Association of Serum Circulating NOSTRIN with Endothelial Dysfunction Markers in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

Abstract No. 29

Balasubramaniyan Vairappan[1]*, Kalaivani MS[1], Deepthi S[1], Sunitha VS[2] and Jayaprakash Sahoo[3]

Departments of Biochemistry[1], Radiodiagnosis[2] and Endocrinology[3], Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry-605006, INDIA.

Background

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is a multisystemic disease with a rapidly increasing global prevalence.
- MASLD complications are an expanding health problem concomitant with endothelial dysfunction (ED) at early stages of the disease.
- To date, food and drug administration (FDA) approved only Rezdiffra (resmetirom) for the treatment of patients with liver scarring due to MASLD.
- Endothelial dysfunction (ED) is an early and persistent condition that holds prognostic significance, as it can predict adverse early hepatic events and increased mortality in patients with advanced liver disease.
- Nostrin, a 58 KDa homotrimeric adaptor protein expressed in vascular endothelial cells, plays a critical role in the trafficking and regulation of eNOS activity through its C-terminal SH3 domain.
- Our previous preclinical and human studies have demonstrated a potential mechanistic role for the Nostrin-eNOS-NO pathway in cirrhosis and acute on chronic liver failure (ACLF).

Aim/Objectives

- This study aimed to assess a novel endothelial nitric oxide synthase (eNOS) trafficking inducer, Nostrin, as a biomarker in patients with MASLD compared to healthy volunteers (HV).
- Additionally, we investigated the association between Nostrin and endothelial dysfunction (ED) in MASLD patients.

Methods

Study Population: This cross-sectional analytical study included 40 MASLD patients and 40 healthy volunteers (HV) as controls. Established ED biomarkers, such as asymmetric dimethylarginine (ADMA) and cyclic guanosine monophosphate (cGMP), the oxidative stress marker 4-hydroxynonenal (HNE) and Nostrin, were measured using commercially available ELISA kits. Flow-mediated dilation (FMD) of the brachial artery was assessed non-invasively using ultrasonography (USG) to measure endothelial function.

Results

Parameter (Mean ± SEM)	Healthy Volunteers (n=40)	MASLD patients (n=40)	p-value
Age	44.43± 1.85	43.58± 1.48	NS
Weight (kg)	68.60 ± 1.41	69.53 ± 1.81	NS
Height (m)	1.648 ± 0.01	1.559 ± 0.01	<0.0001
BMI	24.55 ± 0.35	29.08 ± 0.82	<0.001
W/H Ratio	0.856 ± 0.003	0.877 ± 0.01	<0.01
Systolic BP (mmHg)	113.8 ± 1.43	125.4 ± 1.72	<0.0001
Diastolic BP (mmHg)	72.85 ± 1.05	79.98 ± 1.44	<0.01
Glucose (mg/dL)	76.58 ± 2.16	100.1 ± 3.41	<0.0001
Total Cholesterol (mg/dL)	145.6 ± 4.41	222.5 ± 8.83	<0.0001
Triglycerides (mg/dL)	101.3 ± 6.17	194.0 ± 13.18	<0.0001
LDL (mg/dL)	89.63 ± 4.15	157.5 ± 7.65	<0.0001
HDL (mg/dL)	38.80 ± 1.376	45.05 ± 1.74	<0.01
VLDL (mg/dL)	22.23 ± 1.91	40.85 ± 2.87	<0.0001
Urea (mg/dL)	22.38 ± 0.46	21.40 ± 1.45	= 0.05
Creatinine (mg/dL)	0.861 ± 0.02	1.083 ± 0.036	<0.001
Total Bilirubin (mg/dL)	0.614 ± 0.05	0.493 ± 0.04	NS
Total Protein (g/dL)	6.978 ± 0.10	7.202 ± 0.10	NS
Albumin (g/dL)	4.245 ± 0.04	4.013 ± 0.09	NS
AST (U/L)	23.08 ± 1.80	33.63 ± 3.04	<0.001
ALT (U/L)	29.28 ± 4.07	32.55 ± 3.38	NS
ALP (U/L)	85.38 ± 3.29	81.65 ± 4.67	NS
GGT (U/L)	26.80 ± 2.83	45.68 ± 3.95	<0.0001

Table 1: Anthropometric and biochemical parameters in MASLD patients and control subjects. Data are expressed as mean ± SEM. Comparisons were made using Mann-Whitney U test with p<0.05 considered statistically significant. Note: BMI, body mass index; W/H, waist-hip; LDL, low density lipoprotein; HDL, high density lipoprotein; VLDL, very low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; γGT, gamma-glutamyl transaminase.

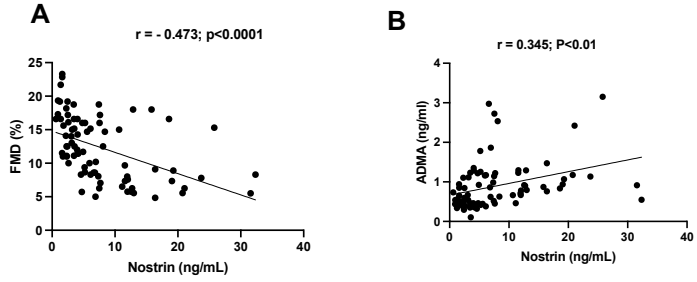

Figure 2 Serum Nostrin concentration was negatively associated with endothelial function marker FMD (A) and positively correlated with marker of endothelial dysfunction ADMA (B) in MASLD patients. Correlation coefficient (r) and statistical significance (p value) are indicated. Individual samples are represented as dots (n=40). Symbols represent **p<0.01; ****p<0.0001.

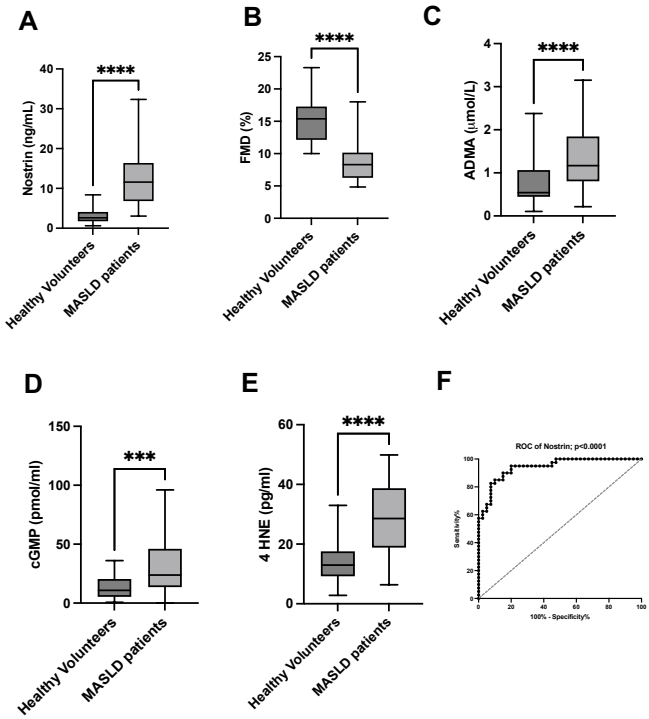

Fig 1. Hepatic Serum Nostrin (A); FMD (B); ADMA (C); cGMP (D) and 4-HNE (E) concentrations were measured by ELISA. F: Receiver Operating Characteristic (ROC) Curve Analysis of NOSTRIN for Predicting MASLD. Data are expressed as mean ± SEM. Comparisons were made using Mann-Whitney U test with p<0.05 considered statistically significant. Symbols represent ***p<0.001; ****p<0.0001.

Conclusions

- Our study demonstrated for the first time that elevated serum Nostrin levels in MASLD patients are negatively correlated with endothelial function and positively correlated with markers of ED.
- These findings suggest that Nostrin may contribute to the vascular impairment observed in MASLD and thus, it holds potential as a novel diagnostic biomarker for identifying and managing ED in patients with MASLD.

Acknowledgement

This work was supported by the JIPMER intramural research grant.

balamaniyan@gmail.com