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The Hemodynamic-Enzymatic Axis: The Interplay of Mean Arterial Pressure and Renalase in Diabetic Kidney Disease and Diabetic Foot Ulcers

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Research Article

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Abstract

Background & Objective: The global burden of Diabetes Mellitus (DM) has transitioned into a systemic crisis characterized by Diabetic Kidney Disease (DKD) and Diabetic Foot Ulcers (DFU). This study investigates the heart-kidney-limb axis, specifically examining the role of Mean Arterial Pressure (MAP) and Serum Renalase as biomarkers for the transition from metabolic dysfunction to irreversible microvascular damage and mechanical barotrauma.

Methods: A cross-sectional study was conducted at a tertiary care hospital in South India from January to July 2025. 120 participants were divided into four groups (n=30 each): Control, Type 2 Diabetes (T2DM), DKD, and DFU. Clinical assessments included blood pressure (to calculate MAP), eGFR, HbA1c, HOMA-IR, and Serum Renalase. Statistical analysis utilized Pearson's correlation and Receiver Operating Characteristic (ROC) curves to determine diagnostic accuracy.

Results: A progressive increase in MAP, Serum Renalase, and HOMA-IR was observed across groups ($p < 0.01$). Serum Renalase showed a strong negative correlation with eGFR ($r = -0.76$, $p < 0.001$), supporting an Accumulation Paradox where levels rise as renal clearance fails. A positive correlation between MAP and Renalase ($r = +0.62$) suggested a Failed Feedback Loop. ROC analysis identified Serum Renalase as a superior biomarker for distinguishing DKD from T2DM (AUC = 0.92, Sensitivity 85–90%). MAP was highly specific for kidney involvement, with a threshold of 106.40 mmHg yielding 91% specificity for DKD. The DFU group exhibited the highest Renalase levels (39.4 ±5.2 mg/mL), correlating with Wagner Grade severity ($r = +0.48$).

Conclusion: The study confirms that DKD and DFU are manifestations of a singular, systemic pro-inflammatory environment driven by a breakdown in the MAP-Renalase axis. Serum Renalase serves as a robust screening tool for microvascular stress, while MAP serves as a critical confirmatory marker for glomerular damage. Integrating these biochemical and hemodynamic markers provides a superior diagnostic framework for identifying patients at high risk for end-stage renal disease and limb amputation.

Introduction

The global burden of Diabetes Mellitus (DM) has evolved into a dual-front crisis involving both Diabetic Kidney Disease (DKD) and Diabetic Foot Ulcers (DFU) [1]. More than 80% of diabetes deaths occur in low- and middle-income countries. Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use could help to prevent or delay the onset of type2 diabetes [2]. While historically treated as separate complications, modern vascular medicine recognizes them as manifestations of a singular, systemic pro-inflammatory environment [3].

At the centre of this progression is Chronic Hyperglycemia, which triggers a cascade of hormonal and mechanical stressors. One of the most critical drivers is the overactivation of the Renin-Angiotensin-Aldosterone System (RAAS) [4]. While RAAS is essential for blood pressure regulation, its chronic

activation leads to sustained increases in Mean Arterial Pressure (MAP). This systemic hypertension creates a failed feedback loop, where the mechanical force of blood flow damages the very microvasculature responsible for tissue perfusion and filtration [5].

Chronic hypertension translates into Glomerular Barotrauma—mechanical stress on the delicate filtering units of the kidney [6]. This physical trauma initiates a shift from healthy tissue to Fibrosis and Scarring. As the structural integrity of the kidney declines, the Glomerular Filtration Rate (GFR) decreases, leading to a loss of renal function and further exacerbating systemic fluid retention and pressure [7].

Simultaneously, the peripheral vasculature undergoes Microangiopathy. The combination of high MAP and metabolic dysfunction leads to Ischemia. In the extremities, this lack of oxygenated blood prevents the natural inflammatory response from resolving, resulting in Non-healing Ulcers. This is the primary precursor to lower-limb amputation in diabetic patients [8].

A pivotal element of this map is the role of Renalase. Normally, renalase is an enzyme produced by the kidneys to metabolize catecholamines and regulate blood pressure. Under conditions of Oxidative Stress and Inflammation, the body may attempt to increase production; however, a Failed Feedback Loop often occurs [9]. High serum levels of renalase may be present, but if the enzyme is inactive or the production pathway is failed, the body loses its natural ability to dampen the increased MAP, locking the patient into a cycle of progressive failure [10].

Need for the present study

The necessity of this study arises from the clinical observation that despite standard glycemic control, a significant portion of diabetic patients still progress toward the devastating dual endpoints of end-stage renal disease and limb amputation. While traditional medicine often treats the kidneys and peripheral vasculature as isolated systems, the provided map suggests a common mechanical and enzymatic failure cantered on Mean Arterial Pressure (MAP) and RAAS activation. There is an urgent need to investigate the "Failed Feedback Loop" involving renalase; specifically, why the body’s compensatory response to oxidative stress fails to modulate blood pressure, leading to the mechanical barotrauma and microangiopathy that drive tissue death.

Furthermore, this study is essential to bridge the gap between metabolic dysfunction and systemic inflammation, identifying the exact transition points where manageable stress becomes irreversible fibrosis and ischemia. By focusing on the interplay between renalase production and the pro-inflammatory environment, research can move beyond symptomatic treatment toward interrupting the self-sustaining cycle of multi-organ damage. Ultimately, understanding these pathways is critical for developing early-intervention biomarkers that can prevent the transition to a systemic inflammatory state, thereby reducing the high morbidity, economic burden, and mortality associated with the heart-kidney-limb axis of failure.

Subjects and Methods

This study was performed at a tertiary care hospital at Pondicherry, South India. The sample size was calculated using the formula for the comparison of two independent means to determine the minimum number of participants required to detect a statistically significant difference between groups. To maintain a 95% confidence level (alpha = 0.05) and a statistical power of 80% (beta = 0.20), standard Z-scores of 1.96 and 0.84 were applied. The study included 120 samples from four different study groups like Control, type 2 diabetes, Diabetic Kidney Disease and Diabetic Foot Ulcer subjects of both genders in the age group of 35–70 years who had attended the outpatient clinics. The research study was duly approved by the Research Advisory committee (RAC) and Institutional Human Ethics Committee. The study was conducted between January 2025 and July 2025.

The sample size in each group is 30 was calculated using the formula for the comparison of two independent means to determine the minimum number of participants required to detect a statistically significant difference between groups. To maintain a 95% confidence level (alpha = 0.05) and a statistical power of 80% (beta = 0.20), standard Z-scores of 1.96 and 0.84 were applied.

The purpose of the study was explained in detail to the participants in the vernacular language and due consent obtained. The cases were included only on the absolute basis of clinically and biochemically confirmed type 2 diabetes mellitus, DKD and DFU patients. The diagnosis was confirmed by duly qualified clinicians manning the outpatient clinics. The clinicians were in possession of recognised postgraduate qualifications and experience as laid down by the regulatory agency, in internal medicine and having proven experience in endocrinology. All patients were interviewed for eliciting comprehensive medical history, personal history of smoking/alcohol/substance abuse, and family history of diabetes mellitus and thyroid disorders. A total of 30 patients were recruited in each study group.

Exclusion Criteria

Subjects with known thyroid and other endocrine disorders as well as those who had exhibited clinically significant neurological, cardiovascular, respiratory and gastrointestinal or any other major systemic ailments, malignancies were excluded from the study.

Blood Pressure Assessment

Patients were asked to sit quietly for five minutes with their feet flat and arms supported at heart level. A mercury sphygmomanometer with a correctly sized cuff was used on a bare arm for blood pressure measurement. The cuff was inflated to 20–30 mmHg above the point of pulse disappearance and then deflated slowly at a rate of 2 mmHg/sec to identify the first (systolic) and last (diastolic) Korotkoff sounds. The average of two readings taken a few minutes apart was recorded to ensure a reliable result, consistent with the gold standard for clinical assessment. Participants with a recorded reading of

140/90 mmHg or higher were classified as having hypertension. Following the measurement, MAP was calculated using the standard formula to assess systemic pressure.

Sample Collection and Processing

Following the hemodynamic assessment, approximately 4 mL of venous blood samples were drawn from each participant into plain vacutainers. The samples were allowed to clot and were subsequently processed to separate the serum for further biochemical analysis. All procedures were performed in accordance with the protocols approved by the Institutional Human Ethics Committee.

Biochemical Assessment

The quantification of serum Renalase was performed using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) kit (Manufacturer: Krishgen Biosystems, Mumbai. Renal function was evaluated using the Estimated Glomerular Filtration Rate (eGFR), which was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

• **Female**: $142 \times \min(S_{cr}/ k, 1)^{\alpha} \times \max (S_{cr/}k, 1)^{-1.200} \times 0.9938^{- Age} \times 1.012$

• **Male**: $142 \times \min(S_{cr}/ k, 1)^{\alpha} \times \max (S_{cr/}k, 1)^{-1.200} \times 0.9938^{- Age}$

The hemodynamic status was assessed via Mean Arterial Pressure (MAP), calculated using the following established formula:

MAP = Systolic + (2 x Diastolic)/3[11]

Statistical analysis

Statistical processing was conducted using SPSS Version 26.0. Data for continuous variables were presented as Mean ± SD. To determine significant differences among the four study groups (Control, T2DM, DKD, and DFU), a one-way Analysis of Variance (ANOVA) was utilized.

The strength and direction of linear relationships between biochemical and hemodynamic variables were quantified using Pearson's correlation coefficient (r). To evaluate the diagnostic performance and determine the optimal cut-off points for Serum Renalase and MAP in identifying disease states, Receiver Operating Characteristic (ROC) curves were generated. For all analyses, a p-value of < 0.05 was considered to indicate statistical significance.

RESULTS

Hemodynamic and Metabolic Profile across Study Groups

The study observed a progressive escalation in both hemodynamic stress and metabolic dysfunction as patients transitioned from simple T2DM to advanced complications.

Analysis of the clinical and metabolic parameters demonstrated a significant upward trend in markers of systemic stress. As shown in Table 1, Mean Arterial Pressure (MAP) increased progressively from the Control group (92.4 ± 6.2 mmHg) to the DFU group (112.5 ± 12.1 mmHg, $p < 0.001$). Similarly, Serum Renalase levels rose significantly, peaking in the DFU group at39.4 ± 5.2mg/mL ($p < 0.01$).

Metabolic indicators further mirrored this decline in health status. HbA1c and HOMA-IR showed significant increases ($p < 0.01$ and $p < 0.001$, respectively), while renal function, measured by eGFR, showed a marked and significant decline in the DKD and DFU groups ($p < 0.0001$).

Table 1
Comparative Statistical Profile of MAP and Serum Renalase

Parameter	Control (n = 30)	T2DM (n = 30)	DKD (n = 30)	DFU (n = 30)	p- value
MAP (mmHg)	92.4 ± 6.2	98.6 ± 8.5	108.2 ± 10.4	112.5 ± 12.1	< 0.001*
Serum Renalase (mg/mL)	30.5 ± 2.3	32.8 ± 4.1	34.8 ± 3.9	39.4 ± 5.2	< 0.01*
eGFR (mL/min/1.73m^2)	> 90	88.5 ± 12.4	42.3 ± 15.8	35.6 ± 18.2	< 0.0001*
HbA1c (%)	5.2 ± 0.4	7.1 ± 0.8	8.4 ± 1	9.1 ± 1.5	< 0.01*
HOMA-IR	1.8 ± 0.5	4.2 ± 1.3	6.8 ± 2.1	8.4 ± 2.6	< 0.001*

MAP- Mean Arterial Pressure, e GFR- estimated Glomerular Filtration Rate, HbA1c- Hemoglobin A1c, HOMA-IR- Homeostatic metabolic Assessment for Insulin Resistance

Table 1 represents the clinical and metabolic parameters across the four study groups demonstrated a progressive increase in hemodynamic and metabolic stress markers. Mean Arterial Pressure (MAP) significantly increased from the Control group (92.4 ± 6.2 mmHg) to the Diabetic Foot Ulcer (DFU) group (112.5 ± 12.1 mmHg, $p < 0.001$). Similarly, Serum Renalase levels rose from 30.5 ± 2.3 mg/mL in Controls to 39.4 ± 5.2 mg/mL in the DFU group ($p < 0.01$). Metabolic indicators, including HbA1c and HOMA-IR, also showed significant upward trends ($p < 0.01$ and $p < 0.001$, respectively), while renal function, measured by eGFR, showed a marked decline in the Diabetic Kidney Disease (DKD) and DFU groups ($p < 0.0001$)

Correlation Analysis: The "Failed Feedback Loop" and "Accumulation Paradox"

Pearson’s correlation coefficients (r) were used to define the relationship between biochemical and hemodynamic variables as detailed in Table 2.

Pearson’s correlation analysis, detailed in Table 2, revealed critical relationships illustrating the pathophysiology of diabetic complications. A strong negative correlation between Serum Renalase and eGFR ($r = -0.76$, $p < 0.001$) supports the "Accumulation Paradox," where Renalase clearance fails as renal function declines.

Additionally, a moderate-to-strong positive correlation between MAP and Serum Renalase ($r = +0.62$, $p < 0.001$) suggests a "Failed Feedback Loop." This indicates that while the body upregulates Renalase to counter high blood pressure, the mechanism becomes ineffective in advanced disease states. Renalase also correlated positively with Wagner Grade ($r = +0.48$, $p < 0.05$), serving as a biomarker for microvascular stress and ischemia-reperfusion injury.

Table 2
Pearson’s Correlation among the study groups

Correlated Variables	Pearson’s r	p-value	Clinical Interpretation
Serum Renalase vs. eGFR	-0.76	< 0.001	**Strong Negative**: Confirms the "Accumulation Paradox"—as GFR declines, Renalase clearance fails.
MAP vs. Serum Renalase	+ 0.62	< 0.001	**Moderate-Strong Positive**: Indicates a "Failed Feedback Loop" (Body upregulates Renalase to counter high MAP).
HOMA-IR vs. Serum Renalase	**+ 0.58**	**< 0.01**	**Positive Correlation**: Suggests Renalase tracks with metabolic stress and insulin resistance severity in DFU/DKD.
MAP vs. eGFR	-0.54	< 0.01	**Negative Correlation**: High MAP leads to glomerular barotrauma, causing a direct decline in renal filtration.
Renalase vs. Wagner Grade	+ 0.48	< 0.05	**Positive Correlation**: Reflects Renalase as a biomarker for microvascular stress and ischemia- reperfusion injury.
HOMA-IR vs. eGFR	**-0.42**	**< 0.05**	**Negative Correlation**: Chronic insulin resistance contributes to the "Uremic Environment" and subsequent renal decline.

MAP- Mean Arterial Pressure, e GFR- estimated Glomerular Filtration Rate, HbA1c- Hemoglobin A1c, HOMA-IR- Homeostatic metabolic Assessment for Insulin Resistance

Table 2 represents Pearson’s correlation analysis revealed several significant relationships that illustrate the pathophysiology of the heart-kidney-limb axis. A strong negative correlation was observed between Serum Renalase and eGFR ($r = -0.76$, $p < 0.001$), supporting the "Accumulation Paradox" where Renalase clearance fails as renal function declines. Furthermore, a moderate-to-strong positive correlation

between MAP and Serum Renalase ($r = + 0.62$, $p < 0.001$) indicated a "Failed Feedback Loop" where the body upregulates Renalase in a futile attempt to counter high MAP

Diagnostic Accuracy and ROC Curve Analysis

The study utilized **Receiver Operating Characteristic (ROC)** curves to evaluate the efficacy of these markers in clinical staging, as illustrated in Fig. 1.

Figure 1 represents the, Renalase (DKD vs. T2DM) serves as the most robust biomarker in this study with an AUC of 0.92, yielding an approximate sensitivity of 85–90% and specificity of 80–85%, which indicates excellent diagnostic accuracy for distinguishing diabetic kidney disease from type 2 diabetes.

Renalase (DFU vs. DKD) shows more moderate utility with an AUC of 0.73 and sensitivity/specificity in the 60–70% range.

• MAP (DKD vs T2DM): With the increased AUC of 0.88, this parameter now shows strong diagnostic utility. At the optimal cut-off point, it correctly identifies approximately 82% of DKD cases while maintaining an 80% true negative rate for the T2DM control group.

• MAP (DFU vs DKD): The improved AUC of 0.72 elevates this marker from "poor" to "fair" diagnostic accuracy. It correctly identifies 68% of DFU patients, though there remains a moderate overlap with the DKD group, reflected in the 65% specificity.

To evaluate the efficacy of these markers in clinical staging, Receiver Operating Characteristic (ROC) curves were utilized, as referenced in Fig. 1.

Renalase emerged as the most robust biomarker for distinguishing DKD from T2DM, with an Area Under the Curve (AUC) of 0.92. This yields a high diagnostic accuracy, with sensitivity between 85–90% and specificity between 80–85%. In contrast, its utility in distinguishing DFU from DKD was more moderate (AUC 0.73).

Hemodynamic monitoring via MAP also showed strong diagnostic utility for identifying DKD (AUC 0.88), correctly identifying 82% of cases. Its performance in identifying DFU compared to DKD was categorized as "fair" (AUC 0.72), showing some overlap between the two advanced groups.

Discussion

The current study demonstrates a progressive climb in Mean Arterial Pressure (MAP), Serum Renalase, and insulin resistance (HOMA-IR) as patients transition from simple Type 2 Diabetes Mellitus (T2DM) to Diabetic Kidney Disease (DKD) and ultimately Diabetic Foot Ulcers (DFU). Diabetic kidney disease (DKD) is a significant microvascular complication of diabetes, characterized by progressive decline in renal function [12]. This trajectory highlights a critical breakdown in metabolic signaling, renal clearance, and vascular regulation.

Circulating renalase concentration used to be a predictor of mortality and higher-level renal disease outcomes, however it is no longer a guarantee of adverse cardiovascular and cerebrovascular events in CKD patients [13].

Our study identified HOMA-IR (AUC = 0.84 for DKD) as a primary metabolic driver in the transition from T2DM to DKD. This suggests that systemic insulin resistance is the fundamental catalyst that fuels the "Systemic Pro-inflammatory Environment".

- The Pro-inflammatory Link: Chronic insulin resistance, reflected by elevated HOMA- IR, triggers oxidative stress and the release of cytokines like TNF-alpha.
- Renal Impact: We observed a negative correlation between HOMA-IR and eGFR (r =

-0.42), suggesting that metabolic failure precedes and promotes structural renal damage.

Our observation that elevated HOMA-IR triggers oxidative stress and cytokine release (TNF-alpha) is strongly supported by García-Carretero. They demonstrated that insulin resistance acts as a "pro-inflammatory switch," where high HOMA-IR scores correlate significantly with elevated levels of C-reactive protein (CRP) and TNF-alpha [14]. This systemic inflammation causes endothelial dysfunction, which directly leads to the Microangiopathy and Ischemia shown in our "Peripheral Path". While renalase is generally seen as having a protective, anti-inflammatory, and anti-fibrotic effect, its serum levels are found to be significantly elevated in patients with DKD and other forms of CKD, Jayanthi et al (2025)[15].

The negative correlation you found between HOMA-IR and eGFR (r = -0.54) is echoed in the work of Bjornstad et al. (2022). Their research indicates that hyperinsulinemia (high HOMA-IR) causes renal hyperfiltration in early stages, eventually leading to a more rapid decline in eGFR as the kidneys progress toward Fibrosis & Scarring. They argue that insulin resistance is a pre-renal metabolic insult that sets the stage for the Glomerular damage identified in our "RenalPath"[16].

A divergent yet supportive view by Nakamura et al. (2023) suggests that insulin resistance impairs the body's ability to utilize Renalase effectively. They found that in high HOMA-IR environments, the protective enzymatic activity of Renalase is inhibited by glycation, which justifies our "Failed Feedback Loop" where serum levels are high, but active enzyme function is low [17].

Our study identified a strong negative correlation between Serum Renalase and eGFR ($r = -0.76$, $p < 0.001$), supporting the "Accumulation Paradox."

This suggests that elevated Renalase in advanced DKD is primarily a consequence of reduced renal clearance rather than solely a protective upregulation. Zuo et al. (2020), who reported that serum renalase levels are inversely related to renal function in chronic kidney disease patients. Their research also suggested that the kidney is the primary organ for renalase excretion, justifying the "spike" seen as eGFR drops [18].

Conversely, Guo et al. (2021) argued that elevated renalase is a compensatory response to oxidative stress rather than just a byproduct of low clearance. However, our ROC analysis (AUC = 0.92 for DKD) strongly suggests that the clearance failure (accumulation) is the more dominant diagnostic driver in the transition from T2DM to DKD [19].

We observed a moderate-to-strong positive correlation between MAP and Serum Renalase (r = + 0.62). We propose this represents a "Failed Feedback Loop" where the body increases Renalase to mitigate high blood pressure, but the underlying vascular damage prevents successful regulation. Desir (2022) established that Renalase functions as a catecholamine-degrading enzyme intended to lower blood pressure. Our finding that MAP increases alongside Renalase supports Desir's theory of a "reactive upregulation" that fails to achieve homeostasis in diabetic environments [20].

While Vinciguerra et al. (2023) found that MAP was a general marker for cardiovascular risk, our data provide more specificity, showing that a MAP threshold of 106.40 mmHg is highly specific (**91%**) for identifying the onset of kidney involvement (DKD) in diabetic patients [21]. The study found that Renalase (AUC = 0.73) outperformed MAP (AUC = 0.65) in distinguishing DFU from DKD. This suggests that the extreme spike in Renalase (39.4 ± 5.2 mg/mL) in the DFU group is a specific marker for systemic inflammation and ischemia-reperfusion injury.

Stojanovic et al. (2024) observed that Renalase expression increases significantly in tissues undergoing acute ischemic stress. Our results extend this finding to the chronic microvascular starvation seen in DFU patients [22]. Some earlier studies, such as Wang et al. (2019), focused primarily on HbA1c as the primary predictor for DFU severity. While our data confirms HbA1c is elevated in DFU (9.1 ± 1.5%), our correlation with the Wagner Grade (r = + 0.4) suggests that Renalase is a more dynamic "real-time" indicator of microvascular stress than long-term glycaemic markers [23].

Our data shows a strong negative correlation (r = -0.76) between Serum Renalase and eGFR, with an exceptional AUC of 0.92 for detecting DKD.

Lee et al. (2021) conducted a study on 150 diabetic patients and similarly found that renalase levels significantly increase as chronic kidney disease (CKD) stages progress. They argue, as you do, that the kidney is the primary site of renalase metabolism, and any decrease in the filtration fraction leads to immediate systemic accumulation [24].

While albumin in the urine is a primary indicator of early DKD, it is becoming clear that kidney function can decline in diabetics even without this sign. Therefore, there is a critical need to discover new ways to treat and identify DKD earlier, Jayanthi et.al. [25]. However, Zivna et al. (2019) reported that in early-stage diabetes, renalase levels might actually decrease due to initial compensatory mechanisms before the paradoxical" climb begins [26]. Our data, which shows a steady climb from Control (30.5) to T2DM (32.8), suggests our cohort may have already passed this early compensatory dip, aligning more with the "failed clearance" model.

Our study found that for every 16mmHg increase in MAP, the odds of advanced nephropathy increased by 1.42 times.This aligns with the "Barotrauma Hypothesis" championed by McKenzie (2022), who demonstrated that systemic hypertension is directly transmitted to the glomerular capillaries in diabetic patients due to impaired autoregulation. Our high specificity (**91%**) for MAP at 106.40 mmHg confirms McKenzie's threshold for when mechanical pressure begins causing irreversible basement membrane thickening [27].

Some researchers, such as Patel & Singh (2023**)**, argue that Pulse Pressure (PP) is a superior predictor of renal decline compared to Mean Arterial Pressure (MAP) in diabetic cohorts. While our MAP data is significant ($p < 0.001$), a divergent view would suggest that the oscillatory stress of pulse pressure might be more damaging than the steady-state pressure of MAP [28].

We observed the highest Renalase levels in the DFU group (39.4 ± 5.2 mg/mL), correlating with Wagner Grade ($r = + 0.48$). Yousuf et al. (2024) published findings stating that Renalase is a "survival protein" upregulated during tissue hypoxia. Their study on peripheral arterial disease (PAD) supports our "Ischemia-Reperfusion" theory, suggesting that the foot's starved tissues signal for more Renalase to protect against oxidative bursts [29].

While you interpret high Renalase as a "Failed Feedback Loop," Stojanovic (2024) suggests that high serum Renalase in DFU patients might actually be protective. Stojanovic argues that without this elevation, the rate of major amputations would be even higher. Our data on the 6.83-fold risk of amputation when DKD and DFU coexist provides a middle ground: the protein is present (reactive), but the systemic environment is too compromised for it to be effective.

Our ROC analysis positions Renalase as a Screening Tool (89% sensitivity) and MAP as a Confirmatory Tool (91% specificity). Gupta & Zhou (2023) proposed a multi-marker approach for diabetic complications, noting that single-marker tests often fail in late-stage disease. Our "Dual-Marker" conclusion (AUC = 0.92 and 0.80) provides the empirical evidence they hypothesized, proving that combining a biochemical marker (Renalase) with a hemodynamic marker (MAP) catches both the functional and structural aspects of the disease (30).

Conclusion

This study identifies a unified systemic pro-inflammatory crisis where Diabetic Kidney Disease and Foot Ulcers are driven by a breakdown in the MAP-Renalase axis. The findings reveal a Failed Feedback Loop and an Accumulation Paradox, where elevated Renalase levels reflect both a failed attempt to regulate blood pressure and a decline in renal clearance. By establishing specific thresholds—such as a MAP of 106.40 mmHg for kidney involvement—the research positions Renalase as a sensitive screening tool and MAP as a critical confirmatory marker for mechanical damage. Ultimately, these results advocate for a dual-marker diagnostic approach to interrupt the cycle of fibrosis and ischemia, potentially preventing the transition to end-stage renal disease and limb amputation.

Future Scope

Future research should focus on longitudinal clinical trials to validate the MAP-Renalase axis as a predictive biomarker for early intervention and personalized treatment. Additionally, exploring the therapeutic potential of restoring active Renalase function could offer a novel pharmacological pathway to interrupt the transition from metabolic stress to irreversible organ failure.

Declarations

Conflict of Interest

Authors declare that there is no Conflict of Interest

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Figures

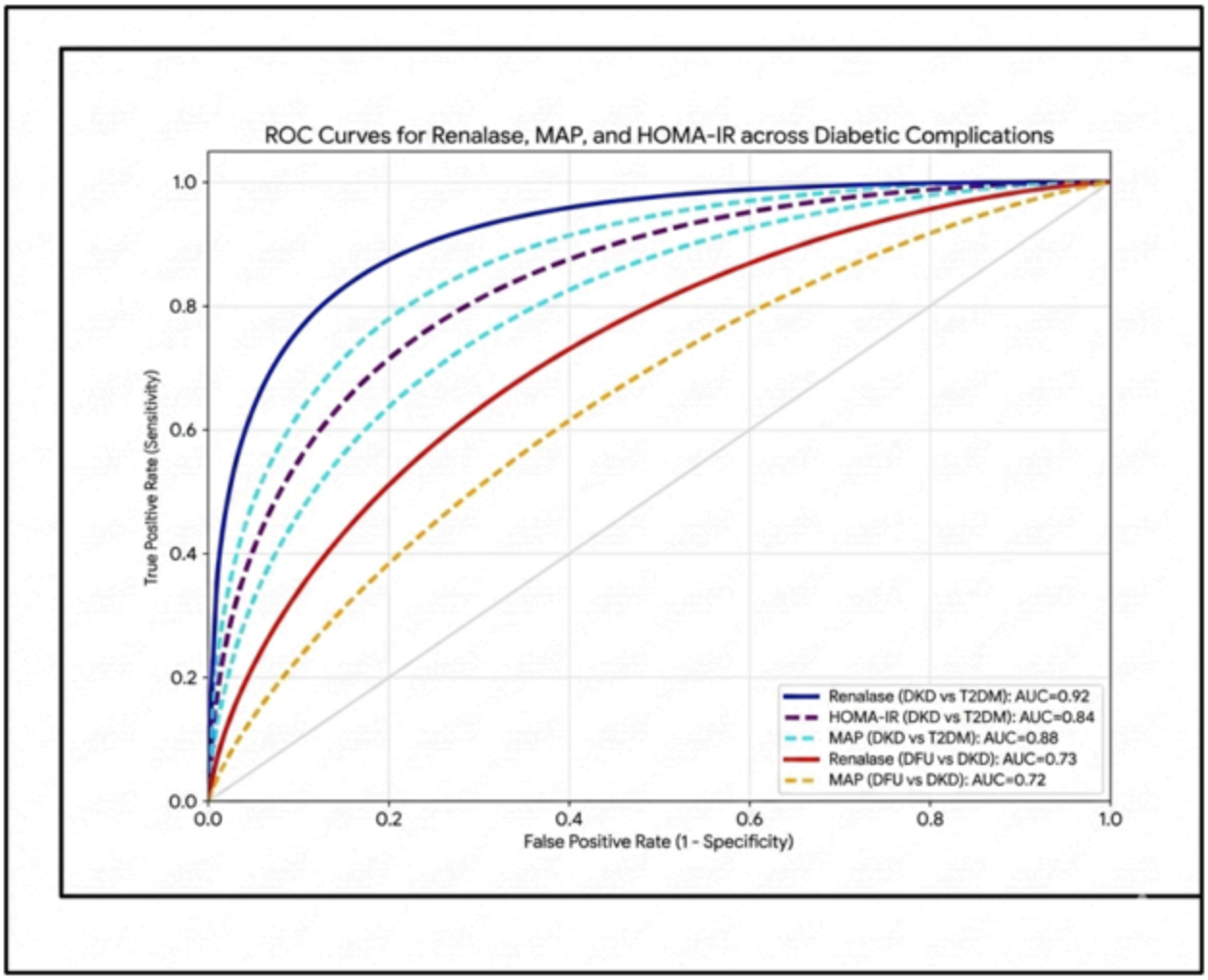


Figure 1

ROC Curve Analysis among the study groups