The role of metabolic disorders in the formation of asymmetric dimethylarginine levels in patients with coronary heart disease

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Aim of the study. The aim of the study was to compare levels of asymmetric dimethylarginine (ADMA) in patients with coronary heart disease (CHD) in the presence or absence of metabolic dysfunction–associated steatotic liver disease (MASLD) and assess the possible association between ADMA and metabolic disorders.

Methods. The study included 50 patients with CHD, divided into two equal groups: 25 patients with MASLD and 25 patients without MASLD. The CHD was diagnosed based on clinical, electrocardiographic, and coronarographic data. MASLD was diagnosed using liver ultrasound. ADMA levels were assessed using enzyme-linked immunosorbent assay (ELISA) of the blood serum sample.

Results. The mean age in the MASLD group was 54.2 years, and in the group without MASLD, it was 53.8 years. The mean body mass index (BMI) of patients with MASLD was significantly higher (32.8 kg/m²) than that of patients without MASLD (27.1 kg/m², $p<0.01$). Arterial hypertension was present in 80% of MASLD patients and 48% of patients without MASLD ($p<0.05$). Type 2 diabetes mellitus (T2DM) was diagnosed in 52% of MASLD patients and 20% of patients without MASLD ($p<0.05$). ADMA levels in patients with MASLD were significantly higher (165.85 ± 24.27 ng/mL) than in patients without MASLD (129.44 ± 20.22 ng/mL, $p<0.001$). Moreover, the presence of three or more metabolic criteria (e.g., obesity, arterial hyper-

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tension, and diabetes mellitus) was associated with even higher ADMA levels (190 ± 20 ng/mL).
Conclusion. The obtained data confirm the necessity of a personalized approach to treating patients with CHD and MASLD, focusing on the correction of metabolic disorders to reduce ADMA levels.
Keywords: coronary heart disease, metabolic dysfunction–associated steatotic liver disease, asymmetric dimethylarginine, endothelial dysfunction, insulin resistance

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Introduction

Coronary heart disease (CHD) remains one of the leading causes of death and disability worldwide [1]. According to the World Health Organization (WHO), cardiovascular diseases (CVDs), including CHD, account for approximately 17.9 million people yearly, making up to 32% of all deaths. CHD alone is responsible for more than 7 million deaths each year[1]. The European Society of Cardiology reports that CHD is the primary cause of death in Europe [2], accounting for 38% of all CVD-related deaths.

CVDs continue to be a leading cause of mortality and disability in Uzbekistan. According to the Ministry of Health of the Republic of Uzbekistan, circulatory system diseases account for more than 50% of total mortality[2]. Recent WHO data (Global Health Estimates, 2024 revision) indicate that the age-standardized mortality rate from all CVDs in Uzbekistan in 2021 was ≈780–800 per 100,000 population (both sexes).This is approximately 3.5 times higher than the average rate for the WHO European Region (≈220 per 100,000) and nearly twice the global average (≈250 per 100,000) [3]. There has been an increase in the incidence of CHD, hypertension, and other cardiovascular conditions. Reports from several regional cardiology centers indicate a 10–15% rise in primary incidence rates over the past 5 years [3]. Concurrently, there has been an increase in the prevalence of risk factors (RFs) such as obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome, further exacerbating the epidemiological situation[4]. Recently, researchers have increasingly focused on comorbidity of somatic diseases as a key factor affecting work capacity and prognosis in patients with cardiovascular pathology [4]. This encompasses not only pathogenetically linked disorders but also independent diseases of various organs and systems, which adversely affect the course of CVDs [5].

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health problem affecting up to 25% of the world's adult population [6]. Among patients with obesity and T2DM, the prevalence of MASLD reaches 70–90% [6]. Research indicates that MASLD is associated with an increased risk of cardiovascular events such as myocardial infarction (MI) and stroke, independent of conventional risk factors [7, 8]. According to the European Association for the Study of the Liver, MASLD is recognized not only as a liver disease but also as a significant cardiometabolic condition affecting the prognosis of patients with CHD [9, 10].

Contemporary studies demonstrate that MASLD increases the risk of atherosclerosis development and CHD progression through mechanisms involving systemic inflammation, oxidative stress, insulin resistance, and lipid metabolism disorders [11]. A large meta-analysis conducted by the Department of Medicine, University of Verona (Italy) revealed that patients with

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[4] International Diabetes Federation (IDF). IDF Diabetes Atlas. 10th ed. Brussels: 2, IDF; 2021. https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf

MASLD have a significantly higher risk of cardiovascular complications (CVCs), including atherosclerotic vascular lesions, compared to those without this condition [6]. Other researchers reached similar conclusions, notably the group led by S. Francque from the Department of Gastroenterology and Hepatology at the University of Antwerp (Belgium). They identified a strong association between the severity of liver fibrosis in MASLD and increased cardiovascular mortality [11]. Pathogenetically, this is attributed to systemic manifestations of metabolic dysfunction: heightened inflammatory response, activation of oxidative stress, development of insulin resistance, and progressive alterations in lipid metabolism, which collectively promote the formation and progression of atherosclerosis and CHD [4].

Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, plays a key role in the development of endothelial dysfunction, which underlies atherosclerosis and CHD [12]. ADMA levels increase in the presence of MASLD, as confirmed by data from large-scale studies (NHANES and ATHEROGEN) [13]. In patients with coexisting MASLD and CHD, ADMA levels may serve as a marker of cardiovascular risk [14]. However, there is insufficient data in the scientific literature regarding its clinical significance in this patient population.

Given the global epidemic of obesity and metabolic disorders, studying the impact of MASLD on CHD progression and related biochemical markers such as ADMA is of critical importance [15]. This will enable the improvement of diagnostic, therapeutic, and preventive strategies for CVCs in this patient group [16].

The aim of the study was to compare ADMA levels in patients with CHD with and without MASLD and to assess the potential association between ADMA levels and metabolic disorders.

Methods

A pilot, open-label clinical study was conducted at the Department of Cardiometabolic Disorders of the Republican Specialized Scientific and Practical Medical Center of Cardiology from July to December 2024. The study included 50 patients with CHD, equally divided into two groups: 25 patients with MASLD and 25 without MASLD.

Inclusion Criteria:

- Confirmed diagnosis of CHD (stable exertional angina, functional class I–II)
- Age 34–70 years
- Signed informed consent

Exclusion Criteria:

- Unstable angina, acute coronary syndrome, or history of myocardial infarction.
- Chronic heart failure NYHA class III–IV or left ventricular ejection fraction <40%.
- Severe comorbidities affecting ADMA levels or endothelial function, such as chronic kidney disease (GFR <45 mL/min/1.73m²), liver cirrhosis or severe chronic liver disease, active malignancies, significant systemic inflammatory or autoimmune disorders.
- Decompensated type 1 diabetes, uncontrolled type 2 diabetes (HbA1c >9% at enrollment, patients required treatment adjustment prior to assessment)
- Use of ADMA-affecting medications within 4 weeks prior to enrollment (e.g., high-dose L-arginine, PDE-5 inhibitors)

CHD was confirmed through clinical evaluation, electrocardiography (ECG), and coronary angiography (CAG) [2]. MASLD was diagnosed via liver ultrasound, supplemented by elastography for fibrosis staging when indicated. All participants underwent standardized laboratory testing, including complete blood count, comprehensive biochemistry panel, lipid profile, fasting glucose and insulin with HOMA-IR calculation. Serum ADMA levels were quantified using enzyme-linked immunosorbent assay (ELISA) with certified commercial kits (Beijing Solarbio Science & Technology Co., Ltd.).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software. Normally distributed data are presented as mean ± standard deviation, with between-group comparisons made using Student's t-test. For non-normally distributed data, the Mann-Whitney U test was applied. Statistical significance was defined as $p < 0.05$.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committee. All patients received detailed information regarding study aims and potential risks, and signed an informed consent for participation and processing of their medical data.

Results

The study included 50 patients with CHD, divided into two groups: 25 with MASLD and 25 without MASLD.

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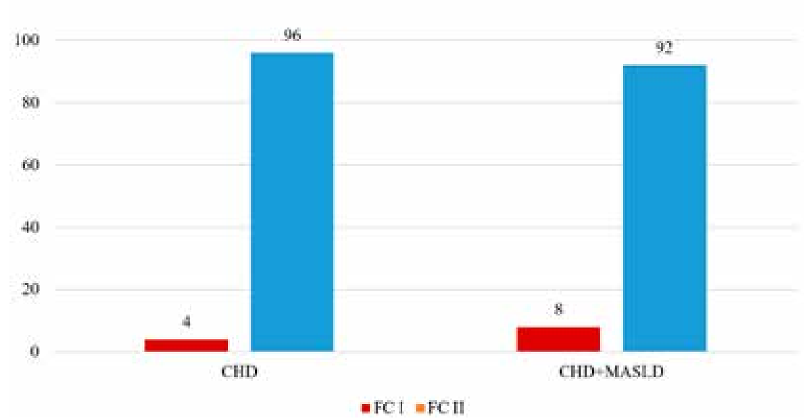

Fig. 1. Distribution of patients by angina functional class

The mean age was 54.2 years in the MASLD group and 53.8 years in the non-MASLD group, with no statistically significant difference (p = 0.73). Males comprised 56 % of the MASLD group and 60 % of the non-MASLD group (p = 0.64). All patients had stable CHD classified as Canadian Cardiovascular Society (CCS) functional class (FC) I–II (Fig. 1). CHD diagnosis was established based on medical history, ECG, and CAG when clinically indicated. Patients received guideline-directed medical therapy including antianginal agents, antiplatelet therapy, and lipid-lowering treatment. Thus, group allocation was based exclusively on MASLD status, with comparable age-sex distributions and identical CHD functional class severity between groups.

Patients with MASLD had a significantly higher mean body mass index (BMI) (32.8 kg/m²) compared to the non-MASLD group (27.1 kg/m², p < 0.01). Arterial hypertension (AH) was present in 80 % of MASLD patients versus 48 % in non-MASLD patients (p < 0.05). T2DM was diagnosed in 52 % of MASLD patients and 20 % of non-MASLD patients (p < 0.05). Low-density lipoprotein (LDL) levels were higher in the MASLD group (4.7 mmol/L) than in the non-MASLD group (3.1 mmol/L, p < 0.01) (Table 1).

Table 1. **Clinical and Metabolic Characteristics of CHD Patients Stratified by MASLD Status**

Parameter	CHD+MASLD (n=25)	CHD (n=25)	P
Mean age (years)	54.2 ± 6.1	53.8 ± 5.9	-
Male	14 (56 %)	16 (60 %)	-
BMI (kg/m²)	32.8 ± 4.2	27.1 ± 3.5	<0.01
AH (%)	80 %	48 %	<0.05
T2DM (%)	52 %	20 %	<0.05
LDL (mmol/L)	4.7 ± 0.8	3.1 ± 0.7	<0.01

ADMA levels were significantly higher in MASLD patients compared to non-MASLD patients. The mean ADMA level in the MASLD group was 165.85 ± 24.27 ng/mL, whereas the non-MASLD group showed significantly lower levels (129.44 ± 20.22 ng/mL). This difference was statistically significant (p < 0.001), indicating significant endothelial dysfunction in MASLD patients (Fig. 2).

Additional analysis revealed significantly higher ADMA levels in patients with a greater number of

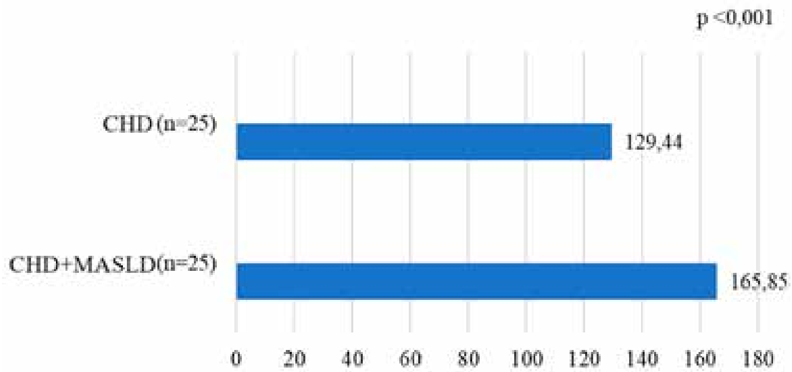

Fig. 2. ADMA levels in study groups

metabolic disorders. Patients with 1–2 metabolic criteria (e.g., hypertension and obesity) had ADMA levels of 140 ± 15 ng/mL. Those with ⩾3 criteria (e.g., obesity, type 2 diabetes, hypertension, dyslipidemia) showed substantially higher ADMA levels, averaging 190 ± 20 ng/mL ($p < 0.01$) (Table 2).

Table 2. **Analysis of ADMA Levels According to Number of Metabolic Criteria**

Study group	ADMA level (ng/mL)	P
1–2 metabolic criteria	140 ± 15	<0.01
3 and more criteria	190 ± 20	-

Discussion

This study presents the first domestic cohort analysis comparing ADMA levels in stable CHD patients stratified by MASLD status. Our findings confirm that MASLD comorbidity is associated with a pronounced elevation of this endothelial dysfunction biomarker. The observed increase (~36 ng/mL, +28 %) aligns with international studies [12]. For instance, Younossi et al. [7] reported 0.09 μmol/L higher ADMA concentrations (≈23–25 ng/mL) in biopsy-confirmed MASLD patients versus controls. Recent MASLD reviews indicate a mean excess of 0.1 μmol/L. Thus, our data demonstrate consistent manifestation of this phenomenon across diverse ethnic and geographic populations.

The causal relationship between MASLD and elevated ADMA is largely mediated by insulin resistance and chronic systemic inflammation [11]. Insulin resistance suppresses dimethylarginine dimethylaminohydrolase (DDAH) activity, the enzyme responsible for ADMA degradation, leading to its accumulation. Concurrently, proinflammatory cytokines (TNF-α, IL-6) and oxidative stress in the liver and vascular wall further inhibit DDAH while enhancing arginine methylation in proteins, thereby increasing ADMA synthesis [5].

ADMA itself competitively inhibits endothelial nitric oxide synthase, reducing nitric oxide bioavailability, enhancing vascular tone, and promoting atherogenesis. This mechanism explains the more frequent and severe coronary artery involvement in patients with combined MASLD and CHD [12].

Notably, in our cohort, ADMA levels exhibited a proportional increase with the number of metabolic disorders: patients with ⩾3 criteria showed 35 % higher values than those with 1–2 criteria. A similar gradient was demonstrated in untreated hypertensive patients (ADMA↑ ~20 %), reinforcing the concept of an ADMA-NO "metabolic cascade". Consequently, ADMA may serve as an integrative biomarker of cumulative metabolic burden on the endothelium [14]. The elevated ADMA levels observed in MASLD patients have significant clinical relevance: they enable more accurate cardiovascular risk stratification in stable CHD patients where conventional scores (SCORE2, GRACE) underestimate hepatic comorbidity impact [7]; underscore the necessity for early lifestyle modification and pharmacological management of insulin resistance to reduce ADMA and improve vascular prognosis; and function as a treatment response biomarker, where ADMA reduction during statin or combination lipid-lowering therapy correlates with atherosclerotic plaque regression [1].

As a pilot investigation, this study has inherent limitations: its single-center design and restricted sample size reduce the generalizability of findings. The single-timepoint measurement of ADMA precludes assessment of its dynamics in response to therapeutic interventions. The absence of instrumental endothelial function evaluation (flow-mediated dilation, FMD) [10] limits direct validation of ADMA as a surrogate marker. Future large-scale prospective studies employing multivariate models (incorporating ADMA + FMD + liver fibrosis indices) are needed to determine whether including ADMA enhances predictive accuracy for CVCs in MASLD patients. Furthermore, therapeutic strategies targeting ADMA reduction, such as pharmacologic DDAH activation or L-citrulline supplementation [15], remain promising yet underexplored avenues in cardiometabolic pharmacology.

Conclusion

This study demonstrated significantly higher ADMA levels in CHD patients with comorbid MASLD compared to those without MASLD. A positive correlation was observed between the number of metabolic disorders (obesity, hypertension, type 2 diabetes) and elevated ADMA concentrations, suggesting its potential role in the pathogenesis of endothelial dysfunction and CVCs. These findings support the need for a personalized approach to diagnosing and treating CHD patients that accounts for concomitant metabolic disorders, while highlighting the potential utility of ADMA as a cardiovascular risk stratification biomarker.

Conflict of interest: none declared.

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