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Study of the Proportion of Microalbuminuria in Non-Diabetic Patients

Authors
Dr Sarath Kumar S, Dr Radha T.R.
Kottayam Medical College

Introduction

Ischemic heart disease is one of the known global killers and in India the estimated prevalence is approximately 6-9%. As of now it is a leading cause of mortality and morbidity in India.

Since the pioneering work of the Framingham study, many prospective and clinical studies have identified a series of independent risk factors for ischemic heart disease among which age, male gender, a positive family history of premature atherosclerotic disease, smoking, diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia and low HDL cholesterol are considered as classical risk factors. The interest in improving cardiovascular risk assessment, resulting from a better understanding of the pathogenesis of atherosclerosis and identification of new targets for anti-atherosclerotic drug therapy has stimulated the search for novel risk factors.

One such novel risk factor is microalbuminuria which has emerged as an independent and robust risk factor. Microalbuminuria is a well-accepted marker for micro and macrovascular damage in patients with diabetes mellitus. However more and more evidence is accumulating that microalbuminuria is an important cardiovascular risk factor even in those without diabetes.It is a surrogate marker for endothelial dysfunction and is independently associated with atherosclerosis in diabetic and in non-diabetic patients.

The inclusion of microalbuminuria as an additional risk factor for ischemic heart disease may be warranted.

Objectives

Primary Objective

To estimate the prevalence of microalbuminuria in non-diabetic ischemic heart disease patients.

Secondary Objective

To correlate microalbuminuria with known risk factors other than diabetes and hypertension.

Methodology

Study Design

Observational study – Descriptive Study

Study Location

This study was conducted in the Department of General Medicine, Kottayam Medical College, Kerala.

Study Population

The study population were the patients admitted in the General Medicine ward of Kottayam Medical College.

Sample Size

Sample size for the study = 100

Formula used: Sample size = $\frac{Z^2 \times p \times q}{d^2}$

Where, Z = Z value

Z value at 95% confidence interval = 1.96; Z^2 = 3.84 rounded to 4

p= prevalence; q = (1-p); d = relative precision = 10% of p

Here, p = 72%

The value of p has been taken from the pilot study by Suthar et al(101)

Therefore, sample size = $\frac{4\ x\ 72\ x\ 28}{(10.8)^2}$ = $\frac{8064}{116.64}$ = 69.

(Pilot study: Suthar N, Khambholja J, Suthar A, Patel K, Parikh A. Relationship of Microalbuminuria with Ischemic Heart Disease in Non-Diabetic Subjects. Natl J Integr Res Med. 2014;5 (3):51–6)

Period of Study

1st January 2015 to 1st November 2015 (Ten Months)

Inclusion Criteria

The patients included were those that were diagnosed with Ischemic Heart Disease (Acute Myocardial Infarction) based on the clinical features, 12 lead ECG and cardiac enzyme estimation.

Exclusion Criteria

1) Diabetic patients diagnosed by ADA criteria (2004).
2) Congestive cardiac failure at presentation.
3) Urine showing
   Macroalbuminuria (dipstick positive albuminuria)
   RBCs > 50/µl
   Leucocytes > 75/µl
4) Female patients with vaginal discharge.
5) Those on drugs like ACE inhibitor and ARB inhibitors.
6) Those diagnosed with other renal disorders known to cause albuminuria
7) Hypertension

Materials & Methods

After attaining clearance from the Institutional Review Board, this hospital based observational study was conducted in the patients admitted in the ward under the Department of General Medicine. A total of hundred subjects was selected after explaining the purpose of the study and procedure in detail and, after attaining their consent in written format for each. Data collection was by clinical history, examination and investigations. The patients included in the study were those who were admitted with Ischemic heart disease (infarct/ischemia) based on clinical features, ECG and cardiac enzyme.A preset proformawas used to collect data regarding age, sex, address, occupation, history of present illness, past history, drug history and personal history including smoking and alcoholic history. Height and weight were recorded and BMI was calculated. The investigations collected were FBS, PPBS, Troponin and ECG. Urine examination was performed as described below.

All the patients in the study had clinical history of chest pain typical of cardiac chest pain. ECG findings that were considered to diagnose ischemic heart disease were as follows: -

- New or presumed new ST-segment depression: horizontal or down sloping ST depression ≥0.05 mV in 2 contiguous leads and/or T inversion ≥0.1mV in 2 contiguous leads with prominent R wave or R/S ratio >1.
- New or presumed new T-wave inversion: T-wave inversion of at least 0.1mV in 2 contiguous leads.
- Transient ST-segment elevation lasting <20 min: new ST-segment elevation at the J point in 2 contiguous leads with the cut points ≥0.1 mV in all leads other than leads V2 through V3, where the following cut points apply: ≥0.2 mV in men age ≥40 y, ≥0.25 mV in men age <40 y,or ≥0.15mV in women.
- New persistent LBBB.
- Abnormal, persistent Q or QS waves

- Signs of evolving injury current > 1 day
- Serial, equivocal changes > 1 day
- Symmetrical T wave inversions
- Conduction disturbances suggestive of ischemic heart disease

The patients were designated as those with or without ECG abnormalities. Similarly the cardiac biomarker used in this study was the Troponin (T/I) and a qualitative measurement was taken.

Procedure in detail - Timed urine collection (24 hours)

Patient was advised to start collecting their urine in the morning. They were asked to empty their bladder when they first get up and that sample was not collected. They were advised to write down the time they urinated to mark the beginning of the 24-hour collection period. For the next 24 hours, all of their urine was collected. Patient was asked to urinate into a small, clean container first and then pour the urine into a larger container to avoid contamination. Finally, at or just before the end of the 24-hour period the patient was asked to urinate for the last time and that sample of urine was added to the large container with time being recorded. The container was sent for estimation of microalbuminuria level by the immunoturbidimetry method. The result was reported as x mg/day of albumin.

The normal rate of albumin excretion is < 20 mg/day (15µg/min); persistent albumin excretion between 30 and 300 mg/day (20-200 µg/min) is called microalbuminuria and albuminuria > 300mg/day (> 200 µg/min) represents overt or dipstick positive proteinuria (also called macroalbuminuria).

In this study those having 24 hour urine albumin excretion between 30 and 300 mg/day were considered to have microalbuminuria. s

Statistical Analysis

Data analysis was done with the help of SPSS version 20. Tables and graphs were created with the help of SPSS and Microsoft Excel. Descriptive data that included numbers and percentages were calculatedfor all the categories. Categorical data were analyzed by Chi square tests for statistical significance. A p-value (two tailed) of
< 0.05 was considered statistically significant. The Pearsons correlation coefficient was calculated for continuous variables to find out the relation between them.

Definitions

1) Smoker – one who has smoked at least 100 cigarettes in their lifetime.
2) Alcoholic - For men, consuming 15 drinks or more per week and for women8 drinks or more per week.
3) Prior MI - if the patient has had at least 1 documented previous myocardial infarction.
4) Acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, the following criteria meets the diagnosis for MI:

   Detection of the rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99thpercentile and with at least 1 of the following:

   — Symptoms of ischemia
   — New or presumed new significant ST-T changes or new LBBB
   — Development of pathological Q waves on the ECG
   — Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
5) STEMI is defined as an ACS in which there is cardiac marker evidence of myocardial necrosis (eg. positive cTn or CK-MB) and new (or presumably new if no prior ECG is available) ST-segment elevation or LBBB on the admission ECG.
6) NSTEMI is defined as an ACS in which there is cardiac marker evidence of myocardial necrosis (eg, positivecTn or CK-MB) without new ST-segment elevation

7) UA is defined as angina pectoris (or equivalent type of ischemic discomfort) with any 1 of the 3 following features:
   I. Angina occurring at rest and prolonged, usually ≥10 min
   II. New-onset angina of at least CCS classification III severity
   III. Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class to at least CCS class III
8) The patient must also not have any biochemical evidence of necrosis.
9) CCS classes of angina:
   • Class 0: none

• Class I: ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
• Class II: slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, or in cold, in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking >2 blocks on the level and climbing >1 flight of ordinary stairs at a normal pace and in normal conditions.
• Class III: marked limitation of ordinary physical activity. Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.
• Class IV: inability to perform any physical activity without discomfort.
Anginal symptoms may be present at rest.

Results & Observations

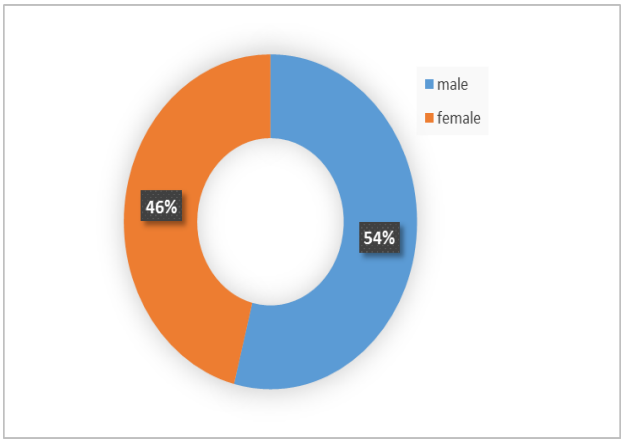
Age Characteristics

Table 1: Sex wise Age Distribution

Age Group	Patients Sex		Total
	Male	Female	
25 - 34	0	2	2
35 - 44	9	7	16
45 - 54	13	12	25
55 - 64	17	11	28
65 - 74	11	10	21
75 - 84	3	4	7
85+	1	0	1
Total	54	46	100

Sex Distribution

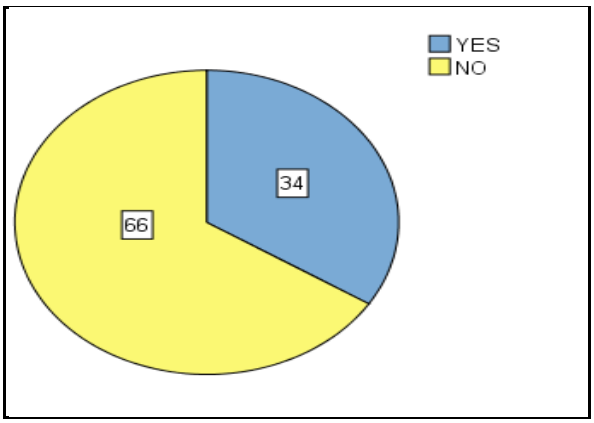
Figure 1: Sex distribution of the study population



In this study, male patients were more compared to the females the numbers being 54 and 46 respectively.

History of Prior Ischemic Heart Disease

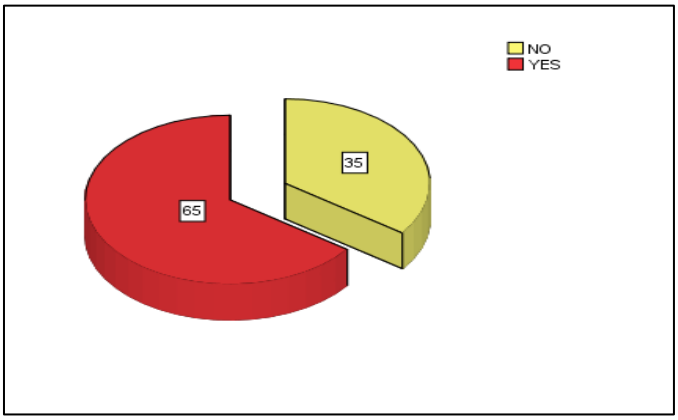
Figure 2: Past history of Ischemic heart disease



This study had 100 subjects and only 34 of them gave history of ischemic heart disease.

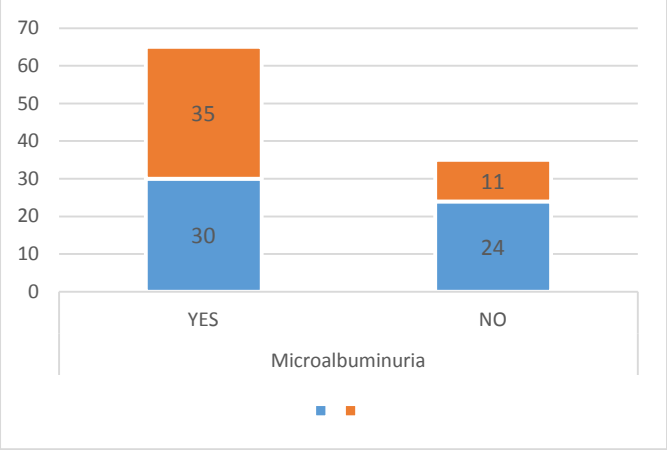
Microalbuminuria

Figure 3: Proportion of subjects with microalbuminuria



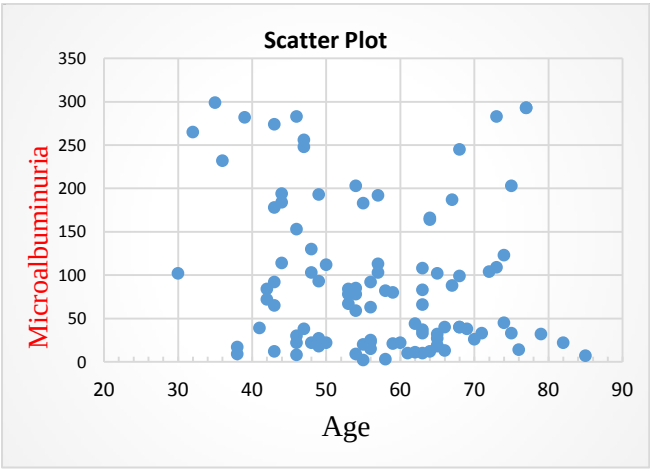
In this study the number of subjects who were found to have microalbuminuria were 65. This high proportion in the study can be translated to the fact that microalbuminuria is indeed present in ischemic heart disease and warrants
its use as a predictive marker.

Figure 4: Sex wise distribution of microalbuminuria



Independent t-test was performed on the patients with microalbuminuria with relation to sex. The t-value was 0.682. The t-distribution for 98 degrees of freedom gives the 5% level at 1.98 hence p value is > 0.05 thus not statistically significant.
Hence, we do not reject the null hypothesis and there is no evidence to say that there is a difference between the levels of microalbuminuria and sex of individual.

Figure 5: Scatter plot of Microalbuminuria versus age



The above figure (figure 5) shows the distribution of microalbuminuria with respect to age of the study subjects. Since both were continuous variables the correlation between them was calculated by the Pearson's coefficient. The Pearson's correlation coefficient was -0.19 and it indicates that there is a negative but weak correlation between the two.

Table 2: Correlations of Microalbuminura with other variables

		Patients Age	BMI of patient	FBS of patient	PPBS of patient
Microalbuminuria	Pearson Correlation	-.187	.129	-.007	.082
	p-value	.063	.202	.942	.417

Microalbuminuria and Sex

Table 3: Sex wise distribution of patients with respect to microalbuminuria

		Microalbuminuria		Total	Percentage
		NO	YES		
Patients Sex	Male	24	30	54	55.5
	Female	11	35	46	76.0
Total		35	65	100	

$X^2 = 4.60$; p value =0.03(<.05)

It is evident in this study that males were predominant in those without microalbuminuria and that females were more in those with microalbuminuria.
The Chi-square statistic is 4.60. The P value is 0.03.
This result is significant at $p < 0.05$.
Hence 76 % of female subjects with ischemic heart disease have microalbuminuria compared to 55% of males and this difference is statistically significant.

Microalbuminuria and Family history of Ischemic heart disease

Table 4: Distribution of patients with family history of ischemic heart disease

		Microalbuminuria		Total
		NO	YES	
Family history of IHD	NO	27	39	66
	YES	8	26	34
Total		35	65	100

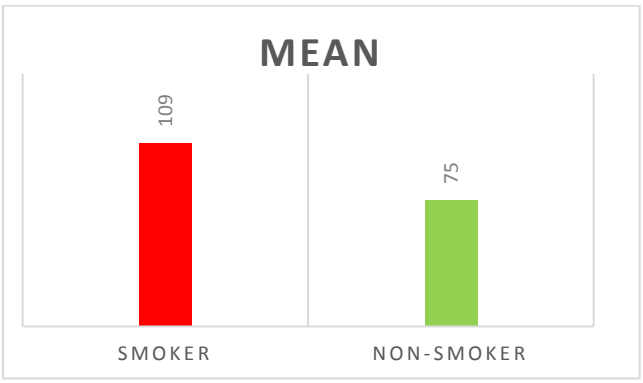
$X^2 = 2.98$; p value = 0.08 (>0.05)

The Chi-square statistic is 2.98. The P value is 0.084.

This result is not significant at $p < 0.05$.

Hence, we cannot reject the null hypothesis and we can conclude that there is no evidence to say that there is the difference can be attributed to sampling error and there lies no association between them.

Figure 6: Microalbuminuria mean between smokers and non-smokers



On comparing the means of microalbuminuria between smoker and non-smokers, the t value = 2.0213 and the two-tailed P value equals 0.046.

By conventional criteria, this difference is considered to be statistically significant.

Hence, we have evidence to say that smokers are prone to have microalbuminuria when compared with non-smokers.

The Pearson's correlation coefficient was +0.13 and it indicates that there is a positive but weak correlation between the two.

Microalbuminuria and prior history of ischemic heart disease

Table 5: Microalbuminuria versus history of ischemic heart disease

			Microalbuminuria		Total	Percentage
			NO	YES		
h/o Ischemia	NO	Count	33	32	65	49.23
	YES	Count	2	33	35	94.28
Total		Count	35	65	100	

$X^2 = 20.30$; p value < 0.0001 (<0.05)

The Chi-square statistic is 20.30. The P value is less than 0.0001.

This result is extremely significant at $p < 0.05$.

We conclude that the difference between microalbuminuria and previous history of ischemic heart disease is not by chance and that they are dependent on each other.

Microalbuminuria and Troponin Positivity

Table 6: Troponin versus Microalbuminuria

			Microalbuminuria		Total	Percentage
			NO	YES		
Troponin positive	NO	Count	19	10	29	34.5
	YES	Count	16	55	71	77.4
Total		Count	29	71	100	

$X^2 = 16.72$; p value =0.0001(<.05)

The Chi-square statistic is 16.72. P value is less than 0.0001.

This result is extremely significant at $p < 0.05$.

There is enough evidence to suggest that troponin positivity and microalbuminuria are associated and not independent.

Discussion

Prevalence and incidence of microalbuminuria

This study was done to find out the proportion microalbuminuria in non-diabetic ischemic heart disease patients and to look for any association with other known risk factors.

After analysis of the study data 65 % of the study population had microalbuminuria. In an Indian study conducted by Suthar et al[1], of the 50 non-diabetic patients with ischemic heart disease 36 had microalbuminuria i.e. 72% of the study population.

Microalbuminuria and sex

This study comprised of 100 patients in total of which 54 of them where males and the rest females. Of the total 100 study population 65 patients had microalbuminuria while the rest 35 were not positive for microalbuminuria. In those who had microalbuminuria 30 were male patients and 35 were female patients. In this study, 76 % of female subjects with ischemic heart disease had microalbuminuria compared to 55% of males and this difference is statistically significant.

Microalbuminuria and age

The minimum age was 30 and the maximum being 85. The mean age of the study population

was 56.90 ± 12.00 years. This is comparable with the study by Suthar et al[1] in which the mean age of the study population was 55.8 ± 3.67 years. On comparing the means with respect to sex of the patient it has been found that this study had a mean of 56.94±11.52 for the males and 56.85±12.68 for the females. The age group with the most number of patients was the group from 55 to 64, which comprised of 28 of the total study group. Of this 28 patients 17 were male and the rest, 11 were females.

Microalbuminuria and smoking

In this study, history of smoking was present in 54% of the study subjects indicating that smoking is an important risk factor for ischemic heart disease. Of the smokers 41 were males and 13 were females. Thus 75.9 % of males were smokers and 28.2% of females were smokers. Umesh N Khot et al[2] had found a prevalence of 76.9% in males and 36.3% in females in their study for smoking as a risk factor. The mean urinary albumin level among smokers was 109 ± 97 mg/day and 75 ± 65 among non-smokers mg/day. The t-value = 2.0213 and the p-value equals 0.0460. By conventional criteria, this difference is considered to be statistically significant. In another study by RK Gupta et al[3], smokers had a 4-fold higher prevalence of microalbuminuria than non-smokers.

The heart outcome prevention evaluation study[4] documented that smoking was an independent determinant of microalbuminuria in all participants, i.e., non-diabetic and diabetic patients with a high cardiovascular risk profile. The PREVEND study[5,6]showed statistically significant difference in urinary albumin excretion in non-smokers and smokers.

Microalbuminuria and family history of ischemic heart disease

There was a positive family history of ischemic heart disease in 66 patients. The p-value was not significant for less than 0.05. There are hardly any studies in literature that have commented on an association between microalbuminuria and family history of ischemic heart disease.

Microalbuminuria and Body mass index

The mean BMI of this study group was 24.4 ± 2.27. Majority of the patients i.e. 53 had a BMI in the range of 25 to 29.9.The relationship between microalbuminuria and BMI is a positive one with a Pearson correlation coefficient of +0.13. One cross-sectional population study showedthat prevalence of albuminuria increased with increasing body mass index[7]; another found slightly higherbody mass indices in subjects with slight albuminuria than in those with normal albuminuria[8].The BMI was >25kg/m2 in majority of the study group. This prevalence was much higher than that obtained by Singh R.B. et al[9] (11.0% in rural and 27.2% in urban).

Microalbuminuria with FBS AND PPBS

Microalbuminuria is a sign of progression towards nephropathy in patients with diabetes[10]. It is a clue which helps us predict the occurrence of cardiovascular disorders in both patients with or without diabetes[11,12]. The risk of microalbuminuria is correlated with plasma glucose level, and the duration of hyperglycemia in patients with diabetes[13,14]. Glycemic control in these patients can prevent the development, and progression of microalbuminuria, but this issue has not been well-documented about IGT and IFG-related disorders yet. In this study the mean FBS of the study population was 99.68 ± 10.73 and for the PPBS it was 150.5 ± 15.84. The distribution of FBS of patients is not the same across the categories of those with and without microalbuminuria(p value = 0.18; significant). The same was not got with respect to PPBS where the p-value was 0.795.

On attempting to correlate these two variables with microalbuminuria, the Pearson coefficient correlation of FBS and PPBS are +0.07 and +0.82. This only just signifies a weak but positive correlation.In the Monica study on Italian subjects, the prevalence of microalbuminuria were 6.9%, 5.6%, and 4.3% in impaired fasting glucose, impaired glucose tolerance and normal glucose tolerance groups, respectively[15]. The prevalence of microalbuminuria was 8.3% in impaired fasting

glucose, 9.9% in impaired glucose tolerance, and 4.3% in normal glucose tolerance groups in Robyn study in Australia[16]. The difference in prevalence reported by different studies can be attributed to the differences in population indexes such as race, laboratory techniques for urine albumin measurement, and the differences in the definition of microalbuminuria, impaired glucose tolerance, and diabetes mellitus.

Microalbuminuria with cardiovascular disease

In the present study the proportion of ischemic heart disease patients with microalbuminuria was 65% hence, the fact that microalbuminuria is a risk factor for cardiovascular disease can be understood. The PREVEND study[17] showed that in a multivariate model adjusted for established cardiovascular risk factors, microalbuminuria was independently associated with infarct pattern (7.1%) (OR-1.61), major ischemia (10.6%) (OR-1.43) and minor ischemia (15.1%) (OR-1.32).Microalbuminuria was detected in 14.8% of those without Diabetes Mellitus at baseline in a cohort of Heart Outcomes Prevention Evaluation Study conducted between 1994 and 1999[18].

Microalbuminuria with ECG changes

In non-diabetic subjects, the result from several studies have indicated that MAU is a marker of cardiovascular risk, moreover, several studies have demonstrated that MAU is an independent predictor of cardiovascular morbidity and mortality in non-diabetic population[8,11]. The presence of ECG changes in the study group was not found to be statistically significant. However, there are many studies in literature to support otherwise. In a study by Hilal et al[19], microalbuminuria was more common in patients with ischemic ECG changes than in those without.

Microalbuminuria with Troponin

In this study when comparing microalbuminuria with troponin positivity, it has been found that among the troponin positive patients, 71% had microalbuminuria compared to 34 % of troponin negative patients. This finding was significant (p = 0.0001).

Conclusions

- The prevalence of microalbuminuria in the study population was 65.
- Female subjects with ischemic heart disease are more prone to develop microalbuminuria when compared to males with ischemic heart disease (p=0.03).
- Those with a previous history of ischemic heart disease are more likely to have microalbuminuria (p<0.0001).
- Smokers are more prone to develop microalbuminuria than non-smokers (p=0.03).
- Those with a positive troponin are more likely to have microalbuminuria when compared to those with a negative troponin (p<0.0001).

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