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ORIGINAL RESEARCH

Action of irbesartan on blood pressure and glucose/lipid metabolism, in hemodialysis patients with hypertension

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Background: Irbesartan has been reported to have beneficial effects on glucose/lipid metabolism in addition to an antihypertensive effect; however, such effects have not been clarified in hemodialysis (HD) patients. We investigated the effects of irbesartan on blood pressure (BP) as well as glucose/lipid metabolism, in HD patients with hypertension.

Methods: Seventeen HD patients with hypertension, aged 62.7 ± 12.5 years, were treated with daily oral administration of 50 to 100 mg of irbesartan for 12 weeks. Then, the changes of BP as well as glucose metabolism (random serum glucose level and serum glycosylated hemoglobin [HbA_{1c}] level) and lipid metabolism (serum low-density lipoprotein cholesterol [LDL-chol] level, serum high-density lipoprotein cholesterol [HDL-chol] level, and serum triglyceride [TG] level) were evaluated.

Results: Irbesartan significantly reduced systolic BP (154.9 ± 12.8 to 139.4 ± 13.1 mmHg ($P < 0.01$) and diastolic BP (78.9 ± 9.1 to 72.2 ± 9.7 mmHg, $P < 0.01$). It also reduced LDL-chol (77.6 ± 19.1 to 72.0 ± 18.6 mg/dL, $P < 0.05$), whereas it did not significantly affect random serum glucose (129.3 ± 46.9 mg/dL to 130.6 ± 47.2 mg/dL), HbA_{1c} (5.58% ± 1.41% to 5.49% ± 1.11%), TG (104.3 ± 65.8 mg/dL to 100.2 ± 59.9 mg/dL), or HDL-chol (44.8 ± 17.1 mg/dL to 45.7 ± 15.6 mg/dL).

Conclusion: Irbesartan is effective for BP control and may have beneficial effects on lipid metabolism in HD patients.

Keywords: irbesartan, hemodialysis patients, blood pressure, glucose/lipid metabolism

Introduction

Hypertension is a major risk factor for the development of cardiovascular events and increases mortality in patients with end-stage renal disease undergoing hemodialysis (HD).[1,2] Activation of the renin-angiotensin-aldosterone system (RAAS) plays a pivotal roles in the pathogenesis of hypertension in HD patients,[3–5] although volume overload is considered the most critical factor.[5–8] Repeated clinical trials reported that RAAS blockers, such as angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), can reduce blood pressure (BP), cardiovascular events, and mortality in HD patients.[4,5,9] These lines of evidence suggest that RAAS blockers would have beneficial effects in the treatment of hypertension in HD patients.[4,5,9] Therefore, they are recognized as first-line drugs for the treatment of hypertensive HD patients.[4,10,11]

Glucose and lipid abnormalities have also been shown to increase the risk factors of arteriosclerosis, leading to the development of cardiovascular events in HD patients.[6,7,12,13] A previous clinical study reported that high serum non-high-density

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lipoprotein cholesterol non-(HDL-chol) level and serum low-density lipoprotein cholesterol (LDL-chol) level were associated with an increased risk of cardiovascular disease in HD patients.[7] Hyperlipidemia leads to the accumulation and deposition of lipid in blood vessels and can act to trigger inflammation by stimulating the infiltration of macrophages, which in turn, secrete proinflammatory cytokines.[14] Other clinical studies suggested that poor glycemic control was also associated with an increased risk of cardiovascular disease and high mortality in HD patients.[15,16] Hyperglycemia has been reported to induce atherosclerosis through multiple mechanisms, for example, by producing advanced glycation end products, by increasing oxidative stress, and by activating protein kinase C.[17] Therefore, appropriate control of glucose and lipid metabolism should be important to improve the survival of HD patients.

Irbesartan, an ARB, has been reported to reduce BP and cardiovascular events in hypertensive patients by blocking the effects of angiotensin II, which induces vasoconstriction and the secretion of aldosterone. Furthermore, it has also been reported to have beneficial effects on glucose/lipid metabolism, by acting as an agonist of peroxisome proliferator-activated receptor (PPAR)-γ, in hypertensive patients with metabolic syndrome.[18] A clinical study showed that the administration of irbesartan at 150 or 300 mg/day decreased fasting serum glucose, glycosylated hemoglobin (HbA_{1c}), LDL-chol and triglyceride (TG) and increased HDL-chol in hypertensive patients.[19] However, the effects of irbesartan on glucose/lipid metabolism have not been elucidated in HD patients. Therefore, in this study, we investigated the effects of irbesartan on glucose/lipid metabolism, along with its antihypertensive effects, in hypertensive HD patients.

Materials and methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Jichi Medical University. Written, informed consent was obtained from all patients.

Patients

Seventeen HD patients with hypertension were enrolled in this study between February 2012 and May 2012. Patients were included if they were classified as hypertensive HD and were not being treated with ARBs. Patients were classified as hypertensive when the clinic BP was ≥140 mmHg systolic and ≥90 mmHg diastolic before an HD session on the last HD day of the week. The upper limits of BP were not set. Whether or not the patients had abnormal glucose/lipid metabolism was not considered for recruitment. The exclusion criteria were: patients who had already received ARB treatment; hyperkalemia (>5.5 mEq/mL) before the HD session; type 1 or type 2 diabetes mellitus with poor glucose control (serum HbA_{1c} level >9%); coronary heart disease; severe arrhythmia; cerebrovascular disease or any medical condition that may have affected the pharmacokinetics of the study drug; and pregnancy.

Study protocol

This was a 16-week, multicenter study consisting of a 4-week observation period, followed by a 12-week irbesartan treatment period (Figure 1). In the observation period, patients' dry weight and the doses of any drugs, including antihypertensives and medications taken for glucose and lipid metabolism, were not changed. Then, all enrolled patients entered the treatment period, during which they received irbesartan at 50 mg orally once daily in the morning, in addition to the drugs that they had been taking in the observation period. BP was measured before all HD sessions. If the BP had not decreased to less than 140/90 mmHg by 4 weeks after the administration of 50 mg of irbesartan, the treatment dose was increased to 100 mg/day, with careful attention to BP decrease during the HD (by ultrafiltration) sessions. If the BP did not decrease to less than 140/90 mmHg with the administration of 100 mg of irbesartan, the addition of another class of antihypertensive agent that the patient had not previously been taking would be considered. Blood samples were obtained from an arteriovenous shunt at the start of the first HD session in a week, at the same time of day for each patient. The plasma renin activity, plasma aldosterone concentration, random serum glucose level, serum HbA_{1c} level, serum total cholesterol level, serum TG level, serum HDL-chol level, and serum LDL-chol level were measured at baseline (week 0) and at week 12 in the treatment period, before the HD sessions. The standard laboratory tests were performed in the observation period and at baseline, week 4, and week 12 in the treatment period. All the blood parameters were measured by a commercial laboratory (SRL, Inc, Tokyo, Japan).

Statistical analysis

All data were expressed as the mean ± standard deviation (SD). Comparisons of BP at weeks 0, 4, 8, and 12 were performed by one-way repeated measures analysis of variance (ANOVA). Comparisons of blood parameters were performed by paired *t*-test. Differences with a *P*-value <0.05 were considered to be statistically significant.

Results

Seventeen HD patients were enrolled in the treatment period after the 4-week observation period. All patients had oliguria or anuria. Among them, one patient dropped out of the study owing to symptomatic hypotension. This patient was a 70-year-old male who had been on HD for 6 years and 8 months. His initial nephropathy was chronic glomerulonephritis. He had not been taking other antihypertensives. His BP prior to the HD session decreased from 148/65 mmHg at baseline to 99/48 mmHg at 8 weeks after the start of irbesartan treatment. His symptomatic hypotension recovered to the basal level soon after the withdrawal of irbesartan. The remaining 16 patients completed the study and were analyzed (Figure 1). Table 1 shows the characteristics of these patients. For one of these 16 patients, the dose of irbesartan was increased from 50 mg/day to 100 mg/day at week 4 because his BP before the HD session had not decreased to less than 140/90 mmHg. Further antihypertensives of other classes were not added in any patients in the treatment period. Table 2 shows the clinical characteristics of the study patients before and after irbesartan treatment, including the changes of BP and the dosage of antihypertensives and the drugs for glucose/lipid control. Antihypertensives that had been taken by the study patients before the treatment period included calcium antagonists (eleven patients), ACEIs (two patients), direct renin inhibitor (one patient), α-blockers (four patients), and an αβ-blocker (one patient). Two patients had been taking statins (pravastatin 10 mg/day and atorvastatin 10 mg/day, respectively). Six patients had been diagnosed with diabetes mellitus and of these, two patients were treated with insulin and an α-glucosidase inhibitor, one patient was treated with an α-glucosidase inhibitor. Three patients were not treated with any drugs.

Table 1 Patients' baseline characteristics

Number	16
Age (years)	62.3 ± 12.7
Gender	
Male	15
Female	1
Body mass index (kg/m^2)	21.1 ± 2.3
Duration of hemodialysis (years)	7.6 ± 8.1
Initial nephropathy	
Chronic glomerulonephritis	5
Diabetic nephropathy	6
Nephrosclerosis	1
Polycystic kidney disease	1
Gouty kidney	1
Unknown	2
Systolic BP (mmHg)	154.9 ± 12.8
Diastolic BP (mmHg)	78.9 ± 9.1
PRA (ng/mL/hr)	1.92 ± 2.44
PAC (pg/mL)	388.7 ± 1045.9
LDL-chol (mg/dL)	77.6 ± 19.1
HDL-chol (mg/dL)	44.8 ± 17.1
TG (mg/dL)	104.3 ± 65.8
Random glucose (mg/dL)	129.3 ± 46.9
HbA_{1c} (%)	5.58 ± 1.41

Abbreviations: BP, blood pressure; HbA_{1c}, glycosylated hemoglobin; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; PRA, plasma renin activity; PAC, plasma aldosterone concentration; TG, triglyceride.

The effect of irbesartan on BP

Systolic BP significantly decreased from 154.9 ± 12.8 mmHg at baseline to 139.4 ± 13.1 mmHg at week 12 ($P < 0.05$) (Figure 2). Diastolic BP also significantly decreased from 78.9 ± 9.1 at baseline to 72.2 ± 9.7 mmHg at week 12 ($P < 0.05$) (Figure 2).

Effects of irbesartan on RAAS

As shown in Figure 3, plasma renin activity increased from 1.92 ± 2.44 ng/mL/hour at baseline to 3.19 ± 3.66 ng/mL/hour at week 12 ($P < 0.05$). The plasma aldosterone concentration levels were not significantly altered (388.7 ± 1045.9 pg/mL at baseline to 196.6 ± 488.51 pg/mL at week 12).

Effects of irbesartan on glucose/lipid metabolism

LDL-chol was significantly decreased (77.6 ± 19.1 mg/dL at baseline vs 72.0 ± 18.6 mg/dL at week 12) ($P < 0.05$) (Figure 4). HDL-chol and TG were not significantly different: the HDL-chol was 44.8 ± 17.1 mg/dL at baseline vs 45.7 ± 15.6 mg/dL at week 12, whereas the TG level was 104.3 ± 65.8 mg/dL at baseline vs 100.2 ± 59.9 mg/dL at week 12 (Figure 4). The random serum glucose and HbA_{1c} were also not significantly different: the random serum glucose was 129.3 ± 46.9 mg/dL at baseline vs 130.6 ± 47.2 mg/dL at week 12, whereas the HbA_{1c} was 5.8% ± 1.41% at baseline vs 5.49% ± 1.11% at week 12 (Figure 4).

Discussion

The results in the present study show that irbesartan significantly decreased systolic and diastolic BP in hypertensive HD patients. It also significantly decreased LDL-chol, whereas it did not affect HDL-chol, TG, random serum glucose, or HbA_{1c} level. Regarding the RAAS components, plasma renin activity was significantly increased with the administration of irbesartan, suggesting negative feedback after blocking of the angiotensin II receptor.[20]

Table 2 Patients' clinical characteristics before and after irbesartan treatment

No	Gender	Age (years)	Duration of HD (years)	Initial nephropathy	Antihypertensives (/day)	Irbesartan dose (/day)	Drugs for glucose and lipid control (/day)	BMI (kg/m^2)	Systolic BP (mmHg)		Diastolic BP (mmHg)	
									Baseline	Week 12	Baseline	Week 12
1	Male	65.1	1.8	Diabetic nephropathy	None	50 mg	Insulin Acarbose 150 mg	19.4	140	142	90	72
2	Male	70.7	0.7	Polycystic kidney disease	Cilnidipine 20 mg	50 mg	None	19.7	150	145	80	76
3	Male	72.0	1.7	Diabetic nephropathy	Amlodipine 10 mg	50 mg	None	23.5	148	136	80	70
4	Male	79.6	1.2	Nephrosclerosis	Nifedipine 40 mg Doxazosin 2 mg Imidapril 10 mg	50 mg	None		149	123	61	59
5	Male	66.8	5.8	Diabetic nephropathy	Nifedipine 40 mg	50 mg	Insulin Acarbose 150 mg Atorvastatin 10 mg	25.4	146	138	80	74
6	Male	54.0	20.3	Unknown	Amlodipine 2.5 mg Enalapril 2.5 mg	50 mg	None	23.7	152	140	76	80
7	Male	27.4	1.9	Unknown	Nifedipine 40 mg Doxazosin 4 mg	50 mg	None	18.6	156	146	76	71
8	Male	70.8	11.7	Chronic glomerulonephritis	None	50 mg→100 mg	None	21.2	148	140	79	70
9	Male	79.9	13.6	Chronic glomerulonephritis	None	50 mg	None	20.6	151	139	75	69
10	Male	63.0	30.2	Chronic glomerulonephritis	None	50 mg	None	23.6	161	125	82	71
11	Male	52.7	14.3	Chronic glomerulonephritis	Amlodipine 10 mg Doxazosin 1 mg	50 mg	None	18.0	150	136	92	86
12	Female	54.0	12.0	Diabetic nephropathy	Benidipine 8 mg Doxazosin 4 mg	50 mg	None	19.9	150	120	60	50
13	Male	48.0	6.0	Gouty kidney	Aliskiren 150 mg	50 mg	None	20.9	170	135	83	64
14	Male	63.0	0.1	Chronic glomerulonephritis	Benidipine 8 mg	50 mg	None	22.1	182	160	73	80
15	Male	61.0	0.2	Diabetic nephropathy	Carvedilol 2.5 mg	50 mg	Pravastatin 10 mg	18.3	143	134	85	73
16	Male	60.1	4.3	Diabetic nephropathy	Benidipine 4 mg	50 mg	Voglibose 0.9 mg	23.7	183	173	91	90

Abbreviations: BMI, body mass index; BP, blood pressure; HD, hemodialysis.

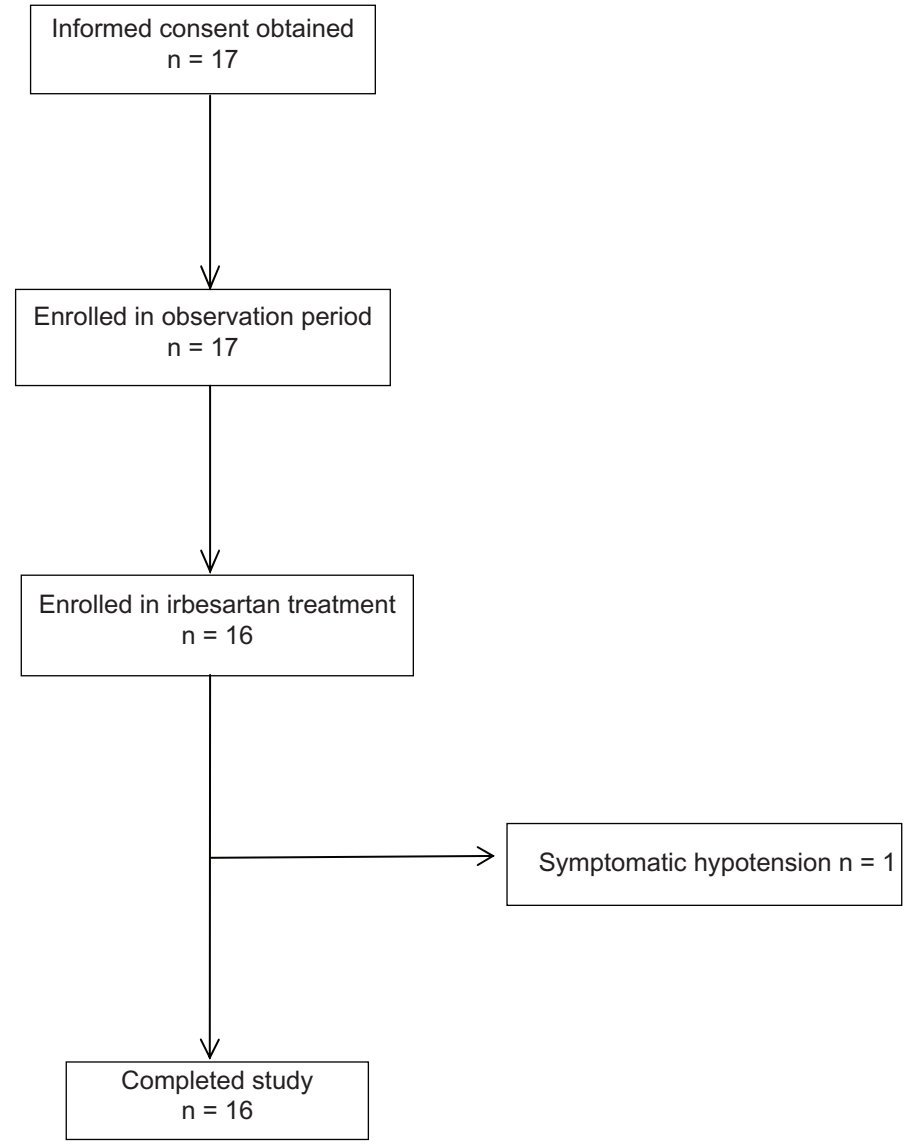

Figure 1 Patient flow chart.

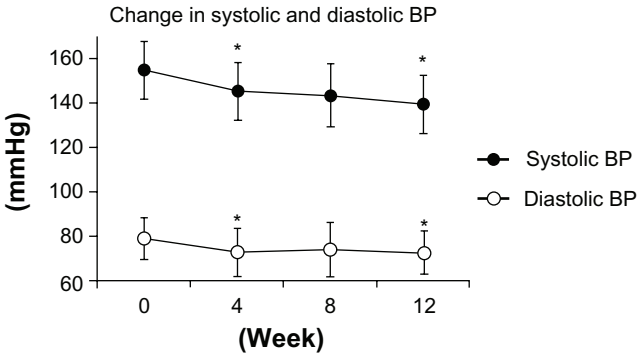

Figure 2 Changes of systolic blood pressure (BP) and diastolic BP from baseline (week 0) to week 12.
Note: *$P < 0.05$.

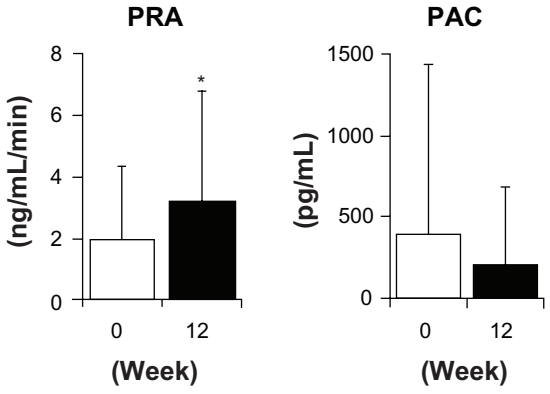

Figure 3 Changes of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) from baseline (week 0) to week 12.
Note: *$P < 0.05$.

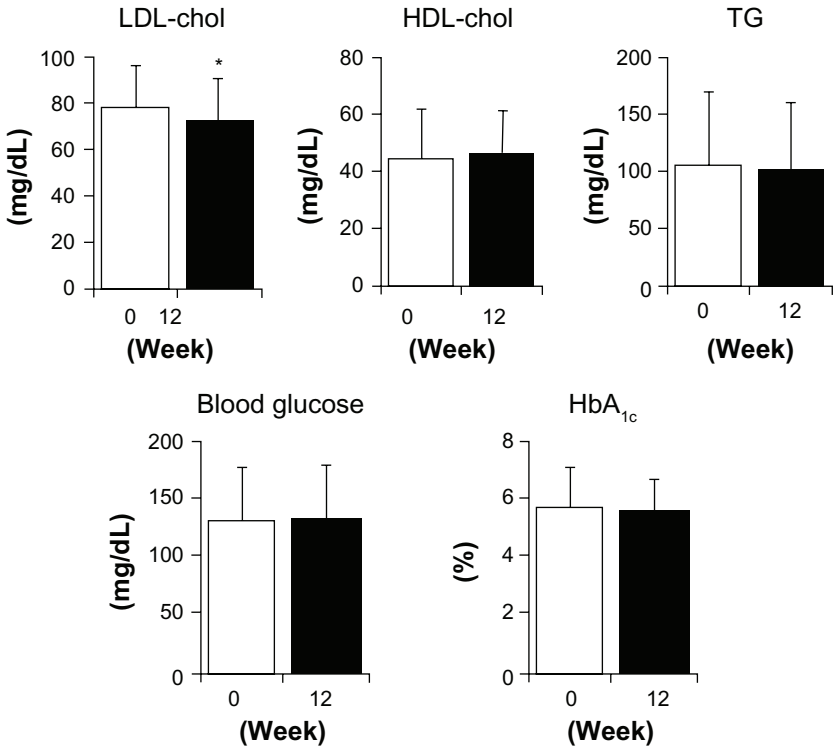

Figure 4 Changes of serum low-density lipoprotein cholesterol (LDL-chol) level, serum high-density lipoprotein cholesterol (HDL-chol) level, serum triglyceride (TG) level, random serum glucose, and serum glycosylated hemoglobin (HbA_{1c}) level from baseline (week 0) to week 12.
Note: *$P < 0.05$.

Cardiovascular disease is a major factor that contributes to the morbidity and mortality of HD patients.[21] Since hypertension is a representative risk factor for the development of cardiovascular disease and has a high prevalence in HD patients, the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines indicate that patients' BP before an HD session should be less than 140/90 mmHg.[11] In the present study, irbesartan significantly decreased systolic BP and diastolic BP in hypertensive HD patients. These results suggest that irbesartan is effective in controlling BP in HD patients.

Along with hypertension, abnormalities of glucose/lipid metabolism have been reported to be risk factors for arteriosclerosis and cardiovascular diseases in HD patients. Repeated clinical studies have shown that poor glycemic control was associated with an increased risk of cardiovascular disease and mortality in HD patients.[13,15,16] In terms of the lipid metabolism in HD patients, a clinical study reported that abnormal lipid metabolism, such as high non-HDL-chol or LDL-chol level, was associated with an increased risk of cardiovascular disease in HD patients.[7] On the other hand, another clinical study demonstrated that cholesterol-lowering therapy provided by atorvastatin did not decrease cardiovascular events or mortality in HD patients with type 2 diabetes mellitus.[22] As such, further studies to investigate lipid metabolism in relation to cardiovascular disease and mortality in HD patients are clearly needed. However, the very abnormal lipid metabolism was generally considered to have been corrected, the K/DOQI clinical practice guidelines recommend that non-HDL-chol should be less than 130 mg/dL in HD patients.[11] In the present study, irbesartan significantly decreased LDL-chol in hypertensive HD patients (Figure 3). These results suggest that irbesartan would also have beneficial effects in the control of lipid metabolism in hypertensive HD patients. Random serum glucose, HbA_{1c}, TG, and HDL-chol were not significantly decreased by irbesartan. The small number of subjects and the short study period might explain why the changes in these parameters of glucose/lipid metabolism were not significantly altered by irbesartan.

In the present study, irbesartan treatment was discontinued in one patient owing to a finding of hypotension after an HD session. This hypotension recovered to the basal level soon after the withdrawal of irbesartan. No other side effects of irbesartan, including hyperkalemia, were detected in any patients throughout the follow-up period.

There are significant limitations to the present study. First, it was a single-arm trial without a control group.

Second, the sample size was small, and the treatment period was short. Third, whether the improvement of lipid metabolism by irbesartan was independent of the BP lowering or not was not clear owing to the lack of control groups treated with other classes of antihypertensives. In addition, we cannot rule out the influence of cointerventions, such as the change of patients' water and nutrition intake and lifestyle behavior, and of factors like the Hawthorne effect.[23] Further large-scale, double-blind and long-term clinical trials are needed to confirm the efficacy of irbesartan in HD patients.

In conclusion, irbesartan significantly decreased BP and LDL-chol levels in hypertensive HD patients. These results suggest that it would be effective for BP control as well as for lipid metabolism control in hypertensive HD patients.

Disclosure

The authors report no conflicts of interest in this work.

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