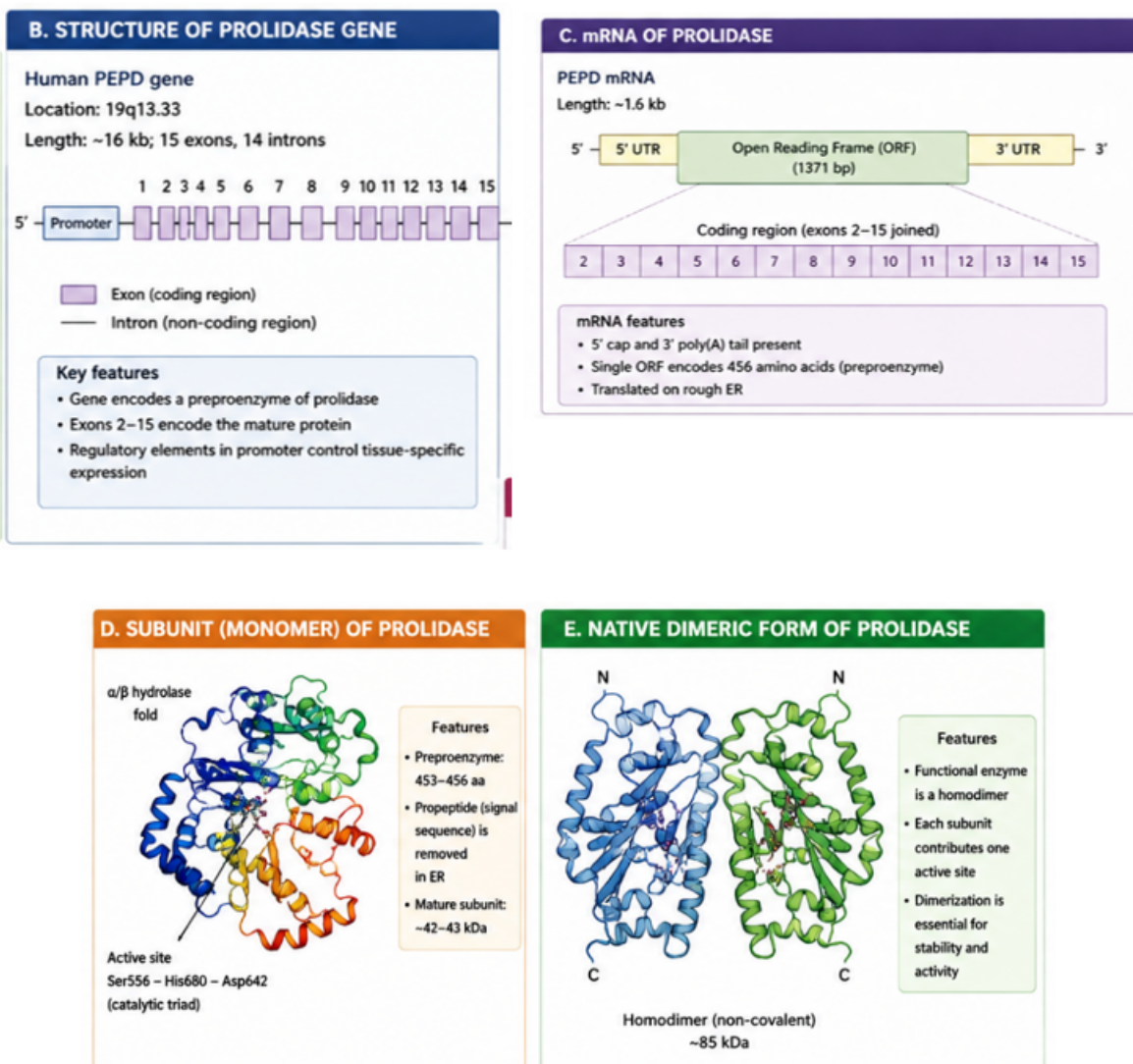


Fig 5: Structure of prolidase gene, its mRNA, subunit and native dimeric form of the enzyme

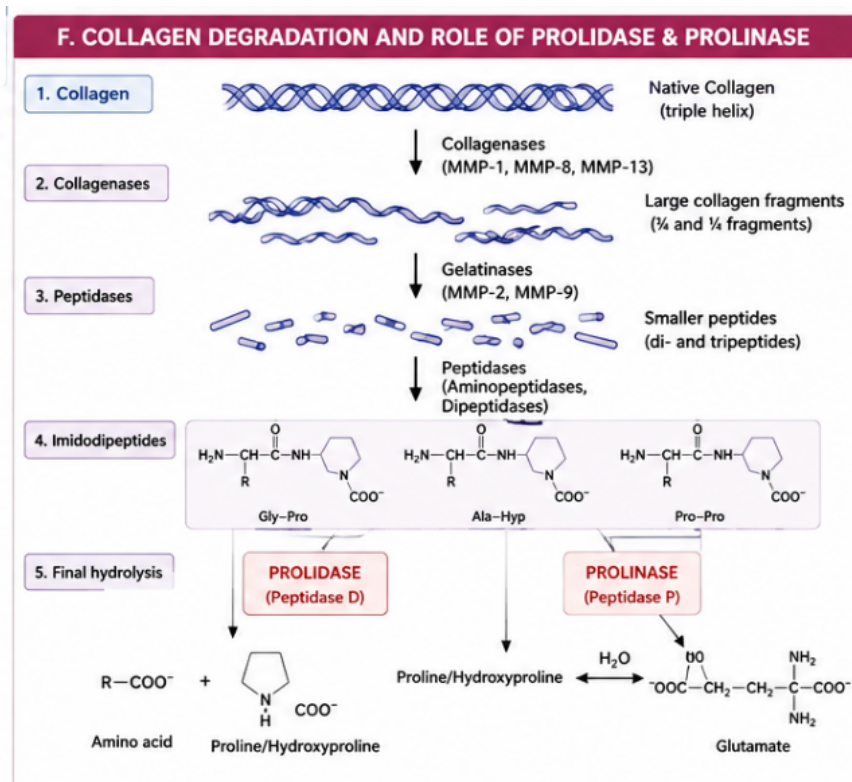


Fig 6. Diagram of collagen degradation resulting in imidodipeptides that are hydrolysed by prolidase and prolinase.

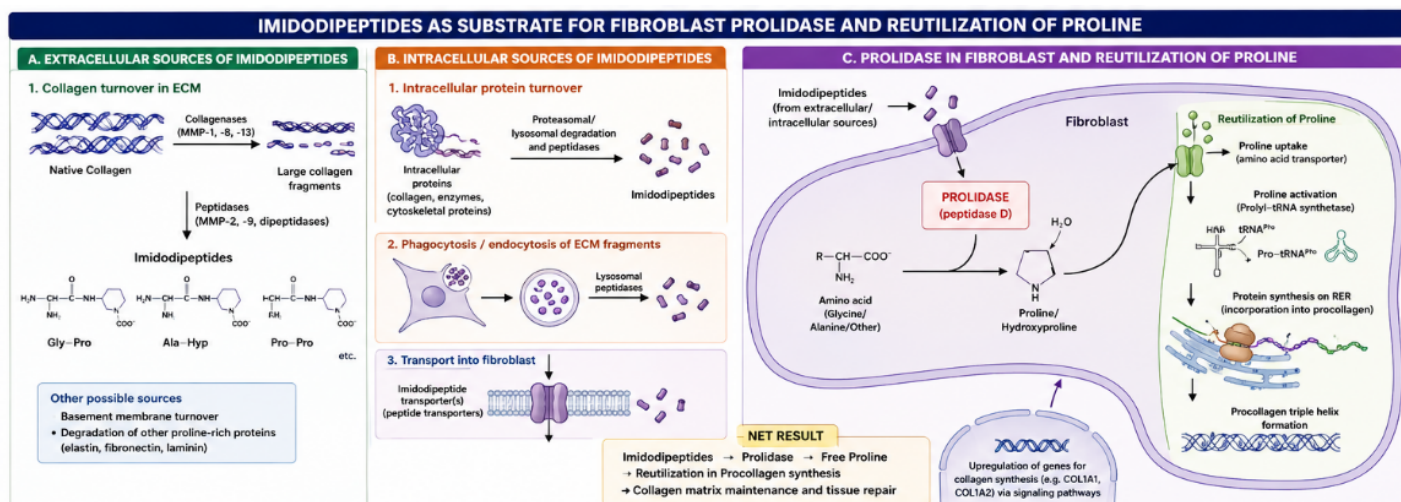


Fig 7: Extracellular and intracellular sources of imidodipeptides, representing substrate for fibroblast's prolidase and its role n reutilization of proline for procollagen synthesis

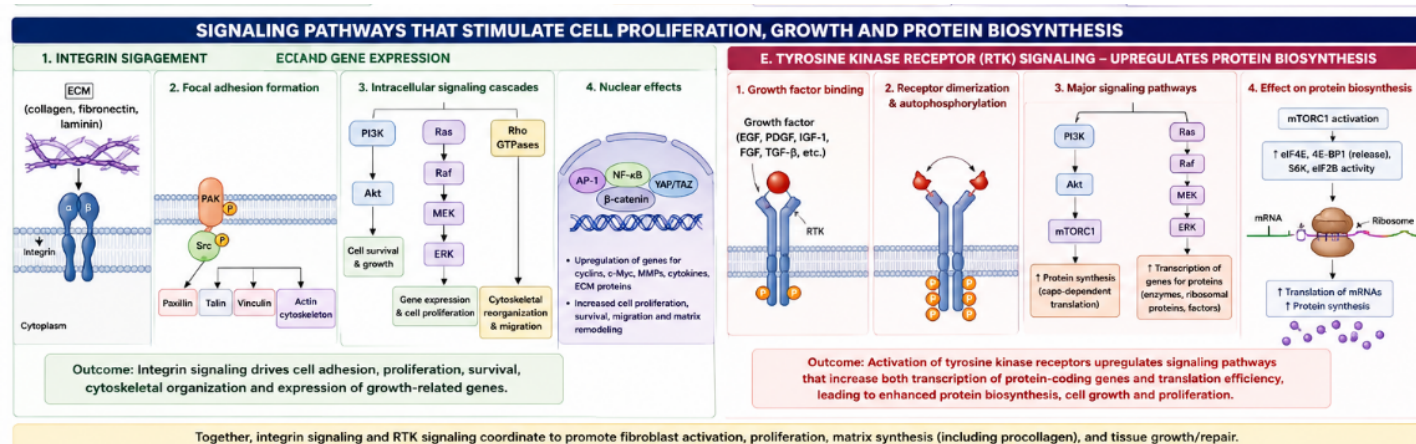


Fig 8: Integrin signaling contributes to stimulation of cell proliferation, growth and gene expression. Whereas, activation of tyrosine kinase receptors (eg. growth factor receptors) contributes to upregulation of signaling for protein biosynthesis

Inflammation, tissue repair, mechanical stress, and abnormal bone production are all closely related processes rather than distinct ones, according to current knowledge of axial spondyloarthritis. While WNT/ β -catenin and other pathways aid in the production of new bone, TNF- α and IL-17A are involved in inflammatory and bone-remodeling processes. Thus, it is possible that an enzyme engaged in collagen turnover represents a part of this remodelling process. The significantly higher ESR and CRP in the patients was a significant finding (10, 11). The mean CRP was 78.09 ± 61.37 mg/L compared with 2.47 ± 1.08 mg/L, and the mean ESR was 69.64 ± 38.45 mm/hr compared with 18.93 ± 5.36 mm/hr in controls; both comparisons were $p < 0.0001$. These results support the study population's significant systemic inflammatory activity. While the mean BASFI was 6.02 ± 1.40 , showing significant functional impairment, the mean BASDAI of 5.82 ± 1.09 was over the standard criterion of 4 for active disease. When monitoring axSpA, current guidelines still place a strong emphasis on assessment utilising clinical indicators, laboratory markers, patient-reported outcomes, and imaging (12, 13).

Serum prolidase did not show statistically significant relationships with BASDAI, BASFI, ESR, or CRP, despite the considerable difference between cases and controls. While there was virtually no link with CRP ($r=0.01$; $p=0.91$), there was a weak positive correlation with BASDAI ($r=0.05$; $p=0.67$) and ESR ($r=0.19$; $p=0.13$). There was a weak negative connection ($r=-0.03$; $p=0.80$) between serum prolidase and BASFI. Therefore, based solely on this study, prolidase cannot be regarded as a reliable indicator of current disease activity or functional impairment, but it may be able to differentiate patients with AS from healthy persons. This result is in contrast to the Baspinar et al. study, which found a substantial correlation between prolidase and disease activity and observed

decreased serum prolidase levels in active AS (15). On the other hand, Uçar et al. found that AS had lower prolidase activity than controls, which they attributed to decreased collagen turnover and fibrosis. As a result, the direction of relationship is significantly different from the current findings. Differences in assay methodology, patient selection, disease duration, treatment status, disease activity, dietary or metabolic variables, and the distinction between assessing prolidase enzyme activity and measuring circulating PEPD levels by ELISA could all contribute to this variance (16, 17).

A key methodological distinction is that the current investigation examined serum PEPD levels instead of enzymatic activity. Patients with both axial and peripheral involvement had a slightly higher prolidase concentration (13.18 ± 5.04 ng/mL) than those with axial disease alone (13.14 ± 3.13 ng/mL). Prolidase also rose quantitatively with the length of the illness, from 13.36 ± 5.44 ng/mL in patients with less than five years of illness to 13.75 ± 4.93 ng/mL in those with five to ten years and 14.33 ± 5.86 ng/mL in those with more than ten years (18). However, no discernible difference was found. These findings imply that persistent structural remodelling may have an impact on prolidase, although the current sample size was insufficient to prove this. CRP and ESR are recognised markers for routine monitoring according to recent axSpA biomarker guidelines, but many new biomarkers are still being assessed. Therefore, rather than justifying the replacement of conventional disease activity markers, the current data should be considered as preliminary evidence supporting additional research (19, 20).

A defined AS population, healthy controls, standardised clinical indices, the elimination of significant systemic confounders, and direct biochemical assessment of PEPD are among the study's strong points. However, generalisability is limited by the small sample size, cross-

sectional methodology, significant male predominance, lack of longitudinal follow-up, and lack of treatment-response evaluation. Prolidase should be assessed in conjunction with BASDAI, ASDAS, CRP, ESR, MRI results, and radiographic progression in larger multicentric prospective studies. Additionally, enzyme activity and circulating PEPD levels should be compared (21, 22).

Conclusion

Ankylosing spondylitis patients had considerably greater serum prolidase levels than healthy controls, suggesting a link between AS and altered collagen-related metabolism. According to BASDAI, the study population had active illness, substantial systemic inflammation, and considerably elevated ESR and CRP. However, there were only modest and statistically insignificant correlations between serum prolidase and BASDAI, BASFI, ESR, and CRP. Prolidase may therefore be useful as a biochemical marker linked to AS, but current research does not prove that it is a reliable measure of disease activity or functional severity. Methodological and demographic variations, especially the measurement of PEPD content rather than enzyme activity, may account for variations from earlier research. Larger longitudinal and multicentric studies incorporating imaging, established activity scores, treatment response, and both prolidase concentration and enzymatic activity are required to clarify its clinical utility.

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