IMPACT OF HYPERLIPIDEMIA ON ENDOTHELIAL DYSFUNCTION AND ARGININE METABOLISM IN DIABETIC PATIENTS: IMPLICATIONS FOR NITRIC OXIDE DYSREGULATION AND INCREASED CARDIOVASCULAR RISK

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BACKGROUND. Type 2 Diabetes Mellitus (T2DM) is a primary public health concern globally, characterized by chronic hyperglycemia, insulin resistance, impaired beta-cell function. Endothelial dysfunction is a hallmark of diabetes and is exacerbated by hyperlipidemia.
AIM. This study investigates the impact of hyperlipidemia on nitric oxide synthesis, arginine metabolism, and vascular health markers in T2DM.
MATERIALS AND METHODS. A total of 120 participants were included in this cross-sectional, comparative study. Serum methylarginine derivatives (Asymmetric dimethyl arginine (ADMA), Symmetric dimethyl arginine (SDMA), L-N Mono-methylarginine (L-NMMA) and related metabolites (arginine, homoarginine, citrulline, ornithine) levels were measured in three groups: diabetes with hyperlipidemia (DM-HL), diabetes with normolipidemia (DM-NL), and healthy controls (HC) using API SCIEX 3200 LC-MS/MS methods. Statistical comparisons between groups were performed using IBM SPSS 26.0 to assess the influence of hyperlipidemia on these markers.
RESULTS. ADMA and SDMA levels were significantly elevated in DM-HL group compared to DM-NL and HC (p=0.001, p=0.000 respectively), indicating increased endothelial dysfunction and potential dyslipidemia-induced renal or vascular impairment. Reduced arginine and homoarginine levels in diabetic groups suggest impaired nitric oxide synthesis and altered urea cycle function (p=0.013, p=0.000 respectively). Notably, the DM-HL group exhibited significantly higher L-NMMA levels (p=0.001). It disrupted metabolic ratios (e.g., SDMA/ADMA, arginine/ADMA, and homoarginine/ADMA), reflecting enhanced nitric oxide inhibition and reduced bioavailability. Hyperlipidemia significantly exacerbated these disruptions, as evidenced by altered citrulline/arginine and citrulline/ADMA ratios, underscoring its additive impact on endothelial dysfunction.
CONCLUSIONS. Hyperlipidemia amplifies the adverse effects of diabetes on endothelial function by exacerbating nitric oxide inhibition, oxidative stress, and arginine metabolism dysregulation. Key biomarkers and metabolic ratios, particularly ADMA and SDMA-related indices, provide valuable insights into cardiovascular risk in this population. Therapeutic strategies targeting lipid management, arginine supplementation, and ADMA reduction could improve vascular health and mitigate cardiovascular complications in DM-HL.

KEYWORDS: ADMA; arginine metabolism; diabetes mellitus; hyperlipidemia; nitric oxide synthase.

ВЛИЯНИЕ ГИПЕРЛИПИДЕМИИ НА ЭНДОТЕЛИАЛЬНУЮ ДИСФУНКЦИЮ И МЕТАБОЛИЗМ АРГИНИНА У ПАЦИЕНТОВ С ДИАБЕТОМ: НАРУШЕНИЕ РЕГУЛЯЦИИ ОКСИДА АЗОТА И ПОВЫШЕНИЕ РИСКА СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ

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АКТУАЛЬНОСТЬ. Сахарный диабет 2 типа (СД2) является одной из основных проблем общественного здравоохранения во всем мире, характеризуется хронической гипергликемией, инсулинорезистентностью и нарушением функции бета-клеток. Эндотелиальная дисфункция является характерным признаком диабета и усугубляется гиперлипидемией.
ЦЕЛЬ. Изучить влияние гиперлипидемии на синтез оксида азота, метаболизм аргинина и маркеры сосудистого здоровья при СД2.
МАТЕРИАЛЫ И МЕТОДЫ. В этом перекрестном сравнительном исследовании приняли участие в общей сложности 120 человек. Уровни производных метиларгинина в сыворотке крови (асимметричный диметиларгинин (АДМА), симметричный диметиларгинин (СДМА), L-N-монометиларгинин (L-NMMA)) и связанных метаболитов (аргинин, гомоаргинин, цитруллин, орнитин) измерялись в трех группах: пациенты с диабетом и гиперлипидемией (DM-HL), пациенты с диабетом и нормолипидемией (DM-NL) и здоровые лица из контрольной группы (HC) с использованием методов LC-MS/MS на приборе API SCIEX 3200. Статистическое сравнение между группами проводилось с использованием IBM SPSS 26.0 для оценки влияния гиперлипидемии на эти маркеры.

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РЕЗУЛЬТАТЫ. Уровни АДМА и СДМА были значительно повышены в группе DM-HL по сравнению с группами DM-NL и НС (p=0,001 и p=0,000 соответственно), что указывает на усиление эндотелиальной дисфункции и потенциальное нарушение функции почек или сосудов, вызванное дислипидемией. Сниженные уровни аргинина и гомоаргинина в диабетических группах свидетельствуют о нарушении синтеза оксида азота и изменении функции цикла мочевины (p=0,013 и p=0,000 соответственно). Следует отметить, что в группе DM-HL уровни L-NMMA были значительно выше (p=0,001). Это привело к нарушению метаболических соотношений (например, СДМА/АДМА, аргинин/АДМА и гомоаргинин/АДМА), что отражает усиление ингибирования оксида азота и снижение его биодоступности. Гиперлипидемия значительно усугубляла эти нарушения, о чем свидетельствуют измененные соотношения цитруллин/аргинин и цитруллин/АДМА, что подчеркивает ее аддитивное влияние на эндотелиальную дисфункцию.

ВЫВОДЫ. Гиперлипидемия усиливает неблагоприятное воздействие диабета на функцию эндотелия, усугубляя ингибирование оксида азота, окислительный стресс и нарушение метаболизма аргинина. Ключевые биомаркеры и метаболические соотношения, особенно индексы, связанные с АДМА и СДМА, дают ценную информацию о сердечно-сосудистом риске в данной популяции. Терапевтические стратегии, направленные на контроль липидов, добавление аргинина и снижение уровня АДМА, могут улучшить здоровье сосудов и снизить риск сердечно-сосудистых осложнений у пациентов с DM-HL.

КЛЮЧЕВЫЕ СЛОВА: АДМА; метаболизм аргинина; сахарный диабет; гиперлипидемия; синтаза оксида азота.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a primary public health concern globally, characterized by chronic hyperglycemia, insulin resistance, impaired beta-cell function and associated with significant metabolic disturbances, including leading to a spectrum of carbohydrate, lipid, and protein metabolic derangements that exacerbate the challenges of the pathophysiological condition [1, 2]. A critical aspect of T2DM pathology involves vascular complications driven by endothelial dysfunction, which contributes to the high prevalence of cardiovascular disease (CVD) in diabetic populations [3].

In recent years, some progress has been made in discovering novel biomarkers associated with the pathogenesis of T2DM and improvements in procedures involved in diagnosing, monitoring, and therapeutic managing the disease [4]. Among these biomarkers, methylarginine has been of special interest due to its effects on endothelial function and nitric oxide (NO) availability [5]. NO signaling in maintaining endothelial health cannot be overstated [6]. NO, a critical vasodilator, is synthesized by nitric oxide synthase (NOS), which requires arginine as a substrate [7, 8] (Fig. 1).

In T2DM, however, NO bioavailability is often compromised, and endothelial dysfunction becomes more pronounced, potentially increasing the risk of atherosclerosis

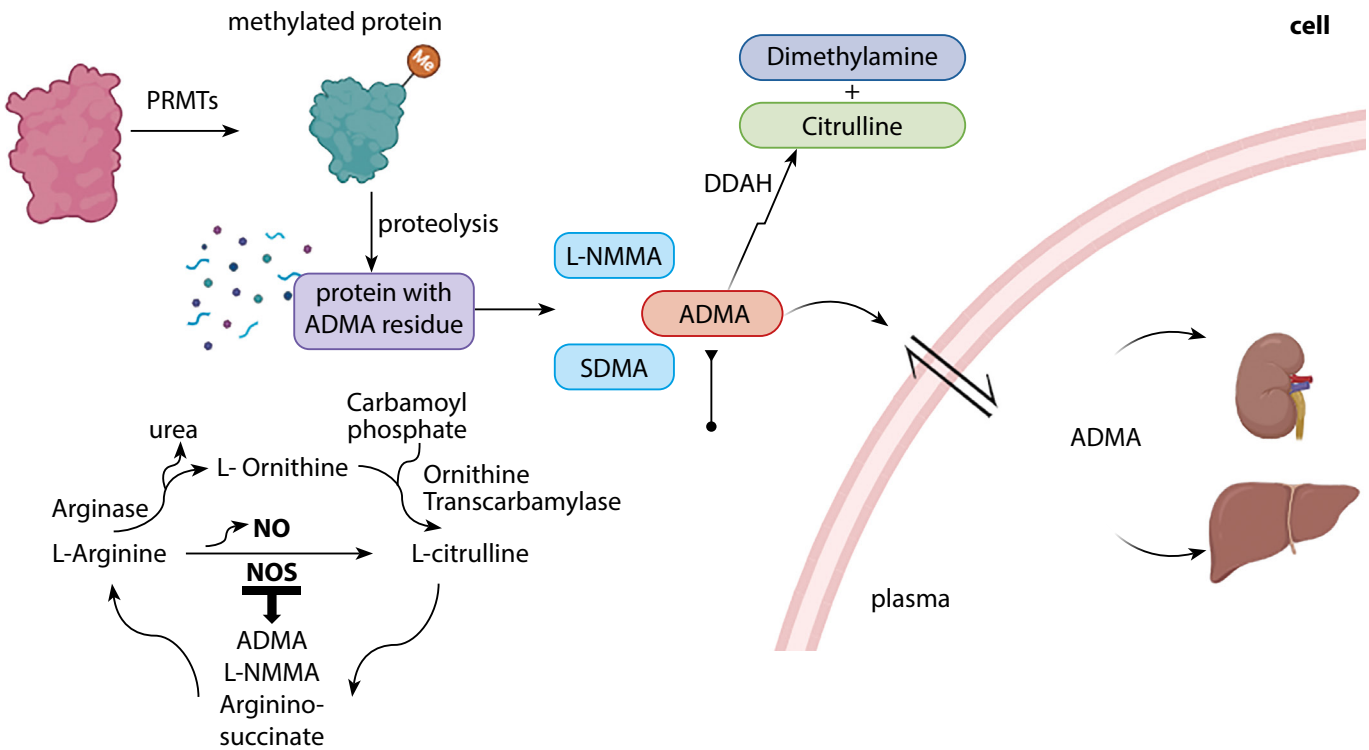

Figure 1. Overview of arginine metabolism and nitric oxide synthesis pathway.

Note. The figure illustrates the role of protein arginine methyltransferases (PRMTs) in the formation of methylarginine derivatives (ADMA, SDMA, L-NMMA) through proteolysis of methylated proteins. ADMA is degraded to citrulline and dimethylamine by DDAH. L-arginine serves as a substrate for NOS, generating NO and L-citrulline. Competing pathways include the conversion of L-arginine to L-ornithine by arginase. The balance of these pathways is critical for endothelial function, with ADMA and L-NMMA acting as NOS inhibitors, impairing NO production. ADMA — asymmetric dimethylarginine; DDAH — dimethylarginine dimethylaminohydrolase; SDMA — symmetric dimethylarginine; L-NMMA — NG-monomethyl-L-arginine; NO — nitric oxide; NOS — nitric oxide synthase.

and related CVD complications [9, 10]. A significant factor contributing to impair NO production in T2DM is the presence of methylarginine derivatives, specifically asymmetric dimethylarginine (ADMA) and L-N Mono-methylarginine (L-NMMA) [11, 12]. These Compounds act as endogenous inhibitors of NOS, reducing NO synthesis and thus limiting vasodilation, which in turn promotes endothelial dysfunction [13, 14] .

Research has established that concentrations of methylarginine and its derivatives are elevated in individuals with T2DM, and this elevation might relate to endothelial dysfunction [15, 16], increased cardiovascular risk [17], and impaired metabolic parameters [18, 19]. T2DM patients frequently experience dyslipidemia — elevated triglycerides, low HDL, and high LDL levels — raising their risk for atherosclerosis and cardiovascular complications [20].

Endothelium plays a crucial role in maintaining vascular homeostasis by regulating vascular tone, vascular smooth muscle cell proliferation, immune cell adhesion, and vascular inflammation through bioactive factors [21]. The molecular mechanisms underlying endothelial dysfunction are complex [10, 22]. They are influenced by multiple pathologic stimuli, including NO, LDL, reactive oxygen species (ROS) and high glucose [23].

Endothelial dysfunction has been associated with diabetic animal models and human patients, and excessive ROS production plays a central role in early microvascular damage [24]. Mitochondrial and cytoplasmic oxidases, such as NADPH oxidase, are significant sources of ROS in endothelial cells [25]. High levels of glucose or fatty acids accelerate this process [26]. Shah et al. suggested hyperglycemia stimulates endothelial cells to overproduce ROS, causing DNA damage [27]. Given this information, it has become necessary to discuss the metabolic pathways of methylarginine within the biochemical cycle of associated molecules such as ADMA, L-NMMA, and symmetric dimethylarginine (SDMA).

RESEARCH AIM

This study examines serum levels of methylarginine derivatives (ADMA, SDMA, L-NMMA) and related metabolites (arginine, homoarginine, citrulline, ornithine) in T2DM patients with hyperlipidemia (DM-HL) and normolipidemia (DM-NL) to determine how lipid status may affect these biomarkers. Understanding these relationships is essential for clarifying the link between dyslipidemia and endothelial dysfunction and could enhance cardiovascular risk prediction in T2DM populations.

MATERIAL AND METHOD

Study Design and Population

This cross-sectional, comparative study was conducted between July 2024 and September 2024, with patient recruitment carried out at the endocrinology outpatient clinics of Selçuk University Faculty of Medicine Hospital. A total of one hundred and twenty individuals over 18 years old participated in this cross-sectional, comparative study. 41 DM-HL aged (55.76±12.5), 42 with DM-NL aged (53.78±10.5) and 37 healthy controls (HC) aged (51.73±9.29).

The Inclusion criteria of this study are individuals with a confirmed diagnosis of T2DM, HbA1c levels above 6.5%, fasting blood glucose levels of more than 6.93 mmol/L, serum cholesterol of DM-HL was more than 5.17 mmol/L and triglyceride were higher than 1.69 mmol/L and stable health conditions with normal kidney and liver function tests. Healthy control subjects were age-sex matched to patient group. They had no history of chronic metabolic or cardiovascular diseases, and normal biochemical and hematological profiles were confirmed prior to inclusion.

We exclude some health conditions, including the presence of other types of DM like gestational and T1DM, Pregnancy or lactation, patients with a history of major surgery, Chronic liver or kidney disease, Substance abuse or alcoholism, and Severe CVD. This selection process was guided by strict ethical considerations, with the study receiving approval from the Selçuk University, Faculty of Medicine, Clinical Research Ethics Committee (Decision No: 2024/324).

Chemicals

Arginine (CAS Number: 202468-25-5), ADMA (CAS Number 220805-22-1), citrulline (CAS Number: 372-75-8), SDMA (CAS Number: 1266235-58-8), L-NMMA (CAS Number: 53308-83-1), ornithine (CAS Number: 3184-13-2), methanol (CAS Number: 67-56-1), HPLC grade water (CAS Number: 7732-18-5), n-butanol (CAS Number: 71-36-3), acetyl chloride (CAS Number: 75-36-5), formic acid (CAS Number: 64-18-6) and d7-ADMA (Catalog No: DLM-7476-5) were purchased from Sigma Aldrich and Cambridge Isotope Laboratories (St. et al., USA) respectively.

Instrumentations

Shimadzu HPLC system (Kyoto, Japan) and Phenomenex C18 HPLC column (50 mm × 4.6 mm) were used for chromatographic separation. The detection was performed using a API 3200 triple quadrupole mass spectrometer equipped with an electrospray ionization interface that was used (Applied Biosystems/MDS Sciex) as detector.

Specimens Collection

Fasting venous blood samples were collected for analysis of serum methylarginine derivatives (ADMA, SDMA, L-NMMA) and related metabolites (arginine, homoarginine, citrulline, ornithine).

Sample Preparation

Serum methylarginine derivatives (ADMA, SDMA, L-NMMA) and related metabolites (arginine, homoarginine, citrulline, ornithine) levels were measured with a modification of the previously published method [28]. The sum of ADMA, SDMA and L-NMMA levels was calculated as a total methylated arginine load [29]. Global arginine bioavailability ratio (GABR) was calculated by the formula as [Arginine / (Citrulline + Ornithine)] [30].

Statistical Analysis

The Statistical analyses were performed using IBM SPSS version 26.0. Data normality was assessed via the Shapiro-wilk test. We employed the Mann-Whitney U test for two group comparisons; for more than two group comparisons One-Way ANOVA test was used for normal distributed parameters while Kruskal-Wallis tests was used for abnormally distributed parameters. Spearman correlation was used. Statistical significance was established at $p<0.05$.

RESULTS

A total of 83 patients diagnosed with DM participated in the study; 55 were female, and 28 were male. The mean age was 56.22±11.4, 51.96±11.5 years respectively. Also 37 healthy controls, 25 were female and 12 were male included in the study. The mean age was 51.72±10.01, 51.75±8.01 respectively.

DM groups had higher fasting blood glucose (FBG), HbA1c, Insulin, HOMA-IR, Triglyceride (TG), Cholesterol (CHE), Low-density lipoprotein (LDL), White blood cell (WBC) and Platelets (PLT) levels than the Control group (p=0.000, p=0.000, p=0.000, p=0.000, p=0.000, p=0.000, p=0.000 p=0.000 and p=0.033 respectively), while High-density Lipoprotein (HDL), Hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were higher in control than DM group (p=0.000, p=0.000, p=0.011, p=0.000 and p=0.000 respectively). The values are shown detailed in Table 1.

When we compared between three groups, ADMA (p=0.001), SDMA (p<0.001), Arginine (p=0.013), Citrulline (p<0.001), L-NMMA (p=0.001), Ornithine (p<0.001), Arginine/ADMA ratio (p=0.028), Homoarginine/ADMA ratio (p<0.001), Citrulline/ADMA ratio (p<0.001), GABR (p=0.002) and Total methylated Arginine load (p<0.001) were statistically significant. The results presented are detailed in Table 2.

Serum ADMA (p=0.033), SDMA (p=0.001), Citrulline (p<0.001), L-NMMA (p<0.001), Citrulline/Arginine (p<0.001), Citrulline/ADMA (p<0.001), GABR (p=0.001) and Total methylated Arginine load (p=0.001) levels were found to be statistically significantly higher in DM-HL group compared to HC group, while serum Homoarginine (p<0.001), Ornithine (p<0.001), Arginine/ADMA (p=0.022) and Homoarginine/ADMA (p<0.001) were found to be statistically significantly lower in DM-HL group compared to HC group.

When DM-NL compared to HC group, serum Citrulline (p=0.002), SDMA/ADMA (p=0.031), Citrulline/Arginine (p<0.001), Citrulline/ADMA (p=0.001) levels were found

Table 1. Shows the demographic, biochemical and hematological parameters of the participants

	DM-HL (n=41)	DM-NL (n=42)	HC (n=37)	P value
Demographic Parameters				
[a]Age (Year)	53.78 ± 10.51	55.76 ± 12.5	51.73 ±9.29	0.087
[c]Gender				
Male	15	13	12	
Female	26	29	25	
[c]Insulin resistance				
+	39	27	-	
-	2	15	37	
Biochemical and hematological tests				
[b]FBG (mmol/L)	10.16 (6.99–22.7)	7.66 (6.94–30.36)	4.83 (3.89–5.49)	0.000[d]
[b]HbA1c (%)	8.9 (6.6–14.6)	7.8 (6.8–15)	5.4 (4.8–5.9)	0.000[d]
[b]Insulin (pmol/L)	96.54(2.78–414.62)	50.00 (2.78–405.59)	56.25(21.53–98.62)	0.000[d]
[b]HOMA-IR	6.8 (0.4–41.4)	2.6 (0.1–24.7)	1.2 (0.5–2.8)	0.000[d]
[b]TG (mmol/L)	3.57 (1.73–8.11)	1.12 (0.68–1.66)	1.3 (0.79–1.53)	0.000[d]
[b]CH (mmol/L)	5.88 (5.34–11.09)	4.29 (3.06–5.15)	4.53 (1.29–4.9)	0.000[d]
[a]HDL (mmol/L)	1.1±0.3	1.34±0.35	1.5±0.26	0.000[f]
[b]LDL (mmol/L)	3.2 (1.29–4.58)	2.39 (0.98–3.57)	2.33 (1.81–4.01)	0.000[d]
[b]WBC (10^9/L)	9 (5.39–14.25)	7.6 (4.65–14.9)	6.3 (4.7–8.4)	0.000[d]
[a]HGB (g/L)	138.0±18.0	131.0±20.3	141.0±10.2	0.041[f]
[a]HCT (%)	42.1±4.2	40.8±5.3	41.4±3.07	0.442[f]
[a]PLT (10^9/L)	318.4±99.9	283.6±70.5	270.9±63.9	0.033[f]
[a]RBC (10^{12}/L)	5±0.54	4.89±0.54	5±0.43	0.542[f]
[b]MCV (fL)	85.3 (64.8–99.2)	85.6 (62.4–101)	87.6 (79–95.5)	0.011[d]
[b]MCH (pg)	28.2 (19.5–34.4)	28.2 (19.5–34.4)	29.3±1.2	0.000[d]
[a]MCHC (g/L)	328.0±14.6	322.0±14.7	341.0±11.4	0.000[f]

Note. [a]Mean±SD; [b]Median (min-max); [c]n; [d]Kruskal Wallis Test; [f]One-Way ANOVA; CH — cholesterol; DM-HL — diabetes with hyperlipidemia; DM-NL — diabetes with normolipidemia; FBG — fasting blood glucose; HbA1c — glycated hemoglobin; HGB — hemoglobin; HC — healthy control; HCT — hematocrit; HDL — high density lipoprotein; HOMA-IR — Homeostasis Model Assessment of Insulin Resistance; LDL — low density lipoprotein; MCH — mean corpuscular hemoglobin; MCHC — mean corpuscular hemoglobin concentration; MCV — mean corpuscular volume; PLT — platelets; RBC — red blood cells; TG — triglyceride; WBC — white blood cell.

Table 2. Methylarginine and its metabolite values

Metabolite	DM-HL (Median, min and max)	DM-NL (Median, min and max)	HC (Median, min and max)	p Value
ADMA (μmol/L)	0.173 (0.059-0.408)	0.087(0.030-0.317)	0.12 (0.032-0.36)	**0.001 P1-2**
SDMA (μmol/L)	0.27 (0.069-0.57)	0.15 (0.065-0.46)	0.14 (0.031-0.503)	**0.000**
Arginine (μmol/L)	57.8 (5.1-202)	41.2 (13.6-146)	62.3 (6.6-278)	**0.013**
HomoArg. (ng/mL)	5.58 (2.06-15.8)	5.3 (1.18-15.4)	10.9 (4.12-126)	**0.000**
Citrulline (ng/mL)	9.9 (0.01-40.6)	5.5 (0.0-16)	2.1 (0.01-13.2)	**0.000**
L-NMMA (μmol/L)	0.038 (0.012-0.096)	0.022 (0.01-0.074)	0.021 (0.006-0.069)	**0.001**
Ornithine	59.1 (3-170)	73.5 (3.4-262)	107 (10.3-324)	**0.000**
SDMA/ADMA	1.63 (0.452-4.270)	1.75 (0.448-4.3)	1.4 (0.224-6.03)	0.072
Arginine/ADMA	382.5 (42.7-1922.4)	474 (43.8-1339.4)	462 (74.3-2139.8)	**0.028**
HomoArg/ADMA	34.7 (15.9-109.9)	61.9 (3.8-178.8)	97.8 (40.4-484.6)	**0.000**
Citrulline/Arginine.	0.19 (0.00-0.744)	0.13 (0.00-0.73)	0.034 (0.001-0.260)	**0.000**
Citrulline/ADMA	62.6 (0.064-276.5)	61.4 (0.016-360)	22.46 (0.08-145.3)	**0.000**
GABR	0.66 (0.31-22.9)	0.533 (0.15-7.33)	0.488 (0.12-1.66)	**0.002**
Total Methylated Arginine load	0.49 (0.16-0.92)	0.285(0.133-0.703)	0.342 (0.098-0.872)	0.000

Note. p-values calculated by Kruskal-wallis test; ADMA — asymmetric dimethylarginine; DM-HL — diabetes with hyperlipidemia; DM-NL — diabetes with normolipidemia; GABR — global arginine bioavailability ratio; HC — healthy control; HomoArg — homoarginine; L-NMMA — NG-monomethyl-L-arginine; SDMA — symmetric dimethylarginine.

to be statistically significantly higher, while Arginine (p=0.026), Homoarginine (p<0.001) and Homoarginine/ADMA (p=0.001) were found to be statistically significantly lower.

Moreover, DM group statistically compared according to lipemic profile and serum ADMA (p<0.001), SDMA (p<0.001), Arginine (p=0.005), Citrulline (p<0.001), L-NMMA (p=0.003), GABR (p=0.014) and Total methylated Arginine load (p<0.001) were found to be statistically significantly higher in lipemic group, while Arginine/ADMA (p=0.029) and Homoarginine/ADMA (p<0.001) were found to be statistically significantly lower. The laboratory parameters of DM and HC groups were described in Figure 2 and Table 3.

Table 3. Methylarginine and its metabolite values between two diabetic groups

Metabolite	DM-HL (Median, min and max)	DM-NL (Median, min and max)	p Value
ADMA (μmol/L)	0.173 (0.059-0.408)	0.087(0.030-0.317)	**0.000**
SDMA (μmol/L)	0.27 (0.069-0.57)	0.15 (0.065-0.46)	**0.000**
Arginine (μmol/L)	57.8 (5.1-202)	41.2 (13.6-146)	**0.005**
HomoArg. (ng/mL)	5.58 (2.06-15.8)	5.3 (1.18-15.4)	0.566
Citrulline (ng/mL)	9.9 (0.01-40.6)	5.5 (0.0-16)	**0.000**
L-NMMA (μmol/L)	0.038 (0.012-0.096)	0.022 (0.01-0.074)	**0.003**
Ornithine	59.1 (3-170)	73.5 (3.4-262)	0.527
SDMA/ADMA	1.63 (0.452-4.270)	1.75 (0.448-4.3)	0.469
Arginine/ADMA	382.5 (42.7-1922.4)	474 (43.8-1339.4)	**0.029**
HomoArg/ADMA	34.7 (15.9-109.9)	61.9 (3.8-178.8)	**0.000**
Citrulline/Arginine.	0.19 (0.00-0.744)	0.13 (0.00-0.73)	0.090
Citrulline/ADMA	62.6 (0.064-276.5)	61.4 (0.016-360)	0.578
GABR	0.66 (0.31-22.9)	0.533 (0.15-7.33)	**0.014**
Total Methylated Arginine load	0.49 (0.16-0.92)	0.285(0.133-0.703)	0.000

Note. p-values calculated by Mann-Whitney U test. ADMA — asymmetric dimethylarginine; DM-HL — diabetes with hyperlipidemia; DM-NL — diabetes with normolipidemia; GABR — global arginine bioavailability ratio; HomoArg — homoarginine; L-NMMA — NG-monomethyl-L-arginine; SDMA — symmetric dimethylarginine.

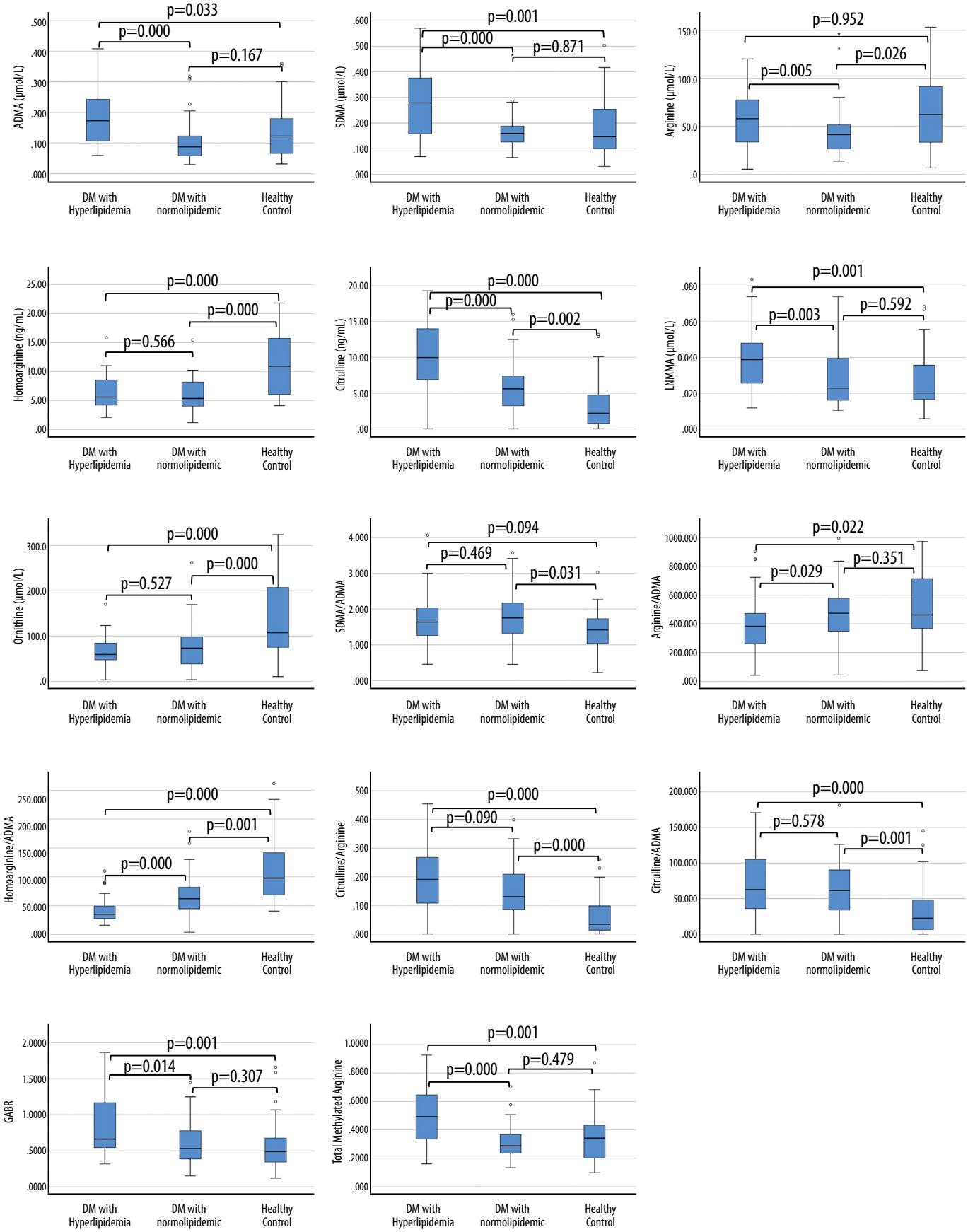

Figure 2. The p-values of Methylarginine metabolites between three groups.

Note. ADMA — asymmetric dimethylarginine; GABR — global arginine bioavailability ratio; SDMA — symmetric dimethylarginine; L-NMMA — NG-monomethyl-L-arginine.

Table 4. Correlation values of methylarginine derivatives and biochemical parameters

		Age	FBG	HbA1C	Insulin	HOMA IR	TG	CH	HDL	LDL	WBC
ADMA (μmol/L)	r	0.083	0.104	.221	.192	0.125	0.233	0.247	-.012	0.082	0.119
	p	0.370	0.257	**0.016**	**0.038**	0.188	**0.010**	**0.007**	0.899	0.381	0.207
SDMA (μmol/L)	r	0.165	.185	.294	.215	.189	.261	0.206	-.110	0.047	.249
	p	0.072	**0.044**	**0.001**	**0.020**	**0.045**	**0.004**	**0.024**	0.231	0.621	0.007
Homoarginine (ng/mL)	r	-.306	-.347	-.310	-.057	-.312	-.158	-.010	0.140	-.059	-.225
	p	**0.001**	**0.000**	**0.001**	0.545	**0.001**	0.086	0.911	0.126	0.529	0.016
Citrulline (ng/mL)	r	0.137	.408	.432	0.147	.300	.354	.292	-.280	.259	.387
	p	0.135	**0.000**	**0.000**	0.114	**0.001**	**0.000**	**0.001**	**0.002**	**0.005**	**0.000**
L-NMMA (μmol/L)	r	.240	0.167	.216	0.014	0.157	.314	.190	-.257	-.037	0.163
	p	**0.008**	0.069	**0.019**	0.884	0.096	**0.000**	**0.037**	**0.005**	0.698	0.084
Ornithine (μmol/L	r	-.220	-.273	-.261	-.006	-.171	-.267	-.090	0.164	-.020	-.236
	p	**0.016**	**0.003**	**0.004**	0.948	0.071	**0.003**	0.326	0.073	0.836	**0.011**
Arginine/ADMA	r	-.129	-.211	-.300	-.114	-.147	-.248	-.130	0.132	-.032	-.142
	p	0.159	**0.021**	**0.001**	0.221	0.119	**0.006**	0.159	0.150	0.738	0.131
Homoarginine/ADMA	r	-.363	-.463	-.529	-.236	-.412	-.383	-.280	0.138	-.170	-.309
	p	**0.000**	**0.000**	**0.000**	**0.011**	**0.000**	**0.000**	**0.002**	0.134	0.069	**0.001**
Citrulline/Arginine	r	0.144	.388	.380	0.022	.206	.249	0.131	-.249	0.146	.363
	p	0.115	**0.000**	**0.000**	0.817	**0.029**	**0.006**	0.155	**0.006**	0.119	**0.000**
Citrulline/ADMA	r	0.096	.287	.240	-.023	0.155	0.151	0.059	-.213	0.124	.241
	P	0.296	**0.001**	**0.009**	0.804	0.101	0.100	0.524	**0.020**	0.188	**0.010**
GABR	r	0.125	0.163	0.166	0.115	0.178	.231	.237	-.063	0.105	0.151
	p	0.172	0.075	0.071	0.217	0.060	**0.011**	**0.009**	0.492	0.265	0.109
Total Methylated Arginine	r	0.151	0.158	.290	.222	0.175	.294	.243	-.088	0.057	.216
	p	0.100	0.085	**0.001**	**0.016**	0.063	**0.001**	**0.007**	0.340	0.548	**0.021**

Note. Spearman correlation test. ADMA — asymmetric dimethylarginine; GABR — global arginine bioavailability ratio; SDMA — symmetric dimethylarginine; L-NMMA — NG-monomethyl-L-arginine. CH — cholesterol; FBG — fasting blood glucose; HbA1c — glycated hemoglobin; HDL — high density lipoprotein; HOMA-IR — Homeostasis Model Assessment of Insulin Resistance; LDL — low density lipoprotein; TG — triglyceride; WBC — white blood cell.

When we performed spearman correlation test on serum methylarginine derivatives and some biochemical parameters, the results showed that ADMA, SDMA, L-NMMA, homoarginine, ornithine, and their derivatives show correlations with glucose metabolism, insulin resistance, and inflammation, potentially linking them to metabolic syndrome and cardiovascular risks, the results presented in Table 4.

DISCUSSION

This study investigates the serum level of methylarginine derivatives (ADMA, SDMA, L-NMMA) and related metabolites (arginine, homoarginine, citrulline, ornithine), which are associated with NO metabolism in DM with and without hyperlipidemia. Unlike previous studies, our study uniquely investigates how hyperlipidemia modulates arginine metabolism and nitric oxide bioavailability in the diabetic state. It allows us to isolate the specific contribution of lipid profile abnormalities to endothelial dysfunction in T2DM patients.

NO is an unstable molecule with a very short half-life (2–6 s) and rapidly oxidizes to nitrite and nitrate. The unstable structure of NO complicates the direct measurement of NO levels [28]. Arginine divided through a reaction catalyzed by NOS to form citrulline and NO [31]. Therefore, in this study, we calculated the citrulline / Arginine ratio, which can be an indicator for NOS activity and NO levels. When we compared the 3 groups the citrulline/Arginine ration were significantly statistically higher in DM-HL than HC (p=0.000) and higher in DM-NL than HC (p=0.000). however, When the results between the two DM groups were examined, no statistical significance was found (p>0.05) (Table 2, Fig. 1).

Rainer H. Böger et al. investigated the levels of ADMA and arginine in hypercholesterolemic and normocholesterolemic participants. 49 hypercholesterolemic and 31 normocholesterolemic participants were included in the study. As a result of the study, plasma ADMA are statistically significantly elevated in hypercholesterolemic than in normocholesterolemic (P<0.05) [32].

Riccioni et al., investigated the level of ADMA and SDMA in asymptomatic carotid atherosclerosis. 180 subjects with carotid atherosclerosis included in this study. 14% had carotid intima-media thickening (CIMT) localized to the common carotid arteries (CCAs), 36% had atherosclerotic plaque in the CCAs, 44% had atherosclerotic plaque in the internal carotid arteries (ICAs) and 6% had atherosclerotic plaque in the external carotid arteries (ECAs). The study found that elderly subjects with asymptomatic carotid atherosclerosis, as measured by CIMT and plaque, had significantly higher plasma concentrations of ADMA and SDMA compared to those without carotid atherosclerosis ($p<0.001$) [33].

In our study, elevated ADMA levels in the DM-HL group compared to both DM-NL and HC groups ($p=0.000$ and $p=0.033$, respectively) indicate that hyperlipidemia exacerbates endothelial dysfunction in diabetic patients. Conversely, the non-significant difference between DM-NL and HC ($p=0.167$) suggests that diabetes alone has a limited impact on ADMA levels. Elevated SDMA levels in DM-HL compared to DM-NL ($p=0.000$) and HC ($p=0.001$) highlight the potential role of SDMA as a marker of dyslipidemia-induced renal or vascular dysfunction. The absence of significant variation between DM-NL and HC ($p=0.871$) supports this interpretation.

Reduced arginine levels in both DM groups compared to HC suggest impaired nitric oxide synthesis, a result of diabetes-associated metabolic disturbances. The lack of a significant difference between the two DM groups ($p=0.952$) implies that hyperlipidemia does not further reduce arginine availability. Additionally, homoarginine levels are markedly lower in DM groups compared to HC ($p=0.000$ for both DM groups), likely reflecting altered urea cycle function or increased protein carbamylation in DM. The absence of significant differences between DM groups ($p=0.566$) suggests that hyperlipidemia does not independently influence homoarginine levels.

Citrulline levels were significantly lower in both DM groups compared to HC ($p=0.000$), suggesting dysregulation in nitric oxide or urea cycle pathways. In addition, the levels of Citrulline were significantly lower in DM-NL compared to DM-HL ($p=0.000$). Elevated L-NMMA levels in DM-HL compared to DM-NL ($p=0.003$) and HC ($p=0.001$) indicate heightened endogenous nitric oxide inhibition in DM-HL, further impairing vascular function. The lack of significant differences between DM-NL and HC ($p=0.592$) emphasizes the more pronounced role of hyperlipidemia in this dysfunction.

The levels of Ornithine showed no significant differences between the two DM groups ($p=0.527$) suggesting that Ornithine serum levels are not affected by dysregulated lipid profile. However, Ornithine levels were reduced in both DM groups compared to HC, highlighting disruptions in the urea cycle and potential shifts in arginine metabolism towards alternative pathways, such as polyamine synthesis or nitric oxide production. This reduction may reflect adaptive or maladaptive metabolic responses to diabetes-induced stress. Restoring metabolic balance through dietary arginine supplementation could be a potential therapeutic strategy to mitigate these disruptions.

Significantly elevated SDMA/ADMA ratios in DM groups, especially in DM-HL suggest an increase in nitric oxide inhibition, which is indicator for endothelial dysfunction. This ratio could be an important marker for identifying individuals at increased risk for cardiovascular complications. Also, the decrease in arginine/ADMA ratio across all DM groups indicates limited substrate availability for nitric oxide synthase due to high ADMA levels. The lack of significant differences between the DM-HL and DM-NL groups suggests that DM is responsible for these alterations rather than lipid status. Since, a low arginine/ADMA ratio strongly predicts CVD risk, the importance of early interventions to preserve endothelial function in diabetes management is mandatory.

The homoarginine/ADMA ratio, an alternative marker of nitric oxide production, was significantly lower in DM-HL. This compounded insufficiency in nitric oxide generation underscores the negative role of hyperlipidemia in vascular dysfunction. Monitoring homoarginine/ADMA ratio may provide valuable vision into the interplay between lipid status and vascular health in DM. Strategies to increase homoarginine levels, such as dietary supplementation, may hold promises for improving vascular outcomes in DM-HL patients.

The citrulline/arginine ratio, reflecting arginine recycling and utilization, was elevated in DM-HL suggesting altered metabolic flux due to increased arginine diversion toward other pathways (e.g., polyamine or proline synthesis). These disruptions contribute to endothelial dysfunction and impaired vascular homeostasis. Modulating arginine metabolism could restore nitric oxide synthesis efficiency and improve vascular function. The citrulline/ADMA ratio, integrating markers of nitric oxide recycling and inhibition, was significantly reduced across all DM groups, particularly in DM-HL. This finding highlights the additive effect of elevated ADMA levels and reduced substrate recycling in worsening endothelial dysfunction. Incorporating lipid-lowering strategies into comprehensive diabetes care is crucial to address these metabolic derangements.

The GABR was significantly lower in both DM groups compared to the HC. GABR reflects the balance between circulating arginine and its primary inhibitors, such as ADMA, and is a critical indicator of nitric oxide bioavailability and vascular health. Both DM and hyperlipidemia are associated with increased oxidative stress and endothelial dysfunction, which reduce arginine availability for nitric oxide production. A reduced GABR in DM groups underscores diminished nitric oxide production capacity, which is pivotal for maintaining vascular tone and preventing atherogenesis. Interventions targeting arginine metabolisms, such as arginine supplementation or ADMA reduction, may improve endothelial function in these populations.

Finally, elevated total methylated arginine levels in DM-HL compared to both DM-NL ($p=0.000$) and HC ($p=0.001$) highlight the additive role of hyperlipidemia in endothelial dysfunction through elevated oxidative stress and impaired protein turnover. The lack of significant elevation in the DM-NL group suggests lipid status is critical in methylation-related dysfunction. Therapeutic strategies to reduce ADMA levels or enhance its clearance (e.g., through dimethylarginine dimethylaminohydrolase [DDAH] activity) could mitigate cardiovascular complications in hyperlipidemic diabetic patients.

CONCLUSION

This study highlights the complex impact of hyperlipidemia on endothelial dysfunction and metabolic disturbances in DM patients. The elevated levels of ADMA, SDMA, and total methylated arginine in the DM-HL group emphasize the additional role of lipid abnormalities in worsening nitric oxide inhibition, oxidative stress, and vascular dysfunction. The significant difference that observed in arginine, citrulline, and related metabolic ratios between patients and control further underline the dysregulation of nitric oxide synthesis and arginine metabolism associated with DM-HL.

These findings suggest that hyperlipidemia amplifies the harmful effects of DM on endothelial function, highlighting the importance of effective lipid management in diabetes care. Biomarkers, such as the SDMA/ADMA, arginine/ADMA, and homoarginine/ADMA ratios, provide valuable insights into the extent of endothelial dysfunction and cardiovascular risk in this population.

Therapeutic interventions targeting metabolic pathways — including arginine supplementation, reduction of ADMA levels, and lipid-lowering strategies — show promise for restoring endothelial function and reducing cardiovascular complications in DM-HL. Future studies should investigate these therapeutic approaches to develop comprehensive strategies for mitigating vascular dysfunction and improving outcomes in this high-risk population.

However, an important limitation of this study is the relatively small sample size, which may reduce the generalizability of the findings to larger populations. Furthermore, the study's cross-sectional nature limits the ability to infer causality between hyperlipidemia, nitric oxide dysregulation, and cardiovascular outcomes. Future research should address these limitations through more extensive, longitudinal studies to confirm these findings and explore causal mechanisms.

OTHER INFORMATION

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