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JIM Journal of Interdisciplinary Medicine

Aims and scope

The Journal of Interdisciplinary Medicine aims to publish top quality papers related to any fields of medicine that present an interdisciplinary dimension.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common situations encountered in the clinical or research practice. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different pathologies from the perspective of various clinical fields.

The Journal of Interdisciplinary Medicine will publish high-quality basic and clinical research related to interdisciplinary medical fields, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to the discovery of new mechanisms involved in the development and progression of a large spectrum of diseases.

The journal will try to provide the entire medical community with the perspective of the regional specifics of Central and Eastern European countries. The journal will primarily focus on publishing original research papers, but also other types of materials (such as review articles, case reports, state-of-the-art papers, comments to editor, etc) will be extremely welcomed.

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Journal of Interdisciplinary Medicine

EDITORIAL

The Role of Healthy Diet and Lifestyle in Preventing Chronic Diseases

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Non-communicable chronic diseases remain the leading cause of death worldwide, with approximately 38 million global deaths annually, according to the latest report released by the World Health Organization (WHO) in 2017.[1] Half of these deaths can be prevented, according to WHO representatives, by taking urgent measures, including changing lifestyle and assimilating a healthy and balanced nutrition. Non-communicable chronic diseases represent the main factors responsible for 70% of planetary mortality.[1]

According to WHO reports of 2017, in Romania, 92% of all deaths were estimated to be caused by non-communicable chronic diseases, of which 56% were cardiovascular diseases, 20% cancers and 5% other chronic diseases, with a total risk of premature death of 21%, of which 29% were men and 12% were women aged 30–70 years.[2] Also in 2017, in Romania, the obesity rate was 25%, the sedentarism rate 38%, the alcohol consumption rate 13%, and the rate of excessive salt consumption 10%.[2]

In the face of this alarming situation, people have to understand that by adopting a healthy lifestyle with a proper diet every day, they can prevent diabetes, obesity, cardiovascular disease, lung disease, and cancer. People who visit an experienced dietitian and follow their recommendations about healthy eating, can have a better quality of life and decrease the risks of developing a non-communicable chronic disease.

The rapid expansion of evidence-based research and epidemiological studies over the past ten years has contributed to clarify the role of healthy eating and lifestyle in preventing and controlling premature morbidity and mortality caused by non-communicable diseases, as well as identifying food-specific components that increase the likelihood of these diseases to occur in individuals and to establish the appropriate interventions in order to modify their impact.[3]

In parallel with the acceleration of industrialization, urbanization, and economic development over the last decade, changes in eating patterns and lifestyle have also taken place, with a major impact on population health and nutrition, especially in developing or transition countries. Although the quality of life has

improved, food availability has expanded, diet has become more diversified, and access to services has increased, account must be taken of several significant negative effects, namely adopting poor eating habits, decreasing physical activity, and increasing tobacco consumption, which can significantly increase chronic diet-related illnesses.[3]

Food and food products have become commodities manufactured and commercialized in a market that has expanded from a key local base to an increasingly global market.[3] Changes in the world food economy have been reflected also in food habits. For example, there is a significantly higher consumption of foods with high fat content, especially saturated fats, food additives, increased amount of salt, and refined carbohydrates (sugar), these characteristics being combined with a sedentary lifestyle, all of which lead to the formation of a vicious circle and to changing attitudes and perceptions of individuals towards balanced nutrition and physical activity.

Given the alarming rates of obesity and chronic illness, now more than ever, strategies for promoting healthy lifestyles must be developed and the efforts of all those involved in the health system must be intensified in order to combat this epidemic.

A study published in this issue of JIM by Cînpeanu *et al.* reported that women have a greater interest in healthy eating than men. However, generally, there is a lack of knowledge about healthy eating, and also the perception and attitude towards healthy eating seems to be influenced by the key messages that are promoted through the main media channels (internet, radio, television).[4] This study underlines that the promotion of the dietitian's profession among the Romanian population can contribute to raising the level of information and education about preventing chronic disease through healthy eating and not only.

CONFLICT OF INTEREST

Nothing to declare.

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STUDY DESIGN

CARDIOLOGY // IMAGING

Factors Associated with Sub-intimal Coronary Artery Dissection in MINOCA Patients with Delayed Washout at Coronary Angiography – Protocol for an Observational, OCT-based Study

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ABSTRACT

Background: Myocardial infarction (MI) with no obstructive coronary arteries (MINOCA) is a special form of the acute coronary syndrome. The heterogeneous pathophysiology of MINOCA is not well elucidated and includes cardiac and non-cardiac causes. Slow flow phenomenon on coronary angiography can be associated with several possible causes of MINOCA confirmed by optical coherence tomography (OCT). Therefore, the aim of this study is to assess the underlying mechanism of the delayed washout phenomenon on coronary angiography and the potential role of subintimal coronary artery dissection (SD) in the setting of an acute MI. **Methods and design:** This clinical prospective, descriptive research will enroll patients diagnosed with acute MI (STEMI or NSTEMI) identified by coronary angiography, followed by OCT imaging of the coronary arteries at the Emergency Clinical County Hospital of Târgu Mureș, Romania. The enrolled patients will be separated into two groups based on OCT examination, patients with SD and patients with no SD. **Conclusion:** The underlying mechanisms of MINOCA with delayed washout phenomenon on coronary angiography is still poorly understood. Modern invasive imaging techniques are capable to assess the microstructure of the coronary artery wall and are able to offer the much needed information to elucidate the pathophysiological changes which ultimately cause the acute event. The current study offers a new, complex – clinical, invasive and noninvasive imaging, as well as biomarker-based – approach, which may lead to a better understanding and treatment of this pathology.

Keywords: myocardial infarction, no obstructive coronary arteries, optical coherence tomography, subintimal coronary artery dissection

INTRODUCTION

The majority of acute myocardial infarctions (AMI) are caused by an intracoronary thrombus with plaque rupture or erosion, and coronary angiography is the gold standard for the diagnosis of coronary artery disease (CAD).[1] In patients with AMI presenting with ST-segment elevation on the ECG, the immediate coronary angiography shows in almost 90% of the cases an occluded coronary artery. In contrast, in AMI patients with no ST-segment elevation on the ECG, this proportion is only 26% when the coronary angiography is performed in the first 24 hours of symptoms onset. DeWood *et al.* demonstrated that around 10% of patients with AMI had no significant lesions on coronary angiography, and this phenomenon was confirmed by some large AMI registries.[2,3]

Myocardial infarction with no obstructive coronary arteries (MINOCA) is a special form of acute coronary syndrome (ACS), present in 5–15% of the cases, typically diagnosed under 50 years of age.[4] MINOCA is characterized by evidence of myocardial injury (elevated cardiac biomarkers) with no significant atherosclerotic coronary plaque (less than 50% on coronary angiography) or flow-limiting obstructions on coronary angiography.[5] The pathophysiology of MINOCA is heterogenous, including coronary artery spasm, coronary dissection, unstable coronary plaque, Takotsubo cardiomyopathy, myocarditis, microvascular coronary artery spasm, or embolization.[6,7] Coronary angiography is able to quantify the coronary stenosis, but unable to identify the plaques at risk, due to the lack of information of the plaque structure or the coronary artery wall. Intravascular imaging, such as optical coherence tomography (OCT) or intravascular ultrasound (IVUS), can visualize the microstructure of the coronary wall and plaque and is able to identify atherosclerotic plaque disruption, plaque erosion, coronary artery dissection, or thrombosis which was not identified during coronarography.[8] OCT can acquire a high-resolution (10–15 μm) image that allows a better understanding of the pathomechanism of MINOCA patients by a punctual assessment of the coronary wall structure.[9] Another key diagnostic tool for this patient category is represented by cardiac magnetic resonance (CMR), which is capable to demonstrate the myocardial damage (late gadolinium enhancement, myocardial edema, wall motion abnormalities).[2]

Spontaneous coronary artery dissection (SCAD) is a rare cause of ACS, which occurs typically in young patients with no cardiovascular risk factors, caused by the disruption of the coronary artery wall, resulting in an intramural hematoma. There are three types of SCAD, and intravascular imaging is necessary to confirm the diagnosis. Nearly half of all cases remain unexplained.[10]

The coronary slow flow phenomenon can be described as a delayed progression of the injected contrast material or delayed distal vessel opacification in the major epicardial coronary vessels.[11] Our previous experience in MINOCA patients detected another phenomenon, which is believed to play a key role in the pathophysiology of these patients. In a variable percentage of MINOCA patients, coronary angiography described a delayed washout of the contrast material, and the OCT examination showed a subintimal dissection (SD) at this level.

The aim of this study is to assess the underlying mechanism of the delayed washout phenomenon on coronary angiography and the potential role of subintimal coronary artery dissection in the setting of an acute myocardial infarction.

STUDY HYPOTHESIS

This study aims to demonstrate the correlation between subintimal dissection in patients with MINOCA and delayed washout, as a variety of the "slow flow" phenomenon. Based on the observation that some of these patients present delayed washout of the contrast material in the coronary arteries, we propose to validate the association between delayed washout of the contrast material and the presence of subintimal dissection on OCT examination. The study will also evaluate clinical and paraclinical characteristics, associations that could influence the aspect and outcome of patients with SD, as well as early and late outcomes of these patients.

MATERIAL AND METHODS

Study population

This clinical prospective, descriptive research will enroll patients diagnosed with AMI (STEMI or NSTEMI) with non-obstructive coronary artery disease identified by coronary angiography, followed by OCT imaging of the coronary arteries, who will be admitted to the Emergency Clinical County Hospital of Târgu Mureș, Romania.

Patients with STEMI are defined as having continuous chest pain longer than 30 minutes, positive cardiac biomarkers (high-sensitive troponin, creatine kinase myocardial band), ST-segment elevation on surface ECG >0.1 mV in two or more contiguous leads or new left bundle-branch block. In patients with NSTEMI, the infarction will be defined as the absence of ST-segment elevation on the ECG

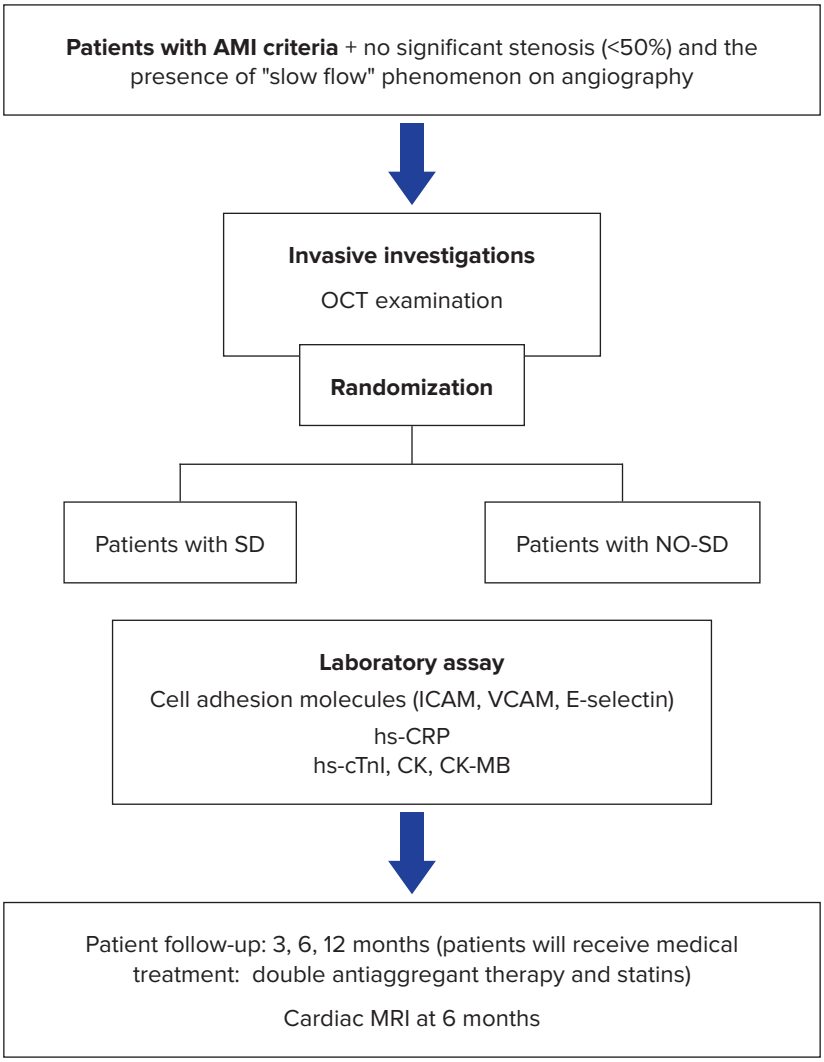

FIGURE 1. Study protocol

with positive cardiac biomarkers and suggestive ischemic symptoms.

Study groups

The enrolled patients will be separated into two groups based on OCT examination, patients with SD and patients with no SD (NO-SD).

Coronary angiography

The coronary angiograms will be performed using the Philips Allura Xper FD20 biplane system. Through radial artery approach, a diagnostic catheter will be introduced into the artery using the Seldinger technique, and by means of a guide wire the catheter will be introduced at the origin of the coronary artery. The coronary arteries will be visualized by means of fluoroscopy and intracoronary injection of iodine-based contrast material (Iomeron). The obtained angiograms will be analyzed by two experienced interventional cardiologists.

OCT examination

OCT imaging will be acquired using an Abbott imaging system and a Dragon Fly catheter (Abbott), after positioning the catheter. Image acquisition of the region will be performed by automatic pullback from distal to proximal to the selected region. To clear the imaging field from blood flow, continuous injection of contrast or saline will be performed.[12] The obtained images will be stored digitally for further analysis.

All the obtained OCT results will be examined by two experienced investigators. If there will be a significant difference between the two evaluations, a third investigator will be included in the process.

Cardiac MRI

We will perform a cardiac MRI for all enrolled patients 6 months after the hospitalization. CMR will be performed using a 1.5 T Siemens scanner, and images will be acquired during repeated end-expiratory breath holds. All CMR images will be reviewed by two experienced readers. Myocardial edema on the CMR image will be considered as an area of high T2 signal intensity on a segmental basis. Late gadolinium enhancement will be determined for each segment, and only the subendocardial and transmural distribution will be considered as ischemic.

Baseline characteristics

The baseline assessment will include physical examination, family history of CAD, previous MI, postmenopausal status, age, gender, cardiovascular disease, peripheral vascular disease, chronic lung disease, weight, current smoking status, arterial blood pressure, ECG, left ventricular ejection fraction, evaluation of risk factors and comorbidities, serum lipids, creatinine, glomerular filtration rate, creatine kinase, creatine kinase-MB, high-sensitive CRP, high-sensitive cTnI, cell adhesion molecules (ICAM, VCAM, E-selectin), quantitative coronary angiography, in-hospital medication, and in-hospital complications.

The enrolled subjects will receive conservative treatment, without percutaneous coronary angioplasty.

Inclusion and exclusion criteria

All patients will sign an informed consent before enrollment in the study.

Inclusion criteria:

- patients with AMI criteria + no significant stenosis (<50%) on coronary angiography and presenting delayed washout phenomenon.

Exclusion criteria:

- patient's refusal to participate in the study;
- sensitivity to the contrast substance;
- pregnancy.

Statistical analysis

We will perform a descriptive statistical analysis. Continuous and categorical data will be presented as mean ± SD or median (interquartile range, IQR), and frequencies. Student's t test and the Mann-Whitney U test will be used for the comparison of continuous variables, as appropriate. Fisher's exact test will be performed to find differences in categorical data. The level of significance will be set at $\alpha = 0.05$.

DISCUSSION

There are several possible etiologies that could lead to myocardial infarction in MINOCA patients, most of them not being elucidated so far. In addition, the all-cause mortality of MINOCA patients is high, estimated at 4.7% at one year. At the same time, a group of these patients will remain without an accurate etiologic diagnosis. Therefore, MINOCA patients are less likely to be prescribed medical therapies for a secondary prevention (statins, antithrombotic medication) than patients with evident coronary lesions on coronary angiogram.[5,13]

Several studies have demonstrated that the majority of myocardial infarction are caused by the rupture of a non-obstructive, non-significant coronary plaque on coronary angiography.[12] OCT examination as a modern invasive investigation can provide a high-resolution longitudinal view and a three-dimensional vessel reconstruction, and can offer detailed information about the vessel wall ultrastructure. Therefore, OCT can characterize plaque ultrastructure and identify the plaques susceptible for rupture.[12]

Because of the lack of information on MINOCA patients with SD in the literature, our study aims to investigate the correlation between subintimal dissection on OCT and the delayed washout phenomenon on coronary angiogram in a group of MINOCA patients. We aim to investigate the clinical evolution of these patients, the effects of dual antiplatelet and plaque stabilization therapy, as well as the assessment of the infarcted area by cardiac MRI.

CONCLUSION

The underlying mechanisms of MINOCA and of the associated delayed washout phenomenon on coronary angiography is still poorly understood. Modern invasive imaging techniques are capable to assess the microstructure of the coronary artery wall and are able to offer the much needed information to elucidate the pathophysiological changes which ultimately cause the acute event. The current study

offers a new, complex – clinical, invasive, and noninvasive imaging, as well as biomarker-based – approach, which might lead to a better understanding and treatment of this pathology.

CONFLICT OF INTEREST

Nothing to declare.

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STUDY DESIGN

CARDIOLOGY // IMAGING

Impact of Coronary Plaque Vulnerability on Acute Cardiovascular Events – Design of a CT-based 2-year Follow-up Study

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ABSTRACT

With coronary artery disease (CAD) projected to remain the leading cause of global mortality, prevention strategies seem to be the only effective approach able to reduce the burden and improve mortality and morbidity. At this moment, diagnostic strategies focus mainly on symptomatic patients, ignoring the occurrence of major cardiovascular events as the only manifestation of CAD. As two thirds of fatal myocardial infarction are resulting from plaque rupture, an approach based on the "vulnerable plaque" concept is mandatory in order to improve patient diagnosis, treatment, and, by default, prognosis. Given that the main studies focus on a plaque-centered approach, this is a prospective observational study that will perform a complex assessment of the features that characterize unstable coronary lesions, in terms of both local assessment via specific coronary computed tomography angiography markers of coronary plaque vulnerability and systemic approach based on serological markers of systemic inflammation in patients proved to be "vulnerable" by developing acute cardiovascular events.

Keywords: vulnerable plaque, acute cardiovascular event, systemic inflammation, vulnerability markers

INTRODUCTION

Coronary artery disease (CAD), the most common cause of myocardial ischemia, represents a modern "epidemic" health problem worldwide, with severe implications in terms of mortality, morbidity, and socioeconomic aspects.[1–3] Given that CAD is projected to remain the leading cause of global mortality, prevention strategies seems to be the only effective approach able to reduce the burden and improve mortality and morbidity rates.[4] At this moment, diagnostic strategies focus mainly on symptomatic patients, totally ignoring the occurrence of major cardiovascular events as the only manifestation of CAD.[5] Coronary atheroma has shown a great diversity in terms of development and progress, demonstrating great variety in growth rate and plaque morphology.[6,7]

In previous studies, coronary plaques prone to rupture proved to have individual morphology features compared to stable atheromas. In clinical practice, this provides the opportunity of early noninvasive imaging identification of high-risk patients, even before devastating adverse clinical events occur.[8,9] As two thirds of fatal myocardial infarctions (MI) and sudden cardiac deaths result from sudden luminal thrombosis due to plaque rupture or erosion, defined as transmural fibrous cap rupture, causing lipid-rich core exposal to blood stream,[5,10–12] the concept of "vulnerable plaque" has emerged, involving massive efforts assigned for its recognition. From this point, substantial results of large studies and trials sustain the mandatory need of an approach based on the "vulnerable" plaque concept, in order to improve patient diagnosis, treatment, and, by default, prognosis. From a histopathological point of view, culprit lesions present large plaque volumes and necrotic cores, covered by a thin fibrous cap infiltrated with macrophages,[13] small calcifications in the fibrous cap having a significant role in plaque instability.[14,15] Moreover, vessels tend to be positively remodeled at the site of atheroma disruption.[16,17] As the histopathological characteristics of culprit lesions are well established, it has been proposed that vulnerable lesions exhibit the same features.[18]

Despite the considerable ongoing efforts of predicting acute coronary events on individual coronary plaque level, the identification of high-risk patients remains a challenging task for cardiovascular imaging technologies.[4,19,20]

Coronary computed tomography angiography (CCTA) has emerged as the best noninvasive imaging modality, allowing, besides coronary lumen and calcium content evaluation, the noninvasive quantitative analysis of coronary atherosclerotic plaques size and composition,[21,22] information with greater potential in predicting further acute coronary events.[23–25] Multiple previous studies proved all CCTA-derived parameters of plaque characterization as significant and independent predictors of future cardiovascular events.[26] In these terms, a recent CCTA study of non-obstructive CAD, with a follow-up of 100 months, confirmed positive remodeling, napkin-ring sign, increased plaque burden, and the presence of low attenuation as being associated with acute coronary syndromes (ACS).[27] As reported in large studies, the presence of multiple high-risk features proved to involve a greater-than-additive risk, as the presence of remodeling index (RI) and low-attenuation plaques (LAP) involved a 22% probability of ACS development over a 27-month follow-up, and the presence of three high-risk features led to a 60% probability of ACS development in the same follow-up time frame.[28,29]

Besides noninvasive imaging, diagnostic techniques for vulnerable plaque detection include serologic markers, as atherosclerosis is known as a chronic immunoinflammatory disease.[30] From this point of view, inflammation has an important impact on the evolution of the atherosclerotic process and the progression of coronary lesions, commonly related to plaque destabilization, as the involvement of inflammatory mechanisms in weakening the collagen structure of the "thin-capped fibroatheroma" is a widely accepted concept at this moment.[22] Of all systemic inflammatory biomarkers, C-reactive protein (CRP) proved to be the most frequently used, due to its predictive value for acute cardiovascular events in various subgroups of patients, as a series of studies suggested that CRP may be considered a culprit in vascular inflammation and plaque instability.[31] In a meta-analysis, involving 52 studies and 246,669 patients, the assessment of CRP level in patients with intermediate cardiovascular risk was able to prevent additional events over a time frame of 10 years.[32] With regard to IL-6, prospective studies proved the association between elevated serum levels in asymptomatic patients and an increased risk of acute cardiovascular events, but IL-6 assessment does not seem to offer any additional value to CRP measurement. Matrix metalloproteinases (MMPs) proved to be involved in vascular remodeling and fibrous cap thinning or rupture, elevated levels being associated with future acute cardiovascular events.[33]

Therefore, focusing only on plaque characteristics will ignore the effects that systemic inflammation processes exert on plaque stability, as plaque destabilization is a complex process which involves structural features and biological processes.[10,11]

We present the study design of a prospective, single-center trial developed with the main purpose of assessing the role of CCTA-derived markers of plaque vulnerability in the development of acute cardiovascular events during a 2-year follow-up, compared to stable atherosclerotic lesions. Furthermore, the trial aims to investigate the involvement of serological markers of systemic inflammation on the rate of major cardiac events in the same time frame.

METHODS

Study objectives

The primary objective of the study is to evaluate the feasibility of CCTA-derived vulnerability markers as prognostic features for the development of acute cardiovascular events in a follow-up period of 2 years. In this regard,

coronary plaques with CCTA vulnerability features will be compared to stable atheromas in terms of major adverse cardiovascular events (MACE) rates. The secondary aim consists in assessing of impact of systemic inflammation on the rate of acute cardiovascular events, based on the evaluation of serological markers.

Study population

This trial will be a single-center, prospective study, which will include 200 patients referred for CCTA examination for chest pain of varying degrees and a probability of CAD ranging between 15–85%, in accordance with the recommendations of the current guidelines of the European Society of Cardiology (ESC).[34]

Inclusion criteria:

- patients with suspected CAD, pre-test probability of CAD between 15–85%, in whom CCTA identified >1 significant coronary lesion;
- age >18 years;
- willingness to participate in the study.

Exclusion criteria:

- documented CAD, ACS, percutaneous coronary intervention (PCI) or bypass grafting;
- moderate or severe valvular heart disease;
- unstable hemodynamic condition;
- cardiac arrhythmia;
- Agatston coronary artery calcium score (CAC) >2,000;
- non-diagnostic CCTA image quality;
- known allergy to contrast agents;
- life expectancy under 2 years;
- chronic kidney disease.

Study groups

Two hundred patients, eligible according to the selection criteria, will be included in two study groups based on the CCTA analysis: group 1 – patients with plaques presenting CCTA-derived markers of vulnerability; group 2 – patients without any marker of vulnerability. In patients with myocardial infarction developed during the follow-up time, a second CCTA evaluation will be performed at 2 years from the baseline assessment. These patients will be divided into two subgroups based on the number of CCTA-derived markers of vulnerability, as follows: group 1A – patients with 1–2 markers of vulnerability; group 1B – patients presenting >2 markers of vulnerability.

Study procedures

CCTA scan protocol

CCTA will be performed using a CT-scanner with 128-multislice dual source (Somaton definition, Siemens Healthcare, Germany), with the following scan parameters: 120 kV tube voltage, gantry rotation time of 0.33 s, 128 × 0.6 collimation, with patients in inspiratory breath-hold position, following the same protocol. All examinations will be performed at a stable heart rate below 60 beats/minute after the administration of an oral beta-blocker. CAC will be assessed during the pre-contrast scan, and a CAC >2,000 will be considered exclusion criteria, as intense calcifications will alter CCTA acquisitions. During an inspiratory breath-hold, 80–100 mL of iodinated contrast agent (Ultravist 370 mgI/mL, Bayer Healthcare, Germany) will be administered according to the patient's body weight, with a flow rate of 5.5 mL/s, followed by 50 mL of 0.9% saline solution at the same flow rate.

Analysis of CCTA

All CCTA acquisitions will be transferred to a Siemens (Siemens AG, Erlangen, Germany) workstation for data processing, measurements, and interpretation, using the QAngioCT RE (Medis, Leiden. Netherlands) dedicated software. Based on current recommendations, coronary arteries with at least 2 mm in lumen will be assessed by a 17-segment model. The quantitative assessment of atherosclerotic lesions will contain atheroma length, atheroma, vessel, and lumen volume, and minimal luminal area. Plaque composition assessment will involve the determination of calcified and non-calcified (lipid-rich and fibrotic) components. Qualitative plaque analysis will include spotty calcifications, positive remodeling, low attenuation core, and napkin-ring sign.

Study definitions

In terms of stenosis severity, plaques will be divided in obstructive (stenosis >50%) and non-obstructive (stenosis <50%). Based on CT density, plaques will be classified in non-calcified (density <30 HU, lipid cores), calcified (density >220 HU), mixed (non-calcified plaques presenting small amounts of calcified elements), and fibrous plaques (density 30–150 HU). Lesions with a low-density core (at-

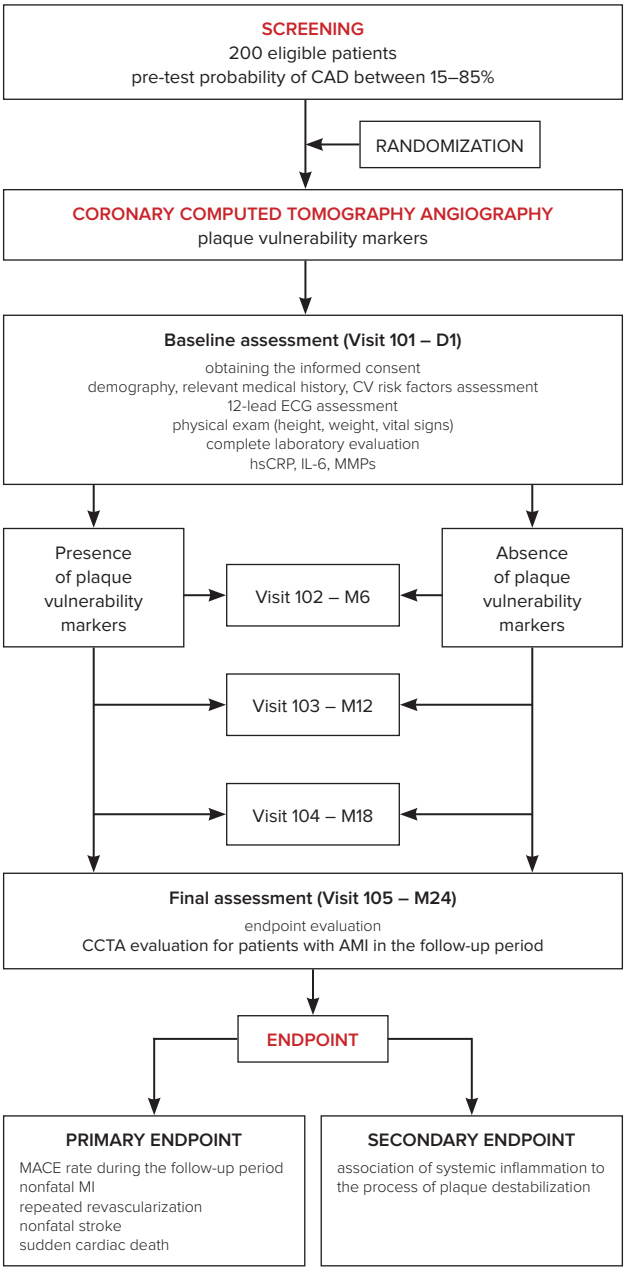

FIGURE 1. Study protocol. CAD – coronary artery disease; CCTA – coronary computed tomography angiography; MACE – major adverse cardiovascular events; AMI – acute myocardial infarction; MMPs – matrix metalloproteinases; hs-CRP – high-sensitivity C-reactive protein; IL-6 – interleukin 6

tenuation <30 HU) and volume larger than 6 mm^3 will be considered LAP. The RI will be defined as the ratio between vessel diameter at the plaque site and a reference diameter. Positive remodeling will be considered in the presence of a RI >1.1. The napkin-ring sign will be considered in the presence of a lesion core presenting low attenuation, surrounded by a rim-like area of high attenuation. Spotty calcification will be considered at a size <3 mm (with density >130 HU).

Study timeline

This clinical study will be conducted between October 2019 and May 2020, with a further 2-year follow-up period, as shown in the study protocol (Figure 1).

Screen – Visit 1

- checking for inclusion/exclusion criteria;

Visit 101 – D1

- obtaining the informed consent;
- CCTA scanning and post-processing;
- demography, relevant medical history, CV risk factors assessment;
- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- complete laboratory evaluation;
- hsCRP, IL-6, MMPs.

Visit 102 – M6

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- relevant medical history;
- MACE.

Visit 103 – M12

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- relevant medical history;
- MACE.

Visit 104 – M18

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- relevant medical history;
- MACE.

Visit 105 – M24

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- CCTA for AMI patients;
- endpoint assessment.

Data analysis

The analyses will be performed with GraphPad Prism 8 (GraphPad Software, San Diego, CA) at a level of significance of 5%. Normality tests will be applied for all study data. Continuous variables will be summarized as mean ± SD and categorical variables as percentages/frequencies. The Chi-square test will be performed in order to compare categorical variables. The Mann-Whitney U test or independent-samples t test will be used for group comparisons. All statistical tests will be two-tailed, and a p value <0.05 will be assigned to determine statistical significance.

Ethics

This study will be carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the local institutional Ethics Committee. Individual informed consent will be signed by each study participant.

Outcome assessment

The primary outcome of the study will be represented by MACE rates during the follow-up time. MACE will be defined as: nonfatal myocardial infarction, repeated revascularization, nonfatal stroke, and sudden cardiac death. Secondary outcome refers to the association of systemic inflammation to the process of plaque destabilization, leading to acute cardiovascular events.

DISCUSSIONS

This study design describes the protocol for a prospective, single-center trial developed with the main purpose of assessing the feasibility of CCTA-derived markers of plaque vulnerability as prognostic features in the development of acute cardiovascular events during a 2-year follow-up, compared to stable atherosclerotic lesions, in patients referred to CCTA evaluation. In this regard, coronary plaques with CCTA vulnerability features will be compared to stable atheromas in terms of MACE rate.

As large studies reported plaque rupture as the substrate for ACS development in at least two thirds of patients,[35–37] the "vulnerable plaque" concept has emerged straight away, with massive efforts assigned for its recognition. From this point, substantial results of studies and trials sustain the mandatory need of an approach based on the "vulnerable" plaque concept in order to improve patient diagnosis, treatment, and, by default, prognosis. Based on previous work, a series of vulnerability features were established on the basis of autopsy findings in culprit lesions, criteria considered to be sufficient and unambiguous for the definition of high-risk plaque. These features are represented by the presence of active inflammation, thin cap fibroatheroma, fissured plaque, calcified nodule, intraplaque hemorrhage, and positive remodeling process. As the histopathological characteristics of culprit lesions are well established, it was presumed that vulnerable lesions exhibit the same features.[18]

Despite the considerable ongoing efforts to predict acute coronary events on individual coronary plaque level, the identification of high-risk patients remains a challenging task for cardiovascular imaging technologies.[4,19,20] Of these, CCTA has emerged as the best noninvasive imaging technique in plaque vulnerability assessment, multiple previous studies proving all CCTA-derived parameters of plaque characterization as significant and independent predictors of future cardiovascular events.[26] From CCTA assessment, at this moment, coronary lesions are most commonly characterized as prone to rupture when possessing large lipid cores with low attenuation and thin adluminal fibrous caps.

In a prospective trial conducted by Motoyama *et al*. in 1,059 subjects, followed over a period of 2 years after CCTA assessment, positive remodeling and low attenuation proved to be specific plaque parameters associated with increased risk of plaque rupture and development of ACS.[28] Another retrospective study identified a significantly higher incidence of positive remodeling, low density plaque components, and spotty calcifications in culprit lesions, all of these features being significant predictors for ACS.[38] In a study conducted by Yamagishi *et al*. although at the time of initial evaluation the lumen area was preserved, coronary culprit plaques exhibited larger plaque volume, with eccentric plaque distribution and echolucent zones in the proximity of luminal surface,[39] this marker proving to be the lipid-rich core, in which metalloproteinases were associated with fibrous cap erosion.[40] These results prove that eccentric plaque distribution involves a higher degree of vulnerability than concentric lesions.[41–43] Another aspect of the presence of rich lipid-core was confirmed by necropsy studies, in which the size of plaque area proved to be less significant than the presence of lipid-rich core.[44] While a series of studies have demonstrated the presence of lipid-rich atheroma with very low CT densities (<30 HU) in culprit lesions as a marker of vulnerability, there is an almost total lack of quantitative assessment of this component.[45,46] A previous study reported larger volumes of low-density lipid-rich cores in unstable plaques, with a critical plaque volume of 6.0 mm^3 and CT density <30 HU as a cut-off value for differentiation between culprit and non-culprit lesions. Besides atheroma composition, a series of morphological characteristics provide prognostic information about plaque vulnerability. The napkin-ring sign, characterized by a plaque core with low attenuation surrounded by a rim-like area of higher attenuation, proved to be a surrogate CT-derived marker of precursor lesions for rupture, independent of other CCTA features.[29] Surprisingly, in a prediction CCTA study, Otsuka *et al*. identified the napkin-ring sign in 41% of ACS events, an even higher incidence compared with intravascular ultrasound investigations.[29]

In this context, the present study will evaluate the feasibility of CCTA-derived markers of vulnerability and structural component parameters as predictive features for further acute cardiovascular events. As the ability to identify "vulnerable" plaques involves major clinical implications, these results may allow the selection of high-risk patients for aggressive risk factor interventions in order to reduce morbidity and mortality.[47]

With the widespread adoption in the literature of the notion that structural plaque features alone can define plaque vulnerability, most efforts have been directed toward correlating imaging features with specific morphologies, leaving aside systemic inflammation and its impact on plaque vulnerability.

As a secondary objective, the trial aims to investigate the impact of serological markers of systemic inflammation on the rate of major cardiac events in the same time frame. A series of studies have suggested the involvement of systemic inflammation, as assessed by C-reactive protein, in the development of ACS.[48] The main concept relies on inflammatory mechanisms as regulators of defective structural stability, combined with the thrombogenic potential of the lipid core. As this concept is widely accepted, however, inflammation may not be responsible for all acute thrombotic events, as one large study has shown that almost half of ACS developed in the absence of high levels of CRP.[49] Moreover, a recent OCT study demonstrated that in one-third of patients with ACS and plaque rupture, there was a lack of inflammatory cell infiltration, with normal levels of CRP.[50]

Despite the recent considerable improvement of imaging techniques' ability to visualize and assess coronary plaques, we are still facing a plaque-centered approach, mainly focused on the precise description of a still frame of the atheroma configuration, not the continuous and variable interaction with its surroundings. Therefore, this study's main contribution is to incorporate both CCTA-derived vulnerability markers and serum biomarkers of systemic inflammation in a complex and complete local and systemic assessment of the patient proved to be "vulnerable" by developing acute cardiovascular events.

CONCLUSIONS

In conclusion, this will be the first study that will perform a complex assessment of features that characterize unstable coronary lesions, in terms of both local assessment via spe-

cific CCTA markers of coronary plaque vulnerability and a systemic approach based on serological markers of systemic inflammation.

CONFLICT OF INTEREST

Nothing to declare.

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STUDY DESIGN

CARDIOLOGY // EMERGENCY MEDICINE

Association between the Incidence of Sudden Cardiac Arrest and the Location of Culprit Lesions in STEMI Patients – Design of a Prospective Clinical Study

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ABSTRACT

Out-of-hospital cardiac arrest (OHCA) has a poor prognosis and is the most severe complication of any cardiac event. It is known from previous studies that the location of the culprit lesion in ST-segment elevation myocardial infarction (STEMI) patients with cardiac arrest may affect the post resuscitation survival rate. However, due to the low number of cases, the association between the localization of the culprit lesion within the coronary tree and the occurrence of cardiac arrest is not widely discussed, because resuscitated cardiac arrest patients are excluded from the vast majority of clinical trials. This is a prospective observational study that aims to develop a prediction model for OHCA in patients who present with STEMI, based on differences related to culprit lesion location. The primary objective of the study is to evaluate the differences related to the location of the culprit lesion in patients with STEMI who present OHCA versus patients without cardiac arrest.

Keywords: cardiac arrest, acute coronary syndromes, culprit lesion, left anterior descending artery

BACKGROUND

Acute myocardial infarction is the most severe manifestation of coronary artery disease, and together with the overall spectrum of ischemic heart diseases, it remains the main cause of mortality worldwide.[1,2] In European countries, the incidence of myocardial infarction ranges from 90 to 312 per 100,000 persons per year.[3] The in-hospital mortality of patients with ST-segment elevation myocardial infarction (STEMI) in European countries varies between 4 to 12%, while the 1-year mortality in case of patients diagnosed with STEMI and treated via angioplasty is around 10%.[4] Older women with STEMI have worse outcomes

compared to older males, and young men are more likely to survive than young women with the same pathology.[5] Advanced age and higher Killip class, longer time until revascularization and treatment strategy, history of myocardial infarction, diabetes mellitus, renal failure, a higher number of affected coronary arteries, and reduced left ventricular ejection fraction (LVEF) increase mortality in STEMI.[4]

Out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) has poor prognosis and is the most severe complication of any cardiac event. The incidence of OHCA in Europe has been estimated at around 275,000 persons per year. The survival rate of OHCA is low; according to different studies, it varies from 11% to 39%.[6,7] Ischemic heart disease is the most frequent cause of OHCA.[8] In patients with resuscitated cardiac arrest complicating STEMI, the six-month survival rate is 54% owing to quick prehospital medical attendance, emergency revascularization, and specific care in the cardiovascular intensive care unit.[9] The factors that can trigger cardiac arrest may be coronary plaque rupture or erosion, or fragmentation and embolization of a thrombus. The survival rate is influenced by gender, hypertension, dyslipidemia, smoking status, age over 59 years, diabetes mellitus, location of arrest at home, and high levels of blood lactate.[7]

The management of cardiopulmonary resuscitation has a relatively low success rate. Therefore, the outcome of resuscitated cases after cardiac arrest with significant coronary stenosis remains poor. Important steps in post-resuscitation care include early coronary artery reperfusion, together with other aggressive post-cardiac arrest therapeutic measures, which can double the rate of survival. It is known from previous studies that the location of the culprit lesion in STEMI patients with cardiac arrest may affect the post-resuscitation survival rate. However, due to the low number of cases, the association between the localization of the culprit lesion within the coronary tree and the occurrence of cardiac arrest is not widely discussed, because resuscitated cardiac arrest patients are excluded from the vast majority of clinical trials.[9]

According to current therapeutic guidelines, in case of patients who have electrocardiographic criteria for STEMI, the treatment method is immediate invasive coronary angiography and, if indicated, percutaneous coronary revascularization. Furthermore, immediate coronary angiography is also indicated in all patients with cardiac arrest in whom an acute coronary syndrome is suspected.

The most common localization of the culprit vessel in cardiac arrest survivors is the left anterior descendent artery (LAD) or the right coronary artery (RCA). The left circumflex artery (LCX) is less frequently identified as a culprit vessel, most likely because the area supplemented by the LCX is an electrically silent zone.[10]

The most common acute complication of myocardial infarction that could lead to cardiac arrest is ventricular fibrillation (VF) and extreme bradycardia that leads to asystole. VF generally occurs if the culprit lesion is located on the LAD, because it carries almost 50% of the blood of the coronary circulation, making it the largest coronary artery. Atherosclerosis or thrombotic occlusion of this vessel involves a large area of the anterior, septal, and apical portions of the cardiac muscle, leading to a serious impairment of cardiac performance.[11] LAD occlusion complicated with cardiac arrest due to VF is more likely associated with a favorable resuscitation outcome, because it is a shockable arrhythmia, making it possible to use a defibrillator. The occlusion of the RCA can result in inferior or right ventricular STEMI, often associated with hypotension, bradycardia, or atrioventricular block, which progress gradually from first degree to complete block, being associated with less favorable outcomes following resuscitation. Cardiac arrest caused by VF is associated with better prognosis compared to bradycardia-asystole. At the same time, occlusion of the LAD increases the predisposition for cardiac arrest due to VF, while RCA occlusion more often leads to fatal outcomes. Left ventricular hypertrophy and multivessel coronary disease is more frequent in patients with fatal infarction, due to the fact that this associated disease increases the electrical instability of the myocardium.[12–14]

The role of cardiac magnetic resonance in risk stratification and follow-up of STEMI patients

Cardiac magnetic resonance (CMR) has an important role in risk stratification, treatment, and long-term follow-up of patients with ischemic heart disease, including patients with STEMI. This noninvasive investigation method is the gold standard technique for assessing the structural and functional features of the left ventricle, as well as the volumes and the size of the replacement fibrosis. Myocardial salvage is a strong predictor of major adverse cardiac events (MACE) and clinical events 6 months after infarction.

Infarct size depends on several factors such as collateral blood flow, time, and efficiency of revascularization. Studies have demonstrated that the quantity of myocardial loss is variable, depending on several factors, thus the follow-up of patients with the use of CMR after coronary reper-

fusion is important for risk stratification and guiding the post-infarction therapies.[15]

STUDY HYPOTHESIS

We hypothesized that patients with acute STEMI, who present culprit lesions at the level of the LAD and a degree of stenosis of less than 50%, are more likely to present sudden cardiac arrest in prehospital settings compared to patients with similar lesions located in the LCX or the RCA. Therefore, the aim of the study is to develop a prediction model for OHCA in patients who present with STEMI at 12 hours from the onset of symptoms, based on differences related to culprit lesion location.

OBJECTIVES

The primary objective of the study is to evaluate the differences related to the location of the culprit lesion in patients with STEMI who present OHCA versus patients without cardiac arrest. Secondary objectives include: (1) to evaluate the impact of culprit lesion location within the coronary tree and the myocardial remodeling process, assessed at one month by using CMR imaging; (2) to assess the role of culprit lesion location on the rate of MACE during a follow-up of 6 and 12 months, respectively.

STUDY DESIGN

This is a clinical, prospective, non-randomized, observational study that will be conducted in the Clinic of Cardiology of the Emergency Clinical County Hospital of Târgu Mureş, Romania, in collaboration with the Laboratory of Advanced Research in Cardiac Multimodal Imaging of the Cardio Med Medical Center Târgu Mureş, Romania. The follow-up will be performed at 30 days after inclusion, as well as 6 and 12 months respectively.

Study population

In total, the study will include 200 patients with acute STEMI, who are admitted through the emergency department for emergency invasive coronary angiography, with or without indication for percutaneous coronary revascularization of the culprit lesions. All patients will undergo complete clinical examination, laboratory testing (full blood count, biochemical analysis, inflammatory biomarkers, and electrolyte levels), transthoracic echocardiographic assessment, 12-lead electrocardiography. Patient inclusion and exclusion criteria are listed in Table 1.

Study groups

The study population will be divided into two main groups: group 1 – patients with location of the culprit lesion at the level of the left anterior descending artery; group 2 – patients with culprit lesion location in the circumflex or the right coronary artery respectively. The main groups will further be divided into subgroups according to the presence or absence of out-of-hospital cardiac arrest, and according to the stenosis degree of the culprit lesion into <50% versus ≥50% stenosis (Figure 1).

STUDY ENDPOINTS

The study endpoints include: (1) left ventricular function and remodeling assessed with CMR, according to location of culprit lesion within the coronary tree, in patients with STEMI, with versus without OHCA; (2) MACE rates at 6 and 12 months after the acute event, according to culprit lesion location. In this study, MACE are defined as the composite endpoint of cardiovascular death, reinfarction, repeated cardiac arrest, heart failure and hospitalizations related to cardiovascular causes.

STUDY PROCEDURES

At baseline, after obtaining the informed consent, all patients will undergo complete clinical assessment, laboratory testing, 12-lead ECG, transthoracic echocardiography, and invasive coronary angiography with or without performing percutaneous coronary revascularization of

TABLE 1. Study inclusion and exclusion criteria

Inclusion criteria
Age over 18 years
Acute ST elevation myocardial infarction, at 12 h from onset of symptoms, who undergo invasive coronary angiography, with or without indication of percutaneous revascularization of the culprit lesion
Exclusion criteria
Non-ST segment elevation acute coronary syndromes (unstable angina, NSTEMI)
Non-ischemic causes of cardiac arrest
Acute myocarditis
Allergy to iodine contrast agent
End-stage renal disease
Pregnant women
Active neoplastic diseases
Patient/patient family refusal to participate in the study

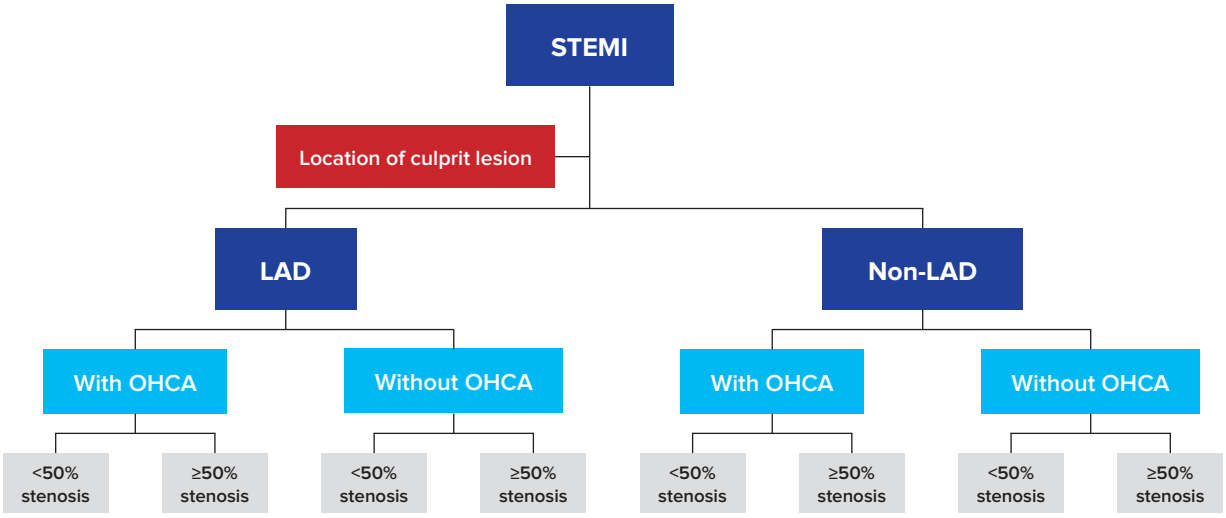

FIGURE 1. Group distribution of the study population according to the location of the culprit lesion within the coronary tree and the degree of stenosis. STEMI – ST-segment elevation myocardial infarction; LAD – left anterior descending artery; OHCA – out-of-hospital cardiac arrest

the culprit lesion, according to the current guidelines of the European Society of Cardiology regarding the management of patients with acute STEMI.

At the one-month follow-up, all patients will undergo assessment of cardiac function and structure, as well as evaluation of the myocardial scar and necrotic area, via CMR imaging with gadolinium tracing, as well as repeated clinical examination, ECG, echocardiography, and endpoint recordings.

The 6- and 12-month follow-up includes evaluation of the incidence of MACE rates, which in the present study are defined as the composite endpoint of cardiovascular death, reinfarction, repeated cardiac arrest, heart failure, and hospitalizations related to cardiovascular causes.

The study procedures are summarized in Table 2.

ETHICAL CONSIDERATIONS

All the study procedures will be conducted according to the ethical principles stated in the Declaration of Helsinki, and ethical approval from the Ethics Committee of both institutes where the study will be conducted

TABLE 2. Summary of the study protocol

	Baseline	1 month	6 months	12 months
Informed consent	■			
Screening for inclusion and exclusion criteria	■			
Demographic data	■			
Medical history	■			
Clinical examination	■	■	■	■
Records of vital signs	■	■	■	■
Pregnancy test	■			
Laboratory testing (CBC, biochemical analysis, inflammatory biomarkers, electrolyte levels)	■			
12-lead ECG	■	■	■	■
Transthoracic echocardiography	■	■	■	■
Invasive coronary angiography ± PCI of culprit lesion	■			
Cardiac MR	■	■		
Endpoint records	■	■	■	■

will be obtained. Signed written informed consent will be obtained from all patients included in the study, and in case of inability of consent from the patient, approval for study enrolment will be obtained from the patients' families.

CONCLUSIONS

In conclusion, the study will research the differences related to the location of the culprit lesion in patients with STEMI, who present OHCA versus patients without cardiac arrest, based on the hypothesis that STEMI patients with culprit lesions located at the level of the LAD, with a less than 50% stenosis, are more likely to present sudden cardiac arrest. At the same time, the study will develop a prediction model for OHCA in patients who present with STEMI, based on differences related to culprit location.

CONFLICT OF INTEREST

Nothing to declare.

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Perception of Healthy Eating among Romanian Adults

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ABSTRACT

Background: Totaling about 60% of all causes of death, chronic illnesses are the main cause of global mortality. Unhealthy behaviors, such as unbalanced eating or insufficient physical activity, can trigger metabolic changes, manifested by hypertension, high blood sugar, hyperlipidemia, obesity. These changes are grouped into the category of metabolic risk factors. Over time, these factors can cause cardiovascular diseases associated with a high mortality rate. **Aim of the study:** To evaluate the perception of healthy eating in a Romanian population. **Material and methods:** We applied a validated online questionnaire aimed to investigate people's attitude towards diet and their motivation regarding food consumption in ten countries, based on an international project. For the present paper, we evaluated a Romanian sample of 821 adult respondents. **Results:** Most of the subjects (82.82%) were from an urban area, and 68.94% were women. Regarding the prevalence of chronic diseases, 3.53% of participants had cardiovascular disease, 6.69% had high cholesterol levels, 7.18% were obese, and 6.57% were suffering from high blood pressure. Significant correlations have been identified between calorie count, excessive sugar and salt consumption, gender variables, cardiovascular disease, obesity, and high blood pressure. Also, tradition is very important in relation to eating behaviors, being highly correlated with obesity. The general direction of answers was correct, even if half of the questionnaire items were formulated in a 'negative' way, and disagreement is needed for a consistent response with a correct perception of healthy diets. The overall perception of healthy eating was consistent with scientific information in the field. **Conclusion:** Women are generally better informed than men regarding healthy eating. Also, there is a possible conflict between traditional food-related cultural values and modern nutritional guidelines based on scientific information.

Keywords: healthy food, chronic diseases, diet, cardiovascular diseases, obesity

INTRODUCTION

A balanced diet with a healthy nutritional intake is a protective factor against all forms of malnutrition and most non-communicable diseases (NCDs) including cardiovascular diseases, diabetes, stroke, and various types of cancer.[1,2]

On the other hand, an unhealthy diet, combined with an insufficient level of physical activity, is a major risk to the health of the person. In order to reduce this risk, a healthy diet is required, even before conception.[3] Breastfeeding supports the healthy development of children, improving their cognitive development and reducing the risk of overweight and obesity, as well as that of developing NCDs during adulthood.[4]

For a healthy life, caloric intake should be kept in balance with energy consumption. Studies show that fat intake should be kept below 30% of the total caloric intake in order to avoid overweight. It is also advisable to consume predominately unsaturated fats at the expense of saturated ones and to avoid industrial trans fats as much as possible.[5]

One of the diseases associated with an unhealthy diet is type 2 diabetes, which can be prevented or its onset delayed by maintaining a healthy diet and an adequate level of daily physical activity, by maintaining body weight within normal limits, and by avoiding smoking. Regular screening, along with treatment measures for associated complications, are also part of the management of type 2 diabetes.[6]

A healthy diet involves reducing sugar consumption below 10% of the total caloric intake; additional health benefits can be achieved by reducing sugar consumption below 5%.[7] Salt consumption is also important in maintaining a healthy diet; studies show that optimum salt intake is less than 5 g per day. Keeping salt intake below this level contributes to preventing the onset of high blood pressure (HBP) and implicitly to reducing the risk of cardiovascular diseases and stroke in adults.[8,9]

As part of a series of global efforts to achieve a healthy life, the World Health Organization (WHO) has set the goal to reduce salt consumption by 30%, and to halt the upward trend in the incidence of diabetes and obesity in adolescents and adults and to reduce the prevalence of overweight in children by 2025.[10]

Both individual and population health are influenced by a number of genetic, environmental, social, and behavioral factors. The latter have a direct influence on health and are the easiest to change.[11] Modern lifestyle has induced certain behavioral patterns related to nutrition, physical activity, and the consumption of harmful substances that contribute to the emergence of health risk factors such as HBP, high cholesterol, or excess weight. These risk factors lead to the onset of cardiovascular disease or various cancers, thus increasing premature mortality. These two types of diseases are the predominant cause of premature death in Europe. Furthermore, eating behavior disorders and an unhealthy lifestyle facilitate the onset of a wide range of NCDs, thus affecting the quality of life of the entire population.

Eating behavior, and lifestyle in general, are also influenced by the cultural, social, and economic patterns of the micro- and macro-groups a person belongs to. According to studies conducted in Western Europe, in recent decades, economic growth seems to have induced an improvement in lifestyle only within a socio-economically disadvantaged population, suggesting that these groups are in a position to more easily adopt a series of behaviors that lead to a healthier life.[12]

WHO studies show that the increasing rate of global mortality is associated with a number of major risk factors such as HBP, high blood glucose, insufficient physical activity, and smoking (active or passive).[13] Contemporary diet is not one that can be considered healthy, and there is a certain degree of awareness regarding this in the general population, most people acknowledging that many foods in the daily basket contain large amounts of food additives. Most of the chicken meat currently on the market has a high content of estrogenic hormones, which represents a risk factor for the appearance of uterine cancer in girls and breast cancer in boys. Much of the food currently consumed globally is genetically modified. This leads to changes in the genetic matrix of the human population, which causes a number of hormonal disturbances among children, including an increase in the prevalence of infant obesity.[14–16]

Due to genetic changes in wheat and the use of food additives, currently marketed bread does not contain enough nutrients. The high level of gluten in flour is associated with the appearance of several conditions such as irritable bowel syndrome, intestinal inflammation, malabsorption, various deficiencies, or various types of anemia. The high starch content of genetically modified wheat makes a large amount of bread consumed by the population lead to the occurrence of conditions such as overweight, obesity, depression, and high triglyceride levels.

Food preparation can also adversely affect consumer health. Frying foods in oils used for a long period of time leads to their contamination with carcinogenic and even neurotoxic substances.

One of the most visible effects of our unhealthy contemporary lifestyle is the increasing prevalence of obesity, and fast food contributes significantly to this phenomenon. This type of diet is rich in saturated fats and salt, contributing to an increased risk of cardiovascular disease among consumers.

The aim of this study was to evaluate the perception of healthy eating in a Romanian population. There is a

wide range of information on this topic on various communication channels (internet, newspapers, magazines etc.), and not all are necessarily based on scientific evidence. Also, Romanian tradition promotes a high-calorie, sugar-rich diet, with a large amount of food at the main meals. In this context, it is of interest to evaluate the perception of people in our country of healthy eating by investigating the extent to which this perception is in accordance with modern scientific evidence of the field of dietetics.

In addition to a general assessment, we consider that it is also of interest to investigate population subgroups, selected according to a number of food-related criteria. Women's eating habits differ from those of men, an urban diet is not similar to that in rural areas, and the level of education can also influence the perception of a healthy lifestyle.

MATERIAL AND METHODS

We used a validated complex questionnaire comprised of 26 questions aimed at investigating people's attitude towards diet and their motivation regarding food consumption in ten countries. The questionnaire was developed in a project coordinated by the CI&DETS Research Center of the Polytechnic Institute of Viseu, Portugal (PROJ/CI&DETS/2016/0008: EATMOT).

For the present paper, we used the results obtained in Romania, by applying the questionnaire to 821 respondents in 2018. All participants were adults, and they answered the questionnaire voluntarily, after informed consent. The application of the questionnaire was done online, respecting the anonymity of the subjects who participated in the study.

The data thus obtained has been centralized and converted into a spreadsheet format using a convenient coding of the answers provided by the participants.

Sections 1–4 of the questionnaire collected demographic data, while sections 16–20 focused on the perception of healthy food by investigating the extent to which this perception is in accordance with modern scientific evidence regarding diet. The questions addressed the presence of chronic diseases among participants and their perception of possible links between diet and chronic diseases, their perception of healthy eating in general, and the sources of information they use in relation to healthy eating. This information was supplemented by general information regarding gender, level of education (gymnasium, high school, or college/university), and living environment (urban, suburban, or rural).

Regarding the three relevant sections of the questionnaire, Section 16 aimed to gather information about possible chronic diseases the study participants were suffering of. They were asked to answer the question "Do you suffer from any chronic disease?". We focused on four conditions present among the answers: cardiovascular disease, high cholesterol, hypertension, and obesity.

Section 19 of the questionnaire included 10 questions regarding the respondents' perception of healthy eating. A 5-level Likert scale was used to collect the answers, which were coded with numbers from 1 to 5, 1 for 'total disagreement' and 5 for 'total agreement'. The neutral point of the scale was score 3, which suggests a non-involvement with the subject. The questions were formulated in a 'positive' or in a 'negative' way: questions where the correct answer was represented by a score higher than 3 or answers such as 'agree' or 'strongly agree', were considered to be 'positive' (questions 3, 4, 5, 6, and 9).

TABLE 1. Section 19 of the questionnaire (respondents' perception of healthy eating)

19.	Please indicate, on the scale below, between 'Totally Disagree' and 'Totally Agree', your opinion on the following statements	Totally disagree	Disagree	Neither agree nor disagree	Agree	Totally agree
19.1	A healthy diet should be based on calorie counting	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.2	We should never consume sugar products	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.3	Fruits and vegetables are very important in the practice of healthy eating	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.4	A healthy diet should be balanced, varied and complete	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.5	We can eat anything, as long as it is in small quantities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.6	Healthy eating is not cheap	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.7	In my opinion, it is strange that some people have the appetite for sweets	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

TABLE 2. Section 20 of the questionnaire (sources of information on healthy eating)

20.	Where do you usually find information about adopting a healthy diet?	Never	Sporadically	Sometimes	Frequently	Always
20.1	Health centers, hospitals, family doctors	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.2	Radio	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.3	Television	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.4	School	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.5	Magazines, books, newspapers	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.6	Internet	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.7	Family, friends	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Conversely, questions where the correct answer was represented by a score lower than 3, or 'disagreement' or 'total disagreement', were considered to be 'negative' (questions 1, 2, 7, 8, and 10). Question 8, "Do you believe that tradition is very important for a healthy nourishment?", could be interpreted as 'positive' or 'negative' depending on the country or region where the questionnaire was applied. For Romania, given the fact that most traditional dishes are rich in saturated fats or sugars, we considered this item to be 'negative'.

Section 20 aimed to gather information about information sources predominantly used by participants to obtain information on healthy eating. The question asked in these section was: "Where do you usually find information about adopting a healthy diet?". A 5-level Likert scale coded with numbers from 1 to 5 (1 for 'never' and 5 for 'always') was used to collect the answers.

To analyze the responses gathered with the questionnaires, we used several descriptive statistical indicators. Thus, the average and the standard deviation of the scores obtained for each question in sections 19 and 20 were calculated.

We also sought to investigate the possible impact of the following respondent-related factors: respondent gender (male, female), education level (general school, high school, university), living environment (urban, suburban, rural), and the presence of chronic diseases or conditions (cardiovascular diseases, high cholesterol level, obesity, HBP).

Average response scores and standard deviations were calculated for each of the above groups. In order to identify significant relationships between the variables we studied, we used the contingency tables and the Chi-square test. The significance threshold used was 5%, the differences being considered significant for $p < 0.05$. Cramer's V test was used to assess the strength of statistical significance. Data centralization was done using Microsoft Excel 2013. Statistical processing was performed using IBM SPSS Statistics v.20 (IBM Corp., Armonk, NY, USA).

RESULTS

Socio-demographic data

The total number of respondents was 821. Of these, 255 (31.05%) were men and 566 (68.94%) women. Regarding the level of education, 9 (1%) respondents finished elementary school, 173 (21.07%) were high school graduates, and 639 (77.83%) had higher education. Most of the participants, 680 (82.82%) came from urban areas, 114 (13.88%) from rural areas, and 27 (3.28%) from a suburban environment.

As far as the prevalence of chronic diseases is concerned, 29 of the participants stated that they suffered from cardiovascular disease, 55 participants had high cholesterol levels, 59 were obese, and 54 suffered from HBP (Figure 1).

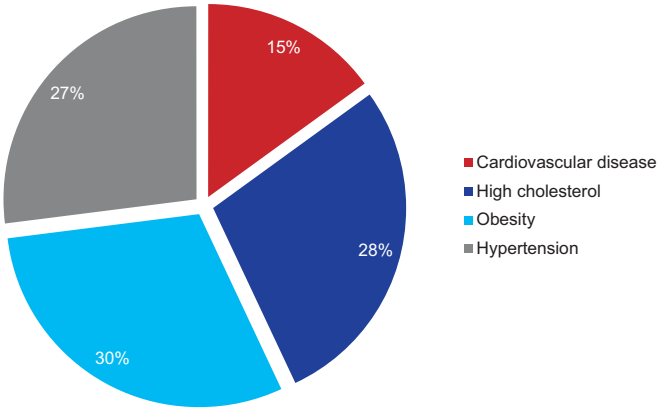

FIGURE 1. The prevalence of chronic diseases in the study population

TABLE 3. The link between questions in section 19 (perception of healthy eating) and different variables

Variable	19.1 – a healthy diet should be based on calorie counting				19.2 – we should never consume sugar products				19.3 – fruits and vegetables are very important in the practice of healthy eating				19.4 - a healthy diet should be balanced, varied and complete				19.5 – we can eat anything, as long as it is in small quantities				19.6 – healthy eating is not cheap				19.7 – in my opinion, it is strange that some people have the appetite for sweets			
	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value
Gender																												
Female	2.76	1.03	42.9	0	2.77	1.08	16.2	0	4.53	0.9	1.55	0.82	4.52	0.94	5.41	0.25	3.72	1.18	13.6	0.01	3.65	1.17	17.22	0	2.24	0.98	8.78	0.07
Male	3.24	1.07	–	–	3.05	1.03	–	–	4.58	0.79	–	–	4.52	0.86	–	–	3.98	1.13	–	–	3.95	1.13	–	–	2.37	0.9	–	–
Level of education																												
Elementary school	2.44	0.88	10.8	0.21	2.56	1.33	13.6	0.09	4.44	0.53	8.07	0.43	4.56	0.53	10.6	0.23	3.78	0.67	13.9	0.09	3	1.41	10.76	0.22	2.22	1.48	15.1	0.06
High school	3.04	1.08	–	–	2.68	1.08	–	–	4.53	0.94	–	–	4.44	0.95	–	–	3.79	1.25	–	–	3.79	1.19	–	–	2.26	1.01	–	–
University	2.88	1.06	–	–	2.91	1.06	–	–	4.55	0.85	–	–	4.54	0.91	–	–	3.81	1.16	–	–	3.74	1.15	–	–	2.29	0.93	–	–
Living environment																												
Rural	2.96	1.01	10.8	0.21	2.81	1.1	5.36	0.72	4.54	0.93	3.88	0.87	4.51	0.91	4.46	0.81	3.83	1.2	11.3	0.19	3.68	1.19	10.84	0.21	2.38	1.02	10.3	0.25
Urban	2.89	1.08	–	–	2.86	1.06	–	–	4.54	0.87	–	–	4.52	0.93	–	–	3.79	1.18	–	–	3.75	1.17	–	–	2.26	0.94	–	–
Suburban	3.11	1.01	–	–	3	1.18	–	–	4.63	0.57	–	–	4.59	0.57	–	–	3.93	0.83	–	–	3.7	0.95	–	–	2.48	1.01	–	–
Chronic diseases																												
Cardiovascular disease – Yes	3.59	1.18	22.3	0	3.07	0.96	2.71	0.61	4.48	0.91	1.75	0.78	4.41	1.12	4.45	0.35	4.41	0.87	10.4	0.03	4.21	1.11	7.54	0.11	2.38	0.86	5.58	0.23
Cardiovascular disease – No	2.89	1.05	–	–	2.85	1.07	–	–	4.55	0.87	–	–	4.52	0.91	–	–	3.78	1.18	–	–	3.72	1.16	–	–	2.28	0.96	–	–
High cholesterol – Yes	2.98	1.01	1.31	0.86	3.15	1.04	4.77	0.31	4.53	0.79	3.32	0.51	4.51	0.81	2.69	0.61	4.13	0.94	5.85	0.21	3.75	1.17	3.98	0.41	2.36	0.95	1.66	0.8
High cholesterol – No	2.9	1.07	–	–	2.83	1.07	–	–	4.55	0.87	–	–	4.52	0.92	–	–	3.78	1.18	–	–	3.74	1.16	–	–	2.28	0.95	–	–
Obesity – Yes	3.08	1.19	13.8	0.01	3.08	1.26	12.9	0.01	4.54	0.88	1.85	0.76	4.61	0.87	3.12	0.54	3.86	1.12	2.46	0.65	3.68	1.15	4.07	0.4	2.17	1	4.4	0.35
Obesity – No	2.89	1.06	–	–	2.84	1.05	–	–	4.55	0.87	–	–	4.51	0.92	–	–	3.8	1.18	–	–	3.74	1.17	–	–	2.29	0.95	–	–
Hypertension – Yes	3	1.24	16.7	0	2.89	1.09	2.82	0.59	4.43	0.98	2.91	0.57	4.59	0.98	4.51	0.34	3.91	1.1	1.23	0.87	3.61	1.2	5.30	0.26	2.61	1.2	15.5	0
Hypertension – No	2.9	1.05	–	–	2.86	1.07	–	–	4.55	0.86	–	–	4.51	0.91	–	–	3.79	1.18	–	–	3.75	1.16	–	–	2.26	0.93	–	–

TABLE 4. The link between questions in section 20 (sources of information on healthy eating) and different variables

Variable	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value	Mean	SD	Chi²	p value
	20.1 – health centers, hospitals, family doctors				20.2 – radio				20.3 – television				20.4 – school				20.5 – magazines, books, newspapers				20.6 – internet				20.7 – family, friends			
Gender																												
Female	2.77	1.13	17.9	0	2.63	1.12	54.6	0	2.93	0.99	52.4	0	2.75	1.2	12.65	0.01	3.48	1.02	11.8	0.02	3.87	0.93	12.7	0.01	3.3	1.01	13.1	0.01
Male	2.71	0.95	–	–	3.22	1.3	–	–	3.26	1.19	–	–	3.03	1.19	–	–	3.69	1.07	–	–	4.01	0.84	–	–	3.53	1.03	–	–
Level of education																												
Elementary school	2.44	1.33	19.2	0.01	2.22	0.97	16	0.04	3.11	0.78	16.8	0.03	2.33	0.71	32.53	0	3.44	0.88	9.46	0.31	3.44	1.13	13.8	0.09	4	0.87	8.90	0.35
High school	2.94	1.17	–	–	2.96	1.27	–	–	3.14	1.16	–	–	3.16	1.25	–	–	3.66	1.1	–	–	3.98	0.94	–	–	3.35	0.95	–	–
University	2.71	1.05	–	–	2.78	1.19	–	–	3	1.04	–	–	2.75	1.18	–	–	3.52	1.03	–	–	3.91	0.89	–	–	3.36	1.04	–	–
Living environment																												
Rural	2.94	1.14	16.4	0.04	2.95	1.2	12.1	0.15	3.07	1.09	9.68	0.29	3	1.2	6.76	0.56	3.59	1	16.5	0.04	3.81	0.91	6.78	0.56	3.3	0.99	8.97	0.34
Urban	2.73	1.07	–	–	2.81	1.21	–	–	3.04	1.06	–	–	2.82	1.21	–	–	3.56	1.05	–	–	3.95	0.9	–	–	3.4	1.02	–	–
Suburban	2.44	1.05	–	–	2.3	0.99	–	–	2.56	0.97	–	–	2.52	1.09	–	–	3.04	0.81	–	–	3.67	0.88	–	–	2.96	1.09	–	–
Chronic diseases																												
Cardiovascular disease – Yes	2.93	1.03	3.85	0.43	3.48	1.33	13.2	0.01	3.62	1.05	14.3	0.01	3.14	1.41	6.51	0.16	3.79	1.21	6.64	0.16	4	0.96	2.03	0.73	3.41	1.09	1.91	0.75
Cardiovascular disease – No	2.74	1.08	–	–	2.79	1.2	–	–	3.01	1.06	–	–	2.82	1.2	–	–	3.54	1.04	–	–	3.92	0.9	–	–	3.37	1.02	–	–
High cholesterol – Yes	2.84	1.07	2.26	0.69	4.76	1.33	8.53	0.07	3.16	0.96	4.02	0.4	2.62	1.18	2.09	0.72	3.64	0.95	2.67	0.62	3.95	0.59	16.1	0	3.64	0.87	5.29	0.26
High cholesterol – No	2.75	1.08	–	–	2.82	1.2	–	–	3.02	1.07	–	–	2.85	1.21	–	–	3.54	1.05	–	–	3.92	0.93	–	–	3.35	1.03	–	–
Obesity – Yes	2.88	1.13	2.42	0.66	2.58	0.97	7.65	0.11	2.9	1.06	3.9	0.42	2.68	1.09	5.70	0.23	3.29	1.02	16.1	0	3.85	1.01	3.2	0.53	3.25	0.98	1.55	0.82
Obesity – No	2.74	1.08			2.84	1.22			3.05	1.06			2.85	1.21			3.57	1.04			3.92	0.9			3.38	1.03		
Hypertension – Yes	2.76	1.23	3.14	0.53	2.59	1.09	7.43	0.12	2.98	1.02	0.8	0.94	2.52	1.24	6.67	0.15	3.26	0.94	9.7	0.05	3.78	0.98	3.69	0.45	3.41	1.02	1.87	0.76
Hypertension – No	2.75	1.07	–	–	2.83	1.22	–	–	3.04	1.07	–	–	2.86	1.2	–	–	3.57	1.05	–	–	3.93	0.9	–	–	3.37	1.03	–	–

Perception of healthy eating

In the section assessing the perception of healthy eating, average response rates and abnormalities within each group were calculated according to the criteria of interest of the study: gender, level of education, living environment, and the presence of one of the targeted chronic diseases (cardiovascular disease, high cholesterol, obesity, HBP).

Question 19.1 – "A healthy diet should be based on calorie counting", has statistically significant links ($p < 0.05$) between gender, cardiovascular disease, obesity, and hypertension.

Question 19.2 – "We should never consume sugar products", identified significant links between gender and obesity.

Questions 19.3 and 19.4 – "Fruits and vegetables are very important in the practice of healthy eating" and "A healthy diet should be balanced, varied and complete", showed no significant links between the variables covered in this study.

Question 19.5 – "We can eat anything, as long as it is in small quantities", showed significant links between gender and cardiovascular diseases.

Question 19.6 – "Healthy eating is not cheap", identified significant links between this question and gender.

Question 19.7 – "In my opinion, it is strange that some people have the appetite for sweets", identified significant links between this question and hypertension.

Sources of information on healthy eating

Section 20 of the questionnaire aimed to gather data regarding preferred sources of information on healthy eating. For each item in this section, the average response rates and deviations in each group of participants were calculated according to the criteria of interest in the study: gender, level of education, living environment, and the presence of one of the targeted chronic diseases (cardiovascular disease, high cholesterol, obesity, HBP).

Item 20.1 – "Health centers, hospitals, family doctors" – Significant links were found between this item, female gender, level of education, and rural environment.

Item 20.2 – "Radio" – Statistically significant links have been identified between radio listeners, female gender, level of education, and cardiovascular disease.

Item 20.3 – "Television" – Significant links have been identified between this item, female gender, level of education, and cardiovascular disease.

Item 20.4 – "School" – Significant links between school, female gender, and level of education were identified.

Item 20.5 – "Magazines, books, newspapers" – Significant data were registered between this item, female gender, obesity, and hypertension.

Item 20.6 – "Internet" – We found significant differences between internet preferences, female gender, and high cholesterol levels.

Item 20.7 – "Family, friends" – We had a significant comparing data between this item and female gender (Table 2).

DISCUSSIONS

Analyzing the response score averages for each question, we observed some general trends in the respondents' perception of healthy eating and their preferences for information sources on the subject. Thus, in Section 19 of the questionnaire, the general direction of the answers was in line with the 'direction' in which the questions were formulated: 'positive' questions (3, 4, 5, 6, and 9) obtained average scores above the neutral value of 3, and 'negative' questions (1, 2, 7, 8, and 10) obtained averages below 3.

Analyzing the results obtained for the different groups of participants, we note that there were significant differences between answers to a series of questions. In the following, we will detail some of these differences, while trying to argue the reasons for their occurrence.

In Section 19 of the questionnaire, assessing the respondents' perception of healthy eating, the response scale has a neutral point between the 'Agree' or 'Disagree' options, corresponding to the 'three' score in our coding. In this context, the significant differences between the average scores of the different groups for which the two averages are located on both sides of the neutral value 3 are particularly interesting. In these situations, the average of a group's responses tends towards an 'agreement' with the content of the question, while the average of the other group's responses tends to a 'disagreement'.

For the question "A healthy diet should be based on calorie counting", there was a significant difference between the average of the answers given by women (2.76) and men (3.24). Women tend to disagree with this statement, while men tend to agree with it. We can attribute this difference to the fact that in Romania, the preparation of household food is made mostly by women, therefore they are better informed regarding healthy eating than men. Women tend to be more involved in nutrition issues, have a better knowledge of food and nutrition, are more prone to follow a diet, and are more likely to perceive having to lose weight.[17] Other significant differences that place two groups on two opposite parts of the neutral point of the scale were found in respondents suffering from cardio-

vascular disease (3.59) vs. respondents who did not suffer from this type of disease (2.89), as well as obese (3.08) vs. non-obese (2.9) respondents. These differences may occur as a result of the diets prescribed for the participants suffering from these two conditions. These diets probably involve a reduction in caloric intake, which justifies the concern of the two groups in this direction.

In case of "We should never eat sugar products", similarly to the previous question, there were also significant differences between women and men (2.77 vs. 3.05), and between obese and non-obese respondents (3.08 vs. 2.84). We consider the potential causes to be similar: the fact that women are better informed on healthy eating and the effects of prescribed diets for obese patients.[18]

For questions "Fruits and vegetables are very important in the practice of healthy eating" and "A healthy diet should be balanced, varied and complete", no significant differences were found between the studied groups. All of the groups have achieved averages over 4, indicating their members' agreement with the statements in question. The two statements coincide with the main messages transmitted in the media (radio, television, and the Internet) through programs promoting healthy eating, and the high scores obtained suggest that these messages have an impact on the perception of the population.[19]

In the case of the question "We can eat anything, as long as it is in small quantities" there were significant differences between the averages of women's and men's responses, as well as of respondents' with and without a cardiovascular disease. The averages of the four groups were all above the neutral point, showing their consent with the asserted claim. This type of message, regarding the control of the quantities of food consumed, also occurs in campaigns promoting healthy eating, but not so often as the previous two messages. This is reflected in the averages of the scores obtained, which are lower than the averages calculated for questions 19.3 and 19.4.

The question "Healthy eating is not cheap" also shows a significant difference between women and men, but the averages denote the agreement of both groups with the assertion (3.65 and 3.95, respectively). There are two observations to be made regarding this question. First, respondents with elementary school as their highest form of education got an average of only 3.00, which overlaps with the neutral answer 'neither agree nor disagree'. We assume these are very young participants, who are not yet involved in the economic management of the diet. Second, the average of respondents suffering from a cardiovascular disease (4.21) is the only one over 4.00 of all groups (although the difference is not statistically significant compared to respondents without a cardiovascular disease). We can interpret this high value as it relates to the cost of recommended diets for this type of affection.[20]

Regarding the question "In my opinion, it is strange that some people have appetite for sweets", there were no differences that would place the groups in antagonistic positions. There was a significant difference between respondents with and without hypertension, but both values denote disagreement with the statement (2.61 vs. 2.26, respectively). All groups expressed their disagreement with the statements, as shown by their scores below 3.

To the question "I think tradition is very important for a healthy diet", most of the groups obtained average scores that disagree with this statement. There is, however, a notable exception. There was a statistically significant difference between obese and non-obese respondents, which places the two groups in antagonistic positions. Thus, obese participants obtained an average of 3.10, indicating to some extent an agreement with the statement, while non-obese participants obtained an average of 2.69, indicating disagreement with the statement. In this context, we can interpret the result as being related to the cultural values of our country, which influence eating behavior towards a hypercaloric diet. This type of cultural value most likely makes its effects felt before the diagnosis of obese patients. It may also conflict with the recommendations made by dietitians to this type of patient.[21]

In case of the "I think biologically produced foods are healthier" item, all groups of study participants have agreed with the statement. There was a statistically significant difference between the averages of women's and men's responses (3.91 vs. 4.00, respectively), but both values are well above the neutral point, denoting the agreement of both groups with this item. In this case, we can also consider that this type of information effectively reaches consumers through media channels.

In case of the item "We should never drink fat products", there were three significant differences between score averages, which place certain groups in antagonistic positions over this claim. Women obtained a score that denotes disagreement with this item (2.49), while men obtained a slightly higher average than the neutral value (3.09), the difference being statistically significant. We can attribute this difference to the greater awareness of women in the field of nutrition in the context of their predominant role in the preparation of the family diet.

Significant differences also occurred between cardiovascular patients (3.55) and those who were not diagnosed with this type of disease (2.64), as well as between respondents with high cholesterol (3.02) and respondents with

normal cholesterol (2.65). A strict diet is recommended for these two conditions, the recommendation being made by a physician. Generally, fat reduction is recommended without providing detailed information about the type of fat to be avoided. From here, a non-discriminatory perception of these types of patients can arise over dietary fats, a perception reflected in the answers to this item of the questionnaire.

Also, there were significant differences between obese (2.32) and normal-weight respondents (2.70), as well as between respondents with hypertension (2.44) and respondents with normal tension (2.69). However, averages values denote the disagreement of these groups with the statement. These types of illnesses are usually chronic, requiring longer diets, and we can assume that this enables patients to be better informed on healthy eating, possibly even dieting.

In Section 20 of the questionnaire, regarding the respondents' preferred sources of information on healthy eating, we can see that the main sources of information are the Internet, magazines, family and friends, and television. Analyzing the differences in score averages among the different groups of respondents, we can see that men are more informed through radio and television than women, similar results being obtained in patients with and without cardiovascular diseases. Out of all the assessed sources of information, the Internet has obtained the highest average scores. Given that the questionnaire was completed exclusively online, we can consider that the respondents had a common profile: above average education, from urban areas, and with access to the internet – which can also be considered a bias.

A healthy diet is a priority for reducing chronic diseases, including obesity, diabetes, cardiovascular disease, and many cancers. This is particularly important for socio-economically disadvantaged populations with limited access to healthy diets and a higher risk of disease. The availability and cultural acceptability of healthy foods are obstacles to promoting a healthy diet.[22] Documented evidence suggests that women are more inclined to buy environmentally friendly foods than men and also tend to adopt behaviors aimed at improving and/or maintaining a good health status, compared to men.[23]

In today's society, with 'fast' lifestyles where people hardly seem to find the time to do everything they wish to, the demand for convenience foods has grown. Many factors can justify this growing trend, such as changes in household structure, intensification of female employment, response of the food industry, marketing campaigns and advertisements, availability of kitchen technology compatible with cooked or pre-cooked meals, individualism, lack of time, or poor cooking skills.[24–27]

CONCLUSIONS

The overall perception of healthy eating in the Romanian population we studied is consistent with scientific information and appears to be influenced by the mainstream messages that are transmitted through media channels. This shows that this type of communication and messages have an impact on the perception of the population. In the future, these digital health interventions could be used to provide more detailed information about a healthy diet, for better outcomes.

Our results suggest that women are generally better informed than men regarding healthy eating. It has also been shown that there is a possible conflict between traditional food-related cultural values and modern guidelines based on scientific information in the field of diet.

Data from certain categories of patients reveal the tendency to follow the diet recommended for the conditions they are suffer from. This may be due to a lack of more detailed information on certain aspects of healthy eating. Increasing the number of dietitians to reach a critical mass, as well as a greater presence of these specialists in the public health system could correct this deficiency.

CONFLICT OF INTEREST

Nothing to declare.

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ETHICAL APPROVAL

The patients signed a written informed consent, and the study procedures were performed according to the ethical principles stated in the Declaration of Helsinki. The study was also approved by the Ethics Committee of CI&DETS, reference no. 03/2015.

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ORIGINAL RESEARCH

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The Relationship between Anxiety and Immunity in Pediatric Oncology Patients

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ABSTRACT

Background: Pediatric onco-hematology is not a frequently encountered medical specialty, and it influences everyday life, basic activities, and the immune system, mostly through psycho-social changes, which may affect every individual and their families differently. Anxiety is the most frequently encountered mental health disorder occurring during childhood and adolescence. The effect of stress and anxiety on the immune system is suggested by the fact that stress hormones elevate proinflammatory cytokines and subsequently lower the anti-inflammatory response. **Objective:** Our main objective was to analyze the relationship between anxiety disturbance and cytokine levels in oncologic pediatric patients from Târgu Mureș in order to answer the following question: does anxiety influence immunity? **Material and methods:** After testing pediatric oncology patients from the Pediatrics Clinic no. 2 of Târgu Mureș, Romania with the SCARED child test, we took blood samples from each participant. IL-6, IL-10, IL-1β, IL-12p40 and TNF-α levels were evaluated with a Human Cytokine Magnetic Panel using the xMAP technique on Flexmap 3D platform (Luminex Corporation, Austin, USA). C-reactive protein levels were determined with the BN Pro Spec nephelometer with CardioPhase hsCRP (Siemens Healthcare Diagnostics, GmbH, Marburg, Germany) reagent. **Results:** The 46 pediatric oncology patients had 6 main diagnostic groups, the most frequent pathology was acute leukemia (58.7%) followed by malignant solid tumors (21.74%) and lymphomas (6.52%). In the anxious group (45.65%) we observed 4 of the 5 studied anxiety types: panic disorder, separation, social, and generalized anxiety. We measured the cytokine levels of all the participants from the two main groups: anxious/non-anxious. Statistical analysis (linear regression) showed statistically significant positive correlations in the anxious group related to the IL-1β and IL-6, a moderate/weak correlation related to IL-12p40, as well as a negative moderate correlation between IL-10 values in the anxious group and a positive trend in the non-anxious group. **Conclusions:** Psycho-oncology is a relatively young specialty with few studies in the last two decades. IL-1β, IL-6, and TNF-α present high levels in anxious patients, while IL-10 and IL-12p40 have low serum levels in mental disorders. C-reactive protein levels are not influenced by anxiety.

Keywords: anxiety disorder, pediatric oncology, inflammatory cytokines, immune response

INTRODUCTION

Pediatric onco-hematology is not a frequently encountered medical specialty, and it presents a heavy psychological and social influence, as these disorders affect both the pediatric patients, as well as their family members, with profound consequences on everyday life and basic human functions, while also impacting the immune system.[1] Therapeutic options vary with each pathology group and consist of chemotherapy, surgical treatment, radiotherapy, and bone marrow transplant according to international protocols for each diagnosis.

Cytostatic courses are followed by temporary medullary aplasia with septic or bleeding complications. In case of acute leukemia, secondary bone marrow aplasia is much longer and more severe than in the case of solid tumors or lymphomas with shorter duration, which are much easier to correct.[2,3]

In pediatric oncology, the prolonged hospitalization period, uncertainty regarding the future, social isolation and seclusion from family members, oncological therapies (radio- and chemotherapies), as well as the presence of intracranial tumors or metastases can have a direct negative impact on the psychological wellbeing of the pediatric patients.[4,5] Furthermore, the harsh and prolonged treatments, as well as the imminent death threat may create traumatic sequelae in the child's psychic function and maturation process.[4]

Children with malignancies and their families must face a prolonged period of medical treatment in the hospital, with a tremendous uncertainty regarding their future. All members of these families can suffer from emotional distress on a short or long term.[5]

Anxiety is the most frequent mental disorder that occurs in children and adolescents, 15–20% of individuals experiencing anxiety at some point in their life. If ignored, the symptoms may prolong throughout adulthood and lead to psychosocial complications.[6] There are different types of anxiety disorders: separation anxiety, selective mutism, specific phobias, social anxiety, drug-induced anxiety, medical conditions-induced anxiety, panic disorder, agoraphobia, generalized anxiety, or school avoidance.[7]

Cytokines, as signaling molecules for the modulation of the immune response, can be present in the circulation in picomolar quantities. In cases of infection or inflammation, cytokine levels can rise to 1,000 times. Some cytokines have a proinflammatory role, others an anti-inflammatory role.[8]

The effect of psychological stress and anxiety on the immune system is triggered by the release of stress hormones, which lead to an overexpression of proinflammatory cytokines (IL-1, IL-6, TNF-α) and low levels of anti-inflammatory cytokines (IL-10, IL-12).[9,10]

Proinflammatory cytokines IL-1, IL-6, and TNF-α, and anti-inflammatory cytokines IL-4, IL-10, and IL-3 have a very important role in the pathogenesis of depression. Different immune responses have been observed according to the severity, nature, and duration of the stress factor: severe stress alters immunity through time, while moderate stress stimulates immune reactions, as shown by Glaser *et al.*[11] The same study demonstrated that the concentration of proinflammatory cytokines rises in the plasma of depressive patients and recedes after healing.[11]

OBJECTIVE

Our main objective was to find a correlation between anxiety disorder and cytokine levels in pediatric oncology patients from Târgu Mureș, Romania. Secondary objectives were to evaluate the frequency of anxiety in the oncologic pediatric population, to identify different anxiety types and compare them with anamnestic data in order to identify certain factors that influence anxiety. Another question that we would like to answer is: does anxiety influence immunity?

MATERIALS AND METHOD

Participants

After their parents completed the consent form, we tested pediatric oncology patients from the Pediatrics Clinic no. 2 of Târgu Mureș, Romania, aged between 7 and 21 years, diagnosed with malignant diseases until the age of 18 years.

Anxiety levels were analyzed using the SCARED child test, created in 1997 by Dr. Boris Birmaher, which can be used without a special license and comprises a personal questionnaire for anamnestic data. By completing the questionnaire, patients can be categorized in 5 types of anxiety disorders: panic disorder, generalized anxiety, separation anxiety, social phobias, and school avoidance.

Laboratory determination

We took blood samples from each participant. The samples were centrifuged, and the serum was stored at –80 °C.

IL-6, IL-10, IL-1β, IL-12p40, and TNF-α levels were measured with a Human Cytokine Magnetic Panel (EMD Millipore Corp, USA) using the xMAP technique. Serum samples were incubated with monoclonal antibody

TABLE 1. Summary of anamnestic data in the studied lot

		N	%
Age groups	7–10 years	16	34.8%
	11–13 years	15	32.6%
	14–16 years	7	15.2%
	17–21 years	8	17.4%
Gender distribution	Male	30	65.22%
	Female	16	34.78%
Provenance distribution	Urban	26	56.52 %
	Rural	20	43.48%
Education level	Primary	17	36.96%
	Middle	17	36.96 %
	Highschool	12	26.9%
Number of truancy months	0–3 months	18	39.13%
	4–6 months	14	30.43%
	7–9 months	4	8.7%
	10–12 months	7	15.22%
	>12 months	3	6.52%
Catheter presence	Yes	32	71.1%
	No	14	28.9%
Treatment phase	Chemotherapy	10	21.74%
	Remission	33	71.74%
	Does not correspond	3	6.54%
Anxiety	Yes	21	45.65%
	No	25	54.35%
Anxiety disorders	Separation	10	47.62%
	Generalized	2	9.52%
	Panic	2	9.52%
	Social	7	33.33%

marker spheres. Different reagent-adding steps were performed, followed by washing in order to obtain sandwich-like antigen-antibody complexes, which were analyzed on the Flexmap 3D platform (Luminex Corporation, Austin, USA).

CRP levels were determined with the BN Pro Spec nephelometer with CardioPhase hsCRP (Siemens Healthcare Diagnostics, GmbH, Marburg, Germany) reagent. The reference interval was <3 mg/L, with a measuring interval of 0.175–11 mg/L, minimal detection limit 0.175 mh/L, intra- and inter-run coefficient of variation <4.0% and <4.6%, respectively.

Statistical data analysis

Data has been centralized in a Microsoft Excel file and processed with the IBM SPSS version 22.0 (IBM Corp, Armonk, NY, USA) statistical program. Cytokine levels were evaluated with descriptive and interference statistics through the Wilcoxon test, and due to the fact that the data was widely spread, we eliminated extreme numerical values with the Grubbs (box-plot) test. The reviewed descriptive analysis enabled the use of the t test and linear regression method to highlight a correlation between anxiety and cytokine levels.

RESULTS

We tested 46 pediatric oncology patients aged between 7–21 years (mean 12.46 years, SD 3.361). Demographic and anamnestic data analysis is presented in Table 1.

Table 1. Summary of anamnestic data in the studied lot

The pathology was split into 6 main diagnostic groups, the most frequent pathology being acute leukemia (58.7%), followed by malignant solid tumors (21.74%) and lymphomas (6.52%).

The age group distribution related to pathology shows that leukemia and solid tumors are more frequent under the age of 13, and that lymphomas are more frequent in the 16–18 years age group.

Based on the SCARED test results we stratified the patients into anxious and non-anxious clusters (Table 1).

TABLE 2. Statistical results of the studied lots (anxious/non-anxious) according to the analyzed parameters

		Anxious		Non-anxious		p value
		N	%	N	%	
Age groups	≥7 ; ≤10	8	38.1%	8	32.0%	
	≥11; ≤13	10	47.6%	5	20.0%	
	≥14; ≤16	1	4.8%	6	24.0%	
	≥17; ≤21	2	9.5%	6	24.0%	0.074
Residence	Urban	11	42.3%	15	57.7%	
	Rural	10	50.0%	10	50.0%	0.604
Catheter	Yes	14	66.7%	19	76.0%	
	No	7	33.3%	6	24.0%	0.484
Diagnosis	Leukemia	10	47.6%	17	68.0%	
	Lymphoma	1	4.8%	2	8.0%	
	Malignant solid tumors	6	28.6%	4	16.0%	
	Border-line solid tumors	1	4.8%	1	4.0%	
	Benign solid tumors	3	14.3%	0	0.0%	
		0	0.0%	1	4.0%	0.283
Gender	Male	13	61.9%	17	68.0%	0.665
	Female	8	38.1%	8	32.0%	
Months of truancy	0–3 months	10	47.6%	8	32.0%	
	4–6 months	8	38.1%	6	24.0%	
	7–9 months	1	4.8%	3	12.0%	
	10–12 months	1	4.8%	6	24.0%	
	>12 months	1	4.8%	2	8.0%	0.277
Mothers' education level	0–4 grades	4	19.0%	0	0.0%	
	8 grades	6	28.6%	4	16.0%	
	High school	7	33.3%	9	36.0%	
	Postsecondary	0	0.0%	1	4.0%	
	University	4	19.0%	11	44.0%	0.060
Treatment	Yes	6	28.6%	4	16.0%	
	No	15	71.4%	21	84.0%	0.303
Siblings	No	4	19.0 %	5	20.0%	
	Yes (≤2)	16	76.2%	20	80.0%	
	Yes (>3)	1	4.8%	0	0.0%	0.719

In the anxious group we have observed 4 of the 5 studied anxiety types: panic disorder, separation, social, and generalized anxiety. None of our patients showed school-related anxiety. The incidence and frequency of different types of anxiety, as well as other anamnestic data are also shown in Table 1.

Most of the patients were admitted to the hospital with a first-degree relative (mother in 91.32% of cases and father in 2.22% of cases). Although there were no statistically significant differences between age groups in relation to the type anxiety disorder ($p = 0.537$), subjects aged under 13 years were more prone to present separation anxiety compared to other age demographics. Treatment complexity correlated with types of anxiety showed a statistically non-significant difference ($p = 0.061$). Correlations between the mother's level of education and the anxiety score show values close to the significant threshold ($p = 0.06$).

The anxiety-gender relationship was statistically non-significant ($p = 0.665$), as shown in Table 2.

Studying immunity in correlation with anxiety

We measured the cytokine levels of all the participants from the two main groups: anxious/non-anxious. The high standard deviation prompted us to identify the extreme values and to exclude them, as highlighted in Table 3.

Correlations between cytokine levels and the presence of anxiety are presented in Table 4.

Statistical analysis (linear regression) showed statistically significant positive correlations in the anxious group related to IL-1β and IL-6, a moderate/weak correlation

TABLE 3. The difference between mean IL serum levels in the studied lots

Anxious	N	Mean	SD	p value
Yes	9	1.82	2.50	0.016
No	34	1.35	1.27	
Yes	6	4.17	2.49	0.148
No	30	3.27	1.63	
Yes	10	12.45	9.61	0.645
No	31	9.61	14.29	
Yes	9	3.57	1.43	0.617
No	32	3.46	1.25	
Yes	9	30.21	12.97	0.680
No	34	25.72	12.77	
Yes	6	0.39	0.45	0.071
No	31	1.15	1.51	

in the anxious group related to IL-12p40, and a negative moderate correlation between IL-10 values in the anxious group and positive trend in the non-anxious group (Figures 1, 2, and 3).

DISCUSSIONS

Current literature data is scarce on the matter of the psycho-social impact of anxiety on pediatric oncology patients or their family members. However, the SCARED measuring tool has been developed for the quantification and categorization of anxiety and may be used without any special license or costs, its efficacy being comparable to other anxiety-measuring tools.

The 46 pediatric oncology patients included in our study had a mean age of 12.46 years (SD 3.361), with a preponderance of patients below the age of 13 years, similarly to other reports in the literature.[12] Male patients represented 65.22% of the study group, similarly to other studies which found that more than 60% of cases manifest in male patients.[13]

The pathology consisted in a variable number of diagnoses comprised in 6 large disease groups, the first and most frequent being acute leukemia in 27 cases (58.69%), followed by malignant solid tumors (bone tumors, renal tumors) in 10 cases (21.73%) and lymphomas in 3 cases (6.52%), similarly to data found in the specialty literature.[13]

Regarding the presence of a catheter, we have established that close to 2/3 of patients had a port system central venous catheter (CVC) or a tunneled central venous line. A CVC helps prevent the direct irritating effect of cytostatic treatments on the veins and provides a safe venous line.[14] We found no statistically significant correlation between the presence of a catheter and anxiety ($p = 0.484$).

In our study, 21 (45.65%) patients presented anxiety based on the SCARED test, this percentage being higher than the one described in the literature. We must mention that the number of studies on this subject is still low.[15] Of the 21 patients with anxiety, separation anxiety was present in 47.62% of cases (n = 10), followed by social anxiety in 33.33% of cases (n = 7). No patient has exhibited school anxiety. According to the data from the specialty literature, as far as chronic pathologies are concerned, the mother-child bond is stronger under the age of 13 years; furthermore, most patients in this age group have not been separated from their families for long periods of time, thus they have a decreased resistance to separation from the family environment.[15]

Separation anxiety is treated according to the age of the child at the time of initial diagnosis, and therapeutic measures often include decorating the hospital room with toys and personal objects from the patient's home. The type of anxiety is correlated with age, and our study found that separation anxiety was more frequent among patients aged

TABLE 4. The correlations between cytokine levels and the presence of anxiety

IL-1	Anxious	$r = 0.532$, $R^2 = 0.283$, $p = 0.019$	Statistically significant positive correlation in anxious patients, negative correlation in the non-anxious group
	Non-anxious	$r = -0.082$, $R^2 = 0.007$, $p = 0.352$	
IL-6	Anxious	$r = 0.742$, $R^2 = 0.551$, $p = 0.002$	Medium positive correlation in the anxious group and a medium negative correlation in the non-anxious group
	Non-anxious	$r = -0.308$, $R^2 = 0.095$, $p = 0.087$	
IL-10	Anxious	$r = 0.220$, $R^2 = 0.048$, $p = 0.365$	Negative correlation in the anxious group and a statistically insignificant positive trend in the non-anxious group
	Non-anxious	$r = 0.153$, $R^2 = 0.024$, $p = 0.248$	
IL-12p40	Anxious	$r = 0.006$, $R^2 = 0.000$, $p = 0.980$	Marked correlation in the anxious group and a weak negative correlation in the non-anxious group, both statistically insignificant
	Non-anxious	$r = -0.065$, $R^2 = 0.004$, $p = 0.385$	
TNF-α	Anxious	$r = 0.244$, $R^2 = 0.059$, $p = 0.314$	A very weak positive correlation in the anxious group and a descending trend in the non-anxious group
	Non-anxious	$r = 0.065$, $R^2 = 0.004$, $p = 0.382$	
CRP	Anxious	$r = 0.198$, $R^2 = 0.039$, $p = 0.445$	A weak positive trend in the anxious group and a slightly descending trend in the non-anxious group
	Non-anxious	$r = 0.192$, $R^2 = 0.037$, $p = 0.208$	

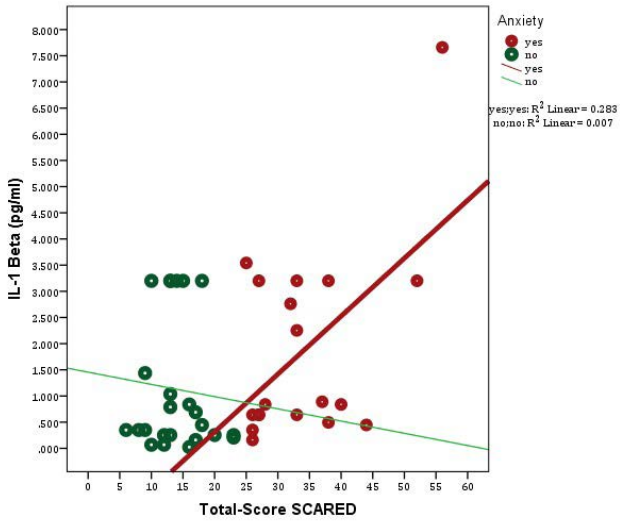

FIGURE 1. Linear regression between IL-1β and anxiety score

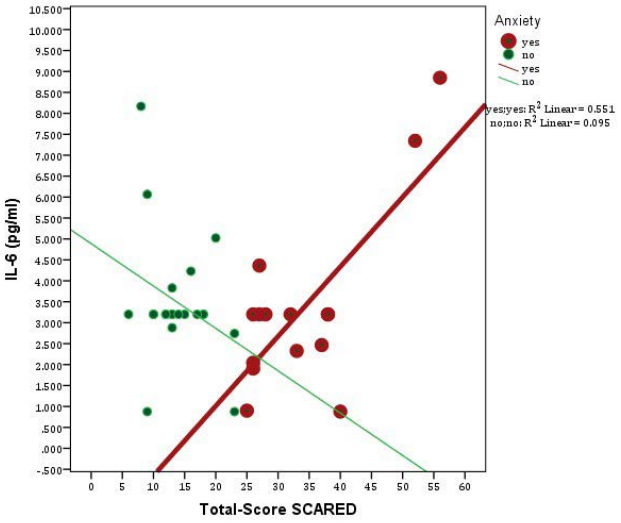

FIGURE 2. Linear regression between IL-6 and anxiety score

13 years or less, which has also been found in other studies throughout the specialty literature.

Regarding the distribution of anxiety by gender, we have not discovered any statistically significant differences in the studied lots (p = 0.665), and neither did other studies in the specialty literature reach a definitive conclusion as to which gender is more vulnerable to anxiety.[16]

The mother's level of education, correlated with the child's anxiety, was close to the threshold of statistical significance; however, the results of the first study that included a larger number of participants have reached statistical significance, suggesting that children from mothers with a higher level of education suffer from lower levels of anxiety than those from mothers with a lower level of education.

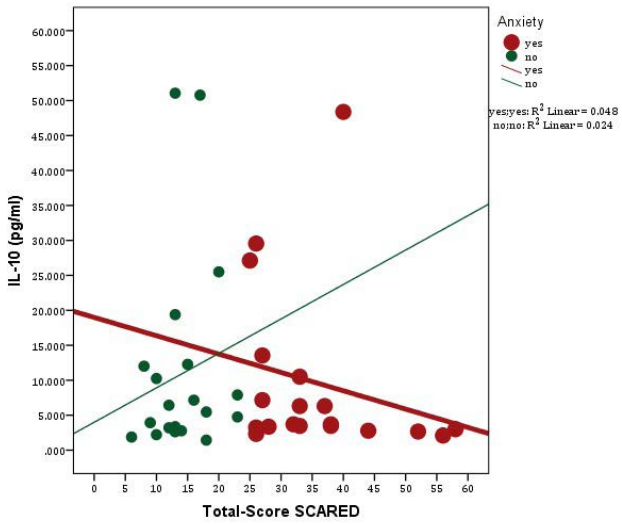

FIGURE 3. Linear regression between IL-10 and anxiety score

As far as we know, this subject has not been discussed yet in the specialty literature.

Age, the presence of a catheter, the type of pathology or the existence of siblings did not influence the level of anxiety. Although we have found no statistically significant data regarding their impact on anxiety, it is still important to pay attention to the siblings of pediatric oncology patients, as suggested by data in the specialty literature.

Correlations related to cytokine levels need to be interpreted restrictively because of the small number of enrolled patients. The mean values of IL-1β and the linear regression analysis carried out on the two lots have identified a significant difference between the group of anxious patients, who presented a positive correlation between the anxiety score and IL-1β serum levels, and the group of non-anxious patients, who presented a negative correlation between these two parameters. Recent studies indicate a marked increase in IL-1β levels in psychiatric disorders. A study of the protective role of probiotics which lower the levels of pro-inflammatory cytokines is under development.[17]

By studying the relationship between anxiety and serum levels of IL-6, we have identified a medium positive correlation in the anxiety group and a medium negative correlation in the non-anxious group. This has been previously described in certain studies, which discuss the key role of IL-6 in the pathogenesis of depression, with high detectable serum levels in such clinical scenarios.[18]

Regarding IL-10 levels, we have observed a difference between the two studied lots (anxious/ non-anxious), highlighting a low negative correlation between the anxiety score and IL-10 levels in the anxious group, as well as

a low positive correlation in the non-anxious group, with a statistical insignificancy. Similar data were reported by recent studies, which have described the protective role of IL-10 in anxiety disorders, describing low levels in anxiety and depression and high levels when no clinical signs of psychiatric afflictions are present.[19]

There was no correlation in the anxious group and a weak negative correlation in the non-anxious group between IL-12p40 levels and the anxiety score. The specialty literature reports low levels of this serum cytokine in anxiety or other psychiatric disorders, thus our results are in line with the ones from these studies.[20]

The evaluated serum levels of TNF-α were higher in anxious subjects compared to non-anxious patients. Recent studies show high levels of TNF-α in patients with psychiatric disorders as well.[20]

Correlations between the serum levels of C-reactive protein and the anxiety score of the two lots do not agree with the existing literature data, a fact owed to the small number of patients in the studied lot. Other studies have shown higher serum levels of CRP in anxiety disorders.[21]

CONCLUSIONS

Psycho-oncology is a relatively new medical field, thus very few scientific studies have been published in the last twenty years. Anxiety disorders are present during childhood and adolescence, and they have been found to be more prevalent in individuals with chronic illnesses, especially in pediatric oncology patients. In the oncologic population included in the present study, 4 types of anxiety were found, with a net predominance of separation anxiety, which was also most frequent in the <13 years age demographic.

Proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, presented high values in anxious subjects; on the other hand, IL-10 and IL-12p40 seemed to have low levels in psychiatric pathologies influenced by anxiety. CRP levels were not influenced by anxiety disorders.

CONFLICT OF INTEREST

We have no conflict of interest to declare.

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CASE SERIES

SURGERY // DERMATOLOGY

Chemical or Surgical Treatment in Ingrown Toenails? Practical Issues from a Case Series

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ABSTRACT

Introduction: An ingrown toenail is a serious medical problem that cannot be overlooked, and the decision of choosing between conservative versus surgical treatment may be difficult in daily practice. **Case series presentation:** We present the cases of two young men with a long history of ingrown toenails, previously treated by complete nail avulsion, numerous topical applications of antibiotics, and 5% silver nitrate, successfully treated with caustic chemical agents, compared to a 19-year-old athlete with debilitating pain, intense inflammatory changes, infection, granulation tissue induced by skin penetration of lateral nail edge by an incurved toenail, in whom surgical treatment was needed. **Conclusion:** Chemical matricectomy in the absence of any surgical intervention, along with patience allowing the nail to grow, could be an option that is easy to perform in case of ingrown nails. However, the selection of cases is important, taking into balance the benefit-risk ratio.

Keywords: ingrown toenail, chemical matricectomy, surgical treatment

INTRODUCTION

An ingrown toenail is a serious medical problem that cannot be overlooked, and the decision of choosing between conservative versus surgical treatment may be difficult in daily practice. We present two cases treated by 70% trichloroacetic acid (TCA) solution, a caustic chemical agent, applied weekly, in comparison to a case that required surgical intervention.

All patients consented to publication of their data, and all the examinations were performed in accordance to the principles stated in the Declaration of Helsinki.

FIGURE 1. Case 1 before treatment

FIGURE 2. Case 1 at the end of treatment

CASE SERIES PRESENTATION

Case 1

A young man with a long history of ingrown toenail stage 3, previously treated by complete nail avulsion, numerous topical applications of antibiotics, and 5% silver nitrate, addressed us searching a totally noninvasive approach to his condition. The patient had no incurved toenail, but he used to perform an improper nail cutting technique deeply into the lateral edge of the nail. At the moment of clinical examination, the lateral edge of the nail was situated at 2/3 of the distance from the distal part of the nail plate (Figure 1).

A close follow-up, right fitting shoes, no cutting of the nails, a short topical antibiotic treatment (fusidic acid twice daily for seven days applied the day after TCA), and 70% TCA application once weekly were strictly recommended. No occlusive dressing, washing using just soap and water, patience, and weekly application of 70% TCA have been done for the following 5 weeks. Slight pain and erythema were described, especially in the first 24 hours after TCA application. However, no surgical technique was performed. The TCA solution was applied on the granulation tissue until white discoloration was observed and moderate pain was felt by the patient. Until the next TCA application fusidic acid cream was used once daily. Good results were observed at the end of the 5-week period, with complete growth of the lateral margin of the nail plate and no signs of ingrown toenail (Figure 2).

Case 2

A 34-year-old man was seeking medical help because of discomfort and intense pain on the right toe caused by an ingrown toenail. At clinical examination it was observed that the nail plate had pierced the lateral nail fold, causing a foreign body reaction, infection, and intense granulation tissue on both lateral edges. The patient was a healthy person, with no anatomical abnormalities of the nail plate (Figure 3). This was his first visit to the doctor's office, no medical or surgical treatments have been done previously. Weekly application of 70%TCA was performed on the granulation tissue, followed by topical antibiotics. Slight erythema, desquamation, and minor pain were reported during therapy. After a 5-week period, a small granulation tissue persisted on the left nail fold, and one more application of 70%TCA was done (Figure 4).

Case 3

A 19-year-old athlete was seen in the Emergency Unit for debilitating pain, intense inflammatory changes, infection,

FIGURE 3. Case 2 – bilateral ingrown toenail

and granulation tissue induced by skin penetration of the lateral nail edge by an incurved toenail (Figure 5). Conservative treatment was denied, and the patient was sent to the Surgery Department for avulsion of the offending toenail border and the excision of any granulation tissue.

FIGURE 5. Case 3 – ingrown toenail with granulation tissue

FIGURE 4. Case 2 – clinical appearance after 5 applications of 70% TCA weekly

DISCUSSIONS

Ingrown toenail is a very painful and debilitating nail disease, commonly seen in young adults. It affects mostly young men, and it is caused by mechanical trauma, unfitted tight shoes, sharp cutting of the marginal edges of the nail plate, congenital abnormalities of the nail plate or associated with subungual exostosis or tumor, arthritis, onychomycosis, toe deformities.[1,2]

Regardless of the cause, the lateral nail edge presses and penetrates into the nail sulcus, leading to intense pain, the formation of granulation tissue, and infection. Based on the clinical signs, three stages have been described: stage 1, represented by erythema, slight edema, and moderate pain declared by the patient, but only correlated to pressure applied on the lateral nail fold; stage 2, in which infection and spontaneous severe pain are added; and stage 3, in which we can observe the presence of granulation tissue.[3,4]

The surgical approach, widely known and performed especially in Surgery Departments, includes nail avulsion, wedge resection, total nail bed ablation, soft tissue resection, partial nail avulsion, and chemical matricectomy.[5] It is an invasive method that carries the risk of infection and recurrence (if destruction of the germinal matrix is not performed) and all the problems related to surgery. It is used especially in cases of nail deformities, like in case 3 from this small series.

During the last years, chemical matricectomy associated with partial nail avulsion has been brought to attention by its easy application, low morbidity, no risk of recurrence, and noninvasive nature.

Chemical matricectomy has been performed with phenol, sodium hydroxide, and trichloroacetic acid.[6,7] Some reports of intense tissue destruction beyond the limits of granulation tissue and prolonged healing have been reported as side effects.[6] Also, the application of phenol has induced digestive problems, cardiac arrhythmias, hemoglobinuria, and local chemical burns in some patients.[8]

Matricectomy with sodium hydroxide has eliminated some of the systemic adverse reactions caused by phenol application, but excessive tissue destruction can occur due to the liquefaction necrosis action of the drug, which is a strong alkali.[9]

TCA is a caustic chemical agent that produces coagulation necrosis, but without systemic reactions. Several studies have reported good results lately in treating ingrown nails with 100% TCA matricectomy after partial nail avulsion with low recurrence rate and minimal local side effects on long-term follow-up.[10,11]

Some cases could be treated with 70% TCA applied once weekly, without any surgical intervention (partial nail avulsion, laser, electrocautery).

CONCLUSIONS

Chemical matricectomy with 70% TCA once weekly in the absence of any surgical intervention, along with patience allowing the nail to grow, could be an option that is easy to perform in case of ingrown nails, similar to the first two cases in this series. However, the selection of cases is important taking into balance the benefit-risk ratio.

CONFLICT OF INTEREST

Nothing to declare.

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CASE REPORT

OCCUPATIONAL MEDICINE // DERMATOLOGY

Unilateral Palmar Post-traumatic Granuloma Annulare – Work-related?

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ABSTRACT

Granuloma annulare (GA) is a granulomatous skin condition that can present with a diversity of clinical manifestations and locations, with an unknown etiology and diagnosed on clinical-pathological grounds/correlations. Although many trigger factors have been described and several pathogenic mechanisms proposed, the etiology of GA remains unknown. We report a case of work-related, isolated, unilateral GA localized on the right palmar area of a young worker, possibly induced by work-related direct trauma.

Keywords: granuloma, annulare, palmar, work, occupational, dermatology

INTRODUCTION

Granuloma annulare (GA) is a granulomatous skin condition that can present with a diversity of clinical manifestations and locations, with an unknown etiology and diagnosed on clinical-pathological grounds/correlations. Although many trigger factors have been described and several pathogenic mechanisms proposed, the etiology of GA remains unknown.

We report a case of work-related, isolated, unilateral GA localized on the right palmar area of a young worker, possibly induced by work-related direct trauma.

The patient consented to publication of his data, and all examinations were performed in accordance to the principles stated in the Declaration of Helsinki.

CASE REPORT

A 37-year-old man presented with a one-week history of annular erythematous lesions on the right palm, distributed mostly on the compression sites. He was a construction worker, handling a hydraulic hand breaker, used for breaking up concrete. The patient described his full-time job as working on average 10 hours daily with a portable jackhammer. He was a strong young, healthy person of 1.82 m height, who had to support the weight of the tool and the vibration induced by the machine and to handle the machine to break up stones, pavements, or concrete. He started this new job a few months before admission to the hospital; his previous jobs had not been in construction and had not been related to physical activity. Before starting work in construction, a careful medical examination was performed, data recorded, and he was declared a healthy person. Skin lesions on the right palm were observed by the patient and confirmed by his general practitioner a few days before admission to the hospital (Figure 1A).

Dermatological examination revealed several scattered round, well-demarcated, erythematous papules with annulare-type distribution, with an inflammatory rim, localized on the right palm and ventral area of digits II, III, and IV. No scratching marks, due to the absence of pruritus, and no other skin lesions on the body could be observed. The patient was otherwise in good health, no drug intake was noted, and no allergy history was reported.

A punch-biopsy was taken from one of the lesions, revealing a moderate superficial mid-dermal perivascular and interstitial infiltrate of lymphocytes and histiocytes, with mucin deposition between the collagen fibers (Figure 1B).

Based on the clinical and histological findings, a diagnosis of localized GA was established. Provocation test with pressure was not done due to time-work correlation and good evolution in the absence of physical vibration or other type of physical trauma on his palms. On admission to the hospital, he was routinely checked, and no systemic diseases were found. Apart from the chronic traumatic trigger factor, no other cause was detected for localized GA on the right palm.

After having been diagnosed with palmar GA, he was advised to change his work duties; he was treated with topical steroids and avoided any type of physical work involving his right hand, working in administration, as a storekeeper. Skin lesions improved gradually. He was transferred to a similar position within the same company in another city. Close follow-up of the cutaneous disease did not show any relapse in the absence of physical effort as it was recorded in his medical documents.

DISCUSSIONS

Granuloma annulare is a benign common disorder, with a variety of clinical aspects and an obscure etiology, several classifications being issued: localized, generalized (generalized annular GA, disseminated papular GA, atypical generalized GA), subcutaneous, and perforating GA.

Localized GA is a benign inflammatory disease of unknown etiology, mostly described in children. The first description of the disease dates from 1895, when Colcott-Fox reported the case of a 11-year-old female child with "ring eruption on the fingers".[1] The name granuloma annulare was given to the cutaneous disease by Radcliff-Crocker in 1902 as a descriptive terminology highlighting the an-

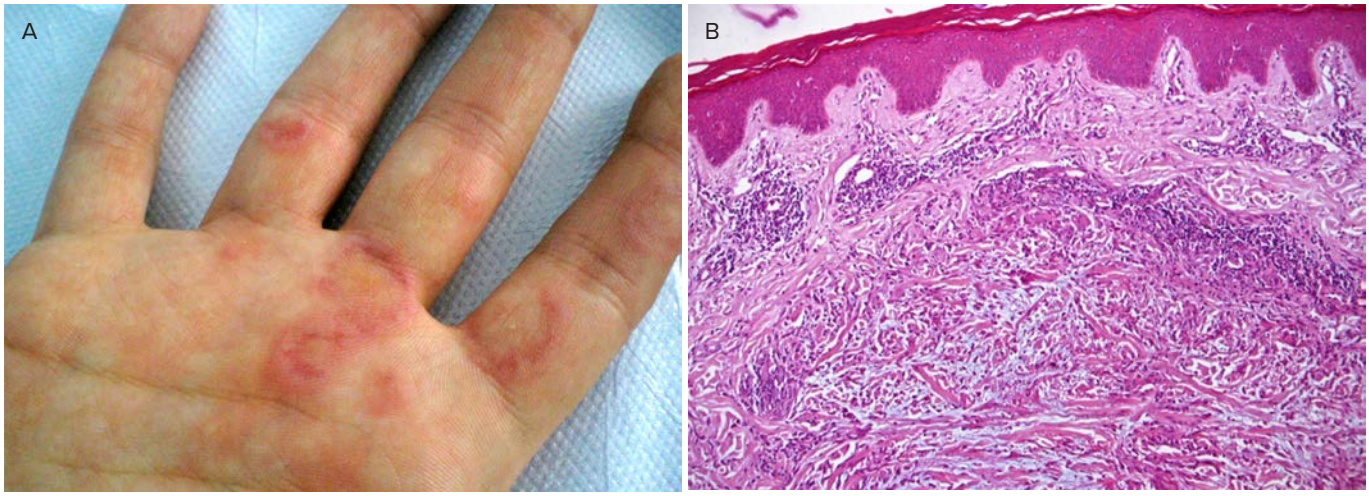

FIGURE 1. **A** – Annular erythematous plaques on the right palmar area; **B** – Histological appearance: moderate superficial and mid-dermal interstitial and perivascular infiltrate, predominantly composed of lymphocytes and histiocytes, and mucin deposition between the collagen bundles/fibers. Hematoxylin and eosin, ×40.

nular (ring-type) distribution of the skin lesions and the granulomatous reaction localized in the dermis and subcutaneous tissue.[2] Localized GA is frequently described in patients not older than 30 years, with papules distributed in annular fashion, free of symptoms or associated with pruritus, burning sensation, localized mostly on the dorsal aspect of the hands, on the elbows, or inferior limbs; GA on the palms is rarely described.

Although the underlying pathogenic mechanisms remain unclear, different theories have been proposed, based on delayed-type hypersensitivity reaction,[3] Th1 involvement,[4] lymphocyte-mediated activation of monocytes,[5] and elastic tissue injury.[6]

Localized forms of GA on the dorsa of the hands have been frequently reported, but the same lesions on the palms are rare.[7] In both situations, localized factors have been correlated with localized GA: ultraviolet light or trauma,[8] arthropod bites,[9] tuberculin skin tests,[10] viral infections,[11] and psoralen plus ultraviolet A photochemotherapy (PUVA).[12] Of interest, GA on the palm has been reported to be associated with systemic disorders such as rheumatic diseases and malignancies.[13,14] A report of GA induced by trauma was published in 1992, when two cases involving the external ears of males were presented.[15] More recently, a case of papular GA of the dorsal aspects of the hands induced by repeated, direct trauma to the site was published, rising therefore the idea of a possible role of direct trauma in the pathogenesis of GA.[8]

CONCLUSIONS

The particularity of the present case is represented by unilateral right palmar type of granuloma annulare in a 37-year-old healthy man, possibly induced by a traumatic trigger factor (vibration and pressure exerted by a hydraulic hand breaker).

CONFLICT OF INTEREST

Nothing to declare.

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GENERAL SURGERY // VASCULAR SURGERY

Aorto-mesenteric Bypass for the Treatment of Chronic Mesenteric Ischemia

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ABSTRACT

Chronic mesenteric artery disease has a much lower incidence than the acute one, but it raises the same problems in terms of patient survival. The long-term outcomes for open surgery are crucial for the right choice of a particular technique. We present the case of a 39-year-old female patient with a history of total nephrectomy, chronic kidney failure, and hypertension, who presented in the Emergency Department with abdominal pain with high intensity, for which she was admitted to the General Surgery Department. Abdominal computed tomography angiography was performed, which indicated the diagnosis of partial upper mesenteric artery stenosis. The patient underwent surgery, during which a retrograde aorto-mesenteric bypass with a Gore-Tex 5 mm diameter prosthesis was performed. In situations where the endovascular approach fails or has no indication (multiple incidence lesions from the origin of the superior mesenteric artery), open surgery is the indication in chronic mesenteric ischemia.

Keywords: chronic mesenteric ischemia, revascularization, bypass

INTRODUCTION

Chronic mesenteric ischemia can result from embolic or thrombotic events, trauma, and distal thoracic or abdominal aortic coarctation. It is an uncommon cause of acute abdomen, accounting for less than 1 in every 1000 hospital admissions, being associated with an increased mortality.[1,2] More than 90% of cases of chronic mesenteric ischemia develop due to atherosclerotic disease that affects the origins of the visceral vessels.[1–3] Early diagnosis and treatment are essential.[2–4]

We present a case of chronic mesenteric ischemia, highlighting the importance of early recognition and timely revascularization.

CASE REPORT

We present the case of a 39-year-old female patient who presented in the Emergency Department for acute abdominal pain, nausea and vomiting, for which she was admitted to the General Surgery Department.

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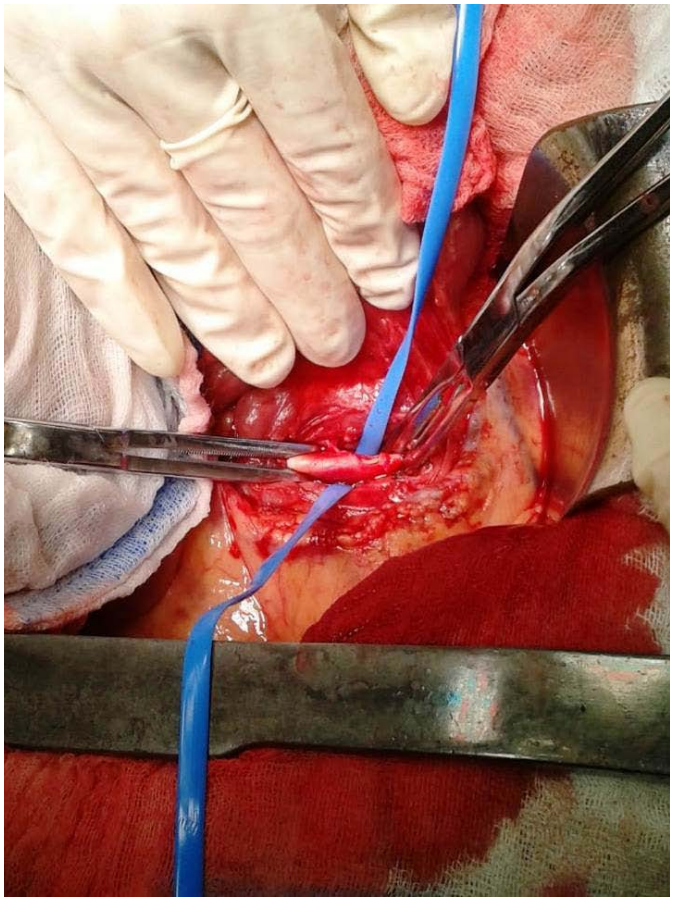

FIGURE 1. Superior mesenteric artery prepared for bypass

FIGURE 2. Aorto-mesenteric bypass with 5 mm Gore-Tex prosthesis (final aspect)

Her past medical history included a total nephrectomy, with secondary chronic kidney failure. Also, she had a risk factor for developing atherosclerosis, due to chronic tobacco use.

On admission, she was hypertensive, but observations were otherwise normal. An abdominal computed tomography angiography (CTA) was performed, which demonstrated a partial upper mesenteric stenosis. We performed a retrograde aorto-mesenteric bypass (Figure 1) with a Gore-Tex prosthesis of 5 mm diameter (Figure 2). Evolution was favorable, and the patient was discharged 6 days after surgery.

The patient remains asymptomatic and continues to be kept under surveillance, with constant follow-up visits.

The patient agreed to the publication of her data and the manuscript was written in accordance with the ethical principles stated in the Declaration of Helsinki.

DISCUSSIONS

Chronic mesenteric ischemia is the most common vascular disorder involving the intestines. The increased utilization of CTA and magnetic resonance angiography (MRA) has increased the recognition of atherosclerotic mesenteric stenoses.[3–5] In our case, we performed an abdominal CTA, in which a partial upper mesenteric stenosis was highlighted.

Open mesenteric revascularization has evolved in the last years and represents the standard method compared to endovascular techniques,[6,7] having low mortality rates and providing excellent long-term primary patency rates.[7,8]

Choosing the technique (reimplantation, endarterectomy, anterograde or retrograde by-pass) is at the discretion of the surgeon, depending on the lesions. Anterograde bypass is more frequently performed because in the overpass portion the aorta is more commonly not affected by atherosclerosis. In contrast, the retrograde technique implies an easier exposure of the in-flow vessel. We performed a retrograde aorto-mesenteric bypass with a Gore-Tex prosthesis of 5 mm diameter. The postoperative evolution was favorable, with no complications on the short- and long-term follow-up.

CONCLUSIONS

In situations where the endovascular approach fails or has no indication, such as multiple lesions initiating from the origin of the superior mesenteric artery, open surgery is the indication in chronic mesenteric ischemia.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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2. Nichols WW, Rourke MF. Aging, High Blood Pressure and Disease in Human. 3rd ed. London/Melbourne: Lea and Febiger; 1990.

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4. Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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