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Effect of Raloxifen on Renal Function in Post-Menopausal Women with Diabetic Nephropathy: a Double Blind Clinical Trial

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Abstract

Background: This study evaluates the effects of the selective estrogen receptor modulators (SERMs), raloxifen, on renal function in post- menopausal women with type 2 diabetes mellitus.

Methods: Thirty-seven post-menopausal women with Type 2 diabetes and diabetic nephropathy included in a 4-month, double-blind, placebo-controlled trial. 18 patients received 60 mg raloxifene per day and 19 patients received placebo. Baseline and end-study body mass index (BMI), blood pressure (BP), fasting plasma glucose (FPG), HbA1C, lipid profiles and serum creatinine (Cr) were measured. Albumin/creatinin ratio (ACR) and GFR were calculated for all the participants.

Results: Mean ACR log was decreased significantly in the raloxifene group (2.4 ± 0.63 µg/mg vs. 1.89 ± 0.8 µg/mg; P=0.009), but slight-non-significant changes in the placebo group were seen (2.16 ± 0.53 vs. 2.12 ± 0.83; P=0.8). In addition, compared with placebo, raloxifene resulted in no significant changes in GFR, HbA1C, lipid profiles and BMI. After considering variables like age, sex, duration of diabetes, duration of menopause, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) as confounding factors the improving effect of raloxifene on ACR remained significant.

Conclusion: These results suggest that raloxifene may limit the progression of albuminuria in post-menopausal women with diabetes; further studies in a larger population may be warranted.

Keywords: Raloxifen; Renal function; Post-menopausal women; Diabetic nephropathy; Diabetes type 2

Introduction

Diabetic nephropathy is a major cause of morbidity and mortality in diabetes mellitus [1,2]. The specific pathological changes in the kidney, the clinical course, and the overall risk to develop nephropathy are quite similar in both types of diabetes [3]. Conclusive evidence exists that strict control of hyperglycemia lowers the risk of nephropathy and other diabetic complications of diabetes mellitus [4,5]. The decline in renal function over time has been shown to relate with the initial glomerular filtration rate, initial urinary albumin excretion rate (UAE), hyperglycemia, hypertension, age and sex [6,7].

Across all ages, the incidence and rate of progression of most nondiabetic renal diseases are markedly higher in men compared with women. It has been known that the female sex is associated with a better clinical outcome in chronic renal diseases [8]. On the other hand, many studies of chronic renal disease have reported more rapid progression of renal insufficiency in male gender [9]. Recent epidemiologic studies indicated that diabetic nephropathy including micro and macroalbuminuria are progressing two folds more in the male diabetic patients [10].

It seems that sex steroids or other pubertal hormones related to sex; influence the risk of diabetic nephropathy and retinopathy [11,12]. Although protective effect of female factors such as sex hormones is not defined clearly, postmenopausal hormone condition might have been accelerating renal failure progression Data suggest that activation of the estrogen receptor pathway limits the incidence and the progression of diabetic nephropathy [13]. In addition, specific modulation of the sexual hormone system, such as selective estrogen receptor modulators (SERMs) may open a new therapeutic option for patients with renal disease [8].

To answer the current deficient knowledge about the effect of SERMs on the progression of nephropathy in type 2diabetes mellitus we designed a 4-month clinical trial with raloxifen in postmenopausal women and aimed to access the effects of raloxifen on renal function in the post- menopausal women with type 2 diabetes mellitus.

Materials and Method

Study population/ Data collection

A double blind- clinical trial was designed to evaluate efficacy of raloxifen, a selective estrogen receptor modulator (SERM), on renal function in post-menopausal women with type 2 diabetes mellitus. The subjects were randomly selected from patients who referred to diabetes clinic of vali-e-Asr hospital, as a referral academic hospital in Zanjan. Fifty-two women with diabetes mellitus whose albuminuria has been confirmed recently by 24-h urinary albumin excretion were enrolled and their albuminuria reconfirmed with ACR ≥ 30 µg/mg [14]. Diabetes mellitus was diagnosed according to World Health Organization (WHO) criteria. Menopausal status was defined as amenorrhea for more than one year and serum FSH level more than 25 mu/L.

All the subjects with history of receiving SERM or estrogen in the

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previous 6 months, tendency to gynecologic or breast cancer or any history of thromboeboli disorders were excluded. We also excluded all the participants with glomerular filtration rate (GFR) less than 30 mL/min, those with other causes of albuminuria, serum triglyceride (TG) concentration more than 400 mg/dl, active liver disease and intolerance to raloxifene.

The details of the study were explained to the participants and informed-consent was obtained. A local ethical committee approved the study. This clinical trial was approved in the Iran registry of clinical trial (IRCT code: 138904151179N4).

Measurements

We registered the subjects' demographic and clinical information including age, sex, weight, height, blood pressure, drug history (ACE or ARB), diabetes and postmenopausal duration, history of ischemic heart disease (according to their medical history or exercise tolerance test or cardio angiography results) and retinopathy(confirmed by an ophthalmologist in the previous 6 months).

Height and weight were measured by standard methods. Weight was measured in minimum dressing by Seca scale with the accuracy of 0.1 kg. Height of the subjects was measured by standard methods and body mass index (BMI) was calculated for all the participants [15]. Blood pressure was measured two times with a 10-minute interval in sitting position and the mean of them was recorded for each of the patients [16]. Blood samples were collected at baseline to measure FPG, HbA1C, lipid profile ((HDL, LDL, triglyceride, total cholesterol) [17], serum creatinine (Cr) and ACR at the first and after the end of the study. Two different urine samples were obtained to measure ACR and mean of them was reported as final ACR result at the two stages of the study. All blood samples for the assessment of lipid profile were obtained after 14 hours of fast. All the laboratory measurements were conducted at the central laboratory of Vali-e-asr Hospital.

All the laboratory examinations were done in one laboratory center and the assays were unchanged during the study period. Creatinine was measure by Jaff method and glomerular filtration rate was calculated using Cockcroft_gault formula; GFR= ([140-age (years)] (×) Weight (kg)/72×Pcr) (×) 0.085.

HemoglobinA1c levels were measured using Ione exchange method by DS_5 device set. Lipid profiles were determined by the colorimetric enzymatic method and by auto analyzer; Cubas Mira. Urine Albumin was checked by nephelometry method and by using Binding Site kits (UK). The inter-assay CV of the kit was 4.1% for higher levels of albumin and 3.1% for lower levels of it. Intra-assay CV for the kit was 2.6% for upper levels and 2.2% for lower levels of albumin.

Study protocol

Thirty- seven out of fifty-two types 2 diabetic-post menopausal women referred to the diabetes clinics that met eligible criteria were included in this study. Participants were assigned randomly into two experimental (n=18) and control group (n=19). Subjects were fully informed about intervention protocol, drug consumption and complication.

18 women in experimental group have treated by 60 mg raloxifene (made by Iran_Hormon Company) for 4 months. 19 subjects in control group have received placebo. The medications were distributed and checked by a third person. Patients were advised to continue their previous medications like angiotensin converting enzyme inhibitors (ACEs) or angiotencin receptor blockers (ARBs) with the same dose throughout the study. After two months, the subjects were reassessed for their blood pressure, weight, BMI and the medication side effects. In order to ensure complete consumption of the drug / placebo, the patients were asked at each visit with the child shell medications bring.

After four months of intervention, subjects were observed again for their blood pressure, weight and BMI. Any documented side effects of the medications were recorded and blood samples were drown after 14 hours of fasting to measure FPG, lipid profile, HbA1C and Cr. Two samples of urine were collected for ACR measurement and the mean of the measures was recorded as the final ACR.

Statistical analysis

All data are showed as mean (± SD). The comparison between the groups of patients was performed using Student t tests for quantitative independent variables and Chi square test for qualitative one. Paired T test was used to evaluate the changes in variables in one group. We used log transformation for ACR to make it a normal distributed variable. For nonparametric data, mann_Witney Test and Wilcoxon Signed Ranks test were applied. Stepwise logistic regression analysis was used to determine the correlations between the independent and the dependent variables. For emission of confounding variables effect, we used multivariate linear regression analysis.

For determination of normal distribution of variables, Komogorov_Sminrnov test was applied. Collected data were analyzed by SPSS version 16. Significance was defined as $P<0.05$.

Results

Basic information

Thirty-seven individuals entered the study (18 subjects in experimental group and 19 in control group). Basal characteristics of the two groups illustrates in Table 1.There were no significant differences between the two groups in term of their clinical characteristics.

Renal function

According to Table 2, there was no significant difference in the GFR at the baseline and also at the end of the study between the two groups. At the end of 4 months of intervention no significant changes in GFR were seen in the individuals within the groups.

Albumin/creatinine ratio (ACR) was approximately similar in both groups before the intervention. At the end of the intervention, ACR decreased significantly in experimental group (P=0.009) but a non-significant rise in ACR was seen in control group (Table 3). Differences between mean of changes of ACR in raloxifene group was statistically significant in comparison to mean of changes of ACR in control group (339.9 µg/mg decrement vs. 260.2 µg/mg increment respectively, P=0.004). Also, ACR log changes within groups have shown significant differences (-0.53 Vs +0.3, P=0.045) (Table 4). Medians of ACR before the intervention were calculated 188 and 117 µg/mg in the experimental and control groups respectively, which were changed to 47 and 117 µg/mg respectively after the intervention.

Linear regression analysis demonstrated that after considering variables like age, sex, duration of diabetes, duration of menopause, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) as confounding factors the improving effect of raloxifene on ACR remained significant.

Variable (Mean+-SD)	Subjects groups		The mean difference	P value
	Experimental/Raloxifene (n=18)	Control/placebo (n=19)		
Age(y)	60.9 ± 7.8	60.5 ± 7.5	0.4	0.891
Duration of diabetes(y)	7.8 ± 4.1	9.6 ± 4.5	1.8	0.244
Duration of menopause(y)	11.3 ± 6.6	12.8 ± 9	1.5	0.595
BMI (kg/m^2)	30.43 ± 4.15	29.29 ± 4.22	1.14	0.446
SBP (mmHg)	145 ± 15.6	143.4v19.9	1.6	0.806
DBP (mmHg)	87.2 ± 8.9	83.8 ± 10.9	3.4	0.337
Variable	**Subjects groups**		**Total number**	
	Experimental/Raloxifene (n=18)	**Control/placebo (n=19)**		**P value**
Ischemic heart disease(IHD) Yes No	5(31.2%) 11(68.8%)	5(31.2%) 11(68.8%)	10(31.2%) 22(68.8%)	1.000
Retinopathy Yes No	7(43.8%) 9(56.2%)	3(18.8%) 13(81.2%)	10(31.2%) 22(68.8%)	0.252
ACEI/ARB history Yes No	13(81.2%) 3(18.8%)	14(87.5%) 2(12.5%)	27(84.4%) 5(15.6%)	0.626

P value< 0.05 is considered statistically significant
BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Table 1: Basic characteristics of diabetic postmenopausal women in experimental and control group.

Variables	groups		Mean of differences	P- value
	Raloxifene/experimental N=18	Placebo/ control N=19		
HbA1C (mg/dL)	7.9 ± 2.5	8.1 ± 1.8	0.15	0.84
TG (mg/dL)	208.5 ± 84.1	167.3 ± 67.5	41.2	0.13
Chol (mg/dL)	209.5 ± 51.7	188.1 ± 43.3	21.4	0.21
HDL (mg/dL)	41.1 ± 5.4	41.3 ± 1.7	0.2	0.86
LDL (mg/dL)	105.4 ± 44.6	111.3 ± 44.8	5.9	0.71
ACR (µg/mg)	844.8 ± 1622.9	347 ± 584.6	497.8	0.22
ACR log	2.4 ± 0.63	2.16 ± 0.53	0.24	0.22
GFR (ml/min)	68.2 ± 12.9	70.4 ± 22.9	1.8	0.78

P value< 0.05 is considered statistically significant
TG: Triglyceride; Chol: Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; ACR: Albumin to Creatinin ratio; ACR log: Logarithm of ACR; GFR: Glomerular Filtration Rate

Table 2: Basic laboratory characteristics of postmenopausal women with diabetic nephropathy.

Variables	Raloxifene/experimental groups N=18		P- value	Placebo/control groups N=19		P- value
	Before	After		Before	After	
BMI (kg/m^2)	30.43 ± 4.15	30.56 ± 4.08	0.471	29.29 ± 4.22	29.35 ± 4.32	0.76
SBP (mmHg)	145 ± 15.6	135 ± 19.9	0.087	143.4 ± 19.9	134.4 ± 17.9	0.13
DBP (mmHg)	87.2 ± 8.9	81 ± 7.5	0.036	83.8 ± 10.9	85.3 ± 10.2	0.453
HbA1C (mg/dL)	7.91 ± 2.54	7.86 ± 2.01	0.916	8.06 ± 1.79	7.72 ± 1.68	0.47
TG (mg/dL)	208.5 ± 84.1	240.4 ± 98.6	0.221	167.3 ± 67.5	165.1 ± 78.2	0.91
Chol (mg/dL)	209.5 ± 51.7	200.6 ± 47.2	0.571	188.1 ± 43.3	186.4 ± 41.7	0.79
HDL (mg/dL)	41.1 ± 5.4	40.9 ± 5.1	0.884	41.3 ± 1.7	43.7 ± 6.4	0.16
LDL (mg/dL)	105.4 ± 44.6	112.2 ± 44.1	0.574	111.3 ± 44.8	108.8 ± 38.1	0.71
ACR Log	2.4 ± 0.63	1.89 ± 0.8	**0.009**[1]	2.16 ± 0.53	2.12 ± 0.83	0.8
GFR (ml/min)	68.2 ± 12.9	66.3 ± 17.1	0.234	70.4 ± 32.9	69 ± 22.9	0.31

1-P value< 0.05 is considered statistically significant
BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, TG: Triglyceride, Chol: Cholesterol, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, ACR: Albumin to Creatinin ratio, ACR log: Logarithm of ACR, GFR: Glomerular Filtration Rate

Table 3: Comparison between the mean values of clinical and biochemical parameters of postmenopausal women with diabetic nephropathy before and after the intervention.

Clinical parameters

Changes of clinical and laboratory parameters after the intervention have been shown in (Table 5).

There was no significant change in BMI at the end of the study in both of the groups. Although SBP decreased with using raloxifene ,its decrement was not statistically significant(P=0.08). Placebo had no remarkable effect on DBP, but after using raloxifene a modulating

Variables	Mean of difference		95%CI	P- value
	Raloxifene/ experimental N=18	Placebo/ control N=19		
BMI (Kg/m^2)	0.13 ± 0.68	0.06 ± 0.84	-0.61_0.49	0.818
SBP (mmHg)	-9.1 ± 19.8	-9 ± 22.7	-15.4_15.4	1
DBP (mmHg)	-5.3 ± 9.2	1.5 ± 8.1	-0.6_13.1	0.051
HbA1C (mg/dL)	-0.05 ± 2.09	-0.34 ± 1.87	-1.72_1.15	0.685
TG (mg/dL)	31.9 ± 99.8	-2.2 ± 81.6	-99.9_31.7	0.299
Chol (mg/dL)	61.4	-1.8 ± 26.6	-27_41.3	0.673
HDL (mg/dL)	6.8 ± 47	2.4 ± 6.5	-1.6_6.8	0.223
LDL (mg/dL)	6.8 ± 47	-2.5 ± 26.7	18.7_-37.2	0.5
ACR (µg/mg)	-339.9 ± 1173.2	260.2 ± 606.6	-73.4_1273.4	0.004[1]
ACR log	-0.53	0.03	0.0104-0.968	0.045[1]
GFR (ml/min)	-2.4 ± 7.7	-1.5 ± 5.6	-3.9_5.8	0.706

1-P value< 0.05 is considered statistically significant
BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TG: Triglyceride; Chol: Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; ACR: Albumin to Creatinin ratio; ACR log: Logarithm of ACR; GFR: Glomerular Filtration Rate

Table 4: Comparison between two groups of post menopausal diabetic women for their mean difference of clinical and biochemical parameters during the intervention.

Variables	groups		Mean of differences	P- value
	Raloxifene/ experimental N=18	Placebo/ control N=19		
BMI (Kg/m^2)	30.6 ± 4.1	29.4 ± 4.3	1.21	0.423
SBP (mmHg)	135 ± 19.9	134.4 ± 17.9	1.5	0.81
DBP (mmHg)	81 ± 7.5	85.3 ± 10.2	-3.4	0.35
HbA1C (mg/dL)	7.9 ± 2.1	7.7 ± 1.7	-0.14	0.83
TG (mg/dL)	240.4 ± 98.6	165.1 ± 78.2	75.3	**0.023**[1]
Chol (mg/dL)	200.6 ± 47.2	186.4 ± 41.7	14.2	0.372
HDL (mg/dL)	40.9 ± 5.1	43.7 ± 6.4	2.8	0.18
LDL (mg/dL)	112.2 ± 44.1	108.8 ± 38.1	3.4	0.81
ACR log	1.89 ± 0.8	2.12 ± 0.83	-0.23	.043
GFR (ml/min)	66.3 ± 17.1	69 ± 22.9	2.7	0.70

1-P value< 0.05 is considered statistically significant
BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TG: Triglyceride; Chol: Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; ACR: Albumin to Creatinin ratio; ACR log: Logarithm of ACR; GFR: Glomerular Filtration Rate

Table 5: Comparison of the mean values of clinical and biochemical parameters in postmenopausal women taking raloxifene with those taking placebo at end of the study.

effect on diastolic pressure was seen (reduction in DBP about 5.3 mmHg, P=0.036) (Table 5).

Metabolic parameters

As illustrated in Table 5, mean of HbA1C had no statistical differences within the groups. Contrary, after four months of intervention a remarkable elevation in triglyceride level in experimental group was seen (P=0.023). Other parameters such as cholesterol, HDL and LDL did not differ.

Discussion

We investigated if raloxifene as a selective estrogen modulating receptor could be able to prevent the progression of albuminuria in post-menopausal type 2 diabetes women. In this double-blind, placebo-controlled, parallel group trial, we found that raloxifene have beneficial effects on ACR which is independent of age, sex, duration of diabetes, duration of menopause, BMI, systolic and diastolic blood pressure. Although a little rise in the concentration of serum TG was seen with raloxifene, no change in BMI and no significant side effect was reported with the medication at least in short term.

Diabetic nephropathy as a leading cause of end-stage renal disease will develop in as many as 40% of type 2 DM patients and is presented by the appearance of proteinuria, elevated arterial BP and diminished GFR [18,19].The mechanisms by which chronic hyperglycemia leads to ESRD involve the effects of soluble factors like growth factors, hemodynamic alterations in the renal microcirculation and structural changes in the glomerulus [18-20]. Some potential risk factors like hypertension, age and sex has been reported to associate with diabetic nephropathy [6,7].

There are previously published evidences that male gender may be associated with a more rapid rate of progression of chronic renal disease [21].In patients with chronic renal diseases, the prevalence of ESRD is higher in males than in females. Influences of gonadal hormones on renal function and structure may cause the differences between two genders for the rate of ESRD. Gonadal hormones may affect directly the renal structures via their receptors on renal cells .Additionally these hormones may cause some effects on other organs like cardiovascular system and indirectly influence the kidneys [22-26].

Mentioned information supports this hypothesis that substitution of substances mediated estrogen effects like SERMs offer promising options for a targeted therapy of renal diseases.

Some previous in vitro and animal studies reported the results of estradiol modulators effect on reduction of diabetic glomerular sclerosis. They demonstrated that raloxifene prohibited transforming growth factor like β-1-induced fibronectin transcription and AP-1 activity. They also illustrated the attenuation of diabetes-associated albuminuria and glomerulo sclerosis with estradiol in rats [25].This effect was thought to be mediated by a decrease in TGF-α concentration [27,28]. Usefulness of raloxifene for treatment of diabetic nephropathy also has been suggested by some other researchers [29,30].

In our study, raloxifene was shown to be effective on albumin/ creatinine ratio in comparison to placebo group without a significant change in GFR which is consistent with two other similar experimental data which reinforced raloxifene may inhibit the progression of albuminuria in post-menopausal women with diabetes [13-31].

Raloxifene mechanism of ACR decrement and kidney protection was not completely clear, but it seems that this type of modulators limit renal damage, independently of metabolic factors like BMI, blood pressure, HbA1C or lipid profile changes which are all considered to be risk factors for progression of diabetic nephropathy. In agreement of our results, it was not indicated remarkable influence of raloxifene (with daily doses of 60 mg) on serum HbA1C by Barrete-Conner, Mtsumura, and Anderson [32,33].

In the present study serum triglyceride had a relative rising after 4 months of receiving raloxifene, although meaningful changes in other markers like LDL-cholesterol and HDL were not seen. Although many studies have shown no significant changes in triglyceride levels with raloxifene, nearly all of the studies excluded individuals who had type 2 diabetes and/or were taking lipid-lowering medications, who may be susceptible to hypertriglyceridemia [34-36].

In contrast of our findings, many studies have shown that raloxifene has a favorable impact on lipid metabolism [37]. For instance raloxifene has been associated with a 10–20% reduction in total and LDL cholesterol [38,39] and an 8% reduction in lipoprotein (a) [39]. Walsh,

Barret_Conner and Droper made it clear that raloxifene reduced serum LDL-C levels [34,37,40,41]. Although most studies to date have not shown changes in HDL cholesterol with raloxifene, some studies have shown that raloxifene significantly increases HDL2 [39]. We couldn't find any significant changes in cholesterol or HDL cholesterol level after four months of raloxifene intake. This may be due to the short-term use of the medication or different effects of raloxifene on lipid profile in diabetic patients. However, we did not find any significant adverse effect with raloxifene.

Also, our results in the line of others [37] showed that raloxifene not only did not have any adverse effect on blood pressure in diabetic patients but also made some reduction in blood pressure especially DBP. We also didn't find any considerable weight gain and BMI elevation with raloxifene. This is considered a topic point for raloxifene as a therapeutic option for diabetic nephropathy in comparison to pure estradiol which is associated with cardiovascular and microvascular complications [42].

Conclusion

Total assessment of our double-blind clinical trial with four months therapy with raloxifene in postmenopausal diabetic women indicated that this modulator might reduce the progression rate of diabetic nephropathy by decreasing albuminuria and without significant effect on GFR, lipid metabolism and blood pressure. However, definite comment about these findings requires a longer and larger population study.

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