Introduction

Acute myocardial infarction (AMI) constitutes a highly frequent and life-threatening cardiac emergency, requiring immediate medical attention.[1] Myocardial infarction is defined as “the
presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia. Troponins are essential biomarkers in the diagnosis of AMI. C-reactive protein (CRP) is another well-studied marker involved in every stage of cardiovascular disease, from atherogenesis to clinical outcomes.

Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) are amino acids intracellularly produced by the posttranslational modification of the L-arginine. In AMI patients, ADMA baseline levels on the 1st day (<24 h) of hospital admission were found to be predictive of mortality on a 1-year follow-up. Concerning SDMA, it is implicated with an altered ventricular ejection fraction of AMI patients, which leads to worse hospital outcomes and it has also been proposed as a therapeutic target in ischemic heart disease.

Due to the possible critical involvement of ADMA and SDMA in AMI’s progression and morbidity, we sought to monitor these markers on the 1st day (<24 h) of admission and on the 3rd post-admission day. Besides, we aimed to identify somatometric, demographic, and lifestyle factors that have an impact on the serum concentration levels of these dimethylarginines upon admission, as well as to assess their reduction or increase on the 3rd day with the presence of these factors.

**Material and Methods**

**Study population**

The current study included 66 consecutive patients admitted for AMI in the Cardiology Department of General Hospital of Chalkida in Greece. Patient inclusion criteria were:

- Confirmed occurrence of AMI
- Age between 30 and 75 years
- Absence of chronic inflammatory and autoimmune disease, diabetes, renal failure, cancer, or any other disease that could severely affect stress markers

**Questionnaire development and distribution**

The participants completed a questionnaire with questions including:

- Sociodemographic characteristics: age, sex, education, occupation, employment status, place of birth
- Somatometric characteristics: weight (current and self-reported lifetime maximum and minimum), height
- Family history: dyslipidemia, hypertension, cardiovascular event
- Patient history: the presence of dyslipidemia, hypertension
- Feelings of high anxiety (yes/no) and anxiety evaluation on an ascending scale of 1 to 7.
- Sleep: hours of sleep per day, daily napping
- Smoking (currently, ex, passive, never) and alcohol consumption (frequency and type of beverage)
- Self-reported physical condition on a scale of 0 (bad) to 4 (excellent), physical requirements for work on a scale of 0 (none) to 4 (excessive)
- Diet: Following a special type (e.g., low cholesterol), eating out/delivery food consumption frequency (never to daily), daily sugar consumption in beverages/coffee (in teaspoons), daily consumption, frequency of eating between meals, preference in biologic products, daily water consumption (in glasses)

The questionnaire was in paper form and its completion required approximately 15 min. The patient filled it on the day of discharge.

**Blood measurements**

Blood samples from 66 patients were obtained < 24 h after admission (1st day). On the 3rd day post-admission, a second blood sample was obtained. Blood was centrifuged and serum was stored at -80°C for future analysis. On each blood sample, troponin T, CRP, ADMA, and SDMA concentrations were measured in the serum. CRP and troponin were promptly available from the laboratory results of the hospital. Quantitative determination of ADMA and SDMA was obtained through competitive enzyme-linked immunosorbent assay (ELISA).

**Statistical analysis**

Statistical analysis was conducted using IBM Statistical Package for the Social Sciences (SPSS) 23 statistics software program. Nominal data are described through frequencies/percentages whereas continuous variables, median, or mean and minimum/maximum values are presented. For continuous variables, independent samples t-test or the nonparametric Mann-Whitney U test was utilized, depending on the occasion. A comparison between 1st and 3rd-day biomarker measurements was conducted through the Wilcoxon signed-rank test. Concerning correlations in continuous variables, Spearman’s (nonparametric) correlation coefficient was calculated. The statistical significance threshold of the current study was set at $P < 0.05$.

**Results**

Regarding patient population characteristics, the median age was 64 (range: 41–70) with 27% (18/66) being females. A positive history for hypertension was present in 67% of patients (44/66) and positive history for dyslipidemia was present in 41% (27/66) of patients. About 58% were current smokers, whereas 3% ex. Height and current weight were available in 59/66 patients, which allowed us to calculate body mass index (BMI). Patients’ mean BMI at the time of the study was 26.63 ± 1.67 kg/m² (21.7–30.9), whereas mean lifetime minimum BMI was 24.84 ± 1.77 kg/m² (range: 20.1–29.4) and mean lifetime maximum was 27.9 ± 1.6 kg/m² (range: 23–32.2).

**Association and correlation of 1st-day marker concentration levels with several factors**

Statistically significant correlations of the examined biomarkers occurred with reported total daily sleeping hours, weekly eating...
out/delivery food consumption frequency, self-reported physical condition status, age, and daily sugar in coffee consumption. Table 1 presents the correlation coefficients as well as the statistical significance of these results.

Furthermore, regarding hypertension, 12 patients reported an unknown history. Of the remaining 54, a positive medical history of hypertension indicated higher ADMA upon admission when compared to a negative one (1,818 ± 0.432 vs 1,568 ± 0.437, P = 0.042).

1st and 3rd-day marker concentration comparison

Between the 1st and 3rd day, a statistically significant decrease in all four markers was observed (P < 0.001), as presented in Table 2. Nonetheless, we observed that ADMA increased in 10/66 patients whereas, in SDMA, the respective fraction was 14/66. After dividing the patients into two groups, those with an increase in ADMA levels had decreased weight (either current or lifetime self-reported maximum-minimum) and height. Regarding SDMA, patients with increased SDMA levels slept more on average in comparison to patients with reduced levels. Table 3 presents the resulting differences among the two groups as well as their statistical significance.

Factors affecting ADMA and SDMA reduction

Among patients, different ADMA and SDMA reductions occurred. We expressed these reductions either as total (e.g., ADMA 1st day – ADMA 3rd day) or as a reduction percentage (e.g., [ADMA 1st day – ADMA 3rd day/ADMA 1st day] × 100%). We subsequently examined several factors of the questionnaire concerning the occurring reductions. Spearman’s rho correlation indicated that self-reported lifetime low BMI was positively correlated with ADMA reduction (r = +0.366, P = 0.009) or ADMA reduction percentage (r = +0.262, P = 0.045). As a result, a higher reduction in ADMA occurred in individuals with higher minimum lifetime BMI, as shown in Figure 1.

In SDMA reduction, statistically significant correlations occurred when examining the daily sleep hours of patients. However, 65/66 patients reported sleeping between 5–8 h per day, whereas only one reported sleeping 9 h. Therefore, the latter was not introduced into the calculation. Spearman’s rho correlation revealed a negative correlation between SDMA decrease and 5–8 daily hour sleep, either as absolute decrease (r = -0.369, P = 0.002) or as a percentage (r = -0.410, P = 0.001). Patients sleeping fewer hours had greater SDMA decrease in comparison to patients sleeping more hours, as presented in Figure 2.

Discussion

This is the first study comparing ADMA/SDMA concentrations with several demographic and lifestyle characteristics of AMI patients on the 1st admission and the 3rd post-admission day. After measuring ADMA and SDMA circulating concentrations on 1st and 3rd-day post-admission for AMI, a statistically significant decrease in both toxic amino acids was revealed. Considering that the same was observed regarding troponin and CRP concentration levels, one could hypothesize that their decrease was expected as part of patients’ clinical remission.

Over the past decades, prospective clinical studies among different patient populations have established a solid relationship between ADMA and cardiovascular risk. The predominant mechanism of action is via inhibiting NO synthesis and impairing the beneficial, vasodilatory impact of NO in normal vascular tone. Following reported literature outcomes, we noticed that patients with a positive medical history of hypertension had higher ADMA levels upon admission. Analogous observations were detected among patients with bad eating habits, possibly due to simultaneous, underlying comorbidities associated with disrupted lipid levels and oxidative stress. Additionally, a negative correlation occurred with self-reported physical condition status, highlighting the possible protective effect of an active lifestyle. SDMA did not correlate with any of the lifestyle factors addressed in the questionnaire. Nonetheless, a positive correlation between 1st-day SDMA and age was observed. SDMA

![Figure 1: Scatterplot depicting self-reported lifetime-minimum body mass index (kg/m²) in X-axis about ADMA reduction expressed as a percentage of the baseline (% of 1st day) concentration on the Y-axis](image)

| Table 1. Factors correlating with 1st day (admission) biomarker concentrations |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| ADMA                        | +0.497, (P<0.001*)          | -                           | -                           | -                           |
| SDMA                        | -                           | -                           | -                           | +0.320, (P=0.009*)          |
| Troponin                    | -                           | -                           | -                           | +0.274, (P=0.027*)          |
| CRP                         | -                           | -                           | -                           | +0.257, (P=0.037*)          |

*Spearman’s rho correlation coefficient
is an endogenous marker of renal function and correlates highly with GFR, explaining the accumulation in older patients who are at an increased risk of renal dysfunction.11 A similar positive correlation was observed regarding 1st-day troponin levels and age, possibly explaining why the conventional cut-off value of troponin for AMI diagnosis provides low specificity in the elderly.12 Notably, SDMA reduction was inversely correlated with total daily sleep duration. In the 5–8 sleep hours range which we were able to study, patients sleeping more had lower SDMA reduction. Besides, patients with an increase in SDMA between 1st and 3rd day slept more on average (7.29 vs 6.67 hours per day). To interpret these findings, we need to consider three facts:

- The predominant excretion of SDMA occurs via the kidneys and may even be a marker of glomerular filtration rate (GFR).11,13
- Previous research findings report that kidney function is associated with a U-shape when considering self-reported daily sleep hours. At extreme sleep hours, (<6 or > 9) kidneys tend to hyperfiltrate.14–17 Notably, this U-shape is more evident in older individuals (>65 years old) and one study concluded that for each 1 h decrease in sleep duration an increase of 1.5 mL/min/1.73 m² in GFR occurs over a decade (estimated from creatinine clearance).15,16
- We only had one patient reporting a daily sleep of 9 h, therefore, we could only report results in the 5–8-h range.

As a result, considering that SDMA is mainly excreted via the kidneys and that GFR increases with less sleep, our results are in accordance with the literature. Nonetheless, we could not exhibit or examine the previously mentioned U-shaped correlation, due to the lack of patients sleeping 9 h or more. Besides, our results revealed a positive correlation of 1st-day ADMA concentrations with reported total daily sleeping hours. Findings connecting ADMA and its degrading enzyme, dimethylarginine dimethylaminohydrolase (DDAH), with sleep parameters or disorders do exist.18–20 Nonetheless, we were not able to identify a possible underlying mechanism to explain this correlation. We should also note that the data analyzed about sleep were self-reported and thus we could not assess sleep quality. The interrelationship of sleep and biomarkers is complex and difficult to investigate; further studies with more meticulous sleeping hours and quality estimation are needed to confirm these findings and investigate the underlying mechanisms.

Concerning AMI mortality, as mentioned, ADMA concentration levels on the 1st day of admission are considered as a prognostic factor.24 Furthermore, among individuals with higher BMI, an obesity paradox exists; a higher BMI correlates with better clinical outcomes.21 This could explain our observation that individuals who maintain a higher lifetime-minimum BMI have a greater decrease in ADMA. Since ADMA is a toxic amino acid, a faster elimination could indicate a prompter clinical remission of AMI. Besides, the only relevant study examining ADMA, BMI, and mortality, recruited a total of 4164 patients with suspected angina pectoris and reported that ADMA is associated with AMI mortality only in individuals with lower BMI (≤26.3 kg/m²). This indicates a disassociation of ADMA and mortality on higher BMI patients.25 Besides, measured ADMA levels were unexpectedly increased on the 3rd post-admission day in only 10/66 patients. These patients weighed less and had a shorter height, with no observations occurring concerning BMI. However, these results again point out to an implication of somatometric characteristics in the course of ADMA concentration levels during AMI. Finally, our study revealed a statistically significant correlation between 1st-day CRP and daily sugar consumption in coffee. This can be considered as an anticipated outcome, considering that sugar consumption in beverages has been shown to promote inflammation.23

Summary of key findings

Hypertension, bad eating habits, more daily hours of sleep, and worse physique were associated with higher ADMA baseline levels in the onset of AMI, whereas regarding SDMA, only increased age correlated with increased baseline levels.

| Table 3: Resulting different characteristics of patients with ADMA or SDMA increase |
|---------------------------------|---------|---------|---------|
| **Reduction** | **Increase** | **P** |
| ADMA (number of patients) | 56/66 | 10/66 | *<0.001* |
| Max-reported weight (kg) | 84.16±7.885 | 79.56±6.444 | 0.030* |
| Min-reported weight (kg) | 77.27±7.634 | 69.11±8.146 | 0.015* |
| Weight (kg) | 82.45±7.654 | 76.44±6.307 | 0.025** |
| Height (m) | 1.757±0.058 | 1.703±0.052 | 0.022** |
| SDMA (number of patients) | 52/66 | 14/66 | *0.016* |
| Daily sleep (h) | 6.67±0.879 | 7.29±0.726 |

*Independent samples Mann-Whitney U test  **Independent samples t-test
Comparing the biomarkers’ concentration levels between the 1st and 3rd day of hospital admission for AMI, both were observed to significantly reduce, on average. Finally, patients maintaining a higher lifetime-minimum BMI exhibited greater reduction in ADMA concentration levels, whereas patients sleeping less (in the 5–8-h range) showed greater SDMA reduction.

Limitations
The relatively small patient database was a limitation for our study, as well as that the questionnaire data collected were self-reported. However, a major strength of this study is that we managed to investigate and study a wide variety of sociodemographic, lifestyle, and somatometric factors.

Implications for primary care practice
AMI prognosis has been reported to be affected by ADMA and SDMA concentration levels; thus, the knowledge that lifestyle and somatometric factors affect these biomarkers may help and guide accordingly primary and hospital care physicians in taking early appropriate action and informing their patients on modifiable factors associated and related with worse outcomes in case of AMI occurrence. Initially, clinicians could increasingly advocate and promote good eating habits, physical exercise, and proper control of hypertension on all patients, since these factors seem to correlate with lower baseline levels of ADMA during AMI. Furthermore, maintaining a normal weight should always be recommended, since obese patients are generally an at-risk group for AMI occurrence.[24]

Conclusion
Overall, all of the investigated marker concentrations seem to decrease on the 3rd post-admission day, probably as a result of patients’ clinical remission. In general, ADMA and SDMA are reported to affect AMI’s prognosis. Interestingly, interventional factors such as sleep duration, BMI, eating habits, physical condition seem to alter their concentration levels during AMI and, therefore, possibly influence prognosis via altering dimethylarginine levels. Larger confirmatory studies and future research could provide more details on these very significant findings and results.

Ethics approval
The study protocol was approved by the Scientific Committee of the General Hospital of Chalkida, Evia, Greece. Informed consent was obtained from all individual participants included in the study.

Consent to publish
All individual participants consented to the publication of the data obtained.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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