Hormones in Wellness and Disease Prevention: Common Practices, Current State of the Evidence, and Questions for the Future

Erika T. Schwartz, MD[a,*], Kent Holtorf, MD[b]

KEYWORDS

• Hormones • Estrogen • Progesterone • Testosterone
• Thyroid • Growth hormone • Wellness • Prevention

The study and use of hormones have long been the domains of endocrinology, which is primarily focused on the pathologic phenomena encountered in the human body as they relate to hormones. No specific field in medicine has been designated to study and analyze the effects of hormones on wellness and disease prevention. As the field of wellness and disease prevention expands rapidly, it behooves the primary care practitioner, the first physician contact between the patient and the health care system, to become conversant and comfortable with hormone treatments as they relate to wellness and disease prevention.

Extensive scientific literature addresses the crucial role hormones play in the physiologic processes that maintain homeostasis. Much controversy surrounds the clinical use of various hormone therapies to support and maintain these processes in the aging patient. This article attempts to clarify some of the confusion and controversy surrounding estrogen, progesterone, testosterone, growth hormone, and thyroid hormones and discuss their roles as supported by the present state of evidence in disease prevention and aging as they apply to the primary care practice.

Hormones represent specific proteins produced by the human endocrine organs: pituitary, adrenals, thyroid, testes, and ovaries. Our focus is limited to estrogen, progesterone, testosterone, growth hormone, and thyroid. In health, all hormones are individually and wholly integral participants to the maintenance of cellular function

[a] 10 West 74 Street, Suite 1A, New York, NY 10023, USA
[b] 23456 Hawthorne Boulevard, Suite 160, Torrance, CA 90505, USA
* Corresponding author.
E-mail address: erika@drerika.com (E. Schwartz).

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and homeostasis. Hormone levels undergo diurnal variation and levels change in response to our environment, thought processes, stress levels, and food intake. Environmental toxins, medications, and pollutants also significantly affect hormone balance.

With the aging process, hormone levels decrease naturally. As these levels decline, problems with health maintenance arise. The diminution in hormone levels that occurs as a result of aging may or may not be compounded by concomitant disease states and environmental factors. In this article, we discuss age-related hormone loss and supplementation therapies for age-related hormonal deficiencies as possible first-line therapeutic modalities to be considered in our search to improve quality of life, prevent chronic illnesses, and maintain wellness.

ESTROGEN, PROGESTERONE, TESTOSTERONE

Scientists have determined the existence of three true end-organ sex hormones: estrogen, progesterone, and testosterone. Both men and women have all three hormones, although levels and ratios of these hormones vary according to gender.

Estrogen and progesterone are the dominant hormones in women. We are often faced with the misconception that estrogen, progesterone, and testosterone act independently of one another. Without fully understanding the inseparable nature of the interaction between all sex hormones, we cannot solve the problems caused by imbalances in their individual levels and the symptoms these imbalances cause.

Estrogen is made in the ovaries, the corpus luteum, adrenal glands, and fat cells. Estrogen is not one big molecule; rather, it is a group of molecules. In humans, the three main identified estrogen molecules are estriol, estradiol, and estrone.

Estradiol is the most active form of estrogen made by the ovaries, adrenals, and fat cells postmenopause. Estradiol directly affects a wide range of cellular functions, as estrogen receptors are ubiquitous.

Estriol is the weakest of estrogens. Estriol is primarily manufactured during pregnancy by the placenta. It attaches to cell receptors affecting hair, nails, and skin. Recorded data on estriol's function demonstrate that estriol's effects are limited mainly to the vaginal walls with a little effect on the heart and bones in nonpregnant women. In the nonpregnant, young, and premenopausal woman, estriol is made in the liver in small doses. Studies on the use of estriol in menopausal women and women with multiple sclerosis have demonstrated promising results.[1]

Estrone is manufactured in fat cells after menopause primarily from testosterone derivatives (androstenedione). Estrone levels tend to rise after menopause and the increase in estrone has been implicated in an increased incidence of breast tumors but most data have been obtained from animal studies. Overweight older women have high circulating levels of estrone.

When the scientific and lay communities refer to estrogen, they typically refer to its three components as one. At times, this oversimplification leads to errors in separating the individual function of the estrogens, particularly when discussing the differences between estrogen preparations used as hormone-replacement therapy available on the market. Although their actions are perceived and often recorded as one, the component molecules of estrogen have different potencies and effects.[2–6]

During the aging process, the ovaries stop producing estrogen on a regular basis. Thereafter the main source of estrogen is from the adrenal glands, primarily in the form of estrone. The body transforms unused testosterone into estrogen (primarily estrone) and releases estrogen stored in fat cells.

Estrogen and progesterone are antagonists. Their actions are designed to balance each other and keep each other in check.[7] We cannot live in a healthy state without hormonal balance. At no time do hormones act independently under normal circumstances in healthy bodies.[7] For example, estrogen increases cell proliferation in the endometrium, while progesterone inhibits cell proliferation. Without progesterone, endometrial hyperplasia occurs in the uterus.[6–8]

Progesterone is manufactured primarily by the corpus luteum (the follicle transformed after ovulation) and also to a small degree by the adrenals. In the ovary, progesterone production is activated at ovulation (15 days before the next menstruation),[7] stimulated by the release of luteinizing hormone from the pituitary gland and is crucial to the survival of the ovum once fertilized. When pregnancy occurs, progesterone production increases rapidly and its manufacture is taken over by the placenta. If a woman does not get pregnant, the corpus luteum involutes and progesterone production diminishes and eventually disappears in parallel with estrogen production, heralding menstruation.

Progesterone is a precursor to most sex hormones, including estrogen in the ovaries, testosterone, all androgens, and other adrenal hormones, making it an extremely important hormone for reasons far beyond its role as a sex hormone. Progesterone in the breast and uterus counteracts the stimulation of cell growth, which is a direct action of estrogen. It accomplishes this action by activating the progesterone receptor, which in turn, down-regulates the estrogen receptor. Because progesterone suppresses estrogen-driven cell proliferation, progesterone in the natural state helps keep breast cell growth in healthy balance.[9]

ESTROGEN AND PROGESTERONE: NOMENCLATURE, COMMERCIAL AVAILABILITY

Among the medications approved by the Food and Drug Administration (FDA) for hormone therapy are two classes of sex steroid hormones: estrogens and progestogens (which broadly include progesterone and progestogens or progestagens, also referred to as ''progestins'' or ''progestational agents''). For better clarification, these medications must further be divided into two groups: (1) bioidentical hormones with molecular structure identical to that of the human hormones and (2) preparations with molecular structures different from that of human hormones (nonidentical). The molecular difference between these two types of hormone formulations affect their actions in the human body.[2,4,7,10]

In 2001, a literature review by Stanczyk[5] scrutinized the various estrogen preparations available on the market. The investigator noted that the scarcity of comparative pharmacokinetic information between various formulas of estrogens created a void in our knowledge of their differential effects and thus hindered our ability to serve the patient. He encouraged comparative studies to help determine the best type of estrogen to be used as therapeutic options to enable individualized treatments and approaches that would fit each woman's risk profile and personal preference.

Hormone Preparations with Molecular Formulas Unlike Those of Human Hormones

Hormone preparations that are molecularly different from human hormones are the most commonly used and marketed hormone-replacement therapy in the United States. They are commonly referred to in the popular literature as synthetic estrogens or pregnant horse urine estrogens. The most popular estrogenic preparations in this category include such oral estrogens as conjugated equine estrogen (Premarin), esterified estrogen (Estaratab, Menest, Cenestin), estrone sulfate (Ogen), and ethinyl

estradiol (Estinyl); and such vaginal creams as estropipate (Ogen) and dienestrol (Ortho-dienestrol).

Progestins

Progestins, which include drug formulations that are also molecularly different from those for human progesterone, were developed to balance the endometrial hypertrophy associated with the use of unopposed conjugated estrogens on the uterus.[7–9,11,12] Progestins are chemical compounds manufactured with two types of primary characteristics: androgenic and nonandrogenic properties. Progestins are manufactured in the laboratory and are not extracted from any known animal sources. They include medroxyprogesterone (Provera, Amen, Cycrin), norethindrone (Micronor, Norlutin), and norethindrone acetate (Norlutate).

Combination Products

Combination products contain combinations of both estrogenic and progestogenic compounds. Some include one hormone that is molecularly identical to human hormones and one that is not, while some contain both the estrogen and the progestogens that are molecularly different from human estrogen and progesterone. They include conjugated estrogen (nonidentical) and synthetic progestin (nonidentical) (Prempro, Premphase);17-beta-estradiol (bioidentical) and norgestimate (nonidentical) (Orthopresfest); ethinyl stradiol (nonidentical) and norethindrone acetate (nonidentical) (FemHRT); and esterified estrogens (nonidentical) and methyltestosterone (nonidentical) (Estratest).

Bioidentical Hormone Preparations

Bioidentical hormones are manufactured to be molecularly identical to hormones found in the human body. Bioidentical preparations include estradiol, estriol, progesterone, and testosterone. Bioidentical hormones are available both in commercial and compounded forms. Bioidentical hormones are not a marketing term. The term has been used for more than a decade in the inserts to all FDA-approved commercial hormone preparations that contain hormones molecularly identical to human hormones. Commercially and compounded available bioidentical hormone preparations include:

17-Beta estradiol (Alora, Climara, Esclim, Estrace)
17-Beta estradiol patches (FemPatch, Vivelle-Dot, Vivelle, Estraderm)
Estradiol transdermal spray (Evamist)
Progesterone in peanut oil capsule (Prometrium)
Progesterone vaginal gel (Crinone)
Micronized progesterone in various compounded forms (capsules, troches, transdermal creams, vaginal suppositories)
Combinations of estradiol and progesterone in compounded formulations as above
Combinations of estradiol, estriol, and progesterone in compounded formulations as above

Beyond the commercial bioidentical hormone formulations, individually compounded preparations of bioidentical hormones are prepared in compounding pharmacies or laboratories (some are FDA approved; all are regulated by the state they operate in) on an individualized basis as prescribed by a physician. These products contain the same active estrogens, progesterone, and testosterone as those found in the commercial preparations listed above. The difference is that they are

individually mixed in tablet, capsule, troches, gels, or creams to the specifications of the prescribing physician for the individual patient. Unlike the commercial preparations, compounded hormone preparations are not manufactured on a large scale and can only be produced for individual patients as prescribed by a physician or other licensed practitioner, depending on the particular state rules.

In a recent review of bioidentical hormones in menopause, Boothby and colleagues[13] reviewed only the compounded formulations of bioidentical. The investigators made no mention of the commercially available bioidentical hormones. This omission inadvertently perpetuated the confusion, credibility, and even existence of bioidentical hormones in FDA-approved commercially available preparations.

Much of the confusion surrounding estrogen and progesterone formulations comes from the lack of clear distinction between their molecular formulas, the lack of focus on their different effects in the human body, and the use of nonspecific nomenclature when referring to estrogen and progesterone regardless of formulaic or activity differences.

The molecular differences between bioidentical and nonhuman identical hormone preparations are illustrated in (**Fig. 1**).

Controversy

The differences in behavior of various hormone formulations in vivo and vitro are directly connected to the differences in molecular structure as described in the scientific literature.[10,14–16] As early as 1976, scientific data demonstrating the safety of bioidentical hormones appeared in the conventional medical literature.[17] Reports of increased risk of endometrial and breast carcinoma among users of synthetic conjugated estrogens also appeared in the scientific literature.[3,8,9,11]

By January 1978, the *Journal of the American Geriatrics Society* addressed the growing concern that treatment with exogenous estrogen alone causes cancer and reported on progestogen as the solution. Adding small doses of a progestogen to either estradiol or conjugated estrogen in a cycled manner was determined to be a safe solution to the concern of increased carcinogenicity found with the use of unopposed estrogen.[18] It is noteworthy that, in 1983, the options for treatment studied included bioidentical estradiol and conjugated estrogens with medroxyprogesterone. The stated goal of the treatment was to help women feel better as they aged and ''not to harm'' them in the process.[19]

As early as 1980 and continuing into the recent literature, untoward side effects of synthetic progestins, such as thrombotic phenomena; breast tissue cell hyperplastic changes; and cardiovascular, cholesterol, carbohydrate, and lipid metabolism changes,[7,10,14] prompted more research into bioidentical (micronized) progesterone as a safer option. An article in the *British Medical Journal* in March 1980 noted: ''Clinically, oral bioidentical progesterone may be of value when synthetic progestogens have caused adverse symptoms that necessitate stopping treatment.''[20]

Recommendations for the use of bioidentical progesterone as a safer alternative were found in the medical literature from Europe as well as the United States throughout the early 1980s.[21–23]

In the 1980s and early 1990s, research scientists expressed concern that the synthetic progestins in hormone therapy could increase the risk of breast cancer.[24,25] About this same time, the scientific literature was replete with studies of safer alternatives in the form of bioidentical estradiol and progesterone, as well as studies comparing bioidenticals to the synthetic hormones and comparing various methods of administration with transdermal method of administration demonstrating the most promise in the area of safety and efficacy. Examples of such scientific literature

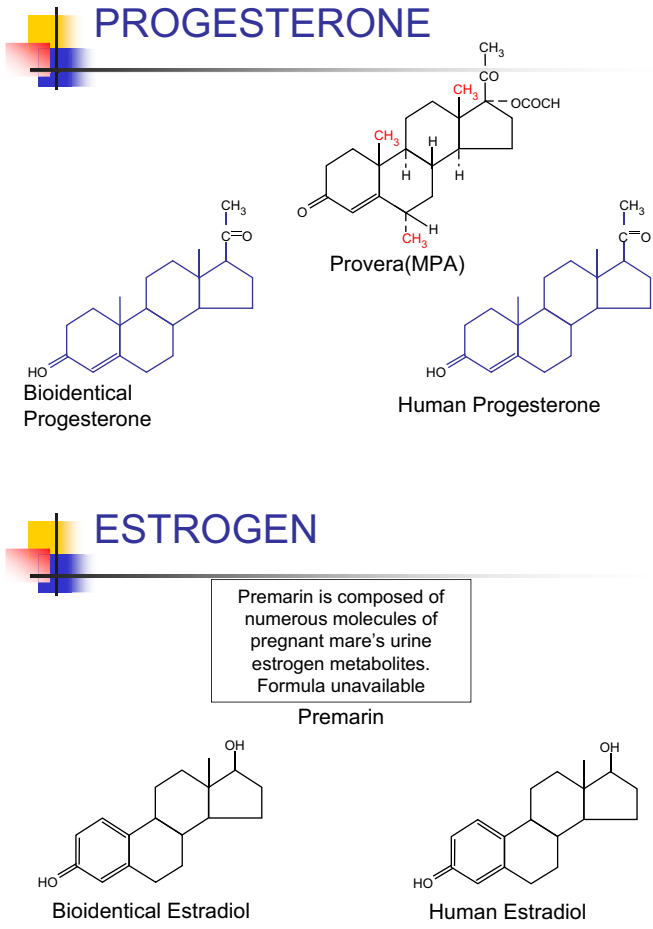

Fig. 1. The molecular formulas of various types of progestagens and estrogens. (*Adapted from* United States Pharmacopeia; and United States National Formulary.)

included an article by Foidart and colleagues,[12] who demonstrated that estradiol and progesterone had less proliferative effects on breast tissue cancer cell lines than did progestins and conjugated estrogens. Franke and Vermes[14] showed that progesterone-induced apoptosis in breast cancer cell lines that were conversely stimulated by synthetic progestins and other androgenic progestins. Place and colleagues[26] conducted a double-blind comparison of estradiol in transdermal form and Premarin that demonstrated improved relief of postmenopausal symptoms in the patient group on estradiol with no side effects. Riis and colleagues,[27] in a double-blind clinical controlled study, demonstrated that bioidentical estradiol and micronized progesterone helped improve bone density in postmenopausal women. Moorjani and colleagues[31] reported on the improved lipoprotein profile in patients receiving oral bioidentical estrogen with progesterone over those on progestins with androgenic action.[9–17,26–33]

Notably, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, a long-term randomized trial of hormone-replacement therapy, compared multiple effects,

including cardiovascular effects, of both synthetic progestins and micronized progesterone in combination with conjugated equine estrogen. The PEPI trial confirmed that over the course of 3 years, oral conjugated estrogen taken alone or with synthetic progestins or micronized progesterone was associated with clinically significant improvement in lipoprotein profile and lowered fibrinogen levels. PEPI also demonstrated significant losses in high-density lipoprotein cholesterol when synthetic progestin was added (significantly reducing the beneficial effects of estrogen). However, when bioidentical progesterone was added, there appeared to be statistically significant endometrial sparing and the bulk of estrogen's favorable effects on risk factors, including high-density lipoprotein cholesterol, were also preserved.[34]

In 1994, the National Institutes of Health began the Women's Health Initiative (WHI), a large-scale prospective double-blind placebo-controlled study. The goal of the study was to evaluate the long-term effect of hormone-replacement therapy versus placebo in the prevention of heart disease, osteoporosis, cancer, and strokes in postmenopausal women. The only form of hormone-replacement therapy used in the study was conjugated equine estrogens (conjugated estrogen [Premarin]) and medroxyprogesterone (synthetic progestins [Provera]). Unfortunately, the WHI did not include a bioidentical arm even though bioidentical hormone usage and statistically significant studies consistently demonstrated positive results and sustainable safety and efficacy records for this therapeutic modality.[10,35–42]

Studies comparing the effectiveness and safety of different methods of administration (oral versus transdermal or vaginal),[26,27,29–33] the use of synthetic versus bioidentical replacement,[26,34,38,40] and the use of estrogen only versus combined estrogen and progesterone[10,34,37,40–42] have raised more questions about the logic and safety of using conjugated estrogen and synthetic progestins in our patients. Large-scale studies have been conducted in Europe where bioidentical hormone replacement therapy is the main type of hormone supplementation in menopausal women. These studies repeatedly demonstrated effective elimination of menopausal symptoms and a lack of long-term negative side effects with the use of bioidentical preparations. Foidart and colleagues[12] showed in a small study that, within 14 days, exposure to progesterone reduced the estradiol-induced proliferation of the breast epithelial cells in vivo in 40 postmenopausal women. E3N is a large prospective French cohort study that investigated breast cancer risk factors in 98,997 women born between 1925 and 1950. The data were analyzed every 2 years and the conclusion emerged that micronized progesterone regimens, compared to synthetic progestin regimens, were associated with significantly lower breast cancer risks. Additionally, women who took the hormone-replacement therapy consistently were at lower risk than women who took the hormones occasionally.[43] De Lignières and colleagues[44] reported the results of an 8.9-year study of a cohort of 3175 postmenopausal women using mainly transdermal estradiol and progesterone. No increased risk of breast cancer was found (risk ratio [RR] of breast cancer per year of use was 1.005). Stahlberg and colleagues[40] reported on the Danish Nurse Cohort Study commenced in 1993, which followed 19,898 women aged 45 and above. The highest risk of cancer was found in the women who used continuous combined estrogen with synthetic progestin. Nelson[41] reviewed the studies that evaluated the short-term effectiveness of conjugated estrogen and estradiol as treatments for relief of hot flashes. The conclusion was that they both have comparable short-term effects. The overarching problem with conjugated estrogen is the long-term increased risk of breast cancer, stroke, and myocardial infarction, which was proven by the WHI initiative.

This situation leaves us with the very important knowledge that hormone-replacement therapy is an important tool in wellness and prevention. The type of

hormone therapies we choose for our patients is what makes the difference and must be carefully considered.[10,12,21,22,25,40–44]

Risks/Benefits

Scientific reviews of the pharmacology and action of progestins demonstrate that all progestins and progestogens are not created equal, and their action varies significantly according to their molecular structure. In the studies reviewed, bioidentical progesterone proved to be safer and more effective in all trials that involved its usage[10,43,44] and numerous studies have shown that any estrogen (conjugated estrogen or bioidentical estradiol) combined with synthetic progestin doubles the risk of breast cancer.[28,45–49] Unlike synthetic progestins, bioidentical progesterone has been shown to have a consistently beneficial effect on breast cell proliferation.[50] The E3N and Danish Nurses studies, which address large populations taking various types of hormone-replacement therapy for more than 5 years, did not find progesterone to be an increased risk factor for breast cancer while progestin was. When estradiol was used in studies that evaluated its effectiveness in relieving menopausal symptoms, including hot flashes, night sweats, insomnia, and mood swings,[51,52] and in improving sleep patterns[53,54] and lipid profiles,[55] the results were consistently positive.

The WHI study came to an abrupt halt in July 2002 primarily because the interim data demonstrated increased risk of myocardial infarction, stroke, and breast cancer in the conjugated estrogen and synthetic progestin arm of the study.[56–59] Since that time, the suggestions to use hormone-replacement therapy in menopausal women has raised fears, doubts, and confusion. Millions of women, exposed to the media frenzy caused by the WHI's unsettling results, abruptly stopped taking their hormone therapies at the advice of their physician and on their own. This situation required physicians to rethink hormone-replacement therapy and to look at other options for relief. Much time and effort has been spent on reevaluating the results of the WHI. This reexamination has brought to light many questions about the validity of the findings and soundness of the study.[60–66] Despite questions raised about the validity of the WHI study, the study itself still provides grounds for caution. The use of synthetic estrogen and progestin replacement remains questionable at best.

Even though the only long-term study on hormone-replacement therapy in the United States was conducted on synthetic hormones and the data clearly established increased risk of cancers and strokes with the use of conjugated estrogen and progestins, hormone therapies are still the most effective therapeutic modalities for the elimination of symptoms of menopause and should be considered an integral part of the overall well-being of the aging woman. While in the short term, the type of hormones used may or may not be as significant as in the long run, the question is: What are the best options for the short and long terms for the women we treat?

An epidemiologic review of the rise in incidence in breast cancer in 1990 looked at the receptor status and the relationship to stage. Of interest is the fact that the investigator found that the incidence in older women increased and the cancers were more likely to be estrogen receptor positive. These cancers carry better prognosis because they tend to grow more slowly and are sensitive to hormonal manipulation.[25] This information is useful for the primary care physician when deciding therapeutic course of action over the long term.

Subsequent to the discontinuation of the WHI study, hormones that are synthetic and molecularly dissimilar to human hormones can no longer be prescribed without hesitation. A growing number of physicians involved in prevention and wellness, in response to concerns raised by the WHI and to requests and demands from patients,

have created study groups and forums within alternative and integrative medical organizations, have written books, and are conducting seminars sharing their clinical experience and research data on the use of bioidentical formulations of estrogen and progesterone. Risks associated with the use of conjugated estrogen and progestins, including the increased risks of breast cancer and cardiovascular events,[10,40,43–46,56–59] have not been reported with the use of bioidentical hormones.[50–55]

Based on the extensive scientific data we have reviewed for this article, it is unclear whether any absolute circumstance calls for synthetic versions of hormone-replacement therapy and such use appears unwise. Given the easy commercial availability of bioidentical formulations and the lack of negative data on these hormones, primary care physicians can easily access them for their patients. When faced with the need to treat a woman with hot flashes, night sweats, insomnia, mood changes, loss of libido, and other symptoms of menopause, the primary care physician must choose wisely the safest and most effective way of improving the quality of life for the patient. While further long-term randomized trials would be helpful to quantify the difference in RRs between synthetic and bioidentical hormone replacement over the long term, the current state of evidence demonstrates bioidentical hormones as a safe and effective option to be considered separate and distinct from its synthetic counterparts.

TESTOSTERONE

Female

Although estrogen remains the central female hormone most frequently used in both wellness and disease prevention, much less controversy surrounds the use of testosterone in women, though the evidence either supporting or discouraging its use is scarce. Nicknamed "the hormone of desire" and promoted in the popular media as the rescuer from the plight of decreasing libido in aging women, testosterone has gained rapid acceptance in the prevention and wellness arenas at a time when controversy and confusion surround estrogen and progesterone therapies.

Testosterone is produced by the ovaries and adrenals in young women in low doses (free testosterone levels range between 2–8 pg/mL). The bulk of the present research on the use of testosterone has been conducted on women with surgical menopause, hypopituitarianism, anorexia nervosa, and primary adrenal insufficiency; patients with HIV and low body weight;[67] and patients with glucocorticoid- and oral contraceptive–induced suppression of endogenous androgens. There has been little if any formal study on testosterone use in normal aging in women.

Benefits

Muscle mass The addition of testosterone to conjugated estrogen results in an increase in fat-free body mass and mitigates central fat deposition associated with estrogen use.[68,69] In a double-blind placebo-controlled small study of androgen-deficient women, testosterone replacement demonstrably increased thigh muscle mass as measured by CT scanning.[70] The data is very limited and its value and usefulness on large populations unknown. Further evaluation and research must be conducted as we address the possibility of usage of testosterone in the aging female to help improve muscle mass and decrease central adiposity.

Libido Loss of libido in the aging female is the most common complaint that leads physicians to consider testosterone deficiency as a possible cause and the main consideration for treatment with testosterone. Multiple factors directly affect sexual inclination. Poor relationship status, self-image issues, multiple medications and their

side effects, other stress factors, aging, and concurrent chronic or acute illnesses are some of the most frequently encountered deterrents of sex drive. Many of these factors cannot be altered, and all factors should be taken into account. Even so, testosterone appears to be effective in offsetting some of the effects from these factors, leading primary care physicians involved in integrative and wellness practices to make testosterone supplementation more popular.

Lack of training in the area of loss of libido and lack of concrete diagnostic criteria have created difficulties for the primary practitioner when attempting to address this problem. While circulating testosterone levels are not very helpful in diagnosing low testosterone as the cause for loss of libido, it may be helpful to keep in mind that premenopausal women have a range of 20 to 75 ng/dL total testosterone while postmenopausal women can present with values as low as 5 to 10 ng/dL. Because we rarely have comparative levels of testosterone on a patient before they come in with the complaint, it is almost impossible to determine whether the testosterone levels correlate in any way with the appearance of symptoms.[71]

The seminal study on impaired sexual function improvement with supplemental testosterone comes from oophorectomized women. Seventy-five women 31 to 56 years old postoophorectomy and -hysterectomy were randomly assigned to receive conjugated estrogen and various doses of transdermal testosterone. The women who received the higher dose of testosterone reported a two- to threefold increase in sexual desire, masturbation, sexual intercourse, and sense of positive well-being as compared with placebo or conjugated estrogen alone.[72]

Breast cancer Acting through androgen receptors, testosterone opposes estradiol-induced proliferation of human breast cell lines.[73] Cases where endogenous testosterone levels are elevated, such as with polycystic ovary syndrome, are associated with breast tissue atrophy and a decreased risk of breast cancer.[74] There are, however, conflicting data on the potential role of supplemental testosterone in the development of breast cancer and under no circumstances should testosterone be given without regular follow-ups.

Testosterone replacement considerations

Variation in dosing, method of administration, and duration of treatment are important determinants of safety and efficacy. To date, the medical literature contains little data on this topic. One is left with a smattering of information to help the patient rely on hopeful but dubious information obtained on the Internet and from popular literature.

Under these circumstances, a growing number of physicians involved with menopausal women's wellness are using testosterone supplementation to provide improvement in libido and mood simply based on clinical findings and blood levels. A popular literature book *The Hormone Of Desire* by Susan Rako, MD, published in 1999, was followed by hundreds of articles in popular science that led to the rise of testosterone supplementation as a potentially helpful resource in the plight of aging women.

Formulations

Testosterone formulations include testosterone gel (Androgel), which is not FDA-approved for women, and various compounded formulations of testosterone in cream, subcutaneous pellets, oral, and sublingual forms. In summary, though treatment with testosterone in the aging woman is gaining popularity, there is a definitive need for studies specific to this population to evaluate the safety and efficacy of testosterone as a therapeutic modality for postmenopausal women, as well as for younger women with loss of libido, to define its best use in prevention and wellness. Studies are

needed to help determine the safest and most efficacious methods for aging females to use testosterone.

Male

Testosterone is the primary androgen produced by the testes and it plays an essential role in the health of the male. Beyond determining the male sex characteristics, testosterone is a determinant of muscle strength, bone mass, libido, potency, and spermatogenesis.

Androgen deficiency

Androgen deficiency includes but is not limited to symptoms of decreased body hair, reduction in muscle mass and strength, increase in fat mass, decreased hematocrit, decreased libido, erectile dysfunction, infertility, osteoporosis, depression, and mood changes. Androgen deficiency may occur secondary to testicular or pelvic trauma or surgical removal, hypogonatropic hypogonadism, or with normal aging.[75]

The normal aging process leads to adult hypogonadism with a decrease in levels of testosterone with age and the development of some or all of the symptoms enumerated above. The condition of androgen deficiency in aging is also known as andropause.

Androgen deficiency or hypogonadism is the result of subnormal production of testosterone by the testes. Its prevalence in healthy males over the age of 40 is demonstrated in observational studies, but there is no agreed upon blood level that defines deficiency.

Common causes of hypogonadism include but are not limited to:

Primary testicular failure
- Klinefelter syndrome
- Cryptorchidism
- Orchitis
- Trauma
- HIV/AIDS
- Myotonic muscular deficiency
- Retroperitoneal fibrosis
- Aging

Hypogonadotropic hypogonadism
- Kallman syndrome
- Prader-Willi syndrome
- Idiopathic hypopituitarism
- Pituitary tumors
- Suprasellar tumors
- Hemochromatosis
- Inflammatory, traumatic, vascular lesions of pituitary and hypothalamus
- Obesity
- Severe chronic illnesses
- Medication
- Andropause

The risk of having low testosterone levels is significantly higher in men with hypertension (RR 1.84), hyperlipidemia (RR 1.47), diabetes (RR 2.09), obesity (RR 2.38) and asthma or chronic obstructive pulmonary disease (RR 1.40) than in men without these conditions. The prevalence of hypogonadism (defined as a total testosterone level below 300ng/dL) in 2162 men aged 45 years or older presenting to primary care offices was 38.7% in a study by Mulligan and colleagues.[76]

Controversy

Perhaps the most significant controversy related to testosterone is the debate over its role in prostate health. For more than 60 years, traditional medical wisdom regarded testosterone as a significant risk factor for prostate hypertrophy and assumed that high testosterone levels served as fuel for prostate cancer. Hormone blockade and or estrogen therapy are still standard of care for prostate cancer therapy even today. Clinicians have hesitated to treat aging males with testosterone because of the belief that high levels of testosterone cause prostate cancer or speed up its growth. More than a decade ago, Shippen, Fryer, and Wright took the view that testosterone is actually protective and should be used.[77] A ground-breaking study released in November 2007 provided a whole new set of data and a new perspective on testosterone.[78] The results of this large-scale prospective study revealed that high endogenous levels of testosterone are associated with low mortality from all causes. The study suggests that low testosterone may be a predictive marker for those at high risk of cardiovascular disease.

Shores and colleagues[79] investigated the correlation between testosterone levels (defined as total testosterone <250 ng/dL or free testosterone <0.75 ng/dL) and mortality in 858 males followed for up to 8 years. The results demonstrated that men with low circulating levels of testosterone had an 88% increased risk of mortality.

Benefits

Cardiovascular Experimental studies suggest that androgens induce coronary vasodilatation. A placebo-controlled double-blind (PCDB) study performed in the United Kingdom followed 46 men with stable angina randomized to receive either a 5-mg testosterone patch or placebo in addition to their current medicines for 12 weeks. Both groups were then monitored for changes in treadmill exercise time before the onset of myocardial ischemia. The results of the treatment group compared with the placebo group were statistically significant (22% improvement in exercise time before onset of ST depression) without effect on prostate-specific antigen (PSA), hemoglobin, lipids, or coagulation profile during the duration of the study. Low-dose supplemental testosterone treatment in men with chronic stable angina increased exercise time preceding induced myocardial ischemia as defined by ST depression on EKG.[80] Testosterone replacement therapy has also been proven to reduce insulin resistance, visceral adiposity, and cardiovascular risk.[81–83] Additionally, a relatively low testosterone, independent of adiposity, is a risk factor for insulin resistance and type II diabetes and vice versa (insulin resistance and diabetes mellitus II are risk factors for low testosterone).[84–86]

Anemia Anemia is a frequent feature of male hypogonadism and antiandrogenic therapies. In a study that evaluated hemoglobin levels in 905 persons 65 years or older, of which 31 men and 57 women had anemia, hemoglobin levels were evaluated after 3 years. The participants were patients without cancer, renal insufficiency, or antiandrogenic treatments. Statistical evaluation of the results showed that older men and women with low testosterone levels had a higher risk of anemia.[87]

Mood and quality of life There is a compelling need for therapies that prevent Alzheimer's disease, defer its onset, slow its progression, and alleviate its symptoms. In a study that evaluated the effects of testosterone therapy on cognition, neuropsychiatric symptoms, and quality of life in male patients with Alzheimer's disease and healthy elderly men, 16 male patients with Alzheimer's disease and 22 healthy male controls were treated with testosterone and a placebo gel daily. Patients receiving testosterone had significant improvement in quality-of-life scores and the treatment was well

tolerated. Testosterone had minimal effects on cognition and the treated group showed more numerical improvement and less decline in visuospatial functions.[88]

Osteoporosis and musculoskeletal Untreated hypogonadism is a prominent cause of osteoporosis in men[89] and bone mineral density significantly increases with testosterone treatment.[90] Older men are as responsive to the anabolic effects of testosterone as young men. Testosterone induces skeletal muscle hypertrophy that leads to improved muscle strength in the leg as demonstrated in this study. A reciprocal change in lean and fat mass is observed but further studies are needed to determine the exact mechanism of change and the therapeutic doses needed for older men to obtain optimal results with minimum side effects.[91]

Libido and sexual function Treatment with testosterone improved sexual function in hypogonadal males in this very small study as measured by frequency and duration of erection and frequency of ejaculation.[92–95] More studies in this important area must be undertaken to provide much-needed information. Perceived risks associated with testosterone treatments and its abuse in the areas of athletic enhancement have caused much confusion without scientific basis.

Risks

Prostate cancer The connection between higher testosterone levels and growth of prostate cancer originated in 1941 with the publication of two papers by Huggins and colleagues.[96,97] The data reported were based on one patient and, despite 67 years of subsequent studies that failed to establish scientific support for this theory, we are still faced with reluctance to treat men with testosterone supplementation for fear of giving them prostate cancer or fueling prostate cancer already present at a subclinical or microscopic level.

More than 430,000 men were part of longitudinal studies over the course of the past 67 years, and no well-designed study has ever shown a direct correlation between total testosterone levels and prostate cancer. A 2007 review out of Harvard concluded that:

> *Although there is yet to be a large, long term, controlled study on the effect of TRT [testosterone replacement therapy] on PCa [prostate cancer] risk, it should be abundantly clear that raising T [testosterone] in hypogonadal men has little, if any, impact on PCa risk or growth in the short to medium term. The withholding of TRT in men because of fear of PCa risk or progression is no longer tenable in an age of evidence-based medicine, because neither evidence nor theory supports this position.*

This article reviewed the state of the evidence and, based on the prospective longitudinal studies, concluded that "men who develop prostate cancer do not have higher baseline testosterone levels and men with higher testosterone levels are at no greater risk for developing prostate cancer than men with lower testosterone levels."[98]

The primary care physician needs to address each patient individually and decide on the use of testosterone based on more than just testosterone levels or fear of prostate cancer. Follow-up with serial blood tests and PSAs is still an important part of the clinical follow-up and should be used for the protection of the patient.

Aromatase One of the most important factors affecting testosterone levels in aging men is the enzyme aromatase, which is found in fat tissue. Aromatase converts testosterone into estrogen, thus changing the ratio of estrogen to testosterone.[99,100] Men who have excessive body and abdominal fat are likely to have increased estrogen

levels caused by aromatase activity. This condition has been linked to decreased insulin sensitivity and metabolic syndrome.[100]

Diagnosis

When a history and symptoms of hypogonadism are clear, the diagnosis is relatively easy. However, often the patient presents with nonspecific history and symptoms and an unremarkable clinical history, making the diagnosis more difficult. Clinically, the typical adult hypogonadism patient is above 50, fatigued, has difficulty building muscle in spite of consistent workout regimen, complains of unexplained weight gain, may be mildly depressed, and may experience erectile dysfunction and loss of libido. In this clinical setting without diagnosable disease, the diagnosis of a relative age-related adult-onset hypogonadism is gaining popularity and treatment with testosterone is becoming more common in the integrative medicine and urology fields.

Thus, it becomes important for the primary care physician, who is the first line of diagnosis and treatment, to feel comfortable with the use of testosterone as a viable and safe short- and medium-term option in the therapeutic armamentarium of healthy aging and wellness preservation. Understanding and considering hypogonadism in every adult aging male is an integral part of prevention and wellness.

Primary testicular failure is associated with elevated follicle-stimulating hormone and luteinizing hormone levels. A baseline PSA and a complete blood cell count should be obtained before starting testosterone supplementation. Estrogen, progesterone, and dihydrotestosterone levels may also be of value.

There is no agreed total or free testosterone cut-off level to define testosterone deficiency.[101] Total testosterone is the most common measure of androgen activity, but is a poor indicator of tissue activity, demonstrating little correlation with clinical status, and is an unreliable indicator of response to therapy.

Free testosterone is a more accurate indicator of hypogonadism,[102] but normal ranges for total and free testosterone vary widely among laboratories, even among those using the same assay, and the reference ranges show little or no correlation to clinical findings.[103] When testing the testosterone levels of a patient who is considering testosterone supplementation to maintain and improve wellness, it is unusual to have available prior testosterone levels when that patient was younger, healthier, and symptom free. Thus, a result that appears to be within normal range may not necessarily reflect what is normal for that particular patient. This situation must be taken into account since it emphasizes the importance of clinical assessment and patient involvement in the decision to treat.

The use of population-based statistically determined normal testing ranges is also limited by the fact that the average testosterone level in men today is less than the average level in men of the same age 15 years ago. This concerning fact is possibly due to environmental suppression of the hypothalamic-pituitary-testicular axis[104] and may also be a contributing factor to diminished sperm counts and increased incidence of infertility.[105]

Testosterone levels decrease with age and illness. Typically, men with hypogonadotropic hypogonadism have low plasma testosterone and luteinizing hormone levels. Prolactin levels should be checked if the total testosterone level is below 250 ng/dL to rule-out a pituitary tumor.

Fifty percent of circulating testosterone is bound to sex hormone–binding globulin, which directly affects free testosterone levels. Free testosterone levels can be obtained to clarify testosterone status. However, variations are greater among free testosterone assays than among total testosterone assays. Also, reference ranges are not as standardized for free testosterone assays as they are for total testosterone

assays. When borderline levels of testosterone are found, or the clinical picture and the blood tests disagree, a low or low-normal free or total testosterone level may be used to support a clinical diagnosis of androgen deficiency, but should not be used to exclude it.[101]

Treatment

Testosterone supplementation has gained popularity over the past 20 years. The benefits of testosterone supplementation include improved energy, greater muscle mass, increased stamina, greater strength, increased confidence, greater motivation, and enhanced libido.[102–106]

Present formulations of testosterone include the following:

Testosterone gel (Androgel)
Testosterone patches (Androderm)
Compounded testosterone creams or gels
Injectable testosterone
Subcutaneous testosterone implants

Monitoring

While it is useful to follow PSA levels during the course of testosterone replacement and supplementation, it is more important to track the velocity PSA increase. There is often a slight bump, a rise above 4.0 ng/mL, or a sudden increase in PSA with the initiation of testosterone therapy, followed by a stable constant level. An increase in PSA more than 0.35 ng/mL per year warrants further evaluation and a referral to the urologist.[107]

While using testosterone in disease prevention and wellness is relatively new to the primary care field, it holds much promise and meets with much support and enthusiasm from patients. The data we reviewed and our clinical experience support the use of testosterone as a first-line hormone supplementation in the aging male. More research is needed to substantiate and define the parameters necessary for its long-term use.

For now, as the esteemed Dr. Morgantaler said:

> *… the diagnosis of androgen deficiency requires only an ear attuned to the characteristic symptoms and blood test providing evidence of reduced levels of total or free testosterone. Treatment provides an opportunity for gratifying results, for patients and clinicians alike.*[108]

GROWTH HORMONE

As the proportion of aging people continues to rapidly rise, reducing the burden of age-related diseases becomes increasingly important in primary care. A controversial hormone that is center stage in the debate over the use of hormone therapies in prevention and wellness is growth hormone.

Growth hormone, a single-chain polypeptide produced in the pituitary gland, has a wide range of metabolic and cellular effects. Growth hormone plays an important role in the regulation of body composition, lipid profiles, tissue repair, cardiac and neuronal functioning, and maintenance of bone mineral density. Growth hormone is secreted in pulsatile fashion, especially during stage III and IV deep sleep. It acts on liver and other tissues to stimulate the production of insulinlike growth factors (IGFs), including IGF-1, which is also known as somatomedin C, and the production of IGF-binding proteins (IGFBPs), which also have direct cellular actions. The most abundant IGFBP is IGFBP-3.

A large percentage of growth hormone effects are mediated through IGF-1. Because of the pulsatile nature of growth hormone production and short half-life (20–50 minutes), routine serum growth hormone levels cannot be used to determine overall production. While there are many influences on the production of IGF-1, levels correlate with overall growth hormone production, are relatively stable in the serum, and are currently the best estimate of growth hormone production and effect. While a low IGF-1 is a strong indicator of abnormally low growth-hormone production, an IGF-1 level in the normal reference range does not rule out deficiency.[109]

While there is considerable variation in growth hormone production among individuals of the same age, there is a progressive decline in average growth-hormone production and IFG-1 levels after age 20, with average levels declining by 30% to 60% by age 40 to 60, and by 50% to 80% after age 60.[110–114] Low growth-hormone levels and production are associated with low quality of life as measured by numerous criteria, including the Nottingham Health Profile and the Psychologic General Well-Being Index.[113,115–118] Gibney and colleagues[119] reviewed 10 years of use of growth hormone in adult growth-hormone deficient patients and found it to be of significant benefit.

A large number of peer-reviewed research, including long-term randomized controlled trial data, has demonstrated that growth hormone replacement improves energy,[119,120] strength,[119] cardiac function,[121–123] blood pressure,[124] cholesterol levels,[124–126] insulin sensitivity[124,127] cognitive function,[128,129] immunity,[130,131] and psychologic well-being;[113,116,118,126] decreases body fat;[121,124,125,127–133] increases lean muscle;[121,124,132] prevents and reverses heart disease;[121,134,135] prevents and improves osteoporosis;[121,125,136] and improves quality of life.[116,118,119,126]

Controversy

Controversial issues regarding growth hormone supplementation include the use of growth hormone as a therapeutic modality for age-related deficiency; the accuracy and necessity of commonly used stimulation testing when considering growth hormone usage in well patients; the need for guidelines for safe and effective treatment; and potential side effects of treatment.

Diagnostic Testing

The diagnosis of growth hormone deficiency is difficult for a number of reasons. As discussed, random serum growth-hormone levels are not indicative of the overall growth hormone production and, while IGF-1 levels do correlate with overall growth hormone production, IGF-1 levels lack sensitivity to detect significant deficiency (IGF-1 levels are often in the normal range even if a significant deficiency exists).

With growth hormone stimulation testing, serum growth-hormone levels are measured after a variety of agents and protocols are used to stimulate the release of growth hormone from the pituitary. Such tests are often promoted as the means of differentiating growth hormone deficiency from normal state. Many endocrinologists believe the diagnosis of adult growth-hormone deficiency can only be made with the use of growth hormone stimulation testing. Such testing has proven to be inaccurate, highly variable, nonphysiologic, and lacking adequate sensitivity to detect relative growth-hormone deficiencies. The use of arbitrary cutoffs to define abnormality does not correlate with response to therapy.[137–145] Studies demonstrate that using the same agent to perform stimulation tests multiple times on one patient do not consistently produce congruous results, thus bringing the usefulness of the test into question.[138,139] Side effects of stimulation testing include significant hypotension, venous thrombosis, nausea, and vomiting.[129] Deaths and neurologic damage have also been reported.[134]

Because stimulation tests are clinically and physiologically unreliable, they are also unreliable for determining growth hormone deficiency. Currently the most appropriate means of diagnosing age-related growth-hormone deficiency is clinical recognition and a low-normal (below the mean) IGF-1 level.

Clinical Diagnosis

The adult age-related clinical syndrome of growth hormone deficiency includes increased fat mass, decreased muscle mass and strength, decreased bone density, elevated lipids, insulin resistance, decreased psychosocial well-being and depression, fatigue, increased social isolation, inability to handle stress, cardiovascular disease, memory decline, overall deterioration in quality of life, frailty, thin dry skin, increased wrinkles, and diminished exercise tolerance.

Clinicians commonly encounter these clinical symptoms in the aging patient. If considered appropriate by physician and patient, a 6-month therapeutic trial with growth hormone could be considered, dosed to keep IGF-1 levels in the upper quartile. Patients should be evaluated for symptomatic and metabolic improvements at a minimum at 3 and 6 months to decide if treatment should be continued.

Treatment

The treatment of age-related adult growth-hormone deficiency remains controversial even though the literature reports significant benefits from growth hormone supplementation. The main sources of concern associated with growth hormone replacement in somatopause include, in no particular order, significant cost of therapy from $250 to $1500 per month (depending on dose and manufacturer), side effects of water retention resulting in joint pain and carpal tunnel syndrome, temporary reduction in insulin sensitivity, and theoretic risk of cancer. Most short-term side effects are diminished with reduction in dose.[146–148]

While there is a long-held theoretic belief of an increased risk of cancer, based on the growth hormone's antiapoptotic and mitogenic effects, neither long-term nor short-term data support this theory. Conflicting data on the relationship between IGF-1 levels and the risk of cancer abound. Some frequently cited epidemiologic studies have found an increased correlation between elevated IGF-1 and breast,[149] prostate,[150] and colorectal cancers,[151] while the majority of studies failed to document increased risk of cancer (or have shown a decreased risk) with increasing IGF-1 levels.[152–165] In addition, one frequently cited study that did connect increased IGF-1 levels and cancer, by Chan and colleagues,[150] is very controversial because the blood was stored for 5 to 15 years before it was tested. Also, IGF-1 levels in the highest quartile group were over three times the upper limit of normal for this age group, suggesting that IGF-1 in the patients studied may not have been measured accurately. Hankinson and colleagues[149] found a trend for decreased risk of breast cancer in postmenopausal women with increased IGF-1 levels but an increased risk in premenopausal women. Palmqvist and colleagues[151] reported increased association between IGF-1 and colon cancer, but a decreased risk of rectal cancer.

The secretion and regulation of IGF-1 is extremely complex and their reported association with cancer must also take into consideration numerous other potential confounding etiologic factors, whether environmental, nutritional, or other yet unidentified. Growth hormone stimulates the production of IGFBP-3, which has cancer-protective characteristics and may counteract increased risk of cancer associated with an increase in IGF-1, if present. There is evidence that tumors secrete IGF-1, which makes it a potential marker for cancer in some individuals and not necessarily a cause. Typical growth hormone supplementation for an age-related deficiency

results in small increases in IGF-1 that remain in the normal age-matched references range, so risk would not be expected to be different than that for controls.

None of the long- and short-term studies have shown an increased risk of cancer, recurrent or de novo, with the use of growth hormone,[166–177] and some of the studies have shown a decreased risk. Among these studies are studies on more than 19,000 children representing of 47,000 patient years of growth hormone treatment;[176] a prospective study of 100 adult growth hormone–deficient patients followed for 1 to 4 years,[177] a study of 910 children treated with growth hormone for 11 years,[175] a study of 32 adults and children followed for up to 40 years treated with growth hormone (average 10.8 years);[166] a study of 180 growth hormone–treated children followed for over 6 years with reduced cancer recurrence risk (RR 0.6);[169] a prospective analysis of 289 growth hormone–deficient adults who, after 5 years of growth hormone therapy, showed lower risk of malignancy (RR 0.25) and decreased risk of myocardial infarction (RR 0.19) and early mortality (RR 0.22) compared with the untreated group.[172]

In 2001, the consensus statement by the Growth Hormone Research Society noted that the data demonstrate that the concern for increasing the risk of cancer with the use of growth hormone is unfounded:

> *The current labeling for GH [growth hormone] states that active malignancy is a contraindication of GH treatment. There are, however, no data to support this labeling. Current knowledge does not warrant additional warning about cancer risk on the product label.*

Supraphysiologic doses of growth hormone are shown to antagonize the effects of insulin. While short-term studies using large doses of growth hormone may potentially worsen insulin resistance,[178] low physiologic doses of growth hormone have demonstrated improvement in insulin resistance and decreased risk of diabetes.[179–182] If treatment is contemplated, low physiologic doses should be used to keep IGF-1 in the upper limit of normal.

In conclusion, aging adults have a relative deficiency of growth hormone and supplementation with growth hormone may be of significant benefit. A clinical diagnosis of growth hormone deficiency can be made with support of low-normal IGF-1 levels alone. Although no long-term studies have assessed side effects with low physiologic doses of growth hormone supplementation in somatopause, the studies we reviewed above have confirmed that low doses, titrated to keep IGF-1 levels in the upper limit of normal, are safe, well tolerated, and associated with a plethora of clinical benefits.

Treatment with growth hormone is presently limited to an affluent and highly motivated population. Cost and risk/benefit ratio over time must be taken into consideration. As our patients age, the challenge of maintaining quality of life for them becomes more difficult and must be considered in the design of future studies. For supplementation with growth hormone to become a first-line therapeutic option in the aging population, additional and more extensive randomized trials that evaluate results of growth hormone treatment in age-related deficiency must be undertaken, and cost factors must be addressed.

THYROID

Hypothyroidism is a common disorder with inadequate amounts of thyroid hormone present at the cellular level. Typical symptoms include fatigue, weakness, weight gain, cold intolerance, muscle aches, headaches, decreased libido, depression, hair

loss, and dry skin. Signs include edema, dry skin, pallor, hair loss, loss of temporal eyebrow hair, and cold extremities. Conditions associated with hypothyroidism include hypertension, atherosclerosis, hypercholesterolemia, hyperhomocysteinemia, menstrual irregularities, infertility, premenstrual syndrome, chronic fatigue syndrome, fibromyalgia, fibrocystic breasts, polycystic ovary syndrome, depression, diabetes, and insulin resistance.

There is a two- to threefold increase in the incidence of thyroid dysfunction with age, including overt and subclinical hypothyroidism (elevated thyrotropin with normal thyroxine and triiodothyronine levels).[183] There is also an age-related decrease in thyroid function that results in diminished tissue thyroid levels and may result in clinically symptomatic hypothyroidism that is not detected with the standard use of thyrotropin, thyroxine, or triiodothyronine levels.

Historically, an elevated thyrotropin with normal thyroxine and triiodothyronine levels has been considered compensated or subclinical hypothyroidism and diagnosed as euthyroid with no requirement for treatment. A plethora of studies have, however, demonstrated that, in spite of the normal triiodothyronine and thyroxine values, subclinical and nondiagnosed hypothyroidism is often associated with significant symptoms and an increased risk of morbidity and mortality.[184–211] In light of this, it has been proposed that the term subclinical hypothyroidism be replaced by the term mild thyroid failure (MTF).[184]

The diagnosis of MTF is particularly important in the aging population in the areas of prevention and wellness. MTF is a treatable condition associated with increased cardiovascular risk and numerous signs and symptoms that might otherwise be attributed to "usual" signs and symptoms of aging, including fatigue, depression, memory loss, cognitive dysfunction, dry skin, constipation, leg cramps, cold intolerance, weakness, water retention, diminished sweating, weight gain, and diminished exercise tolerance.[184–211] Significant improvements may occur with treatment.[185,190,192,193,196,198,202]

Numerous studies have demonstrated increased cholesterol levels in patients with MTF.[184,202,206,207,211] Thyroid replacement results in a significant reduction in the cholesterol levels.[205–207] In addition to the increase in total and low-density cholesterol seen with MTF, endothelial dysfunction with impaired vasodilatation have also been demonstrated, further increasing the risk of cardiovascular events.[210]

The Rotterdam study investigated the association between MTF and aortic atherosclerosis and myocardial infarction in 1149 menopausal women. After adjustment for multiple known coronary artery disease risk factors, the investigators found that MTF significantly increased the risk for arthrosclerosis (odds ratio 1.9) and myocardial infarction (odds ratio 3.1).[204] This important study found that subclinical hypothyroidism was a greater risk for myocardial infarction than hypercholesterolemia, hypertension, smoking, or even diabetes, and that MTF was a contributing factor in 60% of the myocardial infarctions in the patients studied.

In a 20-year longitudinal study, Walsh and colleagues[211] also examined the association between MTF, cardiovascular disease, and mortality in over 2000 individuals (approximately half men and half women) with a mean age of 50 years (age range 17–89). In this study, MTF was associated with a 2.2-fold increased risk of coronary artery disease and 1.5-fold increased risk of cardiovascular mortality after adjustment for multiple known cardiovascular risk factors.

Diagnostic Testing

Thyrotropin is considered the most sensitive marker of peripheral tissue levels of thyroid hormone, and it is widely assumed that thyrotropin levels within the normal

range indicate the person is euthyroid. With significant physiologic stress, illness, inflammation and aging, however, there is demonstrable suppression of thyrotropin, making the thyrotropin test unreliable.[212–231] With significant physiologic stress, illness, inflammation, and aging, tissue-specific alterations also reduce tissue triiodothyronine levels by reducing uptake of thyroxine into tissues and decreasing thyroxine-to-triiodothyronine conversion.[217–228] The decreased serum thyroxine levels caused by the suppressed thyrotropin production is offset to varying degrees by the diminished uptake of thyroxine into the cell and the decreased thyroxine-to-triiodothyronine conversion. This situation tends to be misread as an indication of adequate tissue thyroid levels and makes thyroxine levels of little use, except in extreme cases.[223–225]

With physiologic stress, inflammation, illness, and aging, the correlation between serum thyrotropin and thyroxine levels and peripheral thyroid activity no longer follows.[212–231] Thyrotropin and thyroxine levels cannot be relied upon to detect diminished cellular triiodothyronine levels for aging patients and patients under stress. Instead of thyroxine normally converting intracellular to the active triiodothyronine in peripheral tissue, thyroxine is preferentially converted to reverse triiodothyronine. Serum reverse triiodothyronine levels may be useful because diminished cellular uptake of thyroxine, diminished thyroxine-to-triiodothyronine conversion, and diminished cellular triiodothyronine levels inversely correlate with serum reverse triiodothyronine levels.[212,222,223,225,229,230]

When the physiologic stress or illness is acute and severe, the significantly diminished thyroid levels in the peripheral tissues no longer correlate with thyrotropin levels. This is termed nonthyroidal illness or euthyroid sick syndrome. In these cases, the thyrotropin level cannot be relied upon as an accurate measure of tissue thyroid effect.[212,213,226] The same physiologic changes also occur with chronic physiologic stress, chronic illness, inflammation, calorie reduction, and aging.[216–245] Changes can be metabolically significant and can cause serious symptoms. Treatment may be warranted despite normal thyrotropin and thyroxine levels.[224,235,246,247] The use of thyroxine preparations in the treatment of nonthyroidal illness found in acute conditions, such as trauma, surgery, and sepsis, has shown little benefit. The ineffectiveness of thyroxine preparations in these cases is most likely due to the diminished use and uptake of thyroxine in these conditions. In contrast, treatment with triiodothyronine has proven quite beneficial in studies of severely ill patients,[247–252] as well as in chronic conditions,[246,253–255] which correlate well to the aging patient.

Similar to significant physiologic stress and illness, aging is associated with significant alterations in the hypothalamic-pituitary-thyroid axis that result in a reduction of thyrotropin levels[244,250] (in contrast to MTF's increase in thyrotropin) while tissue-specific alterations reduce the supply of triiodothyronine (via reduced thyroxine-to-triiodothyronine conversion and reduced uptake of thyroxine) to the body tissues.[244,256–262]

With aging, as with nonthyroidal illness, thyrotropin and thyroxine are not indicative of tissue levels of triiodothyronine, making the interpretation of thyroid function tests increasingly complicated and difficult. Aging may be considered a chronic nonthyroidal illness leading to decrease in basal metabolic rate[259,263,264] and reduction in thyrotropin and triiodothyronine levels without a significant decrease in thyroxine and free thyroxine[244,256–258,261,262] (**Fig. 2**). Elevation in reverse triiodothyronine level is also seen[240,244,265,266] as a consequence of diminished use of thyroxine, diminished thyroxine-to-triiodothyronine conversion, and diminished tissue levels of triiodothyronine.[212,222,223,225,232] Another finding in the aging patient is the significantly reduced thyrotropin response to thyrotropin-releasing hormone

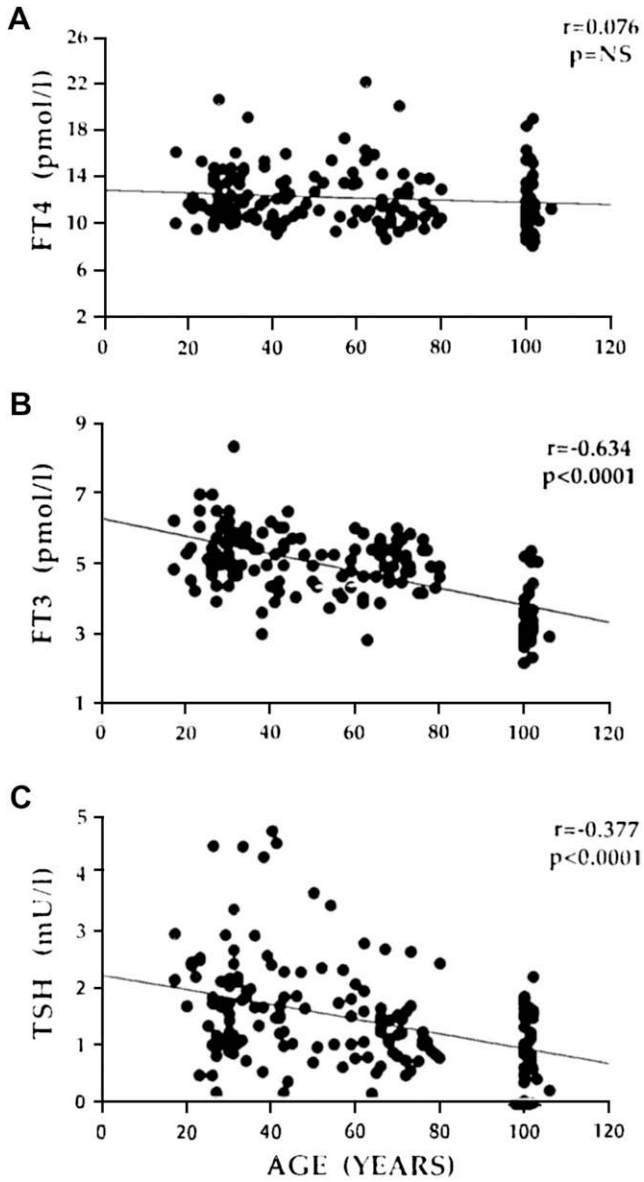

Fig. 2. Age-dependent variations in (*A*) free thyroxine (FT4), (*B*) free triiodothyronine (FT3), and (*C*) thyrotropin (TSH). All healthy subjects in the study (groups *A*–*C*) were pooled for this analysis. (From Mariotti S, Barbesino G, Caturegli P, et al. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Met 1993;77(5):1132; with permission. Copyright © 1993, The Endocrine Society.)

that is similar to that found in severely ill patients with documented nonthyroidal illness.[260,262,267]

Further contributing to potential inaccuracies of standard thyroid testing in this population is the increasing incidence of systemic illness and the increased use of medications that directly affect thyroid function. In aging patients who present with

symptoms consistent with hypothyroidism but have a normal thyrotropin and thyroxine level, obtaining free triiodothyronine, reverse triiodothyronine, and triiodothyronine/reverse-triiodothyronine ratios may help obtain a more accurate evaluation of tissue thyroid status and may be useful to predict those who may respond favorably to triiodothyronine supplementation.[212,222,223,225,232]

The inaccuracy of thyrotropin and thyroxine levels in this potentially large group of individuals, including those with chronic physiologic stress, illness, and advancing age, has potentially profound implications. Studies that do not address the complex interactions of the aging thyroid and illness and use thyrotropin and thyroxine levels alone to determine thyroid status may be significantly flawed. With increasing knowledge of the complexities of thyroid function at the cellular level, it is becoming increasingly clear that the thyrotropin may not be as reliable a marker of tissue thyroid levels as once thought, especially with chronic physiologic stress, illness, inflammation, and aging. It is possible that many symptomatic patients with low tissue levels of active thyroid but normal thyrotropin and thyroxine levels would benefit from thyroid replacement both short and long term. Increasing evidence shows that thyroxine is not an optimal treatment for conditions associated with diminished use of thyroxine. Conversion of thyroxine to triiodothyronine (increased formation of reverse triiodothyronine) should lead the clinician to consider treatment with triiodothyronine.

Thyroid Preparations

Thyroid preparations include triiodothyronine (Cytomel); thyroxine (Synthroid, Levothyroxine); combinations of triiodothyronine, thyroxine; and compounded thyroid formulations (including thyroxine/triiodothyronine and timed-released triiodothyronine preparations).

Further studies are needed regarding the use of triiodothyronine preparations in the aging population and long-term outcomes based on treatment strategies that use improved methods for determining tissue thyroid levels instead of sole reliance on thyrotropin testing. With so much potential for inaccuracy in our present standard thyroid testing, the importance of additional or alternative methods for clinical assessment cannot be overemphasized. New methods of determining tissue levels of thyroid in the aging patient must be developed and used to better assess both short-term and long-term treatment effects and to help the primary practitioner assess tissue thyroid activity in the aging patient with symptoms and normal thyrotropin, thyroxine, and triiodothyronine levels.

SUMMARY

In summary, we believe the well-informed use of hormones in wellness and disease prevention will result in symptomatic improvement and should be considered an integral part in the armamentarium of options we offer our patients. Definitions and testing of hormone deficiency that apply to illnesses do not apply to wellness and prevention and need to be reevaluated while we develop new treatment paradigms to best care for our patients. With the limited amount of research focused primarily on the areas of wellness and prevention, we must acknowledge the infinite number of variables that confound the results of every study. Ultimately we must focus on the individual patient and his or her need and that is the area where the doctor–patient relationship is of utmost importance and is the key to true prevention and wellness.

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