

# The effects of hormonal therapy on lipid profile and renal function in diabetic postmenopausal women

## Abstract

**Aim.** Hormonal therapy (HT) has been known to have beneficial effects on cardiovascular outcome in the general population of post-menopausal women. To evaluate the effects of HT on lipid profile and renal factors, we evaluated the changes using different enzymes and inflammatory acute markers in postmenopausal women with diabetes mellitus (DM). **Methods.** The study was conducted on 190 postmenopausal women from CI Parhon, National Institute of Endocrinology Bucharest who were randomly divided as follows: Group 1 (n=120) placebo, who refused the HT and Group 2 (n=70) those who received HT. The patients from Group 1 were divided in patients with DM (n=21) and patients with normal blood sugar (n=99). The women from the 2<sup>nd</sup> Group were divided into patients with DM (n=12) and patients with normal blood sugar (n=58). The erythrocyte sedimentation rate (ESR), cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), urea and creatinine were analysed. **Results.** The ESR in the 1<sup>st</sup> Group without HT showed a reduction comparing with the 2<sup>nd</sup> Group with HT. Total cholesterol showed to decreased in Group 2 with HT especially on those with normal blood sugar comparing with the 1<sup>st</sup> Group without HT, sustaining the beneficial effect of HT on lipid enzymes. The lowest value in terms of TG was from the 2<sup>nd</sup> Group (with HT) with DM comparing with the rest of the values which were similar sustaining in this case also the beneficial effect of HT on lipid profile. In the case of HDL-C, the highest values were recorded in the 2<sup>nd</sup> Group with HT, sustaining along with cholesterol and TG the same results of beneficial HT effect. When testing the renal function, the urea serum values showed to be decreased in the patients from the 2<sup>nd</sup> Group with HT, sustaining a better renal function in comparison with the 1<sup>st</sup> Group without HT. Creatinine showed the lowest values (<1 mg/dl) in the 2<sup>nd</sup> Group with HT, especially those with normal blood sugar in comparison with the 1<sup>st</sup> Group, showing the fact that HT could sustain a better glomerular filtration rate. **Conclusions.** The above results suggest that HT has favorable effects on cardiovascular outcome in postmenopausal women with or without DM based on cholesterol, TG and HDL-C. Regarding the renal function, it was seen that HT could sustain a better function and a normal glomerular filtration rate. However, the present study indicated the need for long-term prospective trials of large number of patients to determine whether HT should be routinely prescribed in postmenopausal women with or without DM.

**Keywords:** estrogen, cholesterol, triglycerides, urea menopause, diabetes mellitus

Mihaela  
Nicoletta Sandu<sup>1</sup>,  
Tony L. Hangan<sup>2</sup>,  
Matei Dumitru<sup>3</sup>

1. Family Medicine,  
"Carol Davila" University  
of Medicine and Pharmacy,  
Bucharest, Romania  
2. Faculty of Medicine,  
"Ovidius" University  
of Constanta, Romania  
3. Family Medicine,  
"Carol Davila" University  
of Medicine and Pharmacy,  
"Alfred Rusescu" Institute  
for Mother and Child Care,  
Bucharest, Romania

Correspondence:  
Dr. Mihaela Nicoletta Sandu,  
e-mail: sandu\_mihaela44@  
yahoo.com

## Introduction

Some studies have found that hormonal therapy (HT) is associated with a better cardiovascular health profile in healthy postmenopausal women<sup>(1)</sup>. Research on the beneficial effect of HT in postmenopausal women with or without diabetes mellitus (DM) is still controversial<sup>(2,3)</sup>. The affected lipid profile and cardiovascular diseases were detected especially in menopausal loss of estrogen<sup>(4)</sup>. Contrary, it was shown that postmenopausal women receiving HT could have a smaller relative risk of such diseases in comparison with women who do not use HT<sup>(5)</sup>. Some studies sustain the fact that the cardiovascular risk reduction from HT is a consequence of their effect on lipid function of being postmenopausal<sup>(6)</sup>. Moreover, the affected lipid profile and renal outcome have been referred to menopausal loss of estrogen<sup>(7)</sup>.

Multiple risk factors have been identified as contributory to the development of cardiovascular disease. There are several risk factors for accelerated cardiovascular disease and atherosclerosis in postmenopausal women including

lipid abnormalities (i.e. diminished high-density lipoprotein cholesterol (HDL-C), triglycerides (TG)) and renal indexes (i.e. urea and creatinine serum)<sup>(8,9)</sup>. This further implies that for most of the researchers it become more difficult in establishing a correlation between lipid profile and cardiovascular disease in postmenopausal women with or without DM<sup>(10)</sup>.

In the general population of postmenopausal women, hormonal therapy (HT) showed to reduce the cardiovascular risk by up to 50%<sup>(11)</sup>. Only 25% of this reduction has been attributed on decreasing the lipid parameters<sup>(12)</sup>. In the same context, oral estrogen intake showed to decreased LDL-C and increased HDL-C and TG in normal women<sup>(13)</sup>.

In the present study, we performed a prospective research to evaluate the effects of HT on lipid profile and to estimate glomerular filtration rate including inflammatory acute markers on postmenopausal women with or without DM.

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## Methods

A total of 190 postmenopausal women from CI Parhon, National Institute of Endocrinology Bucharest, Romania were enrolled in the study. The women were randomly divided starting from 2012 till 2015 into Group 1 (placebo), who refused the HT (n=120) and Group 2, those who received HT (n=70). The patients from Group 1 were divided in patient with DM (n=21) and patients with normal blood sugar (n=99). The women from the 2<sup>nd</sup> Group were divided into women with DM (n=12) and women with normal blood sugar (n=58). The erythrocyte sedimentation rate (ESR), cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), urea and creatinine were analysed.

Additionally, ESR was determinate by Westergren method<sup>(14)</sup>. The rest of the samples were centrifuged immediately at 3000 rpm for 5 min and divided aliquots were stored until assay. Serum total cholesterol and TG were measured by enzymatic methods using a Hitachi chemical autoanalyser. HDL-C was analysed enzymatically after precipitation of other lipoprotein with heparin<sup>(15)</sup>.

Further to measure liver function and to assess renal function we used urea serum and for the estimation of glomerular filtration rate we used creatinine serum. Blood urea was determined by enzymatic reaction, and serum creatinine was measured by the Jaffe method<sup>(16)</sup>.

Exclusion criteria in both groups included hypertension (systolic blood pressure  $\geq 140$ ), anemia, renal insufficiency, evidence of significant liver disease and hysterectomy. The inclusion criteria were as follows: perimenopausal and menopausal status based on anamnesis following the installation age or after follicle stimulating hormone level ( $> 25$  UI/L).

All postmenopausal women were randomly allocated HT (i.e. Climene (2 mg estradiol valerate micronized and 1 mg cyproterone acetate micronized), Estraderm and Dydrogesteron (estradiol patch, TTS 25, 50, 100 mg), Livial (2.5 mg tibolone), Premarin (0.625 mg conjugated estrogens), Kliogest (1 mg estradiol/norethisterone acetate), Femoston (1mg estradiol or a combination of 1mg estradiol and 10 mg dydrogesterone), one each day or the placebo. Only the patients hosted in 2015 in the Institute gave written informed consent. The protocol was approved by the CI Parhon, National Institute of Endocrinology Bucharest from Romania.

## Statistical analysis

The features were compared between two groups and simple regression analysis was performed to assess the linear relationship between study parameters and descriptive statistics were used for baseline data. Results were considered significant at  $p < 0.05$ . All p values were 2-tailed.

## Results

The ESR in the 1<sup>st</sup> Group had a mean age of  $7.90 \pm 0.889$  mm/h for those with DM and  $18.93 \pm 15.727$  mm/h for those with normal blood sugar. In the 2<sup>nd</sup> Group, the mean ESR was  $19.08 \pm 8.107$  mm/h for those with DM and  $19.19 \pm 11.67$  mm/h for those with normal blood

sugar (Figure 1). In this case it can be seen a reduction of inflammatory marker in the 1<sup>st</sup> Group without HT comparing with the 2<sup>nd</sup> Group with HT.

The patient from the 1<sup>st</sup> Group, without HT had a mean of total cholesterol of  $263.27 \pm 34.75$  mg/dl for those with DM and  $211.62 \pm 26.53$  mg/dl for those with normal blood sugar. In the 2<sup>nd</sup> Group, with HT the mean of total cholesterol was  $228.16 \pm 38.02$  mg/dl for those with DM and  $219.34 \pm 47.10$  mg/dl for those with normal blood sugar. Therefore, here the total cholesterol showed to decreased in Group 2 with HT especially on those with normal blood sugar (i.e.  $219.34$  mg/dl) comparing with the 1<sup>st</sup> Group without HT, sustaining the beneficial effect of HT on lipid enzymes (Figure 2).

The women from the 1<sup>st</sup> Group had TG values of  $190.15 \pm 17.62$  mg/dl for those with DM and  $120.11 \pm 46.91$  mg/dl for those with normal blood sugar. In the 2<sup>nd</sup> Group, it was registries values of  $109.10 \pm 64.64$  mg/dl for those with DM and  $135.36 \pm 68.34$  mg/dl for those with normal blood sugar. Therefore, the lowest value was from the 2<sup>nd</sup> Group (with HT) with DM (i.e.  $109.10$  mg/dl) comparing with the rest of the values which were similar sustaining in this case also the beneficial effect of HT on lipid profile (Figure 3).

In the case of HDL-C the 1<sup>st</sup> Group had values of  $49.54 \pm 3.40$  mg/dl for those with DM and  $52.84 \pm 9.22$  mg/dl for those with normal blood sugar. In the 2<sup>nd</sup> Group, it were registries values of was  $54.12 \pm 10.35$  mg/dl for those with DM and  $53.76 \pm 7.72$  mg/dl for those with normal blood sugar. In this case, the highest values were recorded in the 2<sup>nd</sup> Group with HT and with or without DM, sustaining together with cholesterol and TG the same results of beneficial HT effect (Figure 4).

The postmenopausal women were further indirectly assessing the renal function status using urea serum. It was seen that in the 1<sup>st</sup> Group the values were  $39.61 \pm 4.32$  mg/dl with DM and  $24.76 \pm 8.99$  mg/dl with normal blood sugar. In the 2<sup>nd</sup> Group with HT, the values were  $24.33 \pm 10.69$  mg/dl for the patients with DM and  $29.41 \pm 11.86$  mg/dl for the patients with normal blood sugar (Figure 5). Here the lowest values were observed at the patients from the 2<sup>nd</sup> Group with HT, sustaining a better renal function in comparison with the 1<sup>st</sup> Group without HT.

In the case of creatinine, in the 1<sup>st</sup> Group, the group without HT, the values were  $1.11 \pm 0.19$  mg/dl for the patients with DM and  $0.80 \pm 0.30$  mg/dl for the patients with normal blood sugar. From the 2<sup>nd</sup> Group with HT, the values were  $1.09 \pm 0.365$  mg/dl for the patients with DM and  $0.78 \pm 0.361$  mg/dl for the patients with normal blood sugar (Figure 6). Also in this case, the lowest values ( $< 1$  mg/dl) were presented by the 2<sup>nd</sup> Group with HT, especially those with normal blood sugar (i.e.  $0.78$  mg/dl) in comparison with the 1<sup>st</sup> Group, showing the fact that HT could sustain a better glomerular filtration rate.

## Discussion

The present study shows that HT has a favourable effect on lipoproteins in respect with cholesterol, TG and HDL-C in postmenopausal women with DM comparing

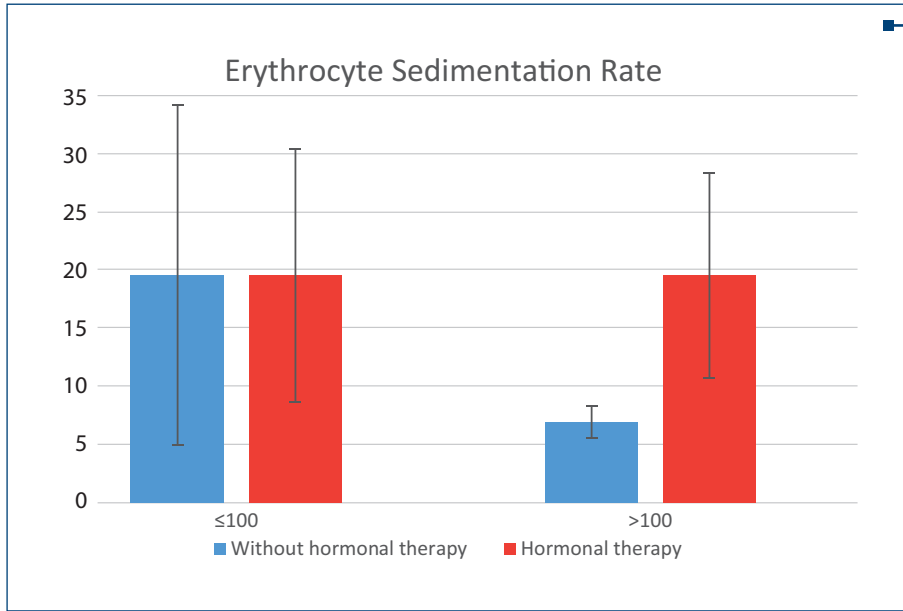


Figure 1. The distribution of ESR at the women with or without HT and with or without DM

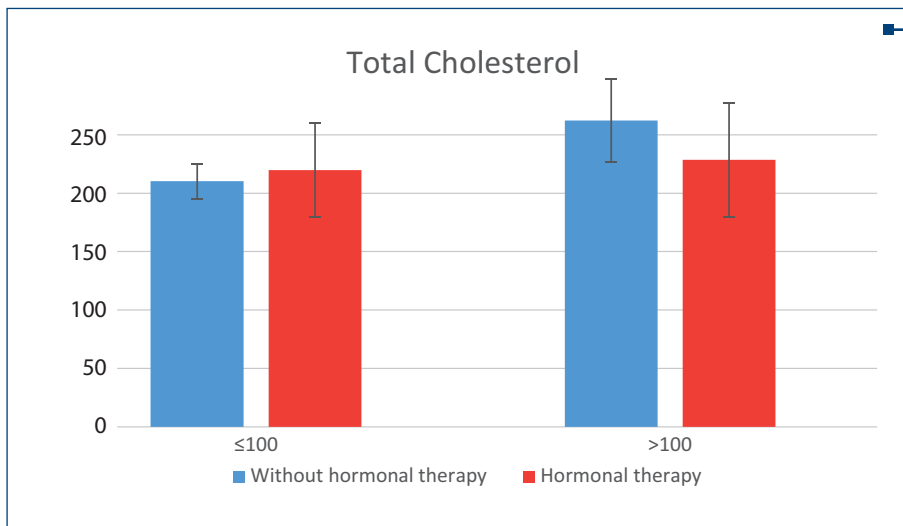


Figure 2. The distribution of cholesterol at the women with or without HT and with or without DM

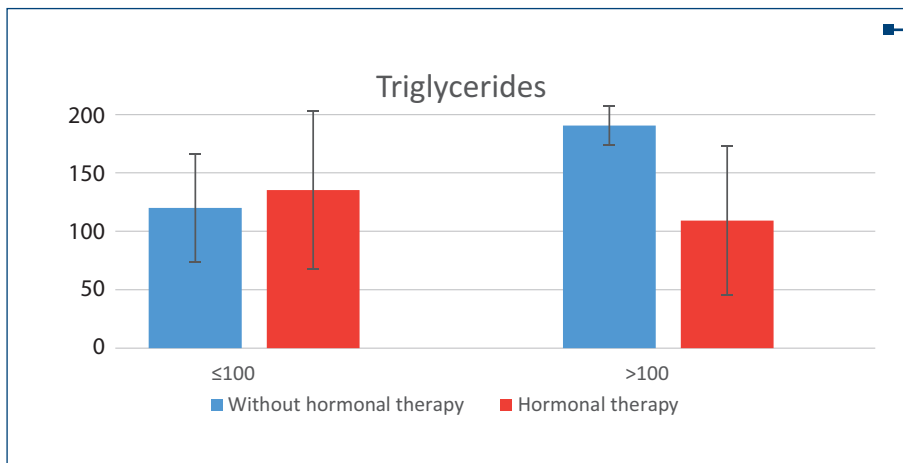


Figure 3. The distribution of TG at the women with or without HT and with or without DM

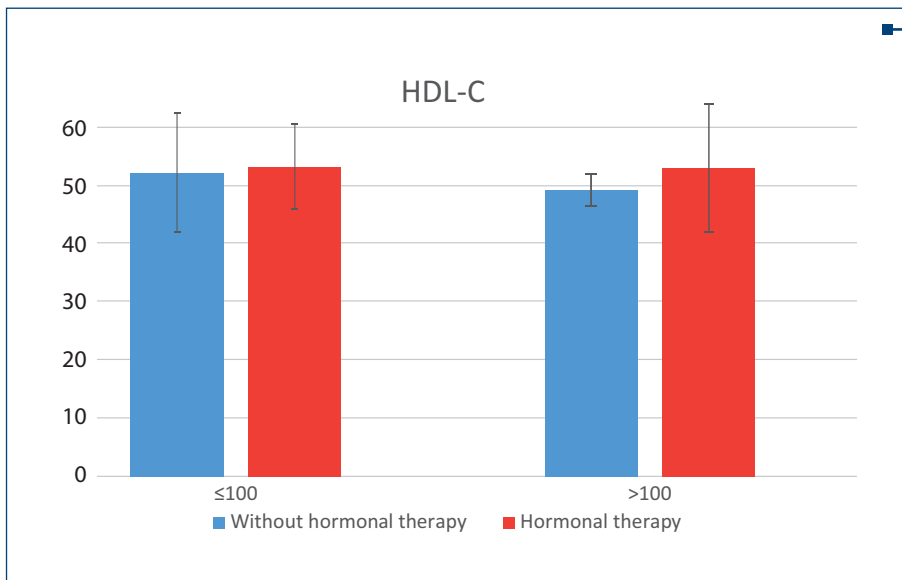


Figure 4. The distribution of HDL-C at the women with or without HT and with or without DM

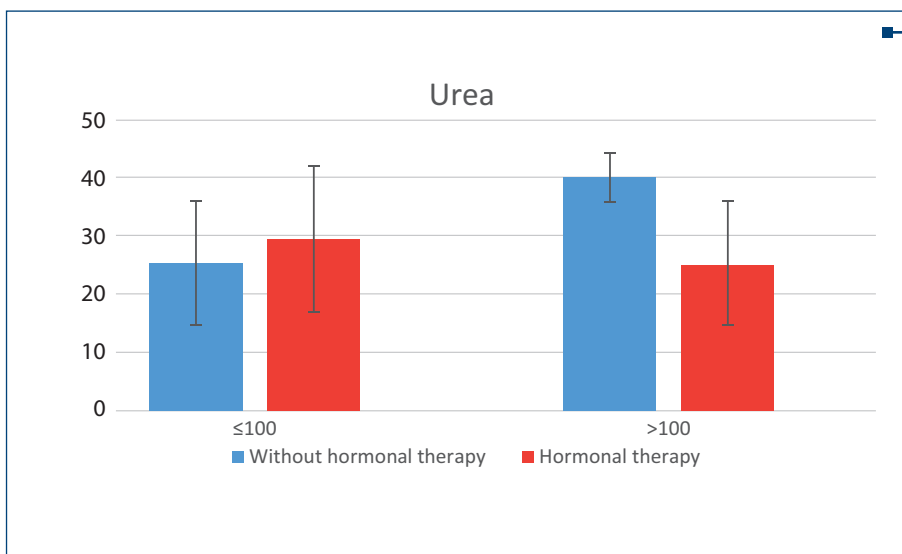


Figure 5. The distribution of urea at the women with or without HT and with or without DM

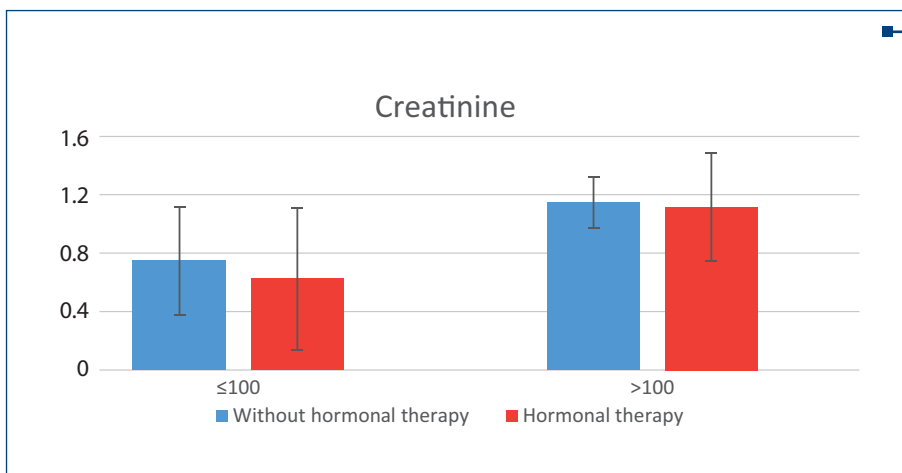


Figure 6. The distribution of creatinine at the women with or without HT and with or without DM

with postmenopausal women with normal blood sugar, although the inflammatory marker user (i.e. ESR) has presented opposite effects.

Ginsburg and contributors<sup>(17)</sup>, evaluated HDL-C and showed to be elevated by 16% after estradiol treatment for 8 weeks in 11 postmenopausal women with renal disease. Other study showed that the effect of estrogen on lipoproteins was reported to be smaller more on diabetic patient<sup>(18)</sup>. This study showed similar results for the lipid profile. When we analysed our data according to the presence of DM, the significant changes in cholesterol, TG, and HDL-C in HT Group (Group 2) seems to be absent in DM patients whereas all these were still significant in non-DM HT patients.

The HDL-C could be seen often by a lowest values, excepting the patients with chronic renal insufficiency<sup>(19)</sup>. In the present study, HDL-C values were within the normal range. However, oral HT increased the serum HDL-C in the group with HT comparing with the group without HT. Previous studies in patients with normal renal function suggest that the increased HDL-C could reduce the cardiovascular risk<sup>(20)</sup>. The TG concentration was not significantly decreased by HT replacement, but the lack of our results may be due in part to the small sample size of the present study. Whatsoever, the mean TG values were not in the normal range for both groups. In hemodialysis patients, the TG were increased maybe taken into account the defective TG removal<sup>(21)</sup>. Until presence, it was not found any correlation between the increased HT concentrations and HDL-C in the same

time, being most probably impossible to evaluate if higher HT concentrations will improve HDL-C:LDL-C ration or other lipid enzymes<sup>(22)</sup>.

However, this study was performed on limited numbers of patients and with a limited treatment duration and the side-effects of HT replacement could not be evaluated. Moreover, in the case of renal function, both urea and creatinine serum values showed that HT could maintain a better function and a constrictive glomerular filtration rate.

In the design of future studies based on HT, consideration should be made of their potential to improve other comorbidities such as prevention of osteoporosis<sup>(23)</sup>, symptoms of urogenital atrophy<sup>(24)</sup>, skin wrinkling<sup>(25)</sup>, and a decreased risk of Alzheimer's disease<sup>(26)</sup>. In patients with degraded renal function, it was showed to have better benefits especially on glomerular filtration rate<sup>(27)</sup>.

## Conclusions

Our results suggested that HT had a beneficial effect on lipid profile in terms of cholesterol, TG and HDL-C in postmenopausal women comparing with postmenopausal women without HT, although the inflammatory acute marker do not showed the same result. Regarding the renal function, it was seen that HT could sustain a better function together with a normal glomerular filtration rate. The present study, however, indicated the need for long-term prospective trials of large number of patients to determine whether HT should be routinely prescribed in postmenopausal women with or without DM. ■

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