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The Effects of Hormone Replacement Therapy on the Human Body

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Abstract

Hormone replacement therapy has been used for decades to treat hormonal imbalances in women and more recently men. The purpose of this literature review was to evaluate different hormones used in this common practice and evaluate them for efficacy and safety. Research was conducted using PubMed and other databases from the Grand Valley State University Library. Keywords such as “hormone replacement therapy,” “estrogen risks,” and “hypogonadism” were used to evaluate peer-reviewed articles from 1993-2014. There is overwhelming evidence to suggest that testosterone seems to be an effective treatment for hypogonadism. Estrogen may also be effective if risk factors for breast cancer are taken into consideration. Hormone replacement therapy should utilize individual dosing and not be used long term until further research is conducted.

Introduction

Hormone replacement is a newer form of therapy that has been integrated into common medicinal practices today. It began to appear in the 1960s to treat menopausal symptoms, and by the 1970s its popularity grew to millions of women (14). HRT today is used to treat women's menopausal symptoms such as hot flashes, mood swings, and vaginal dryness as well as other more serious ailments. Men have also joined the movement to treat low testosterone levels which may help prevent other diseases such as dementia (5). The reason why hormone replacement is growing in popularity is due to its treatment of hormone imbalance. Rather than treating the symptoms themselves, it treats the underlying cause. Hormone replacement therapy is a prescription program that consists of sex hormones such as estrogen or testosterone administered to various sites of the body. Testosterone is essential for the development and maintenance of reproductive organs such as the testis, prostate, epididymis, seminal vesicles, and penis (17). It is also used to develop secondary sex characteristics such as increased muscle strength, hair growth, and others (17). Estrogen is a substance that "maintains secondary sex characteristics and organs such as mammary glands, uterus, vagina, and fallopian tubes" (8). The major estrogenic substances are estradiol, estriol, and estrone (8). In order to receive this type of treatment, the physician has to be specially trained, and the medication must be compounded at a specialized pharmacy. HRT is said to have many benefits, but recent studies suggest that the costs may outweigh them. There are certain health hazards that are concerning when placed on hormone therapy. Is it worth it to be on hormones if other complications arise? This literature review will assess the benefits and risks of testosterone and estrogen specifically in hormone replacement therapy and determine whether or not they are viable methods of treatment.

Literature Review

Supporting Evidence for Testosterone Replacement Therapy

A testosterone study performed by Muraleedharan et al. (16) suggests that replacement therapy may increase survival of type 2 diabetics. Type 2 diabetics tend to have low testosterone. The researchers analyzed 581 men with type 2 diabetes and had their testosterone levels measured. The effects of testosterone replacement therapy were assessed with the low testosterone group. Mortality was increased in the low testosterone group by 17.2% compared with the normal testosterone group (9%). The association was significant ($p=0.003$). Testosterone replacement therapy was associated with a reduced mortality of 8.4% compared with the untreated group's 19.2% ($p<0.002$). The researchers concluded that lower testosterone levels predict an increase in mortality in the long term and that testosterone may improve survival rates for men with type 2 diabetes.

Testosterone replacement therapy may also be used to treat men from suffering from both hypogonadism and HIV/AIDS. Those suffering from HIV/AIDS tend to also have low levels of testosterone. A study performed by Blick et al. (3) explored this usage of testosterone. 849 men participated in a cohort where they were treated for 12 months with Testim, a testosterone supplement. The researchers monitored total testosterone and free testosterone, symptoms of depression, sexual dysfunction, body composition, and prostate-specific antigen levels. Those suffering from HIV/AIDS and those who did not both experienced an increase in testosterone levels to normal ranges. Sexual function and depression scores improved and antidepressant use decreased in both sides. However, body composition only improved significantly in those

without HIV/AIDS ($p<0.05$). The researchers determined that testosterone replacement may provide some clinical benefits regardless of whether or not a patient has HIV/AIDS.

Testosterone replacement therapy can possibly be used to help treat inflammation as well. A study by Tsilidis et al. (23) examined the association of sex hormone-binding globulin with C-reactive protein and white blood cell count. Data from 809 adult males in the National Health and Nutrition Examination Survey from 1999-2004 was used in the study. Upon analyzing the data, they concluded that high concentrations of testosterone were associated with significantly lower concentrations of C-reactive protein, a protein commonly seen in inflammation. However, no significance was seen with a lower count of white blood cells. There is evidence in this finding to suggest that testosterone replacement therapy may have some anti-inflammatory benefits.

Testosterone has been seen to improve psychological distress and quality of life according to a study done in China by Zhang et al. (26). They wanted to analyze the relationship between testosterone deficiency and psychological well-being as well as quality of life. 160 participants were randomized into an experimental or placebo group and asked to complete questionnaires about aging male symptoms, anxiety, depression, stress, and overall health. Men received treatment for six months. Anxiety improved significantly in the experimental group after six months ($p<0.05$) as well as depression scores ($p<0.05$). The scores regarding stress also decreased significantly ($p<0.05$) as well as scores for overall health ($p<0.05$). There was no measureable change in the control group after six months. Researchers concluded that testosterone replacement not only improves deficiency symptoms but may also improve psychological issues.

Testosterone replacement for hypogonadism alone was observed by Miner et al. (15) for twelve months. They used the Testim Registry in the United States to conduct their research. The Testim Registry is a prospective, observational cohort of men who were prescribed Testim. This registry has measurements of total testosterone and free testosterone, prostate-specific antigen, sexual function, mood/depression, and cardiometabolic criteria before and after testosterone replacement. 849 participants were used, and 743 of them were given the drug. Mean total and free testosterone increased significantly after the use of TRT ($p<0.001$ and $p<0.001$ respectively). Mean PSA levels also increased significantly ($p<0.004$). There were significant improvements in sexual function, mood, depression, and cardiometabolic measurements as well. As a result, the researchers established that testosterone deficiency symptoms improved with TRT in men.

Another trial with testosterone that yielded positive results for men with hypogonadism was performed by Dobs et al. (7). This was an open label, noncomparative trial of men with low testosterone. The goal of the study was to determine the pharmacokinetics and safety of a testosterone 2% gel. 129 patients were included in the results. After three months, 100 patients had total testosterone concentrations within the normal physiological range. The gel was well-tolerated with only mild to moderate skin reactions. 2% testosterone restored testosterone levels in 75% of patients with only a low risk of high levels. The researchers determined testosterone replacement therapy of this sort to be safe and effective with minimal adverse effects.

Opposing Evidence for Testosterone Replacement Therapy

Despite all the positive factions associated with testosterone therapy, He et al. (11) studied the cardiometabolic risks that may be associated with it. They recruited 112 men ages 65-

90 to participate. The research was double blind and used a placebo to ensure quality. Transdermal testosterone was administered for 16 weeks. Testosterone levels, body composition, and cardiometabolic risk factors such as upper body fat, blood pressure, insulin sensitivity, fasting triglycerides, and HDL-cholesterol were measured. The researchers found that some of the cardiometabolic factors such as total fat, triglycerides, and HDL-cholesterol improved. Other risk factors such as systolic blood pressure and insulin sensitivity worsened. Overall, cardiometabolic risk scores improved significantly ($p<0.001$). The study concluded that there are diverse changes in cardiometabolic risks, but overall testosterone therapy did not appear to worsen the risk in healthy older men.

Supporting Evidence for Estrogen Replacement Therapy

Estrogen is another popular hormone used in replacement therapy for women. One of the ways that it may be beneficial for people is to treat hormone imbalances and resulting menopausal symptoms. Therefore, many clinical trials have been studied for this purpose. One such study was done by Botelho et al. (4). They analyzed the effects of a hormone supplement and its use to treat menopausal symptoms. The supplement consisted of estradiol, estriol and progesterone. 66 women with symptoms received transdermal hormones in the forearm for 60 months. An improvement was made in symptoms for 92.5% of women. Researchers also found no adverse effects. A mammography was performed to check for breast cancer or abnormalities. As a result of this study, researchers concluded that hormone replacement with this design was safe and effective in treating menopausal symptoms.

Another study by Chittacharoen et al. (6) corroborates these results. An open, uncontrolled phase IV clinical trial was performed on 39 perimenopausal or postmenopausal

women. They received an oral supplement of estradiol and levonorgestrel for six cycles. A menopause rating scale was used to measure severity of symptoms. During the first treatment, the general score decreased by 34.9% after 3 months. Psychological complaints decreased by 34.1% and urogenital complaints decreased by 29.3% after three months. It appears as though at least three months of administration of this supplement caused alleviation of menopausal symptoms by a considerable amount.

Saure, Planellas, Poulsen, and Jaszczak (19) studied a newer combination of hormones and its alleviation of menopausal symptoms. This new formulation, an estradiol combination supplement called Liesta, was compared to another common hormone replacement treatment. 376 perimenopausal women were randomly selected to receive Liesta or the other treatment for six cycles. All the treatments resulted in reduced menopausal symptoms. Hot flashes were no longer present in 71% of the women in the Liesta group and 62% of the other women. Perspiration decreased from 80 to 65% of women in the Liesta group and from 82 to 63% in the other group. Mood swings also decreased from 82 to 52% in the Liesta group. There is evidence to support that both regimens alleviated menopausal symptoms.

A study performed by Ushiroyama, Atsushi, Sakuma, KouUeki, and Minoru (24) examined estrogen's specific effect on a common complaint of menopausal women. They looked at the association between blood flow in the extremities and hot flashes compared to changes in blood flow after estrogen replacement therapy. The study utilized 131 post-menopausal women and treated them with HRT. Before treatment, those who experienced hot flashes had higher blood flow under the jaw than those who did not. Once the estrogen treatment was administered, blood flow at the site decreased significantly ($p<0.0001$). HRT may have therapeutic effects for post-menopausal women suffering from hot flashes.

Besides menopausal symptoms, estrogen replacement may also have other benefits. Estrogen may promote skeletal muscles regeneration. A study by Velders and Diel (25) suggests this notion based on several animal and controlled human studies that they analyzed. Skeletal muscle normally declines with age, but sex hormones may be able to slow the process. The animal studies they studied used estrogen receptor antagonists and receptor selective agonists as their method of measurement. The studies determined that estrogen reduces leukocyte invasion and increases satellite cell numbers during the regeneration of skeletal muscle. Human studies have not been as clear, but they do support this concept. It appears as though hormonal therapies plus exercise help increase tissue mass.

Estrogen may also be able to help manage oxidative stress and improve quality of life according to Sanchez et al. (21). They executed a clinical trial that was controlled and had 111 perimenopausal participants. The women were divided into three groups: premenopausal women in a control group, postmenopausal women receiving HRT, and postmenopausal women receiving a placebo. Lipoperoxides were used as the biochemical marker to measure oxidative stress levels. The results were that levels of lipoperoxides were higher in postmenopausal women with low quality of life ($p<0.05$). Those who received the estrogen supplement with a lower quality of life saw diminished plasma lipoperoxides in six months ($p<0.01$). Therefore, the researchers decided that estrogen therapy improves quality of life and reduces lipoperoxides in postmenopausal women.

Estrogen therapy may also be possibly used to treat asthma according to Ticconi, Pietropolli, and Piccione (22). Their review analyzed many studies performed to determine whether estrogen replacement therapy is a viable treatment for asthmatic symptoms. Their reason for doing this is that estrogen has significant effects on normal airway function. It can work

directly on airway reactivity or indirectly through regulation of inflammation and immune response in the lungs. Naturally it would seem that replacing estrogen would improve asthma symptoms. Unfortunately, the impact of ERT on asthma was not determined at the end of this review. The extensive available data shows that estrogen has a large impact on airway function, but it is inconsistent and unclear.

Recently it has been thought that estrogen may be used to improved cognitive function as well. However another study by Espeland et al. (9) suggests otherwise. Cognitive testing on postmenopausal women was performed 7.2 years after the hormone therapy was administered to them. 1326 women with a mean age of 67.2 years participated in the study. Global cognitive function scores were similar for those who received treatment and those who were given a placebo ($p=0.66$). There was also not a difference in any other areas of cognition that were measured ($p=0.15$). The researchers determined that there was neither benefit nor risk to taking hormone replacement therapy with cognition.

Opposing Evidence for Estrogen Replacement Therapy

As effective as estrogen therapy may seem to appear, it has also been the subject of recent debate. Several publications have come out that indicate serious adverse effects that may be associated with HRT. Amadou et al. (1) demonstrate this in their research of cancer. Data from a Mexican multi-center population-based case-control study of women was analyzed. Over 2000 participants were analyzed from 2004-2007 using a questionnaire. The result of this study was that there was a significant increase in the odds ratio risk of breast cancer in individuals using hormone replacement therapy (OR: 1.45). Therefore, the researchers concluded that HRT had a significant effect on post-menopausal breast cancer in this population of Mexican women.

Another study of hormone replacement therapy's association with cancer was published by the Journal of the Gynecological Endocrinology (12). This article offers a mechanism behind sex therapy's cancer-causing ability as well as the risk of long-term usage. Sex hormones are not known to damage DNA directly, but they can stimulate or inhibit cell proliferation. Since tumors are the result of uncontrolled cell proliferation, hormones can manipulate tumor progression. According to their study of long term usage, the risk of having breast cancer diagnosed increases by 1.023 each year. As a result, this study suggests that HRT should only be used as treatment if patients suffering from menopausal symptoms have not experienced relief from alternative methods. It is also suggested that patients give informed consent before making the decision to proceed with therapy.

Breast cancer risk has been noticed in other studies of ERT as well. A study by Farhat et al. (10) suggests that estradiol and estrone replacement may increase the risk. A nested case-control study within the clinical trial performed by the Women's Health Initiative was done using 16608 postmenopausal women. Women were 50 to 79 years of age and had no history of breast cancer. 348 breast cancer subjects and 348 controls were selected and matched. Sex hormone levels were measured at baseline and then again one year later. Statistically significant elevations in the risk for breast cancer were seen in those treated with estradiol ($p<0.04$) and estrone ($p<0.007$). Therefore, this is more evidence supporting the idea that ERT may cause cancer.

Despite this evidence for breast cancer, other studies suggest that perhaps estrogen replacement therapy does not cause other types of cancer such as brain tumors. Andersen, Friis, Hallas, Ravn, and Gaist (2) decided to analyze the risk of gliomas in a case-control study. Women from 55-84 years of age with a diagnosed brain glioma were chosen for the study. 658

cases and 4350 controls were used. The odds ratio of hormone replacement therapy and gliomas is 0.9. The researchers concluded that HRT does not increase the risk for glioma in the short term.

A meta-analysis was performed by Qi et al. (18) to determine whether or not HRT increased the risk for other types of cancer. A literature search was done using databases such as PubMed and EMBASE until July of 2013 without any limitations. Twelve case-control and six cohorts were used. The results of this study were that there is an increased risk of a meningioma with hormone replacement therapy (RR=1.19). The researchers concluded that long term use of hormones may increase the risk of meningioma in women, although the mechanism behind it is unknown.

After reviewing the literature, other researchers have formed their own opinions on the topic of risks associated with HRT. For example, Khalil (13) came up with his own solution to hormone replacement therapy. His article suggests that estrogen dosage should be done individually. His research concerned the vascular benefits of estrogen. Cardiovascular disease is less common is premenopausal women than men or postmenopausal women, suggesting that estrogen may provide some vascular benefits. Estrogen receptors in endothelium and smooth muscle can signal pathways that lead to vasodilation and decreased smooth muscle contraction. Khalil reviewed clinical trials performed by the Women's Health Initiative and Heart and Estrogen/progestin Replacement Study (HERS). These studies did not demonstrate vascular benefits and even showed adverse effects. Several variables had an impact on the hormonal effects such as age-related changes, distribution, and post-estrogen receptor signaling. Due to such individual factors determining the effects of HRT, Khalil concluded that hormone therapy should be designed appropriately for each patient.

Estrogen is not the only hormone that people think should be dosed individually. Researchers like Shoupe (20) believe that before hormone replacement therapy is administered, a doctor should review cardiovascular risk in each patient. He thinks that it is important to take into consideration a woman's age, number of years since her menopause, and a number of cardiovascular risk factors. Based on other studies, Shoupe believes that those who have had a recent cardiovascular event, current thromboembolic disease, long-standing immobilization, or severe peripheral arterial disease should not use hormone replacements. Otherwise, they have an increased risk when taking hormone supplements.

Discussion

Hormone replacement therapy can be used to treat many different ailments of the body. Overall, different supplements can be beneficial and restore hormone imbalances when dosed individually. However, long term use is questionable.

There is overwhelming evidence to suggest that testosterone replacement therapy may be used to treat hypogonadism. Treating hypogonadism may indirectly treat other ailments such as type 2 diabetes, HIV/AIDS, inflammation, and psychological distress. Testosterone levels seemed to improve in all the studies. However, to improve research quality more double blind and placebo-controlled studies should be performed. Open label, uncontrolled studies seemed to be common amongst the literature. Testosterone replacement does not appear to have any adverse effects, which is great for individuals at a higher risk. More long-term studies should be conducted to reaffirm this though. Testosterone replacement therapy seems to be safe and effective for healthy individuals without major heart problems.

Estrogen appears to also be beneficial but has more risks associated with it. Estrogen supplementation appears to significantly relieve symptoms of menopause. More double-blind, controlled studies should be performed however to ensure quality of research. Many of the studies that yielded significant results were open label. Also, long-term use of estrogen may increase the risk for breast cancer as well as meningiomas. Therefore, it is not recommended for long term usage. Dosing should be done individually as well. If a patient is to use estrogen replacement, they should be informed of the risk. Evaluating a patient's overall risk factors such as age and cardiovascular trouble should prevent any other complications. Estrogen, although

seemingly beneficial, should be recommended only after other treatments have failed to yield results.

All patients taking hormone replacement therapy, especially women, should talk with their doctor to ensure it is the best method of treatment.

Conclusion

Hormone replacement therapy is a viable method of treatment. Out of the two types of hormones discussed in this literature review, testosterone seems to be the safest due to its lack of adverse effects. Both are effective in relieving hormonal imbalance and seem to be suitable methods of treatment. Estrogen carries with it serious possible side effects that can be deadly in patients with high risk. Long term usage is not recommended for either treatment until higher quality research is performed. Dosing should be individual and take into consideration cardiovascular risks as well as history of breast cancer. This will help determine predisposition to complications. Healthy individuals should consider usage if they are experiencing hormonal imbalance and have not received relief from other treatments.

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