Short-term effects of irbesartan treatment on microalbuminuria in patients with normotensive type 2 diabetes

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ABSTRACT

الأهداف: مراقبة الآثار قصيرة الأمد للمعالجة بعقار إربيسارتان على البول الزلالي الصغير لدى مرضى السكري من النوع الثاني ذوي الضغط المستوي.

الطريقة: شملت الدراسة عدد (40 مريض) مصاب بالسكري من النوع الثاني ومن ذوي الضغط المستوي (متوسط العمر 11.4±55.1 عاما) والذين يعانون من وجود بول زلالي صغير. أجريت هذه الدراسة في مستشفى ايجي الجامعي – بورنوفا – ازمير – تركيا، خلال الفترة مابين يناير 2005م وحتى ابريل 2005م. تمت معالجة المرضى بعقار إربيسارتان بمقدار 300mg في اليوم لمدة ثلاثة أشهر. تم الحصول على الفحص البدني، التاريخ الطبي، مستويات ضغط الدم الانقباضي والانبساطي، البول الزلالي، مؤشرات السكري سكر الصيام وغير الصيام، والهيموجلوبين (HbA1c)، ملف الدهون، الكرياتين، واليوريا عند الخط القاعدي بعد ثلاثة أشهر من العلاج بعقار إربيسارتان. كان التقييم الأولي بناءً على تغير البول الزلال.

النتائج: بلغ مستوى البول الزلالي الصغير الفعلي عند الخط القاعدي (110.8±93.1mg) في الـ 24 ساعة. انخفض بشكل ملحوظ إلى (45.6±62.5mg) في الـ 24 ساعة عند نهاية فترة المعالجة بعقار إربيسارتان لمدة ثلاثة أشهر (p<0.001). عندما تم تطبيق ذلك على المرضى بناءً على تغير حالة البول الزلالي بعد العلاج، 90% منهم إما عادوا إلى البول الزلالي الطبيعي أو انخفض لديهم البول الزلالي الصغير. وُجد أن مستويات ضغط الدم الانقباضي والانبساطي، سكر الدم عند الصيام وغيره، مستوى الهيموجلوبين (HbAlc) جميعها منخفضة بشكل ملحوظ بعد ثلاثة أشهر من المعالجة بعقار إربيسارتان مقارنة مع القيم قبل العلاج. يظهر التأثير الإيجابي للمعالجة بعقار إربيسارتان على البول الزلالي الصغير باستقلالية من الهيموجلوبين وسكر الصيام وضغط الدم.

خاتمة: تعتبر آثار المعالجة بعقار إربيسارتان فعالة في تخفيض البول الزلالي الصغير لدى مرضى السكري من النوع الثاني ذوي ضغط الدم المستوي، ومستقلاً عن أثر مضادات ارتفاع ضغط الدم. نحتاج إلى المزيد من الدراسات الوصفية المتعددة المركز حول هذه الحالة.

Objective: To observe the short-term effects of irbesartan treatment on microalbuminuria in patients with normotensive type 2 diabetes.

Methods: A total of 40 normotensive type 2 diabetes patients (mean age 55.1±11.4 years) who had microalbuminuria were included in this non-comparative and prospective research study. The study took place in Ege University Hospital, Bornova-Izmir, Turkey, between January 2005 and April 2005. Patients were treated with irbesartan 300mg/day for 3 months. Physical examination, medical history, systolic and diastolic blood pressure levels, microalbuminuria, diabetes markers (fasting and non-fasting blood glucose, glycosylated hemoglobin [HbA1c]), lipid profile, creatinine and urea were obtained at baseline and after 3 months of irbesartan treatment. The primary assessment criterion was the change in microalbuminuria.

Results: The mean microalbuminuria level at baseline was 110.8±93.1mg/24 hours. It significantly decreased to 45.6±62.5mg/24 hours at the end of 3 months of irbesartan treatment (p<0.001). When patients were stratified according to the change in the microalbuminuria status after treatment, 90% of them either returned to normo albuminuria or their microalbuminuria decreased. Both diastolic and systolic blood pressures, fasting and non-fasting blood glucose, and HbA1c were found to be significantly decreased after 3 months of irbesartan treatment compared to pre-treatment values. The positive effect of irbesartan on microalbuminuria occurs independently from HbA1c, fasting blood glucose, and blood pressures.

Conclusion: The short-term treatment of irbesartan is effective to decrease microalbuminuria in normotensive type 2 diabetes patients, independent of its antihypertensive effect. There is a need for multicenter prospective studies to investigate this further.

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The incidence of end-stage renal disease, which decreases the life expectancy and quality of life of patients and increases management cost, has risen dramatically, primarily due to an increase in the incidence of diabetes recently. Type 2 diabetes mellitus causes microvascular complications, resulting in retinopathy, neuropathy, and nephropathy. Diabetic nephropathy is the leading cause of end-stage renal disease and develops in 40% of patients with type 2 diabetes.[1] Microalbuminuria is the earliest finding of diabetic nephropathy and eventual end stage renal disease. Some authors previously reported in different studies, that norm albuminuric type 2 diabetic patients have an important glomerular filtration rate (GFR) decrease,[2] which was verified by other authors.[3,4] This potentially reversible condition, which can be easily diagnosed, is associated with an increased risk for progression to diabetic nephropathy.[5] Therefore, it is important to define and treat microalbuminuria in diabetes before diabetic nephropathy and following end-stage renal disease develops. Studies showed that angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists reduced the risk and progression of diabetic nephropathy in patients with type 2 diabetes.[6-8] Three major studies - the reduction of endpoints in non-insulin dependent diabetes mellitus with the angiotensin II antagonist losartan (RENAAL) study,[9] the irbesartan microalbuminuria type 2 diabetes in hypertensive patients (IRMA II) study,[10] and the irbesartan in diabetic nephropathy trial (IDNT) - with 2-3 years duration[11] showed that selective angiotensin receptor blockage is effective in reducing the progression of renal disease in patients with type 2 diabetes and high blood pressure. Irbesartan is a potent and selective angiotensin II subtype 1 receptor antagonist, with an antihypertensive activity, which is comparable to, or superior to other antihypertensive agents with a placebo-like safety profile.[12] It also slows the progression of renal disease in hypertensive patients with type 2 diabetes at both the early and later stages of diabetic nephropathy.[13] Irbesartan has been shown to decrease albumin excretion and protect renal function in patients with type 2 diabetes and microalbuminuria independent of its blood pressure lowering effect.[14,15] Most of the studies on the effect of irbesartan on microalbuminuria in type 2 diabetes patients were reports of the results of long-term use of the drug in hypertensive patients. Therefore in the present study, we aimed to observe the short-term effects of irbesartan treatment on microalbuminuria in patients with normotensive type 2 diabetes.

Methods. This was a non-comparative and prospective research study from Ege University Hospital, Bornova-Izmir, Turkey. Patients with type 2 diabetes were included in the study, which commenced in January 2005 and ended in April 2005. Blood pressure of patients was normotensive and all patients had microalbuminuria. Exclusion criteria were hypertension (>systolic and diastolic blood pressure 140/90 mm Hg), macroalbuminuria (>300 mg/day), norm albuminuria (<30 mg/day), and previous antihypertensive therapy. Patients were treated with irbesartan 300 mg/day for 3 months. Physical examination, medical history, systolic and diastolic blood pressure levels, microalbuminuria, diabetes markers (fasting and non-fasting blood glucose, glycosylated hemoglobin [HbA1c]), lipid profile, creatinine, and urea were obtained at baseline and after 3 months of irbesartan treatment. The primary assessment criterion was defined as the change in microalbuminuria. Urine albumin level was measured using the automated Olympus AU2700 within 24 hours of sample collection. All patients gave signed informed consent, before enrollment to the study. The local Ethics Committee approved the study protocol.

Statistical analysis. The study data were summarized using descriptive statistics (mean, standard deviation, and percent). Baseline and third-month data were compared using paired student's t, or Wilcoxon test according to characteristics of data. *P*-values<0.05 were considered as statistically significant. Statistical Package for the Social Sciences (SPSS, Version 10.0, SPSS Inc., Chicago, Illinois, USA) was used for analysis. The relation between systolic and diastolic blood pressure, HbA1c, fasting blood sugar, and variance in the amount of microalbuminuria at baseline and at the third month were determined by Spearman's correlation test and multivariate analyses.

Results. A total of 40 normotensive type 2 diabetes patients (mean age 55.1±11.4 years, female/male ratio 13/27) who had microalbuminuria were included in the study. The mean duration of diabetes was 8.2±6.9 years. All study patients continued the irbesartan treatment for 3 months and were evaluated at the end of treatment. The mean level of microalbuminuria of patients at baseline was 110.8±93.1 mg/24 hours, and this significantly decreased to 45.6±62.5 mg/24 hours at the end of 3 months of irbesartan treatment period (p<0.001, Wilcoxon test) (**Figure 1**). When patients were stratified according to the change in the microalbuminuria status after treatment, 90% of them either returned to normo albuminuria, or their microalbuminuria decreased (**Figure 2**). The decrease in microalbuminuria in different sub-groups according to the change in the microalbuminuria status after treatment is given in **Table 1**. Among these sub-groups, duration of diabetes was shortest in the group

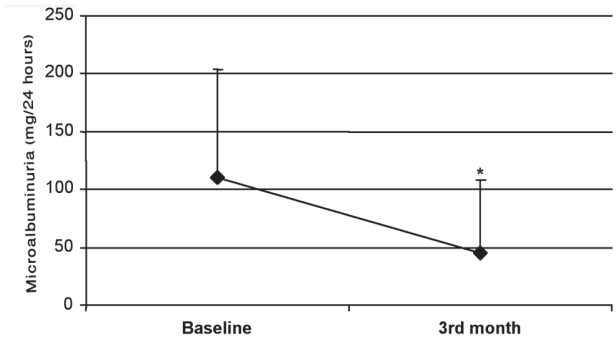

Figure 1 - The mean of microalbinuria levels (mg/24 hours) of patients at baseline and at the end of 3 months of irbesartan treatment period. Upright lines show standard deviation (p<0.001).

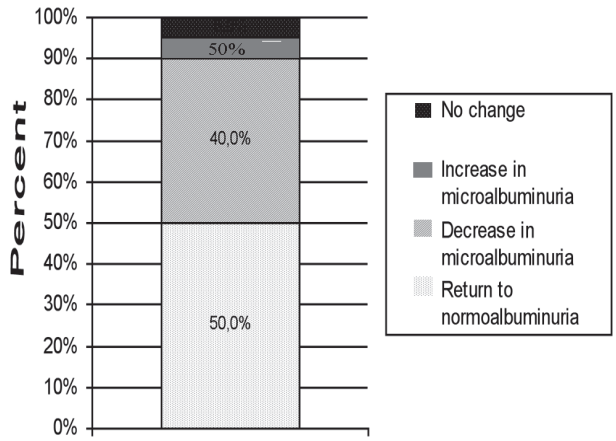

Figure 1 - Stratification of patients according to the change in the microalbuminuria status after treatment.

with no change in microalbuminuria after irbesartan treatment. The mean age of patients in these groups was similar (**Table 1**). The positive effect of irbesartan on microalbuminuria occurs independently from HbA1c, fasting blood glucose, systolic and diastolic blood pressures (**Table 2**). Both diastolic and systolic blood pressures, fasting and non-fasting blood glucose, and HbA1c significantly decreased after 3 months of irbesartan treatment compared to pre-treatment values (**Table 3**). Other laboratory findings did not significantly change during the 3 months of treatment (**Table 3**). Body weight of patients also did not change after treatment (82.4±11.3 kg and 82.0±11.7 kg, p=0.568, student's t test). Similarly, the body mass index of patients was not significantly different after 3 months of treatment compared to baseline (29.4±4.8 kg/m^2 and 29.2±4.9 kg/m^2), p=0.325, Wilcoxon test).

Discussion. We evaluated the short-term effects of irbesartan treatment on microalbuminuria in patients with normotensive type 2 diabetes in the present study. We found that 3 months of irbesartan treatment significantly decreased microalbuminuria, and in most patients, microalbuminuria decreased or returned to the normal level. The results indicate that the positive effect of irbesartan on microalbuminuria occurs independently from HbA1c, fasting blood glucose, systolic and diastolic blood pressures. It is currently known that angiotensin II receptor antagonism prevents the progression of renal disease in patients with type 2 diabetes.[16,17] This idea was first suggested by 3 major studies. In the first study,[9] (RENAAL), losartan was compared in a double-blind, randomized study with placebo, for a mean of 3.4

Table 1 - The amount of decreases in microalbuminuria, duration of diabetes and age in different sub-groups according to the change in the microalbuminuria status after irbesartan treatment.

Changes on microalbuminuria of type 2 diabetic patients	Amount of decrease in microalbuminuria (mg/24 hours)	Duration of diabetes (years)	Age (years)
Return to normoalbuminuria (n = 20)	83.0 ± 95.8	6.9 ± 6.2	55.8 ± 11.5
Decrease in microalbuminuria (n = 16)	76.3 ± 68.4	10.3 ± 7.4	54.3 ± 12.1
Increase in microalbuminuria (n = 2)	-135.0 ± 120.2	9.5 ± 10.6	54.5 ± 13.4
No change (n = 2)	0.0 ± 0.0	3 .0 ± 2.8	54.0 ± 12.7
Total (n = 40)	**65.2 ± 95.5**	**8.2 ± 6.9**	**55.1 ± 11.4**

The data were given as mean±standard deviation

Table 2 - The relations between systolic and diastolic blood pressure, HbA1c, fasting blood glucose, and variance in the amount of microalbuminuria at baseline and at the third month were determined by Spearman's correlation test.

Parameters	n	Spearman's correlation	*P*-value
Baseline			
Systolic blood pressure (mm Hg)	40	0.305	0.055
Diastolic blood pressure (mm Hg)	40	0.309	0.052
HbA1c (%)	40	0.087	0.594
Fasting plasma glucose (mg/dl)	40	0.034	0.834
Third month			
Systolic blood pressure (mm Hg)	40	0.166	0.305
Diastolic blood pressure (mm Hg)	40	-0.038	0.817
HbA1c (%)	40	-0.177	0.274
Fasting plasma glucose (mg/dl)	40	-0.242	0.133

HbA1c - glycosylated hemoglobin

Table 3 - The blood pressure, diabetes markers and other laboratory findings before and after 3 months of irbesartan treatment.

Laboratory findings/durations	Baseline	Third month	P-value
Blood pressure			
Diastolic blood pressure (mm Hg)	80.3 ± 8.3	75.7 ± 8.0	0.009*
Systolic blood pressure (mm Hg)	129.0 ± 12.1	119.2 ± 12.6	<0.001*
Diabetes markers			
HbA1c (%)	7.1 ± 1.3	6.3 ± 0.9	<0.001*
Blood glucose (mg/dL)	202.1 ± 58.1	165.9 ± 57.4	<0.001*
Fasting blood glucose (mg/dL)	145.1 ± 26.5	125.5 ± 30.6	<0.001*
Other findings			
Total cholesterol (mg/dL)	199.6 ± 41.1	189.9 ± 42.5	0.057†
LDL-cholesterol (mg/dL)	122.4 ± 32.6	115.1 ± 30.7	0.089†
HDL-cholesterol (mg/dL)	46.4 ± 8.0	47.7 ± 8.9	0.482*
Triglyceride (mg/dL)	203.3 ± 171.6	171.9 ± 120.7	0.147*
Creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.2	0.451*
Urea (mmol/L)	39.1 ± 15.2	41.3 ± 16.0	0.277*

*Wilcoxon test, †Student's t test, HbA1c - glycosylated hemoglobin

years. During the study period, losartan significantly prevented the rise of serum creatinine levels and end-stage renal disease and microalbuminuria declined by 35%. In the second study,[10] (IRMA-II), which was a large placebo-controlled randomized clinical trial on 590 type 2 diabetes and hypertension patients, irbesartan was associated with a dose-dependent decrease in microalbuminuria although blood pressures were only minimally affected.[10] In the third study (IDNT), Lewis et al[11] compared irbesartan with amlodipine and placebo, in a randomized design over 2.6 years and obtained similar results regarding the incidences of doubling of creatinine levels and end-stage renal disease. In the studies regarding the effects of angiotensin receptor antagonists on renal status of patients with type 2 diabetes and hypertension, the benefits of treatment exceeded those that could be attributed to changes in blood pressure.[18-20] Irbesartan, like other angiotensin II receptor blockers, was demonstrated to prevent or decrease microalbuminuria and delay progression of microalbuminuria in hypertensive type 2 diabetes patients, independent of its effect on blood pressure.[15,21,22] When compared to standard antihypertensive therapy, irbesartan reduced the incidence of end-stage renal disease, extended duration of life, and reduced costs.[23,24] The effect of irbesartan on patients with albuminuria was also shown in primary care settings.[25] Therefore, it was recommended to start irbesartan treatment early, concurrent with microalbuminuria and continue on a long-term basis to improve life expectancy and reduce costs in hypertensive patients with type 2 diabetes and renal disease.[26]

In a randomized double-blind placebo-controlled crossover study, Sasso et al[14] studied micro albuminuric hypertensive and normotensive patients receiving irbesartan or placebo for 2 months. They showed that irbesartan significantly decreased albumin excretion rate (AER) both in hypertensive and normotensive patients, indicating the beneficial effects of irbesartan on AER in type 2 diabetic subjects, independent of its antihypertensive effects.[14] Similar to the result of this study, which evaluated the short-term effect of irbesartan in normotensive patients with type 2 diabetes, the mean microalbuminuria level was significantly decreased in our study after 3 months of irbesartan treatment. Since our patients were all normotensive, the effect of irbesartan on microalbuminuria was thought to be independent of its antihypertensive effect. Although the systolic and diastolic blood pressure of the patients decreased significantly with irbesartan treatment, they did not drop under normal limits. During the 3-month treatment period, the blood glucose, and HbA1c levels of patients were also significantly decreased in parallel with previous studies.[25]

The main limitations of our study are lack of a control group and not controlling for the sodium intake of patients, as the latter may also affect the renin-angiotensin system.

As a conclusion, this study demonstrated that short-term treatment of irbesartan may effectively decrease microalbuminuria in normotensive type 2 diabetes patients and this effect may be independent of its action on hypertension. There is a need for multicenter prospective studies to investigate this further.

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