White Paper Guidance for Physicians on Hormone Replacement Therapy (HRT)

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Endorsing Organizations

Academy of Anti-Aging Medicine - China
Academy of Anti-Aging Medicine - Iberia
Academy of Healthy Aging
Academy of Optimal Aging
Academy of Successful Aging
American Academy of Age Management
American Academy of Anti-Aging Medicine (A4M)
American Academy of Longevity Medicine
American College of Longevity Medicine
American Society of Longevity Medicine
Anti-Aging Medicine Specialisation
Asia-Oceania Federation of Anti-Aging Medicine (AOFAAM)
AustralAsian Academy of Anti-Aging Medicine (A5M)
Belgian Society of Anti-Aging Medicine (BELSAAM)
European Academy of Quality of Life and Longevity Medicine (EAQUALL)
European Organization of Scientific Anti-aging Medicine
European Society of Anti-Aging Medicine (ESAAM)
German Society of Anti-Aging Medicine (GSAAM)
German Society of Hemotoxicology
Hellenic Academy of Antiaging Medicine
Indonesian Society of Anti-Aging Medicine
International Academy of Anti-Aging Medicine
International Academy of Longevity Medicine
International Hormone Society (IHS)
Japan Anti-Aging Medical Spa Association (JAMSA)
Japanese Society of Clinical Anti-Aging Medicine (JSCAM)
Korea Anti-Aging Academy of Medicine (KA3M)
LatinoAmerican Federation of Anti-aging Societies
Romanian Association of Anti Aging Medicine
Sociedad de Medicine Antievejenimiento y Longevidad de Gran Canaria
Society for Anti-Aging & Aesthetic Medicine Malaysia (SAAAMM)
South African Academy of Anti-Aging & Aesthetic Medicine (SA5M)
Spanish Society of Anti-Aging
Thai Academy of Anti-Aging Medicine
Thai Association of Anti-Aging Medicine
Anti Aging Research and Education Society, Turkey
Center for Study of Anti-Aging Medicine - UDAYANA University, Indonesia.
World Academy of Anti-Aging Medicine (WAAAM)
World Academy of Longevity Medicine
World Society of Anti-Aging Medicine (WOSAAM)

Preamble

It is the position of the American Academy of Anti-Aging Medicine (A4M), its numerous worldwide affiliated scientific and medical societies, and befriended organizations, that the use of banned drugs or hormones for athletic enhancement constitutes inappropriate misuse. The A4M, its affiliates, and its befriended organizations (hereinafter referred to as "AM"), do not endorse or condone the use of any illicit substances for the purpose of athletic enhancement or sports cheating.

However, AM is resolute in defending the rights of the patient working in conjunction with their physician in choosing any and all justifiable therapies, drugs and interventions which can be shown to improve either the quality or duration of the human lifespan or the form and function of the individual's physiology in order to achieve greater vitality and health at every age. It is in fact the physician's duty to act as an advocate for the patient's right to obtain the full lawful measure of scientific medical therapeutics necessary for optimum health and personal freedom of choice in healthcare.

Introduction

The American Academy of Anti-Aging Medicine (A4M), its affiliates, and its befriended organizations (hereinafter refered to as "AM), promotes the appropriate application of modern and advanced medical technologies to address the changes in chemical, hormonal, physical, and nutritional needs that occurs with aging. The scientific literature supports the benefits claimed by returning hormones to their physiological state when determined to be deficient.

Experienced anti-aging physicians have been prescribing bio-identical hormone replacement therapy (BHRT) for more than 20 years. For women, benefits may include:

- reduced osteoporosis and restoration of bone strength
- reduced hot flashes and vaginal dryness
- better maintenance of muscle mass and strength
- improved cholesterol levels
- reduced risk of endometrial and breast cancer
- reduced risk of depression
- improved sleep
- better mood, concentration and memory
- improved libido
- fewer side effects than with synthetic hormones

[Reed KD. Natural hormone replacement therapy: what it is and what consumers really want. International Journal of Pharmaceutical Compounding. 2001;5(5):332-335; Drusko J. Natural isomolecular hormone replacement: an evidence-based medicine approach. International Journal of Pharmaceutical Compounding. 2000;4(6):414-442; Boothby L, et al. Bioidentical hormone therapy: a review. Menopause. 2004;11(3):356-367.]

An extensive list of peer-reviewed references documenting the beneficial effects of HRT in adults is presented as Appendix A.

Recent legal actions taken against some compounding pharmacies and physicians continue to be played out in the news. Regardless of the merits or lack of merits to these allegations, these accusations should alert us to the responsibilities that each physician faces with the decision to practice hormone replacement therapy. Attempts are being made to criminalize the practice of medicine where variations to State Board-favored traditional care is undertaken. Thus we are now seeing situations where there are no injured patients and no victims being made the basis of criminal proceedings against health professionals. This is an affront to our profession and the very notion of

optimal healthcare. Errors or debate in prescribing guidelines are administrative issues: for officials to abuse their authority in recasting minor issues as criminal acts is in itself unjust and may be3 considered as criminal abise of their publicly elected positions.

Unfortunately, media confusion and outright deception have muddled the reality of what has occurred in the practice of hormone replacement therapy, where doctors' legal and ethical physiological use of hormones and supplements has been misrepresented as being the inappropriate use of hormones for sports enhancement. Every time that a physician breaches the practice of good medicine by prescribing medications inappropriately under the guise of hormone replacement therapy and/or anti-aging medicine, that physician jeopardizes not only the future of our profession, but the life expectancy of us all.

Using the combined knowledge and skills of a significant and elite group of consultants regarding the medical and legal applications of hormone replacement therapy, The American Academy of Anti-Aging Medicine (A4M), its numerous worldwide affiliated scientific and medical societies, and befriended organizations, offers the following policy positions which may help to offer general recommendations and guidelines to practitioners. However, anything offered herein should *not* be construed as legal or medical advice, and applicable state laws and regulations vary widely and should be strictly adhered to. It is recommended that any practitioner seeking specific advice of this type should contact a duly licensed and knowledgeable attorney in the state of practice and/or the medical licensing board of that state. There is no guarantee that these recommendations will fully protect a practitioner from actions taken by various state medical boards, but it is our hope that they will minimize the extent to which false accusations will be actualized.

Furthermore, the ultimate burdens for both the medical and legal issues rest with the treating physician. Therefore, it is imperative that all practitioners consult with their own State Board, the boards of any other states in which they may be deemed to practice, and legal counsel in all applicable jurisdictions regarding the content of this position paper.

Hormone Replacement Therapy

Introduction

Hormone replacement therapies with controlled substances such as testosterone and growth hormone have been used since many years. The first testosterone treatment of testosterone deficiency in adult men started around 1940 started ands since more than 40 years growth hormone is given to treat short stature children and since 1985 with the safer, not contaminated recombinant growth hormone, product of biotechnology. End of the 1980's, the first trial of adults with growth hormone deficiency were published, and since the beginning 1990s, growth treatment of adult patients started in private medical practice.

Testosterone and growth hormone are natural compounds made by the human body. Both hormones are controlled substances in the USA. They have been and are used in adults to correct testosterone and growth hormone deficiencies, often caused by the natural aging of the endocrine glands. Natural does not mean healthy as many studies have shown the association of various age-related diseases and possibly psychiatric disorders with low levels of these hormones, and their improvement or possibly cure with replacement therapy at small physiological doses.

Most traditional endocrinologists have had no intense training in treatment of testosterone and growth hormone deficiencies. They generally have excellent training in the treatment of diabetes, but lack of interest and expertise in how to treat testosterone and adult growth hormone deficiencies and some other hormone deficiencies that may accelerate aging. Because of this lack of knowledge, many of them have rejected these treatments and confused them with the improper use at excessive doses by

sports athletes searching to improve their performance. The American Academy of Anti-Aging Medicine (A4M), its numerous worldwide affiliated scientific and medical societies, and befriended organizations, do not approve the improper use of these substance in sports, but do point to the right of every patient who is suffering from one of these deficiencies to get relief from their complaints by the adequate hormone treatment.

A. Selection of Patients

Historically, patients who were considered for Hormone Replacement Therapy, other than those with classical hormone deficiency syndromes (i.e., Diabetes, Hypothyroidism, Addison's disease, and Menopause, to name a few) were typically over the age of 45. This age criterion no longer applies when we take into consideration the thousands of individuals who have developed Traumatic Brain Injury-Hormone Deficiency Syndrome, which studies suggest can be treated by the use of Hormone Replacement Therapy.

Therefore, age as the single criterion for patient selection has become a moot point leaving documentation of laboratory defined hormonal deficiencies as the gold standard for any replacement strategy.

I. Recommendations for the Selection of Patients

The same concerns that exist in any other area of medicine, including screenings for contraindications, for example, apply in the field of Hormone Replacement Therapy. Additional considerations include, but are not limited to:

1. Treatment should be based upon having documented hormone deficiencies;
3. Screening should be done for participation in professional sports;
4. Screening should be done for prior hormone use and the following practice should be undertaken:
    - Copies of medical records should be requested from prior physician(s) to document any previous hormone deficiencies. Because individuals who have recently used “steroids”" can transiently depress their hormone levels creating the perception that they are deficient and need hormone replacement therapy.

B. Medical Records

Proper documentation of medical treatment is important and a requirement in all areas of medicine. Illegible or incomplete medical records may subject practitioners to regulatory actions and potential misinterpretation of actual sound medical practice. Many prudent practitioners use a computer based reporting system in which the patient’s visit records are recorded and transcribed. The use of a computerized menu-driven EMR (Electronic Medical Records system) can help avoid the lack of appropriate and illegible documentation.

AM does not endorse or condone the prescription or dispensation of controlled substances or any prescription drugs outside the scope of a bona fide physician-patient relationship. It is incumbent upon every practitioner to comply with the obligations imposed by federal and state laws and regulations in this area. The following subsections present examples of some of the most crucial components to practitioners’ medical records that will be evaluated in determining whether a proper patient-physician relationship exists.

C. Patient History

A comprehensive medical history is essential to document rational support for ordering laboratory tests and for any subsequent treatment which may be required.

Additionally, the documentation of conditions such as Orchitis in a male to account for Hypogoadism, birth control use for prolonged periods of time, Polycystic Ovarian Disease, and a variety of medications and toxic reactions, are important to support the medical need for hormone therapy.

I. Recommendations for the Patient's History

AM recommends that a comprehensive Patient Medical History should be conducted as part of the intake procedure during a patient's initial visit. This history should include a comprehensive system review and comprehensive or interval past, family, and social history as well as a comprehensive assessment/history of prior hormone therapies and pertinent risk factors. The elements of the above history should include all those suggested by the AMA's current procedural terminology codebook.

A review of medical events in the patient's family that includes significant information about: the health status or cause of death of parents, siblings, and children; specific diseases related to problems identified in the chief complaint or history of the present illness, and/or system review; and diseases of family members that may be hereditary or place the patient at risk.

The patient's history should include a chronological description of the development of the patient's present illness from the first sign and/or symptom to the present. This includes a description of location, quality, severity, timing, context, modifying factors, and associated signs and symptoms significantly related to the presenting problem(s).

D. Laboratory Testing

Accusations of insurance fraud may occur when insurance companies believe that physicians are ordering unnecessary laboratory tests on patients. A proper medical history, as outlined above, including a review of symptoms, -- which helps define the medical problem, clarify the differential diagnosis and importantly identify needed testing -- allows for proper documentation that will help support any requested testing. Failure to obtain a proper medical history and review of symptoms can open up the physician to the potential of being investigated for improper ordering of laboratory tests, since states generally have a group of Business and Professional Codes (B&P) that defines and regulates professional conduct expected by businesses. These regulations are state driven and will vary from state to state and practitioners should check with local counsel to determine their state specific requirements. However, most professional conduct regulations encompass similar principles. As an example, in the state of California one of their regulations concerning physician prescribing is as follows:

> Repeated acts of clearly excessive prescribing or administering of drugs or treatment, repeated acts of clearly excessive use of diagnostic procedures, or repeated acts of clearly excessive use of diagnostic or treatment facilities as determined by the standard of the community of licensees is unprofessional conduct for a physician and surgeon, dentist, podiatrist, psychologist, physical therapist, chiropractor, or optometrist. Any person who engages in repeated acts of clearly excessive prescribing or administering of drugs or treatment is guilty of a misdemeanor and shall be punished by a fine of not less than one hundred dollars ($100) nor more than six hundred dollars ($600), or by imprisonment for a term of not less than 60 days nor more than 180 days, or by both the fine and imprisonment. (California B&P section 725)

I. Recommendations for Laboratory Testing

1. Practitioners should always conduct a proper review of symptoms that will support any testing;
2. Never send in a diagnostic code (ICD-9) to justify the ordering of laboratory tests unless that code can be substantiated with proper chart documentation.
3. Never send in an insurance claim for office visits with CPT codes that cannot be substantiated and always ensure that proper documentation of any substantiation is in place. Practitioners should be scrupulous in avoiding Insurance Fraud, or even the appearance of Insurance Fraud.
4. Never prescribe a medication that the patient will receive and the pharmacy will bill to an insurance company unless the rationale for the treatment can be substantiated and proper documentation of that substantiation is in place.

E. Interpretation of Laboratory Results

If there is an area in which the practice of hormone replacement therapy is most unique, and also the most open to a Medical Board's scrutiny, it is the manner in which hormone level results are interpreted. The practice of medicine is being replaced by a financially calculating industry that decides treatment based upon numerical results. These results do not take into consideration the clinical acumen of the practice of medicine that a physician has developed over the years of his/her practice.

Mainstream medicine deals with dichotomic treatment practices on a daily basis. What is the laboratory test for depression, anxiety, bipolar disorder, and other medical conditions that fail to be quantified by a numerical test? In such cases, it becomes the medical judgment of the physician to treat a patient with medication in the absence of a measurable basis.

The use of "natural" thyroid in patients whose TSH levels for example are not yet over 5.5 has stimulated controversial cases where the treating physician has been dragged into court to explain why a thyroid supplement was administered to a patient who is not yet sick? Several, often recent, studies have now been published that show that levels of TSH within the reference range, between 2 and 5.5, in certain categories of patients have been reported to be associated with pathological abnormalities and even diseases. It is therefore to no surprise that the American Association of Clinical Endocrinologists has therefore narrowed in 2002 the serum TSH reference range to 0.3-3.0 mIU/L, lowering the upper reference end to 3. The National Academy of Clinical Biochemistry, the world's most respectful organisation for editing guidelines on laboratory test interpretation, reduced the upper end of the reference range from 5.5 to 4.1 mIU per liter in 2003. The latter group also stated that "more than 95% of healthy, euthyroid subjects have a serum TSH between 0.4 - 2.5 mIU per liter" and that "patients with a serum TSH above 2.5 mIU per liter, when confirmed by repeat TSH measurement made after three to four weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidase antibodies are detected." In 2003, the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, and American Thyroid Association) recommended a target TSH range of 1.0 to 1.5 mIU per liter in patients already receiving thyroxine therapy.

The concept of Interventional Endocrinology acknowledges the fact that not everyone experiences symptoms of deficiency – relative or absolute - at the same levels. Therefore, taking a comprehensive medical history and physical can act to substantiate the application of replacement/supplementation protocols, in accordance with accepted standards of care. Clear documentation in this regard helps support the physician's approach in treating the patient.

F. Physical Examination

A "good faith" physical examination is one of the requirements of having personal knowledge of the medical status of an individual patient. Normally, this includes the standard – hands-on, examination of all systems: HEENT, Cardiovascular, Pulmonary, Gastric, Genitalia, Musculoskeletal and Neurological. This also should include the Vital Signs; Weight, Height, Blood Pressure, Pulse and Respirations.

Additional testing, where appropriate, based upon history and the initial "standard" physical examination might include but are not limited to the following: EKG, Chest x-ray, Ultra-fast CT, Bone Density, and referral for GI assessment.

I. Recommendation for the Physical Examination

1. Before dispensing any prescription medication, a complete Physical Examination should be performed in accord with applicable laws. If indicated perform additional tests to address any suspicious physical findings.

G. Treatment protocols

Treatment protocols should be based upon credible scientific literature and currently accepted practice. . The hormone therapy consensuses of the International Hormone Society that are heavily referenced may serve as a model (visit www.intlhormonesociety.org for details).

H. Prescriptions

To dispense controlled substances, a professional must know the requirements for a valid prescription. A prescription is an order for medication that is dispensed to or for an ultimate user. A prescription for a controlled substance must be dated and signed on the date when issued. The practitioner is responsible for making sure that the prescription conforms in all essential respects to both federal and state laws and regulations.

A prescription order for a controlled substance may be issued only by a physician, dentist, podiatrist, veterinarian, mid-level practitioner or other registered practitioner who is: (1) authorized to prescribe controlled substances by the jurisdiction in which he/she is licensed to practice; and (2) Registered with DEA or exempted from registration (i.e., Public Health Service and Bureau of Prison physicians).

Federal regulations (21 CFR 1306.04(a)) related to prescribing contain two key operational phrases, italicized below:

> (a) A prescription for a controlled substance to be effective must be issued for a *legitimate medical purpose* by an individual practitioner acting in the *usual course of his professional practice*. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.

I. Recommendation for Writing Prescriptions

Generally, a prescription must include the patient's full name and address, and the practitioner's name, address, and registration number. The prescription must also include the drug name, strength, dosage form, quantity prescribed, directions for use, and number of refills. Where an oral prescription is not permitted, a prescription must be written in ink or indelible pencil or typewritten and must be manually signed by the practitioner. The practitioner is responsible for making sure that the prescription conforms to federal and all applicable state laws and regulations.

I. The Office Sale and Dispensing of Medications

Although there are general guidelines set forth by the Federal government [21 CFR 1306.04(b): "A prescription may not be issued in order for an individual practitioner to obtain controlled substances for supplying the individual practitioner for the purpose of general dispensing to patients."], the ability of physicians to distribute medications of all classifications from their offices is regulated by each state. Therefore, it is imperative that physicians review their own state's regulatory laws and guidelines. While state regulations will vary, record keeping and proper labeling of dispensed medications are central to most states' regulatory scheme. As an example, California mandates the following requiring physician dispensing:

> A legally licensed Medical practitioner is in breach of this section of code if they: Fail to keep complete and accurate records of purchases and disposals of substances listed in the California Uniform Controlled Substances Act (Division 10 (commencing with Section 11000) of the Health and Safety Code) or controlled substances scheduled in the federal Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. Sec. 801 et seq.), or pursuant to the federal Comprehensive Drug Abuse Prevention and Control Act of 1970. A physician and surgeon shall keep records of his or her purchases and disposals of these controlled substances or dangerous drugs, including the date of purchase, the date and records of the sale or disposal of the drugs by the physician and surgeon, the name and address of the person receiving the drugs, and the reason for the disposal or the dispensing of the drugs to the person, and shall otherwise comply with all state recordkeeping requirements for controlled substances.

In the government's attempt to prevent the illegal sale and distribution of medications classified as Schedule III, laws have been enacted to make it mandatory to provide additional information about the prescriber (physician) and recipient (patient). This information is computerized and can be used to monitor both physicians and patients in terms of the number and quantity of medication that is prescribed over time.

<u>Schedule III is added to the CURES requirement:</u> As of January 1, 2005, all pharmacies have begun submitting Schedule III prescription information to the Controlled Utilization Review and Evaluation System (CURES) program. The CURES program compiles prescription data in a statewide database to assist state law enforcement and regulatory agencies in their efforts to reduce prescription drug diversion. This was apparently precipitated by the highly publicized prosecutions related to BALCO and allegations of athletic Steroid Abuse. This obviously impacts the sale and distribution of Testosterone and related hormones of treatment.

Prior to this change, pharmacies were required to electronically transmit only Schedule II prescription information to the CURES program. New legislation, Senate Bill 151 (Burton, Chapter 406, Statutes of 2003), requires the same information be transmitted for Schedule III prescriptions.

In addition to requiring submission of Schedule III prescription information, the bill required prescribers **dispensing** these drugs to submit prescription information to the CURES program beginning on July 1, 2004. Physicians "dispensing" from the office must comply with the mandated regulatory filings at the same level as a pharmacy.

In order to comply with the reporting regulations, pharmacies and dispensing prescribers must submit the following information for each scheduled II and III prescription filled:

- Full name, address, gender, and date of birth of the patient;
- Prescriber's category of licensure, license number, and federal controlled substance registration number;
- Pharmacy prescription number, license number, and federal controlled substance registration number;
- NDC (National Drug Code) number of the controlled substance dispensed;
- Quantity of the controlled substance dispensed;
- ICD-9 (diagnosis code), if available;
- Date of issue of the prescription; and
- Date of dispensing of the prescription.

I. Recommendation for the Office Sale and Dispensing of Medication:

1. All states have specific requirements for the dispensing of medication. Practitioners are urged to learn about their own states requirements for dispensing all medications from the applicable state board(s).

2. In accordance with federal law, prescriptions for a controlled substance must affix to the container a label showing the pharmacy name and address, the serial number of the prescription, date of initial dispensing, the name of the patient, the name of the prescribing practitioner, and directions for use and cautionary statements, if any, contained on the prescription as required by law. FDA regulations require that the label of any drug listed as a "controlled substance" in Schedule II, III, or IV of the Controlled Substances Act must, when dispensed to or for a patient, contain the following warning: ***CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.***

3. In many cases state law is more stringent than federal law, and must be complied with in addition to federal law. Professionals dispensing controlled substances should make sure they understand their state and federal controlled substance regulations.

J. Self-Prescribing by Physicians

1. Although there isn't a legal statute that specifically states that a physician cannot write a prescription for personal use, there are a number of Medical Board actions against physicians for the self-dispensing of narcotics and medication of abuse where the stated physician(s) lost their license to practice medicine.

K. Internet Pharmacies

The DEA has provided the following information on its Web Site (http://www.deadiversion.usdoj.gov/faq/internetpurch.htm):

"Federal law requires that 'A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice' (21 CFR 1306.04(a)). Every state separately imposes the same requirement under its laws. Under Federal and state law, for a doctor to be acting in the usual course of professional practice, there must be a bona fide doctor/ patient relationship.

For purposes of state law, many state authorities, with the endorsement of medical societies, consider the existence of the following four elements as an indication that a legitimate doctor/patient relationship has been established:

- A patient has a medical complaint;
- A medical history has been taken;
- A physical examination has been performed; and
- Some logical connection exists between the medical complaint, the medical history, the physical examination and the drug prescribed.

"A patient completing a questionnaire that is then reviewed by a physician hired by or working on behalf of an Internet pharmacy does not establish a doctor/patient relationship. A consumer can more easily provide false information in a questionnaire than in a face-to-face meeting with the physician. It is illegal to receive a prescription for a controlled substance without the establishment of a legitimate doctor/patient relationship, and it is unlikely for such a relationship to be formed through Internet correspondence alone. However, this is not intended to limit the ability of practitioners to engage in telemedicine. For purposes of this guidance document, telemedicine refers to the provision of health care using telecommunication networks to transmit and receive information including voice communications, images and patient records.

"Some Internet sites recommend to the patient that they not take a new drug before they have a complete physical performed by a doctor. These sites then ask the patient to waive the requirement for a physical and to agree to have a physical examination before taking the drug they purchase via the Internet. The physical examination does not take the place of establishing a doctor/patient relationship. The physical exam should take place before the prescription is written. These types of activities by Internet pharmacies can subject the operators of the Internet site and any pharmacies or doctors who participate in the activity to criminal, civil, or administrative actions. For DEA registrants, administrative action may include the loss of their DEA registration. Additionally, providing false material information to obtain controlled substances could be considered obtaining a controlled substance by fraud and deceit, which is subject to Federal and State penalties."

L. Delivery of a Controlled Substance or Drug Product Containing Listed Chemicals to Persons in Another Country

Controlled substances that are dispensed pursuant to a legitimate prescription may not be delivered or shipped to individuals in another country without proper authorization. Any such delivery or shipment is an export under the CSA, and cannot be conducted unless the person sending the controlled substances:

1. Has registered with DEA as an "exporter" (see 21 CFR 1301); and
2. Has obtained the necessary permits(s), or submitted the necessary declaration(s) for export as outlined in 21 CFR 1312.

M. Compounding Pharmacy

Compounding by pharmacists has been a foundational aspect of the practice of pharmacy. While today the majority of prescription medication is mass-produced by pharmaceutical companies, many patients require custom-made preparations that are prescribed by their physician and compounded by a trained pharmacist. These custom-prepared prescription medications must originate from a physician's order and be specifically written to meet that individual patients need. Federal and state laws prohibit the compounding of medication that is not pursuant to a doctor's order.

Compounding pharmacies are strictly regulated by regulations from state boards of pharmacy. However, there have been many efforts recently to allow federal oversight of this practice. Recent legislation has been drafted that would usurp long-established state practices, concerning compounding, and turn the oversight over to the FDA.

Despite this pending legislation, courts have repeatedly upheld pharmacists' rights to compound despite repeated attempts by the FDA to challenge the activity. In May 2006, a U.S. District court judge ruled that the compounding of ingredients to create a customized medication in accordance with a valid prescription does not create a new drug subject to the FDA's approval process (see Medical Center Pharmacy et al. v. Gonzales et al.). Additionally, the U.S. Supreme Court has held as unconstitutional FDA's repeated attempts to regulate pharmacist compounding.

I. Recommendation for the use of a Compounding Pharmacy

The use of customized prescription medications must originate from a physician's order and be specifically written to meet an individual patient's need (i.e., a commercially available product would not meet the patient's need) and be compounded by a trained licensed pharmacist.

With regard to the availability of Human Growth Hormone (HGH) from compounding pharmacies, as of this writing there is no FDA-approved compounded HGH product, only manufactured products.

N. Appropriate Patient Monitoring

Although there are generally no state or federal guidelines for mandatory monitoring of patients receiving Testosterone or Growth Hormone, there is an implied responsibility that would follow the "Standards of treatment" for your specific medical community.

O. Off-Label Prescription Drug Prescribing

It is important for all practitioners to understand the legal basis and ability to prescribe drugs for "off-label" uses, and to adhere to all applicable limitations.

An "off-label" use of a drug or a device is simply a use for a condition or in a manner not appearing on the FDA approved label.[1] The American Medical Association reported in 1995 that approximately half of all prescriptions were written for "off-label" uses. Moreover, the General Accounting Office (GAO) has testified that 90 percent of cancer drug use, 80 percent of pediatric use, and 80-90 percent of drugs used to treat rare diseases are prescribed "off-label."[2] Perhaps the best known example is

[1] James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and* Misconceptions, 53 FOOD & DRUG L.J. 71, 71 n.2, (1998). A recent FDA presentation defined off-label drugs as medicines "use[d] for indication[s], dosage form[s], population[s] or other use parameter[s] not mentioned in the approved labeling." Janet Woodcock, *Lecture to Drug Information Association, A Shift in the Regulatory Approach*, (June 23, 1997), at www.fda.gov/cder/present/diamontreal/regappr/sld001.htm.

[2] *Final Report on the Activities of the House Comm. on Government and Oversight,* 104th Cong. 2d Sess. 104 H. REP. 874 (Section 2), (January 2, 1997) at 114.

aspirin. For years, physicians prescribed aspirin to reduce the risk of heart attacks. However, the FDA did not approve such usage until 1998. While some "off-label" therapies are widely accepted, and doctors could be accused of malpractice if they did not prescribe the drug, others are dangerous and are not an appropriate part of medical care.[3]

The FDA and various court decisions have recognized that "off-label" prescribing is a legitimate part of the practice of medicine. The FDA's policy on "off-label" prescribing states that "a physician may, as part of the practice of medicine lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert." This policy was affirmed by the FDA's Policy office by William B. Schultz, Deputy Commissioner for Policy in the FDA in 1996.[4]

"Off-label" Prescribing of Human Growth Hormone

The federal hGH statute criminalizes whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition where such use has been authorized by the Secretary of Health and Human Services, and pursuant to the order of a physician [21 U.S.C. § 333(e)]. Growth hormone cannot be prescribed or dispensed for non-medical purposes. Since the natural aging process is neither a disease nor any other recognized medical condition, "anti-aging therapy" or "reversing the aging clock" is absolutely not a valid basis upon which to distribute hGH. Of course, "bodybuilding" is not a valid basis nor is improving athletic performance.

The Secretary of Health and Human Services (i.e., the Food and Drug Administration) authorizes the uses for which prescription drugs may be marketed. Pharmaceutical companies can be – and have been – sanctioned by the FDA for marketing products for "unapproved" uses. As previously described, in the case of most pharmaceuticals, the uses for which practitioners may prescribe or dispense FDA-approved drugs include "off label" uses.

The FDA has taken the language of the federal hGH statute to mean that all prescribing of hGH must be "on label" (i.e., for an "authorized use"). Although the treatment of adult growth hormone deficiency is an authorized use of hGH and it is therefore clear that a legitimate prescription for hGH replacement therapy is lawful, controversy continues. There is not yet a consensus among the medical community as to what constitutes a "deficiency" of growth hormone in an adult. Further, controversy has arisen over how to diagnose such a deficiency. For example, some staunch critics of growth hormone replacement therapy have opined that an arginine stimulation test must be administered in order to properly diagnose adult growth hormone deficiency. They point to the language on the package inserts of some commercially available brands of hGH recommending arginine stimulation tests and claim that said language makes this specific test mandatory in order to comply with the statute and avoid the commission of a federal felony. Such an interpretation of the law means that the package insert dictates to a physician not only the approved uses for the product, but in the case of growth hormone deficiency, how the diagnosis should be made. The "no off-label" interpretation held by FDA means that prescribing hGH for an authorized use such as legitimate adult growth hormone deficiency would be lawful, but prescribing for anything other than authorized uses – even to treat serious diseases where research indicates that hGH would be beneficial – would not. While a literal reading of the statute may support this interpretation, it is improbable that Congress ever intended to suppress the development and application of medical uses of HGH to treat disease. The FDA's interpretation of the law places greater limitations on HGH prescribing than exist for

[3] Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 202 n.130.

[4] William B. Schultz, Deputy Commissioner for Policy Food and Drug Administration, Department of Health and Human Services, Before the Committee on Labor and Human Resources, United States Senate, February 22, 1996.

controlled substances such as morphine and opiates, which may be prescribed for any legitimate medical purpose. Nothing in the legislative history proves that Congress ever intended that. In fact, this interpretation of the law seems completely at odds with the intent of Congress to treat anabolic steroids more harshly than HGH, not the other way around. Ultimately, legislative or judicial clarification of these issues may be required. Meanwhile, practitioners are urged to adhere to the strictest standards of the law.

The therapeutic value of HGH was validated by a study conducted in Stockholm, Sweden. Data concerning visits to the doctor, number of days in hospital, and amount of sick leave were obtained from patients included in KIMS (Pharmacia International Metabolic Database), a large pharmacoepidemiological survey of hypopituitary adults with GHD, for 6 months before GH treatment and for 6-12 months after the start of treatment. Assistance required with normal daily activities was recorded at baseline and after 12 months of GH therapy. Quality of life (QoL) (assessed using a disease-specific questionnaire, QoL-Assessment of GHD in Adults) and satisfaction with physical activity during leisure time were also assessed. For the total group (n = 304), visits to the doctor, number of days in hospital, and amount of sick leave decreased significantly ($P < 0.05$) after 12 months of GH therapy. Patients also needed less assistance with daily activities, although this was significant ($P < 0.01$) only for the men. QoL improved after 12 months of GH treatment ($P < 0.001$), and both the amount of physical activity and the patients' satisfaction with their level of physical activity improved after 12 months ($P < 0.001$). In conclusion, GH replacement therapy, in previously untreated adults with GHD, produces significant decreases in the use of healthcare resources, which are correlated with improvements in QoL. [Hernberg-Stahl E, Luger A, Abs R, Bengtsson BA, Feldt-Rasmussen U, Wilton P, Westberg B, Monson JP; KIMS International Board., KIMS Study Group. Pharmacia International Metabolic Database, "Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency," *J Clin Endocrinol Metab*. 2001 Nov;86(11):5277-81]

P. Insurance

Medical liability insurance carriers have recently formed a new medical specialty division for the anti-aging healthcare practitioner. Their position on underwriting coverage for hormones focuses on these specific areas: hands on training combined with your level of experience, FDA approval, and HRT must be performed by a licensed physician, NP, PA or RN. Underwriting makes a decision on whether or not to cover your specific situation. You are covered unless the procedure is specifically excluded.

Several new carriers have entered this market. Their names and contact information are available online at www.worldhealth.net.

Q. Conclusion

In addition to allowing doctors to prescribe approved drugs (other than human growth hormone) for "off-label" uses, the FDA has never sought to restrict the ability of third-parties to publish and disseminate scientific information about "off-label" uses. The FDA has repeatedly recognized the importance of "open dissemination of scientific and medical information regarding these treatments."[5] The FDA has, however, traditionally viewed manufacturer dissemination of such materials as promotion that constitutes advertising and thus violates the FD&C Act.[6] FDA regulation in this area has focused on "determining whether an industry-supported activity is independent and not generally subject to regulation," as opposed to manufacturer-supported and therefore regulated.[7] It is in providing guidance on this issue that the FDA's policies have changed most dramatically in recent years, particularly in response to First Amendment criticisms.

[5] WLF v. Friedman, 13 F. Supp. 2d at 56.
[6] Final Guidance on Industry-Supported Scientific and Educational Activities , 62 Fed. Reg. at 64,076.
[7] *Id.*

Disclaimer

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APPENDIX A

Growth hormone in Adults

Senescence is associated with a decline of the growth hormone (GH) axis:

Senescence is associated with lower GH and IGF-1 levels and increased somatostatin

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GH and psychic well-being

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Lower quality of life and fatigue: the effect of GH and/or IGF-1 treatment

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GH and physical appearance/body composition

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315. Moe KE, Prinz PN, Larsen LH, Vitiello MV, Reed SO, Merriam GR. Growth hormone in postmenopausal women after long-term oral estrogen replacement therapy. J Gerontol A Biol Sci Med Sci. 1998 Mar;53(2):B117-24
316. Guidice LC. Insulin-like growth factors and ovarian follicular development. Endocrine Reviews. 1992;13: 641-69

GH treatment: safety, side effects, complications

317. Monson JP. Long-term experience with GH replacement therapy: efficacy and safety. Eur J Endocrinol. 2003 Apr;148 Suppl 2:S9-14
318. Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D. Carpal tunnel syndrome and gynaecomastia during growth hormone treatment of elderly men with low circulating IGF-I concentrations. Clin Endocrinol Oxf. 1993 ;39:417-25
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320. Ezzat S, Melmed S. Clinical review 18: Are patients with acromegaly at increased risk for neoplasia? J Clin Endocrinol Metab. 1991:72:245-9
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GH secretagogues

329. Borges JL, Blizzard RM, Evans WS, Furlanetto R, Rogol AD, Kaiser DL, Rivier J. Vale W, Thorner MO. Stimulation of growth hormone and somatomedin C in idiopathic GH-deficient subjects by intermittent pulsatile administration of human pancreatic tumor GH-releasing factor. J Clin Endocrinol Metab. 1984;59:1-6
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331. Vittone J, Blackman MR, Busby-Whitehead J, Tsiao C, Stewart KJ, Tobin J, Stevens T, Bellantoni MF, Rogers MA, Baumann G, Roth J, Harman SM, Spencer RG. Effects of single

nightly injections of growth hormone-releasing hormone GHRH 1-29 in healthy elderly men. Metabolism. 1997:46:89-96

332. Khorram 0, Laughlin GA, Yen SSC. Endocrine and metabolic effects of long-term administration of [Nle27] growth hormone-releasing hormone (1-29)NH_2 in age-advanced men and women. J Clin Endocrinol Metab. 1997:82:1472-9
333. Chapman IM, Bach MA, van Cauter E, Farmer M, Krupa D, Taylor AM, Schilling AM, Cole KY, Skiles EH, Pczzoli SS. Stimulation of the growth hormone (GH)-insulin-like growth factor I axis by daily oral administration of a GH secretagogue MK-677 in healthy elderly subjects. J Clin Endocrinol Metab. 1996:81:4249-57
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TOPICS OF DISCUSSION

GH TREATMENT'S INFLUENCE ON GH ENDOGENOUS SECRETION: normally no adverse influence when used at physiological doses

Normal doses of GH do not change the endogenous GH secretion

1. Wu RH, St Louis Y, DiMartino-Nardi J, Wesoly S, Sobel EH, Sherman B, Saenger P. Preservation of physiological growth hormone (GH) secretion in idiopathic short stature after recombinant GH therapy. J Clin Endocrinol Metab. 1990 Jun;70(6):1612-5 *(data show that exogenous GH therapy does not interfere with the maintenance of endogenous pulsatile secretion of GH: pre- and (48 hours after stopping) posttreatment GH secretory profiles were comparable with respect to the number of peaks, mean concentrations, peak amplitude, and secretory rate, even after 12 months of GH treatment)*

Pharmacological doses of GH mildly and temporarily reduce the GH-response to GRF in healthy and diabetics with insulin secretion, but does not influence it in diabetics without insulin secretion

2. Wurzburger MI, Prelevic GM, Sonksen PH, Balint-Peric LA, Wheeler M. The effect of recombinant human growth hormone on regulation of growth hormone secretion and blood glucose in insulin-dependent diabetes. J Clin Endocrinol Metab. 1993 Jul;77(1):267-72 *(The response of GH to GRF in diabetics without residual beta-cell activity (C peptide negative) was almost unchanged after 7 days of high dose 4 IU/day of GH treatment, whereas it became lowered in diabetics with endogenous pancreatic beta-cell activity (C peptide positive) and controls)*

EXERCISE AS AN ALTERNATIVE TO GH TREATMENT

Claim: It is enough to let elderly patients regularly exercise to increase their IGF-1 back to youthful levels, GH therapy is not necessary for them.

Fact: Exercise does generally not significantly increase GH and IGF-1 in elderly persons, and certainly not to youthful levels.

Arguments contra GH therapy

Exercise may increase GH, but more rarely IGF-1 levels, in young adults persons to satisfying levels

1. Kraemer WJ, Aguilera BA, Terada M, Newton RU, Lynch JM, Rosendaal G, McBride JM, Gordon SE, Hakkinen K. Responses of IGF-I to endogenous increases in growth hormone after heavy-resistance exercise. J Appl Physiol. 1995 Oct;79(4):1310-5.
2. Nemet D, Connolly PH, Pontello-Pescatello AM, Rose-Gottron C, Larson JK, Galassetti P, Cooper DM. Negative energy balance plays a major role in the IGF-I response to exercise training. J Appl Physiol. 2004 Jan;96(1):276-82

Exercise causes a significant GH response in elderly men, but not in elderly women (>70 yr)

3. Hakkinen K, Pakarinen A, Kraemer WJ, Newton RU, Alen M. Basal concentrations and acute responses of serum hormones and strength development during heavy resistance training in middle-aged and elderly men and women. J Gerontol A Biol Sci Med Sci. 2000 Feb;55(2):B95-105

Twice a week heavy exercise for 24 weeks in elderly men and women causes a significant GH response, but less than in young men

4. Hakkinen K, Pakarinen A, Hannonen P, Hakkinen A, Airaksinen O, Valkeinen H, Alen M. Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia. J Rheumatol. 2002 Jun;29(6):1287-95

5. Hakkinen K, Pakarinen A, Newton RU, Kraemer WJ. Acute hormone responses to heavy resistance lower and upper extremity exercise in young versus old men. Eur J Appl Physiol Occup Physiol. 1998 Mar;77(4):312-9

16 weeks of training causes a significant GH response after acute exercise in elderly men (60 yrs), but does not change the serum IGF-1

6. Nicklas BJ, Ryan AJ, Treuth MM, Harman SM, Blackman MR, Hurley BF, Rogers MA. Testosterone, growth hormone and IGF-I responses to acute and chronic resistive exercise in men aged 55-70 years. Int J Sports Med. 1995 Oct;16(7):445-50

Conclusion: Only heavy (unhealthy?) exercise acutely increases GH secretion in some studies with elderly persons, but not as much as in young people and it does not increase GH metabolic activity, reflected by serum IGF-1.

Arguments pro GH therapy: Exercise alone does not really help to correct low GH and IGF-1 levels in elderly persons who are usually the ones who need most Gh supplementation

No significant (0 to + 3 %) GH response to exercise in elderly persons

7. Pyka G, Wiswell RA, Marcus R. Age-dependent effect of resistance exercise on growth hormone secretion in people. J Clin Endocrinol Metab. 1992 Aug;75(2):404-7
8. Craig BW, Brown R, Everhart J. Effects of progressive resistance training on growth hormone and testosterone levels in young and elderly subjects. Mech Ageing Dev. 1989 Aug;49(2):159-69
9. Hakkinen K, Pakarinen A. Acute hormonal responses to heavy resistance exercise in men and women at different ages. Int J Sports Med. 1995 Nov;16(8):507-13
10. Figueroa A, Going SB, Milliken LA, Blew RM, Sharp S, Teixeira PJ, Lohman TG. Effects of exercise training and hormone replacement therapy on lean and fat mass in postmenopausal women. J Gerontol A Biol Sci Med Sci. 2003 Mar;58(3):266-70
11. Hakkinen K, Pakarinen A, Kraemer WJ, Hakkinen A, Valkeinen H, Alen M. Selective muscle hypertrophy, changes in EMG and force, and serum hormones during strength training in older women. J Appl Physiol. 2001 Aug;91(2):569-80
12. Kiilavuori K, Naveri H, Leinonen H, Harkonen M. The effect of physical training on hormonal status and exertional hormonal response in patients with chronic congestive heart failure. Eur Heart J. 1999 Mar;20(6):456-64
13. Kostka T, Patricot MC, Mathian B, Lacour JR, Bonnefoy M. Anabolic and catabolic hormonal responses to experimental two-set low-volume resistance exercise in sedentary and active elderly people. Aging Clin Exp Res. 2003 Apr;15(2):123-30

GH TREATMENT AND MUSCLE STRENGTH

Claim: GH treatment does not increase muscle strength in adults, so it is not useful for them.
Fact: GH treatment has been reported to help elderly adults increase their muscle strength.

Welle S, Thornton C, Statt M, McHenry B.Growth hormone increases muscle mass and strength but does not rejuvenate myofibrillar protein synthesis in healthy subjects over 60 years old. J Clin Endocrinol Metab 1996 Sep;81(9):3239-43

GH TREATMENT AND FUNCTIONAL CAPACITIES

Claim: GH treatment does not increase functional capacities.
Fact: It does: breathing capacity in patients with chronic bronchitis for example.

1. Pape GS, Friedman M, Underwood LE, Clemmons DR. The effect of growth hormone on weight gain and pulmonary function in patients with chronic obstructive lung disease. Chest. 1991 Jun;99(6):1495-500

GH TREATMENT AND METABOLIC RATE

Claim: GH treatment does not increase resting metabolic rate.
Fact: On the contrary, it does.

An association between GH production and resting metabolic rate has been found, at least in young adults

1. Jorgensen JO, Vahl N, Dall R, Christiansen JS. Resting metabolic rate in healthy adults: relation to growth hormone status and leptin levels. Metabolism. 1998 Sep;47(9):1134-9 *("in the young subgroup, GH production rate was a positive determinant of resting metabolic rate/lean body mass")*
2. Medical Department M (Endocrinology and Diabetes), Aarhus University Hospital, Denmark.

GH therapy increases resting metabolic rate

3. Snel YE, Doerga ME, Brummer RJ, Zelissen PM, Zonderland ML, Koppeschaar HP. Resting metabolic rate, body composition and related hormonal parameters in growth hormone-deficient adults before and after growth hormone replacement therapy. Eur J Endocrinol. 1995 Oct;133(4):445-50

GH TREATMENT AND ADVERSE EFFECTS

Claim: GH treatment has substantial adverse effects such as edema, etc.
Fact: Substantial adverse effects only appear at overdoses such as is the case for any other medical treatment, it is sufficient to reduce the dose to avoid them.

1. Wuster C, Melchinger U, Eversmann T, Hensen J, Kann P, von zur Muhlen A, Ranke MB, Schmeil H, Steinkamp H, Tuschy U. Reduced incidence of side-effects of growth hormone substitution in 404 patients with hypophyseal insufficiency. Results of a multicenter indications Study. Med Klin. 1998 Oct 15;93(10):585-91
2. Amato G, Izzo G, La Montagna G, Bellastella A. Low dose recombinant human growth hormone normalizes bone metabolism and cortical bone density and improves trabecular bone density in growth hormone deficient adults without causing adverse effects. Clin Endocrinol (Oxf). 1996 Jul;45(1):27-32 *(no adverse effects with doses of 10µg/kg/day or a mean of 500-800 µg /day)*
3. Chihara K, Koledova E, Shimatsu A, Kato Y, Kohno H, Tanaka T, Teramoto A, Bates PC, Attanasio AF. An individualized GH dose regimen for long-term GH treatment in Japanese patients with adult GH deficiency. Eur J Endocrinol. 2005 Jul;153(1):57-65 *("The incidence of oedema and cases with high IGF-I level were less frequent under the IGF-I controlled regimen compared with those during the fixed-dose titration method")*

GH TREATMENT AND THE DIABETES CONTROVERSY

Suspicion: Can GH at physiological doses cause diabetes?
Facts: GH's role is to prevent hypoglycaemia by elevating the low serum glucose levels of GH deficient subjects back to normal. It does not at physiological doses cause diabetes.

Arguments contra GH use

GH is a hyperglycemic hormone

1. Ward PS, Savage DC. Growth hormone responses to sleep, insulin hypoglycaemia and arginine infusion. Horm Res. 1985;22(1-2):7-11

Treatment of GH-deficient children: higher incidence of diabetes

2. Cutfield WS, Wilton P, Bennmarker H, Albertsson-Wikland K, Chatelain P, Ranke MB, Price DA . Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. : Lancet. 2000 Feb 19;355(9204):610-3 *("GH treatment did not affect the incidence of type 1 diabetes mellitus in any age group. … the higher than expected incidence of type 2 diabetes mellitus with GH treatment may be an acceleration of the disorder in predisposed individuals. Type 2 diabetes did not resolve after GH therapy was stopped."; critics: very high GH doses are used in children; no increased incidence of type 2 diabetes has been seen in adults taking GH)*

Serum GH levels are higher in diabetes patients *(critics: yes, two times higher serum GH, but -50% low er serum IGF-1, which reflects GH activity; insulin treatment of diabetes significantly increases serum IGF-1 and lower GH)*

3. Shishko PI, Sadykova RE, Kovalev PA, Goncharov BV. Insulin-like growth factor I in patients with newly detected insulin-dependent diabetes mellitus. Probl Endokrinol (Mosk). 1992 Jan-Feb;38(1):17-9

Acromegaly is associated with an increased incidence of diabetes

4. Mercado M, Espinosa de los Monteros AL, Sosa E, Cheng S, Mendoza V, Hernandez I, Sandoval C, Guinto G, Molina M. Clinical-biochemical correlations in acromegaly at diagnosis and the real prevalence of biochemically discordant disease. Horm Res. 2004;62(6):293-9.
5. Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, Gomez JM, Halperin I, Lucas-Morante T, Moreno B, Obiols G, de Pablos P, Paramo C, Pico A, Torres E, Varela C, Vazquez JA, Zamora J, Albareda M, Gilabert M. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol. 2004 Oct;151(4):439-46
6. Fukuda I, Hizuka N, Murakami Y, Itoh E, Yasumoto K, Sata A, Takano K. Clinical features and therapeutic outcomes of 65 patients with acromegaly at Tokyo Women's Medical University. Intern Med. 2001 Oct;40(10):987-92

Arguments pro GH use:

Insulin secretion: the tonic secretion of insulin from the beta-cells depends on IGF-1

7. Kulkarni RN, Holzenberger M, Shih DQ, Ozcan U, Stoffel M, Magnuson MA, Kahn CR. Beta-cell-specific deletion of the Igf1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter beta-cell mass. Nat Genet. 2002 May;31(1):111-5

GH is an anti-hypoglycemic hormone: it neutralizes hypoglycaemia

8. Ward PS, Savage DC. Growth hormone responses to sleep, insulin hypoglycaemia and arginine infusion. Horm Res. 1985;22(1-2):7-11
9. West TE, Sonksen PH. Is the growth-hormone response to insulin due to hypoglycaemia, hyperinsulinaemia or a fall in plasma free fatty acids? Clin Endocrinol (Oxf). 1977 Oct;7(4):283-8 *(hypoglycaemia per se was the important stimulus to GH secretion and not hyperinsulinaemia or a lowering of plasma free fatty acids)*
10. Khaleeli A, Perumainar M, Spedding AV, Teale JD, Marks V. Treatment of tumour-induced hypoglycaemia with human growth hormone. J R Soc Med. 1992 May;85(5):303

IGF-1 therapy has insulin-like effects: it reduces glycemia and serum insulin in controls and type 2 diabetic patients

11. Moses AC, Young SC, Morrow LA, O'Brien M, Clemmons DR. Recombinant human insulin-like growth factor I increases insulin sensitivity and improves glycemic control in type II diabetes. Diabetes. 1996 Jan;45(1):91-100

Diabetes: the association with lower GH and/or IGF-1 levels

12. Nam SY, Kim KR, Cha BS, Song YD, Lim SK, Lee HC, Huh KB. Low-dose growth hormone treatment combined with diet restriction decreases insulin resistance by reducing visceral fat and increasing muscle mass in obese type 2 diabetic patients. Int J Obes Relat Metab Disord. 2001 Aug;25(8):1101-7

Diabetes patients have high GH, but low IGF-1, marker of GH metabolic activity: *a lower IGF-1 in insulin-dependent diabetes pubers is associated with a higher serum glycosylated hemoglobine HbA1C)*

13. Clayton KL, Holly JM, Carlsson LM, Jones J, Cheetham TD, Taylor AM, Dunger DB. Loss of the normal relationships between growth hormone, growth hormone-binding protein and insulin-like growth factor-I in adolescents with insulin-dependent diabetes mellitus. Clin Endocrinol (Oxf). 1994 Oct;41(4):517-24

Acromegaly: GH production in acromegaly is 10 to 100 times the normal production; 10 to 300 times the doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating a **polyhormonal deficit**: hypothyroidism, hypogonadism, hypocorticism, .., endocrine conditions that increase the risk of glucose intolerance and diabetes. These conditions are not found in corrective GH treatment of GH deficiency.

14. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab. 1994 Dec;79(6):1706-15 *("Patients with active acromegaly …secretion rate per 24 h was 25 times greater in female acromegalics and 100 times greater in male acromegalics than that in the controls")*
15. Lamberton RP, Jackson IM. Investigation of hypothalamic-pituitary disease. J Clin Endocrinol Metab. 1983 Nov;12(3):509-34 *("The possibility of deficiencies of the other pituitary hormones should then be addressed in patients with secretory tumours. In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order. Basal thyroid function tests, serum oestradiol or testosterone, and basal gonodotrophins should be routinely obtained in patients with macroadenomas. Additionally, the integrity of the pituitary-adrenal axis should be determined and an overnight water deprivation test for assessment of neurohypophyseal function is also recommended.")*
16. Snyder PJ, Bigdeli H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD. Gonadal function in fifty men with untreated pituitary adenomas. J Clin Endocrinol Metab. 1979 Feb;48(2):309-14
17. Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN. Diagnosis of pituitary tumors by hormone assays and computerized tomography. Am J Med. 1982 Jun;72(6):861-73

GH therapy increases first, then reduces glycemia when given to HIV-infected patients with fat accumulation:

18. Lo JC, Mulligan K, Noor MA, Schwarz JM, Halvorsen RA, Grunfeld C, Schambelan M. The effects of recombinant human growth hormone on body composition and glucose metabolism in HIV-infected patients with fat accumulation. J Clin Endocrinol Metab. 2001 Aug;86(8):3480-7

GH therapy at physiological doses to type 1 diabetics: no effect on glycemia

19. Bright GM, Melton RW, Rogol AD, Clarke WL. The effect of exogenous growth hormone on insulin requirements during closed loop insulin delivery in insulin-dependent diabetes mellitus. Horm Metab Res. 1984 Jun;16(6):286-9

GH therapy to type 1 diabetics: increased insulin requirements, but improved the control of hypoglycaemic attacks

20. Christ ER, Simpson HL, Breen L, Sonksen PH, Russell-Jones DL, Kohner EM. The effect of growth hormone (GH) replacement therapy in adult patients with type 1 diabetes mellitus and GH deficiency. Clin Endocrinol (Oxf). 2003 Mar;58(3):309-15

Low dose GH therapy (0.10 mg/day) improves insulin sensitivity in young healthy adults

21. Yuen KC, Frystyk J, White DK, Twickler TB, Koppeschaar HP, Harris PE, Fryklund L, Murgatroyd PR, Dunger DB. Improvement in insulin sensitivity without concomitant changes in body composition and cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. Clin Endocrinol (Oxf). 2005 Oct;63(4):428-36 *("The low GH dose (0.10 mg/day) decreased fasting glucose levels (P < 0.01) and enhanced insulin sensitivity (P < 0.02), the standard GH (mean dose 0.48 mg/day) did not modify insulin sensitivity")*

Diabetes: the improvement with GH treatment

22. Gotherstrom G, Svensson J, Koranyi J, Alpsten M, Bosaeus I, Bengtsson B, Johannsson G. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. J Clin Endocrinol Metab. 2001 Oct;86(10):4657-65
23. Svensson J, Fowelin J, Landin K, Bengtsson BA, Johansson JO. Effects of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. J Clin Endocrinol Metab. 2002 May;87(5):2121-7
24. Clayton KL, Holly JM, Carlsson LM, Jones J, Cheetham TD, Taylor AM, Dunger DB. Loss of the normal relationships between growth hormone, growth hormone-binding protein and insulin-like growth factor-I in adolescents with insulin-dependent diabetes mellitus. Clin Endocrinol (Oxf). 1994 Oct;41(4):517-24
25. Yuen KC, Frystyk J, White DK, Twickler TB, Koppeschaar HP, Harris PE, Fryklund L, Murgatroyd PR, Dunger DB. Improvement in insulin sensitivity without concomitant changes in body composition and cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. Clin Endocrinol (Oxf). 2005 Oct;63(4):428-36

GH AND CARDIOVASCULAR SYSTEM

Claim: GH treatment has adverse effects on the cardiovascular system.
Facts: Most studies are reports of beneficial effects of GH on the heart and blood vessels.

Arguments contra GH use: mainly based on studies of excess GH LEVELS and their correction

Acromegalic patients have an increased heart disease mortality *(critics: acromegaly is a disease with GH and IGF-1 levels several times those obtained with a safe corrective GH treatment, with a Gh production that is 25 to 100 times the normal daily production; the acromegalic heart has myocardial hypertrophy with proliferation of the myocardial fibrous tissue, resulting in impaired ventricular relaxation, and eventually heart failure, a condition that is not found in GH deficient adults treated with correct doses of GH)*

1. Erfurth EM, Hagmar L. Cerebrovascular disease in patients with pituitary tumors. Trends Endocrinol Metab. 2005 Sep;16(7):334-42
2. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4

Critics: in acromegaly is the **GH production 10 to 100 times the normal production, 10 to 300 times the doses used in GH therapy.** The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating **a polyhormonal deficit**: hypothyroidism, hypogonadism, hypocorticism, endocrine conditions that increase the risk of glucose intolerance anddiabetes. These conditions are not found in corrective GH treatment of GH deficiency.

3. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab. 1994 Dec;79(6):1706-15 *("Patients with active acromegaly …secretion rate per 24 h was 25 x greater in female acromegalics & 100 x greater in male acromegalics than that in the controls")*
4. Lamberton RP, Jackson IM. Investigation of hypothalamic-pituitary disease. Clin Endocrinol Metab. 1983 Nov;12(3):509-34 *("In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order ")*
5. Snyder PJ, Bigdeli H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD. Gonadal function in fifty men with untreated pituitary adenomas. J Clin Endocrinol Metab. 1979 Feb;48(2):309-14
6. Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN. Diagnosis of pituitary tumors by hormone assays and computerized tomography. Am J Med. 1982 Jun;72(6):861-73

Octreotide therapy of acromegaly suppresses GH production and reverses the heart disease

7. Sacca L, Cittadini A, Fazio S. Growth hormone and the heart. Endocr Rev. 1994 Oct;15(5):555-73
8. Merola B, Cittadini A, Colao A, Ferone D, Fazio S, Sabatini D, Biondi B, Sacca L, Lombardi G. Chronic treatment with the somatostatin analog octreotide improves cardiac abnormalities in acromegaly. J Clin Endocrinol Metab. 1993 Sep;77(3):790-3

Arguments pro GH use: GH treatment improves the failing GH heart of GH deficient persons

GH improves the heart function

9. Cittadini A, Berggren A, Longobardi S, Ehrnborg C, Napoli R, Rosen T, Fazio S, Caidahl K, Bengtsson BA, Sacca L. Supraphysiological doses of GH induce rapid changes in cardiac morphology and function. J Clin Endocrinol Metab. 2002 Apr;87(4):1654-9
10. Napoli R, Guardasole V, Matarazzo M, Palmieri EA, Oliviero U, Fazio S, Sacca L. Growth hormone corrects vascular dysfunction in patients with chronic heart failure. J Am Coll Cardiol. 2002 Jan 2;39(1):90-5
11. Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, Pardo F, Biondi B, Sacca L. A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. N Engl J Med. 1996 Mar 28;334(13):809-14

GH deficient patients have a higher rate of myocardial infarction risk and mortality

12. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

The premature mortality in hypopituitarism (and thus GH deficiency) is due to cardiovascular disease

13. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet. 1990 Aug 4;336(8710):285-8

Coronary heart disease: the association with lower GH and/or IGF-1 levels

14. Conti E, Andreotti F, Sciahbasi A, Riccardi P, Marra G, Menini E, Ghirlanda G, Maseri A. Markedly reduced insulin-like growth factor-1 in the acute phase of myocardial infarction. J Am Coll Cardiol. 2001 Jul;38(1):26-32

Hypopituitarism increases the cerebrovascular mortality

15. Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf). 1997 Jan;46(1):75-81

GH deficient patients have a higher incidence of cerebrovascular events

16. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12
17. Cittadini A, Cuocolo A, Merola B, Fazio S, Sabatini D, Nicolai E, Colao A, Longobardi S, Lombardi G, Sacca L. Impaired cardiac performance in GH-deficient adults and its improvement after GH replacement. Am J Physiol. 1994 Aug;267(2 Pt 1):E219-25

GH TREATMENT

GH therapy to GH deficient patients: normalizes the (excessive) rate of myocardial infarction and its mortality

18. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

GH treatment may improve coronary heart disease

19. 121. Castagnino HE, Lago N, Centrella JM, Calligaris SD, Farina S, Sarchi MI, Cardinali DP. Cytoprotection by melatonin and growth hormone in early rat myocardial infarction as revealed by Feulgen DNA staining. Neuroendocrinol Lett 2002 Oct-Dec;23(5/6):391-395

GH therapy partially normalizes the higher incidence of cerebrovascular events found in GH deficient patients

20. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12
21. Cittadini A, Cuocolo A, Merola B, Fazio S, Sabatini D, Nicolai E, Colao A, Longobardi S, Lombardi G, Sacca L. Impaired cardiac performance in GH-deficient adults and its improvement after GH replacement. Am J Physiol. 1994 Aug;267(2 Pt 1):E219-25

GH AND CANCER

Claim: GH increases the risk of cancer

Facts: The epidemiological studies, which indicate an association between serum IGF-I and cancer risk, have not established causality. An increased cancer risk with GH therapy has not been proven in humans.

Arguments contra GH use:

GH LEVELS: Studies where positive associations between higher serum GH and/or IGF-1 levels and an increased risk of prostate or breast cancer

Studies where a higher serum IGF-1 and/or high IGF-I to IGFBP-3 molar ratio was found associated with an increased risk of prostate cancer *(critics: the increased IGF-1 may be due to local production of IGF-1 by the tumour and may thus be a marker, and not a cause of cancer, or a bias due to nutritional fators - see further)*

1. Peng L, Tang S, Xie J, Luo T, Dai B. Quantitative analysis of IGF-1 and its application in the diagnosis of prostate cancer. Hua Xi Yi Ke Da Xue Xue Bao. 2002 Jan;33(1):137
2. Li L, Yu H, Schumacher F, Casey G, Witte JS. Relation of serum insulin-like growth factor-I (IGF-I) and IGF binding protein-3 to risk of prostate cancer (United States). Cancer Causes Control. 2003 Oct;14(8):721-6
3. Chokkalingam AP, Pollak M, Fillmore CM, Gao YT, Stanczyk FZ, Deng J, Sesterhenn IA, Mostofi FK, Fears TR, Madigan MP, Ziegler RG, Fraumeni JF Jr, Hsing AW. Insulin-like growth factors and prostate cancer: a population-based case-control study in China. Cancer Epidemiol Biomarkers Prev. 2001 May;10(5):421-7
4. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Baltimore Longitudinal Study on Aging. Serum levels of IGF-I, IGF-II, IGF-BP-3, and PSA as predictors of clinical prostate cancer. J Clin Endocrinol Metab. 2000 Nov;85(11):4258-65

Studies where a higher serum GH was found associated with an increased risk of breast cancer *(critic: based on the measurement of the daytime serum GH level, which is not representative of GH 24-hour secretion)*

5. Emerman JT, Leahy M, Gout PW, Bruchovsky N. Elevated growth hormone levels in sera from breast cancer patients. Horm Metab Res. 1985 Aug;17(8):421-4

Studies where a higher serum IGF-1 or IGF-1/IGF-BP-3 ratio is found associated with an increased risk of breast cancer, in particular in women with ≥ 19 CA repeats in IGF-1 gene

6. Yu H, Li BD, Smith M, Shi R, Berkel HJ, Kato I.. Polymorphic CA repeats in the IGF-I gene and breast cancer. Breast Cancer Res Treat. 2001 Nov;70(2):117-22
7. Vadgama JV, Wu Y, Datta G, Khan H, Chillar R. Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. Oncology. 1999 Nov;57(4):330-40 *(up to 7x greater breast cancer incidence in women in the highest quintile of serum IGF-1: serum IGFBP-3 ratio compared to women in the lowest quintile)*

A study where a lower serum IGF-BP-3 was found in breast cancer patients

8. Bruning PF, Van Doorn J, Bonfrer JM, Van Noord PA, Korse CM, Linders TC, Hart AA. Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. Int J Cancer. 1995 Jul 28;62(3):266-70

A study where a higher serum IGF-1 / IGF-BP-3 was found associated with an increased colon cancer risk *(the colon cancer risk was 4 times increased only for subjects in the upper tertile of IGF-1 and lower tertile of IGF-BP-3; for other tertiles or a combination of tertiles there was: no significant association)*

9. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ. Prospecftive study of colorectal cancer risk in men and plasma levels of IGF-1 and IGF-BP-3. J Natl Cancer Inst. 1999; 91: 620-5

In acromegaly, the incidence of and/or mortality from digestive cancer is increased

10. Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni JF Jr. Acromegaly and gastrointestinal cancer. Cancer. 1991 Oct 15;68(8):1673-7 *(but no increase in overall cancer incidence)*
11. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4 *(but decreased overall incidence of cancer in acromegaly, and no increased overall cancer mortality)*

Critics: in acromegaly the GH production is 10 to 100 times the normal production, 10 to 300 times the daily doses used in GH therapy. The pituitary GH-secreting tumor in the sella turcica crushes down the production of other pituitary hormones such as ACTH, LH, FSH, TSH, creating **a polyhormonal deficit**: hypothyroidism, hypogonadism, hypocorticism, .., endocrine conditions that increase the risk of glucose intolerance and diabetes These conditions are not found in corrective GH treatment of GH deficiency.

12. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F. Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab. 1994 Dec;79(6):1706-15 *("Patients with active acromegaly …secretion rate per 24 h was 25 x greater in female acromegalics & 100 x greater in male acromegalics than that in the controls")*
13. Lamberton RP, Jackson IM. Investigation of hypothalamic-pituitary disease. Clin Endocrinol Metab. 1983 Nov;12(3):509-34 *("In patients with large macroadenomas pituitary hormone deficiencies are almost invariable with GH and FSH/LH being the most commonly affected, followed by TSH and ACTH in that order ")*
14. Snyder PJ, Bigdeli H, Gardner DF, Mihailovic V, Rudenstein RS, Sterling FH, Utiger RD. Gonadal function in fifty men with untreated pituitary adenomas. J Clin Endocrinol Metab. 1979 Feb;48(2):309-14
15. Valenta LJ, Sostrin RD, Eisenberg H, Tamkin JA, Elias AN. Diagnosis of pituitary tumors by hormone assays and computerized tomography. Am J Med. 1982 Jun;72(6):861-73

GH TREATMENT WITH HUMAN PITUITARY GH HORMONE

A study where the use of human pituitary GH as therapy to GH-deficient patients treated during childhood and early adulthood up to 1985 was associated with an increased risk of colon cancer and overall cancer mortality *(critics: the data are based on patients having taken GH extracted from human cadavers, now only biosynthetic growth hormone is used; moreoever, the doses used in childhood are extremely high – at least seven times those used in treatment of GH-deficiency in adults)*

16. Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet. 2002 Jul 27;360(9329):273-7

Neutral information and alternative explanations on a possible GH and cancer relation

Possible bias in the studies with increased prostate and breast cancer risk:

Bias 1: The diagnosis of cancer may be more rapidly made in patients with high IGF-1 because they may undergo more intensive scrutiny: *As raised IGF-1 may cause tissue hyperplasia, including increase in size of prostate and breast tissue, the existence of these bigger tissues and possibly of the symptoms they may cause, may lead to more intensive scrutiny, from increased rate of PSA, CEA or C1.25 measurements, to ultrasound and RX examinations, prostate or breast biopsies, and thus an increased rate of detection of very slow, asymptomatic prostate or breast cancers that would have remained undiagnosed or diagnosed much later in patients with low IGF-1. Such higher rate of cancer detection may be particularly the case for prostate cancer, where the number of detected prostate cancer cases is very low compared to the total number of cases found at autotopsy, and premenopausal breast cancer patients who were diagnosed within the 2 years after the first blood sample.*

17. Cohen P, Clemmons DR, Rosenfeld RG. Does the GH-IGF axis play a role in cancer pathogenesis? Growth Horm IGF Res. 2000 Dec;10(6):297-305

Higher levels of IGF-1 or GH or acromegaly have been associated with benign prostatic hyperplasia, but not necessarily with prostate cancer

18. Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Sesterhenn IA, Mostofi FK, Fraumeni JF Jr, Hsing AW. Insulin-like growth factors and risk of benign prostatic hyperplasia. Prostate. 2002 Jul 1;52(2):98-105.
19. Colao A, Marzullo P, Ferone D, Spiezia S, Cerbone G, Marino V, Di Sarno A, Merola B, Lombardi G. Prostatic hyperplasia: an unknown feature of acromegaly. J Clin Endocrinol Metab. 1998 Mar;83(3):775-9

GH and IGF-1 treament of primates can increase breast hyperplasia, not specifically breast cancer

20. Ng ST, Zhou J, Adesanya OO, Wang J, LeRoith D, Bondy CA. Growth hormone treatment induces mammary gland hyperplasia in aging primates. Nat Med. 1997 Oct;3(10):1141-4

Bias 2: After adjustment for prostate volume, no longer significant associations between serum IGF-I and prostate cancer risk may persist *(Serum IGF-I is not useful for diagnosis of prostate cancer, but a marker of benign prostatic hyperplasia and enlargement***)**

21. Finne P, Auvinen A, Koistinen H, Zhang WM, Maattanen L, Rannikko S, Tammela T, Seppala M, Hakama M, Stenman UH. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. J Clin Endocrinol Metab. 2000 Aug;85(8):2744-77

Bias 3: Serum IGF-I may actually be a surrogate marker of nutritional factors *that may increase the cancer risk such as meat and milk intake (persons who eat a lot of protein, especially red meat, have higher IGF-1 levels and an increased cancer risk)*

22. Dai Q, Xiao-ou Shu, Fan Jin, Yu-Tang Gao, Zhi-Xian Ruan, Zheng W. Consumption of Animal Foods, Cooking Methods, and Risk of Breast Cancer. Cancer Epidemiol Biom Prev. 2002;11:801-8

Link between meat, milk and/or protein intake, and prostate or breast cancer

23. Zheng W, Deitz AC, Campbell DR, Wen WQ, Cerhan JR, Sellers TA, Folsom AR, Hein DW. N-acetyltransferase 1 genetic polymorphism, cigarette smoking, well-done meat intake, and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1999 Mar;8(3):233-9
24. Norrish AE, Lynnette R. Ferguson, Mark G. Knize, James S. Felton, Susan J. Sharpe, Jackson RT. Heterocyclic Amine Content of Cooked Meat and Risk of Prostate Cancer. J Nat Cancer Inst. 1999; 91 (23):2038-44
25. Sinha R, Chow WH, Kulldorff M, Denobile J, Butler J, Garcia-Closas M, Weil R, Hoover RN, Rothman N. Well-done, grilled red meat increases the risk of colorectal adenomas. Cancer Res. 1999;59(17):4320-4

26. Butler LM, Sinha R, Millikan RC, Martin CF, Newman B, Gammon MD, Ammerman AS, Sandler RS. Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. Am J Epidemiol. 2003;157(5):434-45
27. Wolk A. Diet, lifestyle and risk of prostate cancer. Acta Oncol. 2005;44(3):277-81
28. Grant WB. An ecologic study of dietary links to prostate cancer. Altern Med Review 1999; 4(3): 162-9 *(in more than 14 European countries)*
29. Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, Willett WC. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst. 2003 Jul 16;95(14):1079-85

Red meat and milk intake is correlated with high IGF-1

30. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, Mantzoros CS. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. J Clin Oncol. 1999 Oct;17(10):3291-8
31. Larsson SC, Wolk K, Brismar K, Wolk A. Association of diet with serum insulin-like growth factor I in middle-aged and elderly men. Am J Clin Nutr. 2005 May;81(5):1163-7
32. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev. 2002 Nov;11(11):1441-8
33. Hoppe C, Molgaard C, Juul A, Michaelsen KF. High intakes of skimmed milk, but not meat, increase serum IGF-I and IGFBP-3 in eight-year-old boys. Eur J Clin Nutr. 2004 Sep;58(9):1211-6

Bias 4: The increases of serum IGF-1 may be produced by the malignant tumour and constitute a consequence and not a cause as suggested in some animal studies.

34. DiGiovanni J, Kiguchi K, Frijhoff A, Wilker E, Bol DK, Beltran L, Moats S, Ramirez A, Jorcano J, Conti C. Deregulated expression of insulin-like growth factor 1 in prostate epithelium leads to neoplasia in transgenic mice. Proc Natl Acad Sci USA. 2000 Mar 28;97(7):3455-60
35. Kaplan PJ, Mohan S, Cohen P, Foster BA, Greenberg NM. The insulin-like growth factor axis and prostate cancer: lessons from the transgenic adenocarcinoma of mouse prostate (TRAMP) model. Cancer Res. 1999 May 1;59(9):2203-9

Bias 5: the variability of serum IGF-1 makes that if two weeks after the initial blood test another measurement of IGF-1 was done, the results of the studies would have been different (about 40° % of participants of the study would have switched from one quartile to the other)

36. Milani D, Carmichael JD, Welkowitz J, Ferris S, Reitz RE, Danoff A, Kleinberg DL. Variability and reliability of single serum IGF-I measurements: impact on determining predictability of risk ratios in disease development. J Clin Endocrinol Metab. 2004 May;89(5):2271-4 *("If fasting serum IGF-1 is measured twice, two weeks apart, individuall differences range from -36.25 to +38.24%, while the mean value for the group of 84 shows high correlation between the two IGF-Is (r=0.922; p<0.0001) and varies much less (mean 120 at first visit) versus 115; p=0.03) in normal volunteers between the ages of 50 and 90 years. When considered in quartiles, IGF-I changed from one quartile to another in 34/84 (40.5%) of the volunteers. When the group was divided in halves, tertiles, quartiles, or quintiles there was an increasing number of subjects who changed from one subdivision to another as the number of gradations increased. These results suggest that the predictive outcomes of earlier studies that used single IGF-I samples for analysis of risk ratios according to tertiles, quartiles, or quintiles could have been different if a second IGF-I was used to establish the risk ratio.")*

No significant associations of serum levels and prostate cancer risk

No difference in plasma GH or IGF-1 between prostate cancer patients and controls

37. Yu H, Nicar MR, Shi R, Berkel HJ, Nam R, Trachtenberg J, Diamandis EP. Levels of IGF-I and IGF BP- 2 and -3 in serial postoperative serum samples and risk of prostate cancer recurrence. Urology. 2001 Mar;57(3):471-5.
38. Hill M, Bilek R, Safarik L, Starka L. Analysis of relations between serum levels of epitestosterone, estradiol, testosterone, IGF-1 and prostatic specific antigen in men with benign prostatic hyperplasia and carcinoma of the prostate. Physiol Res. 2000;49 Suppl 1:S113-8
39. Kurek R, Tunn UW, Eckart O, Aumuller G, Wong J, Renneberg H. The significance of serum levels of insulin-like growth factor-1 in patients with prostate cancer. BJU Int. 2000 Jan;85(1):125-9
40. Cutting CW, Hunt C, Nisbet JA, Bland JM, Dalgleish AG, Kirby RS. Serum insulin-like growth factor-1 is not a useful marker of prostate cancer. BJU Int. 1999 Jun;83(9):996-9
41. Ismail HA, Pollak M, Behlouli H, Tanguay S, Begin LR, Aprikian AG. Serum insulin-like growth factor (IGF)-1 and IGF-binding protein-3 do not correlate with Gleason score or quantity of prostate cancer in biopsy samples. BJU Int. 2003 Nov;92(7):699-702
42. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Res. 2003 Jul 15;63(14):3991-4
43. Ismail A H, Pollak M, Behlouli H, Tanguay S, Begin LR, Aprikian AG. Insulin-like growth factor-1 and insulin-like growth factor binding protein-3 for prostate cancer detection in patients undergoing prostate biopsy. J Urol. 2002 Dec;168(6):2426-30
44. Bubley GJ, Balk SP, Regan MM, Duggan S, Morrissey ME, Dewolf WC, Salgami E, Mantzoros C. Serum levels of insulin-like growth factor-1 and insulin-like growth factor-1 binding proteins after radical prostatectomy. J Urol. 2002 Nov;168(5):2249-52
45. DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1444-51.

In acromegaly, the incidence of cancer, other than possibly colon cancer, does not appear to be significantly increased*; in one study it was even significantly reduced by -14 %. Overall mortality is normal for patients with low posttreatment GH,but increased for patients with high posttreatment GH.*

46. J. Svensson, B.-Å. Bengtsson, T. Rosén, Odén A, Johannsson G. Malignant Disease and Cardiovascular Morbidity in Hypopituitary Adults with or without GH Replacement Therapy . J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12
47. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4 *("The overall cancer incidence rate was 24 % lower than that in the general population of the U.K.; the overall cancer mortality rate was not increased, but the colon cancer mortality rate was increased.")*

No difference in serum IGF-1 between breast cancer patients and controls

48. Li BD, Khosravi MJ, Berkel HJ, Diamandi A, Dayton MA, Smith M, Yu H. Free insulin-like growth factor-I and breast cancer risk. Int J Cancer. 2001 Mar 1;91(5):736-9
49. DeLellis K, Rinaldi S, Kaaks RJ, Kolonel LN, Henderson B, Le Marchand L. Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3): the multiethnic cohort. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1444-51.

GH transgenic mice with high serum IGF-1 do not develop breast, prostate, or colonic malignancies

50. Wennbo H, Gebre-Medhin M, Gritli-Linde A, Ohlsson C, Isaksson OG, Tornell J. Activation of the prolactin receptor but not the growth hormone receptor is important for induction of mammary tumors in transgenic mice. J Clin Invest. 1997 Dec 1;100(11):2744-51
51. Wennbo H, Tornell J. The role of prolactin and GH in breast cancer. Octogene. 2000;19:1072-6

Arguments pro GH use:

Inverse (protective) associations of serum GH/IGF-1 levels and overall cancer risk

Untreated GH deficient patients have an increased overall cancer incidence (2x the normal incidence) and cancer mortality (4x)

52. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

A high serum IGF-1 is found associated with a lower risk of prostate cancer

53. Finne P, Auvinen A, Koistinen H, Zhang WM, Maattanen L, Rannikko S, Tammela T, Seppala M, Hakama M, Stenman UH. Insulin-like growth factor I is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. J Clin Endocrinol Metab. 2000 Aug;85(8):2744-7
54. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum IGF-1: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Res. 2003;15;63(14):3991-4 *(- 48 % for men in the highest quartile of serum IGF-1)*
55. Baffa R, Reiss K, El-Gabry EA, Sedor J, Moy ML, Shupp-Byrne D, Strup SE, Hauck WW, Baserga R, Gomella LG. Low serum insulin-like growth factor 1 (IGF-1): a significant association with prostate cancer. Tech Urol 2000 Sep;6(3):236-9

No significant association between serum IGF-1 and prostate cancer:

GH therapy increases serum IGF-BP-3, *which may protect against cancer: IGFBP-3 causes apoptosis of cancer cells and inhibits IGF action on cancer cells in vitro => Serum IGFBP-3 is in general negatively correlated with the cancer risk cancer: the higher IGF-BP-3, the lower the cancer risk*

56. Wollmann HA, Schonau E, Blum WF, Meyer F, Kruse K, Ranke MB. Dose-dependent responses in insulin-like growth factors, insulin-like growth factor-binding protein-3 and parameters of bone metabolism to growth hormone therapy in young adults with growth hormone deficiency. Horm Res. 1995;43(6):249-56
57. Grimberg A, Cohen P. GH & prostate cancer: guilty by association? J Endocrinol Invest. 1999;22(5 Suppl):64-73

A high serum IGF-BP-3 is associated with a reduced prostate cancer risk (-30%), and/or prostate cancer recurrence

58. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Baltimore Longitudinal Study on Aging. Serum levels of IGF-I, IGF-II, IGF-BP-3, and PSA as predictors of clinical prostate cancer. J Clin Endocrinol Metab. 2000 Nov;85(11):4258-65

Studies where GH therapy given to cancer patients reduced the cancer recurrence, and reduces the cancer mortality or increases survival time

59. Swerdlow AJ, Reddingius RE, Higgins CD, Spoudeas HA, Phipps K, Qiao Z, Ryder WD,Brada M, Hayward RD, Brook CG, Hindmarsh PC, Shalet SM. Growth hormone treatment of children with brain tumors and risk of tumor recurrence. J Clin Endocrinol Metab. 2000 Dec;85(12):4444-9
60. Tacke J, Bolder U, Herrmann A, Berger G, Jauch KW. Long-term risk of gastrointestinal tumor recurrence after postoperative treatment with recombinant human growth hormone. JPEN J Parenter Enteral Nutr 2000 May-Jun;24(3):140-4

Long-term GH replacement (60 months) **reduced the increased cancer risk and mortality of GH deficient patients by half**

61. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

GH or IGF-1 therapy to animals with cancer: may reduce the tumour incidence and/or progression

Combined GH- insulin therapy reduced the development of mammary carcinoma in female rats

62. Bartlett DL, Charland S, Torosian MH. Growth hormone, insulin, and somatostatin therapy of cancer cachexia. Cancer. 1994 Mar 1;73(5):1499-504

GH-therapy reduced the development of lung metastases in rats with prostate cancer

63. Torosian MH. Growth hormone and prostate cancer growth and metastasis in tumor-bearing animals. J Pediatr Endocrinol. 1993 Jan-Mar;6(1):93-7

A lower serum GH level is found in gastric cancer patients

64. Colombo F, Iannotta F, Fachinetti A, Giuliani F, Cornaggia M, Finzi G, Mantero G, Fraschini F, Malesci A, Bersani M, et al. [Changes in hormonal and biochemical parameters in gastric adenocarcinoma] Minerva Endocrinol. 1991 Jul-Sep;16(3):127-39

GH-therapy inhibits the development of liver cancer due to carcinogens (aflatoxin B1 or N-OH-acetyl- aminofluoren) in male rats

65. Liao D, Porsch-Hallstrom I, Gustafsson JA, Blanck A. Sex differences at the initiation stage of rat liver carcinogenesis—influence of growth hormone. Carcinogenesis. 1993 Oct;14(10):2045-9

IGF-1-therapy preserved lean mass in rats with sarcoma and cachexia

66. Ng EH, Rock CS, Lazarus DD, Stiaino-Coico L, Moldawer LL, Lowry SF. Insulin-like growth factor I preserves host lean tissue mass in cancer cachexia. Am J Physiol. 1992 Mar;262(3 Pt 2):R426-31

Conclusion on the cancer studies and GH

- **GH therapy raises both the levels of both IGF-I and IGFBP-3**. **IGF-BP-3** is a potent inhibitor of IGF action in breast and prostate tissues.
- **Autocrine production of IGF's and GH**, have been identified in **cancer cells and tissues**. Thus, serum IGF-I may actually be a confounding variable, serving as a marker for local prostatic IGF-I production.
- Since GH-deficient patients often have a subnormal IGF-I serum level, which normalizes on therapy, the cancer risk on **GH therapy does probably not substantially increase above that of the normal population**. On the contrary, the evidence points to a normalization of the risk.
- It seems prudent that when we treat adult GH deficiency, we should aim to maintain serum IGF-1 in the normal range.

GH AND LIFE SPAN

Claim: GH may have adverse effects on life span
Facts: GH treatment appears to reduce mortality, except for special mice species and humans put in extreme conditions.

Arguments contra GH use

Studies where higher GH and/or IGF-1 levels were found associated with premature death

A high serum GH was associated with premature death in humans *(critics: an old fashioned technique, which lacked assay precision, was used to measure GH; the daytime serum GH were measured, which is not accurate except for acromegaly patients; serum GH does not reflect GH activity, serum IGF-1 does it, but up to a certain degree; an increased serum GH may possibly reflect increased binding of GH to increased serum GHBP and thus inactivation of GH, but the serum GHBP level was not checked in the study)*

1. Maison P, Balkau B, Simon D, Chanson P, Rosselin G, Eschwege E. Growth hormone as a risk for premature mortality in healthy subjects: data from the Paris prospective study. BMJ. 1998 Apr 11;316(7138):1132-3

Acromegaly adults have premature death only when they keep high posttreatment GH *and thus a probably continuing active growth hormone-secreting tumor that crushes down all the other pituitary cells, overall mortality is normal for patients with low posttreatment GH,*

2. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4.

Mice models of genetic pituitary failure with multiple hormone deficiency (Ames and Snell mice) **and GH receptor knockout mice** (primary IGF1-deficiency) **may have a significant higher longevity** *(critics: the heterozygous IGF-I receptor knock-out mutants are special mice species, as are* Ames and Snell mice *. They react in a completely different way to GH than normal mice species. They have a 50 % decrease in IGF-1 receptors, but a 32% higher serum IGF-1; they have more glucose intolerance; are slightly smaller; the lifespan was only significantly longer in female mice (+33%), not in male mice (+16%); the results based on a shortliving species (mise) may not be necessarily true for species with a long life such as humans)*

3. Liang H, Masoro EJ, Nelson JF, Strong R, McMahan CA, Richardson A. Genetic mouse models of extended lifespan. Exp Gerontol. 2003 Nov-Dec;38(11-12):1353-64
4. Holzenberger M. The GH/IGF-I axis and longevity. Eur J Endocrinol. 2004 Aug;151 Suppl 1:S23-7
5. Kulkarni RN, Holzenberger M, Shih DQ, Ozcan U, Stoffel M, Magnuson MA, Kahn CR. beta-cell-specific deletion of the Igf1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter beta-cell mass. Nat Genet. 2002 May;31(1):111-5 *(lack IGF-1 receptors on beta-cells => glucose interance and less beta-cells)*
6. Hauck SJ, Aaron JM, Wright C, Kopchick JJ, Bartke A. Antioxidant enzymes, free-radical damage, and response to paraquat in liver and kidney of long-living growth hormone receptor/binding protein gene-disrupted mice. Horm Metab Res. 2002 Sep;34(9):481-6

Can GH therapy increases mortality?

GH therapy to critically ill patients: doubles the mortality rate

7. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999 Sep 9;341(11):785-92 *(Critics on the study: the doses used were too high doses: 10 to 70 times the normal dose in very weak persons; the control group had an abnormally lower mortality rate than predicted; combined to the high mortality rates of the treatment group, the average mortality rate was very similar to that of a historical cohort; GH treatment lowers cortisol levels, which are crucial to critically ill patients)*

8. Freeman BD, Danner RL, Banks SM, Natanson C. Safeguarding patients in clinical trials with high mortality rates. Am J Respir Crit Care Med. 2001 Jul 15;164(2):190-2

BUT: Studies where GH therapy lowered the levels of cortisol and its metabolites by 20 to 40 %, which is dangerous for critically-ill patients who desperately need cortisol for their survival

9. Vierhapper H, Nowotny P, Waldhausl W. Treatment with growth hormone suppresses cortisol production in man. Metabolism 1998 Nov;47(11):1376-8 ;
10. Rodriguez-Arnao J, Perry L, Besser GM, Ross RJ. Growth hormone treatment in hypopituitary GH deficient adults reduces circulating cortisol levels during hydrocortisone replacement therapy. Clin Endocrinol (Oxf). 1996 Jul;45(1):33-7
11. Weaver JU, Thaventhiran L, Noonan K, Burrin JM, Taylor NF, Norman MR, Monson JP. The effect of growth hormone replacement on cortisol metabolism and glucocorticoid sensitivity in hypopituitary adults. Clin Endocrinol (Oxf). 1994 Nov;41(5):639-48

…and a study where patients who have poor responsive adrenals (poorly able to increase their cortisol production) and are in septic shock, die easier

12. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. Lancet. 1991 Mar 9;337(8741):582-3

.. and studies where glucocorticoid treatments considerably increased survival of critically-ill patients

survival of HIV patient from pneumonia

13. Gagnon S, Boota AM, Fischl MA, Baier H, Kirksey OW, La Voie L. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med. 1990 Nov 22;323(21):1444-50

survival from typhus

14. Hoffman SL, Punjabi NH, Kumala S, Moechtar MA, Pulungsih SP, Rivai AR, Rockhill RC, Woodward TE, Loedin AA. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. N Engl J Med. 1984 Jan 12;310(2):82-8

NEUTRAL information on GH and longevity

No increased mortality in acromegaly if levels of GH are less than 2.5 ng/ml

15. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998 Aug;83(8):2730-4

Arguments pro GH use

GH/IGF-1 LEVELS: Higher serum GH and IGF-1 levels are associated with a higher survival

Persistent GH deficiency (without GH therapy) in humans, is associated with a shorter life expectancy: increased overall and cardiovascular mortality

16. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. Lancet. 1990 Aug 4;336(8710):285-8
17. AS Bates, W Van't Hoff, PJ Jones and RN Clayton. The effect of hypopituitarism on life expectancy. J Clin Endocrin Metab. 1996 Mar;81(3):1169-72

Higher mortality in GH deficient women

18. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

Higher mortality in 11 GH deficient adults suffering from a genetic defect (6.7-kb spanning deletion of genomic DNA of the GH-1 gene) **that causes isolated GH deficiency (hereditary**

dwarfism), *untreated men lost 21 years of life (-25% compared to the unaffected brothers) and women 34 years less (-44% versus unaffected sisters)*

19. Besson A, Salemi S, Gallati S, Jenal A, Horn R, Mullis PS, Mullis PE. Reduced longevity in untreated patients with isolated growth hormone deficiency. J Clin Endocrinol Metab. 2003;88(8):3664-7

Patients with hypopituitarism have increased overall and cardiovascular mortality; *the increased mortality from cerebrovascular disease (esp. in women) was the main contributor to the increased cardiovascular mortality*

20. Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM.Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf). 1997 Jan;46(1):75-81
21. Bengtsson BA, Koppeschaar HP, Abs R, Bennmarker H, Hernberg-Stahl E, Westberg B, Wilton P, Monson JP, Feldt-Rasmussen U, Wuster C. Growth hormone replacement therapy is not associated with any increase in mortality. KIMS Study Group. J Clin Endocrinol Metab. 1999 Nov;84(11):4291-2

GH TREATMENT: Corrective GH hormone treatment increases survival

GH replacement therapy of GH deficient adults lowers the excessive mortality back to normal

22. Bengtsson BA, Koppeschaar HP, Abs R, Bennmarker H, Hernberg-Stahl E, Westberg B, Wilton P, Monson JP, Feldt-Rasmussen U, Wuster C. Growth hormone replacement therapy is not associated with any increase in mortality. KIMS Study Group. J Clin Endocrinol Metab. 1999 Nov;84(11):4291-2
23. Svensson J, Bengtsson BÅ, Rosén T, Odén A, Johannsson G. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004 Jul;89(7):3306-12

GH treatment of normal elderly mice, extended the mean and maximal life span[8-9].

24. Khansari DN, Gustad T. Effects of long-term, low-dose growth hormone therapy on immune function and life expectancy of mice. Mech Ageing Dev. 1991 Jan;57(1):87-100

GH treatment of GH deficient mice extended life span*, but lifespan of (non GH treated) mice was similar to that of normal mice.*

25. Sonntag WE, Carter CS, Ikeno Y, Ekenstedt K, Carlson CS, Loeser RF, Chakrabarty S, Lee S, Bennett C, Ingram R, Moore T, Ramsey M. Adult-onset growth hormone and insulin-like growth factor I deficiency reduces neoplastic disease modifies age-related pathology, and increases life span. Endocrinology. 2005 Jul;146(7):2920-32

Conclusion: Persistent GH deficiency reduces the life expectancy, while GH treatment of GH-deficient patients improves it. Caution should be applied when using GH treatment in critically-ill patients.

DISCUSSIONS ON THYROID DIAGNOSIS

SERUM TSH: IS THE TSH SERUM MEASUREMENT ALONE SUFFICIENT FOR DIAGNOSIS AND FOLLOW-UP OF THYROID DEFICIENCY?

Claim: TSH is the first line test to do. It is sufficient to diagnose all forms of eu-, hypo- and hyperthyroidism. No other test is necessary for the diagnosis.
Facts: TSH is often insufficient on its own to diagnose between eu-, hypo- and hyperthyroidism, particularly to diagnose milder, borderline states of hypothyroidism. Other tests are necessary, as is a complete clinical evaluation (medical history, actual complaints, physical examination) of the patient.

Article defending the serum TSH test as the first line approach to diagnose thyroid dysfunction

1. Nunez S, Leclere J. Diagnosis of hypothyroidism in the adult. Rev Prat. 1998; 48(18): 1993-8.

Doubts on the usefulness of the serum TSH test alone for diagnosis

Overreliance on laboratory tests without clinical evaluation may lead to considerable diagnostic errors

2. Nicoloff JT, Spencer CA. The use and misuse of the sensitive thyrotropin assay. J Clin Endocrinol Metab. 1990;71:553-8.
3. De Los Santos ET, Mazzaferri EL. Sensitive thyroid-stimulating hormone assays: Clinical applications and limitations. Compr Ther. 1988; 14(9): 26-33.
4. Becker DV, Bigos ST, Gaitan E, Morris JCrd, rallison ML, Spencer CA, Sugarawa M, Van Middlesworth L, Wartofsky L. Optimal use of blood tests for assessment of thyroid function. JAMA 1993 Jun 2; 269: 273 ("the decision to initiate therapy shoul be based on both clinical and laboratory findings and not solely on the results of a single laboratory test")
5. Rippere V. Biochemical victims: False negative diagnosis through overreliance on laboratory results—a personal report. Med Hypotheses. 1983; 10(2): 113.

Discussions and controversy in medical associations and journals on the TSH reference range

6. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228–38 *(conclusions of a consensus panel of the Endocrine Society, the American Thyroid Association,and American Association of Clinical Endocrinology. Although the panel concluded that there was good data that patients with slight elevations of TSH above 4.5 may progress to overt hypothyroidism, and that levothyroxine therapy would prevent symptoms, they did not agree that early treatment provided any benefit!)*
7. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9
8. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8 *(remarkable article of which a lot of the following information is extracted)*
9. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab. 2005;90:581–5
10. Surks MI. Commentary: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab. 2005;90:586–7
11. Ringel MD, Mazzaferri EL. Editorial: subclinical thyroid dysfunction: can there be a consensus about the consensus? J Clin Endocrinol Metab. 2005;90:588–90
12. Pinchera A. Subclinical thyroid disease: to treat or not to treat? Thyroid. 2005;15:1–2

Studies that show that the serum TSH reference range of 0.1-5.1 mU/liter for a POPULATION is too large

Studies indicating a population mean value of 1.5 mU/liter for an iodine-sufficient population

13. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995;43:55–68
14. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–99
15. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002;87:1068–72
16. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40
17. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid. 2003 Jan;13(1):3-126

A longitudinal study in diabetics where a baseline TSH levels above the 1.53 mU/liter predicted subsequent thyroid dysfunction, *whereas no thyroid dysfunction if TSH levels < 1.53 mU/liter,* **the reference range for diabetics should then be 0.4-1.52 mU/liter**

18. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7

If the serum TSH reference range would be **based upon a cohort of truly normal individuals with no personal or family history of thyroid dysfunction, no visible or palpable goiter**, **not taking any medication,** who are **seronegative for thyroid preoxidase antibodies, and** whose blood samples are drawn fasting in the morning hours (06–10 h), **the TSH reference range would become 0.4–2.5 mU/L** (Demers & co, Baloch & co.)

19. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40
20. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–99
21. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

When data for subjects with positive TPOAb or a family history of autoimmune thyroid disease are excluded, the normal reference interval becomes much tighter, i.e. 0.4–2.0 mU/liter. *This tighter reference range may certainly be more applicable to African-Americans, who have a lower mean TSH*

22. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002; 87:489–99
23. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40

Publications with data to support a more narrow reference range for serum TSH that would be obtained when persons with diffuse hypoechogenicity of the thyroid on ultrasound, a condition that precedes thyroid peroxidase antibody positivity in autoimmune thyroid disease, **would be excluded**

24. Pedersen OM, Aardal NP, Larssen TB, Varhaug JE, Myking O, Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. Thyroid. 2000;10:251–9

For the American Association of Clinical Endocrinologists the revised reference TSH range is 0.3–3.0 mU/L

25. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2002;8:457–69

Ethnic differences: the mean TSH level in African-Americans is 1.18 mU/liter, *in contrast to a mean of 1.40 mU/liter in Caucasians, due to the greater frequency of autoimmune thyroid disease in whites (12.3%) than in blacks (4.3%), which may have unjustifiedly skewed the upper end of the TSH curve (NHANES data).* **For African-Americans, the TSH reference range should therefore be lower than in whites**

26. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–9

A study, which suggests that the serum TSH cut-off point between hypo- and euthyroidism is 2, not 4 or 5.5

27. Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adampoulos P, Koutras DA. High serum cholesterol levels in persons with 'high-normal' TSH levels: Should one extend the definition of subclinical hypothyroidism? Eur J Endocrinol. 1998 Feb;138(2):141-5(*Treating TPO antibody-positive hypercholesterolemic patients with TSH levels between 2-4 mU/L with low dose levothyroxine normalizes TSH levels and improves the lipid profile)*

In 2003, **the National Academy of Clinical Biochemistry (NACB) has reduced the upper limit of the reference range from 5.5 to 4.1 mU/L,** but stating also that **"greater than 95% of healthy, euthyroid subjects have a serum TSH concentration between 0.4 - 2.5 mU/L". ".. patients with a serum TSH >2.5 mU/L, when confirmed by repeat TSH measurement made after 3 to 4 weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidise antibodies are detected"**

28. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

Supporters of the recommendations of the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, American Thyroid Association) promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy

29. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies

30. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126
31. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77-83
32. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7

33. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34
34. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991;151:165–8
35. Hershman JM, Pekary AE, Berg L, Solomon DH, Sawin CT Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. J Am Geriatr Soc. 1993;41:823–8
36. Parle JV, Maisonneuve P, Sheppare MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet. 2001;358:861–5

The TSH reference range for an INDIVIDUAL is narrower than the reference range for a population

The value of a population-based reference range is limited when the individual patient-based reference range (*i.e.* his personal reference range) **is narrow**

37. Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci. 1989;27:409–37
38. Harris EK. Effects of intra- and interindividual variation on the appropriate use of normal ranges. Clin Chem. 1974;20:1535–42

The individual TSH reference ranges are remarkably narrow within a relatively small segment of the population reference range, *i.e.* confined to only 25% of a range of 0.3–5.0 mU/liter.

A shift in the TSH value of the individual outside of his or her individual reference range, but still within the population reference range, would not be normal for that individual. For example, an individual (as in Anderson's series) with a personal range of 0.5–1.0 mU/liter would be at subphysiological thyroid hormone levels at the population mean TSH of 1.5 mU/liter (as explained by Wartofsky 2005)

39. Andersen S, Petersen KM, Brunn NH, Laurberg P. Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab. 2002;87:1068–72

Studies of twins have data to support that each of us has a genetically determined optimal free T4 (FT4)-TSH set point or relationship

40. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40
41. Meikle AW, Stringham JD, Woodward MG, Nelson JC. Hereditary and environmental influences on the variation of thyroid hormones in normal male twins. J Clin Endocrinol Metab. 1988 ; 66:588–92

A measured TSH difference of 0.75 mU/liter can already be significant in a patient. The NACB guideline 8 states that "the magnitude of difference in ...TSH values that would be clinically significant when monitoring a patient's response to therapy... is 0.75 mU/liter." Greater TSH fluctuations in a specific patient may mean that s/he becomes hypothyroid or hyperthyroid.

42. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

A serum TSH that rises in a given individual from a set point of 1.0 to 3.5 is likely to be abnormally elevated and imply early thyroid failure. A minor change in serum free T4 results in an amplified change in TSH to outside of the usual population-based reference range, although the free T4 is still within its own population-based reference range, because of the the log-linear relationship between TSH and free T4. In the case of **subclinical hypothyroidism,** for example, a slight drop in free T4 results in an amplified and inverse response in TSH secretion (as explained by Wartofsky 2005)

43. Cooper DS. Subclinical hypothyroidism. N Engl J Med. 2001;345:260–5

44. Ayala A, Wartofsky L. Minimally symptomatic (subclinical) hypothyroidism. Endocrinologist. 1997;7:44–50

There is a 3-fold difference between the average daily maximal TSH (3) and minimal TSH (1 mIU/ml)

89. Brabant G, Prank K, Ranft U, Schuermeyer T, Wagner TO, Hauser H, Kummer B,
45. Feistner H, Hesch RD, von zur Muhlen A. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. J Clin Endocrinol Metab. 1990 Feb;70(2):403-9

Conclusion: TSH reference range is too large => need for narrower ranges

46. Pain RW. Simple modifications of three routine in vitro tests of thyroid function. Clin Chem. 1976; 22(10): 1715-8.
47. Dickey RA, Wartofsky L, Feld S. Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9
48. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab. 2005 Sep;90(9):5483-8

Other arguments that may explain why the TSH test alone is not the only test

The TSH test is insufficient to diagnose all forms of hypothyroidism, including the borderline forms.

The frequency of abnormal TSH values

49. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34
50. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7

Longitudinal studies indicating a rate of progression of mild thyroid failure into overt hypothyroidism of about 5% per year *(50% or more in 10 years!): they have to be treated*

51. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995; 43:55–68
52. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77–83
53. Huber G, Staub J-J, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab. 2002;87:3221–6
54. Kabadi UM. 'Subclinical hypothyroidism:' natural course of the syndrome during a prolonged follow-up study. Arch Intern Med. 1993;153:957-61

The pituitary 5'-deiodinase type 2 that converts thyroxine into triiodothyronine (T3), is different than the liver and kidney 5'-deiodinase type 1 that provides the T3 for the rest of the body. This difference may explain why TSH secretion and thus serum TSH secreted by the pituitary gland may be normal, while the rest of the body may be in a thyroid deficient state.

55. Koenig RJ, Leonard JL, Senator D, Rappaport N, Watson A, Larsen PR. Regulation of thyroxine 5'-deiodinase activity by 3,5,3'-triiodothyronine in cultured anterior pituitary cells. Endocrinology. 1984 Jul;115(1):324-9.

In fasting, hypothyroidism or selenium deficiency for example**,** the 5'-deiodinase of **the pituitary gland increases or remains unchanged, while that of the liver decreases.**

56. Suda AK, Pittman CS, Shimizu T, Cambers JB. The production and metabolism of 3,5,3'-triiodothyronine and 3,3',5'-triiodothyronine in normal and fasting subjects. J Clin Endocrinol Metab. 1978 Dec;47(6):1311-9

57. Larsen PR, Silva JE, Kaplan MM. Relationships between circulating and intracellular thyroid hormones: Physiological and clinical implications. Endocr Rev. 1981 Winter;2(1):87-102.
58. Chanoine JP, Safran M, Farwell AP, Tranter P, Ekenbarger DM, Dubord S, Arthur JR, Beckett GJ, Braverman LE Dubord S, Alex S, Arthur JR, Beckett GJ, Braverman LE, Leonard JLl. Selenium deficiency and type II 5'-deiodinase regulation in the euthyroid and hypothyroid rat: evidence of a direct effect of thyroxine. Endocrinology. 1992 Jul;131(1):479-84

A normal or low serum TSH may reflect in elderly persons hypothyroidism in peripheral tissues, and not anymore eu- or hyperthyroidism, because **the pituitary gland has aged. Progressively with increasing age, the serum TSH test becomes less reliable as a diagnostic test.**

59. Urban RJ. Neuroendocrinology of aging in the male and female. Endocrinol Metab Clin North Am. 1992;21(4): 921-31.

Necessity for other tests than the TSH to diagnosis thyroid dysfunction, e.g. the serum free T4

60. Ladenson PW. Diagnosis of hypothyroidism. In Werner and Ingbar's The Thyroid, 7th edition, Braverman LE and Utiger RE, Lippincott-Raven Publishers, Philadelphia. 1996; 878-82
61. Pacchiarotti A, Martino E, Bartalena L, Aghini Lombardi F, Grasso L, Buratti L, Falcone M, Pinchera A. Serum free thyroid hormones in subclinical hypothyroidism. J Endocrinol Invest. 1986 Aug;9(4):315-9
62. Surks MI, Chopra IJ, Mariosh CN, Nicoloff JT, Salomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. JAMA. 1990 Mar 16;263(11):1529-32
63. Davis JR, Black EG, Sheppard MC. Evaluation of a sensitive chemiluminescent assay for TSH in the follow-up of treated thyrotoxicosis. Clin Endocrinol Oxf. 1987; 27(5): 563-70

Serum thyroid hormone levels may not reflect the cellular thyroid status

64. Escobar del Rey F, Ruiz de Ona C, Bernal J, Obregon MJ, Morreale de Escobar G. Generalized deficiency of 3, 5, 3'-triiodothyronine in tissues from rats on a low iodine intake, despite normal circulating T3 levels. Acta Endocrinol (Copenh) 1989; 120: 490-8

Need to analyse valuable indicators of peripheral activity such as the serum levels of plasma binding proteins SHBG, TBG, CBG, or of thyroid-dependent enzymes such as alkaline phosphatase, osteocalcin

65. Smallridge RC. Metabolic, physiologic, and clinical indexes of thyroid function. In Werner and Ingbar's The Thyroid, 7th edition, Braverman LE and Utiger RP, Lippincott-Raven Publishers, Philadelphia, 1996
66. Foldes J, Tarjan G, Banos C, Nemeth J, Varga F, Buki B. Biologic markers in blood reflecting thyroid hormone effect at peripheral tissue level in patients receiving levothyroxine replacement for hypothyroidism. Exp Clin Endocrinol. 1992; 99(3): 129-33

Conditions or factors that DEPRESS the serum TSH

Aging

67. Urban RJ. Neuroendocrinology of aging in the male and female. Endocrinol Metab Clin North Am. 1992;21(4): 921-31
68. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991; 151(1): 165-8

Fasting

69. Croxson MS, Hall TD, Kletzky OA, Jaramillo JE, Nicoloff OA. Decreased serum thyrotropin induced by fasting. J Clin Endocrinol Metab. 1977; 45: 560
70. Borst GC, Osburne RC, O'Brian JT, Georges LP, Burman KD. Fasting decreases thyrotropin responsiveness to thyrotropin-releasing hormone: A potential cause of misinterpretation of thyroid function tests in the critically ill. J Clin Endocrinol Metab. 1983 Aug;57(2):380-3
71. Campbell GA, Kurcz M, Marshall S, Meites J. Effects of starvation in rats on serum levels of follicle stimulating hormone, luteinizing hormone, thyrotropin, growth hormone and prolactin; response to LH-releasing hormone and thyrotropin-releasing hormone. Endocrinology. 1977; 100(2): 580-7
72. Opstad PK. The thyroid function in young men during prolonged physical stress and the effect of energy and sleep deprivation. Clin Endocrinol. 1984; 20: 657-69.

Strenuous physical exercise

73. Scanlon MF, Toft AD. Regulation of thyrotropin secretion. In Werner and Ingbar's The Thyroid, 7th edition

Pregnancy (first trimester)

74. Braverman LE and Utiger RE, Lippincott-Raven Publisers, Philadelphia. 1996; 220-40.

Depression and anxiety disorders

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Non-thyroidal diseases: *diabetes mellitus, Cushing's syndrome, renal failure, cancer, myocardial infarction, AIDS, post-traumatic syndromes, chronic alcoholic liver disease, other illnesses*

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Medications: *thyroid therapy, estroprogestative birth control pills, progestogens, anti-infammatory agents (incl. glucocorticoids and aspirin), antidepressants, L-Dopa, bromocriptine, neuroleptica, anti-hypertensives, antiarrhythmics (amiodarone), hypolipemic agents, IGF-1, somatostatin, etc.*

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Toxic foods: *MSG, alcohol*

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Thyroid diseases*: hyperthyroidism, Graves-Basedow disease, nodular goiter, thyroiditis, secondary or tertiary hypothyroidism, congenital hypothyroidism*

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FACTORS that ELEVATE the serum TSH

Neonatus, stress - emotional arousal, cold exposure, sleep deprivation, adrenal insufficiency, recovery from severe illness, congenital malformations

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128. Sjoberg S, Wemer S. Increased level of TSH can be a sign of adrenal cortex failures: Net necessarily of thyroid gland disease. Lakartidningen 1999; 96(5):464-5
129. De Nayer P, Dozin B, Vandeput Y, Bottazzo FC, Crabbe J. Altered interaction between triiodothyronine and its nuclear receptors in absence of cortisol: A proposed mechanism for increased thyrotropin secretion in corticoid deficiency states. Eur J Clin Invest. 1987 Apr;17(2):106-8
130. Oakley GA, Muir T, Ray M, Girdwood RW, Kennedy R, Donaldson MD. Increased incidence of congenital malformations in children with transient thyroid-stimulating hormonal elevation on neonatal screening. J Pediatr. 1998; 132(4): 573-4

Medications: *iodine, antithyroidea, , lithium, neuroleptica (haloperidol, chlorpromazine), cimetidine, sulfapyridine, clomifen, antidepressants (sertraline), antihistaminic agents, cholestograhic agents, etc.*

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***Auto-immune thyroiditis* and hypothyroidism:** *primary, iodine-deficient, thyroid hormone resistance*

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136. Missler U, Gutekunst R, Wood WG. Thyroglobulin is a more sensitive indicator of iodine deficiency than thyrotropin: Development and evaluation of dry blood spot assays for thyrotropin and thyroglobulin in iodine- deficient geographical areas. Eur J Clin Chem Clin Biochem 1994; 32(3): 137-43
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TSH-secreting tumors (rare)

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FACTORS that ELEVATE or DEPRESS serum TSH

Physiological serum TSH fluctuations

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92. Brabant G, Prank K, Ranft U, Bergmann P, Schuermeyer T, Hesch RD, von zur Muhlen A. Circadian and pulsatile TSH secretion under physiological and pathophysiological conditions. Horm Metab Res Suppl. 1990;23:12-7
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95. Rose SR, Nisula BC. Circadian variation of thyrotropin in childhood. J Clin Endocrinol Metab. 1989; 68(6):1086-90
96. Scanlon MF, Weetman AP, Lewis M, Pourmand M, Rodriguez Arnao MD, Weightman DR, Hall R. Dopaminergic modulation of circadian thyrotropin rhythms and thyroid hormone levels in euthyroid subjects. J Clin Endocrinol Metab. 1980 Dec;51(6):1251-6
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Variations in the biological activity of TSH

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100. Hiromoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, Inada M. Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: Comparison between the in vivo 3,5,3'-triiodo-thyronine response to TSH and in vitro bioactivity of TSH. J Clin Endocrinol Metab. 1995 Apr;80(4):1124-8

TSH test kit imperfections

101. Rasmussen AK, Hilsted L, Perrild H, Christiansen E, Siersbaek-Nielsen K, Feldt-Rasmussen U. Discrepancies between thyrotropin (TSH) meaasurement by four sensitive immunometric assays. Clin Chim Acta. 1997 Mar 18;259(1-2):117-28

102. Libeer JC, Simonet L, Gillet R. Analytical evaluation of twenty assays for determination of thyrotropin (TSH). Ann Biol Clin Paris. 1989; 47(1): 1-11

103. Spencer CA, Takeuchi M, Kazarosyan M, MacKenzie F, Beckett GJ, Wilkinson E. Interlaboratory/intermethod differences in functional sensitivity of immunometric assays of thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations of TSH. Clin Chem. 1995 Mar;41(3):367-74

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106. Schlienger JL, Sapin R, Grunenberger F, Gasser F, Pradignac A. Thyrotropin assay by chemiluminescence in the diagnosis of dysthyroidism with low thyrotropin and normal thyroid hormones levels. Pathol Biol Paris. 1993; 41(5): 463-8

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111. Bartlett WA, Browning MC, Jung RT. Artefactual increase in serum thyrotropin concentration caused by heterophilic antibodies with specificity for IgG of the family Bouidea. Clin Chem. 1986; 32(12): 22(4-9)

112. Csako G, Weintraub BD, Zweig MH. The potency of immunoglobulin antibodies in a monoclonal immunoradiometric assay for thyrotropin. Clin Chem. 1988 Jul;34(7):1481-3

113. Seghers J, Schruers F, De Nayer P, Beckers C. Interference in thyrotropin (TSH) determination: Falsely elevated TSH values in a transplanted patient. Eur J Nucl Med. 1989; 15(4): 194-6

114. Spencer C, Eigen A, Shen D, Duda M, Quails S, Weiss S, Nicoloff J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem. 1987;33(8):1391-6

115. Ealey PA, Marshall NJ, Ekins RP. Time-related thyroid stimulation by thyrotropin and thyroid-stimulating antibodies, as measured by the cytochemical section bioassay. J Clin Endocrinol Metab. 1981;52(3): 483-7

Doubts on the adequateness of measuring the serum TSH as a help to monitor a thyroid treatment (follow-up)

The serum TSH test for follow-up: The risk of misinterpretation increases when monitoring the treatment of hyper- or hypothyroidism

116. Talbot JN, Duron F, Feron R. Aubert P, Milhaud G. Thyroglobulin, thyrotropin and thyrotropin binding inhibiting immunoglobulins assayed at the withdrawal of antithyroid drug therapy as predictors of relapse of Graves' disease within one year. J Endocrinol Invest. 1989; 12(9): 589-95

In 36-47 % of cinically euthyroid patients receiving adequate long-term thyroid therapy for hypothyroidism, an undetectable serum TSH is found

117. Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab 1994; 78(6): 1368-71
118. Gow SM, Caldwell G, Toft AD, Seth J, Hussey AJ, Sweeting VM, Beckett GJ. Relationship between pituitary and other target organ responsiveness in hypothyroid patients receiving thyroxine replacement. J Clin Endocrinol Metab. 1987; 64(2): 364-70

After intake of thyroidhormones, the serum TSH is transitorily depressed within 60 minutes and remains low for up to 9 hours after intake

119. Chopra U, Carlson HE, Solomon DH. Comparison of inhibitory effects of 3,5,3'-triiodothyronine (T3), thyroxine (T4), 3,3,',5'-triiodothyronine (rT3,), and 3,3'-diiodothyronine (T2) on thyrotropin-releasing hormone-induced release of thyrotropin in the rat in vitro. Endocrinology. 1978;103(2):393-402

Some patents who exhibit reversion of an initially high TSH level back into the reference range, are found to subsequently develop mild thyroid failure

120. Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, Trichitta V, Tassi V, Sava L, Vigneri R. Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. J Clin Endocrinol Metab. 2002;87:3209–14

Supporters of the recommendations of the consensus panel promote a target TSH range of 1.0–1.5 mU/liter in patients already receiving T4 therapy, *whereas they refuse to accept TSH levels of 3–10 mU/liter as abnormal in patients not receiving T4 therapy.*

121. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126

The lower end of the normal or reference range for TSH lies between 0.2 and 0.4 mU/liter, as indicated by a number of clinical studies

122. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruj J, Smyth PP, Spencer CA, Stockigt JR, Guidelines Committee, National Academy of Clinical Biochemistry 2003 Laboratory medicine practice guidelines. Thyroid. 2003 Jan;13(1):3-126
123. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf). 1991;34:77-83
124. Warren RE, Perros P, Nyirenda MJ, Frier BM. Serum thyrotropin is a better predictor of future thyroid dysfunction than thyroid autoantibody status in biochemically euthyroid patients with diabetes: implications for screening. Thyroid. 2004;14:853–7
125. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34

126. Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PW, Hershman JM. Low serum thyrotropin (thyroid stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med. 1991;151:165–8
127. Hershman JM, Pekary AE, Berg L, Solomon DH, Sawin CT Serum thyrotropin and thyroid hormone levels in elderly and middle-aged euthyroid persons. J Am Geriatr Soc. 1993;41:823–8
128. Parle JV, Maisonneuve P, Sheppare MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet. 2001;358:861–5

Other tests : urinary T3 as a complementary test

129. Baisier W, Hertoghe J, Eeckhaut W. Thyroid insufficiency Is TSH measurement the only diagnostic tool? J Nutr Environm Med. 2000; 10(3): 109-113

Testosterone in men

Senescence is associated with a decline of the pituitary-testosterone axis in men

Senescence in men is associated with a decline in testosterone levels

1. Deslypere JP, Vermeulen A. Influence of age on steroid concentrations in skin and striated muscle in women and in cardiac muscle and lung tissue in men. J Clin Endocrinol Metab. 1985 Oct;61(4):648-53
2. Deslypere JP, Vermeulen A. Leydig cell function in normal men: effect of age, life-style, residence, diet, and activity. J Clin Endocrinol Metab. 1984 Nov;59(5):955-62
3. Morer-Fargas F, Nowakowski H. The urinary excretion of testosterone in males. Acta endocrinol (Copenh). 1965 Jul;49:443-52
4. Gapstur SM, Gann PH, Kopp P, Colangelo L, Longcope C, Liu K. Serum androgen concentrations in young men: a longitudinal analysis of associations with age, obesity, and race. The CARDIA male hormone study. Cancer Epidemiol Biomarkers Prev. 2002 Oct;11(10 Pt 1):1041-7
5. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001 Feb;86(2):724-31 *(the incidence of (overt) hypogonadal testosterone levels increased to about 20% of men over 60, 30% over 70 and 50% over 80 yr of age, and even greater percentages when free T index criteria were employed)*
6. Drafta D, Schindler AE, Stroe E, Neacsu E. Age-related changes of plasma steroids in normal adult males. J Steroid Biochem. 1982 Dec;17(6):683-7

The speed of age-related decline of serum testosterone in men

7. Vermeulen A. Plasma levels and secretion rate of steroids with anabolic activity in man. Environ Qual Saf Suppl. 1976;(5):171-80

Senescence in men is associated with a decline in metabolic clearance of testosterone

8. Wang C, Catlin DH, Starcevic B, Leung A, DiStefano E, Lucas G, Hull L, Swerdloff RS. Testosterone metabolic clearance and production rates determined by stable isotope dilution/tandem mass spectrometry in normal men: influence of ethnicity and age. J Clin Endocrinol Metab. 2004 Jun;89(6):2936-41
9. Baker HW, Burger HG, de Kretser DM, Hudson B, O'Connor S, Wang C, Mirovics A, Court J, Dunlop M, Rennie GC. Changes in the pituitary-testicular system with age. Clin Endocrinol (Oxf). 1976 Jul;5(4):349-72

Senescence in men is associated with alterations of the circadian cycle of serum testosterone levels: reduced amplitude and desynchonisation of its circadian rhythm

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The age-related decline of serum testosterone starts in middle age in men

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Follow-up of testosterone/androgen treatment in men: judging the efficacy of the androgen replacement by monitoring the patient's clinical and laboratory test responses

396. Santen RJ. Male Hypogonadism. In: Yen SSC, Jaffe RB, eds. Reproductive Endocrinology, 3rd ed. Saunders, Philadelphia, 1991, pp. 739-94
397. Griffin JE, Wilson JD. Disorders of the Testes and Male Reproductive Tract. In: Wilson JD, Foster DW, eds. William's Textbook of Endocrinology, 8th ed. Saunders, Philadelphia, 1992:799-852
398. Nieschlag E, Mauss J, Coert A. Kicovic P. Plasma androgen levels in men after oral administration of testosterone or testosterone undecanoate. Acta Endocrinol (Copenh). 1975;79:366-74
399. Ebert T, Jockenhovel F, Morales A, Shabsigh R. The current status of therapy for symptomatic late-onset hypogonadism with transdermal testosterone gel. Eur Urol. 2005 Feb;47(2):137-46
400. Babar A, Kaachy A, Cutie AJ, Plakogiannis FM. Gas chromatographic method for simultaneous analysis of urinary testosterone, androsterone and etiocholanolone. Determinations after a single dose of testosterone. Pharm Acta Helv. 1988;63(9-10):278-81

TOPICS OF DISCUSSION:

TESTOSTERONE TREATMENT AND TESTICULAR SUPPRESSION

Full recovery of testosterone (endogenous) secretion and serum levels after stopping high dose testosterone–progestogen treatment for contraception

1. Fogh M, Corker CS, McLean H, Hunter WM, Petersen IB, Philip J, Schou G, Skakkebaek NE. Clinical trial with levo-norgestrel and testosterone oenanthate for male fertility control. Acta Endocrino. (Copenh). 1980 Oct;95(2):251-7
2. Foegh M, Damgaard-Pedersen F, Gormsen J, Knudsen JB, Schou G. Oral levo-norgestrel - testosterone effects on spermatogenesis, hormone levels, coagulation factors and lipoproteins in normal men. Contraception. 1980 Apr;21(4):381-91

Full recovery of testosterone production to youthful (young adult) levels in old animals after long-term suppression of endogenous testosterone secretion by high doses of exogenous testosterone (Leydig cell aging was prevented by the high doses of testosterone treatment)

3. Chen H, Zirkin BR. Long-term suppression of Leydig cell steroidogenesis prevents Leydig cell aging. Proc Natl Acad Sci U S A. 1999;96(26):14877-81

Up to 14.5 weeks for recovery of normal sperm production after treatment with high doses of testosterone-progestogen used for contraception (sperm suppression)

4. Ly LP, Liu PY, Handelsman DJ. Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens. Hum Reprod. 2005 Jun;20(6):1733-40

TESTOSTERONE TREATMENT AND PROSTATE CANCER

Prostate cancer: epidemiology

On the important annual incidence of (detected) prostate cancer in men who are alive in the United States

1. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: Cancer statistics review 1973-1986. Bethesda, MD: NIH;1989;III.45

On the very high incidence of prostate cancer when biopsies are made in men aged 62 or over, even with low serum PSA

2. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. J Clin Endocrinol Metab. 1982 Jun;54(6):1104-8 *(Among the 2950 men (age range, 62 to 91 years), prostate cancer was diagnosed in 15.2 %; 14.9 % of the prostate cancers had a Gleason score of 7 or higher. The prevalence of prostate cancer was 6.6 % among men with a PSA level of up to 0.5 ng/ml, 10.1 % among those with values of 0.6 to 1.0 ng/ml,, 17.0 % among those with values of 1.1 to 2.0 ng/ml, 23.9 % among those with values of 2.1 to 3.0 ng/ml, and 26.9 % among those with values of 3.1 to 4.0 ng/ml. The prevalence of high-grade cancers increased from 12.5 % of cancers associated with a PSA level of 0.5 ng/ml, or less to 25.0 % of cancers associated with a PSA level of 3.1 to 4.0 ng/ml. Conclusions: biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to be in the normal range.)*

On the real incidence of prostate cancer: much higher prevalence rate of prostate cancer are found at post-mortem

3. Stemmermann GN, Nomura AM, Chyou PH, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. Cancer Epidemiol Biomarkers Prev. 1992 Mar-Apr;1(3):189-93 *("3.6% of men in life were diagnosed with prostate cancer, whereas 27% of autopsied Hawaii Japanese men who died after 50 years of age had prostate cancer, reaching a frequency of 63% among men over 80 years of age. The volume of 48(60%) of these cancers was less than 150 mm3. These small tumors would probablynot have been discovered in a screening program. Tumors larger than 1000 mm3 would probably be discovered using modern diagnostic procedures but were found in only 13 (4.4%) of the autopsied men)*
4. Oishi K, Yoshida O, Schroeder FH. The geography of prostate cancer and its treatment in Japan. Cancer Surv. 1995;23:267-80 *("The vast majority of cases of prostate cancer remain undetected during life, the prevalence of prostate cancer detected at autopsy being 2800 times that of lethal cancer in Japanese in Japan, 570 times in whites in the USA and 470 times in blacks in the USA. A case-control study of prostate cancer carried out in Japan and the Netherlands revealed a number of statistically significant risk factors, including … no morning erections, , episodes of sexually transmitted disease, lower plasma testosterone and dihydrotestosterone concentrations.")*
5. Sanchez-Chapado M, Olmedilla G, Cabeza M, Donat E, Ruiz A. Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: an autopsy study. Prostate. 2003 Feb 15;54(3):238-47*("The prevalence of prostate cancer (CaP) is 3.58, 8.82, 14.28, 23.80, 31.7, and 33.33% in the 3rd, 4th, 5th, 6th, 7th, and 8th decades, respectively. The rates of high-grade prostatic intraepithelial neoplasia (HGPIN) were 7.14, 11.75, 35.71, 38.06, 45.40, and 48.15% at the 3rd, 4th, 5th, and 8th decades of life….in 21/27 cases (77.7%), an association between CaP and HGPIN was found. The prevalence of both lesions in Caucasian Mediterranean males is significantly lower than in Caucasian American and Afro-American males in all the age groups evaluated.")*
6. Rich AR. J Urol. 1935: 33: 215-33
7. Baron E et al. Arch Path. 1941,32:787-93
8. Dixon RJ et al. Atlas of Tumor Pathology. 1952, p.197

Prostate cancer patients have a low risk of dying from cancer

9. Stemmermann GN, Nomura AM, Chyou PH, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. Cancer Epidemiol Biomarkers Prev. 1992 Mar-Apr;1(3):189-93. *("Prostate cancer was diagnosed in life among 274 of 8006 (3.6%) members of a cohort of Japanese men in Hawaii between 1965 and 1990. Only 55 (20%) of the 274 diagnosed cases died with prostate cancer, and they accounted for only 2% of the 2893 deaths that occurred among the men during this period.")*
10. Quinn M. Cancer Trends in the USA - A View From Europe. J Nat Cancer Inst. 2003;95(17):1258-61

Prostate cancer, esp. non-metasized is rarely a cause of death in men

11. Oishi K, Yoshida O, Schroeder FH. The geography of prostate cancer and its treatment in Japan. Cancer Surv. 1995;23:267-80
12. Oefelein MG, Ricchiuti VS, Conrad PW, Goldman H, Bodner D, Resnick MI, Seftel A. Clinical predictors of androgen-independent prostate cancer and survival in the prostate-specific antigen era. Urology. 2002 Jul;60(1):120-4

Side effects of testosterone/androgen deprivation therapy of prostate cancer

Androgen deprivation therapy may severly impair the quality of life

13. Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. J Am Geriatr Soc. 2006 Jan;54(1):85-90 *("Participants receiving androgen deprivation therapy (ADT) reported significantly poorer quality of life in the areas of physical function (P<.001), general health (P<.001), and physical health component summary (P<.001) than men not receiving ADT; After controlling for comorbidity, total testosterone level rather than ADT accounted for a small yet statistically significant percentage of the total variance of the physical health ..")*
14. Chen AC, Petrylak DP. Complications of androgen-deprivation therapy in men with prostate cancer. Curr Urol Rep. 2005 May;6(3):210-6 *("Androgen-deprivation therapy (ADT) is indicated for the treatment of metastatic prostate cancer and locally advanced disease. In addition to sexual side effects, long-term ADT results in several other changes, including hot flashes; gynecomastia; changes in body composition, metabolism, and the cardiovascular system; osteoporosis; anemia; psychiatric and cognitive problems; and fatigue and diminished quality of life")*

Androgen deprivation causes anemia

15. Choo R, Chander S, Danjoux C, Morton G, Pearce A, Deboer G, Szumacher E, Loblaw A, Cheung P, Woo T. How are hemoglobin levels affected by androgen deprivation in non-metastatic prostate cancer patients? Can J Urol. 2005 Feb;12(1):2547-52 *("The decline and recovery of hemoglobine was closely related to that of testosterone.")*

Androgen deprivation causes impotence

16. Basaria S, Lieb J 2nd, Tang AM, DeWeese T, Carducci M, Eisenberger M, Dobs AS. Long-term effects of androgen deprivation therapy in prostate cancer patients. Clin Endocrinol (Oxf). 2002 Jun;56(6):779-86
17. Potosky AL, Knopf K, Clegg LX, Albertsen PC, Stanford JL, Hamilton AS, Gilliland FD, Eley JW, Stephenson RA, Hoffman RM. Quality-of-life outcomes after primary androgen deprivation therapy: results from the prostate cancer outcomes study. J Clin Oncol. 2001 Sep 1;19(17):3750-7
18. Fowler FJ, McNaughton Collins M, Walker Corkery E, Elliott DB, Barry MJ. The impact of androgen deprivation on quality of life after radical prostatectomy for prostate carcinoma. Cancer. 2002 Jul 15;95(2):287-95

Androgen deprivation therapy may cause urinary incontinence

19. Miller NL, Bissonette EA, Bahnson R, Wilson J, Theodorescu D. Impact of a novel neoadjuvant and adjuvant hormone-deprivation approach on quality of life, voiding function, and sexual function after prostate brachytherapy. Cancer. 2003 Mar 1;97(5):1203-10

Androgen deprivation therapy generates a greater rate of bone loss in men with prostate cancer

20. Preston DM, Torrens JI, Harding P, Howard RS, Duncan WE, McLeod DG. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. Prostate Cancer Prostatic Dis. 2002;5(4):304-10

Testosterone deprivation therapy increases arterial stiffness in men with prostate cancer

21. Dockery F, Bulpitt CJ, Agarwal S, Rajkumar C. Testosterone suppression in men with prostate cancer is associated with increased arterial stiffness. Aging Male. 2002 Dec;5(4):216-22

Dihydrotestosterone deprivation therapy increases the risk of aggressive prostate cancer

22. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003 Jul 17;349(3):215-24

Arguments against population-based PSA screening for prostate cancer and against treatment of prostate cancer:

1. High prevalence rates of prostate cancer at postmortem
2. Increasing biopsy rates leads to overdiagnosis and overtreatment
3. Despite widespread use of such tests in the USA, and apparent incidence rates of detected prostate cancer almost 3 times higher than in the U.K., the mortality in the USA has for many years been almost the same as in the U.K. and other European countries
4. 1/3 of screen-detected cases are incurable
5. No clear benefit of treatment
6. Side effects of prostatectomy include impotence in a large proportion of cases and incontinence in a smaller proportion
7. Screening and follow-up of treatment (much of which may be unnecessary) is expensive (high costs)
8. Few years of life to gain in many elderly patients
9. No consequent reduction in mortality has yet been demonstrated in a randomized controlled trial

23. Quinn M. Cancer Trends in the USA-A View From Europe. J Nat Cancer Inst. 2003; 95 (17): 1258-61

ARGUMENTS PRO TESTOSTERONE THERAPIES

HUMAN STUDIES:

Studies where low testosterone apparently increases the risk of prostate cancer

The urinary free testosterone decreases with aging, while the incidence of prostate cancer increases

24. Morer-Fargas F, Nowakowski H. Die Testosteronausscheidung im Harn bei Männlichen Indivuen. Acta Endocrinol. 1965; 49: 443-52
25. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: Cancer statistics review 1973-1986. Bethesda, MD: NIH;1989;III.45

Low serum testosterone is associated with an increased prostate cancer risk

26. Chen C, Weiss NS, Stanczyk FZ, Lewis SK, DiTommaso D, Etzioni R, Barnett MJ, Goodman GE. Endogenous sex hormones & prostate cancer risk: a case-control study nested within the Carotene and Retinol Efficacy Trial. Cancer Epidemiol Biomarkers Prev. 2003;12(12):1410-6
27. Stattin P, Lumme S, Tenkanen L, Alfthan H, Jellum E, Hallmans G, Thoresen S, Hakulinen T, Luostarinen T, Lehtinen M, Dillner J, Stenman UH, Hakama M. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. Int J Cancer. 2004 Jan 20;108(3):418-24

Low serum testosterone levels have been found in prostate cancer patients

28. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. J Clin Endocrinol Metab 1982 Jun;54(6):1104-8
29. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. Prostate. 1982;3(6):579-88 *(Low testosterone in prostate cancer patients less than 65 years)*
30. Kumar VL, Wadhwa SN, Kumar V, Farooq A. Androgen, estrogen, and progesterone receptor contents and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. J Surg Oncol. 1990 Jun;44(2):122-8
31. Turkes AO, Turkes A, Read GF, Fahmy DR. A sensitive fluorometric enzyme immunoassay for testosterone in plasma and saliva [proceedings] J Endocrinol. 1979 Oct;83(1):31P
32. Vestsi Akademii Medicina Navuk USSR 1980; 3: 72-7 *(mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)°*
33. Revista Experimental Fisiology 1990; 46:63-8 (*mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1))*
34. Revista Experimental Fisiology 1991; 47: 161-6 *(mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1))*
35. Progress in Clinical Biological Research 1975; 6: 143-58 *(mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1))*
36. Zhonghua Yi Xue Za Zhi 1993; 73: 489-90 *(mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1)*

Close to statistical significance lower testosterone levels in prostate cancer patients

37. Hulka BS, Hammond JE, DiFerdinando G, Mickey DD, Fried FA, Checkoway H, Stumpf WE, Beckman WC Jr, Clark TD. Serum hormone levels among patients with prostatic carcinoma or benign prostatic hyperplasia and clinic controls. Prostate. 1987;11(2):171-82
38. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer:a study of a randomized population. Br J Urol. 1996 Mar;77(3):433-40
39. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. Cancer Res. 1988 Jun 15;48(12):3515-7

Low testosterone levels are found in prostate cancer patients and in their (not yet affected) relatives with familial predisposition to prostate cancer

40. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. J Clin Endocrinol Metab. 1982 Jun;54(6):1104-8

A high serum SHBG (and thus less bioavailable testosterone) **is found in men with family history of prostate cancer**

41. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. Cancer Epidemiol Biomarkers Prev. 1995 Oct-Nov;4(7):735-41

A high incidence of prostate cancer is found in patients with low testosterone and normal digital rectal examination and normal PSA (≤ 4 ng/ml)

42. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA. 1996 Dec 18;276(23):1904-6.

Low serum levels of total and bio-available testosterone are found in populations with a higher risk of prostate cancer *(such as African-Americans and whites)*

43. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. Cancer Epidemiol Biomarkers Prev. 1995 Oct-Nov;4(7):735-41 (*Asian-Americans had higher total and bioavailable testosterone compared to African-Americans and whites)*

Studies where a low serum dihydrotestosterone (DHT) was found in prostate cancer patients

44. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. Prostate. 1982;3(6):579-88 *(Low in prostate cancer patients less than 65 years)*
45. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Lagiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). Cancer Causes Control. 1997 Jul;8(4):632-6

A study where DHT is inversely, significantly, and strongly associated with the risk of prostate cancer

46. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Lagiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). Cancer Causes Control. 1997 Jul;8(4):632-6

Studies where close to statistical significance lower DHT levels were found in prostate cancer patients

47. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer:a study of a randomized population. Br J Urol. 1996 Mar;77(3):433-40
48. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. Cancer Res. 1988 Jun 15;48(12):3515-7

High grade prostate cancers are associated with low testosterone levels

49. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM.(editorial note *A Bohle).* Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. Int Braz J Urol. 2005 Nov-Dec;31(6):609
50. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. J Urol. 2005 Dec;174(6):2178-80.
51. Schatzl G, Madersbacher S, Haitel A, Gsur A, Preyer M, Haidinger G, Gassner C, Ochsner M, Marberger M. Associations of serum testosterone with microvessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. J Urol. 2003 Apr;169(4):1312-5

52. Schatzl G, Madersbacher S, Thurridl T, Waldmuller J, Kramer G, Haitel A, Marberger M. High-grade prostate cancer is associated with low serum testosterone levels. Prostate. 2001 Apr;47(1):52-8
53. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol. 2000 Mar;163(3):824-7

Gene polymorphisms with increased risk of high grade prostate cancer are associated with low testosterone levels

54. Schatzl G, Marberger M, Remzi M, Grosser P, Unterlechner J, Haidinger G, Zidek T, Preyer M, Micksche M, Gsur A. Polymorphism in ARE-I region of prostate-specific antigen gene associated with low serum testosterone level and high-grade prostate cancer. Urology. 2005 Jun;65(6):1141-5

Metastatic prostate cancer (PC) is associated with a low serum testosterone compared to localized PC

55. Imamoto T, Suzuki H, Fukasawa S, Shimbo M, Inahara M, Komiya A, Ueda T, Shiraishi T, Ichikawa T. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. Eur Urol. 2005 Mar;47(3):308-12

A low serum testosterone level in patients with metastatic prostate cancer predicts a worse response to androgen withdrawal therapy (progression to androgen-independent prostate cancer)

56. Furuya Y, Nozaki T, Nagakawa O, Fuse H. Low serum testosterone level predicts worse response to endocrine therapy in Japanese patients with metastatic prostate cancer. Endocr J. 2002 Feb;49(1):85-90
57. Imamoto T, Suzuki H, Akakura K, Komiya A, Nakamachi H, Ichikawa T, Igarashi T, Ito H. Pretreatment serum level of testosterone as a prognostic factor in Japanese men with hormonally treated stage D2 prostate cancer. Endocr J. 2001 Oct;48(5):573-8

Lower prostate tissue levels of DHT (but similar levels of testosterone) **are found in men with recurrent prostate cancer compared to men with benign prostate hypertrophy**

58. Mohler JL, Gregory CW, Ford OH 3rd, Kim D, Weaver CM, Petrusz P, Wilson EM, French FS. The androgen axis in recurrent prostate cancer. Clin Cancer Res. 2004 Jan 15;10(2):440-8

Low testosterone levels are associated with an increased prostate cancer mortality in prostate cancer patients

59. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. Am J Clin Oncol 1997 Dec;20(6):605-8
60. Iversen P, Rasmussen F, Christensen IJ. Serum testosterone as a prognostic factor in patients with advanced prostatic carcinoma. Scand J Urol Nephrol Suppl. 1994; 157: 41-7
61. Haapiainen R, Rannikko S, Alfthan O, Adlercreutz H. Pretreatment plasma levels of testosterone and sex hormone binding globulin binding capacity in relation to clinical staging and survival in prostatic cancer patients. Prostate. 1988;12(4):325-32
62. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. Am J Clin Oncol. 1997 Dec;20(6):605-8.

A study where low testosterone levels are found in men with benign prostate hypertrophy

63. Ortega E, Ruiz E, Mendoza MC, Martin-Andres A, Osorio C. Plasma steroid and protein hormone concentrations in patients with benign prostatic hypertrophy and in normal men. Experientia. 1979 Jun 15;35(6):844-5

A study where a low androstanediol glucuronide level was found in patients with benign prostate hypertrophy

64. Wright F, Poizat, Bongini M,Bozzolan F Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. J Clin Endocrinol Metab. 1985; 60 (2) 294-8

Men with chronic prostatis have often low testosterone

65. Yunda IF, Imshinetskaya LP. Testosterone excretion in chronic prostatis. Andrologia. 1977 Jan-Mar;9(1):89-94 *(In 73.1% of patients considerable reduction of testosterone excretion was revealed. Reduction of testicular endocrine function is in direct correlative dependence on severity of clinical symptoms, duration of disease and form of chronic prostatis.")*

A history of prostatitis is positively associated with a history of benign prostatic hyperplasia and cancer

66. Daniels NA, Ewing SK, Zmuda JM, Wilt TJ, Bauer DC; Osteoporotic Fractures in Men (MrOS) Research Group. Correlates and prevalence of prostatitis in a large community-based cohort of older men. Urology. 2005 Nov;66(5):964-70 *("We found positive associations for a history of prostatitis with a history of benign prostatic hyperplasia (odds ratio 8.0, 95% confidence interval 6.8 to 9.5) and a history of prostate cancer (odds ratio 5.4, 95% CI: 4.4 to 6.6)")*

A study where testosterone treatment at high doses prevented the prostate stromal proliferation that estradiol may induce in the presence of physiological concentrations of testosterone

67. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. Cancer Res. 1978 Nov;38(11 Pt 2):4126-34.
68. Feyel-Cabanes T, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on the ventral lobe of the rat postate in organ culture. C R Acad Sci Hebd Seances Acad Sci D. 1977 Oct 31;285(11):1119-22

<u>Studies where testosterone treatment appears to protect against prostate cancer</u>

Studies where testosterone/androgen treatment of patients with advanced prostate cancer increased their survival time and quality of life

69. Morales A, Connolly JG, Bruce AW. Androgen therapy in advanced carcinoma of the prostate. Can Med Assoc J. 1971;105(1):71-2
70. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. Cancer. 1967 Nov;20(11):1871-8

Studies where testosterone /androgen treatment inhibits the proliferation of human prostate cancer cells or induces their apoptosis in vitro

71. Joly-Pharaboz MO, Soave MC, Nicolas B, Mebarki F, Renaud M, Foury O, Morel Y, Andre JG. Androgens inhibit the proliferation of a variant of the human prostate cancer cell line LNCaP. J Steroid Biochem Mol Biol 1995 Oct;55(1):67-76
72. Wolf DA, Schulz P, Fittler F. Synthetic androgens suppress the transformed phenotype in human prostate carcinoma cell line LNCaP. Br J Cancer. 1991 Jul; 64 (1): 47-53
73. Andrews P, Krygier S, Djakiew D. Dihydrotestosterone (DHT) modulates the ability of NSAIDs to induce apoptosis of prostate cancer cells. Cancer Chemother Pharmacol. 2002 Mar;49(3):179-86

Studies where testosterone treatment reduces prostate dysfunction complaints (dysuria, nocturia)

74. Flamm J, Kiesswetter H, Englisch M. An urodynamic study of patients with benign prostatic hypertrophy treated conservatively with phytotherapy or testosterone. Wien Klin Wochenschr 1979 Sep 28;91(18):622-7
75. Kearns WM. Testosterone in the treatment of testicular deficiency and prostatic enlargement. Wisconsin Med J. 1941; 40:927 *(testosterone proprionate therapy did not reduce the size of the prostate, but reduced the dysuria)*
76. Meltzer M. Male hormone therapy of prostatic hypertrophy. Lancet. 1939; 59: 279
77. Trasoff A. The treatment of benign prostatic hypertrophy with testosterone propionate. J Lab Clin Med. 1940; 25: 377
78. Markham MJ. The clinical use of peroral methyltestosterone in benign prostatic hypertrophy. Urol Cutan Rev. 1942; 46: 225
79. Markham MJ. The clinical use of testosterone propionate in benign prostatic hypertrophy. Urol Cutan Rev. 1941; 45: 35

80. Laqueur E. Behandlung der Prostathypertropie mit männlichen Hormone (Hombreol) une experimentell Begründung dieser Therapie. Schweiz Med Wochenschr. 1934; 64: 1116
81. South Med J, 1939, 32: 154

Study where testosterone treatment reduces prostate stromal hyperplasia and prostatic complaints (prostatism)

82. South Med J, 1939, 32: 154

Studies where dihydrotestosterone treatment reduced the prostate volume (-15 to -20% after 1 year treatment)

83. de Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause. Ann Med 1993 Jun;25(3):235-41
84. Swerdloff RS, Wang C. Dihydrotestosterone: a rationale for its use as a non-aromatizable androgen replacement therapeutic agent. Baillieres Clin Endocrinol Metab. 1998 Oct;12(3):501-6
85. Sitruk-Ware R. Contraception, 1989, 39: 1-191

ANIMAL STUDIES:

Studies where androgen deprivation stimulates the progression of hormone-sensitive mouse prostate cancer cells to hormone insensitive in vitro

86. Sato N, Watabe Y, Suzuki H, Shimazaki J. Progression of androgen-sensitive mouse tumor (Shionogi carcinoma 115) to androgen-insensitive tumor after long-term removal of testosterone. Jpn J Cancer Res. 1993 Dec;84(12):1300-8

Studies where antiandrogens (which cause androgen deficiency) **may promote DMAB-induced prostate cancer incidence or increase its malignancy**

87. Akaza H, Tsukamoto S, Morita T, Yamauchi A, Onozawa M, Shimazui T, Ideyama Y, Shirai T. Promoting effects of antiandrogenic agents on rat ventral prostate carcinogenesis induced by 3,2'-dimethyl-4-aminobiphenyl (DMAB). Prostate Cancer Prostatic Dis. 2000 Aug;3(2):115-9
88. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349(3):215-24

A study where significantly lower testosterone (and androstenedione) levels are found in mice with prostate inflamation. This means that testosterone (and androstenedione) may be necessary to counter prostate inflammation.

89. Bondarenko LA, Breslavskii AS, Vartapetov BA, Gladkova AI. Secretion of testicular androgens under conditions of chronic experimental inflammation of the prostate gland. Probl Endokrinol (Mosk). 1977 Jul-Aug;23(4):111-5

A study where testosterone treatment may prevent benign prostate hypertrophy by inhibiting stromal proliferation-induced by estradiol and by keeping prostate glandular cells health, preventing their atrophy in vitro

90. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. Cancer Res. 1978 Nov;38(11 Pt 2):4126-34.

A study where testosterone treatment reduces the proliferation of mouse prostate cancer cells in vitro

91. Suzuki H, Nihei N, Sato N, Ichikawa T, Mizokami A, Shimazaki J. Inhibition of growth and increase of acid phosphatase by testosterone on androgen-independent murine prostatic cancer cells transfected with androgen receptor cDNA. Prostate. 1994 Dec;25(6):310-9

A study where testosterone treatment reduces the proliferation of guinea pig prostate stroma cells in vitro

92. Ricciardelli C, Horsfall DJ, Sykes PJ, Marshall VR, Tilley WD. Effects of oestradiol-17 beta and 5 alpha-dihydrotestosterone on guinea- pig prostate smooth muscle cell proliferation and steroid receptor expression in vitro. J Endocrinol. 1994 Mar;140(3):373-83

A study where testosterone treatment at high doses does not increase the incidence of prostate cancer cells in mice

93. Mainwaring WI. The effect of testosterone on the age-associated changes in the ventral prostate gland of the mouse. Testosterone and ageing of the prostate. Gerontologia. 1968;14(1):133-41

A study where testosterone, DHT and progesterone protects the prostate glandular epithelium against metaplasia and excessive stroma proliferation induced by estrogens in castrated male mice

94. Burrows H. Nature (London). 1936, 138: 164

A study where testosterone treatment of certain species of mice can inhibit prostate cancer growth

95. Umekita Y, Hiipakka RA, Kokontis JM, Liao S. Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride. Proc Natl Acad Sci U S A 1996 Oct 15;93(21):11802-7

Studies where dihydrotestosterone treatment of certain species of rats can inhibit prostate cancer growth

96. Pollard M. Dihydrotestosterone prevents spontaneous adenocarcinomas in the prostate-seminal vesicle in aging L-W rats. Prostate 1998 Aug 1;36(3):168-71
97. Pollard M, Luckert PH, Snyder D.Prevention and treatment of experimental prostate cancer in Lobund-Wistar rats. I. Effects of estradiol, dihydrotestosterone, and castration. Prostate 1989;15(2):95-103

A study where dihydrotestosterone treatment stimulates apoptosis of prostate cancer cells

98. Bruckheimer EM, Kyprianou N. Dihydrotestosterone enhances transforming growth factor-beta-induced apoptosis in hormone-sensitive prostate cancer cells. Endocrinology. 2001 Jun;142(6):2419-26

Breast Cancer in women: protection with testosterone or dihydrotestosterone treatment?

99. Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause. 2004 Sep-Oct;11(5):531-535

NEUTRAL EFFECTS OF TESTOSTERONE THERAPIES

REVIEW STUDIES where the authors did not find an adverse effect of testosterone levels or treatment on the prostate cancer risk

Review studies with conclusions that there is no data to support the view that testosterone treatment could increase the risk of prostate cancer, making e.g. a prostate cancer progress from a preclinical to a clinical stage

100. Rolf C, Nieschlag E. Potential adverse effects of long-term testosterone therapy. Baillieres Clin Endocrinol Metab. 1998 Oct;12(3):521-34.
101. Wirth MP, Hakenberg OW Testosterone and the prostate. Urologe A 2000 Sep;39(5):418-20
102. Morley JE. Testosterone replacement and the physiologic aspects of aging in men. Mayo Clin Proc. 2000 Jan;75 Suppl:S83-7 *("There is no clinical evidence that the risk of either prostate cancer or benign prostate hypertrophy increases with testosterone treatment")*
103. Rhoden NEJM 2004 *("No compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk. In fact, it should be recognized that prostate cancer becomes more prevalent exactly at the time of a man's life when testosterone levels decline. ")*
104. Basaria S, Wahlstrom JT, Dobs AS. Anabolic-Androgenic Steroid Therapy in the Treatment of Chronic Diseases. J Clin Endocrinol Metab. 2001Nov;86(11):5108-17*("..recent reviews suggest that the incidence of prostate cancer is not increased by testosterone administration")*
105. Morales A. Androgen replacement therapy and prostate safety. Eur Urol 2002 Feb;41(2):113-20 *("To date there is no evidence that exogenous androgens promote development of prostate cancer")*
106. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. Cancer Res. 1999 Sep 1;59(17):4161-4 *("… contrary to prevalent opinion, declining rather than high levels of androgens probably contribute more to human prostate carcinogenesis and ;.. androgen supplementation would probably lower the incidence of the disease. … consider the possibility that the growth of androgen-independent prostate cancers might be reduced by the administration of androgens")*

STUDIES with no association between serum androgen levels and prostate disease, including cancer

Studies with no significant difference in plasma testosterone and/or DHT and/or androstanediol glucuronide between prostate cancer patients and controls

107. Heikkila R, Aho K, Heliovaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. Cancer. 1999 Jul 15;86(2):312-5
108. Carter HB, Pearson JD, Metter EJ, Chan DW, Andres R, Fozard JL, Rosner W, Walsh PC. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. Prostate. 1995 Jul;27(1):25-31
109. Nomura AM, Stemmermann GN, Chyou PH, Henderson BE, Stanczyk FZ. Serum androgens and prostate cancer. Cancer Epidemiol Biomarkers Prev 1996 Aug;5(8):621-5
110. Habib FK, Lee IR, Stitch SR, Smith PH. Androgen levels in the plasma and prostatic tissues of patients with benign hypertrophy and carcinoma of the prostate. J Endocrinol 1976 OCT;71(1):99-107
111. Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E. Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. Cancer Epidemiol Biomarkers Prev 1997 Nov;6(11):967-9
112. Wright F, Poizat R, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. J Clin Endocrinol Metab. 1985; 60 (2) 294-8

Studies with no correlation between serum testosterone and serum PSA

113. Monath JR, McCullough DL, Hart LJ, Jarow JP. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. Urology 1995 Jul;46(1):58-61
114. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. Urology 1995 Jul;46(1):62-4
115. Schatzl G, Reiter WJ, Thurridl T, Waldmuller J, Roden M, Soregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. Prostate 2000;44(3):219-24
116. Vijayakumar S, Quadri SF, Dong L, Ignacio L, Kathuria IN, Sutton H, Halpern H. Results of a study to correlate serum prostate specific antigen and reproductive hormone levels in patients with localized prostate cancer. J Natl Med Assoc 1995 Nov;87(11):813-9

A study with no correlation between serum testosterone and prostate tumour volume, weight or Gleason score

117. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. Urology. 1995 Jul;46(1):62-4

A study where therapeutic androgen deprivation (blockade) has no beneficial effect on the evolution of the prostate cancer

118. Young HH 2nd, Kent JR. Plasma testosterone levels in patients with prostatic carcinoma before and after treatment. J Urol. 1968 Jun;99(6):788-92

A study with no significant association of serum testosterone with benign prostate hyperplasia

119. Lagiou P, Mantzoros CS, Tzonou A, Signorello LB, Lipworth L, Trichopoulos D. Serum steroids in relation to benign prostatic hyperplasia. Oncology. 1997 Nov-Dec;54(6):497-501

STUDIES where testosterone/androgen treatments had no adverse effect on the risk of prostate disease, including the risk of prostate cancer

Small clinical studies, performed before the days of PSA, where androgen treatment, usually with small dosages of androgen, did not stimulate the growth of many prostatic tumors and in some cases the tumours were even inhibited by the treatment; the responses were extremely variable

120. Prout GRJ, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. Cancer (Phila.). 1967;*20:*1871-8
121. Trunnell JD, Duffy BJ Jr. The influence of certain steroids on the behavior of human prostate cancer. Trans. NY Acad Sci. 1950;II:12:238-41
122. Brendler H, Lowry O, Brock M. Further investigation of hormonal relationships. Arch Surg. 1950,61:433-40
123. Pearson OH. Discussion of Dr. Huggins' paper: "Control of cancers of man by endocrinological methods." Cancer Res. 1957:17:473-9
124. Morales A, Connolly J, Burr R, Bruce A. The use of radioactive phosphorus to treat bone pain in metastatic carcinoma of the prostate. Can Med Assoc J. 1970;103: 372-3

Studies where testosterone treatment had no significant effect on PSA and/or prostate volume

125. Cooper CS, Perry PJ, Sparks AE, MacIndoe JH, Yates WR, Williams RD. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. J Urol. 1998 Feb;159(2):441-3
126. Cooper CS, MacIndoe JH, Perry PJ, Yates WR, Williams RD. The effect of exogenous testosterone on total and free prostate specific antigen levels in healthy young men. J Urol. 1996 Aug;156(2 Pt 1):438-41
127. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clin Endocrinol (Oxf). 1994 Mar;40(3):341-9
128. Douglas TH, Connelly RR, McLeod DG, Erickson SJ, Barren R 3rd, Murphy GP. Effect of exogenous testosterone replacement on prostate-specific antigen and prostate-specific membrane antigen levels in hypogonadal men. J Surg Oncol. 1995 Aug;59(4):246-50

129. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997 Jun;82(6):1661-7
130. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. J Clin Endocrinol Metab. 1997 Nov;82(11):3793-6
131. Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. Int J Impot Res. 2005 Sep 22 *(No statistical increase: average = 0.31 ng/ml after 1 year of treatment of hypogonadal men)*
132. Shibasaki T, Sasagawa I, Suzuki Y, Yazawa H, Ichiyanagi O, Matsuki S, Miura M, Nakada T. Effect of testosterone replacement therapy on serum PSA in patients with Klinefelter syndrome. Arch Androl. 2001 Nov-Dec;47(3):173-6

A study where dihydrotestosterone treatment had no significant effect on serum PSA

133. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab. 2002 Apr;87(4):1467-72

Studies where testosterone treatment increases the serum PSA but normalizes it in patients with initial atrophic prostate bringing it up to normal levels without any excessive increase

134. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clin Endocrinol (Oxf). 1994 Mar;40(3):341-9.
135. Behre HM, Nieschlag E. Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. J Clin Endocrinol Metab. 1992 Nov;75(5):1204-10
136. Guay AT, Perez JB, Fitaihi WA, Vereb M. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. Endocr Pract. 2000 Mar-Apr;6(2):132-8
137. McClellan KJ, Goa KL. Transdermal testosterone. Drugs 1998 Feb;55(2):253-8; discussion 259
138. Arver S, Dobs AS, Meikle AW, Caramelli KE, Rajaram L, Sanders SW, Mazer NA. Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. Clin Endocrinol (Oxf). 1997 Dec;47(6):727-37
139. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab. 1992 Oct;75(4):1092-8

Testosterone treatment does not increase the incidence of prostate disease

140. Hartnell J, 72nd Endocrine Soc. Meeting, 1990, A 428

A study where previous testosterone propionate treatment (terminated 1 to 7 years before the study) **did not increase the risk of prostate hypertrophy or palpable prostate irregularities in men over 45 years, whatever the treatment length or dose**

141. Lesser MA, Vose SN, Dixey GM. Effect of testosterone propionate on the prostate gland of patients over 45. J Clin Endocrinol Metab. 1955 Mar;15(3):297-300

Studies where DHT treatment had no effect on the prostate volume

142. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab. 2002 Apr;87(4):1467-72.
143. Ly LP, Jimenez M, Zhuang TN, Celermajer DS, Conway AJ, Handelsman DJ. A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. J Clin Endocrinol Metab. 2001 Sep;86(9):4078-88

ARGUMENTS CONTRA TESTOSTERONE THERAPIES:

Studies that suggest that testosterone may increase the prostate cancer risk

Prostate cancer: the association with high free testosterone levels

144. Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. Cancer Epidemiol Biomarkers Prev. 2005 Sep;14(9):2257-60*(critics: a potential bias may come from nutritional factors: individuals who eat a lot of food related to a higher cancer risk such as meat, particularly if cooked well-done, and/or milk, have also higher levels of testosterone as well as of other hormones associated with a higher cancer risk. Moreoever, there is no information in this study on estradiol levels. This is important as the simultaneous presence of high levels of testosterone and estradiol may, following certain reports, increase the prostate cancer (PC) risk, not testosterone levels alone; heavy alcohol drinking, another risk factor for PC, that is in some countries of the world frequent can considerably increase both the estradiol levels and the PC risk in consumers. Other possible bias: data were not adjusted for other PC risk factors such as smoking, nutritional deficiencies, etc.)*
145. Mydlo JH, Tieng NL, Volpe MA, Chaiken R, Kral JG. A pilot study analyzing PSA, serum testosterone, lipid profile, body mass index and race in a small sample of patients with and without carcinoma of the prostate. Prostate Cancer Prostatic Dis. 2001;4(2):101-105 *(critics: no dietary factors were taken into account, only high BMI as a risk factor, nore was serum SHBG analysed: dehydrated persons have usually high SHBG, and thus higher total testosterone, which is bound to it, but generally low active, bioavalable and free testosterone levels)*
146. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst. 1996 Aug 21;88(16):1118-26 *(critics: study did not consider dietary or BMI PC risk factors)*
147. Stahl F, Schnorr D, Pilz C, Dorner G. Dehydroepiandrosterone (DHEA) levels in patients with prostatic cancer, heart diseases and under surgery stress. Exp Clin Endocrinol. 1992;99(2):68-70 *(critic: no estrogen levels, nor dietary factors checked)*

Note: on the importance to check dietary factors:

Studies where the consumption of high amounts of protein and saturated fat such as milk products and meat increased testosterone levels

148. *Sharpe RM, Martin B, Morris K, Greig I, McKinnell C, McNeilly AS, Walker M. Infant feeding with soy formula milk: effects on the testis and on blood testosterone levels in marmoset monkeys during the period of neonatal testicular activity. Hum Reprod. 2002 Jul;17(7):1692-703*
149. *Dorgan JF, Judd JT, Longcope C, Brown C, Schatzkin A, Clevidence BA, Campbell WS, Nair PP, Franz C, Kahle L, Taylor PR.Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. Am J Clin Nutr. 1996 Dec;64(6):850-5*
150. *Hamalainen E, Adlercreutz H, Puska P, Pietinen P. Diet and serum sex hormones in healthy men. J Steroid Biochem. 1984 Jan;20(1):459-64*
151. *Volek JS, Kraemer WJ, Bush JA, Incledon T, Boetes M. Testosterone and cortisol in relationship to dietary nutrients and resistance exercise. J Appl Physiol. 1997 Jan;82(1):49-54*

Milk or meat intake may increase the risk of prostate *(in fact the increased risk may disappear if the vegetable intake which is lower in meat eaters is taken into account)*

Link between meat, milk and/or protein intake, and prostate cancer

152. *Norrish AE, Lynnette R. Ferguson, Mark G. Knize, James S. Felton, Susan J. Sharpe, Jackson RT. Heterocyclic Amine Content of Cooked Meat and Risk of Prostate Cancer. J Nat Cancer Inst. 1999; 91(23):2038-44*
153. *Wolk A. Diet, lifestyle and risk of prostate cancer. Acta Oncol. 2005;44(3):277-81*
154. *Grant WB. An ecologic study of dietary links to prostate cancer. Altern Med Review 1999; 4(3):162-9 (study in 14 European countries)*

A study where higher levels of testosterone were found in patients who are in the advanced D-stage of PC, compared to the levels found in patients in the more moderate B and C-stages of prostate cancer

155. Imamoto T, Suzuki H, Akakura K, Komiya A, Nakamachi H, Ichikawa T, Igarashi T, Ito H. Pretreatment serum level of testosterone as a prognostic factor in Japanese men with hormonally treated stage D2 prostate cancer. Endocr J. 2001 Oct;48(5):573-8 *(note: but those in*

D-stege that had the highest testosterone had the best prognosis, including longer cancer-free survival time)

A study where a higher rate of metastasis (-relapse) is found in prostate cancer patients with testosterone > 500 ng/dl that have been locally irradiated *(critic: the irradiation may change the risk)*

156. Zagars GK, Pollack A, von Eschenbach AC. Serum testosterone - a significant determinant of metastatic relapse for irradiated localized prostate cancer. Urology. 1997 Mar;49(3):327-34

A study where testosterone treatment increases the growth of prostate cancer: in vitro

157. Tymchuk CN, Barnard RJ, Ngo TH, Aronson WJ. Role of testosterone, estradiol, and insulin in diet- and exercise-induced reductions in serum-stimulated prostate cancer cell growth in vitro. Nutr Cancer. 2002;42(1):112-6.

ESTROGENS AND PROSTATE CANCER RISK

Studies that suggest that it is the simultaneous presence of high testosterone levels with high estradiol levels (and with possibly a low DHEA levels) **that may promote prostate cancer**

1. Christov KT, Moon RC, Lantvit DD, Boone CW, Kelloff GJ, Steele VE, Lubet RA, Pezzuto JM. Prostate intraepithelial neoplasia in Noble rats, a potential intermediate endpoint for chemoprevention studies. Eur J Cancer. 2004 Jun;40(9):1404-11
2. Suzuki K, Takezawa Y, Suzuki T, Honma S, Yamanaka H. Synergistic effects of estrogen with androgen on the prostate--effects of estrogen on the prostate of androgen-administered rats and 5-alpha-reductase activity. Prostate. 1994 Oct;25(4):169-76

A study where estrogens inflamed prostate tissues in the presence of testosterone

3. Ho E, Boileau TW, Bray TM. Dietary influences on endocrine-inflammatory interactions in prostate cancer development. Arch Biochem Biophys. 2004 Aug 1;428(1):109-17

Studies that suggest that high estrogen levels alone may promote prostate cancer

A study where a high estrone level was found in men with prostate cancer

4. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. Prostate. 1982;3(6):579-88

A study where increased urinary 16-alpha-OH- estrone and lower 2-OH-estrone metabolites are found in prostate cancer patients *(results nearly reached statistical significance)*

5. Muti P, Westerlind K, Wu T, Grimaldi T, De Berry J 3rd, Schunemann H, Freudenheim JL, Hill H, Carruba G, Bradlow L. Urinary estrogen metabolites and prostate cancer: a case-control study in the United States. Cancer Causes Control. 2002 ;13(10):947-55 State University of New York

A study where higher estradiol and estrone levels and very low testosterone concentrations were found in prostatic fluid than in serum of prostate cancer patients

6. Wynder EL, Laakso K, Sotarauta M, Rose DP. Metabolic epidemiology of prostatic cancer. Prostate 1984;5(1):47-53

Studies where high urinary estrogens are associated with an increased rate of prostate stromal hyperplasia

7. Seppelt U. Correlation among prostate stroma, plasma estrogen levels, and urinary estrogen excretion in patients with benign prostatic hypertrophy. J Clin Endocrinol Metab. 1978 Dec;47(6):1230-5
8. Seppelt U, Buhl K, Drews M. Histologic components of benign prostatic hypertrophy (bph) in relation to the androgen-estrogen status. Urologe A. 1978 Mar;17(2):117-9

A study where estrogen treatment of castrated mice caused metasplasia of prostate glandular cells

9. Burrows H, Nature (London), 1936, 138: 164

A study where anti-estrogen treatment blocked the growth of prostate cancer in mice, although it increased testosterone levels

10. Raghow S, Hooshdaran MZ, Katiyar S, Steiner MS. Toremifene prevents prostate cancer in the transgenic adenocarcinoma of mouse prostate model. Cancer Res. 2002 Mar 1;62(5):1370-6

A study where estrogen treatment stimulate prostate stromal hyperplasia

11. Nakada T, Kubota Y, Sasagawa I, Suzuki H, Watanabe M, Suzuki Y. The effect of oestradiol-17 beta on connective tissue protein in rat prostate. Int Urol Nephrol. 1994;26(3):327-35

A study where testosterone treatment at high doses prevented the prostate stromal proliferation that estradiol may induce in the presence of physiological concentrations of testosterone

12. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. Cancer Res. 1978 Nov;38(11 Pt 2):4126-34.
13. Feyel-Cabanes T, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on the ventral lobe of the rat postate in organ culture. C R Acad Sci Hebd Seances Acad Sci D. 1977 Oct 31;285(11):1119-22

Testosterone in women

Senescence is associated with a decline of the adrenal- and ovarian-testosterone axes:

Senescence is associated with a reduction of the serum testosterone level in women

1. Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. J Clin Endocrinol Metab. 1995 Apr;80(4):1429-30

Testosterone derives in women for more than 90% from the much quicker declining serum DHEA

2. Labrie F, Belanger A, Luu-The V, Labrie C, Simard J, Cusan L, Gomez JL, Candas B., DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: its role during aging. Steroids, 1998;63(5-6):322-8

Testosterone treatment may oppose and testosterone deficiency may trigger some mechanisms of senescence in women

Immune deficiency: *testosterone may improve the immune resistance in certain conditions*

3. Dalal M, Kim S, Voskuhl RR. Testosterone therapy ameliorates experimental autoimmune encephalomyelitis and induces a T helper 2 bias in the autoantigen-specific T lymphocyte response. J Immunol. 1997 Jul 1;159(1):3-6
4. Buggage RR, Matteson DM, Shen de F, Sun B, Tuaillon N, Chan CC.Effect of sex hormones on experimental autoimmune uveoretinitis (EAU). Immunol Invest. 2003 Nov;32(4):259-73
5. Nakazawa M, Fantappie MR, Freeman GL Jr, Eloi-Santos S, Olsen NJ, Kovacs WJ, Secor WE, Colley DG. Schistosoma mansoni: susceptibility differences between male and female mice can be mediated by testosterone during early infection. Exp Parasitol. 1997 Mar;85(3):233-40

Testosterone and psychic well-being in women

Lower quality of life and fatigue in women: the association with lower testosterone levels

6. 323. Abrahamsson L, Hackl H, Lindstrom B, Sogn J. Long-term treatment of virilized women with cyproterone acetate. Wien Klin Wochenschr. 1981 Sep 18;93(17):552-6

Quality of life in women: the improvement with testosterone treatment

7. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause. 2003 Sep-Oct;10(5):390-8

Vasomotor symptoms in women: the improvement with testosterone treatment

8. Simon J, Klaiber E, Wiita B, Bowen A, Yang HM. Differential effects of estrogen-androgen and estrogen-only therapy on vasomotor symptoms, gonadotropin secretion, and endogenous androgen bioavailability in postmenopausal women. Menopause. 1999 Summer;6(2):138-46

Depression in women: the association with lower testosterone levels

9. Rohr UD. The impact of testosterone imbalance on depression and women's health. Maturitas. 2002 Apr 15;41 Suppl 1:S25-46

Depression in women: the improvement with testosterone treatment

10. Sherwin BB. Affective changes with estrogen and androgen replacement therapy in surgically menopausal women. J Affect Disord. 1988 Mar-Apr;14(2):177-87

Negative symptoms in women: the association with lower serum testosterone levels

11. Goyal RO, Sagar R, Ammini AC, Khurana ML, Alias AG. Negative correlation between negative symptoms of schizophrenia and testosterone levels Ann N Y Acad Sci. 2004 Dec;1032:291-4

Anxiety in women: the association with lower testosterone levels

12. Landen M, Baghaei F, Rosmond R, Holm G, Bjorntorp P, Eriksson E. Dyslipidemia and high waist-hip ratio in women with self-reported social anxiety. Psychoneuroendocrinology. 2004 Sep;29(8):1037-46 *(Serum levels of total testosterone (1.6+/-0.8 vs. 2.2+/-1.1, P=0.013) and free thyroxin (14+/-2 vs. 16+/-4, P=0.04) were lower in subjects confirming social anxiety)*

Anxiety in women: the improvement with testosterone treatment

13. Montgomery JC, Appleby L, Brincat M, Versi E, Tapp A, Fenwick PB, Studd JW. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. Lancet. 1987 Feb 7;1(8528):297-9
14. van Honk J, Peper JS, Schutter DJ. Testosterone reduces unconscious fear but not consciously experienced anxiety: implications for the disorders of fear and anxiety. Biol Psychiatry. 2005 Aug 1;58(3):218-25

Memory loss and Alzheimer's disease in women: the association with lower testosterone levels

15. Simpson E, Davis S. Why do the clinical sequelae of estrogen deficiency affect women more than men? J Clin Endocrinol Metab. 1998 Jun;83(6):2214

Memory in women: the improvement with testosterone treatment

16. Wisniewski AB, Nguyen TT, Dobs AS. Evaluation of high-dose estrogen and high-dose estrogen plus methyltestosterone treatment on cognitive task performance in postmenopausal women. Horm Res. 2002;58(3):150-5

Love in women: the association with higher testosterone in women

17. Marazziti D, Canale D. Hormonal changes when falling in love. Psychoneuroendocrinology. 2004 Aug;29(7):931-6

Loss of sexual drive, sexual gratification, intercourse frequency in women: the association with lower testosterone levels

18. Persky H, Lief HI, Miller WR, O'Brien CP. Plasma testosterone level and sexual behavior of couples. Arch Sex Behav. 1978 May; 7(3):157-73

Sexuality decline in women: the improvement with testosterone treatment

19. Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas. 1995 Apr;21(3):227-36
20. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause. 2003 Sep-Oct;10(5):390-8
21. Sarrel P, Dobay B, Wiita B.Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. Sexual behavior and neuroendocrine responses. J Reprod Med. 1998 Oct;43(10):847-56
22. Sarrel PM. Psychosexual effects of menopause: role of androgens. Am J Obstet Gynecol. 1999 Mar;180(3 Pt 2):S319-24
23. Penotti M, Sironi L, Cannata L, Vigano P, Casini A, Gabrielli L, Vignali M. Effects of androgen supplementation of hormone replacement therapy on the vascular reactivity of cerebral arteries. Fertil Steril. 2001 Aug;76(2):235-40
24. Tutten A, Laan E, Panhuysen G, Everaerd W, de Haan E, Koppeschaar H, Vroon P. Discrepancies between genital responses and subjective sexual function during testosterone substitution in women with hypothalamic amenorrhea. Psychosom Med. 1996 May-Jun;58(3):234-41
25. Tuiten A, Van Honk J, Koppeschaar H, Bernaards C, Thijssen J, Verbaten R. Time course of effects of testosterone administration on sexual arousal in women. Arch Gen Psychiatry. 2000 Feb;57(2):149-53
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