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RISK FACTORS FOR ACUTE MYOCARDIAL INFARCTION IN YOUNG PEOPLE: A STUDY ON CAUSES AND ASSOCIATED CONDITIONS

Eduarda Endlich de Freitas
http://lattes.cnpq.br/0250120617173331

Henrique Teixeira Giestas Serpa
http://lattes.cnpq.br/8558327863459829

Dallisy Falcão Leite
http://lattes.cnpq.br/0329557744020068

Sarah Reis Lima
http://lattes.cnpq.br/4578013029598292

Carlos Henrique Fernandes Nassur
https://lattes.cnpq.br/7416864585556736

Danillo da Silva Pires
https://lattes.cnpq.br/6498594582713845

Pedro Simões Wetler
http://lattes.cnpq.br/9497239141093175

Rafaella Curcio Egashira

Renato Giestas Serpa

Guilherme Freitas Fernandes de Oliveira

Abstract : **Introduction**: Acute myocardial infarction (AMI) remains one of the leading causes of global mortality. Despite a reduction in incidence in older populations, there has been a significant increase in cases among young adults (18–55 years), especially women, with distinct and often underestimated risk factors. **Objective:** To identify the main risk factors associated with AMI in young individuals, including genetic, metabolic, behavioral, gender, and ethnic factors. **Method:** A literature review was conducted in the PubMed Central (PMC) database using the descriptors "Acute Myocardial Infarction," "Young Adult," and "Risk Factors," combined with the Boolean operator "AND." Of the 148 articles initially found, 17 met the inclusion criteria (2018–2024), in addition to the inclusion of 1 additional article outside the initial strategy. **Results:** Smoking was identified as the most prevalent risk factor, increasing the risk of AMI in young smokers by up to 13 times. Other relevant traditional factors included obesity, dyslipidemia, hypertension, and metabolic syndrome. Among genetic factors, familial hypercholesterolemia, Apolipoprotein E-related polymorphisms, elevated lipoprotein A, and hyperhomocysteinemia stood out. Inflammatory aspects, such as elevated levels of C-reactive protein , and PCSK9, were also associated with an increased risk of events. Young women showed a more significant increase in AMI rates, with diabetes, depression, and low family income being particularly influential, while ethnic differences showed a higher prevalence of hypertension in blacks and diabetes in Hispanics. **Conclusion:** AMI in young people has a distinct multifactorial profile, in which modifiable risk factors play a predominant role, but genetic and socioeconomic conditions also strongly influence. Early identifi-

cation and individualized management of these factors are fundamental for primary prevention and reduction of the impact of AMI in this population.

Keywords: Acute Myocardial Infarction. Young Adult. Risk Factors. Acute Myocardial Infarction. Young Adult. Risk Factors.

INTRODUCTION

According to Nowbar et al. (apud Gupta et al.), the leading cause of death worldwide is coronary artery disease (CAD), accounting for 9 million deaths per year. According to Arora et al. (apud Gupta et al.), in a more current scenario, the incidence of Acute Myocardial Infarction (AMI) in younger patients (35-54 years) has been increasing. Patients affected by AMI at younger ages have other risk factors when compared to older patients, such as hyperhomocysteinemia, increased lipoprotein A, insulin levels, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), among others. In addition to risk factors and different clinical and angiographic presentations (Pineda et al. apud Gupta et al.), metabolic, inflammatory, and genetic factors (Pineda et al. apud Gupta et al.) may influence the early onset of this younger population (Fischer et al. apud Gao et al). Regarding etiology, atherosclerotic plaque rupture remains the main cause (90% of cases), while the remaining 10% are divided among causes unrelated to atherosclerosis, such as spontaneous coronary artery dissection, coronary vasospasm, coronary embolism, drug use, and hypercoagulable states (Krittanawong et al). Due to the increase in the number of AMI cases in young people, it is important to study which risk factors are associated with the possible development of this condition.

OBJECTIVE

To identify the main risk factors associated with acute myocardial infarction in young individuals, including genetic and behavioral conditions.

METHOD

A literature review was conducted to analyze the main risk factors associated with acute myocardial infarction (AMI) in young individuals. The search was performed in the PubMed Central (PMC) database, using the descriptors "Acute Myocardial Infarction," "Young Adult," and "Risk Factors," combined with the Boolean operator "AND." The initial search resulted in 148 articles.

The inclusion criteria were: (a) articles published between 2018 and 2024; (b) available in English, Portuguese, or Spanish; (c) directly addressing the topic of interest, including systematic reviews and meta-analyses, with access to the full text. The following were excluded: (a) publications available only in abstract form; (b) articles that did not directly address the research question; (c) those that did not meet the other inclusion criteria.

After rigorous application of these criteria, 17 articles were selected to compose the final corpus of this review, in addition to the addition of one article outside the aforementioned search strategy. Critical and detailed reading of the articles allowed for a comprehensive and up-to-date assessment of the available literature, providing a solid basis for understanding the risk factors associated with AMI in young people.

The titles, abstracts, and full text were then read in this sequence. The steps in this article selection process are detailed in the flowchart below (Figure 1).

After reading all the articles included in this review, we articulated and classified the risk factors found for the population in our study as traditional, genetic, sex-related, race/ethnicity-related, and other non-traditional risk factors: associated with changes in C-reactive protein (CRP) concentration, PCSK9, and hyperhomocysteinemia. This division allows for a better understanding of the influence of these factors on the occurrence of AMI independently.

RESULTS AND DISCUSSION

Acute myocardial infarction (AMI) remains one of the leading causes of death worldwide (GUPTA *et al.*, 2018) and accounts for approximately 800,000 hospitalizations per year in the United States (LU *et al.*, 2022). It is undeniable that, in recent decades, several advances have been made in the areas of treatment and prevention of this event, resulting in a significant decrease in the incidence and mortality from AMI (WU *et al.,* 2020). However, this decrease was not observed among younger patients: according to a 2019 study conducted by the Atherosclerosis Risk in Communities Surveillance (ARIC), the proportion of annual admissions for AMI among young patients (aged 35-54) increased from 27% between 1995 and 1999 to 32% between 2010 and 2014. This phenomenon was especially significant for women, who showed a 10% increase between the periods mentioned, compared to 5% among men (ARORA *et al.,* 2019 *apud* WU *et al.,* 2020).

These data show that young people with high cardiovascular risk are often not recognized by health professionals and, consequently, primary prevention strategies are potentially flawed in caring for these individuals. The reality is that AMI in young patients has clinical and pathophysiological aspects that are distinct from those observed in the older population, in addition to covering a different profile of risk factors (GUPTA *et al.,* 2018). The importance of studying this population is therefore understood.

Initially, the definition of young adults in the context of patients affected by AMI must be established. There are many discrepancies in the literature regarding the age range of these individuals: in the studies analyzed, ages ranged from under 35 to under 55, divided between very young (18 to 35 years) or young (36 to 55 years) (WU *et al.,* 2020; ZHANG *et al.,* 2022).

It should be noted that coronary artery disease (CAD) is multifactorial and involves environmental, clinical, biochemical, genetic, ethnic, and socioeconomic parameters. Its risk factors can be divided into modifiable and non-modifiable, most of which affect patients of all age groups. However, what differentiates young patients from others is the higher prevalence of modifiable aspects and their strong association with the development of AMI in the future (KRITTANAWONG *et al.,* 2023; WU *et al.,* 2020). Several studies show that about 90% of young patients had at least one modifiable cardiovascular risk factor prior to their first AMI (HAMMERSHAIMB *et al.,* 2022; WU *et al.,* 2020; ZHANG *et al.,* 2021).

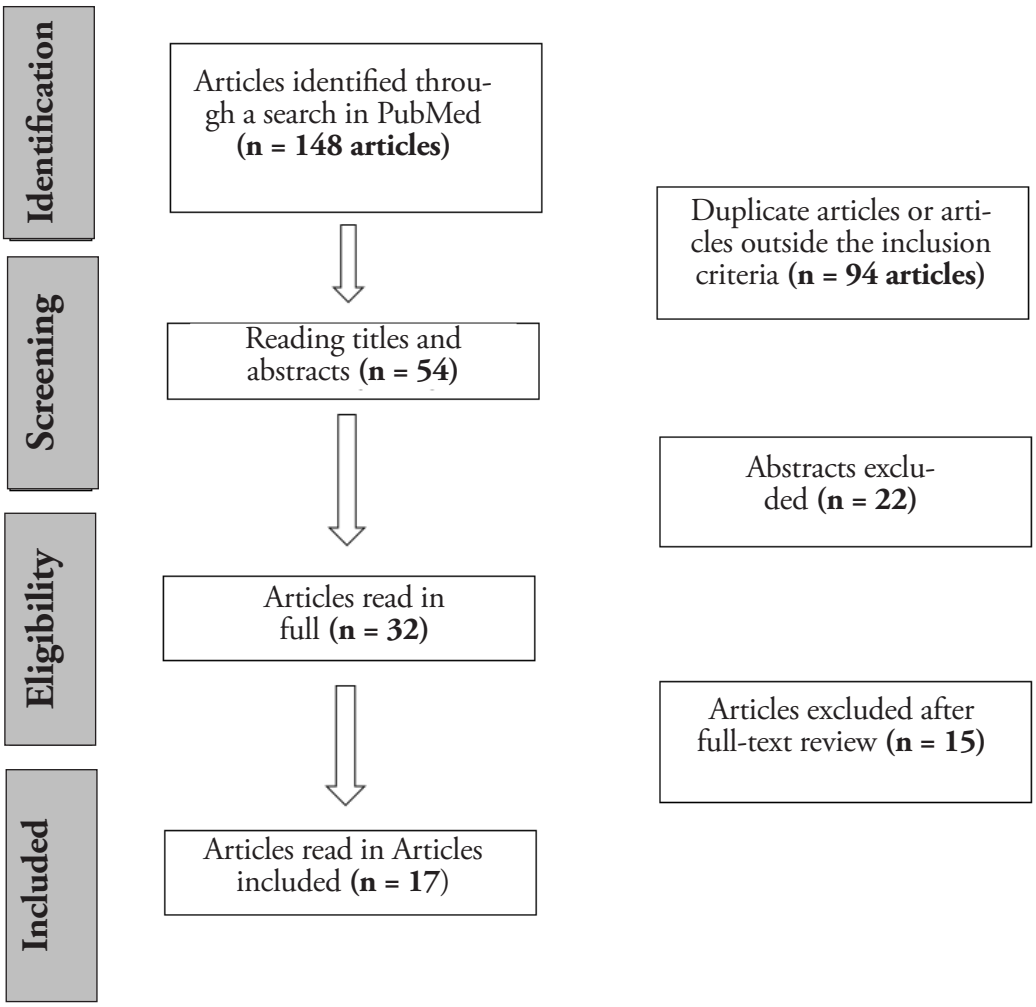

Figure 1 – Flowchart of article search and selection

Source: Prepared by the author

TRADITIONAL FACTORS:

Smoking remains the main and most prevalent risk factor among young people. According to a study by ZHANG *et al.* (2022), which analyzed approximately 9,000 patients diagnosed with AMI between the ages of 18 and 45, about 73.2% were smokers. This factor alone is responsible for a 9-fold increase in the chances of AMI in young men and a 13-fold increase in young women (PALMER *et al.,* 2019 *apud* WU *et al.,* 2020). This is due to the direct relationship between tobacco use and the progression of atherosclerosis: the combination of the cardiovascular effects of smoking (promoting endothelial dysfunction, increasing oxygen demand, and increasing the risk of thrombosis) accelerates the course of the disease (ZHANG *et al.,* 2022). As a result, smokers have heart attacks about a decade earlier than non-smokers and have a worse prognosis, with higher morbidity and mortality rates (ZHANG *et al.,* 2022). A strong predictor for CAD progression and possible future AMI is the age of onset of addiction: young smokers are more likely to have a heart attack than those in any other age group (PALMER *et al.,* 2019 *apud* WU *et*

al., 2020). This is believed to be justified by the longer exposure to tobacco and smoking burden of these individuals, which increases the risk of cardiovascular events (ZHANG *et al.,* 2022).

Other traditional cardiovascular factors, such as obesity, dyslipidemia, and hypertension, are still among the most prevalent aspects in the young population. About 66% of the patients analyzed had obesity and diabetes, 33% were dyslipidemic, and 28% were hypertensive (HAIDER *et al.*, 2023). According to KIM *et al.* (2018 *apud* WU *et al.,* 2020), almost 50% of young people diagnosed with AMI had metabolic syndrome at the time of admission, and these patients had higher rates of reinfarction than the others. Obesity, which has become more prevalent in recent years, with a 98% increase between 2005 and 2015 (YANDRAPALLI *et al.,* 2019 *apud* WU *et al.,* 2020), adds to the list of risk factors.

Regarding dyslipidemia, GUPTA *et al.* (2018) observed that the ratios between TC/HDL, LDL/HDL, and Apolipoprotein B/Apolipoprotein A1 were significantly higher in young patients who had suffered a heart attack. These ratios are known to be the best predictors of CAD and can identify young dyslipidemic individuals at higher risk of an acute cardiovascular event.

GENETIC FACTORS

It is known that the influence of genetic components in the development of atherothrombotic diseases is much more important in young patients than in older patients. The genetics of acute myocardial infarction (AMI) are complex but can be summarized in monogenic and polygenic expression patterns (KRITTANAWONG *et al.,* 2023). Among the monogenic diseases related to early AMI are familial hypercholesterolemia, homocystinuria, antiphospholipid syndrome, fibromuscular dysplasia, and other rare syndromes (STITZIEL, 2014 apud KRITTANAWONG *et al.,* 2023). In addition, there are more complex genes with variable expressivity that interact with other genes and risk factors, whose understanding is still limited and which have not been fully identified.

Isordia-Salas *et al.* (2019) showed that the Thr325Ile polymorphism in the gene encoding thrombin-activable fibrinolysis inhibitor (TAFI) was associated with an increased risk of IAMSST in young Mexicans under 45 years of age (OR 1.62, 95% CI 1.12-2.36, P = 0.01) and a higher risk in those carrying the Ile allele (those with the Thr/Ile and Ile/Ile genotypes) than those with the Thr/Thr genotype, with an OR of 1.62 (95% CI 1.12-2.36, P = 0.01). There was no statistical difference in the distribution of the Ala147Thr genotype (P = 0.24) and in the frequency of the allele (P = 0.46). TAFI is a potent inhibitor of fibrinolysis, and it is known that negative regulation of the fibrinolytic system contributes to the formation of arterial thrombi (BAJZAR, 2000 apud ISORDIA-SALAS *et al.,* 2019). The Thr325Ile polymorphism in the gene encoding TAFI, located on chromosome 13q14.11, causes the substitution of threonine (Thr) for isoleucine (Ile) at position 325, which leads to an increase in the half-life and activity of the protein (BROUWERS, 2001 apud ISORDIA-SALAS *et al.,* 2019). This results in a hypofibrinolytic state with increased platelet aggregation and endothelial dysfunction, which could favor the process of thrombus formation. In several studies, the use of TAFI inhibi-

tors in combination with fibrinolytic agents results in a significant improvement in clot dissolution ( ), highlighting the potential of TAFI inhibitors as adjuvants in intravenous thrombolysis. Inhibition of the TAFI pathway through drugs may represent a new approach to prevent thrombus formation or increase the effectiveness of thrombolytic treatment (MONTANER, 2003 apud ISORDIA-SALAS *et al.,* 2019).

Another polymorphism studied is the Apolipoprotein E (ApoE) polymorphism. ApoE plays a key role in the transport and catabolism of lipoproteins, and its polymorphism is an important genetic factor influencing cardiovascular risk. There are three main known isoforms or alleles of ApoE: E2, E3, and E4, with E3 being the main allele and E4 being the most associated with the risk of AMI (MAHLEY, 2016 apud GUPTA *et al.,* 2018). However, the study was unable to establish statistical significance when analyzing ApoE polymorphism and allele frequency between groups of patients aged between 35 and 80 years and under 35 years (very young), due to the small sample size and low statistical power (GUPTA et *al.,* 2018).

Apolipoprotein A (LpA) plays an important role in determining cardiovascular risk. There is a strong association between high LpA values and the early onset of acute coronary syndrome, being an isolated risk factor mainly in individuals under the age of 60. It is estimated that a serum LpA value greater than or equal to 50 mg/dL increases the risk of acute myocardial infarction threefold in patients under the age of 45. However, it is worth noting that this relationship tends to disappear after the age of 60, being a determining factor for coronary events in younger patients. (RALLIDIS *et al.,* 2018).

An observational study conducted in young patients up to 35 years of age reported higher serum homocysteine (HCY) levels and a higher prevalence of hyperhomocysteinemia in these patients with ACS [for HCY, 16.55 (11.93–29.68) vs. 12.50 (9.71–17.42), P < 0.001; for HHCY prevalence, 62.08% vs. 26.18%, P < 0.001]. The study also demonstrated that hyperhomocysteinemia is an independent predictor of traditional risk factors for ACS (OR, 4.561; 95% CI, 3.288–6.327; P < 0.001), and is associated with a higher prevalence of AMI with ST segment elevation in these patients (P = 0.041) (SUN *et al.*, 2021). This correlation is ly due to the toxic and compromising action of HCY on blood vessels and, more specifically, on their endothelium, in addition to inducing stiffening of the vasculature (BALINT *et al.*, 2020 apud SUN et al., 2021). Although hyperhomocysteinemia is an independent risk factor for AMI in young patients, traditional risk factors such as obesity, smoking, alcohol, caffeine, and insufficient levels of vitamin B and folic acid can elevate serum HCY concentrations (SUN *et al.*, 2021).

The level of C-reactive protein (CRP) has also been shown to be an important predictor of AMI in patients up to 45 years of age. Based on a case-control study that analyzed the predictive value of CRP for cardiovascular risk in a young Chinese female population, CRP was considerably higher in the ACS group (1.30 ± 1.70 vs. 3.33 ± 5.92, respectively, p < 0.001) and was associated with a higher occurrence of major cardiovascular events, such as AMI (7.0% vs. 8.9% vs. 19.30%, respectively, p < 0.05) (LIU *et al.*, 2021). CRP is a protein produced by the liver and activated macrophages in atherosclerotic plaques (CALABRÓ *et*

al., 2003 apud LIU *et al.*, 2021) that has been shown to play a regulatory role in the atherosclerosis process [YAGHOUBI *et al.*, 2015 apud LIU *et al.*, 2021) by forming unstable atherosclerotic plaques and causing the rupture of these plaques (CHENG *et al.*, 2014 apud LIU *et al.*, 2021).

The increased risk of major cardiovascular events and the degree of coronary artery damage in patients with early acute myocardial infarction, i.e., those aged 45 years or younger, especially those with high LDL-C levels, is related to increased serum levels of proprotein convertase subtilisin/kexin type 9, Pcsk9. A prospective cohort study of 332 young men at Tianjin Chest Hospital in China showed that serum Pcsk9 levels were elevated in the group with a high SYNTAX score (SS > 21.5) ($P < 0.05$) compared to the group with low SYNTAX scores ($SS \leq 12$ and $12 < SS \leq 21.5$, respectively). The correlation between serum Pcsk9 levels and the occurrence of these events can be explained by the degradative effect of Pcsk9 on LDL receptors, which increases serum LDL-C levels (GAO *et al.*, 2021).

FACTORS ASSOCIATED WITH GENDER

The ARIC study revealed that the increase in myocardial infarction (MI) rates in young patients was particularly pronounced among young women. The study highlighted a significant increase in the annual proportion of hospitalizations for acute MI in young women, which rose from 21% in the period 1995-1999 to 31% between 2010-2014 ($p<0.0001$), indicating a 10% increase, in contrast to a 5% increase among young men (ARORA *et al.,* 2019 *apud* WU *et al.,* 2020).

In a case-control study of a total of 2,264 patients with a history of AMI between the ages of 18 and 55, of whom 3,122 (68.9%) were women, from various ethnic groups (Hispanic, Black, non-Hispanic White, Asian, among others), seven risk factors, after multivariable adjustment, were significantly associated with a higher probability of AMI among men and women: diabetes, depression, hypertension, current smoking, family history of premature MI, low family income, and hypercholesterolemia. Among women, diabetes was the main associated risk factor, followed by smoking, depression, hypertension, low income, and family history of early AMI. Among men, the main risk factor was smoking, followed by family history, hypertension, hypercholesterolemia, depression, diabetes, obesity, and physical inactivity (LU et al., 2022). The correlations between depression and low family income remain significant even after adjusting for other risk factors, indicating that socioeconomic and psychological aspects play a relevant role in the development of acute myocardial infarction (AMI) in young adults, especially in women. In a French study with a population of 1,912 participants aged ≤ 50 years, among 335 women (17.5%), this group had more hypertension (31.3% vs. 21.9%, $P < 0.001$), peripheral arterial disease (3.6% vs. 1.5%, $P = 0.012$), and chronic obstructive pulmonary disease (5.7% vs. 3.0%, $P = 0.020$), but lower hemoglobin values (13.6 ± 1.5 vs. 15.0 ± 1.47 g/dL, $P < 0.001$) and LDL cholesterol (127 ± 46 vs. 138 ± 46 mg/dL, $P < 0.001$) compared to men (WEIZMAN et al., 2023). These findings indicate the importance of developing gender-specific strategies to modify risk factors and prevent acute myocardial infarction (AMI) in young adults.

FACTORS ASSOCIATED WITH RACE/ETHNICITY

Understanding the risk factors for AMI that are most prevalent in different ethnicities/races contributes to establishing care and prevention measures that are more specific to that particular population. Among 1,753 patients hospitalized for type 1 AMI, aged between 18 and 50 years, compared to white patients, black patients had a higher prevalence of hypertension (53.1% vs. 32.2%, $p < 0.001$), while Hispanic patients were more likely to have diabetes (28.2% vs. 15.5%, $p < 0.001$) and obesity (23.9% vs. 17.7%, $p = 0.008$) (HAMMERSCHAIMB *et al.,* 2023). The higher prevalence of hypertension in Black patients has already been documented, and this evidence is corroborated by previous studies showing that hypertension is a significant risk factor for ischemic heart disease in this population (CARNETHON *et al.,* 2017 apud HAMMERSCHAIMB *et al.,* 2023).

CONCLUSION

Understanding the risk factors for acute myocardial infarction (AMI) in young patients reveals a multifactorial interaction between traditional determinants and genetic factors that should be taken into account. Among the traditional risk factors, smoking stands out as the main factor that, in isolation, increases the risk of AMI in young people (PALMER *et al.,* 2019 *apud* WU *et al.,* 2020). Regarding the metabolic profile, there is a significant prevalence of metabolic syndrome (MS) in the young population with a history of AMI, resulting in higher rates of reinfarction and worse prognosis (2018 *apud* WU *et al.,* 2020). The relationships between TC/HDL, LDL/HDL, and Apolipoprotein B/Apolipoprotein A1 can provide important information regarding the risk of dyslipidemia and the occurrence of acute cardiovascular events (GUPTA *et al.,* 2018).

Genetic factors have a major influence on the risk of AMI in the young population compared to the elderly population. There are several patterns of genetic inheritance that interact with cardiovascular risk, whether monogenic or polygenic, with emphasis on familial hypercholesterolemia. Although more in-depth studies are needed, genetic screening is of great value for the implementation of specific measures for the patient's underlying conditions, with a focus on genetic counseling and primary prevention of cardiovascular events (STITZIEL, 2014 apud KRITTANAWONG *et al.* 2023).

The prevalence of AMI according to the race, sex, or ethnicity of patients is linked to the profile of risk factors prevalent in each population, requiring an approach that addresses behavioral measures and control of comorbidities. in addition, the socioeconomic profile of patients should be taken into account, as it has a direct influence on access to prevention and health promotion measures (WEIZMAN *et al.,* 2023).

Thus, the implementation of primary prevention measures with the modification and control of determining risk factors is essential. Smoking cessation, regular guided physical exercise, and dietary monitoring should be encouraged, with a focus on controlling the metabolic profile in order to reduce the cumulative risk of cardiovascular events. In addition, screening for genetic factors can provide valuable information for patient management, allowing for personalized care and individualized treatment. This is expected to prevent the occurrence

of acute cardiovascular events in the young population, aiming for lasting cardiovascular health.

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