Microalbuminuria as a predictors for detection of silent ischemia in patients with type two diabetes mellitus

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الخلاصة:

إن وجود الزلال في إدرار مرضى السكري يعتبر عامل خطورة و يزيد من نسبة الأصابة لإمراض القلب و أمراض الكلى لديهم . إن السبب الحقيقي ما زال غير معروف, إلا إن الباحثين توصلوا إلى نتيجة إن وجود الزلال في ادرار مرضى السكري يزيد من نسبة الأصابة بإمراض القلب و أمراض الكلى و كذلك إن أمراض القلب و أمراض الكلى تزيد من نسبة الزلال في الإدرار.

هدف البحث: إمكانية الإستعانة بعامل زلال الإدرار في تشخيص حالات الذبحة الصدرية الصامتة لمرضى داء السكري النوع الثاني.

طريقة البحث: تم الإستعانة بمئة و تسعة وستون مريضا بداء السكري النوع الثاني من الذين ليست لهم أمراص القلب في مستشفى التعليمي في الديوانية. بعد إجراء الفحوصات السريرية و المختبرية و أخذ موافقات المرضى. وزعت العينات الى مجموعتين إعتمادا على نتيجة وجود الزلال من عدمه. المجموعة الأولى إحتوت على أربعة و سبعين حالة إيجابية في زلال الإدرار بينما المجموعة تكونت من إثنتا و تسعون حالة لا يوجد لديهم زلال في الإدرار . بعد ذلك أجريت لهم فحص إجهاد القلب أو فحص هولترللكشف حول وجود علامات الذبحة الصدرية الصامتة.

النتيجة: تبين وجود علاقة بين زلال الإدرار عند مرضى السكري و الذبحة الصدرية. كانت هناك ثلاث عشرة حالة إيجابية لفحص اجهاد القلب من أصل أربعة و سبعين في المجموعة الأولى و ثلاثة حالات إيجابية فقط من اصل خمسة و تسعون في المجموعة الثانية

هنك علاقة ما بين زلال الإدرار و أمراض القلب و أمراض الكلى و إرتفاع ضغط الدم. يمكن الإستعانة بفحص كشف زلال الإدرار للكشف عن أمراض الشرايين التاجية الصامتة لمرضى السكري وكذلك علاج العوامل المؤثرة الأخرى بصورة شديدة في حالة وجودها قد يحسن من الحالة المستقبلية لمرضى السكري.

Abstract:

Background: CHD was still the most widespread leading cause of death in worldwide. Many risk factors can play a role in its pathogenesis; DM, HT, dyslipidemia, obesity smoking and microalbuminuria are common known risk factors. Microalbuminuria is independently considered as a risk factor of CHD in patients with diabetes. Its task as a predictor for CHD has not been well examined, and its predictive implication is uncertain.

Aim of study: The purpose of our study was to determine the using of microalbuminuria as a predictor test for detection of silent ischemia in type II DM.

Patient and methods: Selection of 169 patients with type II DM who had neither old nor recent IHD and they hadn't chest pain. According to the results of microalbuminuria, we were dividing those patients into two groups, with and without microalbuminuria. Group one consist of 74 patients with microalbuminuria while group two consist of 92 patients without microalbuminuria. Treadmill test (TMT) or holter studies were done for all patients of both groups after taking their agreement.

Results: the result would reveal that diabetic patients with microalbuminuria are at high risk of ischemia than those without microalbuminuria independently to other risk factors. 16 of 74 patients from group one and only three of 95 from group two show positive features of ischemia during exercise test with statistically significant (p value < 0.001).

Conclusion: In diabetic patients, microalbuminuria is associated with high CHD risk, independently to other known risk factors. As such, any patient with diabetes mellitus type two had microalbuminuria should search for latent IHD independently to other risk factors. So detection of microalbuminuria and trating of other risk factors is mandatory for improved outcome of CHD risk.

Recommendation: Closely follow up of diabetic patients with tight glycemic control in order to reduce incidence of microalbuminuria and any patient with microalbuminuria should search for CHD.

Introduction

Coronary heart disease (CHD) was still the most leading cause of morbidity and mortality in the developed and developing countries, and the incidence is still raising whole over the world [1]. Many modified and unmodified factors play a role in its pathogenesis. Insulin resistance diabetes, hyperlipidemia, obesity, hypertension and microalbuminuria are the most risk factors correlated with the atherosclerosis which is a critical pathology of CHD. The highlighting is being focused on lifestyle modification and control of the risk factors to control or prevent CHD [2].

The patients with CHD often presented with typical central chest pain. Some of those patients, especially patients with diabetes and those with previous ischemic heart attacks had freed of pain even with emotional and physical exertion, which is define as silent ischemia. It is often detected accidentally by routine ECG or can be detected in suspected candidate by an exercise stress test and/or holter monitoring if they had normal resting ECG. [3] It is estimated by AHA that about 3 to 4 millions of Americans have episodes of silent ischemia which is most of them are diabetic [1].

The diabetic patients often complaining from many microvascular and macrovascular complications especially those with poorly control. So, those patients are at high risk for CHD.

The presence of protein in urine was defined as microalbuminuria, which is occurs when there is abnormal high glomeruler permeability for albumin, which is occurring mostly in diabetes mellitus. It's considered as independent risk factor for CHD as well as renal injuries in both diabetic and non diabetic patients.

Microalbuminuria is"defined when there is 30–300 mg of albumine/24 hour urine collection or 30 to 300 mg albumine/L in a spot urine sample. Albumin/creatinine ratio (ACR) was used to compensate the variations in urine spot samples, which is ≥3.5 mg/mmol in female and ≥2.5 mg/mmol in male".[4]

Definitions of microalbuminuria

24h urine collection	**30-300 mg albumin/24 hr**
Spot urine sample	30-300 mg albumin/liter of urine
ACR	3.5 mg/mmol(female), 2.5 mg/mmol(male)

Recently many studies have added findings about the association between microalbuminuria and CHD. Firstly, the risk of microalbuminuria had much lower at ACR of 1 mg/mmol [7]. Second, in diabetic individuals, the cardiovascular event has been increase with the progression of microalbuminuria [8] . Thirdly, LIFE study (Losartan Intervention For Endpoint reduction in hypertension), suggest that any reduction of microalbuminuria was associated with a significant reduction in the cardiovascular disease risk **[9].**

Patient and methods:

This cross-sectional study was conducts on 169 diabetic patients were seen in diabetic center of Al-Diwanyia Teaching Hospital in Al- Diwanyia city. It is carried out from the December 2014 till the end June 2015.

The patients were diagnosed clinically by a physician as having type two diabetes mellitus. Those patients were randomly selected. All included patients were accepting to join in this study.

Patient with type one diabetes mellitus, severe physical or mental disabilities, any patients with known CHD and patients who had bundle branch block (BBB) on ECG were excluded from the study. Any participants with hematuria and those with macroalbuminuria were also excluded.

Careful history, physical examinations and clinical variables such as pulse, BP, height,

weight, and body mass index (BMI), were done to all candidates.

Patients are considered obese when their BMI is over 30 kg/m^2. Hypertension was defined when systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg.

Fasting serum total cholesterol, triglyceride levels, glucose, HbA1c, urea, and creatinine were measured to all patients.

A 24-hour urine collection or a urine spot sample was taken for measurement of microalbuminuria and ACR also was done. An early morning sample is preferred and the patients teach him to avoid doing heavy exercises 24 hours before the test. The diagnosis of microalbuminuria was considered positive according to its definition.

According to the presence of microalbuminuria, the patients were classified into two groups. Group one was consist of seventy four diabetic patients who had microalbuminuria. While group two consists of ninety five diabetic patients had no microalbuminuria.

All patients of both groups after history and full physical examination were sending for resting ECG and echocardiography for more cardiac assessment. Any patient with ECG features of previous or recent ischemia, arrhythmia or bundle branch block were excluded.

Consent of patients was taking for exercise stress test or holter monitoring. All included patients of both groups were underwent exercise stress test or holter monitoring for 48 hours (holter study was done for those who unable or refused exercise stress test).

The exercise test consider positive if the patient had one or more of the following clinical or ECG criteria during exercise test:

- Decrease in systolic BP of (> 10 mm Hg) from baseline or hypertensive response “systolic BP of 250 mm Hg or diastolic BP higher than 115 mm Hg”.
- Typical chest pain.
- Dizziness,
- Cyanosis or pallor.
- Critical arrhythmias.
- ST elevation (> 1 mm)
- Development of bundle branch block

Some patients are unable to do or complete the exercise test, holter study done for at least 48 hours and then assessed the finding.

Statistically assessment of both groups was done by using Chi square for assessment of its significant. The p value of < 0.05 was considered significant.

In this study we focused that an exercise stress test and/or Holter monitoring can be used as screening test in diabetic patients with microalbuminuria, who had no clinical features or ECG changes for IHD, for diagnosis of silent ischemia.

Result:

Table (1): show the demographic distribution of both groups, with no. of each geneders.

Age group	Group 1		Group 2		Total
	male	female	male	female	
30-45	14	19	13	31	77
46-60	13	13	19	16	61
60--70	5	6	8	5	24
>70	2	2	1	2	7
total	34	40	41	54	169

Table one revealed the distribution of patients in both groups according to their age and gender. Group one consist of 74 diabetic patients (34 male and 40 female) had microalbuminuria and most of them in middle age group. While group two consists of 95 diabetic patients (54 male and 41 female) had no microalbuminuria. As in group one most of group two patients are in middle age. Obviously there is no significant between these groups according to their age and gender distribution.

Table (2) distribution of risk factors in each group:

Risk factors	Group 1	Group 2
Hypertension	28	37
obesity	38	46
Hyperlipidemia	45	61
smoking	29	38

Table two will revealed the presence of risk factors other than microalbuminuria in both diabetic groups. In both groups, most of patients had many risk factors; obesity and hyperlipidemia are the most risk factors in both groups. Most of obese patients of both groups had central obesity with high waist circumflex of both gender. Patients are considered obese when their body mass index (BMI) is over 30 kg/m^2. Active current smoking habit was about 40% in both groups, mostly among male group.

The lifestyle of most patients of both groups had poor activities and attitude of exercise. Statistically there is no significant difference of risk factors distribution between these two groups.

Table (3): show the results of exercise stress test of both groups

Result of TMT	Group 1	Group 2	P value
Positive	13	3	0.001
Negative	61	92	0.434
Total	74	95	

Table three will show that thirteen of seventy four patients with microalbuminuria had positive exercise stress test, while only three of ninety five patients will be positive in other group who had no microalbuminuria with statistically significant (P value of < 0.05).

Table (4): show the distribution of patients with positive TMT according to the level of microalbuminuria

Microalbuminuria level	Patients with positive TMT
30-99	3(female =2)
100-199	7(female =3)
200-300	3 (female =1)

The table four obviously shows the distribution of positive TMT patients according to their microalbuminuria, 10 of 13 patients had microalbuminuria level higher than 100 with statistically significance (P value < 0.05).

Discussion:

Microalbuminuria was considering a part of metabolic syndrome beside the HT, insulin resistance, central obesity and dyslipidemia in same subject. It's been consider as predicted of primary CHD events independently of other established risk factors. In our study, although the patients with overt CHD were not included in this study, the incidence of silent CHD significantly high across those with microalbuminuria. A study done by Dinneen and Gerstein in a systematic review, showed that microalbuminuria among patients with

type two diabetes to be associated with a 2.4-fold increased risk for CHD events as compared with normoalbuminuria[11], and this finding was well-matched with our study in which CHD was significantly increase among categories with type two diabetes with microalbuminuria than those without microalbuminuria .

Many other studies for detection of microalbuminuria in population will showed a significant increasing of albuminuria with many other risk factors like age, smoking and some pathological state like hypertension and dyslipidemia in addition to diabetes mellitus [7]. This is also seen in our study, that microalbuminuria was increased in elderly and those with hypertensive but show no significant increased in patients with dyslipidemia.

The prevalence of microalbuminuria was more in the female than men which is compatible with EPIC-Norfolk study, but with no statistically significance. This may be explained by the fact that urinary creatinine levels are higher in men [4] .

Regardless of whether microalbuminuria was a risk factor per se for CHD or resulting from tissue damage from other CHD risk factors, our finding imply that microalbuminuria can be used as a predictor for detection of silent IHD and can identifying whose diabetic patients at high risk of CHD and might be benefit to identified the outcome of those patients.

Conclusions

The relationship between CHD and microalbuminuria needs to be considering bidirectional correlation in diabetic patients. That microalbuminuria cause cardiovascular disease at same time cardiovascular disease may causes microalbuminuria.

In diabetic patient, presence of microalbuminuria associated with high risk of CHD, independent of other cardiovascular risk factors. Although the prognosis of silent ischemia is still controversial, definitely the early detection and treated of silent ischemia can improve the outcome prognosis.

Tightly control of other CHD risk factors is essential in the presence of microalbuminuria [12] to improve the outcome of the diabetic patients.

In the EPIC-Norfolk "European Prospective Investigation of Cancer-Norfolk Study", and HOPE "(Heart Outcomes Prevention Evaluation)" study, both were observed that the incidence of CHD will increased significantly with albuminuria. In our study also showed significantly increased in silent IHD in diabetic patient who had microalbuminuria.

Recommendation:

- Larger number study is indicated.
- Closely follow up of diabetic patients with tight glycemic control in order to reduce incidence of microalbuminuria.
- This study was a single-center experience, large multi-centers study is suggested.