Circulating Angiotensin Peptides as Biomarkers of Rheumatoid Arthritis

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Assistant Professor

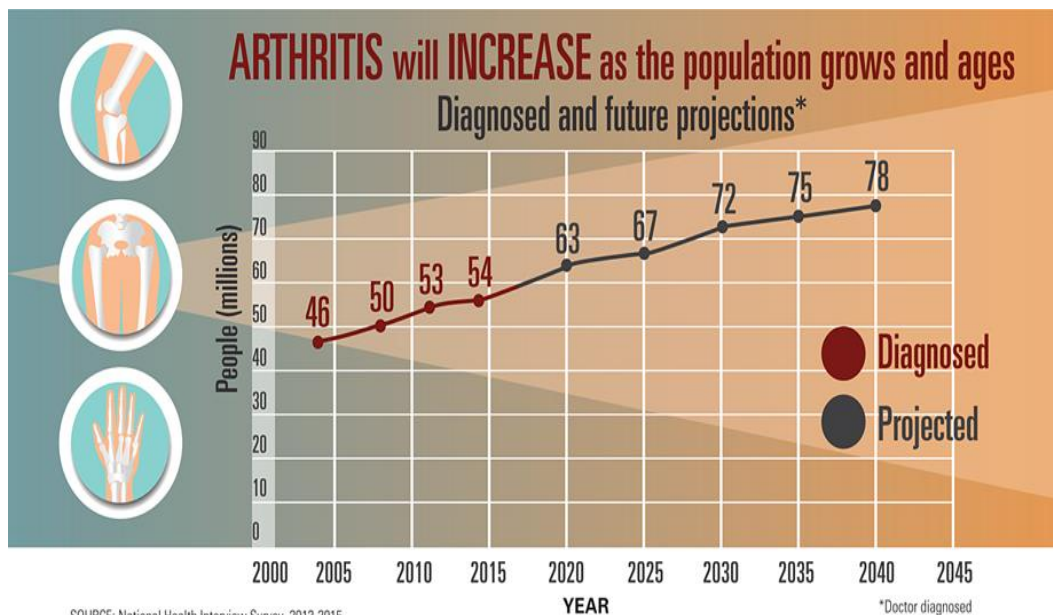**Department of Biomedical and Pharmaceutical Sciences**
College of Pharmacy
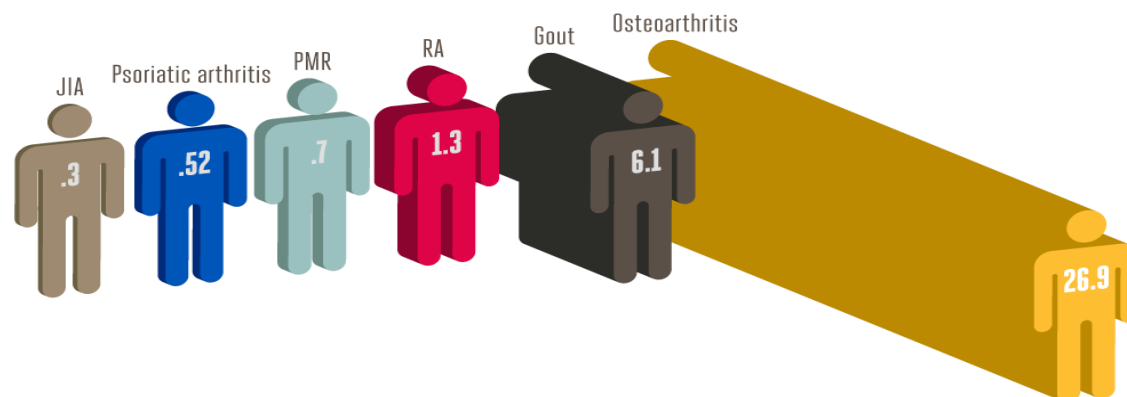
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Idaho State University

ROAR

Arthritis

ARTHRITIS will INCREASE as the population grows and ages
Diagnosed and future projections*

People (millions)

46 50 53 54 63 67 72 75 78

2000 2005 2010 2015 2020 2025 2030 2035 2040 2045
YEAR

● Diagnosed
● Projected

SOURCE: National Health Interview Survey, 2013-2015.

*Doctor diagnosed

Prevalence of common forms of arthritis in the US (in millions)[1,3-5]

JIA .3
Psoriatic arthritis .52
PMR .7
RA 1.3
Gout 6.1
Osteoarthritis 26.9

RA: rheumatoid arthritis; JIA: juvenile idiopathic arthritis (juvenile rheumatoid arthritis); PMR: polymyalgia rheumatica.
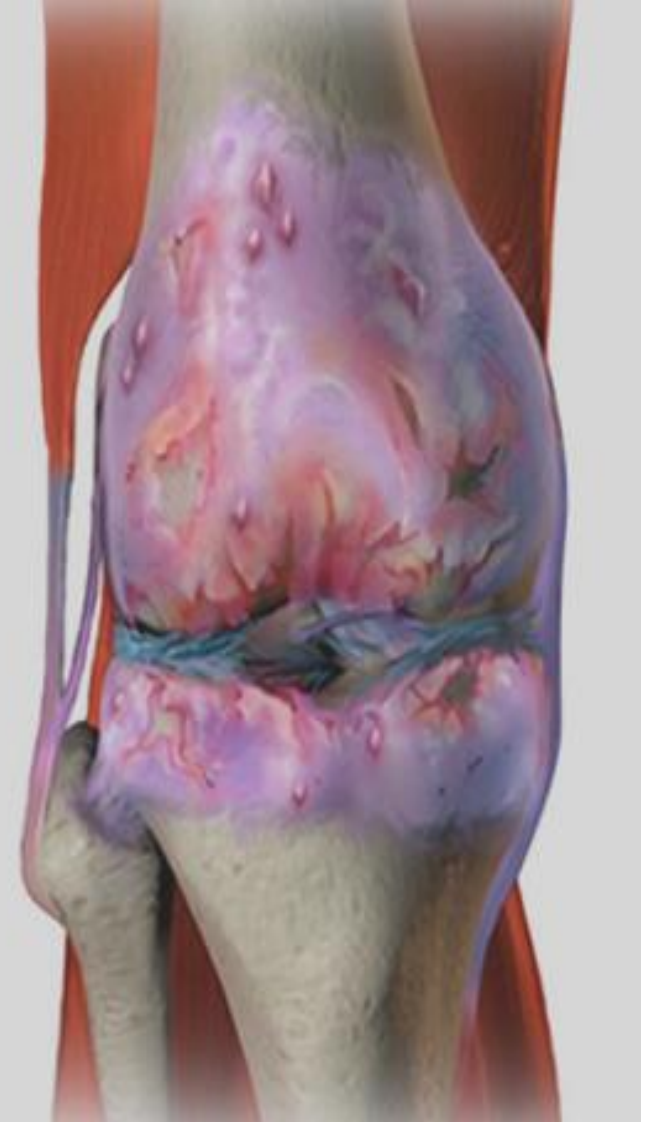
Rheumatoid Arthritis

Rheumatoid Arthritis

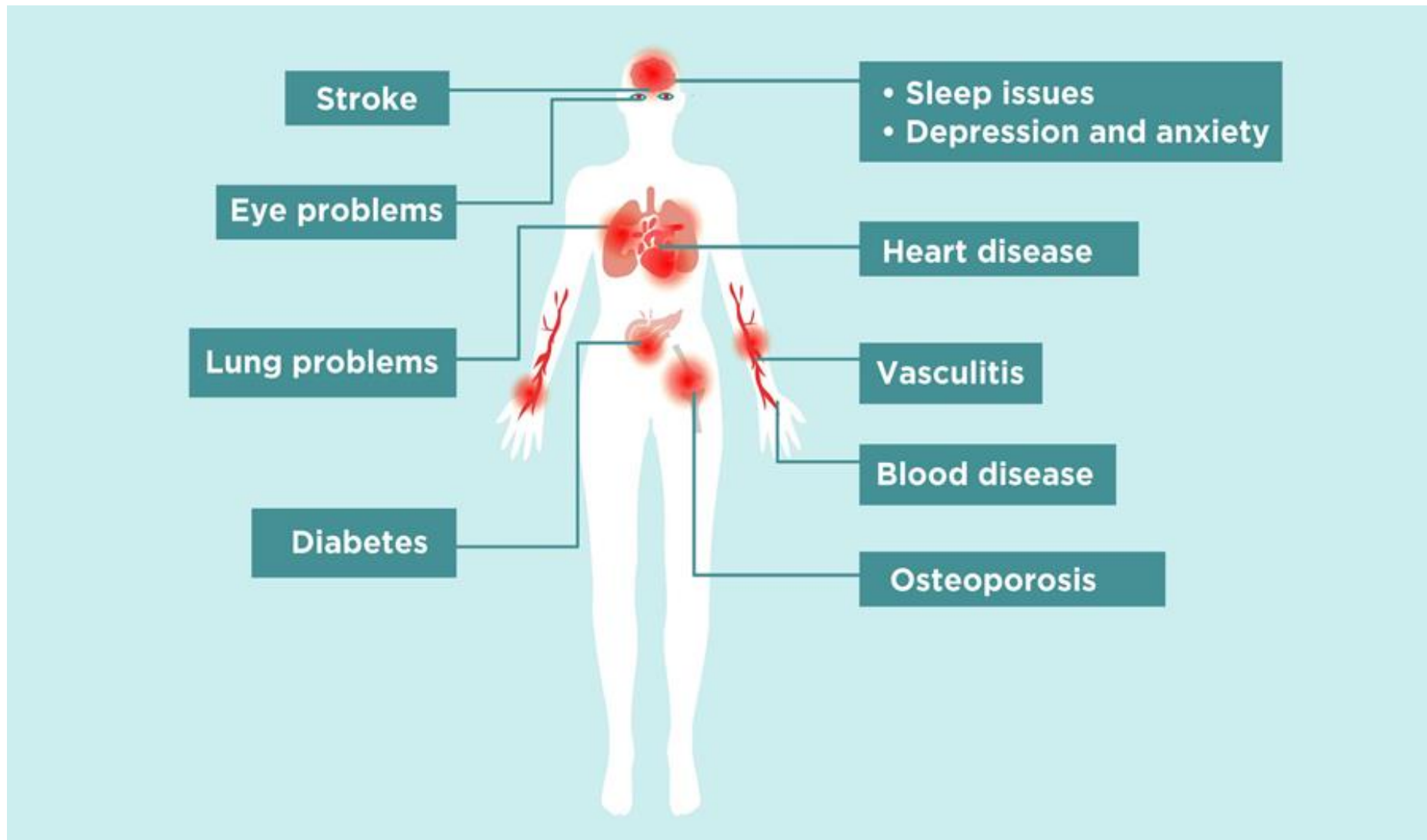## SYMPTOMS ASSOCIATED WITH RHEUMATOID ARTHRITIS

- Swelling, pain, and stiffness in the joints in the hand.
- A warm feeling around the joint.
- Deformities and contractures of the joint.
- Weakness due to anemia caused by low red blood cell count.
- Nodules, or lumps, particularly around the elbow.
- Foot pain, bunions, and hammer toes with long-standing disease.
- Fever.
- Cysts.
- Loss of appetite.
- Decreased energy.
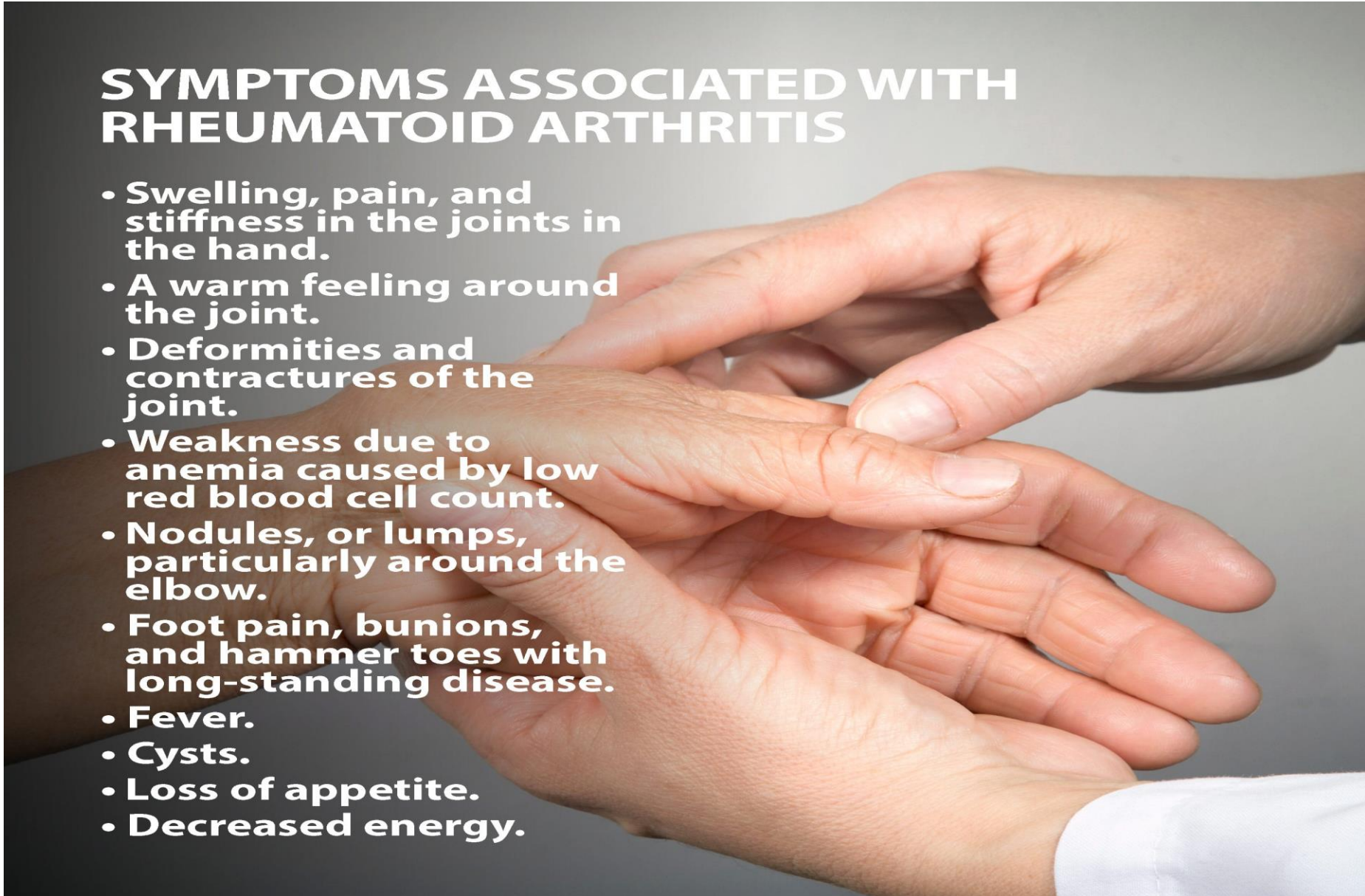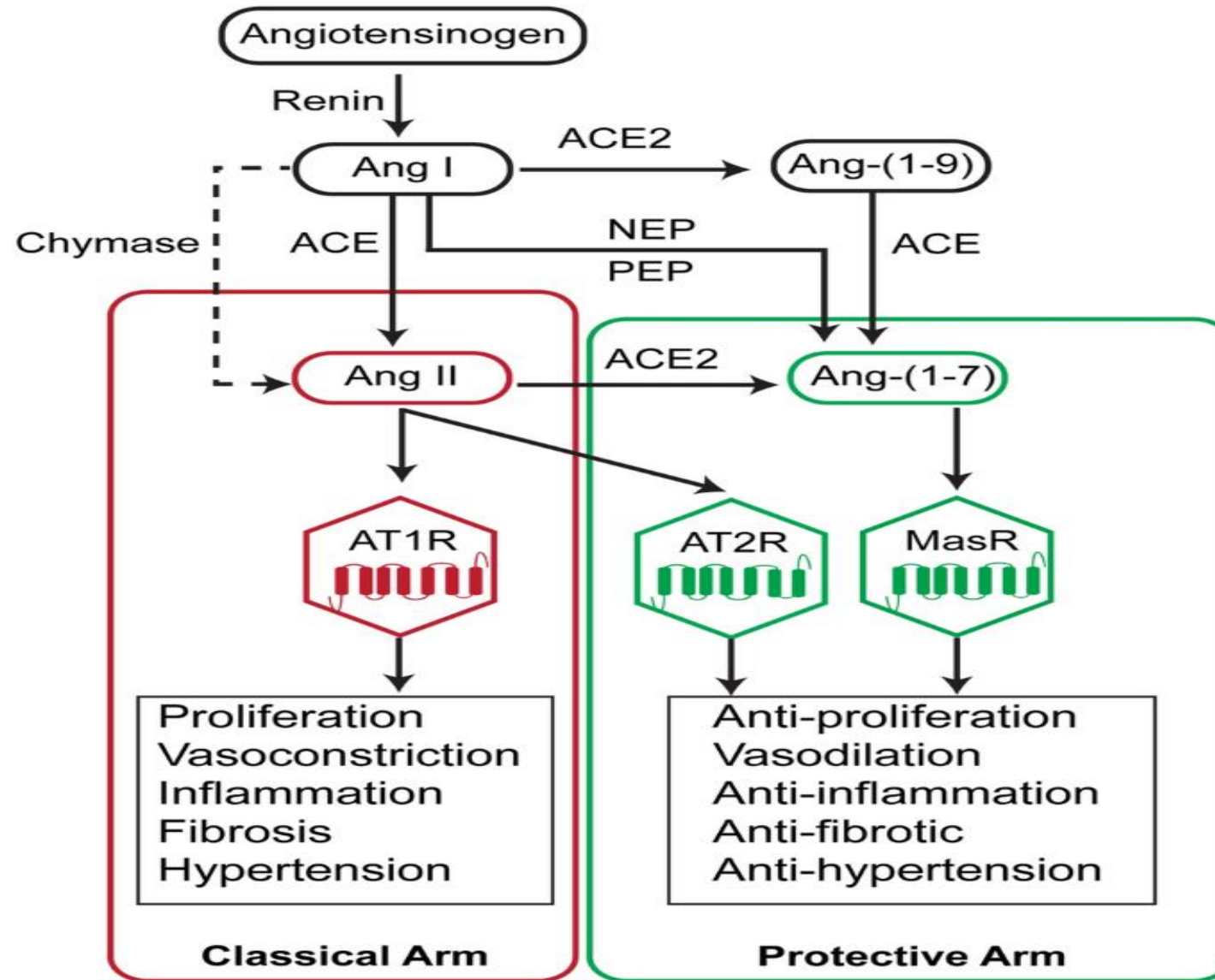
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Arthritis Comorbidities

Arthritis and the RAS
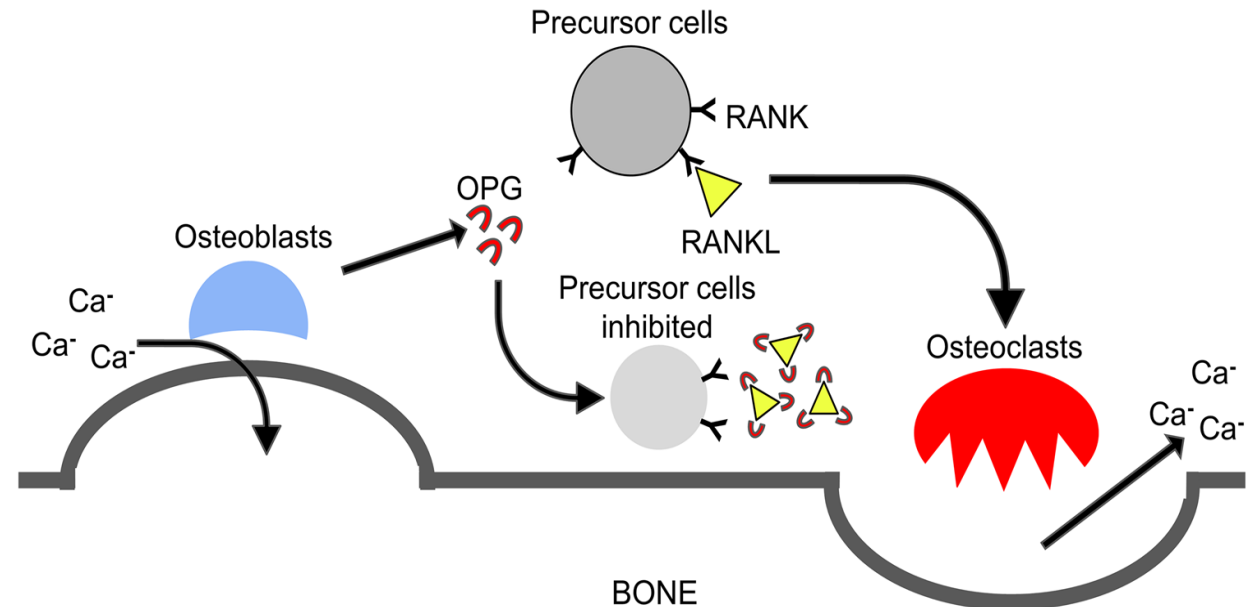
Pathophysiology of Arthritis and the RAS

Inflammatory mechanisms:

- Ang II activates NF-κB, enhances IL-1, IL-6 and TNF-α production, induces the production ROS

Osteopenia:
The classical RAS arm can act on osteopenia by means of three different pathways:
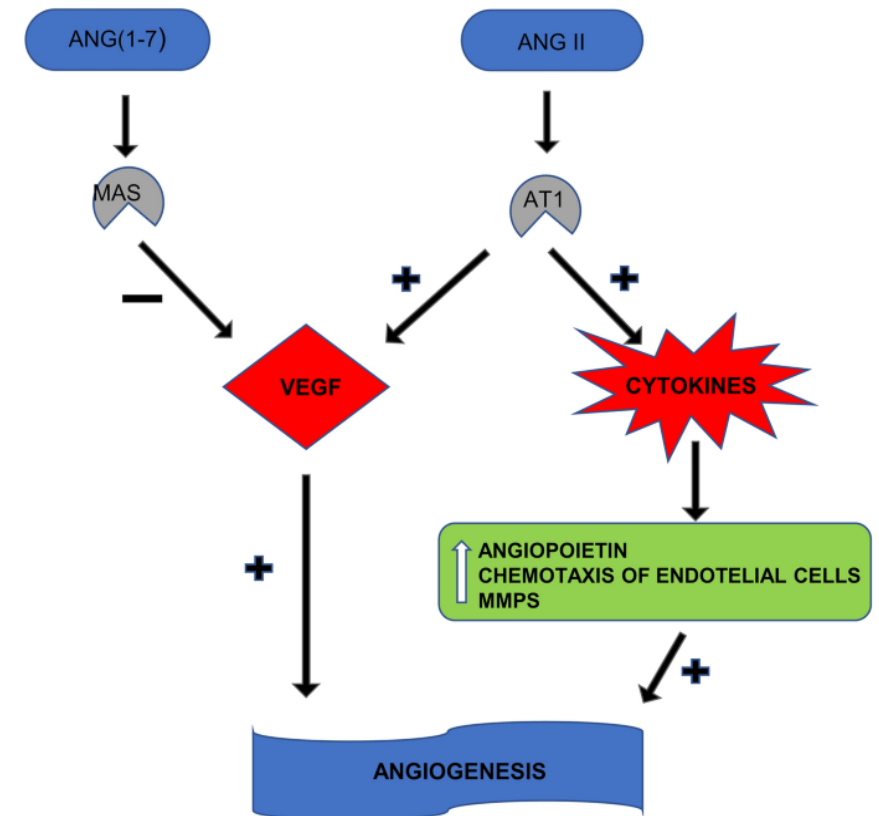
- RANKL pathway
- DKK-1 pathway
- MMPs pathway

Pathophysiology of Arthritis and the RAS

Angiogenesis:

- Has a central role in assisting the invasion of inflammatory cells, which results in characteristic structural destruction of articular tissue.

- AngII interacts with the AT1 receptor and stimulates the production of vascular endothelial growth factor (VEGF) and inflammatory Cytokines

- This increase the production of angiopoietin, Mielometaloproteinases (MMPs) and chemotaxis of endothelial cells.

- These factors, together with the increased VEGF, stimulate **angiogenesis**.

- Ang-(1-7) interacts with Mas receptor and exerts the opposite effect, decreasing VEGF production and **angiogenesis**

Moreira, F.R.C., *et al. Mol Biol Rep* **48**, 6619–6629 (2021).
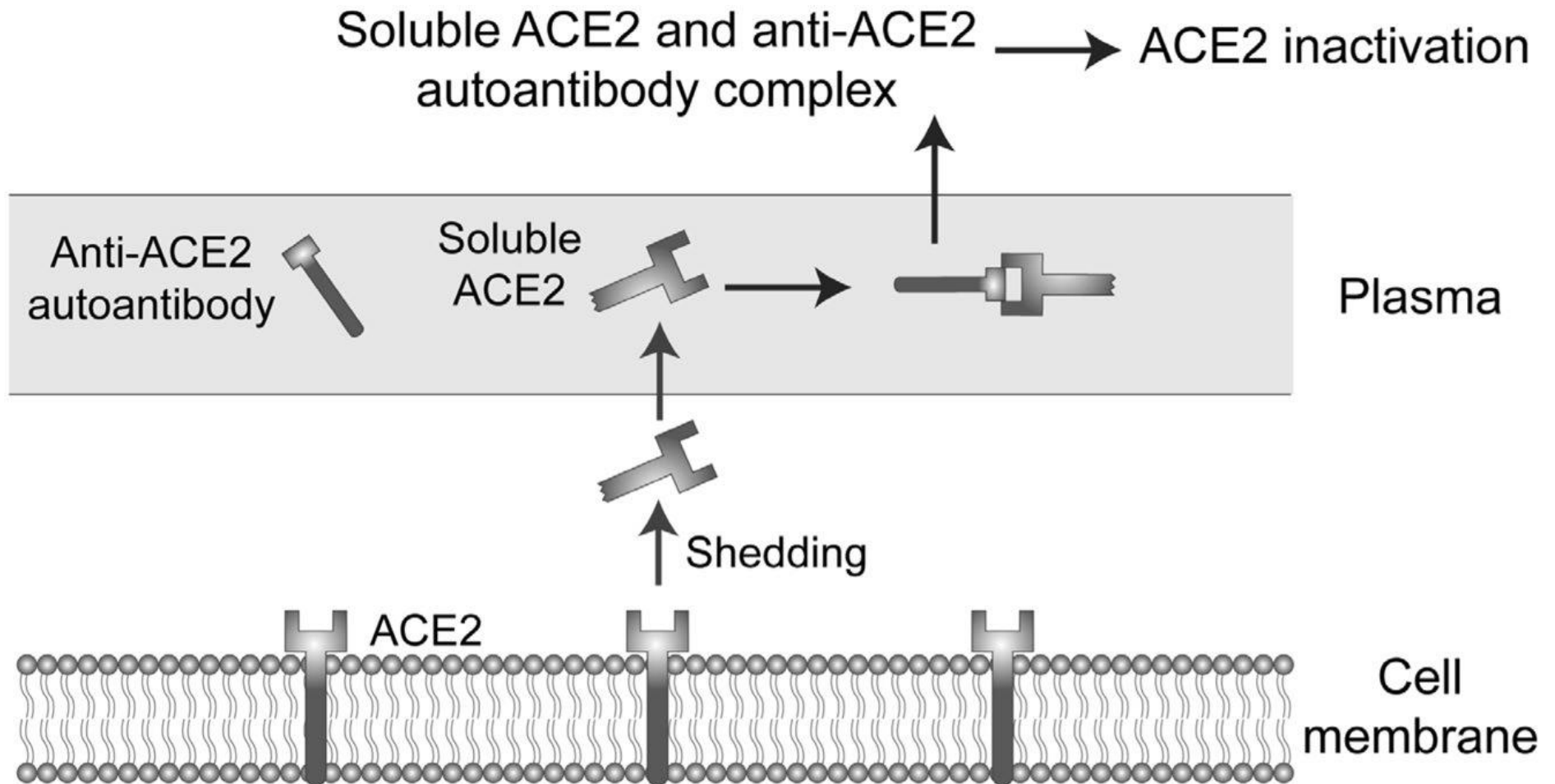
Arthritis and the RAS

- Balance of the RAS arms is essential for homeostasis of the body functions
  - Activation of RAS can result in chronic imbalances potentially leading to pathological conditions (renal, CV, CNS, musculoskeletal).

  - ACE2 keeps Ang II level with in normal level and produces an anti-inflammatory peptide, Ang-(1-7).

  - Circulating ACE2 has been associated with different disease and may be useful diagnostic and prognostic biomarker

  - Despite the higher plasma level of ACE2, patients with those disease presented with reduced ACE2 enzyme activity

  - The sera of patients with vasculopathy, high levels of Anti-ACE2 auto-Ab were detected which strongly correlated with the ACE2 activity

S. Khajeh Pour et al. Inflammopharmacology, 30, 1295–1302 (2022); Takahashi *et al. Arthritis Research & Therapy* 2010, **12**:R85

Anti-ACE2 Autoantibody

Study Significance

- Consistent and reliable measurement of ACE2 activity is difficult.

- Instead, the substrate and product of the ACE2 enzyme can be quantified robustly.

- **This study measured Anti-ACE2 Autoantibody and Ang peptides in blood samples of patients with arthritis to investigate their correlation with RA disease intensity**

Study Design

- This was a pilot study using 12 patients with RA under an approved protocol (IRB-FY2020-273).

Patient's demographic and clinical characteristics of RA patients			
Variable	Remission (N = 7)	Active (N = 5)	p-value
	Mean ± SD	Mean ± SD	
Age	68.29 ± 12.05	68.80 ± 15.22	ns[a]
BMI	28.57 ± 5.71	27.60 ± 5.46	ns[a]
Medication use	7.43 ± 3.78	7.40 ± 2.07	ns[a]
Comorbidities	1.71 ± 1.25	1.80 ± 0.84	ns[a]
CRP (mg/L)	1.59 ± 1.27	16.10 ± 10.97	0.0054*
RAPID3 score	8.29 ± 6.38	19.85 ± 7.64	0.0085*

*One-tailed t-test was performed, $p<0.05$, [a]ns; not significant.

Method

LC-MS/MS analysis of biomarkers

Solid Phase Extraction
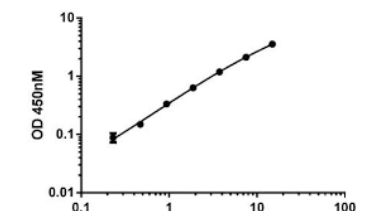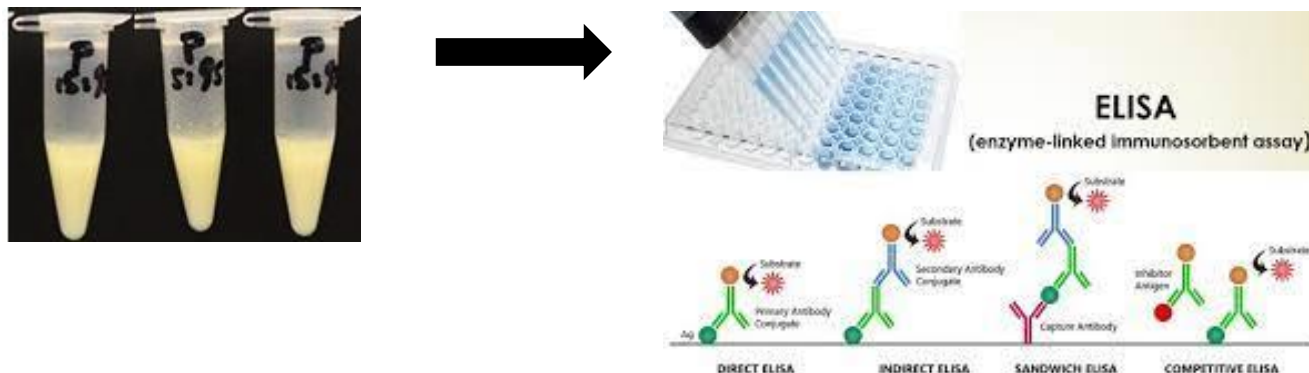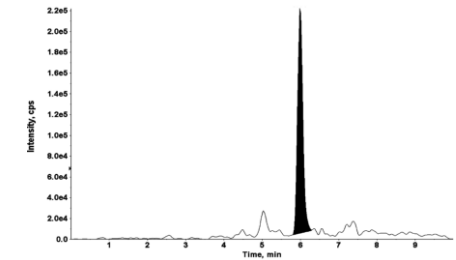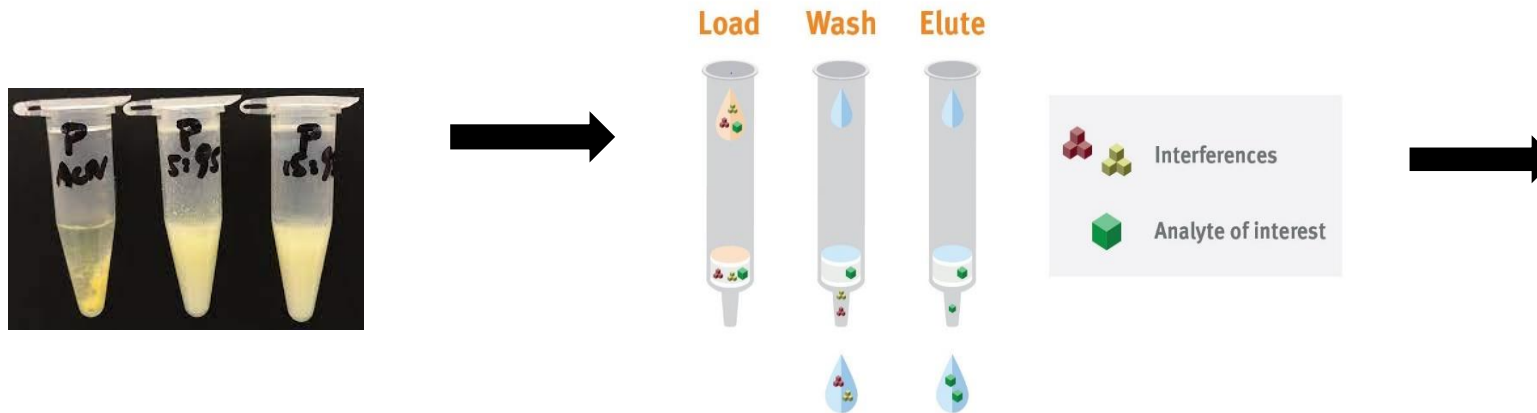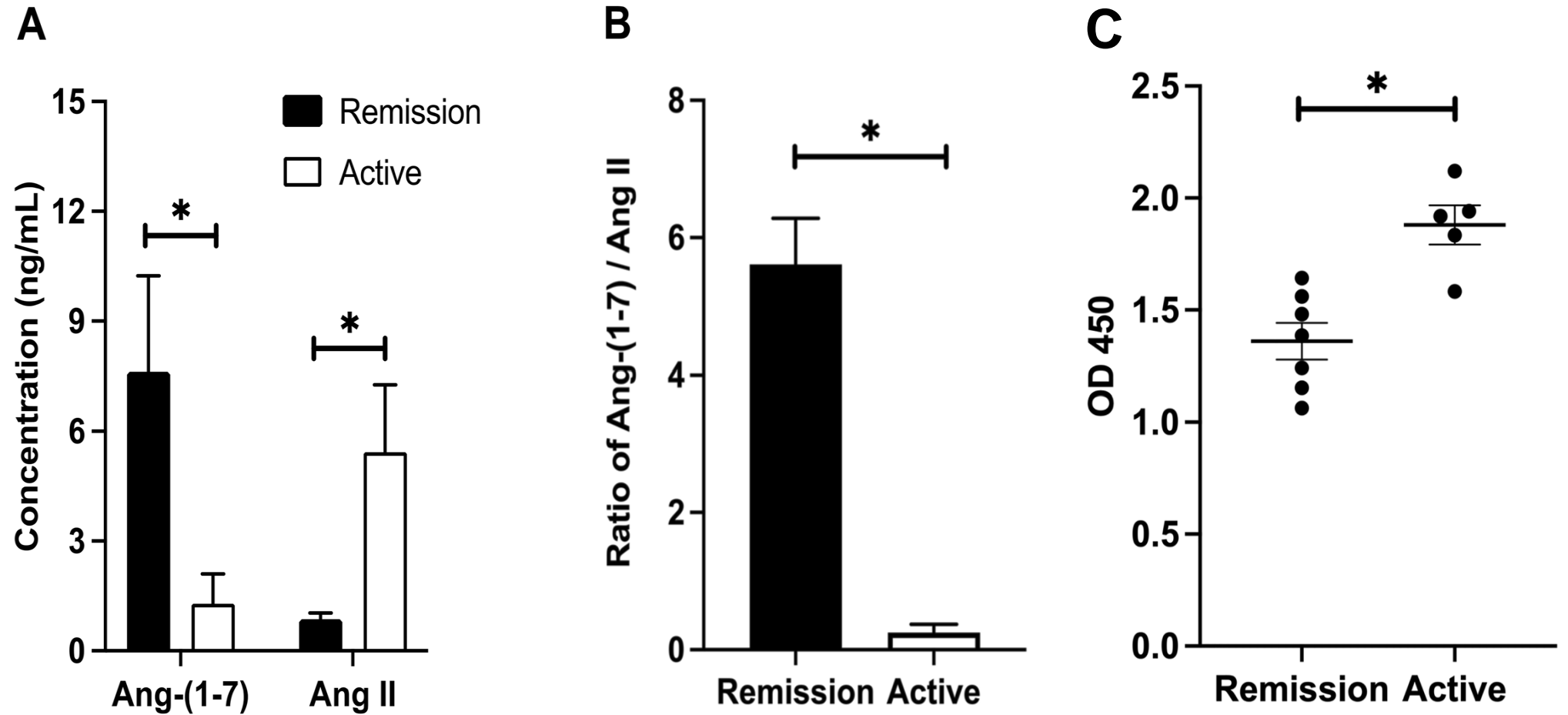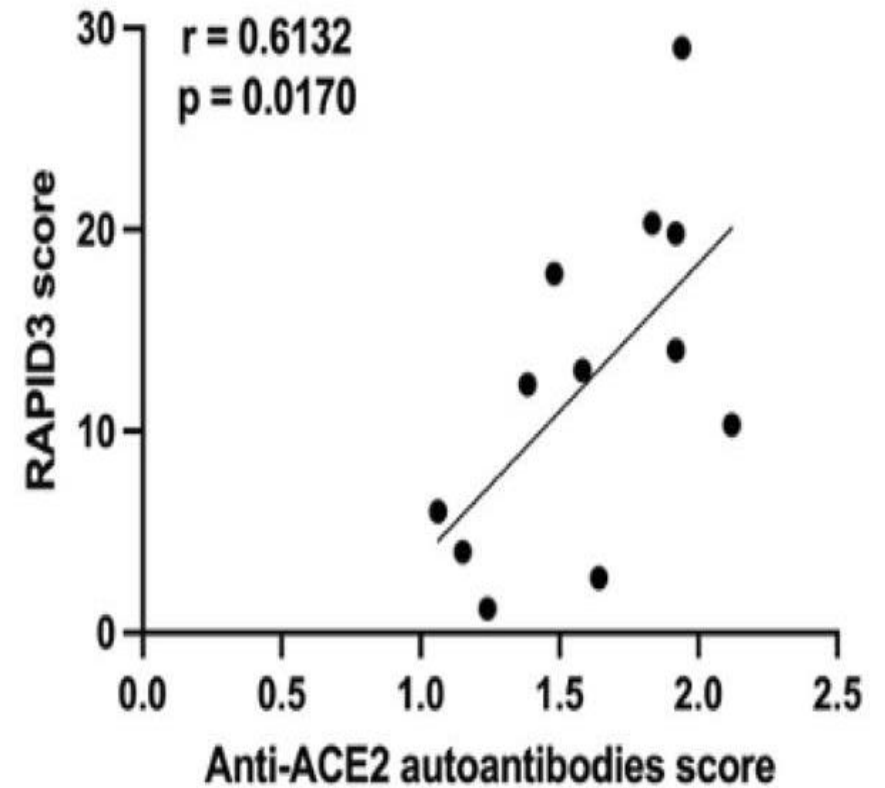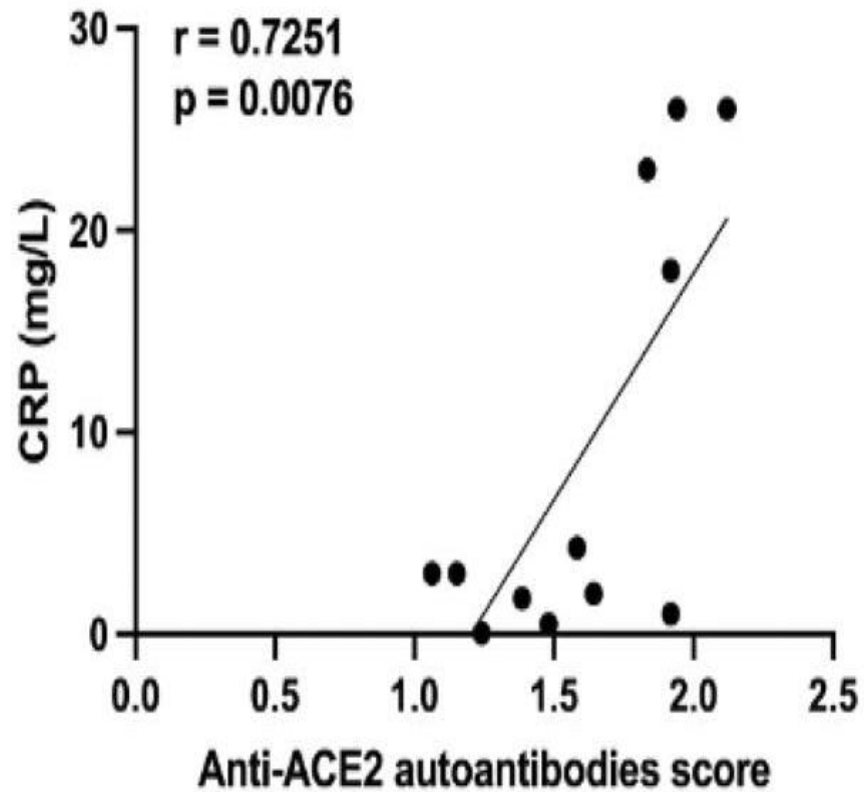
Results and Discussion
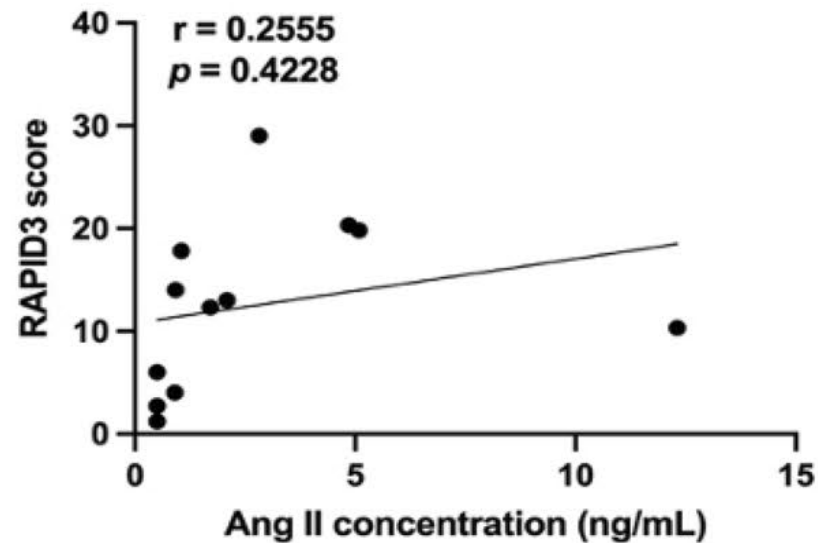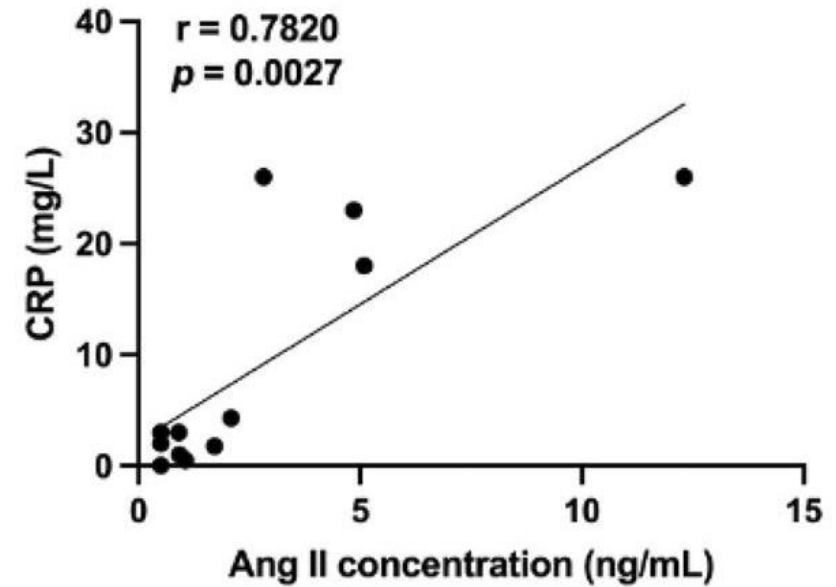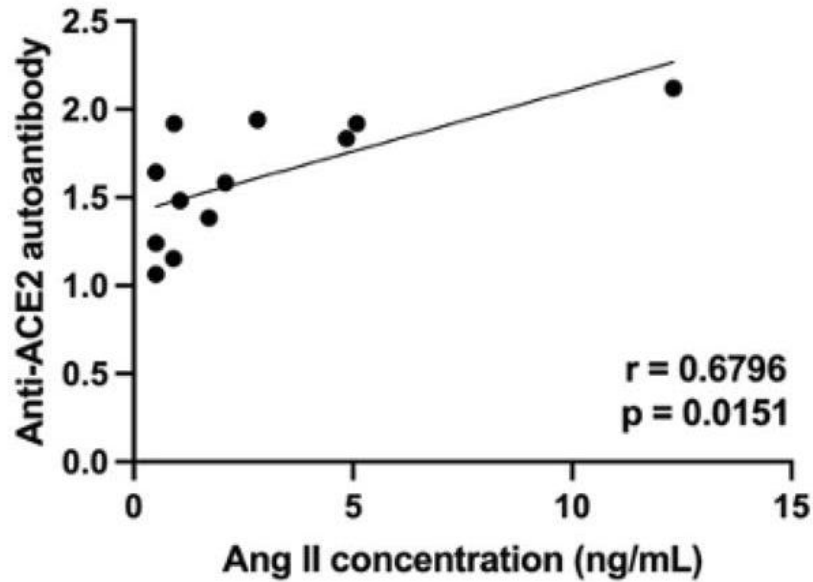
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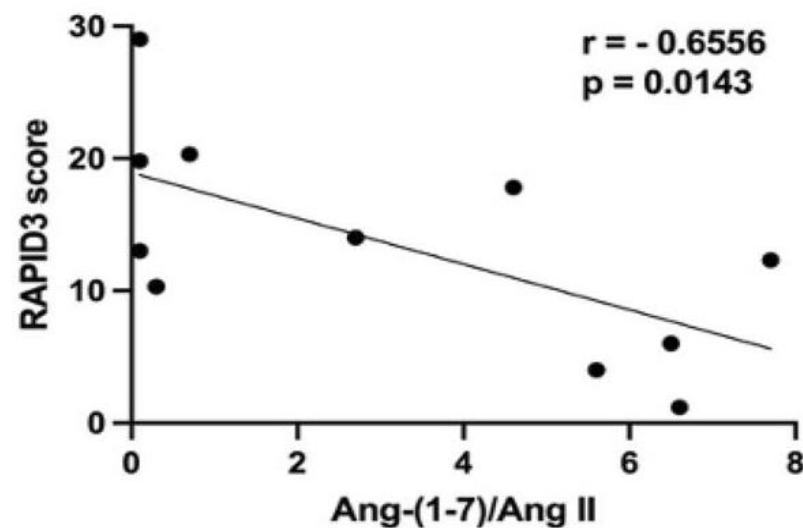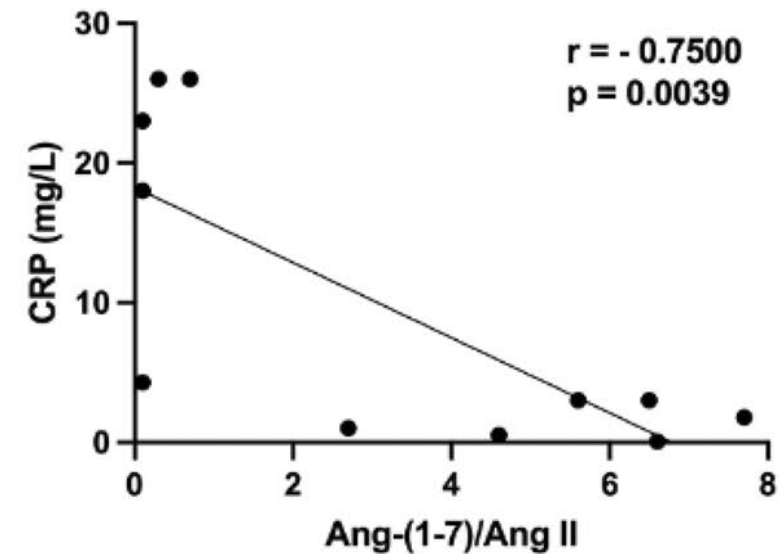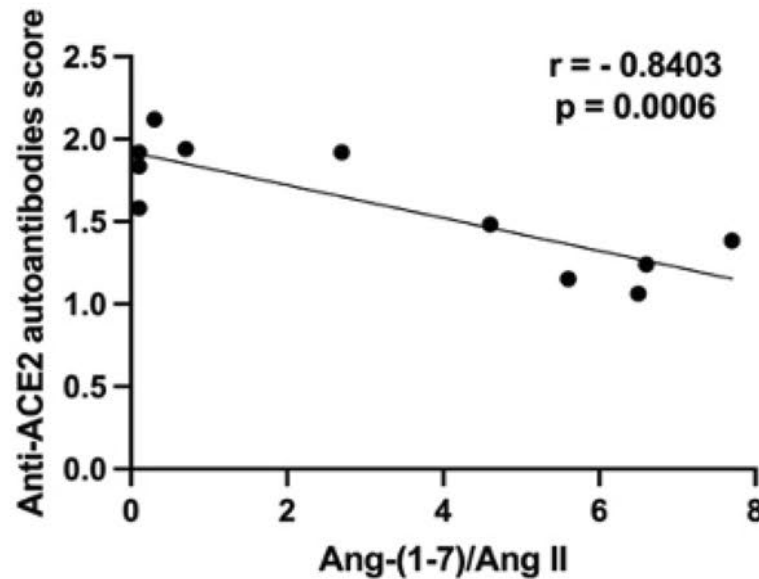
Conclusion

The findings of this study suggest:

- The RAS **classical arm is augmented** and the **protective arm is suppressed** in RA and other inflammatory disease.

- Higher systemic or local Ang-(1–7) levels could put the disease into remission and protect the patient from long-term consequences of RA.

- The RAS components as the biomarkers of RA can serve as a reliable tool for early detection, to help clinicians evaluate the treatment success rate and determine disease prognosis to prevent long-term complications of RA.

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- INBRE/CTR-IN (Year 7)