Cannabis and tramadol addiction: Do they imply additive risk for acute myocardial infarction in adults younger than 45 years?

Hazem Mansour, *Mona Rayan,* *Mina Shnoda*[1], *Diaa Kamal*

Department of Cardiology, Faculty of Medicine, Ain Shams University; Cairo-*Egypt*
[1]Department of Internal Medicine, Allegheny General Hospital; Pennsylvania-*United States of America*

Abstract

Objective: Acute myocardial infarction (AMI) is the main cause of cardiovascular events worldwide. AMI commonly occurs in elderly patients because of atherosclerotic process related to common risk factors. Consequently, the rupture of atheromatous plaque with deleterious sequela is the common etiology of the disease. However, there are less studied etiological factors in youth compared with the usual population. Therefore, this study aimed to examine the risk profile of Egyptian youth presenting with AMI.

Methods: A study was conducted in 106 patients aged ≤45 years admitted with AMI in our university hospital to explore their clinical profile risk factors.

Results: In the study, 71 (67%) and 35 (33%) patients presented with ST elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI). Anterior wall MI was predominant in 49 patients (46.2%). Moreover, 93 patients (88%) were smokers, 31 (29.2%) used tramadol, 43 (40.6%) smoked cannabis, 50 (47.2%) had poor sleeping habits, 29 (27.4%) had high stress levels, 37 (34.9%) had hypertension, and 22 (20.8%) had diabetes. Twenty (18.9%) patients had a family history of premature coronary artery disease. High and low high-density lipoprotein (HDL) levels were observed in 20 (18.9%) and 47 (44.3%) patients, respectively. The left anterior descending artery (LAD) was involved in 56% of the studied population associated with tramadol use. A significant association was found between both tramadol use and cannabis smoking and presence of heavy thrombus burden on coronary angiography.

Conclusion: AMI in Egyptian youth was predominantly observed in men, with anterior STEMI as the most common presentation. Cannabis and tramadol addiction were high risk factors for AMI in Egyptian youth. *(Anatol J Cardiol 2020; 24: 316-25)*

Keywords: acute myocardial infarction, youth risk factors, cannabis, tramadol

Introduction

AMI in the young is relatively uncommon. However, it is an important problem because the risk parameters, clinical scenario, and prognosis in these patients differ when compared with elderly patients (1). Coronary artery disease (CAD) in the young is referred to CAD occurring in individuals <45 years. However, various studies have considered age varying from 35 to 55 years in the spectrum of CAD in the young (2).

This issue has gained importance recently because of the significant increase of AMI events in the young population as reported by some epidemiological studies (3).

In addition to the conventional risk factors for AMI in the young, data regarding the role of some novel factors, such as cannabis and tramadol addiction are increasing (4). Cannabis has pro-coagulant effects and hemodynamic properties that might promote plaque rupture and stimulate thrombosis (5).

Analgesic doses of tramadol indicates less risk for cardiovascular events. However, tramadol use might cause serotonin syndrome, which might provoke cardiac arrhythmia. Cardiac hazards vary from palpitations to arrhythmias, conduction abnormalities, and cardiac arrest (6).

Because AMI events in the youth in the last decades have significantly increased, this study aimed to clarify the different etiological factors and prevalence in Egyptian youth in addition to the paucity of studies on risk factor profile in AMI in the young.

Methods

Aim

To determine the clinical profile and proportion of different risk factors and demographic data of Egyptian patients presenting with MI for the first time at age ≤45 years.

Address for correspondence: Hazem Mansour, MD, Department of Cardiology, Faculty of Medicine, Ain Shams University; Cairo-*Egypt*
Phone: +201 000 540 100 E-mail: hazemmansour79@gmail.com
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Patient population

Of 1207 patients admitted because of AMI for the first time in our university hospitals between February 2018 and August 2018, only 106 patients achieved our inclusion criteria.

Inclusion criteria

- All patients of both sexes,
- Between 18 and 45 years,
- Presenting with STEMI or NSTEMI.

Exclusion criteria

Patients <18 years and >45 years, those with known CAD or had previous MI or underwent revascularization procedure, certain conditions that may affect the ST segment (e.g., electrolyte disturbance, pericarditis, takotsubo cardiomyopathy, etc.), and those who refused to be part of the study.

Ethical approval and consent to participate

The Local Ethical Committee of the faculty of medicine of our university hospital approved our study protocol, and the participants signed an informed written consent to participate in the study.

Study design

A cross-sectional single-center observational study enrolling young adults (age ≤45 years) with STEMI or NSTEMI. Data on the clinical and demographic characteristics, risk factors, and angiographic variables were collected. Full history was obtained on age, marital status, and detailed risk profile with regard to smoking and the number of cigarettes smoked daily, IV drug abuse, tramadol use, cannabis smoking, hypertension defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure > 90 mm Hg in four readings on two separate occasions and/or taking regular antihypertensive medications or blood pressure >130/85 mm Hg in patients with diabetes (7). Diabetes mellitus diagnosed by blood glucose ≥200 mg/dL or HbA1C ≥6.5% or being a known diabetic and receiving medications (8). Dyslipidemia was diagnosed as serum cholesterol of ≥200 mg/dL, triglyceride >150 mg/dL, low-density lipoprotein (LDL) >100 mg/dL, <70 mg/dL for patients with diabetes or heart disease (9). Family history of premature ischemic heart disease defined as male <55 years or female <65 years in first-degree family members. The presence of poor sleep habits was assessed using the Pittsburgh scale. Stressful life/working conditions were also assessed using the Holmes–Rahe Questionnaire. Standard electrocardiogram was performed in all patients.

All patients underwent coronary angiography with the aim of fixing the culprit vessel

Obstructive CAD was demarcated as ≥70% stenosis in major epicardial arteries or ≥50% stenosis in the left main coronary artery, whereas intermediate disease was demarcated as 50%–69% stenosis, and minimal disease was defined as ≤50% stenosis. The culprit artery was identified angiographically and documented for each patient in the study. The type of lesion and presence of heavy thrombus burden were also detailed.

Statistical analysis

Data were composed, reviewed, coded, and entered in the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges when their distribution was parametric. In addition, qualitative variables were presented as numbers and percentages.

Qualitative data were presented as numbers and percentages. With regard to the qualitative data, the two groups were compared using the chi-squared test. However, the Fisher exact test was only used when the expected count in any cell was <5.

Quantitative data were presented as mean, standard deviations, and ranges. The data distribution was tested using the Kolmogorov–Smirnov test of normality. With regard to the quantitative data, the two groups were compared using independent t-test when the data were parametric, and Mann–Whitney test was used when data were non-parametric, and paired data were compared using paired t-test.

Univariate and multiple logistic regression analyses were used to assess factors related to STEMI presentation and LAD involvement with odds ratio and 95% confidence interval (CI).

The CI was adjusted to 95%, and the margin of error accepted was adjusted to 5%. Thus, $p<0.05$ was considered significant.

Results

Of 1207 patients admitted for the first time with MI, 106 were young, with a prevalence of 8.8% in our center. Of 106 patients, 95% were men, and the mean age was 39 years. STEMI and NSTEMI were found in 71 (67%) and 35 (33%) patients, respectively. Anterior wall MI was present in 49 patients (46.2%). With regard to the risk factor profile, 88% of patients were smokers, 40.6% were hashish smokers, 35% were hypertensive, 21% were diabetic, and 18.9% had low HDL level. Tramadol addiction and hash (cannabis) smoking were reported in 29% and 41% of patients, respectively (Table 1).

With regard to hash smoking, the correlation between patients with STEMI (35, 49.3%) and NSTEMI (8, 22.9%) was highly significant ($p=0.009$) (Table 2).

Univariate logistic regression analysis for factors related to AMI showed that body mass index (BMI), sleeping habits, hash smoking (cannabis), DM, hypertension, LDL level, and family history of premature CAD were significantly associated with the odds of AMI at $p<0.05$. The estimated odds ratio (OR) (95% CI) of hash smoking was 3.281 (1.313–8.200; $p<0.011$) (Table 3).

Affected LAD was significantly correlated with hypertension, peak CKMB, and tramadol use (Table 4).

Univariate and multiple logistic analysis showed that tramadol use was an independent predictor for LAD involvement (Table 5).

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Table 1. Clinical profile and risk factors of the study group

	n=106
Age	
Mean±SD	39.32±5.28
Range	24–55
Sex	
Females	5 (4.7%)
Males	101 (95.3%)
BMI	
Mean±SD	27.81±2.23
Range	23–33
STEMI/NSTEMI	
NSTEMI	35 (33.0%)
STEMI	71 (67.0%)
Anterior/inferior	
Anterior	49 (69.0%)
Inferior	20 (28.2%)
Lateral	2 (2.8%)
Smoking	
No	13 (12.3%)
Yes	93 (87.7%)
IV drug abuse	
Negative	104 (98.1%)
Positive	2 (1.9%)
Tramadol addiction	
Negative	75 (70.8%)
Positive	31 (29.2%)
Hash (cannabis) smoking	
Negative	63 (59.4%)
Positive	43 (40.6%)
Diabetes mellitus	
Negative	84 (79.2%)
Positive	22 (20.8%)
Hypertension	
Negative	69 (65.1%)
Positive	37 (34.9%)
LDL level	
Normal	86 (81.1%)
High	20 (18.9%)
HDL level	
Normal	59 (55.7%)
Low	47 (44.3%)
FH of premature CAD	
Negative	86 (81.1%)
Positive	20 (18.9%)
Peak CKMB	
Mean±SD	242.32±194.37
Range	40–786
LCX	
Negative	88 (83.0%)
Positive	18 (17.0%)
LAD	
Negative	43 (40.6%)
Positive	63 (59.4%)
RCA	
Negative	79 (74.5%)
Positive	27 (25.5%)
NSL	
Negative	103 (97.2%)
Positive	3 (2.8%)

BMI - body mass index; STEMI - ST elevation myocardial infarction; NSTEMI - non-ST elevation myocardial infarction; LDL - low-density lipoprotein; HDL - high-density lipoprotein; FH - family history; CAD - coronary artery disease; LCX - left circumflex artery; LAD - left anterior descending artery; RCA - right coronary artery; NSL - non significant lesion

The culprit lesions showed a highly significant large thrombus burden in both illicit drugs (Table 6).

A significant correlation was found between anterior wall MI and tramadol use among patients presenting with AMI (88.0%) (p=0.035). Furthermore, a significant correlation was found with cannabis (hash) smoking because 58% of tramadol users were smoking cannabis (p=0.018) (Table 7).

A significant association was also found between tramadol use and smoking, as 100% of tramadol users were smokers (p=0.013).

Moreover, a significant correlation was found among tramadol users with LAD involvement (24 patients, 77.4%; p=0.015), and no association was found in other culprit vessels and non-significant lesions. No significant association was found between hash smoking and involvement of any culprit vessel (Tables 5 and 7).

A substantial association was found between illicit drug use and degree of increase in cardiac enzymes. Hash smoking was significantly associated with greater increase of CK total and CKMB that reflects more myocardial injury. No similar association was detected with tramadol use (Fig. 1, Table 7).

Discussion

Egypt, like many other countries, faces a dual disease burden: a persistently diminishing communicable disease burden and a large and rapidly growing non-communicable diseases burden,

Table 2. Relationship between AMI presentation and other parameters

	STEMI/NSTEMI		*P*
	NSTEMI n=35	STEMI n=71	
Age			
Mean±SD	40.77±4.21	38.61±5.62	0.046
Range	31–48	24–55	
BMI			
Mean±SD	28.63±2.29	27.41±2.10	0.007
Range	23–33	23–32	
Sex			
Females	4 (11.4%)	1 (1.4%)	0.022
Males	31 (88.6%)	70 (98.6%)	
Smoking			
No	2 (5.7%)	11 (15.5%)	0.149
Yes	33 (94.3%)	60 (84.5%)	
IV drug abuse			
Negative	34 (97.1%)	70 (98.6%)	0.606
Positive	1 (2.9%)	1 (1.4%)	
Tramadol addiction			
Negative	29 (82.9%)	46 (64.8%)	0.054
Positive	6 (17.1%)	25 (35.2%)	
Hash smoking			
Negative	27 (77.1%)	36 (50.7%)	0.009
Positive	8 (22.9%)	35 (49.3%)	
Diabetes mellitus			
Negative	20 (57.1%)	64 (90.1%)	<0.001
Positive	15 (42.9%)	7 (9.9%)	
Hypertension			
Negative	13 (37.1%)	56 (78.9%)	<0.001
Positive	22 (62.9%)	15 (21.1%)	
LDL level			
Normal	20 (57.1%)	66 (93.0%)	<0.001
High	15 (42.9%)	5 (7.0%)	
HDL level			
Normal	17 (48.6%)	42 (59.2%)	0.302
Low	18 (51.4%)	29 (40.8%)	
FH of premature CAD			
Negative	24 (68.6%)	62 (87.3%)	0.020
Positive	11 (31.4%)	9 (12.7%)	

P>0.05, not significant; *P*<0.05, significant; *P*<0.01, highly significant.
BMI - body mass index; STEMI - ST elevation myocardial infarction; NSTEMI - non-ST elevation myocardial infarction; LDL - low-density lipoprotein; HDL - high-density lipoprotein; FH - family history; CAD - coronary artery disease

such as myocardial ischemia and infarction. However, data on clinical features, risk factors, optimal treatment approach, and outcomes in AMI in Egyptian youth and the middle eastern region were limited compared with older subjects. Thus, this population requires special attention, and developing an approach to the early diagnosis and identification of high-risk patients is a challenge. Therefore, we targeted this population in our study.

With regard to the AMI presentation in the present study, anterior wall MI was the predominant STEMI type in 22 patients (88%) (p=0.035), and consequently, LAD was the most affected vessel (63%). Regarding the extent of CAD, our study showed a predominance of single-vessel disease (VD), which was LAD, followed by two VD and three VD.

A study conducted on 124 patients <40 years presenting with AMI were evaluated. Anterior wall MI was found in 88 patients (71%), denoting that anterior wall MI was the most predominant, with LAD being affected in approximately 2/3 of patients (1).

Another cross-sectional study evaluated 41 STEMI patients and revealed that anterior wall MI was found in 82.9%, with obstructive CAD in 61% of patients due to involvement of LAD in 46.4% (10).

Similarly, a cross-sectional study was conducted on 266 young (≤35 years) patients with clinical diagnosis of AMI. Anterior wall MI was the most common. Most patients showed single VD, followed by double VD. The LAD was the most commonly affected vessel (11).

Regarding the demographic characteristics of the present study population, 95.3% of the patients were men, which was similar to the results obtained by Bhardwaj et al. (1), with 99% being men. Similarly, Incalcaterra et al. (12) found that 91% of the study sample were men. Sinha et al. (13) also found that 91% of the study sample were men, indicating that MI in the young age occurs almost exclusively in men. The male predominance of the study population is accredited to the protective effects of estrogen in preventing the atherosclerotic process, and the dominance of smoking was more common among men, which has been established in various epidemiological studies (14).

A limited percentage of obesity was found among the study group, with a mean BMI of 27.81±2.23 (overweight), whereas the prevalence of obesity (BMI ≥30) was only 8% among the study sample. Obesity was an uncommon risk parameter in many previous studies in young individuals presenting with AMI, with an incidence of 3.3%–0% (15-17).

Bhardwaj et al. (1) showed similar results, with only 4% of patients being obese. However, the results were different from our results in studies by Incalcaterra et al. (12) and Sinha et al. (13), wherein the percentage of obesity in their study samples was 25.1% and 39.1%, respectively. Lakka et al. (18) showed that abdominal obesity was an independent risk factor for acute coronary syndrome (ACS) in middle-aged men, and in addition to smoking, the risk of coronary events increased by 5.5 times.

The majority of patients were smokers (87%), and highlighting smoking was the most significant risk factor in this age group. Cigarette smoking was the most important risk factor for CAD, with involvement ranging from 60% to 90% (15, 16) in many studies. Similar to previous studies, our study population

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Table 3. Univariate and multiple logistic regression analyses for factors related to AMI presentation

	Univariate		Multiple	
	P	OR (95% CI)	P	OR (95% CI)
Age	0.052	0.917 (0.840–1.001)	-	-
BMI	0.010	0.766 (0.625–0.938)	0.925	1.016 (0.725-1.425)
Sex	0.053	9.032 (0.970–84.144)	-	-
Hash smoking (cannabis)	0.011	3.281 (1.313–8.200)	0.289	2.600 (0.444–15.214)
Diabetes mellitus	<0.001	0.146 (0.052–0.408)	0.765	0.724 (0.088–5.993)
Hypertension	<0.001	0.158 (0.065–0.386)	0.098	0.198 (0.029–1.349)
LDL level	<0.001	0.101 (0.033–0.312)	0.165	0.278 (0.046–1.695)
FH of premature CAD	0.024	0.317 (0.117–0.860)	0.197	0.262 (0.034–2.009)

BMI - body mass index; OR - odds ratio; CI - confidence interval; LDL - low-density lipoprotein; FH - family history; CAD - coronary artery disease

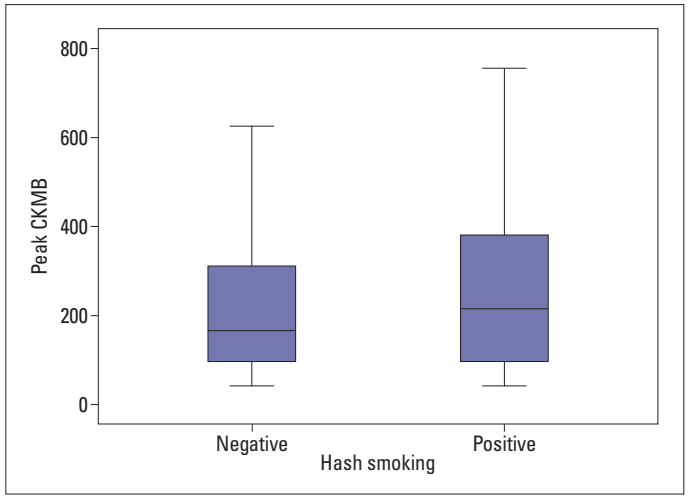

Figure 1. Association between hash (cannabis) smoking and CKMB

included 87% smokers (17). It unfavorably promotes all phases of atherosclerosis by accelerating thrombotic process, endothelial dysfunction, and coronary vasoconstriction, initiates pro-inflammatory effects, and eventually generates thrombotic milieu.

The percentage of traditional risk factors, such as DM, hypertension, and dyslipidemia, were documented in the present study sample. DM was found in 22%, which was consistent with the prevalence in the study by Karim et al. (19). A similar prevalence (20.7%) was found by Incalcaterra et al. (12), and a prevalence of 17.2% was detected by Sinha et al. (13). However, the study by Bhardwaj et al. (1) showed that the percentage of DM was much lower, with only 8% of the study population being diabetic.

The percentage of hypertension in the study group was 34.9%, which was quite similar to the study by Bhardwaj et al. (1), with 44.4% of the study sample being hypertensive. A study by Aggarwal et al. (2) showed that the percentage of hypertension in young people with CAD was 26% compared with only 13% in those without CAD.

Dyslipidemia is considered a major risk factor for CAD in the literature, and our study was concerned with the specific form of dyslipidemia prevalent in this age group. In our study, 44.3% of the study population had low HDL levels, and by stratifying them, 29% of the patients had isolated low HDL levels as the only factor of dyslipidemia, whereas only 3.7% had isolated high LDL levels. The significant prevalence of low HDL level in our study sample matched multiple studies. Among 68 studies involving >300.000 patients in different age groups, HDL was strongly and inversely related to CV events (20).

The study by Bhardwaj et al. (1) showed that the prevalence of low HDL among young adults presenting with AMI was 42.7%, whereas high LDL levels were present in 12.9% only.

The study by Alsheikh-Ali et al. (21) showed consistent results with our study. Approximately 55% of all patients who developed AMI had low HDL-C level, whereas almost half of them already had LDL level within the target range (<100).

The percentage of positive family history for premature CAD was 20% in our study, which was consistent with that by Bhardwaj et al. (1), which was 17.7%. In contrast, a positive family history was present in almost half of patients in both studies by Incalcaterra et al. (12) and Sinha et al. (13). The difference in results can also be explained by a better recall of family history by their study subjects due to better education and medical awareness.

Literature data clearly associated the conventional risk factors with atherosclerosis leading to development of CAD and its complications in young subjects but with different rates and importance of specific risk factors compared with older patients. The PDAY study (22) and Bogalusa Heart study (23) showed that atherogenesis already starts in childhood, and the degree of lipid-rich plaques depends on factors, such as age, HDL level, hypertension, hyperglycemia, obesity, and tobacco smoking. Prospective cohort studies, including the Muscatine study (24) and the Cardiovascular Risk in Young Finns study (25) showed that coronary risk factors recorded in childhood or early adult-

Table 4. Relationship between LAD involvement and other parameters

	LAD		*P*
	Negative n=43	Positive n=63	
Age			
Mean±SD	39.49±5.17	39.21±5.38	0.788
Range	24–55	27–45	
Sex			
Females	1 (2.3%)	4 (6.3%)	0.337
Males	42 (97.7%)	59 (93.7%)	
BMI			
Mean±SD	28.05±1.90	27.65±2.43	0.372
Range	23–32	23–33	
Smoking			
No	2 (4.7%)	11 (17.5%)	0.050
Yes	41 (95.3%)	52 (82.5%)	
IV drug abuse			
Negative	42 (97.7%)	62 (98.4%)	0.784
Positive	1 (2.3%)	1 (1.6%)	
Tramadol addiction			
Negative	36 (83.7%)	39 (61.9%)	0.015
Positive	7 (16.3%)	24 (38.1%)	
Hash smoking			
Negative	25 (58.1%)	38 (60.3%)	0.823
Positive	18 (41.9%)	25 (39.7%)	
Stress level			
Normal	1 (2.3%)	3 (4.8%)	0.659
Low	3 (7.0%)	7 (11.1%)	
Moderate	25 (58.1%)	38 (60.3%)	
High	14 (32.6%)	15 (23.8%)	
Diabetes mellitus			
Negative	31 (72.1%)	53 (84.1%)	0.134
Positive	12 (27.9%)	10 (15.9%)	
Hypertension			
Negative	22 (51.2%)	47 (74.6%)	0.013
Positive	21 (48.8%)	16 (25.4%)	
Peak CKMB			
Mean±SD	194.74±158.79	274.79±210.38	0.037
Range	45–786	40–755	
LDL level			
Normal	34 (79.1%)	52 (82.5%)	0.654
High	9 (20.9%)	11 (17.5%)	
HDL level			
Normal	28 (65.1%)	31 (49.2%)	0.105
Low	15 (34.9%)	32 (50.8%)	
FH of premature CAD			
Negative	34 (79.1%)	52 (82.5%)	0.654
Positive	9 (20.9%)	11 (17.5%)	

P>0.05, not significant; *P*<0.05, significant; *P*<0.01, highly significant.
BMI - body mass index; STEMI - ST elevation myocardial infarction; NSTEMI - non-ST elevation myocardial infarction; LDL - low-density lipoprotein; HDL - high-density lipoprotein; FH - family history; CAD - coronary artery disease; CK-MB: Creatine kinase-MB

hood correlated significantly with the carotid artery intima–media thickness and coronary calcium score.

A high proportion of study samples had poor sleeping habits, with approximately half (47.2%) of the subjects having reported sleeping <6 h daily and/or interrupted sleeping and/or snoring problems. The study conducted by Xie et al. (26) concluded that less sleeping time and increased snoring frequency upsurges the AMI risk with a calculated OR of 1.77 compared with the control group. Poor sleeping habits were associated with tramadol addiction in 25% of patients, which could be a possible association with tramadol use rather than a separate independent risk factor.

Exposure to stressful life as assessed by the Holmes–Rahe Questionnaire recorded 9.4%, 3.8%, 59.4%, and 27.4% had low, normal, moderate, and high stress levels, respectively. In addition, 47.5% of patients with both moderate and high stress levels had other risk factors, such as low HDL level and illicit drug use, indicating a consistent result with the study by Bagheri et al. (27), which showed that total psychological stress is correlated with the existence and severity of CAD considerably, but the correlation was not independent.

Histopathological studies have shown that these plaques have more lipid content with relative deficiency of cellular scar tissue and progress more quickly than plaques seen in older patients. These vulnerable plaques are susceptible to rupture that may account for higher prevalence of STEMI at a younger age than chronic stable angina (16). High frequency of stressful life events might have attributed for the instability of the plaque causing its rupture leading to STEMI development.

The present study showed a high proportion of study subjects used tramadol and smoked hash (cannabis).The percentage of tramadol use and hash smoking was 31% and 41%, respectively, with 17% of patients having concomitant hash smoking and tramadol use.

Cannabis is the most commonly used illicit substance worldwide. Approximately 160 million people aged 15–64 years have used cannabis at least once in their life (28). These substances are obtained from Cannabis sativa. The dried leaves and flowers are called marijuana, and the dried resin from the flower's

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Table 5. Univariate and multiple logistic regression analyses related to LAD involvement

	Univariate				Multiple			
	P	OR	Lower	Upper	*P*	OR	Lower	Upper
Tramadol addiction	0.018	3.165	1.217	8.233	0.032	3.004	1.101	8.195
Hypertension	0.014	0.357	0.156	0.813	0.103	0.459	0.180	1.169
Peak CKMB	0.042	1.002	1.000	1.005	0.374	1.001	0.999	1.004

OR - odds ratio; CK-MB: Creatine kinase-MB

Table 6. Association between illicit drug use and presence of heavy thrombus

		Heavy thrombus burden		
		Negative	Positive	*P*
Tramadol addiction	Negative	50 (66.7%)	10 (32.3%)	0.001
	Positive	25 (33.3%)	21 (67.7%)	
Hash (cannabis) smoking	Negative	43 (68.3%)	17 (39.5%)	0.003
	Positive	20 (31.7%)	26 (60.5%)	

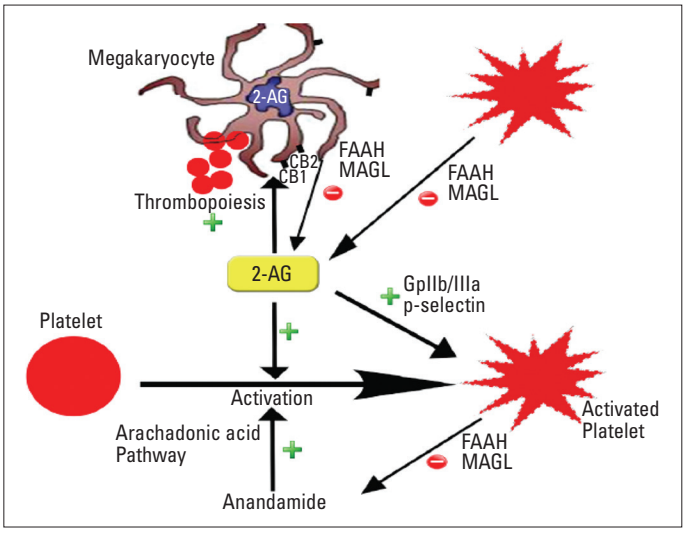

Figure 2. Molecular mechanisms of interplay between cannabinoid system and platelets [Goyal et al., 2017 (5)]

surface is called hash (hashish in Egypt). Cannabis has been suggested to have pro-coagulant properties. Both CB1 and CB2 receptors have been identified on the platelet cell membrane. It has been revealed in vitro that cannabis upsurges expression of glycoprotein IIb–IIIa and P-selectin in a concentration-dependent manner, which predisposes to platelet aggregation and factor VII stimulation. Cannabis is also hypothesized to have hemodynamic effects that could promote plaque rupture and initiate thrombosis (Fig. 2) (5).

A study was conducted to evaluate the percentage of cannabis users among 1116 young STEMI patients, and their mean age was 26±3.9 years. Substance abuse was infrequent, with 52 patients using cannabis (4.6%), which was lesser than that in our study (13).

Univariate logistic regression analysis for factors related to AMI showed that hash smoking (cannabis) was significantly associated with the odds of AMI. The estimated OR (95% CI) of hash smoking was 3.281 (1.313–8.200) (p<0.011).

A large, multi-institutional database retrospective, matched cohort analysis was performed on patients between October 2011 and September 2016. The researchers identified 210,700 patients with cannabis abuse and were compared with 10,395,060 age-matched controls. The 5-year cumulative incidence of MI in the cannabis group was considerably greater than that in the control group [1.28% vs. 0.89%, relative risk (RR), 1.44]. A greater risk was found in the young, with RR of 3.20 and 4.56 individuals aged 25–29 years and 30–34 years (29).

Mittelman et al. (30) evaluated the role of marijuana as an initiator for ACS by conducting a case-crossover study on 3882 patients, and 124 patients had marijuana use in the past year. The authors revealed a raised risk of up to 4.8 times for MI within 1 h of marijuana use. The risk dropped quickly after 1 h. The number of patients who admitted marijuana use was only 3.2% of the whole group. In regular marijuana users, the annual risk of cardiovascular events was augmented by 1.5%–3% (30). Cocaine revealed an OR of 24 compared with 4.8 for marijuana in the study by Mittelman et al. (30). The attributable risk of marijuana was the second lowest among the triggers at 0.8, signifying a low predominance in the population. Although many case reports and *in vitro* studies conveyed that marijuana might cause platelet stimulation and coronary vasospasm, there is no certain evidence for this suggestion (31).

Table 7. Relationship between tramadol addiction and other parameters

	Tramadol addiction		*P*
	Negative n=75	Positive n=31	
Age			
Mean±SD	39.12±5.58	39.81±4.50	0.545
Range	24–55	27–48	
Sex			
Females	5 (6.7%)	0 (0.0%)	0.141
Males	70 (93.3%)	31 (100.0%)	
STEMI/NSTEMI			
NSTEMI	29 (38.7%)	6 (19.4%)	0.054
STEMI	46 (61.3%)	25 (80.6%)	
Anterior/Inferior			
Anterior	27 (58.7%)	22 (88.0%)	0.035
Inferior	17 (37.0%)	3 (12.0%)	
Lateral	2 (4.3%)	0 (0.0%)	
Smoking			
No	13 (17.3%)	0 (0.0%)	0.013
Yes	62 (82.7%)	31 (100.0%)	
Range	6–30	10–30	
IV drug abuse			
Negative	73 (97.3%)	31 (100.0%)	0.359
Positive	2 (2.7%)	0 (0.0%)	
Hash (cannabis) smoking			
Negative	50 (66.7%)	13 (41.9%)	0.018
Positive	25 (33.3%)	18 (58.1%)	
Diabetes mellitus			
Negative	62 (82.7%)	22 (71.0%)	0.177
Positive	13 (17.3%)	9 (29.0%)	
Hypertension			
Negative	48 (64.0%)	21 (67.7%)	0.713
Positive	27 (36.0%)	10 (32.3%)	
LDL level			
Normal	59 (78.7%)	27 (87.1%)	0.313
High	16 (21.3%)	4 (12.9%)	
HDL level			
Normal	43 (57.3%)	16 (51.6%)	0.590
Low	32 (42.7%)	15 (48.4%)	
Peak CKMB			
Mean±SD	231.65±189.25	268.13±207.16	0.382
Range	40–786	40–710	
LCX			
Negative	58 (77.3%)	30 (96.8%)	0.015
Positive	17 (22.7%)	1 (3.2%)	
LAD			
Negative	36 (48.0%)	7 (22.6%)	0.015
Positive	39 (52.0%)	24 (77.4%)	
RCA			
Negative	52 (69.3%)	27 (87.1%)	0.056
Positive	23 (30.7%)	4 (12.9%)	
NSL			
Negative	74 (98.7%)	29 (93.5%)	0.148
Positive	1 (1.3%)	2 (6.5%)	

P>0.05, not significant; *P*<0.05, significant; *P*<0.01, highly significant.
STEMI - ST elevation myocardial infarction; NSTEMI - non-ST elevation myocardial infarction; LDL - low-density lipoprotein; HDL - high-density lipoprotein; FH - family history; CAD - coronary artery disease; LCX - left circumflex artery; LAD - left anterior descending artery; RCA - right coronary artery; NSL - non significant lesion

In the CARDIA (Coronary Artery Risk Development in Young Adults) study, a 15-year longitudinal follow up of 3617 adults was conducted, and no relationship was found between marijuana and cardiovascular risk (32). However, marijuana use was linked to other unhealthy actions, such as high-caloric diet, tobacco smoking, HIV infection, and other illicit drug use, which accounts for poor health consequences. Moreover, other large-sample size, long-term longitudinal studies were unsuccessful to display any statistically substantial escalation in mortality due to cardiovascular events in marijuana users (33, 34). However, marijuana use more than once weekly was accompanied with a threefold increase in mortality in patients who previously had an MI (35).

Although many case reports of ACS after marijuana use have been issued in the literature, assessment of cardiovascular effects of marijuana is complex due to concurrent use of other drugs, such as cocaine, poor quantification, and existence of several chemical compounds in marijuana. Furthermore, there are diverse means of marijuana use that might modify the quantity and types of chemicals consumed. For example, marijuana rolled in tobacco leaves are called blunts, whereas while those rolled in cigarette paper are called joints. Thus, using blunts will yield effects of nicotine in addition to that of marijuana, (36) whereas using joints leads to inhalation of chemicals from the combustion of paper.

Tramadol is used as pain medication in the US and Europe. Tramadol is an atypical opioid that acts centrally to initiate its analgesic effect. It is commonly used in the treatment of moderate to severe pain. It binds to the μ opioid receptors with a low affinity and also inhibits the reuptake of serotonin and norepinephrine. At analgesic doses, it exerts a low risk for devel-

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opment of cardiovascular events. However, tramadol use can predispose to serotonin syndrome, which can initiate cardiac arrhythmia. Cardiac side effects may vary from agitation and palpitations to arrhythmia, conduction abnormalities, and cardiac arrest (6).

In 2018, the Food and Drug Administration has raised a question if tramadol causes ACS; however, well-validated clinical studies evaluating the association between tramadol use and CAD is limited. In contrast with our study, the Nair and Chandy study (40) showed low risk of cardiovascular complication with tramadol use in anesthesia. The main concern raised by the study was tramadol-induced serotonin syndrome, and not CAD, with tramadol use. This factor was not well investigated probably because tramadol is not commonly used as an illicit drug in western countries but used more often as a sedative or in pain management purposes in the short term.

A substantial correlation was established between tramadol use and LAD involvement in our study. However, no statistical significance was found between the use of hash and involvement of any culprit vessel. Unfortunately, a limited number of studies were conducted on that aspect.

Study limitations

Limitations included a limited number of patients and being conducted in a single center. In addition, not adding a control group of patients >45 years to identify whether the subject's age really matters. The education and income levels and employment status are relevant information that could have been useful.

Moreover, the emphasis on the difference between tobacco and tobacco mixed with cannabis should be made clear. Other abused substances, such as cocaine, are famously associated with STEMI, but these were excluded in our study due to common use in the geographical area of the research and because of the socioeconomic status of the subjects.

Therefore, multi-centric broader studies, including a control group >45 years while stressing on other substances of abuse are recommended.

Conclusion

AMI in Egyptian youth predominantly occurred in men, and anterior STEMI was the most common presentation. Cannabis and tramadol addiction are considered high risk factors for AMI in the Egyptian youth. Furthermore, tramadol use was correlated significantly with LAD involvement.

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