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Abstract: The aim of this study was to determine whether isradipine affects microalbuminuria and other biochemical parameters related to glucose and lipid metabolisms. 18 subjects, 40 to 73 years of age, with NIDDM for 0 to 21 years, blood pressure≤140/90 mmHg in the absence of antihypertensive treatment, and persistent urinary albumin excretion rate (UAER) 30 to 300 mg/day, received sustained-release (SRO) formulation isradipine at dosages of 5 mg once daily for 3 months. The effects of isradipine on microalbuminuria, fasting plasma glucose, plasma lipids, plasma creatinin, uric acid, C-peptide, insulin, HbA_{1c}, fructosamine, systolic and diastolic blood pressure and heart rate were assayed. After 3 months of isradipine treatment, UAER fell from 72.5±40.2 to 52.9±39.5 mg/24 h ($p<0.01$). Diastolic blood pressure decreased from 85.8±4.9 to 81.9±3.0 mmHg ($p<0.05$). Other parameters were not significantly influenced by isradipine treatment. After 3 months of therapy, isradipine regressed diabetic nephropathy in normotensive NIDDM patients. No serious clinical or metabolic side effects were observed.

Key Words: İsradipine, microalbuminuria, diabetic nephropathy, antihypertensive treatment.

Introduction

Nephropathy is a major complication in insulin-dependent diabetes mellitus (IDDM) (1). In IDDM, the presence of microalbuminuria reliably predicts the development of diabetic nephropathy, and clinical nephropathy is associated with a higher mortality rate (2-5). Although only a few studies have addressed this topic in NIDDM, the prevalence of microalbuminuria seems to be at least as high as in IDDM and predicts the development of more severe proteinuria and early death (6-11). Furthermore, a relationship between microalbuminuria and cardiovascular diseases has been reported in both nondiabetic and diabetic patients, and it has been considered to be the most reliable predictor of early mortality (12-15).

Many studies have indicated that ACE-inhibitors decrease microalbuminuria and retard the progression of renal disease in both hypertensive and normotensive diabetic patients (16-23). But these results are controversial with regard to calcium antagonists (16, 19, 24), and to our knowledge, no data are available about the effect of isradipine, a new antihypertensive dihydropyridine calcium antagonist, on microalbuminuria in normotensive NIDDM patients. Therefore, we investigated whether isradipine decreases microalbuminuria.

Materials and Methods

The study population consisted of 18 normotensive patients (BP ≤ 140/90 mmHg) with NIDDM, all of whom had a UAER 30-300 mg/24 h. The subjects were in good general health, were physically active, had no other significant disease, were not pregnant were taking no drugs known to affect blood pressure, carbohydrate or lipid metabolism. The baseline characteristics of these individuals are shown in Table 1. All subjects had been followed up for treatment of their diabetes in the Endocrinology polyclinic of the Research Hospital of Harran University.

Weight and height were measured with the patients wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Blood pressure (BP)

was measured in both supine and upright positions with a mercury sphygmomanometer after 10 min rest by one observer. Two BP measurements wereade (interval 1.5 min), and the mean calculated. A subject was excluded if systolic blood pressure (sBP) was > 140 mmHg, diastolic blood pressure (dBP) was > 90 mmHg, or if the subject was receiving drug treatment for hypertension. Smoking was defined as whether the subject was a current smoker.

Blood samples were taken between 08:00 and 09:30 after a 12-h fast. Plasma glucose, fructosamine, cholesterol, triglyceride and serum high-density lipoprotein (HDL) cholesterol concentrations were assayed by an autoanalyzer (Hitachi 911) using commercial kits. Serum low-density lipoprotein (LDL) cholesterol concentration was calculated with the Friedwald equation in patients with triglyceridemia < 400 mg/dl (25). Plasma insulin level was determined from samples stored at -20˚C by radioimmunoassay (RIA) (DPC, Los Angeles, USA). Plasma C-peptide level was determined by luminoimmunoassay (LIA) (Immulyte hormone analyzer). HbA_{1c} level was determined with the microcolumn method (Biosystems, Barcelona, Spain) and quantitative colorimetric determination (Stanbio, San Antonio, Texas).

Urinary albumin concentration was determined as the mean of two 24-h urine samples collected at home during normal activity in monthly separate determinations. Urinary albumin was measured from samples stored at -20˚C by a commercial immunoturbidimetry assay (Orion, Espoo, Finland). Sediment in fresh urine was assayed in each sample and was normal in all cases.

Data analyses were performed with the SPSS *f*or Windows 5.1 program. The results were expressed as means±SD. The differences between before and after treatment concerning the continuous variables were

Table 1. Baseline characteristics of the study population

Variable		Range
n	18	
Sex (M/F)	11/7	
Age (years)	52±11	40-73
BMI (kg/m^2)	27.2±4.3	19.8-35.5
Diabetes duration (years)	5±7	0*-21
sBP (mmHg)	127±12	110±140
dBP (mmHg)	86±5	80-90
Smokers *n* (%)	7 (39)	

Data are means±SD. *Diabetes duration <6 monnths

Table 2. Biochemical and clinical parameters

Variable	Before treatment	After treatment	p value
UAE (mg/24h)	72.5±40.2	52.9±39.5	<0.01
FPG (mg/dl)	174.7±75.8	177.1±44.6	NS
Urea (mg/dl)	35.3±10.4	35.8±8.3	NS
Creatinin (mg/dl)	0.85±0.15	0.9±0.13	NS
Uric acid (mg/dl)	4.4±1.2	4.5±1.0	NS
Total Cholesterol (mg/dl)	236.3±33.3	232.2±31.8	NS
HDL cholesterol (mg/dl)	44.1±6.5	42.6±7.5	NS
LDL cholesterol (mg/dl)	145.3±31.0	147.5±29.8	NS
Total triglyceride (mg/dl)	224.7±98.4	218±130.3	NS
Fructosamine (mmol/L)	3.8±0.6	3.7±0.6	NS
HbA1 (%)	8.7±1.2	8.5±1.4	NS
C-peptide (ng/ml)	2.9±1.5	2.6±2.1	NS
Insulin (μU/ml)	9.8±5.8	10.2±7.1	NS
sBP (mmHg)	127±12	125±10	NS
dBP (mmHg)	86±5	82±3	<0.05
Heart rate (b/min)	89±11	93±13	NS

Data are means±SD. NS means Not Significant (statistically)

Table 3. Spearman correlation coefficients of UAER

Parameters	*n*	*r*	*P* value
HbA1	18	0.57	0.01
Fructosamine	18	0.45	0.05
Total Cholesterol	18	0.45	0.05

n= number of subjects, *r*= Sperman correlation coefficient

analyzed using the Wilcoxon test. Correlations between variables were tested with the Sperman correlation coefficient. *P* values < 0.05 were considered to be statistically significant, but *P* values <0.10 are also shown.

Results

There were 18 patients in this study. The base line characteristics of the patients are shown in Table 1. When the 18 patients were grouped according to BMI, 1 patient was lean (<20 kg/m^2), 5 were normal (20-24.9kg/m^2), 8 were overweight (25-30kg/m^2), 4 were obese (>30kg/m^2). 3 patients were only put on diets, 11 had oral hypoglycemic treatment, and 4 had insulin treatment. After 3 months of isradipin treatment, UAER decreased from 72.5±40.2 to 52.9±39.5 mg/24 h($p<0.01$), diastolic blood pressure (as the mean of readings in the supine and upright positions) fell from 85.8±4.9 to 81.9±3.0 mmHg ($p<0.05$). Other parameters did not significantly change after the treatment (Table 2).

UAER obtained before the treatment showed a significant positive correlation with HbA_{1c}, and a weak positive correlation with total cholesterol, and fructosamine levels (Table 3). The calcium antagonist, isradipine, was well tolerated. Only 3 patients reported mild, transient headaches during treatment. Orthostatic hypotension was not observed before, during or after the treatment.

Discussion

Our study was designed to evaluate the effects of isradipine on some clinical and metabolic parameters (especially on UAER). Despite isradipine being an antihypertensive drug, it was used in normotensive NIDDM subjects because the onset of microalbuminuria or the elevation of BP (above 120-140/80 mmHg) are predictive of a poor evolution and require appropriate preventive therapeutic interventions, which include an optimal control of hyperglycemia, dietary proteins and salt restriction, and prescription of antihypertensive drugs, with a particular benefit ascribed to angiotensin converting enzyme (ACE) inhibitors (and possibly certain calcium channel blockers) (16). Several studies have demonstrated that antihypertensives prevent the progression of nephropathy and also regress the nephropathy in both IDDM and NIDDM patients (17-23, 26, 27).

Microalbuminuria is defined as urinary excretion of albumin persistently above normal, but below the sensitivity of conventional semiquantative test strips (28, 29). We conducted this study on patients with UAE of 30-300 mg/24 h as most researchers have (30-33).

There is still controversy as to whether increased UAER in patients with NIDDM has similar pathognomonic relevance as in IDDM and whether antihypertensive treatment may beneficially influence increased UAE in patients with NIDDM to the same extent as in patients with IDDM (34). Many studies have suggested that ACE inhibitors may be effective in preventing the onset of nephropathy and its treatment in hypertensive and normotensive diabetic patients (18, 20, 23, 35). However, few studies have assessed the effects of other antihypertensives on UAER in diabetic patients, and the results are controversial (36-44). Some researchers have reported that nifedipine increased UAER in normontensive microalbuminuric insulin-dependent diabetic subjects, in contrast to captopril or placebo (24, 37, 38). Some of them have reported that calcium antagonists did not change UAER (42, 44). But others have reported beneficial nephroprotective effects of calcium antagonists on diabetic patients (16, 19, 39-41, 43). Norgaard K et al. have suggested that isradipine did not change UAER in hypertensive IDDM patients (45). In contrast, Frishman WH and Guistino A et al. have reported a favorable renal effect profile of isradipine in essential hypertension (46, 47). In this study, isradipine led to a decrease in UAER. This decrease was not attributable only to its beneficial blood pressure lowering effect because it decreased only diastolic blood pressure and also this decrease ($p<0.05$) was not as significant as the decrease in UAER ($p<0.01$). Similarly several prospective studies have claimed that antihypertensives exert nephroprotective effects beyond their BP lowering effects (19, 20, 26).

Like previous researchers (48, 49), we observed that isradipine did not significantly affect the mean levels of FPG, total cholesterol, HDL cholesterol, LDL cholesterol,

urea, cretainin, uric acid, glycosylated hemoglobin, fructosamine, C-peptid or insulin. Therefore, such drugs (ACE inhibitors, calcium antagonists, and α-Adrenergic inhibitors) are called metabolic neutral drugs, and they are referred in the treatment of diabetic patients (19, 50). However, their potential adverse effects should be considered. Hyperkalemia is common with the use of ACE inhibitors. Pregnancy or possible pregnancy is a contraindication of the use of ACE inhibitors. α-Adrenergic inhibitors may cause persistent orthostatic hypotension and fluid retention in diabetic patients (50, 51). Isradipine has some adverse effects related to vasodilatation (such as ankle edema, headaches and dizziness) (48, 52-55). In this study, no serious clinical or metabolic side effects were noted, except headaches in 3 patients, but they did not require discontinuation of the treatment. Furthermore, isradipine did not cause ortostatic hypotension.

In basal conditions, neither sBP nor dBP was significantly correlated with UAER (r=0.36, p=0.13 and r=-0.13, p=0.58, respectively). This finding is consistent with previous observations (7-10, 26). These data suggest that blood pressure NIDDM patients, unlike in IDDM patients, does not strictly depend on the degree of renal impairment. This assumption is confirmed by the fact that approximately 20% of NIDDM patients are hypertensive before diagnosis, with several other pathogenic mechanisms playing a major role (26, 50). However, UAER was strongly correlated with glycosylated hemoglobin (r=0.57, p=0.01) and weakly correlated with fructosamine and total cholesterol (r=0.45, p=0.05; and r=0.45, p=0.05; respectively).

In conclusion, isradipine is safe and well tolerated by normotensive microalbuminuric patients with NIDDM. Isradipine treatment reduces urinary albumin excretion. Although the mechanisms of the renal effects o f isradipine have not been fully elucidated, these results indicate the potential use of this drug in the long-term renal protection of normotensive microalbuminuric patients with NIDDM.

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