



Nontraditional Risk factors in Women with Angina- An Outpatient Study

Authors

Harharpreet Kaur^{1*}, Kiranjit Kaur², Sukhraj Singh³, Arvinder Kaur⁴
Sourya Kanti Dass⁵, Randhir Singh⁵

¹Professor and Head, Department of Medicine, MM Medical College, Kumarhatti, Solan

²Professor, Department of Biochemistry, MM Medical College, Kumarhatti, Solan

³Assistant Professor, Department of Medicine, MM Medical College, Kumarhatti, Solan

⁴Senior Resident, MM Medical College, Kumarhatti Solan

^{5,6}Junior Resident, Department of Medicine, MM Medical College, Kumarhatti, Solan

*Corresponding Author

Dr Harharpreet Kaur

Professor Medicine, MM Medical College, Kumarhatti, Distt. Solan, Himachal Pradesh, India

Abstract

Background: *It is a myth that ischemic heart disease (IHD) is a man's disease. Angina is a frequent complaint amongst women visiting medical outpatient departments. It is a distinct entity which is poorly understood and misdiagnosed due to vague symptoms. It is thought to be microvascular in origin, usually stable and often associated with inflammation and endothelial dysfunction (ED).*

Aims and Objectives: *Were to study the gender differences in risk profiles and to explore novel female specific/ nontraditional risk factors (RF) / comorbid conditions in angina patients which could not only help in its identification but also provide new insights into the pathophysiology of angina in women.*

Material and Methods: *445 consecutive patients of angina from OPDs of two tertiary hospitals of Punjab and Himachal were included.*

Results: *Males /Females were 20% /80%. SLE, hypothyroidism, thyrotoxicosis, migraine, hysterectomy, PCOS, ulcerative colitis, asthma and anemia were most common associations found in women especially in age group between 31-40 yrs. The traditional RF were more frequent beyond the age of 40. Smoking, alcoholism and diabetes were more common in males. Stroke, Pulmonary and, renal disease, fatty liver, hyperuricemia, aortic stenosis, stress and viral infections were other comorbidities present in both sexes. Thus unconventional RF should be looked for in females with angina especially younger ones which may be associated with coronary inflammation and ED.*

Keywords: *Angina, Women, Non Traditional Risk factors.*

Introduction

The popular perception that ischemic heart disease (IHD) is a man's disease is really a myth. Angina is a common presenting symptom of this disease and is a frequent complaint amongst women visiting the medical outpatient departments. Studies such as Women's Ischemia Syndrome

Evaluation (WISE)¹ have provided new insights into the pathophysiology and clinical presentation of IHD in women which differs from men in many ways and underline the need for more research in this field. Angina in women is a distinct entity. It is thought to be microvascular in origin which explains the higher rates of angina and acute

coronary syndromes in women in the absence of obstructive coronary artery disease.¹ Stable ischemic heart disease (SIHD) is quite prevalent in women. The Framingham Heart study showed that stable angina was more common in females (47% in women compared to 26% in men). The determinants of angina in women are poorly characterized. Traditional cardiac risk factors are highly prevalent in women, and many of these risk factors have either a greater impact or a higher prevalence, or both, in women.¹ The results of the recent 10 year mortality WISE study showed that mortality was more frequently associated traditional risk variables such as diabetes, hypertension, elevated serum triglyceride, age, smoking, postmenopausal status and metabolic syndrome which can be modified.² However little is known about the non-traditional risk factors (RF) that may predispose to endothelial dysfunction and cause angina in younger women.³ Because of the atypical symptoms angina in women is often misdiagnosed. There is a lack of understanding and dearth of studies pertaining to ischemic heart disease in women.

Aims and Objectives

The objective of this study was to compare the differences in risk profiles in males and females.

And at the same time explore novel risk variables/comorbidities associated with angina in women. This would help to understand gender differences in underlying pathophysiology and thus enable early diagnosis and treatment.

Material and Methods

It was an observational study of 496 consecutive patients who presented with history of angina in the medical OPDS in two tertiary hospitals of Punjab and Himachal Pradesh from 2018 to 2019. Data was collected from the patient's old medical records, clinical examination, and relevant investigations. Angina was assessed through a series of detailed questions as described in standard questionnaires. The inclusion criteria were patients with typical angina which was

defined as the presence of substernal chest pain or discomfort (pressure, heaviness, squeezing, burning, or choking sensation) that was provoked by exertion, eating, exposure to cold or emotional stress, lasting for about 1-5 minutes and relieved by rest and/or nitroglycerin. Patients with stabbing pain and pain radiation to atypical locations and patients with atypical anginal symptoms who were relieved by nitrates were also included. Patients with STEMI (usually present in the emergency department) were not included. Those who did not respond to nitrates were excluded. Patients with pain which changed with respiration, cough, or change in position and where alternative etiology could be identified were excluded.

Traditional risk factors studied were hypertension, diabetes mellitus, dyslipidemia, body mass index (BMI), smoking and alcohol use. Any other concurrent disease/comorbidity associated with patients of angina as diagnosed from history, clinical examination, investigations or old medical records was noted. Anthropometry, blood pressure, electrocardiogram, and biochemical investigations were done using standard protocols. The risk factors were defined using standard criteria. Data was analyzed by excel and SPSS 20.0 software.

Results

445 patients of angina were studied. 205 from Punjab and 240 from Himachal Pradesh. The females /males having angina were 174/31 (84.87% /15.12%) in Punjab and 181/59 (75%/25%) in Himachal. Thus angina was more common in women.

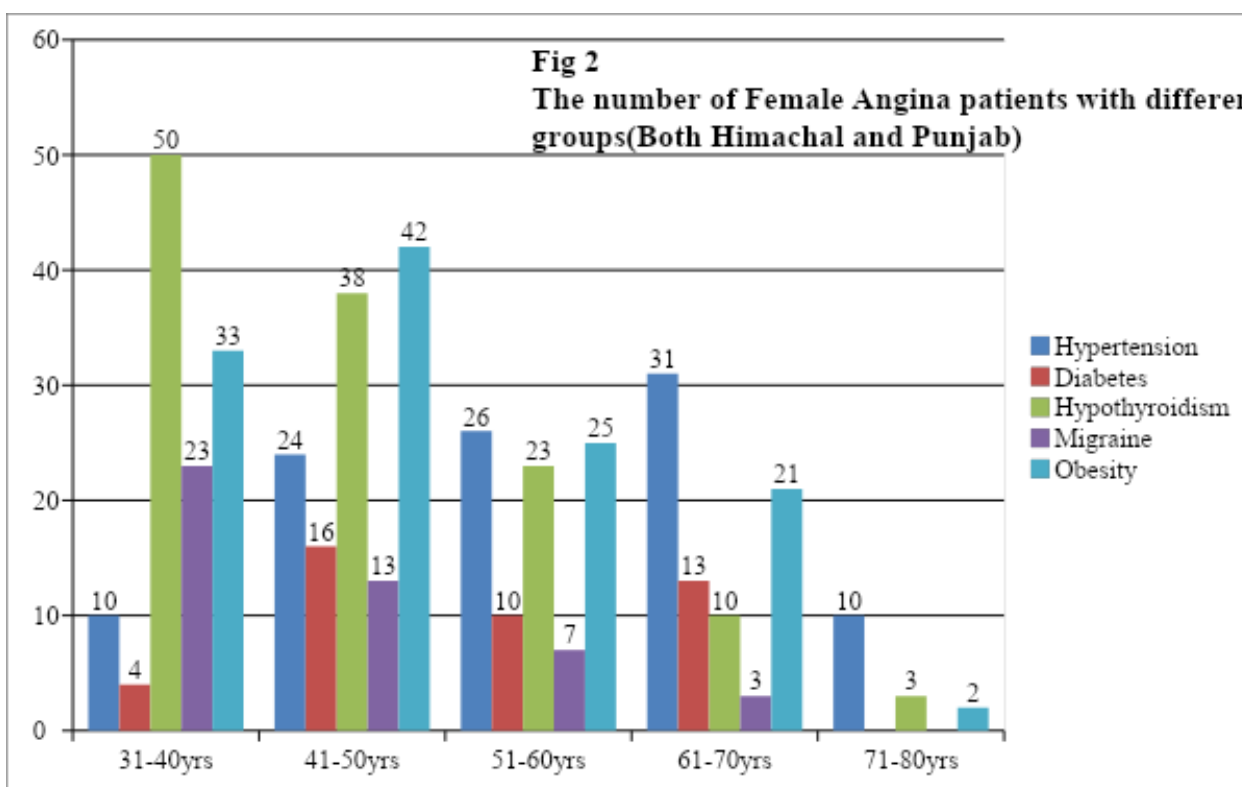
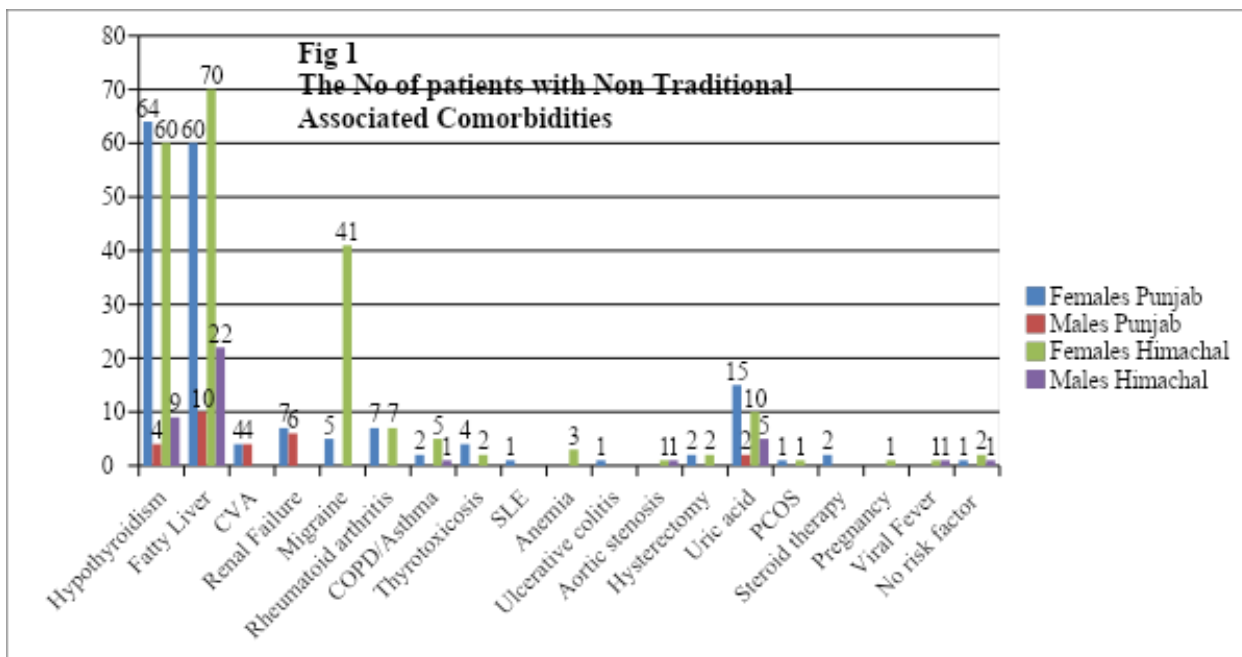
Number of patients (Both states) having traditional Risk factors like Obesity and diabetes and hypertension are depicted in Table 1.

The No. of patients with Non Traditional RF and Associated Comorbidities in males and females of both states is shown in Fig 1

The number of Female Angina patients (Both Himachal and Punjab) with different RF and their distribution in different age groups can be seen in Fig 2.

Table 1 Number of patients (Both states) having Traditional Risk factors

	Obesity	Dyslipidemia	Hypertension	Diabetes	Smoking	Alcoholism
Females	124 -(35%)	80(23%)	101(29%)	44(12%)	0	0
Males	17(19%)	15(17%)	23(28%)	20(22%)	11(12%)	12(13%)



Discussion

Our results show that the number of females suffering from angina was significantly higher as compared with males. This is in conformity with

the 31 country study by Hemmingway which found that women have 20% higher prevalence of stable angina even though more men suffer from myocardial infarctions.⁴ In our study with regard

to nontraditional risk factors and comorbidities rheumatoid arthritis (RA), SLE, thyrotoxicosis, hysterectomy, PCOS, ulcerative colitis, steroid therapy, asthma and anemia were exclusively found in women though the number was small.⁽¹⁻⁷⁾ (Fig 1) A pregnant female also presented with atypical anginal symptoms. Many patients had more than 1 comorbidity.

Associated migraine and hypothyroidism were more common in females (124 and 46 as compared to 5 and 0 respectively in males). The number of migraine and hypothyroid patients were more frequent in females between the age of 31-40 yrs and declined with increasing age (Fig 2). The number of diabetic and hypertensive women were lesser in the age group of 31-40 and the number increased subsequently after the age of 40 yrs. (Fig 2) The patients of rheumatoid arthritis (RA), anemia, asthma, PCOS, hysterectomy and ulcerative colitis were in the age group of 20- 45 . One female of RA however was 70 years old and had the disease for many years and had hypertension also.

Other studies also have observed that the younger women suffer from IHD which is distinct not only in its risk profile but also pathophysiology. These women represent a heterogeneous and a distinct group. It is believed that these women have non-obstructive coronary artery disease (CAD) and coronary vasomotor disorders with endothelial and microvascular coronary dysfunction (MCD) of the coronary tree in comparison with the traditional obstructive CAD as seen in men.^{5,6} There appears to be a heightened sensitivity of the coronary microcirculation to vasoconstrictor stimuli in the small intramural prearteriolar coronary arteries with decreased blood flow to the heart but with normal coronary arteries. They also tend to suffer from diseases with an enhanced inflammatory state such as rheumatoid arthritis, systemic lupus erythematosus and chronic intestinal bowel syndromes.⁷ In these cases myocardial ischemia occurs due to pro-inflammatory molecules like TNF- α which promote endothelial and microvascular

dysfunction by reducing the synthesis and bioavailability of nitric oxide (NO). Elevated plasma C-reactive protein levels, a marker of inflammation, has been shown to correlate with endothelial dysfunction in these diseases.⁷ Recio-Mayoral et al demonstrated the presence of coronary microvascular dysfunction (CMD) using PET scans in RA patients.⁸ It can explain the persistence of anginal symptoms, despite successful myocardial revascularization in >20% of patients.⁹ Anti-inflammatory treatment for RA has been shown to improve microvascular endothelial function. Thus inflammation is related to CMD in women.

The coexistence of hypothyroidism (which is associated with inflammation and atherosclerosis) and angina has been observed for many decades. Some of the cardiovascular effects can be explained by a higher prevalence of hypertension and dyslipidemia in patients with hypothyroidism but not all have high blood pressure or lipid profiles. Endothelial dysfunction is an early event in the pathogenesis of atherosclerosis and is characterized by decreased availability of endothelial nitric oxide. It may play an important role in patients with hypothyroidism.¹⁰ Coronary vasospasm has been documented in one case of hypothyroidism.¹¹ The large number of patients in our study could be due to a rise in prevalence of hypothyroidism in India¹² The prevalence of hypothyroidism in India is 11%, compared with only 2% in the UK and 4.6% in the USA. It may also be linked to an increase in incidence of obesity. Subclinical cases are equally important and were included. 53% of the subclinical hypothyroid subjects were positive for anti-thyroid peroxidase antibodies.¹² All patients with subclinical hypothyroidism who were included were those who were given low dose thyroxin and responded to and tolerated it well in addition to antianginals. The presence of hypothyroidism can help to diagnose angina in women with obscure anginal symptoms.

The other important association found in our study was migraine. Some other studies also have found

an increased risk of vasospastic disorders such as migraine in cases of microvascular angina. Vascular reactivity disproportionately affects women with migraine headaches.¹³ It is not surprising that vascular reactivity would be present in the coronary circulation of women as well. Cerebral perfusion changes similar to the migraine complex were observed on functional brain imaging during the symptomatic phase of angina.^{14,15,16} Endothelial dysfunction and mediators, such as endothelin, may be connecting factors between microvascular angina also known as cardiac Syndrome X (CSX) and migraine headache. It is believed that CSX may be another migraine equivalent or a manifestation of migraine. In one study 3 groups were studied: a CSX group, a coronary artery disease (CAD) group and a healthy group. The prevalence of migraine was 60% in CSX group, 16% in the CAD group and 22% in the healthy group ($p < 0.0001$).¹⁷ The association of migraine in women of Himachal Pradesh was surprising but on search of literature it was found in one study that a much higher proportion of patients living at high altitude were diagnosed with migraine compared to patients living at sea level. (53.8% vs 16.1%, respectively; $P < 0.001$)¹⁸ The cold weather may also play a role.

Obesity was present in all groups including younger ones. It is also characterized by a state of low-grade inflammation and capable of producing microvascular angina.¹⁹

Individuals with microvascular angina are typically younger than those with angina due to obstructive coronary artery disease.²⁰ The impact of vascular dysfunction is thought to decrease as the age advances with the increase in vascular stiffness and atherosclerosis. Beyond 60 years of age, the traditional RF tend to overrule the nontraditional ones and the pattern of IHD shifts to a more obstructive one.⁶ This trend has been shown in our study.

According to the WISE study many of the traditional risk factors have either a greater impact or a higher prevalence in women as compared to

men eg hyperlipidemia, obesity and diabetes. In our study though the percentage of obesity and dyslipidemia was more in females the percentage was equal for hypertension and diabetes was more in males (Table 1) It may be due to a smaller sample size in males (31 and 59) and therefore larger studies are needed.

Smoking and alcoholism were more prevalent in males. Cerebrovascular accident, COPD fatty liver, hyperuricemia, aortic stenosis, renal disease, and viral infections were some lesser known comorbidities and present in both sexes. 3 cases had no risk factor. The mechanism of angina in aortic stenosis is known. Renal disease, hyperuricemia and COPD are associated with other traditional risk factors. Asthma and viral infections are associated with inflammation. Stress may be associated in cases where no risk factor was found.

The lower percentage of males with angina in our study as compared to other studies may be due to small size of the study.

Conclusion

Women with angina often have vague atypical symptoms and present in medical OPDs and are often referred to psychiatry department. Women in the age group from 30-40 should be suspected of angina symptoms in case they are also having nontraditional risk factors. Thus it is important to ask for risk factors both traditional and nontraditional and co-morbidities when considering the diagnosis of angina in women. They may also be a guide for the treatment. Future research needs to be directed towards a greater understanding of the nontraditional risk variables for angina/SIHD in women so that a sex-specific algorithm can be formulated for angina in women. No other similar study has been conducted to explore the non-traditional risk factors in angina in women presenting in OPDs.

References

1. Gulati, M; Shaw, LJ; Bairey Merz, C. Noel. "Myocardial ischemia in women:

- lessons from the NHLBI WISE study". (2012) *Clinical Cardiology*. 35 (3): 141–148.
2. Tanya S , Kenkre , Pankaj M et al Ten-Year Mortality in the WISE Study (Women's Ischemia Syndrome Evaluation) December 2017. *Circulation* Vol 10, Issue 12
 3. Elias-Smale SE, Günal A, Maas AH. Gynecardiology: Distinct patterns of ischemic heart disease in middle-aged women. *Maturitas*. 2015 Jul;81(3):348-52.
 4. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA*. 2006; 295: 1404–1411
 5. Marzilli M, Merz CNB, Boden WE, Bonow RO, Capozza PG, Chilian WM, et al. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! *J Am Coll Cardiol*. 2012;60(11):951–6
 6. Maas, A.H.E.M. Characteristic Symptoms in Women with Ischemic Heart Disease *Curr Cardiovasc Risk Rep* (2019) 13: 17
 7. Faccini A, Kaski JC, Camici PG. Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases. *Eur Heart J*. 2016;37(23):1799–806
 8. Recio-Mayoral A, Mason JC, Kaski JC, Rubens MB, Harari OA, Camici PG. Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. *Eur Heart J* 2009;30:1837–1843.
 9. Cohen DJ, Van Hout B, Serruys PW, Mohr FW, Macaya C, den Heijer P, Vrakking MM, Wang K, Mahoney EM, Audi S, Leadley K, Dawkins KD, Kappetein AP; Synergy between PCI with Taxus and Cardiac Surgery Investigators. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 2011;364:1016–1026.
 10. Jaskanwal D Sara,1 Ming Zhang, Hossein Gharib, Hypothyroidism Is Associated With Coronary Endothelial Dysfunction in Women *J Am Heart Assoc*. 2015 Aug; 4(8): e002225.
 11. Osken A, Yaylaci S, Aydin E, Kemalolu Oz T, Ipek G, Atasoy I, Zehir R, Dayi SU. Diffuse coronary vasospasm in a patient with hypothyroidism. *Thyroid Res Pract* 2016;13:89-91
 12. Lathia T. Rising prevalence of thyroid disorders. *J Mahatma Gandhi Inst Med Sci* 2015 ;20:125-7.
 13. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol*. 2009;54: 1561–1575
 14. Saghari M., Assadi M., Eftekhari M., et al. Frequency and severity of myocardial perfusion abnormalities using Tc-99m MIBI SPECT in cardiac syndrome X. (2006) *BMC Nuclear Med* 6:1.
 15. Leon-Sotomayor L.A. Cardiac migraine—report of twelve cases. *Angiology*(1974) 25:161–17
 16. Prinzmetal M, Kennamer R, Merliss R, et al. Angina pectoris. I. A variant form of angina pectoris; preliminary report. *Am J Med*. 1959;27:375–388
 17. Reza Nemati, Association Between Migraine Headache and Cardiac Syndrome X *Journal of the American College of Cardiology* .Volume 67, Issue 17, May 2016
 18. Arregui A, Cabrera J, Leon-Velarde F, et al. High prevalence of migraine in a high-altitude population. *Neurology*. 1991;41: 1668-1670.
 19. Mohammed S. Ellulu,1 Ismail Patimah, Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci*. 2017 Jun; 13(4): 851–863.
 20. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J Am Coll Cardiol*. 1995 Mar 15. 25(4):807-14.