ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Postmenopausal Hormone Replacement improves Proteinuria and Creatinine Clearance in Type 2 Diabetes Mellitus and Hypertension

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Abstract
Background: Hypertension and diabetes frequently result in renal microvascular damage which progress to induce proteinuria. Also, menopause is associated with progression of vascular diseases. **Aim:** determine if hormone replacement therapy (HRT) can establish renal microvascular damage in type 2 diabetes mellitus and hypertension which is determined by proteinuria and GFR or not . **Patients and methods:** Administration of a cyclic combination of oestradiol and norgestrel orally for 3.5 monthly cycles to 21 postmenopausal women. **Results** Comparing the baseline values, mean (SD) 24-hour urine protein excretion decreased from 0.3 g/24h (0.32) to 0.2 g (0.29) (P <0.001) and creatinine clearance improved from 97-119 mL/min to 99-126 mL/min (P <0.001).it was worth mentioning that HbA1c , post prandial blood glucose and Random blood sugar were decreased significantly with (P<0.001 ,0.022 and 0.001) respectively without any additional anti diabetic treatment. **Conclusion** This study showed that hormone replacement therapy may reduce proteinuria, and even improve creatinine clearance in diabetic and hypertensive postmenopausal women.
Keywords: Postmenopausal Hormone Replacement, Proteinuria, Type 2 Diabetes Mellitus and Hypertension.

Introduction:

Hypertension occurs in about 50% of Type II diabetic patients and is therefore a major pathophysiological mechanism for arterial damage. The resulting arterial damage is usually progressive and accelerates the development of diabetic nephropathy and end-stage renal disease (ESRD) **(1)**.Postmenopausal Women are more susceptible to cardiovascular diseases during this period, considering that the ovarian hormones would be has a protective effect on the cardiovascular system, by acting at various levels, contributing to the body homeostasis **(2).**exogenous supplementation of female sex hormones (estrogen and/or progestin) was the primary choice to diminish the risks of CVDs and control menopausal symptoms. However, over the last two decades, the use of HRT has doubts and uncertainties following the results of several studies **(2).**

material and Methods:

This randomized controlled trial conducted on 21 postmenopausal diabetic and hypertensive women age 47-57 years, with proteinuria (300-750 mg/24h), recruited from the outpatient clinic of internal medicine department, Minia University Hospital, Egypt from January to May 2021. All hypertensive and diabetic medications were left unchanged during the study period. None of the women had had a hysterectomy, received HRT previously or had any known contraindication including prior thromboembolic event . The mean duration of diabetes was10 years . The study was approved by the ethical committee of faculty of medicine, Minia University and a written informed consent was obtained from each participant. All women have been studied in a paired fashion as following: 1st without hormone replacement therapy and 2nd after 14 weeks of receiving oral estradiol 2 mg/day (days 1-22 of each month) and oral norgestrel 0.5 mg/day (days 12-22) in an unblinded manner. All participants are subjected to thorough history taking, full clinical examination and anthropometric measurements including weight, height, BMI and blood pressure. Blood samples for all patients were drawn before the beginning of HRT and after the end of 14 weeks for the following: 24-hour urine protein,urea,creatinine ,fasting,random and2 hour post prandial blood glucose level ,HbA1c ,cholesterol, triglycerides and complete blood count. All measures were performed by standard clinical

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methods .GFR calculated according to MDRD equation = 186 × [serum creatinine(mg/dL)]−1.154× [age]−0.203 × [0.742 if patient is female] × [1.21 if patient is African-American] (3)

Statistical Analyses:

The collected data were coded, tabulated and statistically analyzed using SPSS program (Statistical Packed for Social Sciences) software version 25. Descriptive statistics were done for parametric quantitative data by mean ± standard deviation. Pearson's correlation coefficient was employed to test the correlations between different variables

Results:

This randomized controlled trial conducted on 21 postmenopausal diabetic and hypertensive women whose ages ranged from 47 to 57 years. Their weight was ranged from 74-103 kg which did not change significantly during the study as body mass index (BMI).there was no significant changes in urea ,Hb , platelets or fasting blood glucose before and after HRT, But there was significant decrease in Systolic & diastolic blood pressure, creatinine ,HbA1c ,Random blood sugar and post prandial blood glucose, cholesterol, triglycerides and TLC with Pvalue < 0.002,0.002, 0.001, 0.0010.001, 0.001, 0.001 ,0.022 and 0.02). respectively. No thromboembolic events occurred during the study period. proteinuria significantly decreased after 14 weeks of HRT (p=0.001)and creatinine clearance improved significantly (p=0.001)**.** there was significant positive correlation between24 h proteinuria and BMI,systolic Bp,Hb and platelets.An univariate regression analysis was done to clarify the association between patient's risk factors and 24h proteinuria show that the most important predictors of proteinuria were Hb level, platelet count, BMI and systolic BP. But, there were no significant association with other elements and Multiple Stepwise Linear regression analysis of variables were done revealed that the most predicting elements are HB and BMI.

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Table(1): Demographic data of patients included in the study and Comparison between pre and post HRT

		Pre N=21	Post N=21	P value
Age(years)		(47-57) 51.6±3.2		
Weight	Range Mean ± SD	(74-103) 85.4±10.2	(73-105) 86.1±11.3	0.070
BMI	Range Mean ± SD	(27.5-38.3) 31.9±3.6	32.1±4	0.267
HTN duration	Range Mean ± SD	(7-12) 9±1.9		
DM duration	Range Mean ± SD	(7-13) 10±2.2		
Urea	Range Mean ± SD	(10-22) 16.3±4	(10-24) 17.1±4.9	0.343
Creatinine	Range Mean ± SD	(1-1.5) 1.3±0.2	(0.9-1.4) 1.2±0.2	<0.001*
HbA1c	Range Mean ± SD	(5-9) 7±1.4	(5-8) 6.3±1.1	<0.001*
Fasting blood glucose	Range Mean ± SD	(127-210) 175.7±32.3	(130-210) 167.7±31.5	0.053
Post prandial blood glucose	Range Mean ± SD	(156-330) 233.3±53.9	(167-295) 221.6±45	0.022*
Random blood glucose	Range Mean ± SD	(192-343) 272±49.9	(198-306) 246.3±42.9	<0.001*
Cholesterol	Range Mean ± SD	(188-410) 262.7±73.6	(182-384) 242±67.2	**<0.001***
Triglycerides	Range Mean ± SD	(223-381) 311.3±62.2	(219-392) 291.6±66.5	**<0.001***
TLC	Range Mean ± SD	(4-7.1) 5.1±1.1	(4-8) 5.6±1.2	0.020*
Hemoglobin	Range Mean ± SD	(9-11) 10.3±0.7	(9.8-11.4) 10.6±0.5	0.075
Platelets	Range Mean ± SD	(280-400) 327±39.5	(298-376) 328.4±29.6	0.656
Systolic blood pressure	Range Mean ± SD	(130-165) 145.7±10.4	(130-160) 142.1±9.8	**0.002***
diastolic blood pressure	Range Mean ± SD	(90-100) 95.7±4.3	(80-100) 92.9±6.6	**0.002***
24h proteinuria	**Range Mean ± SD**	**(0.2-0.4) 0.32±0.07**	**(0.2-0.4) 0.29±0.08**	**<0.001***
Creatinine Clearance	**Range Mean ± SD**	**(97-119) 107.9±6.6**	**(99-126) 112±9.2**	**0.001***

Paired samples (t) test for quantitaive data between pre and post.

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Table 3: Correlation between 24h proteinuria and (BMI, SBP, DBP, TLC, Hb, platelet count, Cholesterol, Triglycerides, HbA1c, Creatinine clearance, Urea, Creatinine).

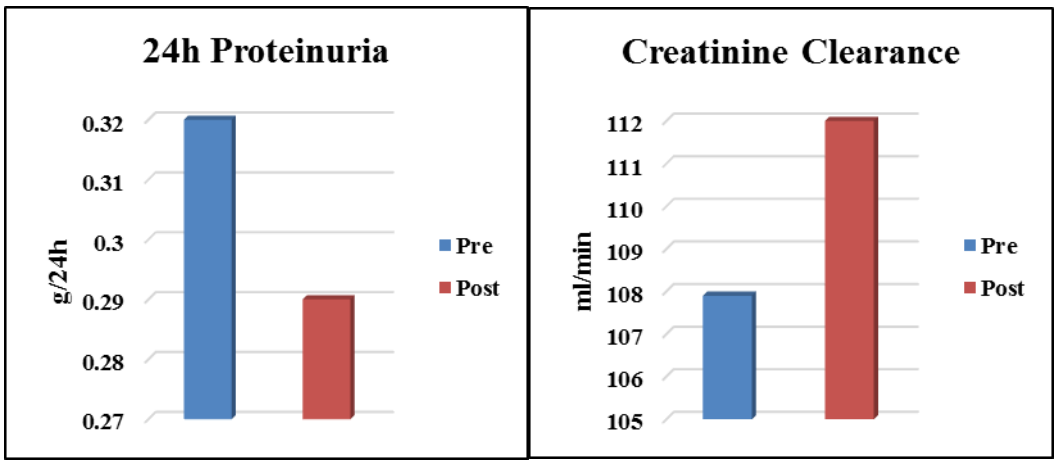
	24h proteinuria	
	Range	**P value**
BMI	**0.433**	**0.049***
Systolic Blood Pressure	**0.455**	**0.038***
Diastolic Blood Pressure	0.216	0.348
Total Leuckocytic Count	0.325	0.150
Hemoglobin	**0.891**	**<0.001***
Platelet count	**0.491**	**0.024***
Cholesterol	0.400	**0.073**
Triglyceride	-0.22	0.926
HbA1C	0.209	0.364
FBS	0.239	0.296
2HPP	0.164	0.478
RBS	-0.010	0.965
Creatinine clearance	-0.031	0.895
Urea	0.008	0.973
Creatinine	-0.029	0.899

Pearson's correlation

***: Significant level at p value < 0.05.**

Figure 1: Show comparison between pre and post HRT in 24h proteinuria and creatinine clearance

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021



Discussion

Hypertension and diabetes frequently result in renal microvascular damage that followed by the development and progression of proteinuria and the decrease of GFR. **(4)** .Menopause is associated with progression of vascular diseases **(5)**. Ten to 15 years after menopause, women lose most or all factors that protecting from cardiovascular diseases compared with men **(6)**.There are several possible mechanisms by which HRT might decrease proteinuria and improve creatinine clearance including changes in systemic and/or intraglomerular pressure, improving glomerular endothelial function and/or glomerular capillary wall integrity, and indirect metabolic effects such as increasing insulin sensitivity, decreasing glucose levels, and decreasing cholesterol or triglyceride levels **(7&8).**Free radical accumulation has also been reported as a causative factor for nephropathy **(9)**. Several studies describe the ability of estrogen to increase nitric oxide production and to reduce oxidative stress which appears to have arule in the improvement of nephropathy seen in our study **(10).** In our study, HRT was associated with significant improvement in HbA1c ,random blood sugar, post prandial blood glucose at P value (P<0.001,0.001,0.022) but there was no significant changes in fasting blood glucose in contrast to other studies report that estrogen therapy does not affect carbohydrate metabolism **(11)**.It is properly known that better control of plasma lipids can decrease the vascular complications of diabetes **(12)**. Interestingly, we found a significant decrease in plasma cholesterol and triglycerides levels (p<0.001) in contrast to a study by **Szekacs et al., (13)** that had no significant changes in lipid profile**. Gregersen et al.,** confirm a strong effect of HRT on atherogenic lipids with a large reduction in the pro-thrombotic lipoprotein (a), apolipoprotien (B) and total cholesterol suggesting an overall favorable effect on thrombogenicity after HRT replacement therapy in post-menopausal women **(14)**. BMI showed no significant changes during our study which is similar to the study performed by **Szekacs et al., (13).** In our study, there was a significant decrease insystolic&diastolic blood pressure at P value (p= 0.002).That was similar to **Fung et al.** (**15**) and **Mueck & Seeger** who found that both primarily normotensive and hypertensive postmenopausal women had a very low risk of BP increase during HRT, indeed, BP was often lowered **(16)** In our study, there is a significant decrease in proteinuria after 14 week of HRT with P value (p=0.001) which was similar to **(13),**and in agree with **kattah et al.,** they proved that HRT is associated with significant decreased in proteinuria with P value <0.001**(17).**Unlike another study performed by **Fenkci et al.,(18)**who showed no improvement in proteinuria after HRT. Another similarity in our study and **(Szekacs et al.)** that show a significant improvement in creatinine clearance with p value 0.001**(13)**. But was in contrast to **Ahmed et al.** who showed a greater decline in eGFR **(19).** the improvement in proteinuria might result from decreased systemic blood pressure and decreased intraglomerular pressure. Estrogen replacement is reported to increase vasodilatation in coronary and other large arteries in postmenopausal women **(20)**.These divergent results may be due to important factors related to HRT, such as route of administration, timing of initiation

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

and type of concomitant progestin therapy, which were not always reported in these studies, all of which can contribute to the wide variations in outcomes **(21).**

Conclusion: hormone replacement therapy may reverse established proteinuria and improve creatinine clearance in diabetic and hypertensive postmenopausal women.

Recommendations: Further studies are required to confirm the possible benefits of HRT in patients with nephropathy due to diabetes or hypertension alone

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