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Exploring a Possible Link between Myocardial Infarction and Erectile Dysfunction: A Literature Review

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Abstract

A decrease in the blood flow through the vessels due to endothelial dysfunction is the reason for both acute myocardial infarction (AMI) and Erectile dysfunction (ED). Intimal thickening in the coronary artery and decreased availability of nitrous oxide in penile arteries link ED and AMI. Fatigue, depression, and ED are generally seen in patient's post-hospital discharge after AMI. ED affects many men and their partner's quality of life, and the prevalence increases with age. The most common cause of ED is psychogenic. However, organic causes, like atherosclerosis, and genetic and environmental factors, play a significant role. Data were collected from studies like systematic reviews, cohort, case-control, prospective, and retrospective studies, all of which give us similar findings discussed in this review article. Several extensive studies in different countries link the two diseases together. Therefore, the health care providers can consider the in-depth screening of patients with a long history of low sex interest to find any possibility of ischemic heart disease. The International Index of Erectile Function (IIEF-5) is used to help physicians to assess the problem of ED. Fluorine-18 sodium fluoride (NaF) is a bone-seeking radiopharmaceutical used as a tracer to detect bone metastases.

NaF uptake in penile vessels could be used as a marker of atherosclerosis causing ED.

Introduction and Background

Acute myocardial infarction (AMI) is a life-threatening emergency condition that affects around 40% of men above the age of 40 [1]. Reduced or stoppage in the blood supply to a portion of the heart leads to cardiac muscle necrosis, which causes AMI, also called a Heart Attack in layman's terms [2]. In the early 20th century, AMI was generally considered a fatal event diagnosed only at autopsy. Until the 1970s, with more understanding of its clinical presentation and diagnosis, it was managed with prolonged bed rest and with a sedentary lifestyle. Since then, there has been new information evolved which has changed our understanding of it is pathogenesis and markedly altered our treatment options [2]. Globally, it is estimated that up to 3 million people suffer from ST-segment elevation myocardial infarction, while a further 4 million suffer from non-ST segment elevation myocardial infarction [1]. In the assessment of AMI, health care providers have reported the use of cardiac screening tools, specialized equipment like an electrocardiogram, stress electrocardiograms, and measurement of the cardiac enzyme to aid in the diagnosis of AMI [1].

Erectile dysfunction (ED) is defined as the chronic inability to either achieve or maintain a penile erection [3]. Along with the sexual distress that is caused due to ED, it is also thought to be an indicator of cardiovascular disease (CVD), as both are vascular diseases with similar risk factors. Like diabetes, dyslipidemia, hypertension, smoking, and obesity [4]. ED is the common underlying pathophysiological process that links both the diseases, and the prevalence of ED after an AMI is well documented [1].

Patients with ED have a 55% higher risk of developing AMI, and coronary artery disease (CAD) is 50% more likely to occur in patients with ED [4]. ED was considered to be caused by psychogenic factors, but recent research has suggested it to be more connected to vascular factors [5]. ED affects a large population of men; the estimated number by 2025 could reach as high as 300 million worldwide [6]. ED affects the partner's quality of life and can have implications on mental health [5]. ED is thought to increase in prevalence with age, varying from 19% to 39% in a European study on men aged 18-75 years [6]. ED has started to be considered one of the critical risk factors for heart disease, diabetes, and even young age sudden death [7].

The percentage of diabetic patients with ED varies from 35% to 90% [8]. The multiple risk factors that play a role in this considerable percentage are age, a long history of diabetes, poor blood sugar control, smoking, and a sedentary lifestyle. A Meta-analysis study has connected ED with an increased risk of AMI in diabetic patients [8]. ED, peripheral artery disease, and the cardiovascular system could have the same underlying pathophysiological processes due to atherosclerosis, which causes blockage in the blood flow through the vessels.

Atherosclerosis occurs due to genetic and environmental factors, and this interaction between the two factors increases the association between ED and heart attack [9]. Male sex hormone testosterone levels decrease with age leading to decrease muscle mass, reduced bone mineral density, lower libido, vasomotor changes, fatigue, depression, and ED [10]. Multiple studies show a significant association between low serum testosterone levels and cardiovascular mortality [11]. Furthermore, Androgen deficiency has become one of the factors in AMI and heart attacks, such as glucose level, low-density lipoprotein, and increased production of inflammatory cytokines [12]. This review article summarizes the risk of developing AMI in patients with a history of ED.

Search Strategy

Using AMI, ED, risk factors of MI and ED, the clinical picture of MI and ED, nitrous oxide, and Fluorine-18 sodium fluoride (NaF) as search keywords, articles were retrieved that analysed the connection between AMI and ED. The age of literature examined was from 2012-2022 except for two articles. PubMed and PubMed Central (PMC) were used as the primary databases. The different studies used to collect the data analysed were traditional reviews, systematic reviews, clinical trials, retrospective, and cohort studies. There were no demographical, age, or ethnicity limitations in the search. Articles only published in the English language were considered, and no translated papers of different languages were considered in this review.

Review

This section will discuss the risk factors, causes, pathophysiology, and clinical picture of AMI and ED and explain their link with each other, and also sheds light on the role of Fluorine-18 sodium fluoride (NaF) in detecting micro-calcification of the penile artery.

Risk Factors and Etiology of ED and AMI

Atherosclerosis affects small arteries more than large arteries. Both penile arteries and coronary arteries are small in size. Atherosclerosis with subsequent inflammation is the most common and most important driver of thrombosis [1]. 50% of men with significant coronary artery disease after cardiac

catheterization have a history of ED [13]. 40% of men with ED have a history of hypertension, and 42% of men who suffer from hyperlipidemia have ED.

In addition, 28% of diabetic men have ED compared to non-diabetic patients [13]. ED has also been seen in multiple cases post rectal surgery. In China, in a questionnaire survey to evaluate sexual function after rectal surgery, the ED percentage was seen in 25% of males, and the number participating in the study was 984 subjects [14].

Mostly, the cause of ED is considered to be multi-factorial. However, the specific reasons for ED could be psychological causes and organic causes, anxiety, depression, aging, cardiovascular disease, diabetes mellitus, hypertension, hyperlipidemia, and neurological diseases like multiple sclerosis [13].

Other causes of ED are sexual disorders and hormonal disorders such as thyroid dysfunction, low testosterone levels, and late onset hypogonadism [12].

MI risk factors were used in a study named (Nterheart) diet, cigarette smoking, diabetes, hypertension, obesity, high lipid, alcohol, physical activity, and psychological factors [15]. The number of participants in the diseased group was 12,461 and 14,637 in the control group. Hypertension, elevated lipid levels, diabetes, and smoking were present more in the younger subjects.

Smoking was considered to be one of the most significant risk factors along with MI, which ranged from 64.5% to 93.7%.

Homocystinuria causes MI and leads to endothelium changes followed by atherosclerosis and plaque instability. Homocysteine prevents the dilator effect on the vessel. Instead, it leads to vasoconstriction after reducing the availability of Nitrous oxide (NO), which is responsible for dilating the penile vessel during erection leading to ED [15].

Chronic kidney disease is present in older patients with heart attacks [16]. Raised systolic blood pressure, male sex, and diabetes have a stronger association with MI [17].

One study linked differentially expressed genes (DEGs), GSE 114695 and GSE 69187, with a younger patient with a history of MI and a high-fat diet; it is interesting to see in future research if this gene could play a role in ED at a younger age [18].

CHA2DS2-Vasc score risk assessment for thromboembolic stroke and ED is considered a vascular component of this score to assess emboli risk [19]. Table 1 lists the prevalence of ED associated with systemic diseases and post rectal surgery.

Table 1

Prevalence of ED in relation to some diseases [4,8,13].

DISEASE	ED percentage
AMI	55%
Diabetes mellitus	35-95%
Post rectal surgery in men	25%
Post rectal surgery in women	22.5%
After catheterization + CAD	50%
Hypertension	40%
Hyperlipidemia	42%

Table credit: Author. Baradeiya A M

AMI: Acute Myocardial Infarction

CAD: Coronary Artery Disease.

Pathophysiology of ED and MI

Nitrous oxide (NO) plays a significant role in erection and arousal. NO works in the paraventricular nucleus and some other regions of the brain. NO functions as a dilator of penile arteries leading to more blood flow and causing an erection.

Phosphodiesterase 5 (PDE5) enzyme breaks down cGMP (nitric oxide - cyclic guanosine monophosphate) at cavernosal smooth muscle cells. As a result, Ca-dependent potassium channels open, and potassium and calcium out-flux and cell hyperpolarization relaxes smooth muscle cells and increase blood flow through the arteries. Furthermore, this pathway also dilates the systemic vessels and coronary arteries, explaining the connection between AMI and ED [20].

The most common reason for thrombosis is the inflammation that happens at the endothelial level due to atherosclerosis. Atherosclerosis is an inflammatory process that affects the intima, which is the inner wall of the vessels. The inflammatory process will release the macrophage, monocyte, T lymphocyte, lipids, and platelets.

As a result, intimal thickening and fibrous cap formation called the atheroma, decrease in the blood supply to the coronary arteries, and development of angina and MI. It also affects the penile arteries too, causing ED due to reduced blood flow [2]. Smoking increases and speeds up this process causing direct damage to the vascular endothelial system causing a vascular clot, and increased sympathetic activity, leading to AMI [15]. Figure 1 explains the role of NO in erection [20].

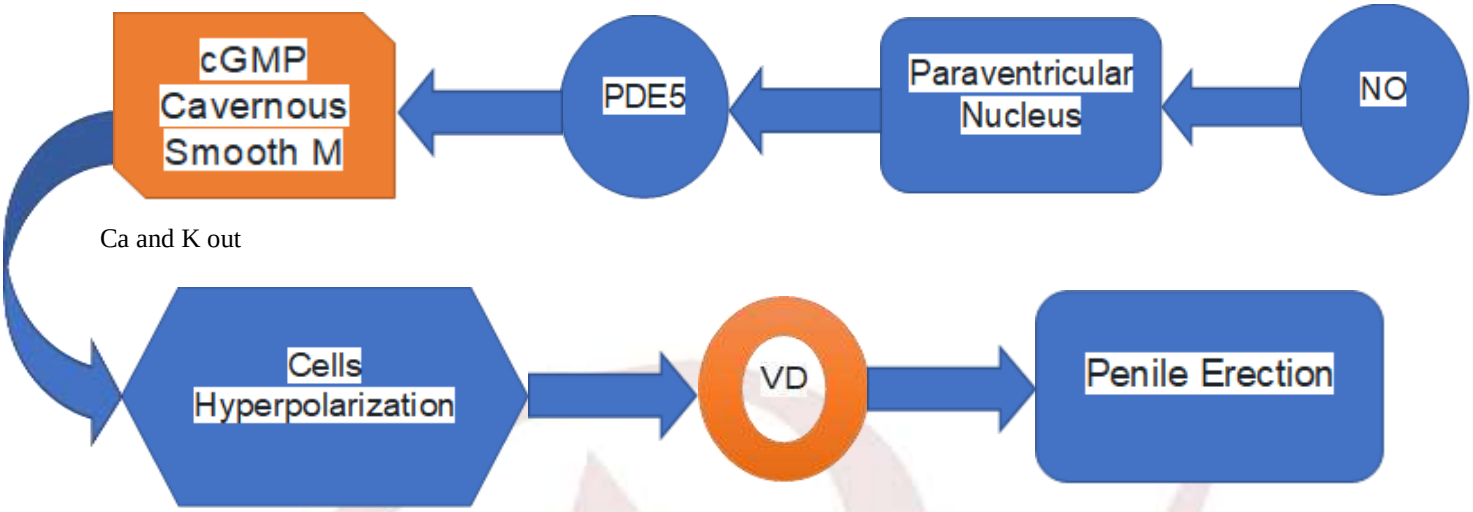

Figure 1: Role of NO on erection

The figure is adapted from [20] Anatomy, Pathophysiology, Molecular Mechanisms, and Clinical Management of Erectile Dysfunction in Patients Affected by Coronary Artery Disease: A review.

Figure credit: Author. Baradeiya A M

NO: Nitrous oxide.

PDE5: Phosphodiesterase type 5.

cGMP: Nitric Oxide - Cyclic Guanosine Monophosphate.

Ca: Calcium.

K: Potassium.

VD: Vasodilation.

The Clinical Picture of ED and MI

Knowing the causes of ED and its presenting symptoms is essential. It could be psychogenic due to post-traumatic accidents, psychological problems, or different kinds of stress present as a patient can reach a self-stimulated erection, loss of sustained erection, or normal nocturnal erection. And most of the patient's symptoms improved after using a phosphodiesterase type 5 (PDE5) inhibitor. While organic causes like the vascular and neurological present as gradual onset, normal libido, loss of morning erections, and poor response to PDE5 inhibitor [21, 22]. Even though the loss of interest in sex is the primary male sexual complaint, the percentage of males seeking help for ED is around 6% [23]. Vasculogenic erectile dysfunction is the most common vascular disorder in the younger generation [21].

Presenting symptoms in MI patients could be typical symptoms like chest pain radiating to the left arm or jaw, pain being described as dull, heavy aching, crushing, squeezing, or atypical burning, stabbing pain radiating to the epigastric area or the back [24]. The VIRGO study recruited patients hospitalized with AMI between August 2008, and January 2012, from 103 different hospitals across the united states. Participants were asked about what symptoms they had before arriving at the hospital and what they thought was causing their symptoms; possible responses included acid reflux, flu, stomach illness, muscle pain, and stress, and they were asked why they decided to get help for their symptoms. Responses included symptoms that would not go away, pain severe to ignore, worrying about heart problems, and a family or friend telling them to get help [25]. Fatigue is one of the most bothersome physical symptoms of MI. Fatigue is an unpleasant feeling ranging from tiredness to exhaustion resulting from mental and physical illness or post-traumatic stress disorder. Depression plays a significant role in sexual capability and maintaining erections [26]. The International Index of Erectile Function(IIEF-5) questionnaire was given to young patients less than 45 years post-AMI to assess ED. Mild symptoms of ED occurred in 26%, while severe symptoms occurred in 7%. In the older group, mild ED occurred in 52 %, and 38% had severe symptoms [27]. Table 2 shows the prevalence of ED and AMI.

Table 2

Prevalence of ED and AMI

Author (Year)	Study design	Risk factors	Association between ED and AMI %	Assessment	Conclusion
Abdelhamed A *et al.* (2016) [8]	Prospective study	DM	95%	Multidetector computed tomographic coronary angiography. (MDCT-CA)	MDCT-CA can be used to identify silent MI (SMI) in diabetic patients with ED, especially in severe ED.
		HTN	45%		
		Smoking	55%		
		Dyslipidemia	30%		
Canat L *et al.* (2013) [9]	Observational study	Single vessels disease	45.36%	Coronary angiography after AMI	The severity of ED correlated with the number of occluded vessels documented by coronary angiography
		Two vessels disease	64.5%		
		Three vessels disease	65.7%		
Rinkūnienė E *et al.* (2021) [5]	Retrospective study	Dyslipidemia	100%	Anthropometric measurement, CVD risk factor, and IIEF-5	ED is common in patients after a MI. The prevalence of CVD risk factors is high in patients with ED.
		Arterial hypertension	90.0%		
		DM	14.0%		
		Smoking	23.3%		
		CVD positive family history	43.7%		
		Insufficient physical activity	54.5%		

Table credit: Author. Baradeiya A M

DM: Diabetes Mellitus

HTN: Hypertension

CVD: Cardiovascular Disease

Summary of the Studies Showing the Relationship Between ED and MI

Multiple studies connect MI and ED. In a large meta-analysis of 12 prospective cohort studies, which included 36,744 subjects, Dong *et al.* [28] showed that men with ED increased the relative risk of CVD. 55% of men with a history of ED presented with the acute coronary syndrome. In a retrospective case-control study by Hodges *et al.* [29], it was compared to 43% in matched controls. In the department of preventive cardiology at VUH Santaros Klinikos, a retrospective analysis study showed that 62% of patients who visited the center after AMI experienced ED, and the prevalence of ED increased with age [5].

A study done by Montorsi *et al.* [30] showed similar data, which showed the prevalence of ED is 42-57% in patients with cardiovascular disease. Four related studies, including a systematic review and meta-analysis, Li D *et al.* [31], Montorsi *et al.* [30], and Kumar *et al.* [32], showed ED as a risk factor for coronary artery disease, except Banks *et al.* [7] showed no relationship.72,2% of 396 urologists doctors believed these two diseases present with each other, and 88.2 % asked their patients about a history of CVD [31]. Table 3 summarizes the studies and shows the relationship between ED and other diseases.

Studies (Year)	Study Method	Assessment	Disease	ED %
Hodges LD *et al.* (2007) [29]	Case-control study	IIEF-5 questionnaires	CVD	66%
Montorsi *et al.* (2006) [30]	Case-control study	IIEF-5 questionnaires	CVD	42-57%
Li D *et al.* (2020) [31]	Prospective study	Urologist online questionnaires response	CVD	72.2%
Kumar *et al.* (2019) [32]	Case-control study	IIEF-5 questionnaires	Hypertensive	61.79%
			Normotensive	20.28%

Table credit: Author. Baradeiya A M

CVD: Cardiovascular Disease

IIEF-5: The International Index of Erectile Dysfunction

A prospective population-based Australian study (the 45 and Up Study) collected questionnaire data from 2006 to 2009 with the first CVD related hospitalization and severity of ED based on age, smoking, alcohol consumption, marital status, income, education, physical activity, body mass index, diabetes, hypertension, and hypercholesterolemia treatment. Table 4 shows the prevalence of the study populations between the history of CVD and the severity of ED. Banks E *et al.* [7].

Table 4

Prevalence of ED and history of CVD in Australian populations [7].

Characteristic	Degree of Erectile Dysfunction for Individuals with No Previous CVD (n=65,495)				Degree of Erectile Dysfunction for Individuals with Previous CVD (n=29,323)			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
N	31,256	17,710	10,561	5,968	7,174	6,492	6,995	8,662
Mean age (years)	55.9 (7.3)	59.5 (8.4)	64.2 (9.5)	71.2 (10.5)	59.8 (8.4)	64.0 (8.9)	68.8 (9.2)	75.1 (9.0)
Ever smoker	44%	48%	55%	58%	52%	56%	60%	63%
≥15 alcoholic drinks/week	25%	27%	26%	23%	24%	25%	23%	19%
Mean BMI (kg/m2)	27.0 (3.9)	27.1 (4.1)	27.4 (4.4)	27.1 (4.6)	27.7 (4.2)	27.8 (4.3)	27.8 (4.5)	27.5 (4.8)
Tertiary education	33%	30%	23%	18%	28%	25%	19%	15%
Household income ≥AU$70,000	47%	37%	24%	13%	37%	27%	16%	8%
Married/living with a partner	86%	82%	79%	78%	85%	81%	79%	76%
Highest physical activity tertile	41%	39%	34%	30%	39%	37%	32%	24%
Doctor-diagnosed diabetes	4%	6%	11%	17%	10%	13%	21%	28%
Current treatment for hypertension	13%	18%	25%	29%	29%	35%	39%	41%
Current treatment for hypercholesterolemia	10%	13%	15%	16%	22%	26%	28%	27%

Reprinted with permission from Banks E *et al.* [7] Erectile dysfunction severity as a risk marker for cardiovascular disease hospitalization and all-cause mortality: a prospective cohort study. Source: *PLOS Medicine*. (2013)

Fluorine-18 Sodium Fluoride (NaF) and Micro-calcification of the Penile Artery.

Fluorine-18 sodium fluoride (NaF) is a bone-seeking radiopharmaceutical used as a tracer to detect bone metastases. NaF identifies the process of micro calcification in atheromatous plaques of the penile artery. NaF uptake in ED patients is significantly higher than in patients with no ED [33]. To determine if atherosclerosis of penile arteries plays a role in ED, NaF positron emission tomography-computed tomography bone scans were evaluated in 437 prostate cancer patients. Prostate cancer patients who had NaF bone scans for detecting osseous metastases were enrolled in this study. Of the result of 437 patients, 336 (76.9%) had prevalent ED, 60 incident ED (13.7%), and 41 had no ED (9.4%).

Approximately 70 minutes after intravenous injection of NaF, whole-body Positron Emission Tomography and Computed Tomography (PET-CT) images were acquired to evaluate NaF uptake in penile arteries at the base of the penis. Penile NaF uptake was commonly observed in ED patients. The uptake was observed from the urethral activity in the cavernous and dorsal penile arteries. Quantitative penile NaF uptake in prevalent ED was significantly higher than in no ED [34]. NaF uptake in penile vessels could serve as a marker of atherosclerosis causing ED.

Limitations

The search strategy for this review article was limited to two databases, PubMed and PubMed Central (PMC). The search was restricted to studies published in the last ten years. Additionally, statistical analysis was not the primary purpose of the supporting point. This literature review included data from a patient who had MI and then ED and also incorporated patients who first had ED and then MI.

Conclusion

MI and ED have common pathological processes that play a significant role in their link. Patients with a history of ED have a probability of developing a new onset MI. Multiple factors, such as diabetes, hypertension, hyperlipidemia, smoking, and alcohol, connect both MI and ED. The patient presenting ED should be investigated further for any heart-related diseases. Encouraging the physicians to use questionnaires to assess for a history of ED will let them find more cases. Focusing on the organic causes of ED is as essential as focusing on psychogenic etiology. Analysing various studies published in the last ten years points out the possibility of the relationship between ED and MI. Suggestions for future trials include performing statistical analyses focusing specifically on data from patients with a history of ED developing MI.

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