

## **EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR {CAPTOPRIL} AND SELECTIVE $\beta_1$ -ADRENERGIC RECEPTORS BLOCKER {ATENOLOL} ON PROTEINURIA IN HYPERTENSIVE DIABETIC PATIENTS**

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### **Abstract**

Diabetes mellitus is one of the common health problems. It has many serious complications among them are hypertension and diabetic nephropathy which may lead to renal failure. The first sign of early stage renal of failure or diabetic nephropathy is proteinuria which {presence of an abnormal amount of protein in urine} which leads to hypertension. As its known that hypertensive patients need treatment and those with diabetes and proteinuria need more attention to be given during choosing their antihypertensive medications by using effective drugs with less side effects and comply with many aspects that are looked for by both the physician and the patient. This study was conducted on {28} diabetic patients using insulin for treatment , those patients were newly diagnosed to have hypertension as a complication of diabetes. The medications that are used as antihypertensive for them are either angiotensin converting enzyme inhibitors {ACEI} or Atenolol {tenormin}. According to the antihypertensive drugs used for treatment they were classified into two groups :

Group-A- ACEI patients, and group-B- Atenolol patients. The aim of this study was to find whether Atenolol has an effect on proteinuria or not and to compare this effect if any with ACEI, despite the fact that ACEI has a renoprotective effect on kidney but because Atenolol became widely used for the management of hypertension whatever the aetiology of hypertension. As it is known well that for every medication there are side effects some of them might be serious so Atenolol needed to be used cautiously in diabetic patients because it causes masking of hypoglycemia in addition to other side effects but its widely used by our physicians in diabetic patients so we want to demonstrate here whether it has an effect on the level of proteinuria which might be a cause, or a result of hypertension in diabetic patients, in order to decrease the unwanted side effects on those patients and to pay more attention during choosing the medications used for such patients. Therefore {24} hour urine was collected for each patient and total protein in urine was measured before starting treatment and after different periods from using medications, in addition to monitor blood pressure and blood glucose levels. From the results obtained it was clear that ACEI still the effective drug, it significantly (  $p < 0.05$ ) lowers both blood pressure and the level of proteinuria in contrast to Atenolol which was not significant in lowering the level of proteinuria but effectively lowered blood pressure .

It was concluded that ACEI still the best to be the first choice medication for diabetic hypertensive patients, while Atenolol needs more attention and follow up for the patients when its decided to be used.

## تأثير العقار المثبط للإنزيم المحول للأنجيوتنسين (كابتوبريل) والعقار الانتقائي الذي يعمل على غلق مستقبلات بيتا 1 (الاتينولول) على مستويات البروتين في إدرار مرضى داء السكر و فرط ضغط الدم.

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### الخلاصة

داء السكري هو أكثر الأمراض شيوعاً ، و المضاعفات التي يسببها كثيرة و البعض منها تكون خطيرة، و من أكثر المضاعفات شيوعاً هي: ارتفاع ضغط الدم و تلف الكلى و الذي ينتهي بالفشل أو العجز الكلوي. من أولى علامات العجز الكلوي نتيجة داء السكر هي الإدرار الزلالي (وجود البروتين في الإدرار) و الذي يؤدي إلى فرط ضغط الدم .

كما هو معروف فإن مرضى فرط ضغط الدم يحتاجون للعلاج و أولئك الذين يعانون من داء السكر والإدرار الزلالي بالإضافة إلى أن فرط ضغط الدم بحاجة إلى عناية أكثر عند اختيار العقار لعلاج ارتفاع ضغط الدم لديهم وذلك بان يكون العلاج المستخدم ذو تأثيرات جانبية قليلة و فعالية عالية و يلبى الأهداف و الجوانب المرجوة من استخدامه لكل من الطبيب و المريض. هذا البحث اجري على (28) مريضاً يعانون من داء السكر منذ سنوات و يستخدمون الأنسولين في العلاج ، وهؤلاء المرضى يعانون من ارتفاع ضغط الدم كأحد مضاعفات داء السكر و تم استخدام إما عقار التينورمين أو مثبط الإنزيم المحول للأنجيوتنسين لعلاج ارتفاع ضغط الدم . قُسم هؤلاء المرضى اعتماداً على نوع العقار الذي وصف من قبل الطبيب لعلاجهم إلى مجموعتين: المجموعة الأولى: استخدمت العقار المثبط للإنزيم المحول للأنجيوتنسين. المجموعة الثانية: استخدمت عقار التينورمين. كان الهدف من البحث هو معرفة فيما إذا كان لعقار التينورمين تأثير على مستويات البروتين في الإدرار في مثل هكذا مرضى و مقارنة هذا التأثير مع العقار المثبط للإنزيم المحول للأنجيوتنسين المعروف بفعاليتيه في تقليل مستويات البروتين في الإدرار و فعاليتيه في حماية الكلى، و لكن أُختير عقار التينورمين لأنه أصبح واسع الاستعمال في علاج اغلب حالات ارتفاع ضغط الدم مهما كان المسبب لارتفاع ضغط الدم و المعروف أن لكل دواء هناك حالات يجب أن يستخدم فيها و أخرى يفضل فيها عدم استخدامه و بالنسبة لعقار التينورمين فإن احد تأثيراته الجانبية هو التأثير على مستوى السكر في الدم {masking of hypoglycemia} وقد يؤدي إلى ارتفاع مستوى السكر في الدم إضافة إلى تأثيراته الجانبية الأخرى و لكن وبالرغم من هذا إلا انه يستخدم و بشكل كبير لهؤلاء المرضى فما أردناه هنا هو تسليط الضوء و التركيز فيما إذا كان لهذا العقار القدرة على تقليل مستويات البروتين في الإدرار (الإدرار الزلالي) لمرضى داء السكر والذي ربما يكون سبباً أو نتيجة لفرط ضغط الدم في هؤلاء المرضى و لغرض التقليل من التأثيرات الجانبية غير المرغوب بها والانتباه أكثر عند اختيار العلاجات والأدوية. تم جمع عينات الإدرار لمدة (24) ساعة لكل مريض و قيست مستويات البروتين الكلي قبل البدء بالعلاج و بعد فترات زمنية مختلفة من استخدام كلا العقارين بالإضافة إلى مراقبة مستويات السكر في الدم و مستويات ضغط الدم .

من النتائج التي تم الحصول عليها اتضح أن العقار المثبط للإنزيم المحول للأنجيوتنسين قلل وبشكل ملحوظ مستويات كل من البروتين في الإدرار ومستويات ضغط الدم و بمعنوية  $P < 0.05$  أما بالنسبة للتينورمين فلا يكون تأثيره ملحوظاً بصورة كبيرة في خفض مستويات البروتين في الإدرار و لكنه فعال في خفض ضغط الدم مما تقدم يتبين و بشكل واضح بان العقار المثبط للإنزيم المحول للأنجيوتنسين يبقى هو الخيار الأمثل لعلاج فرط ضغط الدم لدى مرضى داء السكر و ذلك لفعاليتيه في أكثر من جانب من جوانب العلاج مما يساعد على تقليل كمية الأدوية المستخدمة و عددها و نوعيتها وبالتالي يساعد المريض على التجاوب أكثر في الالتزام بالعلاج على العكس فيما إذا كانت الأدوية كثيرة - وهذا أيضاً ما أردنا توضيحه- فلو استخدم عقار التينورمين الذي يعمل على خفض مستويات ضغط الدم المرتفعة فإنه ستكون هناك حاجة لاستخدام عقار آخر

معها لخفض مستويات البروتين في الإدرار ، ناهيك عن التداخل الدوائي الذي يحدث عند استخدام أكثر من عقار وغيره من التأثيرات الجانبية .

## Introduction

Proteinuria is described as a condition in which urine contains an abnormal amount of protein (greater than 0.03 gm/day). The main protein that most likely appears in urine is albumin, that's why its also called "albuminuria"(1).

There are two types of albuminuria according to the amount of albumin that presents in urine (2):

\*Microalbuminuria: when the amount of albumin (0.03-0.3)gm/day.

\*Macroalbuminuria: when the amount of albumin in urine (0.3-3)gm/day or more .

Proteinuria is one of the common complications of diabetes mellitus, it leads to hypertension and renal failure so, diabetes is a leading cause for end stage renal disease {ESRD} in both type I and type II diabetes, therefore, It is considered as a major health problem leading to vast derangements in glucose and lipid homeostasis with disastrous vascular complications. Hypertension and diabetic nephropathy are two common complications of diabetes, they are in a close association to each other, the mechanisms by which hypertension develops in diabetic patients (3):

1-Hyperlipidaemia, due to lipid metabolism abnormalities.

2-Renin Angiotensin Aldosterone System (RAAS)which promotes both systemic and glomerular hypertension, it can induce haemodynamic injury to the vascular endothelium, so its intimately involved in the development of atherosclerosis and arteriosclerosis, the initial atherosclerotic lesion of lipids, monocytes and T-lymphocytes is thought to be an inflammatory reaction involving endothelial cells and subendothelial tissues, with ongoing inflammation, subendothelial smooth muscle cells proliferate and migrate area of injury, increasing the tissue mass of inflammatory response and ultimately cause typical atherosclerotic plaque, it promotes endothelial cell dysfunction and increases oxidative stress which ends with hypertension.

3-diabetic nephropathy and end stage renal disease (ESRD).

So hypertension can be a cause, a result and a complication of renal disease in diabetic patients, and has been identified as a key

modifiable risk factor in patients with decreased renal function.

Diabetic nephropathy is a single most important cause of end stage renal failure, it accounts for about (30%) of all renal failure patients(4),it presents at first as intermittent microalbuminuria, progressing to persistent microalbuminuria, and then macroalbuminuria, with progression of the disease, the glomerular filtration rate decreases dramatically and ESRD ensues(5).

The mechanism by which diabetic nephropathy develops is due to the effect of renin angiotensin Aldosterone system {RAAS}, in the kidney; its responsible for constriction of the glomerular efferent arterioles which increase blood pressure within the glomerular capillaries bed and leads to structural damage (shear injury) to the glomeruli which is an important step in the development of vasculopathy, and nephropathy, this vasculopathy causes nephron ischaemia, with nephrosclerosis, consequently the kidneys lose their ability to regulate glomerular filtration flow and pressure with resultant hyperfiltration, manifested as albuminuria and proteinuria(6). When proximal convoluted tubule reabsorbs the excess protein, secretion of vasoactive substances damage the glomerular tubular apparatus; nephrons damage further and activate RAAS, resulting in increased sympathetic tone and fluid overload compounding the progression of hypertension and increased nephron loss(7), this leads to an axis of amplification between hypertension and renal dysfunction, whereby (90%) of patients with diabetic nephropathy have hypertension, therefore, the benefit of strict control of blood pressure is for slowing of progression of kidney disease and protection against renal dysfunction(8), from this point of view it was important to choose a proper antihypertensive medication that provide renoprotective benefits beyond blood pressure lowering property, that's why two groups of antihypertensive medications were chosen in this study which are the common in use in our country these two groups are: Angiotensin enzyme inhibitors group{ACEI} which include (Captopril, Lisinopril and Enalapril).

Their main action is inhibiting of angiotensin converting enzyme in humans and animals, and

causing suppression of renin angiotensin Aldosterone system and that results in decreasing plasma angiotensin II and causing decrease in vasopressor activity and decrease Aldosterone secretion, which leads to vasodilatation and therefore lowering blood pressure, they do not appear to bind to serum proteins other than angiotensin enzyme and they do not undergo metabolism, they are excreted unchanged entirely in the urine, this mechanism of action has important role in protection against progression of diabetic nephropathy(9).

The other group is  $\beta$ -adrenergic receptor blocker and the medication which was chosen is Atenolol(tenormin) because it is wide commonly used medication of this group, Atenolol like any other antihypertensive medication lowers both systolic and diastolic blood pressure by its ability to bind to  $\beta$ -receptors and prevents their stimulation by catecholamines, Atenolol has a selective effect on  $\beta_1$ -receptors which are present in the heart, therefore its considered a cardioselective antihypertensive agent. Its water soluble, cleared and excreted via kidneys in urine in an unaltered manner(10).

### Subjects and methods

This study was conducted in Al-Medina medical hospital. Twenty eight(28) diabetic patients(females) were included in the study with mean age (48.82+8.85)years, the mean duration of diabetes (15.21+2.71)years, with mean body mass index (21.92+2.8)Kg/m<sup>2</sup> they were newly diagnosed as hypertensive, the criteria for diagnosing of their hypertension based on measuring of the blood pressure three times at different occasions which were high in those patients, in addition most of the patients have one or more high measurement done outside the hospital before coming to see the physician.

According to antihypertensive medications they received which were prescribed by the physician, the patients were divided into two groups:

**Group A:** consists of (14) patients with who received the angiotensin converting enzyme inhibitor with a dose of (25)mg Captopril.

**Group B:** consists of (14) patients, received Atenolol (100)mg daily.

In order to study the effect of these two groups of medications on proteinuria (24)hour urine

collection was obtained from each patient included in the study and levels of total protein in urine were measured in different occasions before starting their medication and after 2, 4, 6 and 8 weeks from using their medication, in addition their blood pressure and blood glucose level were monitored.

The total protein in urine was measured by Randox kit method(Randox laboratories Ltd.,Ardmore, Crumlin, Co.Antrim, united kingdom, BT294Qy) the principle of this method is that pyrogallol red complexes with proteins in an acid environment containing molybdate ions, the resulting blue-coloured complex absorbs maximally at 600 nm, therefore, the optical density at 600 nm is directly proportional to the protein concentration of the samples(15) Blood pressure was measured by mercury sphygmomanometer.

The results were obtained, and analyzed statistically. All data were expressed as mean +standard deviation, significance was defined as  $p < 0.05$  by using student T-test.

### Results

**Group A :** which received ACEI(captopril) :

- 1- The mean of 24 hour urinary protein excretion (albumin) decrease from (2.97+0.63)gm/24hr before treatment to (2.68+0.63)gm/24hr 2 weeks after starting the use their antihypertensive medication, it is clear that they had macroalbuminuria.
- 2- Four weeks later the mean level of albuminuria decreased to (2.51+0.59)gm/24hr.
- 3- Going on with treatment the mean level became (2.2+0.56) after 6 weeks.
- 4- Eight weeks later it became(1.9+0.53)gm/24hr

It appears that: the levels of proteinuria was significantly ( $p < 0.05$ )decreased gradually with carry on treatment as shown in table-1-

The average mean for different measurements of blood pressure before starting the use of antihypertensive medication was (150.61+8.79)mmHg systolic pressure and (100.67+6.65)mmHg diastolic pressure. Two weeks after starting the treatment with antihypertensive the mean of blood pressure was(143.76+9.25)mmHg systolic and (95.81+3.65) diastolic pressure, within the 4 weeks later it became (140.35+4.47)mmHg systolic and (93.52+6.86)mmHg diastolic.

Six weeks later the systolic blood pressure decreased to be (139.26+5.81)mmHg and diastolic (90.16+4.32)mmHg. On continuing treatment it became (138.45+3.50)mmHg systolic and diastolic(87.35+4.65)mmHg within the later 8 weeks, the lowering effect of ACEI on the level of blood pressure was significant ( $p<0.05$ )as illustrated in (table 3).

The mean levels of blood glucose were as follow :

The mean of blood glucose levels before starting the antihypertensive treatment was (5.47+1.16) mmol/L , and became (5.27+0.87) mmol/L 2 weeks from starting the antihypertensive agent , within 4 weeks it became (4.62+0.72)mmol/L , 6 weeks later it was (4.49+0.68)mmol/L, and on the 8weeks later was(4.42+0.49)mmol/L as it showed in (table 2).

It can be noticed that there is a non significant decrease in the level of blood glucose within the period of treatment for this group.

**Group B:** the patients of this group received Atenolol and the results were as follow :

- 1- mean level of proteinuria before starting medication (3.002+0.61)gm/24hr.
- 2- Two weeks later it was (2.71+0.39)gm/24hr.
- 3-After 4 weeks (2.61+0.23)gm/24hr.
- 4-With continuing Atenolol use for 6 weeks mean level of proteinuria (2.60+0.38) gm/24hr, and in the next 8 weeks it was (2.68+0.31)gm/24hr.

The results of group B showed slight a non significant decrease in the levels of proteinuria in comparison to these for group A as shown in (table 1) .

The average mean of blood pressure for the patients of this group before starting the antihypertensive medication was (150.14+5.49) mmHg systolic blood pressure and (101.18 +7.22) mmHg diastolic. The mean of the blood pressure after starting the use of Atenolol after 2 weeks (141.78+5.04)mmHg systolic and (92.5+6.12)mmHg diastolic, after 4 weeks (139.73+4.77)mmHg systolic and (90.92+8.05)mmHg diastolic, on 6 weeks later was (139.78+5.02)mmHg systolic and (88.78+6.55)mmHg diastolic blood pressure. On the 8 weeks it was (137.14+4.95)mmHg systolic and (88.28+5.38) mmHg diastolic blood pressure. The lowering effect of Atenolol for blood pressure was significant ( $p<0.05$ )as seen in (table 3).

The result of means of blood glucose level were: The mean of blood glucose before treatment was (5.53+0.96) mmol/L, 2 weeks late it was (4.9+0.93)mmol/L, after 4 weeks was (5.55+0.93)mmol/L, within 6 weeks was (5.10+1.00)mmol/L, and after 8 weeks became (4.97+0.83)mmol/Las shown in (table 2).

**Table 1: Levels of proteinuria (gm/day) in group A and B(Mean+SD)**

Level of proteinuria (gm/24hr)					
	Average mean before treatment	2weeks after treatment	4weeks after treatment	6weeks after treatment	8weeks after treatment
<b>Group -A-</b>	2.97±0.63	2.68±0.63	2.51±0.59*	2.2±0.56*	1.9±0.53*
<b>Group -B-</b>	3.00±0.61	2.71±0.39	2.61±0.23	2.60±0.38	2.68±0.31

\*statistically significant changes(  $P<0.05$ ).

Table 2: Levels of blood glucose (mmol/L) for group A and B (Mean±SD)

Level of blood glucose (mmol/L)					
	Average mean before treatment	2weeks after treatment	4weeks after treatment	6weeks after treatment	8weeks after treatment
Group -A-	5.47±1.16	5.27±0.87	4.62±0.72	4.49±0.68	4.42±0.49
Group -B-	5.53±0.96	4.9±0.93	5.55±0.93	5.10±1.00	4.97±0.83

Table 3: Levels of blood pressure (mmHg) in group -A- and -B- (Mean±SD)

		Levels of blood pressure (mmHg)											
		Average mean before treatment		2weeks after treatment		4 weeks after treatment		6 weeks after treatment		8weeks after treatment			
		systolic	diastolic	systolic	diastolic	systolic	diastolic	systolic	diastolic	systolic	diastolic		
Group -A-		150.61±8.79	100.67±6.65	143.76±9.25	95.81±3.65	140.35±4.47	93.52±6.86	139.26±5.81	90.16±4.32	138.45±3.50	87.35±4.65		
Group -B-		150.14±5.49	101.18±7.22	141.78±5.04	92.5±6.12	139.73±4.77	90.92±8.05	139.78±5.02	88.78±6.55	137.14±4.95	88.28±5.38		

## Discussion

As it has been mentioned in the mechanisms of development of hypertension in diabetic patients that renin angiotensin system is implicated in the development of hypertension, atherosclerosis, nephropathy and vascular complications. Angiotensin converting enzyme inhibitors have known renoprotective effects so, they are benefit in treating diabetic nephropathy, therefore they should be recommended as initial antihypertensive agents for patients with diabetes and albuminuria(11,12). Both hypertension and chronic hyperglycaemia of diabetes are associated with endothelial dysfunction which allows protein particularly albumin to be excreted in the glomerular capillaries, only small amount is excreted at first but this albuminuria is a sign of endothelial dysfunction and increased vascular permeability, this endothelial dysfunction is the earliest stage in the development of atherosclerosis, thus albuminuria is also a marker for early cardiovascular diseases in patients with diabetes(13). Lowering blood pressure with angiotensin converting enzyme inhibitors protected diabetic patients from deteriorating renal function; the degree of protection was much greater than what would be expected by reduction of blood pressure alone by using another medication this is suggesting that renin angiotensin system {RAS} plays an important role in diabetic nephropathy(14). Angiotensin II plays a key role in the development of hypertension and renal disease. Tissue derived angiotensin II appears to be involved in many disease process, including those leading to atherosclerosis, insulin resistance and glomerulosclerosis(15).

In this study it was noticed that urinary protein excretion significantly decreased after ACEI but did not changed significantly after Atenolol, according to those results, it can be hypothesized that inhibition of tissue angiotensin formation and its related changes on the glomerular permeability rather than renal and systemic haemodynamic features, seems to be the common mechanisms by which ACEI decrease albuminuria in those patients. The time course of antiproteinuric response is due to renal haemodynamic changes during ACEI which occur during the first hour after administration of ACEI where as reduction of proteinuria occur after (4)weeks of ACEI(16), ACEI restored glomerular size selectively at time of maximal antiproteinuric effect.

Angiotensin II, the major hormone of the renin-angiotensin system, and plays an important role in the pathogenesis of hypertension and atherosclerosis (17).

Several lines of evidence have suggested that angiotensin II impairs insulin sensitivity, causing insulin resistance and glucose intolerance(18), and this promotes the development of hypertension by upregulating the number and activity of angiotensin II receptors, resistance has been improved in response to treatment with angiotensin I converting enzyme inhibitors (ACEI) (17, 19). ACEI has been recommended as first lines of anti-hypertensive treatment in patients with diabetes, The degree of blood pressure reduction in the group-A- who use ACEI was quite significant, typically reducing both systolic and diastolic blood pressure by at least 10 mmHg.

It was noticed also that in group-A- who used ACEI there was reduction in the levels of blood glucose although was not significant, this reduction can be explained due to the inhibition of ACEI which can improve insulin sensitivity, so the inhibition of angiotensin enzyme is the important for reduction of blood pressure, blood glucose levels and proteinuria in diabetic patients, this is contrast to what has been noticed in the patients of group -B- who used Atenolol, there was no effect or increase in the levels of proteinuria and there was increase in the levels of blood glucose in some periods of treatment despite this increase was not significant, this might be due to the mechanism of action of Atenolol which acts directly on cardiac muscle causing decrease in myocardial contractility and that decrease in the cardiac out put cause decrease in the blood supply to the tissues of the body and increase need for oxygen and energy for metabolic processes which may end with disturbances of metabolism, this decrease in the cardiac out put causes decreasing in renal blood flow and this may cause increase in capillary pressure so it has no effect on permeability of the glomeruli or it may increase it and thus there is no change or increase in the level of proteinuria(20), in addition it has no effect on angiotensin converting enzyme(9), but it significantly reduced both systolic and diastolic blood pressure. In conclusion ACEI still more effective than  $\beta$ -adrenergic blocking agent in delaying and /or decrease the progression of nephropathy and Atenolol should be used in caution when needed to be used in such patients.

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