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Luis Eduardo Del Moral , Claudia Lerma , Hector González-Pacheco , Alan Cristhian Chávez-Lázaro , Felipe Massó , Emma Rodriguez *

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Article

Correlation of Plasmatic Amyloid Beta Peptides (Aβ-40, Aβ-42) with Myocardial Injury and Inflammatory Biomarkers in Acute Coronary Syndrome

Luis Eduardo Del Moral [1], Claudia Lerma [1], Hector González-Pacheco [3], Alan Cristhian Chávez-Lázaro [1], Felipe Massó [1] and Emma Rodriguez [1, *]

[1] Translacional Research Unit, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City 14080, Mexico; luisdelmoral.contact@gmail.com (L.D.M.); alancristhianchavezlazaro1@gmail.com (A.C.-L.) f_masso@yahoo.com (F.M.); emarod2@yahoo.com.mx (E.R.)

[2] Department of Molecular Biology, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City 14080, Mexico; dr.claudialerma@gmail.com

[3] Coronary Care Unit, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City 14080, Mexico 2; hectorglezp@gmail.com

* Correspondence: emarod2@yahoo.com.mx

Abstract: Ischemic heart disease is the leading cause of mortality worldwide. There is evidence of the participation of Aβ in thrombosis and clinical manifestations of acute coronary syndromes. In this study, we investigated the correlation of Aβ peptides with myocardial injury and inflammation biomarkers in acute coronary syndrome. This is a single-center, cross-sectional, observational, and correlation study that included 65 patients within the first 12 hours after symptom onset (chest pain, shoulder pain, or chest discomfort) with ST-elevation and non-ST elevation myocardial infarction who were admitted in the Coronary Care Unit, biochemical parameters of Aβ peptides levels were evaluated. Our results show that NSTEMI patients had a higher prevalence of hypertension, diabetes, smoking, and prior myocardial infarction when compared to STEMI patients. We observed a higher level of Aβ-42 in NSTEMI, but no difference in Aβ-40 levels. We also found a correlation between age and NT-proBNP with both Aβ peptides (Aβ-40, Aβ-42) in both groups. In this analysis, NSTEMI patients had higher prevalence of cardiovascular risk factors. Considering the toxic properties of Aβ-42 in coronary endothelial cells and cardiomyocytes, this peptide may be useful in risk stratification scores in patients with NSTEMI.

Keywords: acute myocardial infarction; beta amyloid; Aβ-42; Aβ-40; NT-proBNP

1. Introduction

Ischemic heart disease is considered the leading cause of mortality worldwide and the main cause of disease burden in developed countries, accounting for nearly 9.4 million deaths in 2021[1,2]. Acute coronary syndromes encompass a spectrum of conditions that include ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA)[3,4]. Coronary thrombus development in vulnerable atherosclerotic plaque is the primary cause of acute coronary syndrome; nevertheless, a considerable number of patients undergoing ACS may be caused by plaque erosion, calcific nodules, coronary spasm, and spontaneous coronary artery dissection[5,6] [5,6].

Beta amyloid (Aβ) is a peptide with a length of 37-49 amino-acids that are produced by the excision of the amyloid precursor peptide (APP) [7,8]. Aβ-40 and Aβ-42 are the primary isoforms found in vascular lesions and parenchymal lesions in the brain [9]. An experimental study has demonstrated an early peak of soluble amyloid precursor peptide (sAPP) preceded the liberation of myocardial injury enzymes [10]. There is evidence of the participation of Aβ in thrombosis [11] and clinical manifestations of acute coronary syndrome [12]. Furthermore, Aβ-40 stimulates the activation

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and adhesion of platelets [13–16] and can induce the release of matrix metalloproteinases (MPP) by monocytes, increasing the vulnerability of the plaque [17]. Moreover, Aβ-42 affects coronary endothelial cells and cardiomyocytes, reducing mitochondrial respiration and disruption of fatty acid metabolism in both cell types [18]. However, there are limited studies that addressed the circulating levels of these peptides and conventional biomarkers in ST-elevation and non-ST myocardial infarction. In this study, we investigated the correlation of Aβ peptides with myocardial injury and inflammation biomarkers in acute coronary syndrome.

2. Materials and Methods

2.1. Study Population

This single-center, cross-sectional, observational, and correlation study included patients within the first 12 hours after onset of symptoms (chest pain, shoulder pain, or chest discomfort) with acute coronary syndrome who were admitted to the Coronary Care Unit at the Instituto Nacional de Cardiología Ignacio Chávez from Mexico City. Patients' exclusion criteria were as follows: patients with a history of renal disease, liver failure, autoimmune or autoinflammatory disease, and malignant or hematological disorders. Patients with inadequate blood sample volume to evaluate Aβ peptide (Aβ-42, Aβ-40) concentration, a period of more than 180 minutes between the collection of blood sample and storage at -80° C or those who wish to withdraw consent were eliminated.

The institutional Research and Ethics committees approved the study (protocol number 21-1275) in compliance with principles outlined in the Helsinki Declaration. Informed oral and written consent was given by all the subjects participating in this study.

2.2. Sample Size Determination

There are no previous studies on the association between the plasmatic levels of Aβ peptides (Aβ-42 and Aβ-40) and biomarkers of myocardial injury or inflammation in patients with acute coronary syndrome. Therefore, we proposed an expected minimal Pearson correlation coefficient between Aβ peptides (Aβ-42, Aβ-40) and myocardial injury or inflammation biomarkers of 0.3. Assuming a unilateral alfa risk of 0.05 and a statistical power of 80%, we estimated a necessary sample size of 68 subjects.

2.3. Data Collection

The patients' hospital charts and electronic medical history were reviewed to obtain all clinical data from patients. Clinical characteristics included age, sex, body mass index (kg/m), presence of diabetes, hypertension, dyslipidemia, previous myocardial infarction, smoking status, New York Heart Association (NYHA) class, Killip-Kimball class, Global Registry of Acute Coronary Events (GRACE) score, Thrombolysis In Myocardial Infarction (TIMI) score for ST-elevation myocardial infarction (STEMI), TIMI score for unstable angina / non-ST elevation myocardial infarction (UA/NSTEMI) score, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcome with Early implementation of the American College of Cardiology/ American Heart Association Guidelines (CRUSADE) score, left ventricular ejection fraction (LVEF %). We also gathered time parameters (minutes) such as symptom-to-door, symptom-to-blood sample (*time between symptom onset and blood sample collection*), door-to-electrocardiogram (ECG), door-to-needle, door-to-balloon, and symptom-to-catheter.

Biochemical values obtained from the electronic medical history included high sensitivity troponin I (hs-cTnI [pg/ml]), N-terminal pro-B natriuretic peptide (NT-proBNP [pg/ml]), high sensitivity c reactive protein (hs-CRP [mg/dl]), total cholesterol (mg/dl), high-density lipoprotein (HDL [mg/dl]), low-density lipoprotein (LDL [mg/dl]), triglycerides (mg/dl), atherogenic index of plasma (AIP), albumin (g/ml). In addition, we quantified plasmatic levels of Aβ-42 (pg/ml), Aβ-40 (pg/ml), and Aβ-42/40 ratio from a blood sample.

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2.3. Assessment of Plasmatic Aβ Peptides (Aβ-42, Aβ-40)

Peripheral blood from subjects was obtained in a 4 ml BD K2EDTA Vacutainer tube. The blood was then centrifuged (1500 rpm, 15 min at 4 °C) and plasma was collected and stored in 200 µL aliquots at -80 °C until Aβ peptide analysis.

After thawed at room temperature, plasmas were used to measure Aβ-42 and Aβ-40 levels with High Sensitivity Human Amyloid Aβ-42 ELISA Kit (EMD Millipore) and High Sensitivity Human Amyloid Aβ-40 ELISA Kit (EMD Millipore) following the manufacturer's instructions. Absorbance measurements were taken using an imaging reader (Cytation 3, BioTek) at 450 nm and 590 nm. The measurement range was 16-500 pg/ml for Aβ-42 and Aβ-40. The intra- and inter-assay coefficients of variation of ELISA kits were <10%. No cross-reactivity was observed between Aβ-42, Aβ-40 antibodies.

2.4. Statistical Methods

Categorical variables are presented as frequencies and percentages. Comparisons were made using the chi-squared test or Fisher´s exact test. The normal distribution of continuous variables was tested using the Kolmogorov-Smirnov method. Continuous variables with normal distribution are described as mean ± SD and were compared using the Student´s t-test. Otherwise, the Mann-Whitney's U test was used, and variables were described as median (percentile 25 – percentile 75). We calculated the correlation between Aβ peptides (Aβ-42, Aβ-40) and continuous variables with the Pearson correlation test or Spearman correlation test as applicable. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Overall Patient Characteristics and Demographics

The study sample included 65 patients, with a mean age of 59 ± 13 years. Fifty-one patients (78.5%) were male. Fifty-nine patients (90.8%) had at least one SMuRF (standard modifiable cardiovascular risk factor). The number of patients with risk factors were: arterial hypertension 42 (64.6%), diabetes mellitus 14 (21.5%), dyslipidemia 12 (18.5%), smoking 44 (67.7%), and previous myocardial infarction 27 (41.5%).

Ten patients (15.%) had an NYHA two and above class, 14 (21.5%) with a Killip-Kimball two and above class, 40 (61.53%) with an intermediate-high risk GRACE score, 42 (64.61%) with an intermediate-high risk TIMI score, 29 (44.6%) with a moderate-high risk CRUSADE score, 19 (30.6%) patients had mid-range LVEF (left ventricular ejection fraction), and 15 (24.2%) with reduced LVEF. The mean symptom-to-door time was 339 ± 191 minutes, symptom-to-blood sample time was 390 ± 194 minutes, and symptom-to-catheter time was 2147 ± 2203 minutes.

Biochemical levels of Aβ-42 were 38.39 (35.39-43.63) pg/ml, Aβ-40 176.20 ± 79.35 pg/ml, Aβ-42/40 ratio was 0.25 (0.20-0.31), hs-cTnI was 333.0 (67.10-1617.0) pg/ml, NT-proBNP was 342.0 (111.0-975.0), hs-CRP was 4.57 (2.26-9.50) mg/dl, albumin was 4.04 ± 0.48 g/dl, total cholesterol 165.0 ± 40.7 mg/dl, triglycerides was 157.1 ± 63.3 mg/dl, HDL was 37.6 ± 8.3 mg/dl, LDL was 106.5 ± 38.1 mg/dl, and AIP was 0.23 ± 0.21.

3.2. Aβ Peptides Correlation Analysis

We analyzed the data recovered from our constructed database and Spearman's correlation test was applied. Table 1 shows the correlation between Aβ-42, Aβ-40 and Aβ-42/40 ratio with our study variables. We found a positive correlation between Aβ-42 and Aβ-40 with age, Aβ-42 and Aβ-40 with NT-proBNP, and Aβ-40 with ≥1 SMuRF. Conversely, we found a negative correlation between Aβ-42 and albumin, and Aβ-42/40 Ratio with ≥1 SMuRF ($\rho = -0.251$, $p = 0.044$). There was no correlation with statistical significance between Aβ-42, Aβ-40, Aβ-42/40 ratio and other biochemical variables such as hs-cTnI, hs-CRP, albumin, total cholesterol, HDL, LDL, triglycerides, AIP.

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Table 1. Shows the correlation between our study variables and Aβ peptides (Aβ-42, Aβ-40), Aβ-42/40 ratio in patients with acute coronary syndrome. Data was analyzed using Spearman's correlation test.

Variable	Aβ-42 (pg/ml)		Aβ-40 (pg/ml)		Aβ-42/40 ratio	
	Rho	p-value	Rho	p-value	Rho	p-value
Age (years)	0.303	0.014	0.389	0.001	-0.224	0.073
BMI (Kg/m²)	-0.050	0.694	-0.084	0.507	-0.031	0.805
One or more SMuRF	0.167	0.184	0.298	0.016	-0.251	0.044
High sensitivity troponin I (pg/ml)	-0.021	0.869	0.063	0.617	-0.142	0.260
CRP (mg/dl)	0.073	0.584	0.174	0.190	-0.155	0.247
NT-proBNP	0.417	0.001	0.374	0.002	-0.129	0.305
Albumin (g/dl)	-0.284	0.048	-0.173	0.234	0.048	0.741
Total cholesterol (mg/dl)	-0.153	0.274	-0.089	0.526	0.061	0.664
HDL (mg/dl)	-0.005	0.972	0.061	0.657	-0.043	0.757
LDL (mg/dl)	-0.147	0.285	-0.096	0.484	0.090	0.515
Triglycerides	-0.074	0.611	-0.051	0.726	-0.051	0.725
AIP	-0.073	0.617	-0.079	0.585	-0.024	0.869
Symptom-to-blood sample[ǂ]	0.012	0.923	-0.142	0.259	0.049	0.697

[ǂ] Time between symptom onset and blood sample collection.

Figure 1 provides scatterplots wth marginal histograms to represent visually the correlation of Aβ-42, Aβ-40 and Aβ-42/40 with age, NT-proBNP and albumin. At first glance, we observed a right skewness in the distribution histograms of Aβ-42, Aβ-40, Aβ-42/40 ratio and NT-proBNP; additionally in the scatterplots of these variables some data points were extreme values regarding the main distribution and are considered outliers.

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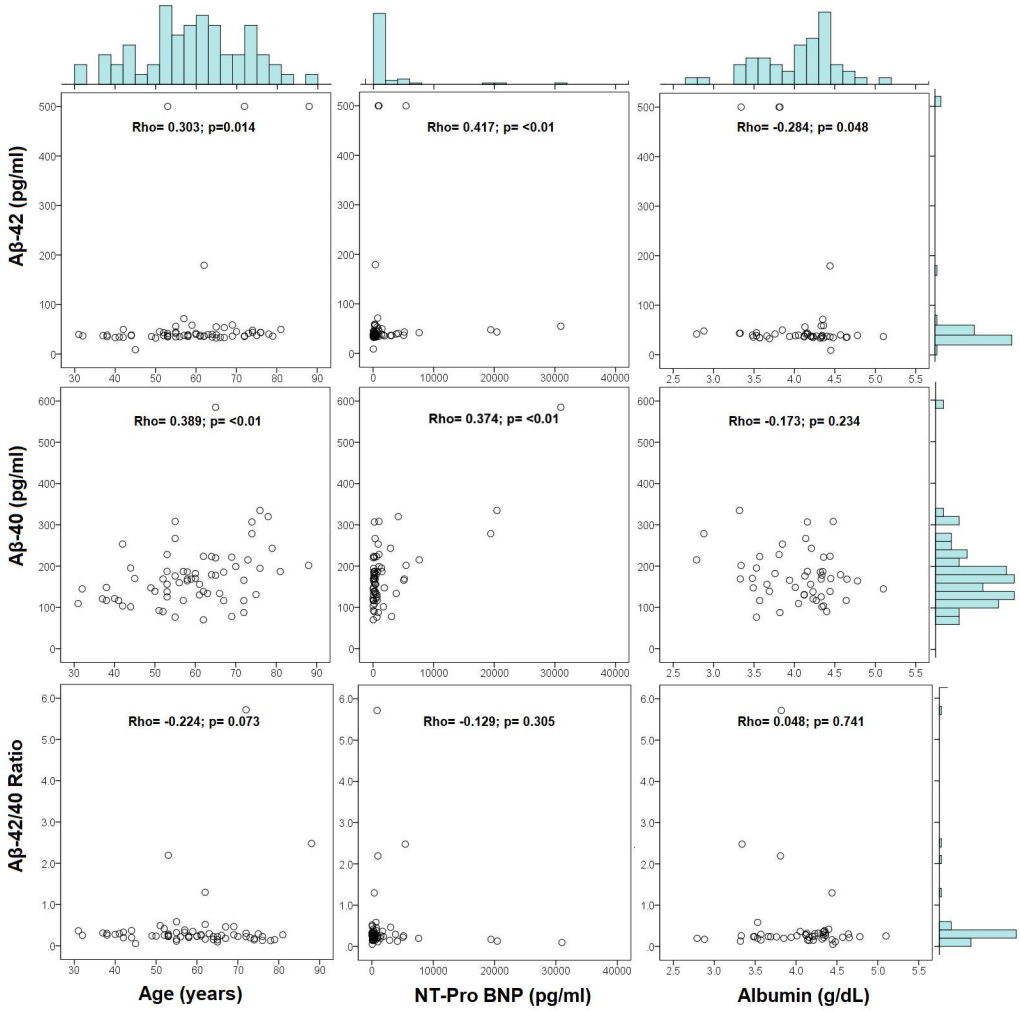

Figure 1. Scatterplot matrix and marginal histograms (with Spearman's correlation coefficients) showing the relation between **Aβ-42** vs age, NT-proBNP and albumin (top row); **Aβ-40** vs age, NT-proBNP and albumin (middle row); **Aβ-42/40 Ratio** vs age, NT-proBNP and albumin (bottom row).

Considering the potential heightened effect of these outliers in the correlation between our study variables, we established cut-off values and repeated the correlation analysis. Outliers were defined by Aβ-42 <20 pg/ml or >100 pg/ml, Aβ-40 >400 pg/ml, Aβ-42/40 ratio <1.0, and NT-proBNP >10,000 pg/ml. After this additional anallysis the positive correlation between Aβ-40 with age, Aβ-42 and Aβ-40 with NT-proBNP was maintained, in addition we observed a negative correlation between Aβ-42/40 ratio with age. The rest of the correlations were not statistically significant.This analysis is available in the supplementary material (Table S1, Figure S1)

3.3. Comparison of Demographic, Clinical and Biochemical Characteristics Between Groups

Table 2 presents the demographic and laboratory baseline characteristics. There were 34 patients in the STEMI group (52%), and 31 patients in the NSTEMI group (47%). We observed a higher prevalence of diabetes, hypertension, smoking, and previous myocardial infarction in the NSTEMI group compared to the STEMI group. When repeating this analysis without outliers, the higher prevalence of hypertension ($p = 0.046$), previous MI ($p = 0.01$) and smoking ($p = 0.005$) of the NSTEMI group when compared to the STEMI group was preserved. This data is available in the supplementary material (Table S2).

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Table 2. Demographic characteristics of 65 patients admitted to the coronary care unit grouped by ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI). Data is shown as mean ± standard, median (percentile 25 – percentile 75), and absolute value (percentage).

Variable	STEMI (N = 34)	NSTEMI (N = 31)	p value
Age (years)	58 ± 12	60 ± 12	0.503
Sex			
Male	29 (85.3%)	22 (71.1%)	0.135
Female	5 (14.7%)	9 (29.9%)	
Body mass index (Kg/m²)	28.28 ± 4.15	27.83 ± 3.70	
Overweight	14 (41.2%)	14 (45.2%)	0.652
Obesity	12 (35.3%)	9 (29.0%)	
Overweight/Obesity	26 (76.5%)	23 (74.0%)	
Diabetes	4 (11.8%)	10 (32.3%)	0.043
Hypertension	18 (52.9%)	24 (77.4%)	0.039
Dyslipidemia	6 (17.6%)	6 (19.4%)	0.859
Previous myocardial infarction	9 (26.5%)	18 (58.1%)	0.010
Smoking status			
Current smoker	16 (47.1%)	5 (16.1%)	0.003
Former smoker	6 (17.6%)	17 (54.8%)	
Nonsmoker	12 (35.3%)	9 (29.1%)	
Number of SMuRFs			
One or more	29 (85.3%)	30 (96.3%)	0.121
None	5 (14.7%)	1 (3.7%)	
NYHA			0.572
≥2 Class	5 (14.7)	5 (16.1%)	
Killip-Kimball			0.240
≥2 Class	9 (26.5%)	5 (16.1%)	
GRACE			0.583
Intermediate-High Risk	22 (64.7%)	18 (58.1%)	
TIMI			0.615
Intermediate-High Risk	21 (61.8%)	21 (67.7%)	
CRUSADE			0.559
Moderate-High Risk	14 (41.2%)	15 (48.4%)	
LVEF			
Mid-range ejection fraction	9 (27.3%)	6 (20.7%)	0.618
Reduced ejection fraction	11 (33.3%)	8 (27.6%)	
Symptom-to-door time (minutes)	392 ± 196	280 ± 171	0.018
Symptom-to-blood sample time (minutes)	418 ± 198	364 ± 193	0.221
Door-to-electrocardiogram time (minutes)	6 (5-8)	5 (5-7)	0.143
Door-to-balloon time (minutes)	508 (98-2377) (n = 31)	2030 (1085-3576) (n = 16)	0.001
Symptom-to-catheter time (minutes)	1700 ± 1889	3070 ± 2562	0.992

We observed no difference of hs-cTnI, NT-proBNP, hs-CRP, albumin, total cholesterol, triglycerides, HDL, LDL, and AIP between our study groups (Table 3).

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Table 3. Biochemical values from 65 patients admitted to the coronary care unit grouped by ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI). Data is shown as mean ± standard deviation or median (percentile 25 – percentile 75).

Variable	STEMI (N = 34)	NSTEMI (N = 31)	p value
Aβ-42 (pg/ml)	35.96 (34.27-39.14)	41.76 (38.99-47.75)	0.001
Aβ-40 (pg/ml)	169.38 ± 88.26	183.68 ± 68.96	0.472
Aβ-42/40 ratio	0.25 (0.21-0.30)	0.24 (0.20-0.38)	0.708
High sensitivity troponin I (pg/ml)	368.5 (67.1-4742.0)	249 (65.3-1299.0)	0.281
NT-proBNP (pg/ml)	257.5 (104.0-643.0)	516.0 (199.0-643.0)	0.097
High sensitivity CRP (mg/dl)	4.98 (2.47-9.50)	4.46 (1.63-10.40)	0.569
Albumin (g/dl)	4.14 ± 0.42	3.95 ± 0.52	0.149
Total cholesterol (mg/dl)	170.3 ± 43.7	157.5 ± 35.7	0.264
Triglycerides (mg/dl)	162.2 ± 65.8	149.4 ± 60.3	0.490
HDL (mg/dl)	38.65 ± 8.81	36.21 ± 7.65	0.285
LDL (mg/dl)	112.9 ± 41.4	98.1 ± 32.3	0.155
AIP	0.23 ± 0.23	0.23 ± 0.20	0.992

Regarding Aβ peptides, we observed (Figure 2) that circulating levels of Aβ-42 were higher in the NSTEMI group compared to the STEMI group (median level 41.76 [38.99 - 47.75] vs 35.96 pg/ml [34.27- 39.14]; p = 0.001). There was no evident difference in Aβ-40 and Aβ-42/ Aβ-40 Ratio between both groups (Table S3). Interestingly, when repeating this analysis without outliers (Table S4), the plasmatic levels of Aβ-42 were higher in the NSTEMI group compared to the STEMI group (median level 40.26 [37.64 – 45.13] vs 35.39 pg/ml [34.27-37.64]; p = 0.001), no difference between Aβ-42 and Aβ-42/40 Ratio when compared in both groups was found.

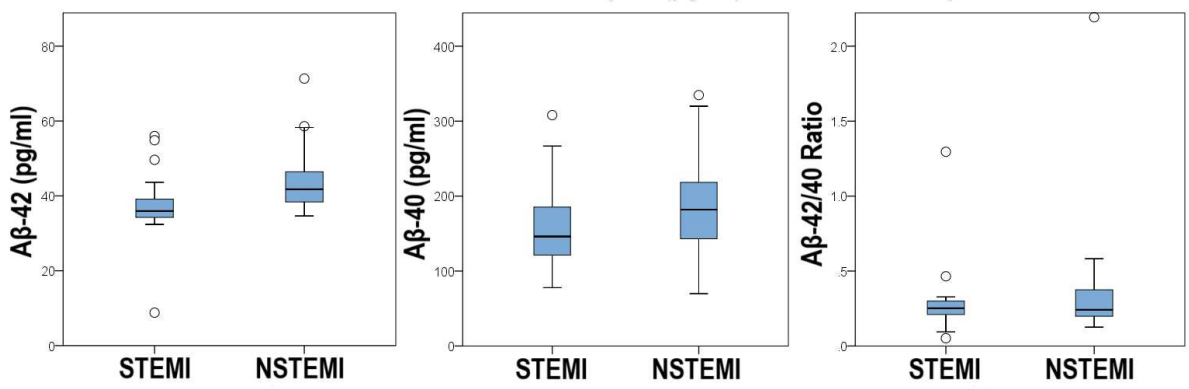

Figure 2. Box plot showing a comparison of circulating levels of Aβ-42, Aβ-40, and Aβ-42/40 between STEMI group (n=34) and NSTEMI group (n=31), p = <0.01.

3.4. Comparison of Aβ-42 and NT-proBNP with Cardiovascular Risk Factors

Table 3 shows the mean levels of plasmatic Aβ-42 and NT-proBNP between several cardiovascular risk factors incluiding: diabetes, hypertension, dyslipidemia, smoking, prior MI, and two or more SMuRFs. We observed higher levels of Aβ-42 in patients with hypertension compared to those without hypertension, plasmatic levels of Aβ-42 had a tendency to be higher in patients with diabetes, and prior MI when compared to patients without these risk factors. Conversely, Aβ-42 was higher in nonsmokers and without dyslipidemia when compared to those who smoked and had dyslipidemia.

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Table 3. Aβ-42 and NT-proBNP compared by the presence of cardiovascular risk factors including diabetes, hypertension, dyslipidemia, smoking, and prior myocardial infarction. Data is shown as median (percentile 25 – percentile 75). .

Variable	All subjects (N=65)			
	Aβ-42 (pg/ml)	p value	NT-proBNP (pg/ml)	p value
Diabetes				
Yes:	42.50 (36.51-47.75)	0.075	3978.0 (226.0-7611.0)	0.004
No:	37.64 (35.01-43.63)		277.0 (110.0-690.0)	
Hypertension				
Yes:	39.70 (36.51-49.62)	0.006	551.0 (181.0-1862.0)	0.056
No:	36.14 (34.64-39.51)		231.0 (110.0-522.0)	
Dyslipidemia				
Yes:	37.07 (35.58-39.13)	0.393	415.5 (76.7-1192.5)	0.819
No:	38.76 (35.39-44.38)		342.0 (125.0-974.0)	
Smoking				
Yes:	38.39 (35.39-43.25)	0.624	226.0 (99.0-975.0)	0.060
No:	38.57 (35.76-48.68)		642.5 (257.5-1125.0)	
Prior MI				
Yes:	40.26 (36.14-53.37)	0.066	516.0 (199.0-1862.0)	0.197
No:	37.45 (35.01-41.76)		257.5 (110.0-766.0)	
SMuRF				
≥One:	38.76 (35.76-45.13)	0.039	315.0 (110.0-978.0)	0.910
None:	35.01 (33.52-37.64)		470.0 (234.0-642.0)	

4. Discussion

The traditional classification of acute myocardial infarction (AMI) based on electrocardiogram findings (STEMI or NSTEMI) for the patient's initial management has led to a more guided approach to the different clinical presentations in the spectrum of acute coronary syndrome [4]. Even though STEMI and NSTEMI have been associated with similar pathophysiologic mechanisms sharing standard modifiable cardiovascular risk factors (SMuRFs) [19], they show different prevalence of these risk factors, including age.

Aβ peptides have been associated with peripheral atherosclerotic manifestations [20], vascular inflammation [9], myocardial dysfunction [21,22], mortality, and adverse cardiovascular outcomes [23,24]. Aβ-40 is related to subclinical cardiovascular disease and has been used for risk stratification in NSTE-ACS [22,25]. However, there are no studies on the role of Aβ-42 in STEMI and/or NSTEMI. We aimed to investigate the correlation between plasmatic levels of beta-amyloid peptides (Aβ-42, Aβ-40, Aβ-42/40 Ratio) with myocardial injury and inflammatory biomarkers in patients with acute coronary syndrome.

Our results showed that NSTEMI patients had different prevalence of risk factors and Aβ levels. We observed a greater prevalence of hypertension, diabetes, and previous myocardial infarction in NSTEMI when compared to STEMI. These findings were consistent with previous studies done in the US and Europe [26–28]. However, we also found that smoking was more prevalent in NSTEMI patients opposing the previously reported higher prevalence of smoking in STEMI patients. This difference could be explained because of the inclusion of former smokers in our study as part of the categorization of smoking status. The National Health Interview Survey defined former smokers as adults who had smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of the interview [29]. This additional subcategory was not clear in the aforementioned studies, so further research regarding the impact of former smokers as a risk factor is necessary.

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When comparing Aβ peptides (Aβ-40, Aβ-42) in patients with acute coronary syndrome, we found higher levels of Aβ-42 in the NSTEMI group. The cleavage of APP in endothelial cells [10], macrophages [29], platelets [14], and neurons [31] may be influenced by factors such as aging, ischemia, and inflammation [9]. This enhancement of APP/ Aβ processing and inadequate clearance may favor the accumulation of Aβ peptides in the bloodstream, vascular wall [9], and heart tissue [32]. Notably, in previous studies, STEMI patients had a higher mortality rate compared to NSTEMI, but this tendency changes at one- or two-year follow-up when mortality rates become similar between both groups [19]. This may be due to the greater prevalence of cardiovascular risk factors in NSTEMI and could be correlated with enhancing the APP / Aβ processing and residual inflammation overtime. To our knowledge, there is no evidence of what could modulate the final processing of APP to generate pathologic cleavage products and subsequently an inclination towards a specific length of Aβ (Aβ-40 or Aβ-42) in each of the different cell types. Platelets have a great importance in releasing circulating Aβ peptides [14] along with different pathways of activation in STEMI and NSTEMI, favoring thromboxane receptor and PAR1 pathways, respectively [33]. A recent report demonstrated that human platelets release higher levels of Aβ-42 from α granules in response to the combination of hypoxia and inflammation [34]. In myocardial infarction, platelet activation precedes coronary thrombosis. Therefore, further studies exploring the production or storage Aβ-42 in these phenotypically different platelets may add value to the usage of Aβ peptides in risk stratification.

We also found a correlation between age and NT-proBNP with both Aβ peptides (Aβ-40, Aβ-42), but albumin only correlates with Aβ-42. Aβ peptide production and clearance can be affected by age-related mechanisms. Neprilysin (NEP) is a metallo-endopeptidase that degrades several bioactive peptides including Aβ peptides [35], there is evidence that supports the hypothesis that aging can reduce NEP activity thereby leading to Aβ accumulation [8]. Furthermore, neuronal aging can increase APP endocytosis consequently enhancing Aβ production [36]. A study reported that plasmatic levels of Aβ-42 in cognitively and neurological normal individuals increase with age. However, these levels stabilize after age 65 [37]. With the additional correlation analysis, by excluding potential outliers only the correlation between Aβ-40 with age was conserved.

The use of circulating natriuretic peptides (NPs), including BNP and NT-proBNP, as clinical biomarkers revolutionized the early recognition of patients with heart failure and ruled out other causes of dyspnea [38], as well as risk stratification after acute myocardial infarction. [39]. NPs are secreted by cardiomyocytes through different pathways mainly stimulated by myocardial stretching, neurohormones (endothelin 1 and angiotensin II) and circulating cytokines (IL-1β or TNF), which involve $G_o\alpha$, $G_q\alpha$ or p38 activation [35]. The novel finding of this study is the association of Aβ-42 with NT-proBNP in patients with ongoing acute coronary syndrome. Focusing research on Aβ-42 in acute coronary syndrome in further studies could help explore the underlying participation of this peptide in cardiovascular disease. A study found that plasma Aβ-40 was associated with NT-proBNP, suggesting that Aβ-40 could be involved in early subclinical rise in filling pressure in the general population without overt coronary cardiovascular disease [22]. Moreover, circulating Aβ-40 is a predictor of mortality and can improve risk stratification of patients with NST-ACS over GRACE score [25].

Our results show a negative correlation between Aβ-42 and albumin. Serum albumin has an important role in balancing Aβ peptides between brain and blood plasma due to its capability of binding. A study found that low serum albumin may increase amyloid accumulation in patients with Alzheimer's Disease [40]. Although, the regulation of Aβ peptides by albumin in cardiovascular disease has not yet been investigated.

On the other hand, we did not find a correlation between Aβ peptides (Aβ-40, Aβ-42) and high sensitivity troponin I (hs-cTnI). Cardiac troponin I can be detected in serum early after the onset of acute myocardial infarction and usually peak levels are reached after 12-48 hours [41]. Therefore, the timing of the blood sample could have an influence on this association. A study explored the changes in cardiac troponins I and T beyond the initial hours of symptom onset. They found a peak concentration of 6-12 hours for cTnI and 12-18 hours for cTnT from initial sampling. However, the time between symptom onset and initial sampling is not clear [42].

Finally, there was no correlation between Aβ-42 and high sensitivity C Reactive Protein (hs-CRP) in our population. There is limited information regarding this with ongoing acute coronary syndrome. However, a previous study reported no association between higher levels of CRP and Aβ-42 in cerebral small vessel disease [43].

Our study has some limitations. Firstly, we estimated a population size sample of 68 subjects which is relatively small and will need to be applied in a larger cohort. Secondly, our study groups were predominantly male and older age adults. Therefore, our findings may need further validation and should not be generalized in female subjects and younger populations. Thirdly, due to the cross-sectional nature of our study, we only assessed Aβ peptide, cardiac injury, and inflammatory biomarkers at the admission of patients who arrived in the first 12 hours of symptom onset, although serial determinations of these biomarkers were not part of our objective, further studies regarding the kinetics of these biomarkers are needed. Nevertheless, our results were the first to explore plasmatic levels Aβ-42 with conventional biomarkers in acute coronary syndrome. Additional longitudinal studies are required to determine whether the association of NT-proBNP and both Aβ peptides (Aβ-40, Aβ-42), together with additional echocardiographic measurements may provide insight into heart failure after myocardial infarction.

5. Conclusions

This present study demonstrates the correlation between Aβ-42 and NT-proBNP in patients with ST-elevation and non-ST elevation myocardial infarction. The plasmatic levels of Aβ-42 are higher in NSTEMI when compared to STEMI. Considering the toxic properties of Aβ-42 in coronary endothelial cells and cardiomyocytes, this peptide may be useful in risk stratification scores in patients with NSTEMI. Further longitudinal studies may clarify the role of Aβ-42 in high-risk patients with ongoing acute coronary syndrome.

Supplementary Materials: The following supporting information can be downloaded at: Preprints.org, Figure S1: title; Table S1: title; Video S1: title.

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