ASSESSMENT OF RELATION BETWEEN MICROALBUMINURIA AND ISCHEMIC ELECTROCARDIOGRAM IN IRANIAN GENERAL POPULATION

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Abstract

BACKGROUND: Enhancement of albumin exertion in urine increases the risk of renal and ischemic heart diseases (IHD). We assessed the association of urine albumin and sub-clinical IHD in a random sample of Iranian general population.

METHODS: The random sample in general population in Isfahan County was recruited to the cross-sectional study. From the all sample blood pressure and lipid profile were assessed and morning urine spot was measured for albumin and Creatinine. Microalbuminuria was defined either Albumin-Creatinine Ratio (ACR) was 30-300mg. Also, the standard 12 lead electrocardiogram (ECG) was carried out for all participants. The ECG pattern was divided to two categories; normal or ECG with ischemia. The logistic regression model was determined the odds of albuminuria for ischemic changes in ECG.

RESULTS: 999 subjects, age 35-70 years, participated to study. From all, 40.8% were male. Microalbuminuria was detected in 8% and sub-clinical ECG ischemic changes were found in 23.4%. The most frequent ischemic change was T wave inversion. The mean urine albumin levels in subjects with normal ECG was 9.6±14.6 mg/ml and in ischemic group was 8.5±12.2 mg/ml and they did not have statistically different. The odds ratios of neither Albumin-Creatinine ratio nor microalbuminuria were in significant range for risk to ischemic changes in ECG of apparently healthy participants. They was consecutively OR=0.9 (0.51-1.6), OR=0.99 (0.98-1.004).

CONCLUSION: Our finding didn't declare any association between ACR and IHD. Because of showing this association in the other study; it needs more exploration regarding to association between microalbuminuria and cardiovascular diseases incidence.

Keywords: Ischemic heart diseases, electrocardiogram, Albumin-Creatinine Ratio, Urine Albumin

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Introduction

Ischemic heart diseases (IHD) are on the first rank of all mortality causes and have dedicated the greatest burden of diseases worldwide.[1] There are some recognized risk factors that enhance the incidence of IHD, such as Hypertension, hyperlipidemia, smoking, and diabetes mellitus. Nowadays, investigators seek to find the pathogenesis of the current risk factors and explore the new risk factors to prevent IHD. It has been established that microalbuminuria predicts the cardiovascular disease mortality and morbidity, in diabetic patients.[2,3] Although, in general population – non-diabetics and normotensives – urinary albumin excretion (UAE) increases the risk of cardiovascular diseases and predicts IHD risk and its mortality, too but this relation dose not seem to be causal.[4,5] Low-grade urinary albumin excretion has been related to a

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different group of cardiovascular risk factors, too, even in apparently healthy individuals.[6]

According to the Steno hypothesis, the endothelial cell dysfunction is the outstanding outcome of microalbuminuria, and It is the hallmark of microvascular damage.[7] The engendered microvascular damage is observed in the pathogenesis of hypertension, diabetes mellitus and chronic kidney diseases. Beside, The metabolic syndrome is a well-known predictor of IHD and microalbuminuria is a main component of metabolic syndrome according to the definition of International Diabetes Federation (IDF) and Adult Treatment Panel III (ATP III).[8,9] This component of metabolic syndrome predict the development of albuminuria in apparently healthy population.[10,11] This has led to the concept that microalbuminuria predict the IHD. We have faced on the lack of data regarding the association between microalbuminuria and IHD in the general population. We decided to investigate the association of microalbuminuria and Albumin-Creatinine ratio (ACR) with ischemic electrocardiography (ischemic ECG) changes in apparently healthy subjects in great Iranian population. Additionally, we investigated the relationship between the lipid profile, fasting plasma glucose and blood pressure and UAE and urinary albumin/Creatinine ratio in the population.

Materials and Methods

Setting and subjects selection

This cross-sectional study was set up in Isfahan as the catchments area. Isfahan is the biggest metropolitan in Iran after Tehran- the capital of Iran. It is contained approximately 2,000,000 (70%) urban and (30%) rural populations. Based on the pilot study and standard deviation of 24 hour urinary albumin, the sample size was calculated 1200 subjects in general population. The samples were selected during one year- first of January 2008 to January 2009- from the general population of urban and rural in Isfahan district area, aged 35-70 years. The random cluster sampling was done to select subjects. The clusters were recruited from the poliomyelitis campaign that was conducted by Ministry of Health at 2000. Within household the subjects selected randomly. The trained health professions were going to house and invited individual to the health center. In the health center, initially the informed consent form was filled for each participant. Then the variables were collected as described below.

Measurements and definitions

The blood pressure was measured by a trained health professional in a sitting position, after 10 minutes resting. The calibrated mercury sphygmomanometer with appropriate adult size cuff was used to detect blood pressure for each participant. The measurement was repeated twice at least 10 minutes later. Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or more, or a diastolic blood pressure (DBP) of 90 mmHg or more, or taking antihypertensive drugs.

The trained nurses took 10cc venous blood sample from cubital vein, and sent them to the central laboratory of Isfahan Cardiovascular Research Center (ICRC). ICRC is a World Health Organization (WHO) collaborating center in the non-communicable disease in Eastern Mediterranean region (EMRO). The ICRC laboratory meets the Iranian national reference laboratory criteria and is under external quality control of St Rafael University, Leuven, Belgium.

Serum total cholesterol (TC), triglycerides (TG) and fasting plasma glucose (FPG) were measured enzymatically using an auto-analyzer (Hitachi, Japan). Serum high density lipoprotein cholesterol (HDL) was determined after precipitation of low-density and very low-density lipoproteins with dextran sulfate-magnesium. Low density lipoprotein cholesterol (LDL) was measured directly by Pars Azma kit (Pars Azma, Iran) an auto-analyzer (Hitachi, Japan).

From each participant were requested to collect the all urine during the latter 24 hours in the specific container. Then morning spot urine albumin and Creatinine were measured by photometric analyzer (Hitachi 90Z, Japan).Microalbuminuria was defined Albumin-Creatinine ratio (ACR) between 30-300 mg/gr.[12]

A 12-lead ECG was recorded in each participant. All ECGs were coded and analyzed blindly by both a trained nurse and a cardiologist using Minnesota coding.[13] The ECGs were categorized in five IHD groups; 1- Pathologic Q wave, 2- ST elevation, 3- ST depression, 4- T wave inversion and 5- two or more of the latter groups. Finally the ECG patterns divided into 2 categories; Normal and Ischemic.

Statistical analysis

The analysis was done by SPSS 15th version (SPSS Inc., Chicago, IL). The mean and standard deviation were presented for continuous variable and categorical variables were shown as frequency tables. Fisher's exact test and Mantel-Haenszel test was used for dichotomous variables in univariate analysis, and two samples independent t-test was recruited to compare means between two groups.

The dependent variable was dichotomous – ischemic changes in ECG against normal ECG-, thus two logistic regression models were created to examine the main effect of albuminuria with adjustment of other effective factors. At the first model the odds of increasing of ACR was assessed for ischemic

changes of ECG and was modified for Gender, systolic blood pressure and fasting plasma glucose. The second logistic regression model presented the odds ratio of microalbuminuria for ischemic changes of ECG. Model 2 was adjusted for Gender, systolic blood pressure and fasting plasma glucose, too. The P-value < 0.05 was considered to be significant.

Results

In total, 999 participants, age 35-70 years, completed their questionnaire (84% responce rate). Among these, 408 subjects (40.8%) were male and 591 (59.2%) were female. Table 1 shows the laboratory data of the entire study population. The mean systolic and diastolic blood pressures were 124.1 ± 18.2 mmHg and 77.7 ± 11 mmHg, respectively. Microalbuminuria was shown in 79 (8%) subjects. The ischemic changes in ECG were found in 23.4% of participants. The most common ECG pattern was T wave inversion. There was a significant difference between male and female sex in ECG pattern. In gender differences at ECG pattern, female had more ischemic changes in ECG, as female gender was the risk factor for ischemic changes in ECG in general population in univariate analysis OR = 1.66, 95% CI (1.2-2.3) All ECG changes have been expressed in table 2.

Mean of serum lipids, fasting plasma glucose, urine albumin and Creatinine and ACR was the same in normal and ischemic ECG groups. Only systolic blood pressure was significantly higher in ischemic group (Table 3). No relation was between microalbuminuria and ECG pattern (Fisher's exact test, χ^2 = 0.21, P = 0.99).

Table 1. The laboratory findings of participants

	Mean(± SD)
Fasting plasma glucose (unit)	93(± 28.6)
Total cholesterol(unit)	198.3(± 39)
Triglyceride(unit)	166.7(± 104.8)
HDL(unit)	46.9(± 11.4)
LDL(unit)	117.2(± 27.4)
Urine Albumin(unit)	9.3(± 13.8)
Urine Creatinine(unit)	118.2(± 63.6)
Albumin-Creatinine ratio	0.11(± 0.16)

Table 2. The frequency of the ECG changes in a population-based sample of Iranians

	Frequency	Percent
Normal	751	76.6
Pathologic Q wave	41	4.2
ST segment elevation	8	0.8
ST segment depression	34	3.5
T wave inversion	114	11.6
More than 2 changes	33	3.4

Table 3. Characteristics of participants according to their ECG pattern

	ECG	Mean	Standard deviation	T, P value
Fasting plasma glucose	Normal	92.1	28.1	T=-1.647,
	Ischemia	95.5	27.2	P=0.1
Total cholesterol	Normal	199.2	39.3	T=1.15,
	Ischemia	195.9	38.4	P=0.25
Triglyceride	Normal	168.5	108.2	T=0.997,
	Ischemia	160.7	87.6	P=0.32
HDL	Normal	46.7	11.2	T=-1.029,
	Ischemia	47.6	12.4	P=0.3
LDL	Normal	117.8	27.3	T=1.08,
	Ischemia	115.6	27.9	P=0.28
Urine Albumin	Normal	9.6	14.6	T=1.12,
	Ischemia	8.5	12.2	P=0.26
Urine Creatinine	Normal	118.1	62.4	T=-0.09,
	Ischemia	118.5	68.2	P=0.93
Systolic blood pressure	Normal	123.3	17.9	T=-2.7,
	Ischemia	127	18.9	P=0.007
Diastolic blood pressure	Normal	77.3	10.8	T=-1.82,
	Ischemia	78.8	11.6	P=0.07
Albumin-Creatinine ratio	Normal	0.11	0.15	T=-0.085,
	Ischemia	0.11	0.19	P=0.93

Table 4- The multivariate logistic regression models of factors associated with ischemic ECG

		Model 1			Model 2		
		OR	95% CI	P value	OR	95% CI	P value
Sex	Male	1	-	-	1	-	-
	Female	1.74	1.3-2.4	0.001	1.72	1.25-2.4	0.001
Systolic BP		1.01	1.003-1.02	0.006	1.01	1.004-1.02	0.004
FPG*		1.003	0.99-1.008	0.220	1.003	0.99-1.009	0.170
Albumin					0.99	0.98	1.004
Alb-Cr Ratio**	Negative	1	-	-	-	-	-
	Positive	0.9	0.51-1.6	0.71			

**Fasting Plasma Glucose*
** Albumin-Creatinine ratio

Two logistic regression models were formed. At the first one, effect of ACR on the ECG pattern was assessed considering gender, systolic blood pressure and fasting plasma glucose modification. The second model was based on the effect of microalbuminuria on ischemic changes of ECG with the same adjustment as the first model. The coefficients and OR of both models are demonstrated in table 4. As is seen, neither ACR nor microalbuminuria was the risk factor for ischemic changes in ECG of apparently healthy participants. The OR of microlabuminuria was in the protective range but not significantly. However the female sex and the high systolic blood pressure were the risk factors of ischemia independently.

Discussion

Our findings did not show any significant association between urinary albumin exertion and ischemic changes in the apparently health people. However female sex and high systolic blood pressure were the independent risk factor of ischemia in ECG. The microalbuminuria rate in our study was 15.1%. It was in the range of other reported studies.[14]

The low serum albumin is a previous known risk factor of coronary artery diseases.[15-17] Pursuant to low serum albumin level, albuminuria is mentioned to be an independent cardiovascular risk factor.[4,5,18-20] Many studies have shown sub-clinical cardiovascular diseases like left ventricular hypertrophy and increased carotid artery intima-media thickness associated with microalbumiuria.[14,21-24] In the current study, we assessed the sub-clinical cardiovascular diseases by the ischemic changes of ECG but we could not find any association with microalbuminuria or ACR.

The pathogenesis of microalbuminuria in cardiovascular disease is still unknown. Based on Steno Hypothesis, microalbuminuria makes microvascular damages.[7] It is associated to microvascular dysfunction.[25] Microalbuminuria causes generalized transvascular escape of albumin which is associated with an increased transport of lipoproteins into the endothelium. It is the susceptible marker of atherosclerosis.[26,27] On the other hand, albumin is a negative acute-phase protein, and associated with inflammatory cytokines and cardiovascular diseases associated to inflammation, too.[16] Coagulation and fibrinolytic systems disorders have also considered as a possible link between microalbuminuria and cardiovascular diseases. It has been declared, microalbuminuria has been associated with changes in von Willebrand factor, fibrinogen, thrombomodulin, and plasminogen activator inhibitor-1.[28]

There were many hypotheses to justify the differences between our study and the others. The first one was the variable to show IHD. We used the ECG changes pro IHD. There were some more reliable methods to evaluate IHD.[14] Because of great population in our study, cost and ethical consideration; we could not apply the more reliable methods for IHD evaluation. Third, there was a significant difference in mean systolic blood pressure between two groups in our study. High blood pressure has strong relation to microalbuminuria and IHD.[29-31] Despite, we adjusted the blood pressure effect by logistic regression model; we did not find any relation between ECG pattern and microalbuminuria and ACR. However, in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study determined that treatment and control of blood pressure reduced proteinuria thus the risk of IHD decreased, consequently.[32]

Many limitations existed in this study; at first, we used the morning spot urine sample. Up to one-third of adults in the general population with increased urine albumin exertion in the first urine sample may not have increased urine albumin in a subsequent urine sample.[33] However, Lambers-Heerspink et al have introduced the association of microalbuminuria and IHD. They have pointed out that the spot urine sample results is the same as 24h urine collection.[34] The second, ECG was done in apparently healthy general population and they did not have any symptom of cardiovascular diseases. I could not investigate

more with the other ways such as exercise test, echocardiography, and so on, because of cost.

It was better to adjust ACR with weight; albuminuria changes with weight changes, too.[35] Unfortunately, we did not have the weight of participants in this study. Furthermore, urine Creatinine excretion differs by ethnicity,[36] our population sample in Isfahan is homogenous and we do not have different ethnicity in this region.

At the end, it seems that more investigation is needed to explore the exact relationship between microalbumiuria and IHD. To find this association, the long-term longitudinal study with control for the other cardiovascular risk factors and exact methods for outcome evaluation is needed.

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