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Original research article

To study the traditional, non-traditional and genetic risk factors in premature acute coronary syndrome

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Abstract

Aim: To study the traditional, non-traditional and genetic risk factors in premature acute coronary syndrome
Methodology: The present study was a prospective observational study. The study was carried out in the Kamineni hospital, LB Nagar, Hyderabad. Study period: June 2018-December 2019 Study duration of 18 months. Patients diagnosed Acute coronary syndrome with at least one of the following ST elevation myocardial infarction, Non-ST elevation myocardial infarction and Unstable angina as per AHA guidelines.
Results: In our study the young premature coronary artery disease patients the mean age 38.76± 5.86. Our study showed a male preponderance 89.33%. Chest pain/ angina is predominant symptom in our patients (90.66%). Family history of premature CAD in our study was 16%. In our study, diabetes was present in 12% of patients. In our study, hypertension was present in 34.66% of patients. In our study, raised serum homocysteine levels >15 was present in 40% of patients. In our study, the CC-Genotype MTHFR 80%, CT-Genotype MTHFR 16%, TT-Genotype MTHFR 4%. In our study minor A allel frequency of Prothrombin G20210A was 0.02%.
Conclusion: The present study concluded that One of the most consistently demonstrated risk factors for CAD is male sex, Conventional risk factors like smoking, family history of premature CAD, hypertension and diabetes were proving as the risk factors for CAD in young. Dyslipidemia of high total cholesterol, high triglycerides, high LDL-C and low HDL-C are the risk factors for CAD in young. Genetic analysis of factor V, prothrombin and MTHFR are similar to previous studies, which suggest low statistical significance to CAD in young.
Keywords: Acute coronary syndrome, dyslipidimia, diabetes, prothrombin, MTHFR

Introduction

Cardiovascular diseases are one of the leading causes for mortality and morbidity all over the World. The incidence of acute coronary syndrome varies greatly. In United States and United Kingdom, nearly 650,000 and 180,000 patients respectively, get an acute coronary syndrome every year [1].
Cardiovascular diseases (CVDs), especially coronary heart disease (CHD), have assumed epidemic proportions worldwide. Globally, CVD led to 17.5 million deaths in 2012 [2]. More than 75% of these deaths occurred in developing countries. In contrast to developed countries, where mortality from CHD is rapidly declining, it is increasing in developing countries [3].
This increase is driven by industrialization, urbanization, and related lifestyle changes and is called epidemiological transition [4].
Indians are four times more prone for developing acute coronary syndrome due to a combination of genetic and lifestyle factors. The incidence of acute coronary syndrome in India is 64.37/1000 people with mortality rate of 30% [1].
Other striking features of CVD epidemiology in India are high mortality rates, premature CHD, and increasing burden [5].
Atherosclerotic CAD comprises a broad spectrum of clinical entities that include asymptomatic subclinical atherosclerosis and its clinical complications, such as angina pectoris, myocardial infarction (MI) and sudden cardiac death. In the early 1930s, Carl Miller in Oslo reported the co-segregation of high plasma cholesterol, xanthoma and premature coronary heart disease, providing early clues regarding a genetic component of CAD and its association with cholesterol [6].
Of particular concern to India is not only the high burden of cardiovascular diseases (CVDs), but also the

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effects of these diseases on the productive workforce aged 35-65 years. Heart diseases are rising in Asian Indians 5-10 years earlier than in other populations around the world. The mean age for first presentation of acute myocardial infarction in Indians is 53 years. Coronary artery disease (CAD) that manifests at a younger age can have devastating consequences for an individual, the family, and society. Prevention of these deaths in young people is a nation's moral responsibility. A strategy involving prevention of CVDs long before their onset will be more cost-effective than providing interventions at a stage when the disease is well established. We review the rising trends in CAD with particular emphasis on prevalence of premature CAD and the associated risk factors in young Indian CAD patients. Action strategies to reduce the risk are suggested [7].

Aim

To study the traditional, non-traditional and genetic risk factors in premature acute coronary syndrome.

Objectives

1. To document the conventional /traditional risk factors like hypertension, diabetes mellitus, and dyslipidemia in premature acute coronary syndrome.
2. To assess homocysteine and TSH levels in premature acute coronary syndrome as non-traditional factors.
3. To identify genetic variants in factor V, prothrombin and 5, 10 methyltetra hydrofolate reductase to establish their contribution in premature acute coronary syndrome.

Materials and Methods

Study Design

The present study was a prospective observational study undertaken to "To study the traditional, non-traditional and genetic risk factors in premature acute coronary syndrome".

Study Area

The study was carried out in the Department of Cardiology, Kamineni hospital, LB Nagar, Hyderabad.

Study Duration

Study period: June 2018-December 2019 Study duration of 18 months.

Data Collection

Information collected from the patient demographic characteristics, risk factors, past co-morbids and medical history of present symptoms. General Physical examination included the heart rate, respiratory rate blood pressure systolic and diastolic recorded. All patients investigated for biochemical parameters (fasting lipid profile, serum homocysteine, TSH, fasting blood sugar) and investigation for genetic variant of factor v, Prothrombin, 5,10 Methyl tetra hydrofolate reductase.

Sample size is 75 patients based on prevalence.

Method of Selection

Inclusion Criteria

Patients diagnosed Acute coronary syndrome and admitted to Kamineni Hospital, LB Nagar with at least one of the following:

1. ST elevation myocardial infarction.
2. Non-ST elevation myocardial infarction.
3. Unstable angina as per AHA guidelines.
4. Age >=18 years and =<45 years.

Exclusion Criteria

1. Patients age < 18 years and >45 years.
2. Individuals with Pre-existing: Chronic kidney disease/Hepatic failure/Severe infection/sepsis/ Connective tissue disease/Aortic arteritis Malignancy.
3. Cases with suspected myocarditis, pericarditis, hypothermia, receiving amiodarone treatment etc.

Diagnostic Criteria in Our Study

Hypertension (HTN): history of HTN in the past, systolic blood pressure (SBP) ≥140 mmHg, and or diastolic blood pressure ≥90 mm hg.

Diabetes: History of diabetes; fasting blood glucose >126 mg/dl or 2-h postprandial blood glucose >200 mg/dl, HbA1C >6.5.

Smoking: if the patient was a current smoker or had quit smoking in the past 6 months.

Body Mass Index (BMI): More than ≥30kg/m2 is obese.

Dyslipidemia: Total cholesterol > 200mg/dl, Low density lipoprotein >140mg/dl High density

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lipoprotein < 40mg/dl, Triglycerides >150mg/dl.
Serum Homocysteine levels: >15micromoles/litre is elevated.

An aliquote of the blood sample will be used for DNA isolation from the salting method, as per established from the laboratory. Polymerase chain reaction-based evaluation of gene variants for factor v, prothrombin and 5,10 Methyl tetra hydrofolate reductase will be performed as described by kamineni group earlier [12].

Data Collection

- All patients investigated for biochemistry
  - Lipid profile-(Total cholesterol, HDL, LDL and TGs)
  - Serum homocysteine
  - Thyroid stimulating hormone)
- An aliquote of the blood sample will be used for DNA isolation from the salting method, as per established from the laboratory. Polymerase chain reaction-based evaluation of gene variants for factor v, prothrombin and 5,10 Methyl tetra hydrofolate reductase will be performed as described by kamineni group earlier [12].

Sample Size

Sample size of 75 patients has been calculated as appropriate, based on last 2 years prevalence, Statistical analysis.

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Continuous data was represented as percentage mean +/- standard deviation and frequency. Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs. Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Table 1: Age and gender distribution

Parameters		**Mean± Standard deviation**	
Age (Yrs)		**38.76±5.86**	
		n(75)	**Percent**
Sex	Male	67	89.33
	Female	8	10.66

Table 2: Distribution of various symptom presentation in patients

Symptoms	**n(75)**	**Percent**
Chest pain/discomfort	68	90.66
Breathlessness	27	36
Epigastric discomfort	22	29.33
Nausea/Vomiting	17	22.66
Palpitations	24	32

Table 3: Risk factors distribution in the patients

Risk factors	**Mean (Percent)**
Family-h/o-MI	12(16%)
Smoking	47(62.66%)
Diabetes	9(12%)
Hypertension	26(34.66%)

Table 4: Biochemical data-Mean and SD analysis of the patients

Parameters	**Mean**	**SD**
Total cholesterol (mg/dL)	203.92	36.15
HDL. Cholesterol (mg/dL)	42.7	9.06
lDL. Cholesterol (mg/dL)	129.65	30.16
Triglycerides (mg/dL)	217.65	78.81
S. homocysteine (μmol/l)	16.03	9.81
FBS (mg/dL)	111.42	25
TSH	2.6	1.55

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Table 5: Distribution of dyslipidemia, Fasting blood Sugar and TSH

Parameters	N(75)	Percent
Total cholesterol (≥200 mg/dL)	35	46.66
HDL. Cholesterol (<40 mg/dL)	22	29.33
lDL. Cholesterol (>130 mg/dL)	33	44
Triglycerides (>150mg/dL)	66	88
S. homocysteine (≥15 µmol/l)	30	40
FBS (≥126 mg/dL)	13	17.33
TSH (>4.5<10 mIU/L)	8	10.66

Table 6: Diagnostic spectrum of acute coronary syndrome in the patients

Diagnosis	n(75)	Percent
Unstable	2	2.66
Nstemi	6	8
Stemi	67	89.33

Table 7: Distribution of MTHFR Gene variant

Genetic variant	n(75)	Percent
MTHFR-Wild Type	60	80
Heterozygotic-MTHFR C677T	12	16
Homozygotic-MTHFR C677T	3	4

Table 8: Distribution of Factor V Gene variant

Genetic variant	n(75)	Percent
Factor V-Wild Type	72	96
Heterozygotic- FVL	3	4
Homozygotic-FVL	0	0

Table 9: Distribution of Prothrombin Gene variant

Genetic variant	n(75)	Percent
Prothrombin-Wild Type	72	96
Heterozygotic-Prothrombin G20120A	3	4
Homozygotic-Prothrombin G20120A	0	0

Table 10: Distribution of minor allel frequencies of MTHFR, Factor V and Prothrombin gene variants

Gene Variant	Allel	MAF
Mthfr C667T	T-Allel	0.12
Factor V Leiden	A-Allel	0.02
Prothrombin G20120A	A-Allel	0.02

Discussion

Cardiovascular disease (CVD) is a worldwide health epidemic. Over 80% of CVD deaths take place in low- and middle-income countries. Death due to cardiovascular disease strikes Indians at an earlier age and thus kills or disable many in their productive mid-life [2]. Factors responsible for premature CAD in Indian subjects could be multiple-ranging from social, economic, psychological (stress), lifestyle (smoking, sedentary lifestyle, improper diet), biological (abnormal lipids, hypertension, diabetes, obesity [5], and thrombotic risk factors [6, 7]. There are reports from India which analyzed different thrombotic factors [1].

Although family history has long been identified as a risk factor for CAD, elucidation of the genetic architecture of CAD, found that the predictive ability of genetic information, largely independent of established risk factors for CAD, complements (rather than replaces) conventional risk factors [2].

In our study the young premature coronary artery disease patients the mean age 38.76± 5.86, in other young CAD studies as in Shanker *et al*., [8] 41.92±13.8, George *et al*. [9] 45.8±6.6, Bhardwaj *et al*. [10] 35.94±4.89, Kaur *et al*., [11] 36.4±4.5 this was the mean ± SD age distribution different studies conducted prior. Premature MI was considered to be in ≤ 55 years, but study population that was selected in different studies is different. So the mean age ranged from 26-46 years. In George *et al*. [9] study population was ≤ 55 years. In our study age group was ≤ 45years, so there is mean age distributed between 26-46 years according to the study population selected.

Our study showed a male preponderance 89.33%. Inother studies George *et al*., [9] 84%, Bhardwaj *et al*. [10] Was 99.19%, Kaur *et al*., 96.2%, [11] these all studies showing male population is high effected with CAD. Male gender is more prone for young MI, as similar finding seen in other studies compared. This might be due smoking habit more prominent in male population, and estrogen hormone protective effect

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in young females. Chest pain/angina is predominant symptom in our patients (90.66%). Family history of premature CAD in our study was 16%, in other studies as in Bhardwaj *et al*. [10]. Was 17.7%, Kaur *et al*., 23.4%, (11) George *et al*., 36%, [9] Amitesh *et al*., 64%. [12] Family history of CAD is an important independent risk factor for CAD in younger cases emerging out of various Indian studies discussed above. which quote data varying from 10% to 25%. How a positive family history increases the risk of MI in young patients is not known, although it may involve inherited disorders of lipid metabolism, blood coagulation, or other genetic factors.

In our study, diabetes was present in 12% of patients, in other similar studies like Amitesh *et al*. was 14.3% [12], Shanker *et al*., 11.4% [8], Bhardwaj *et al*. 8.06% [10], Kaur *et al*., 14.1% [11].

In our study, hypertension was present in 34.66% of patients, in other similar studies like Amitesh *et al*. Was 25% [12], Shanker *et al*., 15.9% [8], Bhardwaj *et al*. 8.06% [10], Kaur *et al*., 39.7% [11].

In our study, smokers were 62.66% of patients, in other similar studies like J. Shanker *et al*., 14.2%, Bhardwaj *et al*., 58.8% [10], Kaur *et al*., 61.4% [11]. Regular home check-up of blood pressure and blood sugar, with good control of diabetes and hypertension, with healthy life style modification by healthy diet, regular physical activity and compliance with medication. Cessation of smoking habit. Can break the chain of cumulative increase of risk to cause CAD, between the hereditary risk factors, modifiable risk factors and environmental factors.

Serum Homocysteine

In our study, raised serum homocysteine levels >15 was present in 40% of patients, in other similar studies raised serum homocysteine seen in 26.6%, Bhardwaj *et al*. 19.2% [10].

Genetic risk factor discussion

Gene variant:	Kaur *et al*. 2014	Our study
GG-Genotype of Factor V	92.9%	96%
GA-Genotype of Factor V	7.1%	4%
CC-Genotype MTHFR	65.2%	80%
CT-Genotype MTHFR	29.9%	16%
TT-Genotype MTHFR	4.9%	4%

In our study, the GG-Genotype of Factor V is 96%, GA-Genotype of Factor V is 4%, similar study Kaur et.al.GG-Genotype of Factor V is 92.9%, GA-Genotype of Factor V is 7.1% and no patient was detected to have homozygous Factor V mutation.

In our study, the CC-Genotype MTHFR 80%, CT-Genotype MTHFR 16%, TT-Genotype MTHFR 4%, similar study Kaur *et al*., [11] the CC-Genotype MTHFR 65.2%, CT-Genotype MTHFR 29.9%, TT-Genotype MTHFR 4.9%.

In our study, the GA-Genotype of Prothrombin(G20210A) is 0.02%, these results as to the prior other studies low risk to causation of MI and no patient was detected to have homozygous prothrombin mutation.

In our study minor A-allel frequency of Factor V was 0.02%, in other similar study of Mannucci *et al*. [13] 2.6% which showed an association to young MI with gain of function of variant F5 G1691A. So our study is dissimilar to prior stuy.

In our study minor A-allel frequency of Prothrombin G20210A was 0.02%, similar to Mannucci *et al*., [13] these findings of the variant F2G20210A confirmed the previously reported results, but that study revealed that this gene variant is not significantly associated to young MI.

This analysis of our study compared to the other study, show low risk with Factor V, Prothrmbin variant and MTHFR variant to young MI, but needs further studies to get more satisfied conclusion.

Smoking, alcohol intake, and elevated plasma Hcy are the risk factors for AMI among young patients. However, hypertension is the major risk factor for AMI among elderly patients. Absence of any difference in the genetic profile of the young and elderly patients with AMI was observed in our study. Knowledge of risk factors that selectively operate in young and elderly north Indians can help in planning appropriate preventive strategies that can target the different age-groups independently. This can also help to formulate investigations that can be done for the patients and their relatives. Strategies of smoking and alcohol cessation have to be targeted in the youth which can prevent the occurrence of AMI in the young patients. Diet rich in folate and vitamin B12, which can lower the plasma hcy, should be recommended. In addition, the preventive measures to control hypertension in the elderly patients should be emphasized in north Indian population.

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Conclusions

One of the most consistently demonstrated risk factors for CAD is male sex, whereas the female is protected by the effects of estrogens in preventing atherosclerosis and low prevalence of smoking in female, which was much more common among male. Conventional risk factors like smoking, family history of premature CAD, hypertension and diabetes were similar to previous study proving as the risk factors for CAD in young. Dyslipidemia of high total cholesterol, high triglycerides, high LDL-C and low HDL-C in our study population, is also similar to prior studies, is risk factor for CAD in young. Hyperhomocysteinemia in our study, was similar to prior studies, but homocysteine levels not only depend on genetic factors but also environmental factors, of dietary intake of folic acid, vegetarian diet, Vitamin B12. So hyperhomocysteinemia can occur due to inheritance and dietary habits. Genetic analysis of factor V, prothrombin and MTHFR are similar to previous studies, which suggest low statistical significance to CAD in young.

Recommendations

Patients with family history of premature CAD, familial dyslipiemia/dyslipidemia, should be recommended for regular exercise, smoking cessation and on follow up, evaluate and as required individualised to start on statin.

Regular physical activity lower systolic and diastolic blood pressure, improves insulin sensitivity and glycemic control, in patients diagnosed to be hypertensive and diabetic (primary prevention).

Individualised statin therapy is the best available pharmacologic intervention, cost-effective preventive strategy.

Awareness on this primordial, primary prevention of CAD in young, and importance of golden hour and early diagnosis and treatment will have huge economic impact as sizeable number of patients present late.

Limitations

This study was conducted only of the diseased patients, they was no control group, to compare and analyse statistical significance of the data collected. Only three genetic variants were studied in the study, there are many other dyslipidemia and hypertension causing gene variants, causing atherothrombus independently leading to CAD. Inflammatory markers are not considered in the study, which was considered to be important risk factor CAD. Studies are required to exploit the novel pathways in regard to genetic variants and inflammatory markers for vascular prevention of thrombus formation leading to CAD. Various risk factors were causative and various risk factor cumulative association was causative for the increasing prevalence of MI in young, so if number, of the study population is large, the statistics can give better conclusions. To individualise the preventive strategies according to the risk factor of the individual, for cost-effective benefit in developing countries like India.

Conflict of Interest: None.

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