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Evaluation of pathogenicity-related oxidative stress biomarkers as well as clinical characteristics, management, and outcomes in acute coronary syndrome

Ph.D. Thesis booklet

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1. Introduction

Acute coronary syndrome (ACS) describes a broad spectrum of clinical symptoms compatible with acute myocardial ischemia, from unstable angina to non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI)(Kumar & Cannon, 2009; Zakaria et al., 2018). These symptoms are consequences of partial or complete thrombus formation related to the rupture of coronary atherosclerotic plaques. Reactive oxygen species (ROS) play a vital role in vascular inflammation during atherogenesis, from the onset of fatty streak development to plaque rupture (Bonomini et al., 2008). ROS or free radicals can be any chemical species (atom, ion, or molecule) that contains a single, unpaired electron in its outer orbit conferring very high reactivity; examples include hydrogen peroxide (H_2O_2), singlet oxygen ($1O_2$), superoxide radical ($O^{\bullet -}_2$), and hydroxyl radical (•OH)(Lee & Song, 2009; Leiris et al., 2006; Misra et al., 2009; Nita & Grzybowski, 2016).

Oxidative stress refers to conditions caused by an imbalance between ROS and antioxidant systems, in which either excessive amounts of free radicals are produced or the antioxidant capacity is decreased; such conditions can result in the oxidation of proteins, lipids, carbohydrates, and DNA (Lee & Song, 2009; Leiris et al., 2006; Misra et al., 2009). Under conditions of oxidative stress in which the levels of free radicals are elevated, hydroxyl radicals can oxidize the benzyl ring of phenylalanine (Phe), producing various tyrosine (Tyr) isomers (meta-tyrosine, ortho-tyrosine, and para-tyrosine; m-, o-, and p-Tyr). These Tyr isomers differ, depending on the location of the hydroxyl group on the benzyl ring (Ipson et al., 2019; Ipson & Fisher, 2016; Molnár et al., 2016). According to previous studies(Ipson et al., 2019; Ipson & Fisher, 2016; Molnár et al., 2016), Phe can be enzymatically transformed into physiological p-Tyr. Additionally, p-Tyr can also be nonenzymatically produced by reactions involving hydroxyl radicals during oxidative stress. However, the enzymatically produced p-Tyr is more plentiful than the free radical-derived p-Tyr. Therefore, p-Tyr is viewed as the physiological isoform (Ipson et al., 2019; Ipson & Fisher, 2016; Molnár et al., 2016).

Furthermore, in humans, m- and o-Tyr amino acids cannot be formed enzymatically; instead, they are produced as a result of the reaction between the hydroxyl free radical and the benzyl ring of Phe. Therefore, m-Tyr and o-Tyr are viewed as free radical markers (Ipson et al., 2019; Ipson & Fisher, 2016; Molnár et al., 2016), which may play a role in chronic inflammation during the initiation and progression of ACS (Kun et al., 2015; Szélig et al., 2016).

2. Aims

The overall aim was to evaluation of pathogenicity-related oxidative stress biomarkers as well as clinical characteristics, management, and outcomes in acute coronary syndrome.

The specific aims of my study are the following:

2.1. Serum concentrations of phenylalanine and tyrosine isomers in patients with acute coronary syndrome (I.).

- We aimed to examine the association of Phe and Tyr isomers (*m*-, *o*-, and *p*-Tyr) with oxidative stress following myocardial injury.

2.2. Assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation versus non-ST-segment elevation myocardial infarction (II.).

- We aimed to compare patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) and the serum levels of Phe and Tyr isomers at the aortic root and distal to the culprit lesion in both groups.

2.3. Comparison of baseline characteristics, clinical management and outcomes for patients with acute coronary syndrome (III.).

- We aimed to describe current characteristics of patients admitted for ACS in Hungary compared to Iraq and to analyses whether in-hospital and 30 days post discharge outcomes variations are explained by differences in patients' baseline characteristics and clinical management.

3. Materials and Methods

3.1. Main study: Serum concentrations of phenylalanine and tyrosine isomers in patients with acute coronary syndrome (I.) and assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation versus non-ST-segment elevation myocardial infarction (II.)

***Study population*:** In connection with our examinations regarding serum concentrations of phenylalanine and tyrosine isomers in patients with acute coronary syndrome (I.), a cohort of 44 patients (11 men, 33 women) admitted to the Department of Interventional Cardiology of the Heart Institute of Pécs University Clinical Center (Pécs, Hungary) were part of this case-control study of ACS patients. Patients aged 30 years and older with confirmed diagnosis of STEMI or NSTEMI were included. The exclusion criteria comprised the lack of serum samples of adequate volume or an uncertain diagnosis of ACS. None of the ACS patients had inflammatory disease or cancer that could impact the tyrosine isomer concentration. Control serum samples were obtained by collecting blood from 26 healthy volunteers who were healthcare workers at the same Heart Institute mentioned above, with a gender distribution of 11 men and 15 women. A biobank similar to that of ACS patients was obtained by selecting volunteers aged 25-72 years. None of the volunteers had cardiovascular disease, risk factors of CAD, or used immunosuppressive drugs. In connection with our examinations regarding assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation versus non-ST-segment elevation myocardial infarction (II.), a prospective study was conducted on 44 patients diagnosed with ACS who were part of the above study.

Clinical and angiographic evaluation: In both studies, general medical history was collected and physical examinations, standard laboratory tests, and 12-lead electrocardiograms were performed in all patients upon admission. The type of ACS was assigned based on American Heart Association and American College of Cardiology guidelines (Amsterdam et al., 2014). The extent of coronary artery disease (CAD) was ascertained by coronary angiography and was categorized according to the number of coronary arteries with obstructive CAD (defined as angiographic stenosis of ≥50%) into 0-, 1-, 2- or 3-vessel disease.

Blood collection and laboratory analysis: In first study, blood samples were drawn from the aortic root and the radial artery for ACS patients, while for the control group, they were drawn by venipuncture. In second study, arterial blood samples were taken from the aortic root using a guiding catheter and from the culprit vessel segment distal from the primary lesion using an aspiration catheter, during the percutaneous coronary intervention. In both studies, serum was

obtained through centrifugation (3000 rpm, 10 min) and was stored at −80°C until further examination. Afterwards, 125 μL of trichloroacetic acid (Reanal Private Ltd., Budapest, Hungary) was added to 500 μL of serum and the samples were incubated on ice for 30 minutes. The precipitate was subsequently separated by centrifugation. The supernatant was filtered by a syringe filter (0.2 μm; Millipore, Billerica, MA, USA) before analysis. Serum *m*-Tyr, *o*-Tyr, *p*-Tyr, and Phe levels were determined using reversed-phase-high performance liquid chromatography (rp-HPLC), using a C18 silica column (250 × 4 mm) with isocratic sodium acetate/acetic acid as the mobile phase, on a Shimadzu LC-20 system (Shimadzu USA Manufacturing Inc., Canby, OR, USA) with fluorescence detection (Shimadzu, RF-10Axl; λ_{ex} = 275 nm/λ_{em} = 305 nm for Tyr, λ_{ex} = 258 nm/ λ_{em} = 288 nm for Phe), as described in more detail previously (Molnár et al., 2005). Concentrations of the compounds were calculated using an external standard, and in some cases, ratios of the individual amino acids were also used.

Ethics: Both studies were approved by the Regional and Institutional Research Ethics Committee (4511/2016) of the University of Pécs and were conducted in accordance with the ethical guidelines of the 2003 Declaration of Helsinki. All participants gave their informed consent.

Statistical analysis: SPSS software, version 22.0 (IBM Corporation, Armonk, New York, United States) was used for statistical analysis. Continuous variables were expressed as mean (SD) or median and interquartile range. Categorical variables were expressed as percentages or frequencies. Normal distribution was assessed with the Shapiro‑Wilk test. In first study, comparisons between the ACS patient and healthy controls were performed using the $\chi 2$ test for categorical variables, the t test for normally distributed continuous variables, and the Mann‑Whitney test for skewed continuous variables. In second study, differences between the STEMI and NSTEMI groups were assessed using the $\chi 2$ test for categorical variables, the t test for normally distributed continuous variables, and the Mann‑Whitney test for skewed continuous variables. For pairwise comparisons of each group, the Wilcoxon test was used, depending on the normal distribution. In both studies, to assess the correlation between the amino acid parameters and baseline characteristics of patients with ACS, we used the Spearman's rho test. P values of less than 0.05 were considered statistically significant.

3.2. Sub-study: Comparison of baseline characteristics, clinical management and outcomes for patients with acute coronary syndrome (III.)

Study population: A prospective cohort study was conducted at two cardiac centers between May 1, 2018, and May1, 2019. The study included 164 ACS patients; 64 patients from the Pécs

Heart Institute in Hungary and 100 patients from Al-Nasiriyah Heart Center in Iraq. The study complies in accordance with the ethical guidelines of the Declaration of Helsinki 2003, and was approved by the local ethical committee of the Doctoral School of Health Sciences of the University of Pécs and Dhi-Qar health director/Al-Nasiriyah Heart Center. Written consent was obtained from each patient after they were informed clearly about the details of the study. The diagnosis of ACS was defined as follows: STEMI and NSTEMI/UA. ACS diagnosis was based on ESC and AHA/ACC guidelines (Amsterdam et al., 2014; Arnett et al., 2019; Collet et al., 2021; Roffi et al., 2016). Specifically, present chest pain, changes in the ECG and levels of cardiac biomarkers.

Patient characteristics, management and outcomes: Baseline variables of study interest include: demographic data (age and gender), risk factors (smoking, DM, HT, dyslipidemia and family history of CAD, previous medical history (prior UA, prior MI, prior renal failure, prior PCI and prior CABG. Key hospital presentation variables included symptom onset, heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) on arrival, creatinine levels, troponin levels, and ejection fraction (EF); in-hospital clinical management variables included angiography, PCI and CABG; in-hospital and 30 days post discharge outcomes.

Statistical analysis: SPSS software, version 22.0 (IBM Corporation, Armonk, New York, United States) was used for statistical analysis. Continuous variables were expressed as mean (SD) or median and interquartile range. Categorical variables were expressed as percentages or frequencies. Differences between the two countries were assessed using the $\chi 2$ test for categorical variables, the t test for normally distributed continuous variables, and the Mann-Whitney test for skewed continuous variables. Univariate multivariate logistic regression was performed to assess for predictors of in-hospital and 30 days post discharge major adverse cardiovascular events (MACE, defined as death, re-infarction and stroke). We included covariates from the Global Registry of Acute Coronary Events (GRACE) Risk Model to serve as the basis of our investigation into potential in- and post-hospital targets for intervention. P values of less than 0.05 were considered statistically significant.

4. Results

4.1. Results of serum concentrations of phenylalanine and tyrosine isomers in patients with acute coronary syndrome (I.)

A comparison of baseline characteristics and amino acid parameters for ACS patients showed no significant differences between the STEMI and NSTEMI subgroups; therefore, ACS patients were treated as a single group. Similar results have been published previously(Al- Sadoon et al., 2021). Gender distribution did not differ significantly between ACS patients and healthy controls (men /women, 11/33 vs 11/15, respectively; $P = 0.13$), but the mean age was significantly higher in the ACS group (mean [SD], 68.1 [9.4] years vs 47.5 [12.7] years, respectively; $P = 0.02$). Our data showed that while serum phenylalanine concentrations did not differ between ACS patients and controls, serum *p*-Tyr levels were significantly lower in the ACS group than in controls (median, 34.9 vs 54.1 μmol/l; $P < 0.001$). Serum *m*-tyrosine concentrations were significantly higher in ACS patients than in controls (median, 14.6 vs 6.1 nmol/l; $P < 0.001$), whereas serum *o*-tyrosine concentrations did not differ between the two groups. Moreover, the serum *p*-tyrosine/ phenylalanine ratio was lower in ACS patients compared with controls (median, 0.9 vs 1.4 μmol/μmol; $P <0.001$). In contrast, the serum *m*-tyrosine/ phenylalanine ratio was higher in ACS patients compared with controls (median, 0.3 vs 0.1 nmol/μmol; $P <0.001$). When comparing serum *p*-tyrosine/ phenylalanine ratios from our recalculated data on different illnesses, we found that this ratio was significantly lower in all patients compared with controls. In both ACS patients and controls, no gender differences were found for phenylalanine or *p*-, *m*-, or *o*-tyrosine. None of these amino acid parameters were correlated with age in either group. Moreover, creatinine levels and estimated glomerular filtration rates were not significantly correlated with either phenylalanine or *p*-, *m*-, or *o*-tyrosine in ACS patients. Serum *m*-tyrosine levels did show a positive correlation with *p*-tyrosine/ phenylalanine ratios in different vessel segments.

4.2. Results of assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation versus non-ST-segment elevation myocardial infarction (II.).

Forty-four patients were included in the study: 23 with STEMI and 21 with NSTEMI. The mean age of the participants was 68.1 ± 9.4 years, and most were female (75.0%). A previous history of hypertension, smoking, and diabetes mellitus was found for 79.5%, 38.6%, and 36.4% of the patients, respectively. Moreover, most patients (84.1%) had one-vessel disease. There was no significant difference in smoking, diabetes mellitus, and extent of CAD, with the exception of

hypertension, between patients with STEMI and NSTEMI. Serum Phe levels were significantly higher distal to the culprit lesion than at the aortic root (44.7 vs. 35.5 μmol/L, P = 0.002) in patients with STEMI. Serum p-Tyr/Phe and m-Tyr/Phe ratios were significantly lower distal to the culprit lesion than at the aortic root (0.7 vs. 0.9 μmol/μmol, P = 0.024; 0.1 vs. 0.4 nmol/μmol, P = 0.018, respectively) in patients with STEMI. There were no statistically significant differences with respect to changes in serum levels of Phe and Tyr isomers distal to the culprit lesion compared to the aortic root in patients with NSTEMI. There were no significant differences between patients with STEMI and NSTEMI with regard to serum levels of Phe and Tyr isomers, whether distal to the culprit lesion or at the aortic root. We examined the associations of the amino acid parameters with demographics and clinical data for patients, according to their diagnoses. Subject age, gender, smoking status, hypertension, and diabetes mellitus all failed to show any significant correlation with amino acid parameters at the aortic root or distal to the culprit lesion in patients with STEMI and NSTEMI. Serum m-Tyr levels at the aortic root showed a negative correlation with the extent of CAD in patients with NSTEMI (rho = –0.446, r2 = 0.096; P = 0.043), whereas there was no significant correlation in patients with STEMI (rho = –0.236-, r2 = 0.050; P = 0.129).

4.3. Results of comparison of baseline characteristics, clinical management and outcomes for patients with acute coronary syndrome (III.)

The overall demographic and clinical characteristics of patients in the two countries showed some similarities, but there were many notable differences. The patients were younger in Iraq (61 vs. 68 years, P=0.001) and often had a family history of CAD (9.4% vs 24.0%, P=0.018) than those in Hungary. Conversely, Hungarian patients more often had hypertension (89.1% vs. 68.0%, P=0.002), dyslipidemia (64.1% vs. 42.0%, P=0.006), prior MI (98.4% vs. 24.0%, P=0.000), prior PCI (92.2% vs. 23.0%, P=0.000) and prior CABG (21.9% vs. 1.0%, P=0.000) than Iraqi patients. As regards clinical characteristics at admission, Iraqi patients were more often presented with typical chest pain (96.0% vs. 82.8%, P=0. 004), higher creatinine levels (85.0 vs. 75.0 μmol/L, P=0. 005) than Hungarian patients. By contrast, Hungarian patients were more often presented with higher diastolic blood pressure (90 vs. 80 mm Hg, P=0.020) than Iraq patients. Overall, Iraqi patients were more often diagnosed with STEMI (64.0% vs. 26.6%). In contrast, Hungarian patients were more often diagnosed with NSTEMI (73.4% vs. 36.0%). Concerning management strategies overall, PCI was performed more often in Hungary (92.2% vs. 70.0%, P=0.001) than in Iraq. Likewise, CABG was performed in Hungary (10.9% vs. 0.0 %, P=0.001) while not performed in Iraq. With regard reperfusion therapy for patients diagnosed

with STEMI, primary PCI has also been performed more frequently in Hungary (94.1% vs. 71.9%, P = 0.048) than in Iraq. During hospital admission, there were no statistically significant differences between Hungary and Iraq in relation to mortality rate (6.3% vs. 3.0%; respectively), cardiogenic shock (7.8% vs. 5.0%, respectively), stroke (0.0% vs. 2.0%, respectively) and MACE (14.1% vs. 11.0%, respectively). However, Hungarian patients had a higher rate of in-hospital re-infraction (14.1% vs. 4.0%, P=0. 020) than Iraqi patients. There were no statistically significant differences when comparing out-hospital events between Hungary and Iraq with regard mortality rate (1.7% vs. 3.1%, respectively), re-infraction (8.3% vs. 13.4%, respectively), cardiogenic shock (0.0% vs. 3.1%, respectively), stroke (6.3 % vs. 2.0 %, respectively), and MACE (15.0% vs. 13.5%, respectively). Patients presenting with STEMI had a higher risk of in-hospital MACE [odds ratio (OR), 95% confidence interval = 0.087, 95% CI 0.020 to 0.376, P= 0.001] and 30 days post discharge MACE (OR = 0.308, 95% CI 0.101 to 0.937, P= 0.038) than patients presenting with NSTEMI/UA. Furthermore, symptom onset to presentation >6 hr was associated with both in-hospital MACE (OR = 1.858, 95% CI 0.556 to 6.215, P= 0.021) and 30 days post discharge MACE (OR = 1.143, 95% CI 0.395 to 3.309, P= 0.018).

5. Discussion

5.1. Serum concentrations of phenylalanine and tyrosine isomers in patients with acute coronary syndrome (I.)

In the present study, we found that the serum *p*-tyrosine concentration and the *p*-tyrosine/ phenylalanine ratio were both lower in ACS patients compared with controls. Similar results were described in patients with diseases associated with inflammation and immune activation, such as sepsis, diabetes, and renal failure as well as in burn patients(Kovacs et al., 2020; Kun et al., 2014; Molnár et al., 2005; Szélig et al., 2016). It is worth noting that there are several possible explanations for the existence of lower serum *p*-Tyr levels in patients. One possible explanation is that the levels of the precursor phenylalanine were low. In the current study, we found that serum phenylalanine levels in our patients were not lower than those of the controls. This finding helped exclude the possibility that lower levels of phenylalanine precursors were the primary cause for the lower serum levels of *p*-Tyr. Another possible explanation has to do with impaired renal synthesis of serum *p*-Tyr (Szélig et al., 2016). In previous studies, it has been reported that low serum *p*-Tyr levels caused by low PAH activity are mainly recognised in patients with severe impairment of glomerular function (Szélig et al., 2016). In our study, no correlation could be found between serum creatinine levels and serum *p*-Tyr levels (data not shown). This finding suggests that at this phase of renal damage, lower *p*-Tyr levels could occur

without severe impairment of glomerular function. A third possible explanation is that lower serum p-Tyr levels-caused by reduced PAH activity-could be a result of a deficiency of the enzyme cofactor BH4 which is used in the enzymatic reaction (Szélig et al., 2016). The current data are in line with the results obtained from our previous studies that we recalculated (Kovacs et al., 2020; Kun et al., 2014; Murr et al., 2014; Szélig et al., 2016). These results further support the idea that diminished conversion of phenylalanine to tyrosine by PAH may be due to increased production of reactive oxygen species, which can cause a decrease in the enzyme cofactor BH4 that takes part in the enzymatic reaction (Kovacs et al., 2020; Molnár et al., 2005; Murr et al., 2014; Szélig et al., 2016). Therefore, the observed decrease in the serum *p*-tyrosine concentration and the *p*-tyrosine/ phenylalanine ratio could be attributed to reduced enzymatic production of cofactor BH4.

Another important finding was that the serum *m*-tyrosine concentration and the *m*-tyrosine/ phenylalanine ratio were both higher in ACS patients compared with controls. Similar results were detected in patients with diseases in which oxidative stress is thought to play a pivotal pathological role, such as sepsis, lens cataracts, as well as in burn patients and those after trauma and acute ischemic stroke (Ipson & Fisher, 2016; Kovacs et al., 2020; Molnár, 2015; Molnár et al., 2016). These results indicate that increased serum concentration of *m*-tyrosine and the *m*-tyrosine/ phenylalanine ratio in ACS patients may reflect oxidative stress induced by inflammation (Ipson & Fisher, 2016; Molnár, 2015; Molnár et al., 2016; Szélig et al., 2016).

5.2. Assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation versus non-ST-segment elevation myocardial infarction (II.)

In the current study, there were significantly higher levels of serum Phe distal from the culprit lesion compared to the aortic root in patients with STEMI; while there were slightly higher levels in patients with NSTEMI, this difference was not significant. Similar results have been described in patients suffering from diseases associated with inflammation and immune activation, such as ovarian carcinoma, HIV-1 infection, and sepsis, as well as in patients after trauma and acute ischemic stroke (Ormstad et al., 2016; Ploder et al., 2008; Ribas et al., 2011; Zangerle et al., 2010). These findings may be explained by the fact that increased serum Phe levels can be caused by the diminished conversion of Phe into Tyr by phenylalanine hydroxylase (Murr et al., 2014; Ormstad et al., 2016; Ploder et al., 2008; Ribas et al., 2011; Zangerle et al., 2010). The observed increase in serum Phe levels in STEMI patients could be attributed to the number of damaged cells and disruptions in tissue function.

However, the results of the current study revealed that serum p-Tyr levels were slightly higher, while serum m-Tyr and o-Tyr levels were slightly lower, in the distal region of the culprit vessel compared to the aortic root in patients with STEMI. In contrast, serum p-Tyr and o-Tyr levels were slightly lower, while serum m-Tyr levels were slightly higher, in the distal region of the culprit vessel compared to the aortic root in patients with NSTEMI. These findings were unexpected and suggest that serum p-Tyr levels clearly differ from those of m-Tyr and o-Tyr in patients with STEMI and NSTEMI. A possible cause of this difference may be the two pathways of tyrosine isomer synthesis: p-Tyr is primarily produced enzymatically under physiological conditions, mainly in the kidneys, and is synthesized to a much lower extent under conditions of oxidative stress, whereas m-Tyr and o-Tyr are only formed nonenzymatically under conditions of oxidative stress (Szélig et al., 2016). The results of this study showed no significant association between serum amino acid parameters and baseline patient characteristics except for serum m-Tyr levels; they are negatively correlated with the extent of CAD at the aortic root in patients with NSTEMI. These results suggest that serum amino acid changes may be caused by the effects of oxidative stress and inflammation during myocardial infarction.

5.3. Comparison of baseline characteristics, clinical management and outcomes for patients with acute coronary syndrome (III.)

Our findings showed that there were many notable differences upon demographic and clinical characteristics in this comparisons. The younger age of the patients in Iraq may reflect the unphysical activity, a higher prevalence of diabetes, stress and the genetic factor of family history of CAD. These findings were consistent with several records proving that the prevalence of patients with ACS in the Arab Middle East are about a decade younger than in developed countries and have a higher prevalence of diabetes (Almahmeed et al., 2012; Suwaidi et al., 2010; Zubaid et al., 2017). However, both of countries patients were older adult. The higher prevalence of hypertension, dyslipidemia, previous MI and previous PCI in Hungary may indicate unhealthy lifestyles. According to the latest finding of a population survey in the Hungarian countryside, HT affect approximately 2.4 million people out of a total population of 10 million in Hungary. Additionally, the prevalence of HT in the age group of around 60 years is comparable to the values observed in other parts of the world (Farsang et al., 2004). The results indicate that Iraqi patients were more often diagnosed with STEMI. The higher prevalence of STEMI among Iraqi patients can be explained by the younger age and one another possible reason is that the study was conducted in CCU where all patients with STEMI were admitted while NSTEMI and UA included those patients with serious condition only, according to the number of patients and the hospital's ability to receive cases. Interestingly, the use of

angiography was higher in Iraq than in Hungary, but PCI and CABG rates were significantly lower. With regard reperfusion therapy for patients diagnosed with STEMI, primary PCI was treated more frequently in Hungary than in Iraq. This finding was consistent with data recorded form Hungarian Myocardial Infarction Registry, where primary percutaneous coronary intervention (PPCI) was performed in 91.1% of STEMI patients. However, this major issue lies in the impact of financial and administrative factors on the medical decision-making process and the quality of the services provided. Where, there is a shortage of hospitals with cath laboratory facilities and equipment in Iraq, despite the large numbers of patients. The present study confirmed the results of previous clinical trials that showed a wide variation in practical performance between countries in managing ACS patients(McNamara et al., 2014). However, these basic findings are consistent with research showing that patterns of management within a clinical trial do not necessarily reflect management in routine clinical practice (McNamara et al., 2014).

6. Conclusions

6.1. Main study: Serum concentrations of phenylalanine and tyrosine isomers in patients with acute coronary syndrome (I.)

The results of this study showed that increased serum *m*-tyrosine levels can reflect oxidative stress induced by inflammation after myocardial injury, similarly to the observed decrease in *p*-tyrosine levels.

6.2. Main study: Assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation versus non-ST-segment elevation myocardial infarction (II.)

Our data suggest that changes in serum levels of different Tyr isomers can mediate the effects of oxidative stress during myocardial infarction. The contribution of this study is to confirm the association of changes in the Phe and Tyr isomers with oxidative stress following myocardial injury.

6.3. Sub-study: Comparison of baseline characteristics, clinical management and outcomes for patients with acute coronary syndrome (III.)

Our results showed that variations in ACS outcomes are due to differences in socio-economic characteristics, disease severity, and therapeutic management in both countries.Moreover, there is a obvious impact of financial and administrative factors on medical decision-making and quality of services provided.

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List of Publications

In extenso publications

Articles related to the dissertation

1. Al-Sadoon, I., Wittmann, I., Kun, S., Ahmann, M., Konyi, A., & Verzár, Z. (2021). Assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation vs non-ST-segment elevation myocardial infarction. Journal of Clinical Laboratory Analysis, 35(2), e23613. https://doi.org/10.1002/jcla.23613. Q 2, IF 2.352.
2. Al-Sadoon I, Wittmann I, Molnár GA, et al. Serum concentrations of phenylalanine and tyrosine isomers in patients with acute coronary syndrome. Pol Arch Intern Med. 2021; 131; 16107. doi:10.20452/pamw.16107. Q3, IF 3.277.
3. Al-Sadoon, I. (2020). Phenylalanine, para-tyrosine, ortho-tyrosine and meta-tyrosine for ST-segment elevation VS. Non-ST-segment elevation acute coronary syndrome. 1. [Data set]. Mendeley. https://doi.org/10.17632/tgr3dd7wj4.1

Articles in the field of the dissertation

1. Qasim Ali Khasal, Ied AlSadoon, Fatima J Shinjar. (2020). STRESSFUL LIFE EVENTS OF PATIENT WITH ISCHEMIC HEART DISEASE AT AL-NASIRIYA HEART CENTER – International Journal of Psychosocial Rehabilitation,24(6), 7414-7423. https://www.psychosocial.com/article/PR260746/18854/

Articles in other topics

1. Nahla Saleh Hasan, Murtadha Kadhim Yasir, Qasim Ali Khasal, Mishaal Zoori Jabbar, Abdulrahman Abbas Jasim, Ied Al_Sadoon (2020). The Use of Complementary and Alternative Medicine among Diabetic Patients in Nasiriya City, Medico Legal Update, 20 (1): Medico Legal Update.
2. Khasal, Q. A., Dabis, H. A., Al_Sadoon, I., & Sachit, A. A. (2019). Assessment of Metered-dose Inhalers Technique among Patients with Chronic Respiratory Disorders at Al-Hussein Teaching Hospital in Al-Nasiriyah City. Indian Journal of Forensic Medicine & Toxicology, 13(3), 243. https://doi.org/10.5958/0973-9130.2019.00203.2

Abstracts and oral presentations

1. Ied Al Sadoon , István Wittmann Prof. Dr , Szilárd Kun MD PhD , Mercedes Ahman , Attila Konyi MD PhD , Zs.Verzár MD PhD, Assessment of Oxidative Stress Markers in Patients with Acute Coronary Syndrome: Potential to Modify Risk Stratification and Treatment, In: Csiszár, Beáta; Bódog, Ferenc (ed.) Medical Conference for PhD Students and Experts of Clinical Sciences: Book of abstractsPécs, Hungary: University of Pécs Doctoral Student Self-Government , (2019) p. 9.
2. Ied Al-Sadoon, István Wittmann, GA Molnár, Szilard Kun, Mercédesz Ahmann, Attila Konyi, Zsófia Verzár (2020). Investigation of Serum Phenylalanine and Tyrosine Isomers in Acute Coronary Syndrome Patients. 9th INTERDISCIPLINARY DOCTORAL CONFERENCE 2020 BOOK OF ABSTRACTS. Pécs, Hungary : Doctoral Student Association of the University of Pécs (2020) 384 p. pp. 55-55. , 1 p.
3. Ied, A. S., Wittmann, I., Kun, S., Ahmann, M., Pakai, A., Oláh, A., Boncz, I., & Verzár, Z. (2020). PCV95 SERUM Phenylalanine and Tyrosine Isomers in ACUTE Coronary Syndrome Patients. Value in Health, 23, S503–S504. https://doi.org/10.1016/j.jval.2020.08.586
4. Ied, Al-Sadoon; Mercédesz, Ahmanna; Hussein, Al-Kenzawib; Zsófia, Verzár. Comparison of baseline characteristics, clinical management and outcomes for patients with acute coronary syndrome. Medical Conference for PhD Students and Experts of Clinical Sciences 2021: Book of Abstracts. Pécs, Hungary: Doctoral Student Association of the University of Pécs (2021) 128 p. pp. 6-6. , 1 p.