Effects of Hormone Replacement Therapy on Insulin Resistance in Postmenopausal Women

POSTMENOPOZAL KADINLARDA HORMON REPLASMAN TEDAVİSİNİN İNSÜLİNE DİRENÇ ÜZERİNE ETKİLERİ

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Summary

Our aim was to investigate the effect of hormone replacement therapy (HRT) on insulin resistance in postmenopausal women.

Initially, 39 postmenopausal women were enrolled in the study. Fifteen patients out of 39 were found to have insulin resistance, and placed on hormone replacement therapy, consisting of conjugated equine oestrogen (0.625 mg/day) and medroxyprogesterone acetate (10 mg/day) for 3 months. Euglycaemic hyperinsulinemic clamp technique was used to determine insulin resistance before and after HRT.

The mean age was 50.6±6.4 (ranged between 37-59) years. The mean pretreatment level of M value was 3.3 ±0.6 mg/kg/min while the same value after 3 months' hormone replacement therapy was 4,54 ±0.9 mg/kg/min (p<0.001). The M value, which was the main objective of our study, was increased 28% by HRT (p<0.001). Additionally, HRT caused significant decreases in the levels of low density lipoprotein cholesterol (p<0.044), total cholesterol (p<0.016), serum insulin (p<0.022), and an increase in high density cholesterol (p<0.009) level while there were no statistically significant changes in the levels of C-peptide, glycaemia and triglyceride (p>0.05).

Our study showed that HRT improves insulin resistance and hyperinsulinemia, both of which have important role in the progression of atherosclerosis. Additionally, HRT offers a number of other advantages such as improvements in serum lipids and reduction in menopausal symptoms. As a result, HRT is beneficial in postmenopausal women who do not have contraindications to use these agents.

Key **Words:** Hormone replacement therapy, Insulin resistance, Postmenopause

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Özet

Bu çalışmada amacımız, hormon replasman tedavisinin (HRT) postmenopozal kadınlarda insuline direnç üzerine etkilerini incelemekti.

Postmenopozal dönemde olan 39 olgu çalışmaya alındı. Olguların çalışmaya dahil edilebilmeleri için diabètes mellitus, glukoz tolerans bozukluğu, obezite ve sistemik hastalığı bulunmaması ve daha önceden HRT yapılmamış olması koşulları arandı. Çalışmaya alınan 39 hastanın 15'inde insuline direnç tesbit edildi. İnsüline direnç saptanan 15 hastaya 3 ay süreyle konjüge östrojen (0.625 mg/gün) ve medroksiprogesteron asetat (10 mg/gün) verildi. Tedavi öncesi ve sonrası hiperinsülinemik öglisemik klemp tekniği kullanılarak insüline direnç araştırıldı.

Çalışmaya alınan olguların yaş ortalaması 50.6 ±6.4 (37-59) idi. incelenen parametreler olan M değeri, serum insülin ve C-peptid, total kolesterol (TK), trigliserid (TG), yüksek dansiteli lipoprotein kolesterolü (HDL-K) ve düşük dansiteli lipoprotein kolesterolü (LDL-K) düzeyleri sırasıyla şöyle idi; 3.3 ± 0.6 mg/kg/dk, 39.0 ±10.1 mIU/ml, 3.0 ±1.1 ng/ml, 230 ± 43 mg/dl, 152 ± 65 mg/dl, 41.8 ± 6.1 mg/dl ve 188 ± 6.4 mg/dl. Aynı parametrelerin 3 aylık HRT sonrası düzeyleri ise, yine sırasıyla, 4.54 ± 0.9 mg/kg/dk, 26.6 ± 10.1 mIU/ml, 3.57 ± 0.6 ng/ml, 209 ± 27 mg/dl, 132 ±37.9 mg/dl, 48.4 ±3.9 mg/dl ve 161 ± 8.2 mg/dl idi. HRT ile M değeri ortalama %28 artma gösterdi (p<0.001). Ayrıca, LDL-K %2 (p<0.044), TK %9.1 (p<0.016) ve insülin düzeyi %33 (p<0.022) azalma, HDL-K ise %17 (p<0.009) artma gösterdi. Buna karşılık, TG, C-peptid ve glisemi düzeylerinde anlamlı ölçüde bir değişme olmadı (p>0.05).

Çalışmamızda HRT ile hem insülin direncinde hem de serum insülin düzeyinde anlamlı bir iyileşme sağlandığını tesbit ettik. Bu nedenle, eğer ciddi bir kontrendikasyon yoksa, postmenopozal kadınlarda HRT uygulanmasının yararlı olacağını söyleyebiliriz.

Anahtar Kelimeler: Hormon replasman tedavisi, insüline direnç, Postmenopozal dönem

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Coronary artery diseases, hypertension, stroke, vasomotor disturbances, osteoporosis and resulting fractures begin to rise in women with the termination of reproductive life although these conditions

are rather rare before menopause (1). This rise is believed to be due to deficiency of oestrogen hormone in the postmenopausal period. So, hormone replacement therapy (HRT) in this period seems to be an appropriate approach to lower these undesired risks.

The increased incidence of coronary heart disease in women with sex hormone deficiency may be lowered by use of HRT (2). Although the relation between coronary artery disease and the loss of ovarian functions has been known for a long time, benefits of HRT have recently become to be clear (3,4). In the population studies, it was evidently showed that HRT had beneficial effects on coronary artery disease (5). Though HRT has some good effects on lipids and lipoproteins, it is not possible to explain its all beneficial effects on coronary artery disease with only this mechanism. Disorders of glucose and insulin metabolism have important role in the development of coronary artery disease. It is a well-known fact that coronary artery disease is more common in men than in women. This condition suggests that female sex hormones may have a number of effects on carbohydrate and insulin metabolism (6). Impaired glucose tolerance is an independent risk factor for the development of coronary artery diseases and it is claimed that this feature is related to insulin resistance and hyperinsulinemia. Currently, the clamp technique is known to be the most sensitive method for the measurement of insulin resistance (7). In postmenopausal women, it is claimed that insulin resistance may contribute to the increase in mortality of coronaiy events, by accelerating the atherosclerosis. For this reason, HRT has recently come to light to improve the insulin resistance in such conditions. But many studies about this subject performed rather insensitive methods and the data obtained is not conclusive. While some authors reported that HRT had no good effect on insulin resistance, even more increased it, the others reported that HRT had beneficial effects on the insulin resistance (8,9). So, we planned this study to investigate the effects of HRT on insulin resistance, by using hyperinsulinemic euglycaemic clamp technique, which is accepted as the most sensitive method in this field.

Subjects and Methods

Initially, 39 postmenopausal women were enrolled in the study. The diagnosis of menopause was confirmed with the serum levels of follicle stimulating (>40 mlU/ml) and luteinizing hormones (>25 mlU/ml), and oestradiol (<30 pg/ml) in addition to history of absence of menses at least for one-year. A11 participants gave written informed consent to be included in the study. Exclusion criteria were as follows; diabetes mellitus, impaired glucose tolerance, obesity (body mass index >30 kg/m2), systemic diseases, or history of previous hormone replacement therapy.

After having medical history, we performed a detailed physical examination in all patients. Gynecologic examination was made by one of the gynaecologists of our hospital. Then, mammographic examinations of breasts, ultrasonographic examination of the breasts and the whole abdominal region were performed. PAP smear was obtained to exclude the existence of any cervical malignancy. After history, physical examination and laboratory investigations, we assessed the state of insulin sensitivity in those 39 patients by using hyperinsulinemic euglycaemic clamp technique. Of these, then, 15 postmenopausal women with insulin resistance were given hormone replacement therapy, consisting of conjugated equine oestrogen 0.625 mg daily and medroxyprogesterone acetate 5 mg daily for 3 months. After a 3-month period of therapy, we measured insulin sensitivity again, in addition to hormonal and biochemical measurements, which we made at the beginning also.

After over-night fasting, blood samples were obtained from antecubital vein. In these samples biochemical parameters and hormone levels were measured. Complete blood counts were made with the aid of an automatic device (HI Technicon, USA) and routine biochemical measurements were performed by using an outoanalyser (RA 1000 Technicon, USA). Serum insulin levels were measured by the coated-tube method (DPC, USA) and C-peptide leves were measured by radioimmunoassay method (DSL, USA). Normal levels for insulin were below 30 mU/ml, for C-peptide below 3.5 ng/ml.

Hyperinsulinemic euglycemic clamp technique, described by DeFronzo et al (10), was used to detect the existence of insulin resistance in the subjects. After over-night fasting, the patients were studied at 09.00 a.m. The temperature of the room was around 20 °C, the patients were kept in supine position during the study. During this test basal glycaemia before the test and blood glucose levels at every 10 minutes for 120 minutes were measured using a glucometer (B-Glucose, Hemoccue AB, Sweden). Crystalline insulin (Humulin R, Lily Inc., USA) solution, of 300 mlU/ml concentration, was prepared in isotonic saline solution. Four-ml blood, which was obtained from the study subject, was added into this solution to prevent insulin to adhere to the wall of plastic tube. Insulin and 20% dextrose solution was given by infusion pumps intravenously (Abbot-Show, Life Care Pump). The infusion rate of this insulin solution was adjusted according to the formula described by DeFronzo et al. Four minutes after the onset of insulin infusion, glucose infusion, at a rate of 2 mg/kg/min, was started to prevent hypoglycaemia and resultant contra-regulator responses. The rate of this infusion was increased to 2.5 mg/kg/min at tenth minute and then was adjusted according to the prevailing glycaemia, measured at every 10 minute. The glycaemia values, which were measured at every ten minutes for 120 minutes, were separated into 5 groups. Based on these measurements, glucose disposal rate was calculated for every 20-minute period and these were referred as M1-5. Arithmetic mean of these M1-5 values gave us a mean M value (Mm), which denotes total glucose disposal rate. This M value, also calculated by the formula defined by DeFronzo et al. (10), was used to establish whether insulin resistance existed. The subjects who had M value less than 4 mg/kg/min were accepted as insulin resistant.

Statistical calculations were made by Wilcoxon paired sign test with the aid of a PC compatible statistics program, SPSS 6.0 for Windows. P values less than 0.05 were accepted as statistically significant.

Results

The study group was composed of postmenopausal women. The mean age was 50.6±6.4 (ranged between 37-59) years. Of the patients, 3 (aged 37, 43, and 45 years) were surgically menopaused whereas the others were normal menopausal women.

Table 1. Study parameters before and after hormone replacement therapy

Parameter	Pretreatment	Posttreatment	p value
"average (mg/kg/min)	3.3±0.6	4.54±0.9	0.001
Insulin (mlU/ml)	39±11	26.6±10.1	0.022
C-peptide (ng/ml)	3.0±1.1	3.57±0.6	0.167
TC (mg/dl)	230±43	209±27	0.Q16
TG (mg/dl)	152±65	132±37.9	0.551
HDL-C (mg/dl)	41.8=1=6.1	48.4±3.9	0.009
LDL-C (mg/dl)	188±6.4	161±8.2	0.44

The mean pretreatment levels of M, insulin, C-peptide, total cholesterol, triglyceride, high density-lipoprotein cholesterol, and low density-lipoprotein cholesterol were 3.3±0.6 mg/kg/min, 39±10.1 mIU/dl, 3.0±1.1 ng/ml, 230±43 mg/dl, 152±65 mg/dl, 41.8±6.1 mg/dl and 188±6.4 mg/dl, respectively. Same values following 3-month hormone replacement therapy were as follows; 4,54±0.9 mg/kg/min, 26,6±10.1 mIU/dl, 3,57±0.6 ng/ml, 209±27 mg/dl, 132±37.9 mg/dl, 48.4±3.9 mg/dl and 161±8.2 mg/dl. These results altogether are shown in Table 1. With the hormone replacement therapy, meaningful improvements occurred in the levels of insulin, LDL-C, HDL-C, and the M values. However, there were no statistically significant changes in the levels of triglyceride, C-peptide, and basal glycaemia. The M value (shown in Figure 1), which was the main objective of our study, increased 28% with HRT and this increase was statistically significant (pO.001). Also, there was 2.9% decrease in LDL-C ($p<0.044$), 9.1% in TC ($p<0.016$), 33% in serum insulin ($p<0.022$) and 17% increase in HDL-C ($p<0.009$) levels while there were no statistically significant changes in the levels of C-peptide and TG ($p>0.05$). These results are also shown as graphics in Figure 1.

Discussion

Our results demonstrate HRT has significantly useful effects on both insulin resistance and plasma insulin levels, both of which are believed to have a

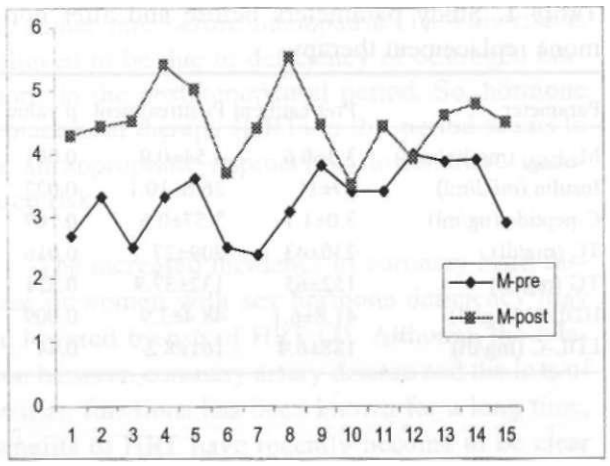

Figure 1. Pre- and posttreatment M values.

central role in the development of atherosclerosis and related conditions. Disturbances of carbohydrate metabolism and insulin sensitivity play an important role in the development of coronary heart diseases. Impaired glucose tolerance is a well-known risk factor for the development of coronary artery diseases and this condition may be related to hyperinsulinemia and insulin resistance (11). Lindheim and coworkers reported that there was insulin resistance in 44-60% of healthy postmenopausal women, by using insulin tolerance or intravenous glucose challenge tests (8). It has been known that there is a close relation between the increase in the risk of coronary artery disease and loss of ovarian function (3,4). Basal serum insulin levels are frequently found increased in both female and male patients with coronary heart disease. Some researchers found that there was insulin resistance in syndrome X cases, irrespective of gender (11). Insulin resistance is due not only to changes in lipoproteins, but also to blood pressure, android type obesity and increased plasminogen activator inhibitor-I (12). Hyperinsulinemia may cause an increase in the risk of coronary diseases by directly triggering atherosclerosis. It was also shown that there was increased insulin resistance in premature coronary disease (11).

Although it is generally agreed that estrogen hormone has a protective effect against cardiovascular diseases in women it is disputable how estrogen exerts this effect. Although it was claimed that the use of combined oral contraceptive pills caused impaired glucose tolerance, this intolerance may result from the progesterone component of the pill rather than estrogen. Women taking oral contraceptives, especially the older formulations, have hyperinsulinemia and sometimes glucose intolerance. The degree of hyperinsulinemia seemed to correlate with the progestin component of oral contraceptive pills (13). Some authors reported that progestins significantly reduce both insulin binding and glucose transport whereas estrogens actually increase insulin-binding (14). It has been suggested that estrogen replacement therapy may improve insulin sensitivity. A study by Hargreaver et al. showed that there was a 25% increase in the insulin sensitivity by use of replacement (15). A study by Godsland et al. (16) also claimed that oral contraceptives cause insulin resistance. The results of a study by Elkind-Hirsch et al. (17) showed a significant decrease in sensitivity to insulin associated with combined estrogen-progesterone treatment but no apparent changes in insulin sensitivity during estradiol-only phase of cyclic steroid replacement therapy in young women with premature ovarian failure.

A study performed in surgically postmenopausal cynomolgus monkeys demonstrated that progestins alone or in combination with estrogens could induce insulin resistance while having no effect on plasma lipid concentrations or glucose effectiveness (18). Some authors reported that hormone replacement therapy may modestly decrease fasting levels of insulin and glucose but increases postchallenge glucose concentrations (19). A study, by Miller et al., showed that HRT caused 4.8% reduction in LDL-C and 12-19% in LDL-C (20). In agreement with the results of these studies our results also demonstrated hormone replacement therapy has beneficial effects on plasma lipids. Moderate effects of therapy were found on insulin resistance in postmenopausal women, although long-term, controlled trials using accurate measurements of insulin sensitivity are lacking. Treatment with progestins exerts moderate deleterious effects on insulin sensitivity, which may be attributable to the partial androgenicity of progestins used (19).

Our study shows that HRT can improve insulin resistance and hyperinsulinemia, both of which have important role in the development of atherosclerosis. Additionally, HRT offers a number of other advantages such as improvement in serum lipids and reduction in menopausal symptoms. It is concluded that the increased incidence of cardiovascular disease in postmenopausal women may be attributable to a number of adverse factors including insulin resistance. As a result, therapies aiming to improve these changes, such as hormone replacement therapy, are likely to provide metabolic and cardiovascular benefits for women's health.

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