Impediment of the Progressions of Microalbuminuria and Hyperlipidemia in Normotensive Type 2 Diabetes by Low-Dose Ramipril†

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Abstract

In a randomized, double-blind, placebo-controlled study, we investigated in normotensive type 2 diabetics with microalbuminuria the effect of ramipril, an ACE inhibitor, on urine albumin excretion and serum lipids. A total of 1,882 patients were screened for urine microalbumin consecutively by dipstick test, Rapi Tex®-Albumin test and RIA. The final 28 normotensive and microalbuminuric patients were assigned to receive either ramipril (1.25 mg/d, n=16) or placebo (n=12) for 12 weeks. Throughout the study, both groups had no changes in blood pressure, fasting plasma glucose, HbA_{1C}, serum creatinine and electrolytes and no difference in creatinine clearance. At week 12 only the placebo group showed the significant increment of urine albumin excretion and triacylglycerol (30.6±38.3 to 39.0±19.7 and 167±64 to 208±77 mg/dl, respectively) but the decrement of HDL-cholesterol (46±16 to 35±6 mg/dl). During a 3 month period, increased urine albumin excretion was observed in normotensive type 2 diabetes with microalbuminuria who received only placebo. We conclude that ramipril may arrest the progression of albumin excretion and had favorable effects on serum lipids. Ramipril was safe and well-tolerated without untoward side effects during the study period.

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Microalbuminuria (MAU) has been recognized as an independent and reliable predictor of future development of overt proteinuria in diabetic patients[1]. It is associated with high mortality from end stage renal failure as well as cardiovascular diseases[1,2]. Since the progressions of MAU or proteinuria as well as renal failure are accelerated by hypertension, angiotensin-converting enzyme (ACE) inhibitor has been used to lower both systolic and diastolic blood pressures in hypertensive diabetic patients in order to delay such progressions[3-5].

Independent of antihypertensive property, ACE inhibitor at low dosage which has no effect on blood pressure (low dose), also shows its specific advantageous effect on reducing the albumin excretion rate and retarding the decline of the glomerular filtration which consequently preserves renal function and survival in diabetic patients with nephropathy[6-8]. The latter benefit has made ACE inhibitor capable of stopping the progression of proteinuria and deterioration of renal function in mild hypertensive and normotensive diabetic patients as well[8-10]. Although the information on this benefit has been confirmed among type 1 diabetes, it is still inconclusive and controversial in type 2 diabetes whose large proportion constitutes those patients who develop end-stage renal disease[10-12].

Since ramipril has been accepted worldwide as an effective and safe ACE inhibitor, it is recommended as the first-line drug in the management of hypertensive subjects with type 2 diabetes mellitus[4]. At the low dose of 1.25 mg daily, ramipril was shown to have no significant antihypertensive effects in animal models or humans [10,13,14]. Our study aimed to evaluate the effects of a short-term therapy with ramipril at low dosage (1.25 mg/day), which has no effect on blood pressure level, on the progression of microalbuminuria. The study also looked at the effect of ramipril on the status of plasma lipids in the type 2 diabetes mellitus with incipient nephropathy. In order to assure the aforesaid qualification, the subjects were then carefully selected from patients who attended the diabetic clinic according to the repetitively-screening cascade. The study was performed in a randomized, double blind and placebo-controlled clinical trial of 1 2 weeks' duration.

Method

Patients

Patients of both sexes (aged 30-85 years) who attended the out-patient department of the diabetic clinic of Theptarin General Hospital, Bangkok, were selected for the study. They had type 2 diabetes mellitus diagnosed according to World Health Organization criteria of at least 6 months' duration. A history of unstable angina, heart failure, liver and/or gastrointestinal diseases were reasons for exclusion. The study recruited real normotensive patients with MAU and without apparent proteinuria according to the screening cascade described as follows. Those with systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 were not eligible for the study. Of the 1,889 type 2 diabetic patients, 625 patients whose casual urine samples showed apparent proteinuria with dipstick test (Labstick^{TM}, Bayer Australia Ltd., Pymble, N.S.W., Australia) were excluded. All inclusive patients were screened for MAU by checking their urine specimens triplicately with Rapi Tex®-Albumin test (Behringwerke AG, Marburg, Germany) and those whose at least 2 in 3 tests demonstrated positive response were recruited in the study. Among the qualified 256 patients, 47 patients who showed proteinuria were excluded and the remaining 209 patients without proteinuria were asked to collect urine during 3 hours for MAU measurement utilizing radioimmunoassay technique with double antibody Albumin kit (Euro/DPC Ltd., Llanberis, Gmynedd, U.K.). The results revealed the existence of MAU in 78 patients. Among them, 7 patients with poorly controlled diabetes confirmed by their hemoglobin A_{1C} (HbA_{1C}) > 10 per cent as well as 30 patients whose $HbA_{1C} \leq 10$ per cent but had undergone hypotensive medications were ruled out from the subject list. One inclusive patient died and at the end 40 normotensive and well glycemic-controlled patients with MAU were invited to participate in the study.

Study Design

The study protocol was approved by Theptarin Hospital's ethics committee. After handing in informed consent of participation, 40 patients with type 2 diabetes were enrolled in the 12 week study. Patients were randomized into 2 groups of 20 in a double-blind fashion. They received either 1.25 mg

ramipril or an indistinguishable placebo capsule once daily and underwent clinical evaluation at weeks 0, 6 and 12 or before, during and after the study. Monitoring of medication intake was done by counting their remaining capsules at each visit. Oral hypoglycemic agents were prescribed regularly throughout the study. Dietary regimen and sodium intake of the patients were kept unchanged under supervision and counsel of the Hospital's registered dietitian. At each outpatient visit before intake of morning medication, blood pressure was measured on the same arm with the patient supine or seated for 5 min and with the patient standing for 2 min by means of a standard mercury sphygmomanometer. The mean of two blood pressure readings taken during each visit was used for the analysis. During the study, 8 patients in the placebo group and 4 in the ramipril group dropped out. At the end of the protocol, 12 patients in the control group and 16 in the treated group completed the study. Adverse effects and intercurrent illnesses were recorded separately at each visit and have not been included in this report.

Laboratory Analyses

Determination of all biochemical variables in blood samples taken before, during and after or at respective weeks 0, 6 and 12 of the study was performed at the hospital's central laboratory. The afore-mentioned MAU measurement by means of radioimmunoassay technique was performed at Radio-Immunoassay Center (R.I.A. Center), Bangkok. Serum glucose, creatinine, albumin and lipids were analyzed by conventional laboratory techniques employing Technicon RA 2000 auto-analyzer (Technicon Instrument Corp., Terrytown, N.Y., U.S.A.). Serum and urinary sodium and potassium were measured by Ciba Corning 644 FAST 4 System (Ciba Corning Diagnostics Corp., Medfield, M.A., U.S.A.). The concentrations of serum lipids: triacylglycerols (TG), total cholesterol (TC), cholesterol of high density lipoprotein (HDL-C), were assessed biochemically whereas low density lipoprotein-cholesterol (LDL-C) was obtained from the calculation (LDL-C = TC - TG/5 - HDL-C). Serum HbA_{1C} was analyzed by HPLC technique using Variant Hemoglobin Testing System (Bio-Rad Diagnostics Group, Herules, C.A., U.S.A.).

Statistics

Results are presented as mean ± SD. Figures in parentheses shown in the Tables are the number of patients. All statistical significances were calculated by one-way analysis of variance (ANOVA) with Duncan's new multiple range test by programme of SPSS/PC+ for windows and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Data

Forty patients who fulfilled all inclusion criteria were randomized to receive ramipril or placebo. During the study, 3 in the ramipril group and 4 in the placebo group were unavailable for follow-up, 1 in each group forgot to take medication, 2 in the ramipril group were found later to take hypotensive medication from other hospitals and 1 in the placebo group was hospitalized with acute pyelonephritis. They all were withdrawn from the study and thus there were 28 patients (16 in the ramipril *vs* 12 in the placebo groups) remained and completed the study. Both groups were well matched at the baseline regarding sex distribution, body mass index, medication intake, systolic and diastolic blood pressures at three different postures and all biochemical parameters in both serum and urine (Table 1). Age ranges of both groups were slightly but non-statistically different. Fasting blood glucose and glycosylated hemoglobin (HbA_{1C}) of both groups were in normal levels with mean values ranging 167-172 mg/dl and 8-8.5 per cent, respectively. No statistically significant difference between patients administered with ramipril and placebo was found in any biochemical parameters of serum lipids. Although serum TG levels of ramipril group were slightly higher than those of placebo group (188±114 *vs* 167±64 mg/dl), the difference between groups failed to reach statistical significance (Table 1).

Blood Pressure and Biochemistry

Many patients in both groups had no data of blood pressure in baseline as well as during the study. Results of diastolic (DBP) and systolic blood pressures (SBP) from week-6 and week-12 treatment phases were compared with baseline data (Table 2). After 12 weeks of the study, DBP and SBP at three different postures: supine, sitting and standing, remained unchanged. Nonhypotensive

Table 1. Baseline demographic and laboratory data of normotensive type 2 diabetic patients.

	Ramipril group	Placebo group
No. of patients (M:F)	16 (11/5)	12 (8/4)
Age (years)	41±10.4 (32-85)	54±14.9 (30-68)
Body mass index (kg/m^2)	27.8±3.3	27.1±3.5
Medication intake (tablets)	85±7	83±6
Systolic blood pressure (mm Hg)		
- Supine	133±35 (14)	136±15 (10)
- Sitting	134±12 (10)	130±13 (7)
- Standing	127±6 (3)	130 (1)
Diastolic blood pressure (mm Hg)		
- Supine	80±4 (14)	83±11 (10)
- Sitting	79±5 (10)	80±8 (7)
- Standing	80±0 (3)	70 (1)
Serum		
- Fasting blood sugar (mg/dl)	167±35	172±51
- Hemoglobin A_{1C} (%)	8.0±1.3	8.5±1.7
- Triacylglycerols (mg/dl)	188±114	167±64
- Total Cholesterol (mg/dl)	220±27	213±33
- HDL-cholesterol (mg/dl)	44±8	45±14
- LDL-cholesterol (mg/dl)	138±29	133±43
Urine		
- Microalbuminuria (mg/l)	29.5±23.5	30.6±19.7

Data are means ± SD.
Figures in parentheses are gender for the first row , age range for the second row and all othersare number of patients. Unless otherwise stated, number of patients are 16 in ramipril group and 12 in placebo group.

Table 2. Blood pressures (BP) measured at 3 different postures at week 0 (before the study), week 6 (during study period) and week 12 (at the end of the study) in type 2 diabetic patients with micro-albuminuria treated with ramipril or placebo.

	Treatment	wk 0	wk 6	wk 12
Systolic BP (mm Hg)				
- Supine	Placebo	136±15 (10)	137±17	131±13
	Ramipril	133±35 (14)	135±12	131±12
- Sitting	Placebo	130±13 (7)	131±9	129±6 (8)
	Ramipril	134±12 (9)	132±15 (14)	130±14 (12)
- Standing	Placebo	130 (1)	132±9 (7)	130±5 (8)
	Ramipril	127±6 (3)	136±11 (12)	131±14 (11)
Diastolic BP (mm Hg)				
- Supine	Placebo	83±11 (10)	80±10	82±6
	Ramipril	80±4 (14)	78±7	78±7
- Sitting	Placebo	80±8 (7)	76±7	80±5 (8)
	Ramipril	79±5 (9)	77±9 (14)	78±6 (12)
- Standing	Placebo	70 (1)	76±8 (7)	80±5 (8)
	Ramipril	80±0 (3)	78±6 (12)	78±6 (11)

Data are means±SD.
Figures in parentheses are number of patients. Unless otherwise stated, number of patients are 16 and 12 in ramipril and placebo groups, respectively.

dose of ramipril at 1.25 mg did not provide any effect to blood pressures of normotensive type 2 diabetic patients. Neither significant difference was found when the corresponding data of both groups of treatment were compared to each other.

Table 3 shows routine blood biochemical parameters at baseline and at 6 and 12 weeks of treatment with ramipril compared to placebo. Values of fasting blood glucose (FBG) of the ramipril group were slighly lower than those of the placebo group in all corresponding periods (167±35 *vs* 172±51 mg/dl at wk 0, 151±40 *vs* 184±54 at wk 6, 155±27 *vs* 155±27 *vs* 158±41 at wk 12). However, the differences were not statistically significant. Noticeably, a small but non-significant decline was observed in FBG concentrations of both groups at the end of the study compared to baseline (172±51 dropped to 158±41 and 167±35 dropped to 155±27 mg/dl for the placebo and ramipril groups, respectively). The concentrations of glycosylated hemoglobin, serum creatinine, serum albumin, serum electrolytes: sodium and potassium, were unaffected by treatment and remained unchanged in both groups throughout 12 weeks of the study.

Microalbuminuria and Serum Lipids

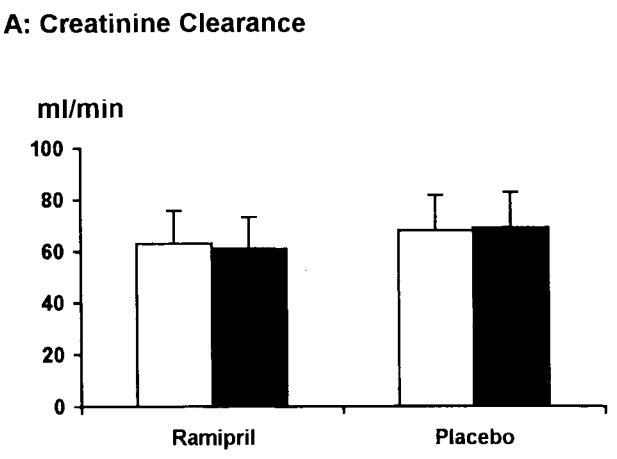
Creatinine clearance in urine was stable in both groups of treatment throughout the study (Fig. 1A). Despite having MAU at baseline, the type 2 diabetic treated with placebo for 12 weeks still showed the significant progression of MAU in 24 h urine compared to baseline (30.6±38.3 to 39.0±19.7 mg/dl; $p<0.05$). However, those treated with low dose ramipril showed no change in MAU during the same period (29.5±23.5 to 27.7±22.0 mg/dl) (Fig. 1B). As shown in Table 4, urinary excretion of electrolytes: sodium, potassium and chloride, of both groups were stable throughout the study. Body mass index of both groups of patients were also well controlled throughout the study along with well-controlled glycemia as one can see in FBS and HbA1C in Table 3. Serum total cholesterol were also kept constant during the study (Table 4). LDL-cholesterol of both groups tended to increase but did not reach statistical significance (138±29 rose to 142±31 and 133±43 to 139±35 mg/dl for placebo and ramipril-treated groups, respectively).

Treatment with placebo (Fig. 2), TG concentrations of patients markedly rose after 12 weeks (167±64 to 208±77 mg/dl; $P<0.05$) whereas HDL-cholesterol dropped significantly during the same period (46±16 to 35±6 mg/dl; $P<0.05$). However, both parameters of lipids did not alter after the treatment with ramipril (TG 188±112 to 187±90 mg/dl and HDL cholesterol 44±8 to 40±10 mg/dl). No adverse effects of ramipril as well as placebo were observed throughout the study period (Fig. 2A and 2B).

Table 3. Fasting blood glucose, hemoglobin A_{1C}, serum creatinine, serum albumin and serum electrolytes (Na^+/K^+) at week 0 (before the study), week 6 (during study period) and week 12 (at the end of the study) in type 2 diabetic patients with microalbuminuria treated with ramipril or placebo.

	Treatment	wk 0	wk 6	wk 12
Fasting blood glucose, mg/dl	Placebo	172±51	184±54	158±41
	Ramipril	167±35	151±40	155±27
Hemoglobin A_{1C},%	Placebo	8.4±1.4	8.5±1.7	8.4±1.3
	Ramipril	8.0±1.3	7.9±1.2	8.1±1.0
Serum creatinine, mg/dl	Placebo	1.15±0.17	1.24±0.14	1.17±0.20
	Ramipril	1.20±0.20	1.31±0.29	1.18±0.22
Serum albumin, g/dl	Placebo	4.35±0.37	4.28±0.41	4.29±0.29
	Ramipril	4.41±0.22	4.30±0.20	4.24±0.37
Serum sodium, mEq/l	Placebo	142±3	142±2	141±3
	Ramipril	142±5	141±2	141±2
Serum potassium, mEq/l	Placebo	4.8±0.6	4.5±0.2	4.6±0.3
	Ramipril	4.9±0.7	4.9±0.4	4.7±0.4

Data are means±SD.



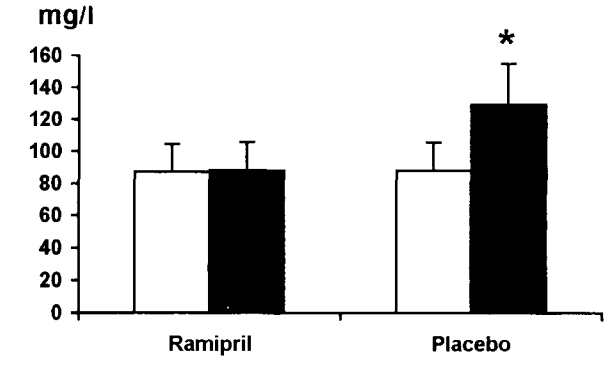
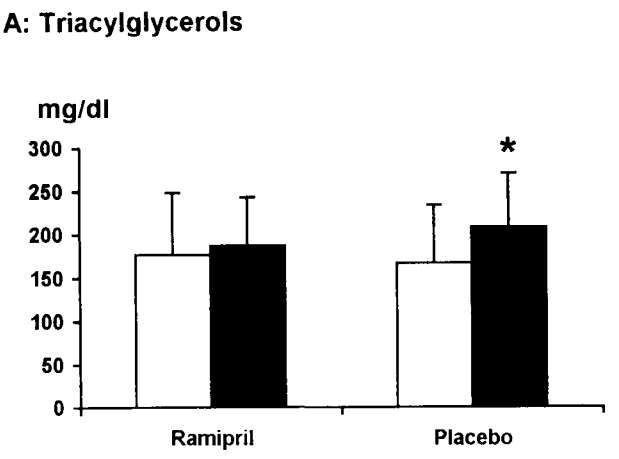


Fig. 1. Creatinine clearance in ml/min (A) and microalbuminuria in 24 h urine (B) in type 2 diabetic patients with microalbuminuria at week 0 (open columns) and week 12 (solid columns) of treatment with ramipril or placebo. Values are means ± SD. Asterisk indicates P < 0.05 for wk 12 *vs* wk 0.



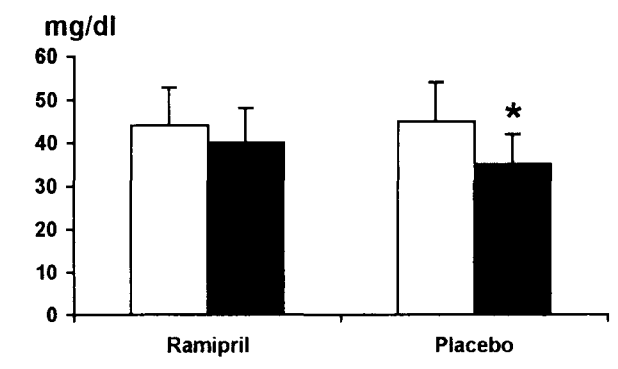


Fig. 2. Serum lipids: triacylglycerols (A) and HDL-cholesterol (B) in type 2 diabetic patients with microalbuminuria received either ramipril (1.25 mg/d) or placebo capsules for 12 weeks. The results expressed in means ± SD comparing wk 0 (open column) with wk 12 (solid column). Asterisks indicate P < 0.05 for wk 12 *vs* wk 0.

DISCUSSION

In the past, the study of diabetic nephropathy has always been with type 1 diabetes patients despite the fact that the majority of the diabetic population are type 2. Since the progression of nephropathy is comparable in both types of diabetics[15] and type 1 diabetes is found much less frequently among Asian populations than among Caucasians[16], in most places the majority of the end stage renal failure patients are type 2 diabetics[3,11,17]. Prevention of the progression of the proteinuria and onset of end stage renal failure is therefore of utmost epidemiological importance particularly among the Asian population. Definitive evidence showed the beneficial effect of ACE inhibitors in the preservation of renal function, stopping progression of proteinuria and reducing mortality independent of their antihypertensive property. This has been shown in both macroproteinuria and microproteinuria patients.

Table 4. Body mass index, serum lipids and urine electrolytes before and at the end of the study in type 2 diabetic patients with microalbuminuria treated with ramipril or placebo.

	Ramipril		Placebo	
	wk 0	wk 12	wk 0	wk 12
Body mass index (kg/m^2)	27.8±3.3	27.1±3.3	27.1±3.5	27.0±3.2
Serum				
- Total cholesterol (mg/dl)	220±27	220±33	213±33	215±28
- Triacylglycerols (mg/dl)	177±114	187±90	167±64	208±77*
- HDL-cholesetrol (mg/dl)	44±8	40±10	45±15	35±6*
- LDL-cholesterol (mg/dl)	138±29	142±31	133±43	139±35
Urine				
- Sodium (mEq/l)	105±55	95±54	87±44	87±63
- Potassium (mEq/l)	22±11	20±11	17±9	17±7
- Chloride (mEq/l)	108±50	96±46	89±39	89±61

Data are means ± SD.
Asterisk (*) indicates $p < 0.05$ for wk 12 vs wk 0.
The p value at 12 wks of the effects of ramipril *vs* placebo for triacylglycerols (TG), HDL-cholesterol (HDL), ratio of TG:HDL and microalbuminuria are not significant at 0.526, 0.087, 0.252 and 0.15, respectively.

Although the majority of diabetic patients with proteinuria are type 2 diabetes it is only recently that clinical trials of the effect of antihypertensive medications on the progression of proteinuria have been conducted in type 2 diabetes. Enalapril is the most extensively tried ACE inhibitor. It has been tried in both macroproteinuria and microproteinuria patients, in both hypertensive and normotensive patients. Ravid et al[18] have shown that long term treatment with enalapril could stabilize the level of proteinuria in normotensive diabetic type 2 patients over a period of five years while those treated with placebo showed marked deterioration of proteinuria as well as renal function. The deterioration of proteinuria among the placebo group could be arrested after switching to treatment with enalapril during the next two years (year 6 and 7)[19]. Ahmad et al[20] showed that enalapril initiated during the period of microproteinuria could decrease the amount of proteinuria with the number of patients progressing from microproteinuria to macroproteinuria markedly reduced by 66.7 per cent.

Schnack et al[21] compared the effect of ramipril (2.5-5.0 mg/day) with atenolol (50-100 mg/day) in type 2 diabetic patients with microproteinuria and hypertension. In this one year study they found that both atenolol and ramipril caused an almost identical reduction of blood pressure but only the group with ramipril maintained the albumin/creatinine ratio while those with atenolol showed deterioration of albumin/creatinine ratio. Trevisan et al[10] used a low dose of ramipril (1.25 mg/day) in type 2 diabetic patients with microalbuminuria and normotensive or mild hypertension. The study was done in a randomized double blind placebo-controlled multicenter trial for a period of 6 months. They measured the albumin excretion rate (AER) and found the stabilizing effect of ramipril even at one month of treatment. The authors suggested that the effect of the low dose ACE inhibitor may be related to acute intrarenal hemodynamic changes. This is supported by evidence in animal studies which showed that ACE inhibitors lower intraglomerular pressure[21] and suppress the growth of glomerular and mesangial cells[23,24].

The present study performed in a randomized, double blind placebo controlled trial in two groups of type 2 diabetes patients, carefully screened for microproteinuria and normotension as well as excluded those with poorly controlled diabetes. A three months trial showed a significant increase of proteinuria in the placebo controlled group compared to the group on a low dose (1.25 mg/day) of ramipril. Our observation confirmed the finding of Trevisan et al[10] that low dose ACE inhibition with ramipril could arrest the progressive rise in albuminuria in type 2 diabetic patients with persistent microalbuminuria. In this study,

unlike other studies mild hypertension was already excluded yet ramipril at low dosage still can impede the progression of proteinuria at a very early stage of treatment. The low dose of ramipril had no significant effect on the blood pressure but still had the effect on the proteinuria reflecting the intraglomerular hemodynamic effect of ACE inhibitor. It has been shown that administration of ramipril 1.25 mg once a day inhibits ACE activity for 24 hour after the last intake without any significant antihypertensive effect. A low dose of 1.25 mg of ramipril gives equal activity in inhibiting ACE activity as 5 mg of ramipril and even improved the regression of left ventricular hypertrophy. A study is being done to see if the low dose of ramipril can reduce the morbidity and mortality of the normotensive or hypertensive type 2 diabetic patients with microalbuminuria or proteinuria.

Concerning cardiovascular disease (CVD), it has been well recognized that type 2 diabetes mellitus is associated with an increased cardiovascular risk[25]. Meanwhile in type 2 diabetic patients, MAU and proteinuria are strong independent predictors for increased cardiovascular mortality[1,2]. Coincidentally, type 2 diabetes with MAU complication may accelerate the patients to the higher risk of CVD. Since ACE inhibitor suppresses the development of MAU as explained earlier, reduction of CVD risk in type 2 diabetes treated with ACE inhibitor is thus expected. However, studies on the effects of ACE inhibitor administration on cardiovascular morbidity and mortality are not currently available. Passa and Chatellier[14] investigated the effect of a low daily dose of 1.25 mg ramipril treatment in 2,000 type 2 diabetic patients in their 3 years' follow-up study started in 1995. The efficacy of ramipril in their study was evaluated by the major endpoints e.g., cardiovascular death, sudden death, myocardial infarction, stroke, renal replacement therapy. The study is still underway and the results are expected to be summarized in the near future. The effect of ACE inhibitor and vitamin E administrations on the progression of renal and cardiovascular disease in patients with diabetes was also assessed in another study performed by Gersein et al[26] without any conclusion. Thus, the effect of ACE inhibitor administration in diabetic patients on morbidity and mortality of cardiovascular disease is still inconclusive. Nevertheless, the risk of CVD may be assumed from the incidence of hyperlipidemia in type 2 diabetes.

Since hypertriacylglycerolemia as well as hypo-HDL cholesterolemia are known as risk factors of CVD, the prevalences of both abnormalities are roughly double the norm in type 2 diabetes which made the patients more prone to develop CVD[27]. Hypertriacylglycerolemia in type 2 diabetes is a result of both increased very low density lipoproteins (VLDL) biosynthesis and impaired VLDL catabolism[27,28]. In contrary, plasma TG level is also an independent risk factor for the development of type 2 diabetes among nondiabetics. Yang et al[29] investigated the relationship between baseline fasting plasma triacylglycerol (TG) level and the incidence of type 2 diabetes mellitus in 432 Chinese nondiabetics. After a long-term follow-up study of 6 years, they reported the statistically significant relationship between the progression of hypertriacylglycerolemia and development of type 2 diabetes. Therefore, reduction of hypertriacylglycerolemia is not only beneficial by lowering the risk of CVD but improves the diabetic status as well.

In order to properly manage type 2 diabetes, the therapeutic aims must be set for three parameters: plasma lipids, plasma glucose and blood pressure[30]. There are many means of treatment to reduce plasma TG levels in patients; with or without hypotriacylglycerolemic medication. Lehmann et al[24] trained patients with regular moderate aerobic exercise at 50-70 per cent maximal effort over 3 months. They found the decrement of plasma TG in type 2 diabetes for 20 per cent along with the increment of HDL cholesterol for 23 per cent. Lee and Reasner[31] supplemented the patients with chromium picolinate for 2 months and reported the significant reduction of plasma triacylglycerol concentrations of the patients for 17.4 per cent. Gans et al[32] prescribed either cilazapril or placebo to hypertensive type 2 diabetes and found no alteration of TG and other plasma lipids through 8 weeks of the study. Leonhardt et al[33] described in their review literature on the efficacy of acarbose, alpha-glucosidase inhibitor, on lipids in NIDDM that it sometimes reduces serum TG while it has little or no effect on serum cholesterol. Trevisan et al[10] treated type 2 diabetes with either 1.25 mg ramipril daily or placebo for 6 months, they also reported no alteration of plasma TG in both groups.

In the present study, we demonstrated that without the treatment of MAU and plasma lipids, type 2 diabetic patients developed hypertriacylglycerolemia with hypo-HDL cholesterolemia. These abnormal lipid alterations thus prone the type 2 diabetic patients to the higher risk of CVD. Interestingly, arresting the incipient diabetic nephropathy in type 2 diabetic patients from its progression with low-dose ramipril could also impede the development of hypertriacylglycerolemia as well as hypo-HDL cholesterolemia. This may be beneficial to the patients in the prevention of CVD. The real mechanism of how ramipril impedes hypertriacylglycerolemia in type 2 diabetes is still unexplained. It probably reduces postprandial hyperinsulinemia and subsequently improves the metabolism of TG in VLDL as explained for acarbose(33).

In summary, our study demonstrates that after the treatment of normotensive, incipient-nephropathic and well glycemic-controlled type 2 diabetic patients with either placebo or 1.25 mg of ramipril daily for 12 weeks, there was no change in blood pressures measured either at supine, sitting or standing postures every 6-week period throughout the study. No alterations of serum albumin, fasting blood sugar, glycosylated hemoglobin, creatinine, electrolytes were found in both groups. However, significant rise of MAU as well as progressive rise of TG and reduction of HDL-cholesterol were observed in the placebo group, whereas, they were found to be unchanged among patients administered with ramipril.

We thus conclude in our investigation that low dose ramipril arrests the development of MAU and hyperlipidemia in type 2 diabetic patients with incipient diabetic nephropathy. Impediment of the progressions of the hypertriacylglycerolemia and hypo HDL-cholesterolemia by ramipril probably reduces the type 2 diabetic patientsí proneness to the risk of CVD. Long-term studies and larger numbers of subjects are needed to determine this extraordinary benefit.

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ลามิพริลขนาดต่ำชะลอการพัฒนาของภาวะไมโครอัลบุมินนูเรียและไฮเปอร์ลิพิดีเมีย ในผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลินที่มีความดันโลหิตปกติ

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การศึกษาครั้งนี้ทำโดยคัดเลือกผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลินที่เริ่มมีปัญหา microalbuminuria (MAU) แต่ไม่มีความดันโลหิตสูง เลือกผู้ป่วยเบาหวานได้ 1,882 คน คัดผู้ที่มี proteinuria ชัดเจนออก ในที่สุดได้ผู้ป่วย 28 คน แบ่งโดยวิธี randomized, double-blind เป็น 2 กลุ่ม 16 คนได้รับยา ramipril ซึ่งเป็นยาในกลุ่ม ACE inhibitor ปริมาณ 1.25 มก./วัน 12 คนได้รับยาหลอก นาน 12 สัปดาห์ ทำการเก็บตัวอย่างเลือดที่สัปดาห์ที่ 0 และ 12 ผลการศึกษาไม่พบการเปลี่ยนแปลงของความดันโลหิตทั้งไม่พบความแตกต่างของ fasting plasma glucose, HbA_{1C}, serum creatinine และ electrolytes ระหว่าง 2 กลุ่ม ขณะที่พบ urine albumin excretion และ serum triacylglycerols เพิ่มสูงขึ้น (30.6±38.3 สู่ 39.0±19.7 และ 167±64 สู่ 208±77 mg/dl ตามลำดับ) และ HDL-cholesterol ลดลง (46±16 สู่ 35±6 mg/dl) ในกลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ กลุ่ม ramipril ไม่พบการเปลี่ยนแปลง การศึกษาครั้งนี้ไม่พบผลข้างเคียงของการใช้ ramipril สรุปผลได้ว่าผู้ที่ได้รับยาหลอกจะมีการพัฒนาของปัญหา MAU และ hyperlipidemia การรับประทานยา ramipril อาจช่วยหยุดยั้งการพัฒนาภาวะที่ไม่ต้องการนี้ได้

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