COMPLEX HRT CASES IN MEN

Neal Rouzier, M.D.

[redacted] A Medical Group, Inc.

August 3, 2015

[redacted]

changes). Your vitamin D level was 30.9 which is low normal. Your b12 and folic acid levels were normal. Your total testosterone was 1,296 which is very elevated (target for testosterone replacement is above 300 and normal is 241-827) and your free testosterone was 253 which is also very high (normal is 20-150).

Your testosterone levels are way too high on compounded testosterone 1g twice a day. Too high a testosterone level can lead to benign prostatic hypertrophy (which you do not have), possibly an increased risk for prostate cancer, and possibly and increased risk for symptomatic coronary artery disease and heart attack. It can also increase the risk for polycythemia (to many red blood cells) which can increase the risk of blood clotting, heart attack or stroke. So I recommend that you reduce the testosterone dose by 50% by either decreasing to 1/2g twice a day OR 1g once a day. You should return for a repeat testosterone level on this lower dose after about 6 weeks. This repeat testosterone dose should be drawn 1-3 hours after one of your doses.

With your previous non-zero Coronary Artery Calcium Score, your target LDL cholesterol is below 100 and you are at 135. So you would be better to be on a low dose statin. You elevated cardiac C-Reactive Protein also suggests a statin would be wise

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What about men?

- 58 y/o male with Syndrome X is treated with testosterone. Total testosterone is 1800 but the free testosterone is still low at 75ug/ml (Quest normal 50-210).
- Should the testosterone Rx be lowered?
- Raised?
- Treatment for Syndrome X in men?
- What are the recent AACE recommendations for treating men?

What is the best treatment that can be offered to men to treat/prevent hair loss?

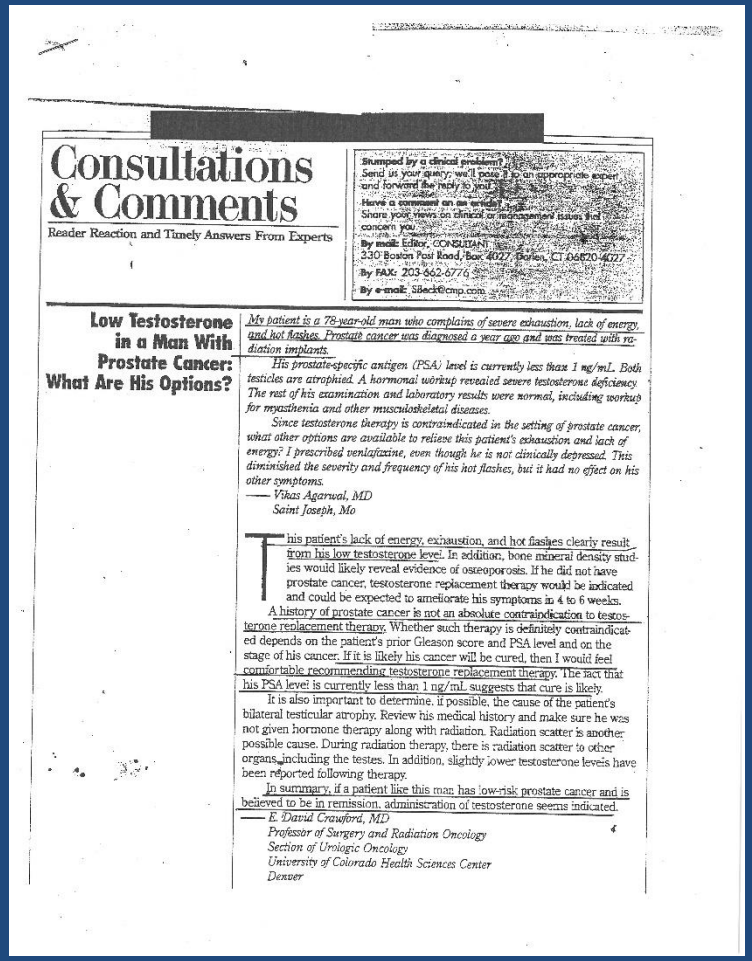
Dutasteride (Avodart) blocks 5 alpha-1 and 5 alpha-2 enzymes and has a half life of 72 hours.

True: Dose is 0.5 mg twice per week.

Eucapril (Fluridil) is most potent topical hair protector.

True: In phase III trials. Obtain on internet from Czech republic.

Low Testosterone in a Men With Prostate Cancer: What Are His Options?



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Low Testosterone in a Man With Prostate Cancer: What Are His Options?

My patient is a 78-year-old man who complains of severe exhaustion, lack of energy, and hot flashes. Prostate cancer was diagnosed a year ago and was treated with radiation implants.

His prostate-specific antigen (PSA) level is currently less than 1 ng/mL. Both testicles are atrophied. A hormonal workup revealed severe testosterone deficiency. The rest of his examination and laboratory results were normal, including workup for myasthenia and other musculoskeletal diseases.

Since testosterone therapy is contraindicated in the setting of prostate cancer, what other options are available to relieve this patient's exhaustion and lack of energy? I prescribed venlafaxine, even though he is not clinically depressed. This diminished the severity and frequency of his hot flashes, but it had no effect on his other symptoms.

— Vikas Agarwal, MD
Saint Joseph, Mo

This patient's lack of energy, exhaustion, and hot flashes clearly result from his low testosterone level. In addition, bone mineral density studies would likely reveal evidence of osteoporosis. If he did not have prostate cancer, testosterone replacement therapy would be indicated and could be expected to ameliorate his symptoms in 4 to 6 weeks.

A history of prostate cancer is not an absolute contraindication to testosterone replacement therapy. Whether such therapy is definitely contraindicated depends on the patient's prior Gleason score and PSA level and on the stage of his cancer. If it is likely his cancer will be cured, then I would feel comfortable recommending testosterone replacement therapy. The fact that his PSA level is currently less than 1 ng/mL suggests that cure is likely.

It is also important to determine, if possible, the cause of the patient's bilateral testicular atrophy. Review his medical history and make sure he was not given hormone therapy along with radiation. Radiation scatter is another possible cause. During radiation therapy, there is radiation scatter to other organs, including the testes. In addition, slightly lower testosterone levels have been reported following therapy.

In summary, if a patient like this man has low-risk prostate cancer and is believed to be in remission, administration of testosterone seems indicated.

— *E. David Crawford, MD*
Professor of Surgery and Radiation Oncology
Section of Urologic Oncology
University of Colorado Health Sciences Center
Denver

- Q: “My patient is a 78 year old man who complains of severe exhaustion, lack of energy, and hot flashes. Prostate cancer was diagnosed a year ago and was treated with radiation implants”.
- A: This patient’s lack of energy, exhaustion, and hot flashes clearly result from his low testosterone level.
- A history of prostate cancer is not an absolute contraindication to testosterone replacement therapy.

Low Testosterone in a Man With Prostate Cancer: What Are His Options? *Consultant Live*. 2006 Dec 31. News article.

Testosterone and Prostate CA

- If it is likely his cancer will be cured, then I would feel comfortable recommending testosterone replacement therapy.
- His PSA level is currently less than 1 ng/mL and suggests that a cure is likely.
- In summary, if a patient like this man has low-risk prostate cancer and is believed to be in remission, administration of testosterone seems indicated.

Morgentaler in JAMA



men with metastatic prostate cancer who underwent bilateral orchiectomy. Nevertheless, the limited clinical trials to date have shown a risk of prostate cancer in men undergoing TRT of approximately 1%, a rate not different from untreated men undergoing screening.[77] Moreover, population-based studies have failed to demonstrate that men with higher levels of testosterone are at any increased risk of developing prostate cancer or that men with low testosterone levels are somehow protected against developing prostate cancer.[75,78] Furthermore, only 1 of 20 hypogonadal men at high risk for prostate cancer based on a prior history of prostatic intraepithelial neoplasia developed cancer after 1 year of testosterone treatment,[48] suggesting that TRT may not adversely affect progression of prostate cancer.

Who Should Be Referred for Prostate Biopsy in Association With TRT?

Men with an elevated PSA level or an abnormal DRE finding should undergo biopsy prior to initiation of TRT. Prostate biopsy should also be performed if the PSA rises above the normal range or the DRE becomes abnormal during treatment. There is ongoing debate whether the historical upper PSA threshold of 4.0 ng/mL should be lowered to 2.6 ng/mL.[79,81] A rapid rise of PSA is a further indication for biopsy, since this may be a sign of prostate cancer as well. Bhasin and colleagues recommend biopsy for a rise of 1.0 ng/mL or greater within the first 6 months of treatment, and for any rise of 0.4 ng/mL per year after that time.[48] Although most clinicians currently reserve prostate biopsy for the indications above, it has been my own practice to perform prostate biopsy prior to initiation of TRT in all men age 45 years or older, since 14% of hypogonadal men with a normal DRE and PSA less than 4.0 ng/mL have biopsy-detectable prostate cancer.[81] There is evidence that high-grade prostate cancer, Gleason 8-10, is particularly associated with low testosterone.[82]

Once treatment has been initiated, men should be monitored with PSA and DRE, as well as hemoglobin or hematocrit, 2 to 3 times within the first year, and 1 to 2 times per year thereafter.[21,74]

Who Should Treat the Man With ED?

Most men with ED can be effectively treated by their primary care physicians. Men with physical abnormalities of the penis, such as Peyronie disease, should be referred to a urologist. If oral medication fails or is contraindicated, then the man should be referred to a specialist in sexual dysfunction, which in most cases will be a urologist. Sexual problems related to hypogonadism may also be treated by the primary care physician or referred to a urologist or endocrinologist. Referral to a psychotherapist is indicated for significant personal or relationship issues that appear to be more complicated than a straightforward complaint of ED or low sexual desire.

The Competing Issues of Hypogonadism and ED

The 2 primary treatment options offered to Mr G, testosterone and sildenafil, have widely different actions. Sildenafil effectively improves blood flow to the penis, thus aiding erection, but has no direct effect on libido. Testosterone supplementation, on the other hand, has a wide variety of potential benefits, including improved erections, libido, mood, strength, and sense of well-being. Men who respond to TRT often report that they "feel normal again."

As a rule, I treat hypogonadal men with TRT first, since this may offer a more complete response than addressing ED alone. If ED does not respond to testosterone treatment, I then prescribe a PDE 5 inhibitor. If the man has experienced benefits from TRT, such as improved libido, he may continue both treatments together. If no symptomatic improvement resulted from TRT itself, it is my practice to discontinue it. However, some clinicians choose to continue treatment to address the metabolic effects of hypogonadism.

Recommendations for Mr G

I would first offer Mr G a trial of TRT in the form of a topical gel, adjusting dosage and mode of therapy as needed to achieve physiological testosterone levels. It is my own practice to perform prostate biopsy before initiating treatment because of the substantial prevalence of biopsy-detectable cancer in this population. However, this approach is impractical for nonurologists, and a reasonable alternative strategy is to monitor with PSA and DRE at 3, 6, and 12 months, reserving biopsy for worrisome changes. If Mr G noted improvement in ED and libido with testosterone supplementation, I would continue this treatment indefinitely. If he notices no benefit at all despite mid- to high-normal testosterone levels, I would discontinue the testosterone trial. I would then offer treatment with one of the oral PDE 5 inhibitors. If libido improves with TRT but ED persists, I would continue TRT and add a PDE 5 inhibitor to the treatment regimen.

Given Mr G's concerns regarding risks, I would reassure him that both testosterone and PDE 5 inhibitors have been widely studied and both appear to have good safety profiles. I would specifically add that sildenafil by itself has not been found to be dangerous for the heart, that it can be taken together with his antihypertensive medications, and that priapism is extremely rare and treatable. I would emphasize that he will require monitoring of his prostate and hematocrit indefinitely while receiving TRT. I would then encourage him to begin treatment if he wishes.

It is my own belief that the mission of physicians must include doing our best to improve the quality of life of our patients. Given the importance of sexuality in human life, I encourage clinicians to become knowledgeable in the area of male sexual dysfunction to ably assist their patients to experience full, satisfying, and loving lives.

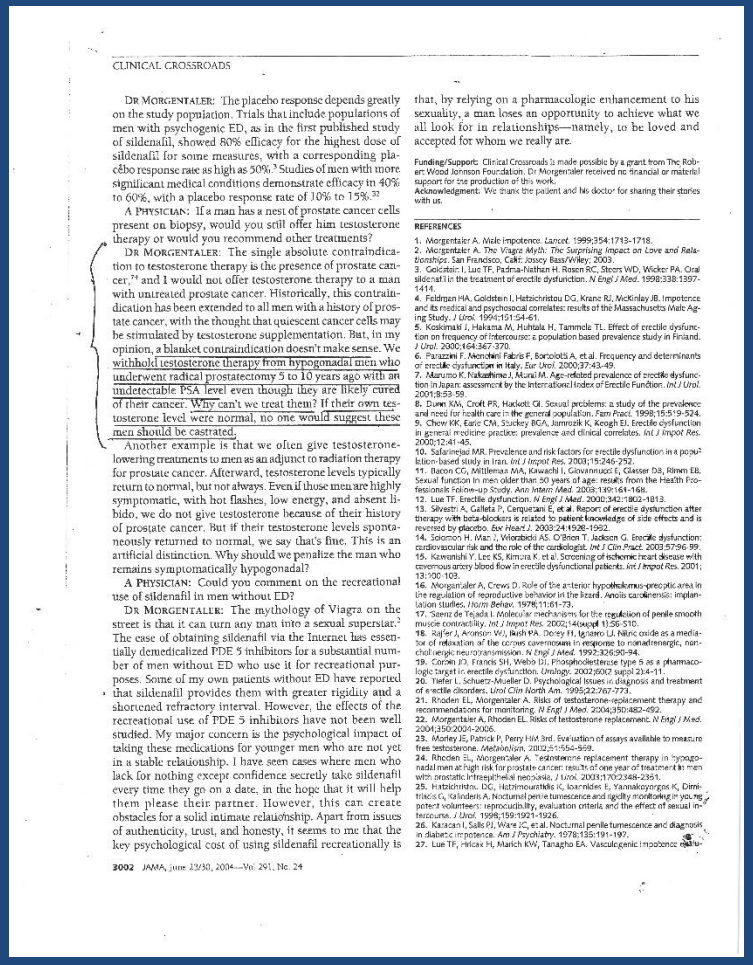
QUESTIONS AND DISCUSSION

A PHYSICIAN: You mentioned that sildenafil worked in 80% of psychogenic and 65% of organic cases of ED. What about placebo response in each group?

- Nevertheless, the limited clinical trials to date have shown risk of prostate cancer in men undergoing TRT to be approximately 1%, a rate not different from untreated men.

Testosterone Tx With PCa

- Studies have failed to demonstrate that men with higher levels of testosterone are at any increased risk of developing prostate cancer or that men with low testosterone levels are somehow protected against developing prostate cancer.
- 1 of 20 hypogonadal men at high risk from prostate cancer based on a prior history of prostatic intraepithelial neoplasia (PIN) developed cancer after 1 year of testosterone treatment, suggesting that TRT may not adversely affect progression of prostate cancer.



CLINICAL CROSSROADS

DR MORGENTALER: The placebo response depends greatly on the study population. Trials that include populations of men with psychogenic ED, as in the first published study of sildenafil, showed 80% efficacy for the highest dose of sildenafil for some measures, with a corresponding placebo response rate as high as 50%.[3] Studies of men with more significant medical conditions demonstrate efficacy in 40% to 60%, with a placebo response rate of 10% to 15%.[32]

A PHYSICIAN: If a man has a nest of prostate cancer cells present on biopsy, would you still offer him testosterone therapy or would you recommend other treatments?

DR MORGENTALER: The single absolute contraindication to testosterone therapy is the presence of prostate cancer,[74] and I would not offer testosterone therapy to a man with untreated prostate cancer. Historically, this contraindication has been extended to all men with a history of prostate cancer, with the thought that quiescent cancer cells may be stimulated by testosterone supplementation. But, in my opinion, a blanket contraindication doesn't make sense. We withhold testosterone therapy from hypogonadal men who underwent radical prostatectomy 5 to 10 years ago with an undetectable PSA level even though they are likely cured of their cancer. Why can't we treat them? If their own testosterone level were normal, no one would suggest these men should be castrated.

Another example is that we often give testosterone-lowering treatments to men as an adjunct to radiation therapy for prostate cancer. Afterward, testosterone levels typically return to normal, but not always. Even if those men are highly symptomatic, with hot flashes, low energy, and absent libido, we do not give testosterone because of their history of prostate cancer. But if their testosterone levels spontaneously returned to normal, we say that's fine. This is an artificial distinction. Why should we penalize the man who remains symptomatically hypogonadal?

A PHYSICIAN: Could you comment on the recreational use of sildenafil in men without ED?

DR MORGENTALER: The mythology of Viagra on the street is that it can turn any man into a sexual superstar.[2] The ease of obtaining sildenafil via the Internet has essentially demedicalized PDE 5 inhibitors for a substantial number of men without ED who use it for recreational purposes. Some of my own patients without ED have reported that sildenafil provides them with greater rigidity and a shortened refractory interval. However, the effects of the recreational use of PDE 5 inhibitors have not been well studied. My major concern is the psychological impact of taking these medications for younger men who are not yet in a stable relationship. I have seen cases where men who lack for nothing except confidence secretly take sildenafil every time they go on a date, in the hope that it will help them please their partner. However, this can create obstacles for a solid intimate relationship. Apart from issues of authenticity, trust, and honesty, it seems to me that the key psychological cost of using sildenafil recreationally is that, by relying on a pharmacologic enhancement to his sexuality, a man loses an opportunity to achieve what we all look for in relationships—namely, to be loved and accepted for whom we really are.

Funding/Support: Clinical Crossroads is made possible by a grant from The Robert Wood Johnson Foundation. Dr Morgentaler received no financial or material support for the production of this work.
Acknowledgment: We thank the patient and his doctor for sharing their stories with us.

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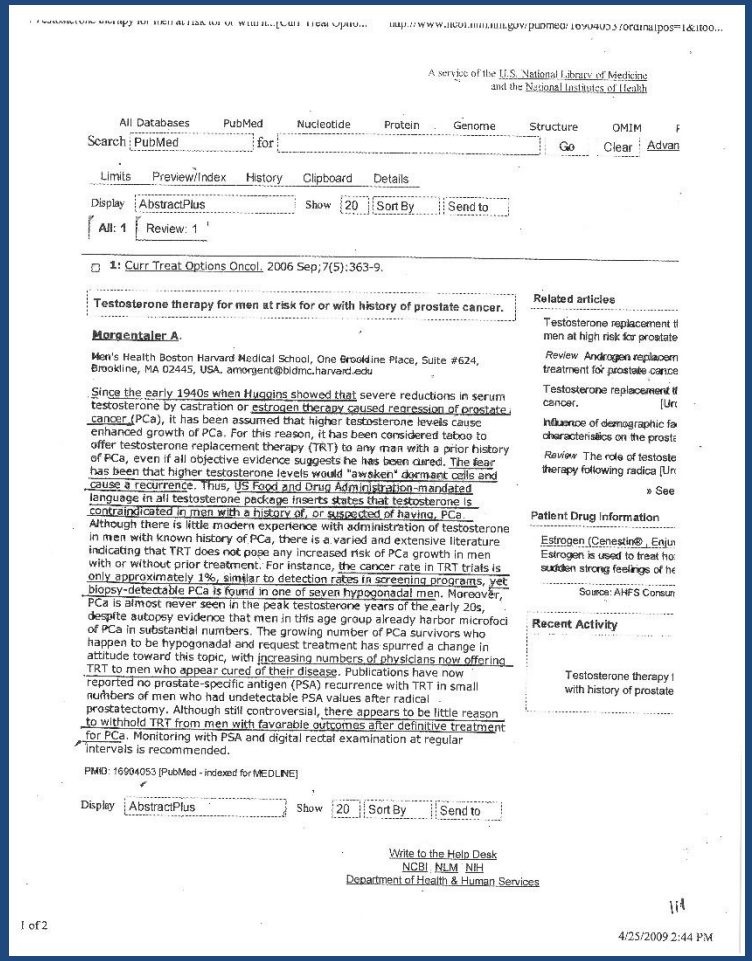
Testosterone Therapy for Men At Risk For or With History of Prostate Cancer



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Testosterone therapy for men at risk for or with history of prostate cancer.

Morgentaler A.

Men's Health Boston Harvard Medical School, One Brookline Place, Suite #624, Brookline, MA 02445, USA. amorgent@bidmc.harvard.edu

Since the early 1940s when Huggins showed that severe reductions in serum testosterone by castration or estrogen therapy caused regression of prostate cancer (PCa), it has been assumed that higher testosterone levels cause enhanced growth of PCa. For this reason, it has been considered taboo to offer testosterone replacement therapy (TRT) to any man with a prior history of PCa, even if all objective evidence suggests he has been cured. The fear has been that higher testosterone levels would "awaken" dormant cells and cause a recurrence. Thus, US Food and Drug Administration-mandated language in all testosterone package inserts states that testosterone is contraindicated in men with a history of, or suspected of having, PCa. Although there is little modern experience with administration of testosterone in men with known history of PCa, there is a varied and extensive literature indicating that TRT does not pose any increased risk of PCa growth in men with or without prior treatment. For instance, the cancer rate in TRT trials is only approximately 1%, similar to detection rates in screening programs, yet biopsy-detectable PCa is found in one of seven hypogonadal men. Moreover, PCa is almost never seen in the peak testosterone years of the early 20s, despite autopsy evidence that men in this age group already harbor microfoci of PCa in substantial numbers. The growing number of PCa survivors who happen to be hypogonadal and request treatment has spurred a change in attitude toward this topic, with increasing numbers of physicians now offering TRT to men who appear cured of their disease. Publications have now reported no prostate-specific antigen (PSA) recurrence with TRT in small numbers of men who had undetectable PSA values after radical prostatectomy. Although still controversial, there appears to be little reason to withhold TRT from men with favorable outcomes after definitive treatment for PCa. Monitoring with PSA and digital rectal examination at regular intervals is recommended.

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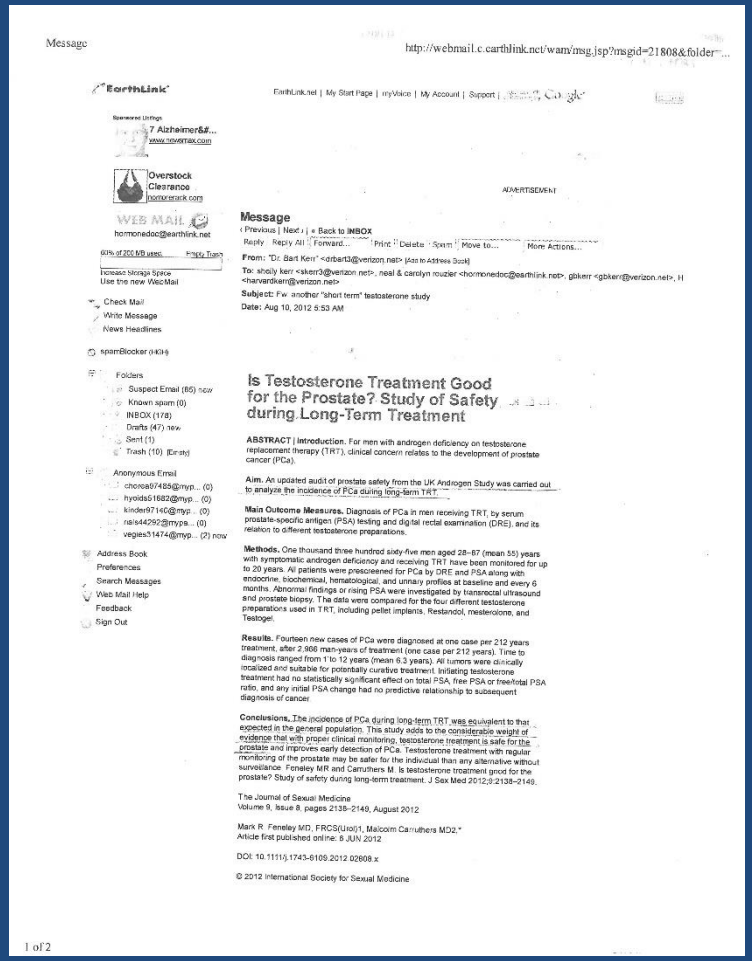
- In the early 1940s Huggins showed that estrogen therapy caused regression of prostate cancer.
- The fear has always been that higher testosterone levels would “awaken” dormant cells and cause a recurrence of prostate cancer.

Morgentaler A. Testosterone therapy for men at risk for or with history of prostate cancer. *Curr Treat Options Oncol*. 2006 Sep;7(5):363-9.

- US Food and Drug Administration-mandated language in all testosterone package inserts states that testosterone is contraindicated in men with a history of, or suspected of having, PCa.
- The cancer rate in TRT trials is only approximately 1%, similar to detection rates in screening programs, yet biopsy-detectable PCa is found in one of seven hypogonadal men.
- We see increasing numbers of physicians now offering TRT to men who appear cured of their disease.
- There appears to be little reason to withhold TRT from men with favorable outcomes after definitive treatment.

Is Testosterone Treatment Good For the Prostate? Study of Safety During Long-Term Treatment



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Is Testosterone Treatment Good for the Prostate? Study of Safety during Long-Term Treatment

ABSTRACT | Introduction. For men with androgen deficiency on testoste/one replacement therapy (TRT), clinical concern relates to the development of prostate cancer (PCa).

Aim. An updated audit of prostate safety from the UK Androgen Study was carried out to analyze the incidence of PCa during long-term TRT.

Main Outcome Measures. Diagnosis of PCa in men receiving TRT, by serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE), and its relation to different testosterone preparations.

Methods. One thousand three hundred sixty-five men aged 28–87 (mean 55) years with symptomatic androgen deficiency and receiving TRT have been monitored for up to 20 years. All patients were prescreened for PCa by DRE and PSA along with endocrine, biochemical, hematological, and urinary profiles at baseline and every 6 months. Abnormal findings or rising PSA were investigated by transrectal ultrasound and prostate biopsy. The data were compared for the four different testosterone preparations used in TRT, including pellet implants, Restandol, mesterolone, and Testogel.

Results. Fourteen new cases of PCa were diagnosed at one case per 212 years treatment, after 2,966 man-years of treatment (one case per 212 years). Time to diagnosis ranged from 1 to 12 years (mean 6.3 years). All tumors were clinically localized and suitable for potentially curative treatment. Initiating testosterone treatment had no statistically significant effect on total PSA, free PSA or free/total PSA ratio, and any initial PSA change had no predictive relationship to subsequent diagnosis of cancer.

Conclusions. The incidence of PCa during long-term TRT was equivalent to that expected in the general population. This study adds to the considerable weight of evidence that with proper clinical monitoring, testosterone treatment is safe for the prostate and improves early detection of PCa. Testosterone treatment with regular monitoring of the prostate may be safer for the individual than any alternative without surveillance. Feneley MR and Carruthers M. Is testosterone treatment good for the prostate? Study of safety during long-term treatment. J Sex Med 2012;9:2138–2149.

The Journal of Sexual Medicine
Volume 9, Issue 8, pages 2138–2149, August 2012

Mark R. Feneley MD, FRCS(Urol)1, Malcolm Carruthers MD2,*
Article first published online: 6 JUN 2012

DOI: 10.1111/j.1743-6109.2012.02808.x

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1 of 2

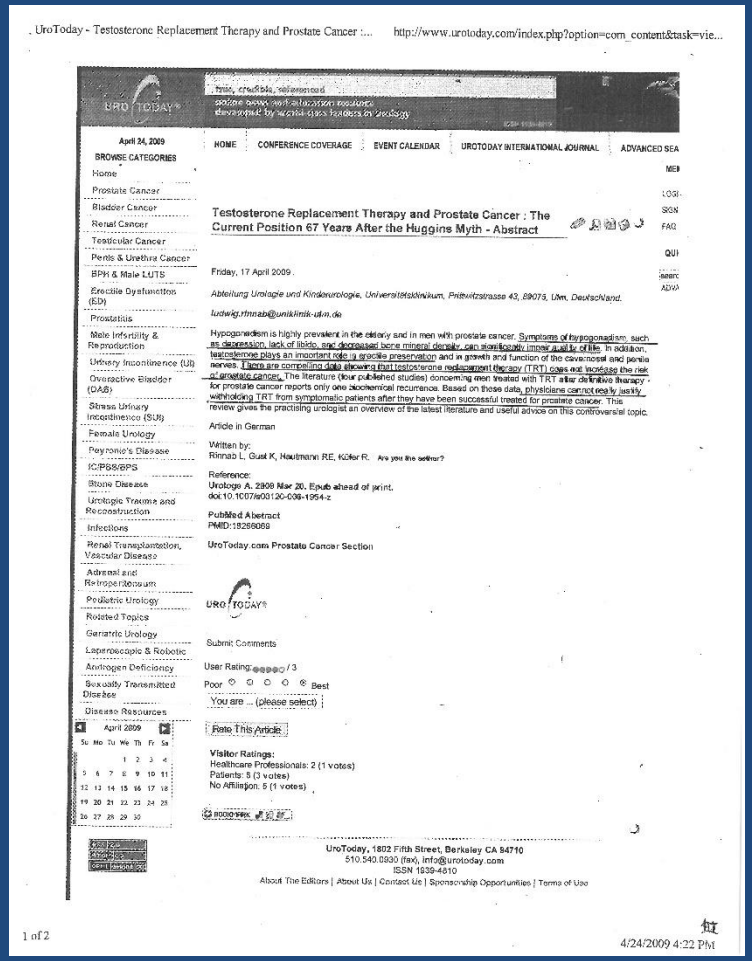
- An updated audit of prostate safety from the UK Androgen Study was carried out to analyze the incidences of PCa during long-term TRT.
- The incidence of PCa during long-term TRT was equivalent to the expected in the general population.
- This study adds to the considerable weight of the evidence that with proper clinical monitoring, testosterone treatment is safe for the prostate.

- How can the results of these various studies be reconciled with the indisputable and dramatic regression of PCa that occurs when T is lowered by chemical or surgical castration? And how is it possible to cause PCa regression by lowering T, yet not cause enhanced PCa growth by raising T? Both questions are resolved by a single word- saturation.
- Essentially all biologic systems become saturated at some concentration of substrate, meaning that there is a concentration for a chemical, in this case T, beyond which addition of more substrate has no effect. Clearly, at the extreme low end of serum T concentration we see PCa regression.

- Raising T levels in men with metastatic PCa who already have castrate T levels does indeed cause PCa growth. But it has been nearly impossible to show that raising T causes any incremental increase in PCa growth beyond the near-castrate range for T.
- Recently published landmark study in which hypogonadal men receiving testosterone therapy for 6 months failed to demonstrate an increase in prostatic concentrations of T or DHT, nor in markers of cellular proliferation, despite a substantial increase in serum T and DHT levels. Nishiyama et. al. also found no correlation between serum T or DHT and prostate tissue concentrations of DHT.
- I therefore believe we should discard the old analogy that “T acts like food for a hungry tumor” because higher T does not appear to cause greater PCa growth.

- “T is like water for a thirsty tumor,” because once the tumor is no longer “thirsty,” additional amounts are treated as excess.
- If true, then perhaps we can drop the traditional prohibition against offering T therapy to men with a prior history of PCa. In one recent report of 31 men who were treated with testosterone for a median of 4.5 yr following brachytherapy for PCa, none developed evidence of cancer recurrence, 74% maintained PSA < 0.1 ng/ml, and all had PSA < 1.0 ng/ml.

Testosterone Replacement Therapy and Prostate Cancer: The Current Position 67 Years After The Huggins Myth - Abstract



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Testosterone Replacement Therapy and Prostate Cancer : The Current Position 67 Years After the Huggins Myth - Abstract

Friday, 17 April 2009.

Abteilung Urologie und Kinderurologie, Universitätsklinikum, Prittwitzstrasse 43, 89075, Ulm, Deutschland.

ludwig.rinnab@uniklinik-ulm.de

Hypogonadism is highly prevalent in the elderly and in men with prostate cancer. Symptoms of hypogonadism, such as depression, lack of libido, and decreased bone mineral density, can significantly impair quality of life. In addition, testosterone plays an important role in erectile preservation and in growth and function of the cavernosal and penile nerves. There are compelling data showing that testosterone replacement therapy (TRT) does not increase the risk of prostate cancer. The literature (four published studies) concerning men treated with TRT after definitive therapy for prostate cancer reports only one biochemical recurrence. Based on these data, physicians cannot really justify withholding TRT from symptomatic patients after they have been successful treated for prostate cancer. This review gives the practising urologist an overview of the latest literature and useful advice on this controversial topic.

Article in German

Written by:
Rinnab L, Gust K, Hautmann RE, Küfer R. Are you the author?

Reference:
Urologe A. 2009 Mar 20. Epub ahead of print.
doi:10.1007/s00120-009-1954-z

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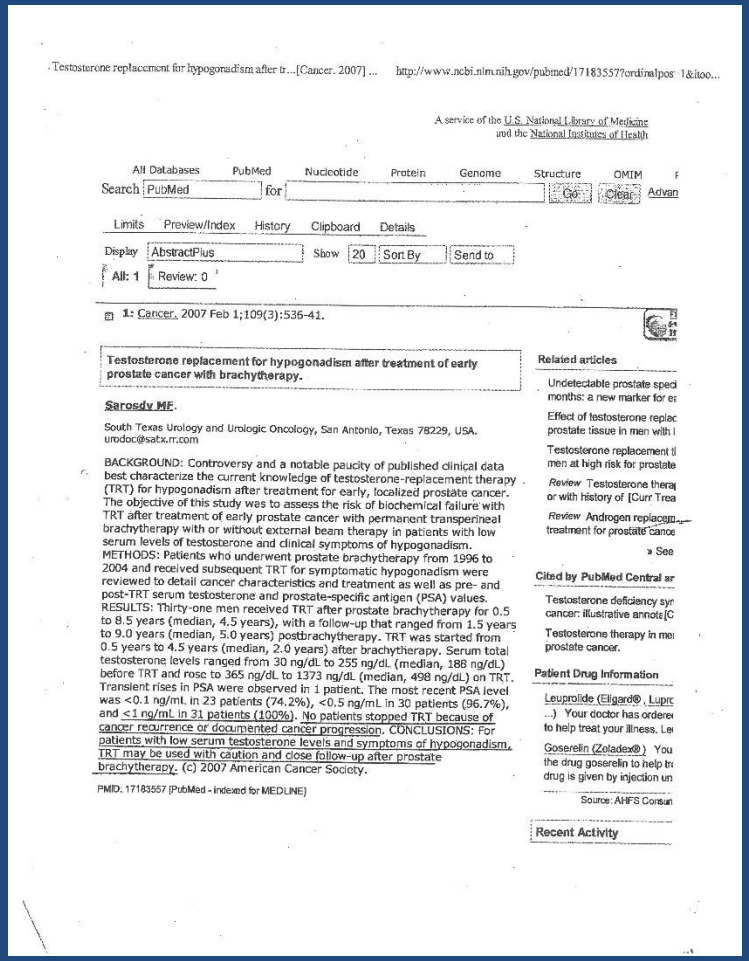
1 of 2 4/24/2009 4:22 PM

- Symptoms of hypogonadism, such as depression, lack of libido, and decreased bone mineral density, can significantly impair quality of life… testosterone plays an important role in erectile preservation.
- There are compelling data showing testosterone replacement therapy (TRT) does not increase the risk of prostate cancer.
- Physicians cannot really justify withholding TRT from symptomatic patients after they have been successfully treated for prostate cancer.

Rinnab L, Gust K, Hautmann RE, Küfer R. Testosterone replacement therapy and prostate cancer. The current position 67 years after the Huggins myth. *Urologe A.* 2009 May;48(5):516-22.

Testosterone Replacement for Hypogonadism After Treatment of Early Prostate Cancer with Brachytherapy



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1: Cancer. 2007 Feb 1;109(3):536-41.

Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy.

Sarosdy MF.

South Texas Urology and Urologic Oncology, San Antonio, Texas 78229, USA. urodoc@satx.rr.com

BACKGROUND: Controversy and a notable paucity of published clinical data best characterize the current knowledge of testosterone-replacement therapy (TRT) for hypogonadism after treatment for early, localized prostate cancer. The objective of this study was to assess the risk of biochemical failure with TRT after treatment of early prostate cancer with permanent transperineal brachytherapy with or without external beam therapy in patients with low serum levels of testosterone and clinical symptoms of hypogonadism. METHODS: Patients who underwent prostate brachytherapy from 1996 to 2004 and received subsequent TRT for symptomatic hypogonadism were reviewed to detail cancer characteristics and treatment as well as pre- and post-TRT serum testosterone and prostate-specific antigen (PSA) values. RESULTS: Thirty-one men received TRT after prostate brachytherapy for 0.5 to 8.5 years (median, 4.5 years), with a follow-up that ranged from 1.5 years to 9.0 years (median, 5.0 years) postbrachytherapy. TRT was started from 0.5 years to 4.5 years (median, 2.0 years) after brachytherapy. Serum total testosterone levels ranged from 30 ng/dl. to 255 ng/dL (median, 188 ng/dL) before TRT and rose to 365 ng/dL to 1373 ng/dL (median, 498 ng/dL) on TRT. Transient rises in PSA were observed in 1 patient. The most recent PSA level was <0.1 ng/mL in 23 patients (74.2%), <0.5 ng/mL in 30 patients (96.7%), and <1 ng/mL in 31 patients (100%). No patients stopped TRT because of cancer recurrence or documented cancer progression. CONCLUSIONS: For patients with low serum testosterone levels and symptoms of hypogonadism, TRT may be used with caution and close follow-up after prostate brachytherapy. (c) 2007 American Cancer Society.

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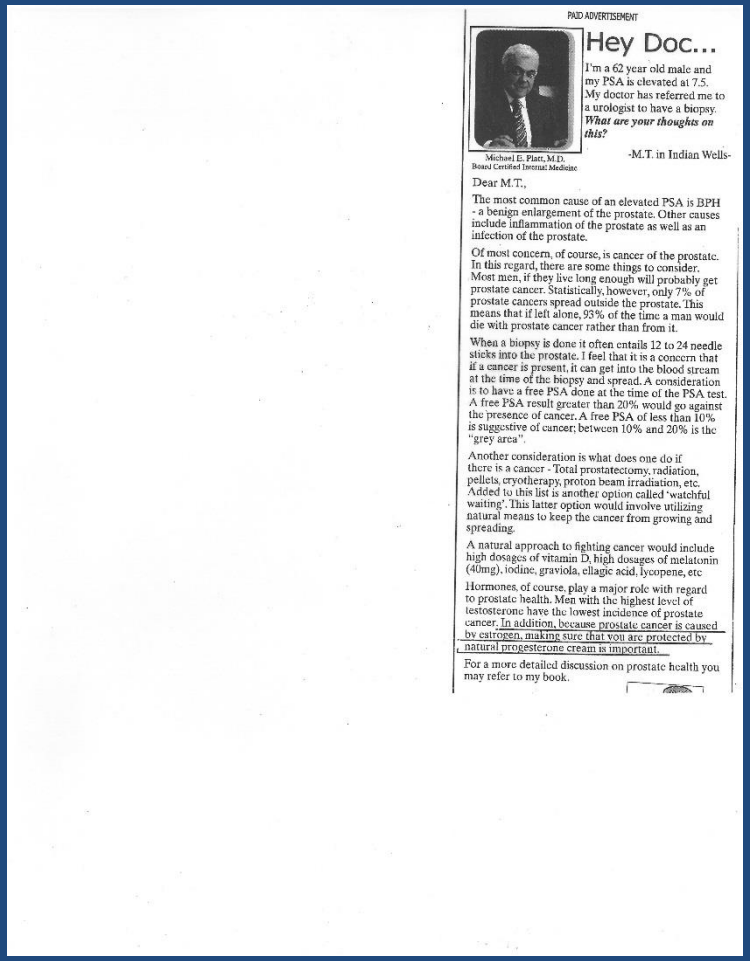
- No patients stopped TRT because of cancer recurrence or documented cancer progression.
- In patients with low serum testosterone levels and symptoms of hypogonadism, TRT may be used with caution and close follow-up after prostate brachytherapy.

Hey Doc



PAID ADVERTISEMENT

Hey Doc...

I'm a 62 year old male and my PSA is elevated at 7.5. My doctor has referred me to a urologist to have a biopsy. ***What are your thoughts on this?***

-M.T. in Indian Wells-

Michael E. Platt, M.D.
Board Certified Internal Medicine

Dear M.T.,

The most common cause of an elevated PSA is BPH - a benign enlargement of the prostate. Other causes include inflammation of the prostate as well as an infection of the prostate.

Of most concern, of course, is cancer of the prostate. In this regard, there are some things to consider. Most men, if they live long enough will probably get prostate cancer. Statistically, however, only 7% of prostate cancers spread outside the prostate. This means that if left alone, 93% of the time a man would die with prostate cancer rather than from it.

When a biopsy is done it often entails 12 to 24 needle sticks into the prostate. I feel that it is a concern that if a cancer is present, it can get into the blood stream at the time of the biopsy and spread. A consideration is to have a free PSA done at the time of the PSA test. A free PSA result greater than 20% would go against the presence of cancer. A free PSA of less than 10% is suggestive of cancer; between 10% and 20% is the "grey area".

Another consideration is what does one do if there is a cancer - Total prostatectomy, radiation, pellets, cryotherapy, proton beam irradiation, etc. Added to this list is another option called 'watchful waiting'. This latter option would involve utilizing natural means to keep the cancer from growing and spreading.

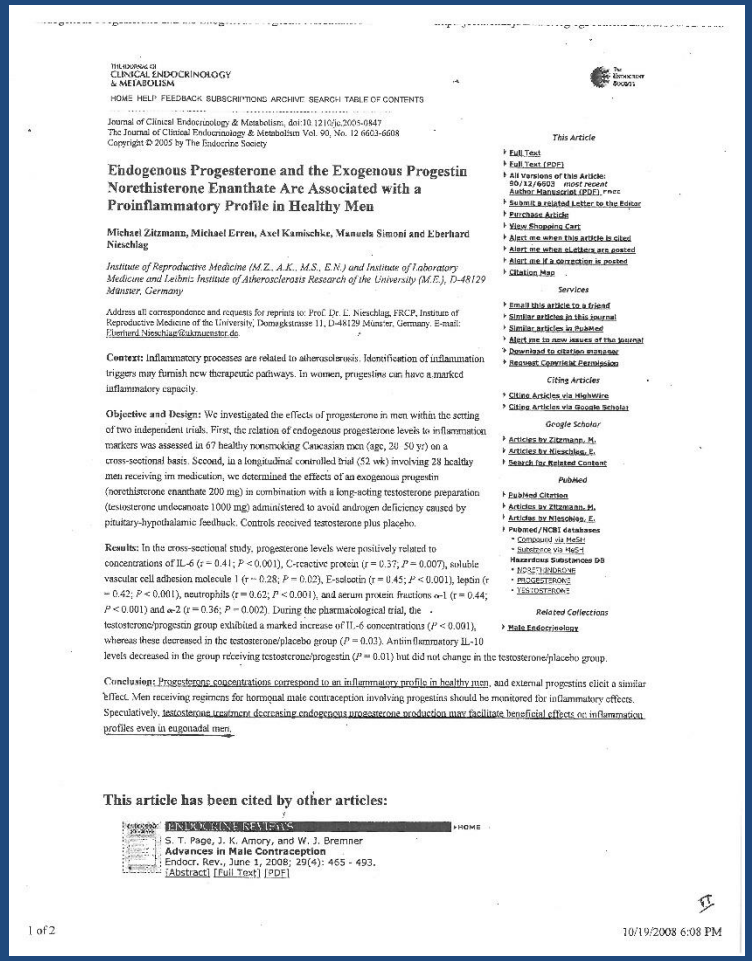
A natural approach to fighting cancer would include high dosages of vitamin D, high dosages of melatonin (40mg), iodine, graviola, ellagic acid, lycopene, etc

Hormones, of course, play a major role with regard to prostate health. Men with the highest level of testosterone have the lowest incidence of prostate cancer. In addition, because prostate cancer is caused by estrogen, making sure that you are protected by natural progesterone cream is important.

For a more detailed discussion on prostate health you may refer to my book.

- In addition, because prostate cancer is caused by estrogen, making sure that you are protected by natural progesterone cream is important.

Endogenous Progesterone and the Exogenous Progestin Norethisterone Enanthate Are Associated with a Proinflammatory Profile in Healthy Men



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Journal of Clinical Endocrinology & Metabolism, doi:10.1210/jc.2005-0847
The Journal of Clinical Endocrinology & Metabolism Vol. 90, No. 12 6603-6608
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Endogenous Progesterone and the Exogenous Progestin Norethisterone Enanthate Are Associated with a Proinflammatory Profile in Healthy Men

Michael Zitzmann, Michael Erren, Axel Kamischke, Manuela Simoni and Eberhard Nieschlag

Institute of Reproductive Medicine (M.Z., A.K., M.S., E.N.) and Institute of Laboratory Medicine and Leibniz Institute of Atherosclerosis Research of the University (M.E.), D-48129 Münster, Germany

Address all correspondence and requests for reprints to: Prof. Dr. E. Nieschlag, FRCP, Institute of Reproductive Medicine of the University, Domagkstrasse 11, D-48129 Münster, Germany. E-mail: Eberhard.Nieschlag@ukmuenster.de.

Context: Inflammatory processes are related to atherosclerosis. Identification of inflammation triggers may furnish new therapeutic pathways. In women, progestins can have a marked inflammatory capacity.

Objective and Design: We investigated the effects of progesterone in men within the setting of two independent trials. First, the relation of endogenous progesterone levels to inflammation markers was assessed in 67 healthy nonsmoking Caucasian men (age, 20–50 yr) on a cross-sectional basis. Second, in a longitudinal controlled trial (52 wk) involving 28 healthy men receiving im medication, we determined the effects of an exogenous progestin (norethisterone enanthate 200 mg) in combination with a long-acting testosterone preparation (testosterone undecanoate 1000 mg) administered to avoid androgen deficiency caused by pituitary-hypothalamic feedback. Controls received testosterone plus placebo.

Results: In the cross-sectional study, progesterone levels were positively related to concentrations of IL-6 ($r = 0.41$; $P < 0.001$), C-reactive protein ($r = 0.37$; $P = 0.007$), soluble vascular cell adhesion molecule 1 ($r = 0.28$; $P = 0.02$), E-selectin ($r = 0.45$; $P < 0.001$), leptin ($r = 0.42$; $P < 0.001$), neutrophils ($r = 0.62$; $P < 0.001$), and serum protein fractions α-1 ($r = 0.44$; $P < 0.001$) and α-2 ($r = 0.36$; $P = 0.002$). During the pharmacological trial, the testosterone/progestin group exhibited a marked increase of IL-6 concentrations ($P < 0.001$), whereas these decreased in the testosterone/placebo group ($P = 0.03$). Antiinflammatory IL-10 levels decreased in the group receiving testosterone/progestin ($P = 0.01$) but did not change in the testosterone/placebo group.

Conclusion: Progesterone concentrations correspond to an inflammatory profile in healthy men, and external progestins elicit a similar effect. Men receiving regimens for hormonal male contraception involving progestins should be monitored for inflammatory effects. Speculatively, testosterone treatment decreasing endogenous progesterone production may facilitate beneficial effects on inflammation profiles even in eugonadal men.

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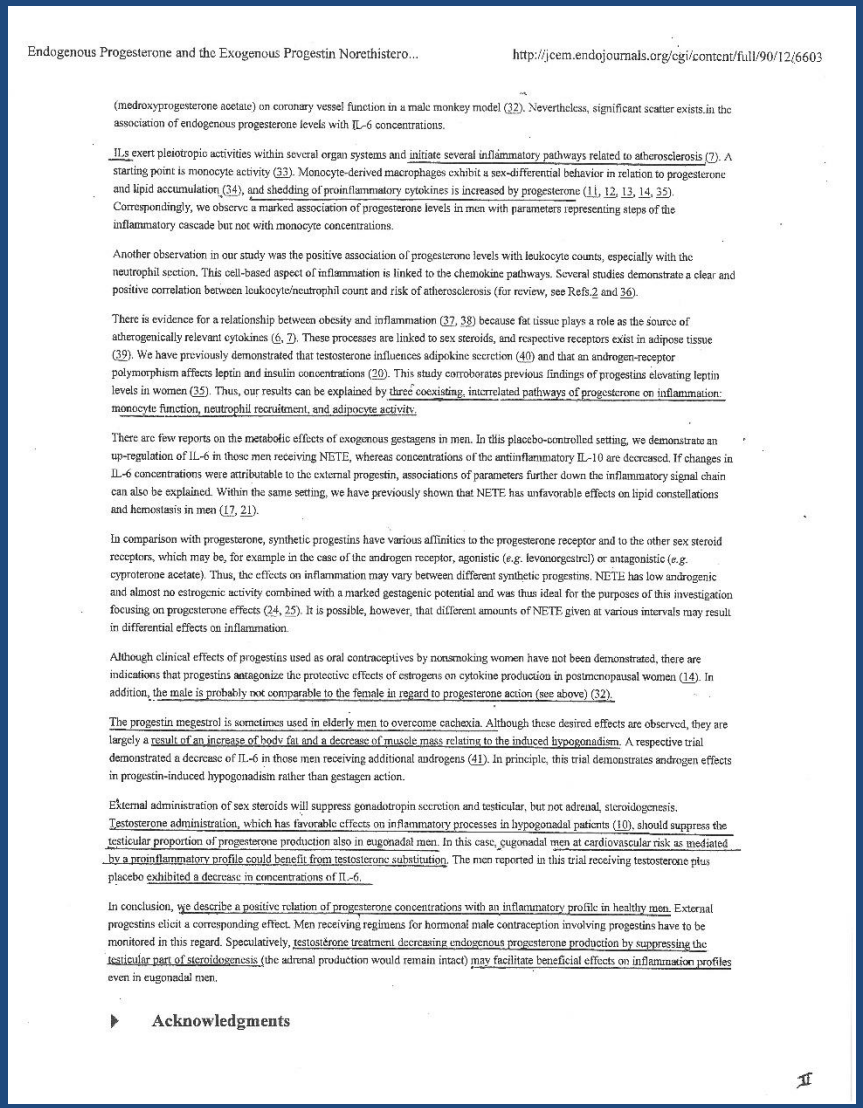


(medroxyprogesterone acetate) on coronary vessel function in a male monkey model (32). Nevertheless, significant scatter exists in the association of endogenous progesterone levels with IL-6 concentrations.

ILs exert pleiotropic activities within several organ systems and initiate several inflammatory pathways related to atherosclerosis (7). A starting point is monocyte activity (33). Monocyte-derived macrophages exhibit a sex-differential behavior in relation to progesterone and lipid accumulation (34), and shedding of proinflammatory cytokines is increased by progesterone (11, 12, 13, 14, 35). Correspondingly, we observe a marked association of progesterone levels in men with parameters representing steps of the inflammatory cascade but not with monocyte concentrations.

Another observation in our study was the positive association of progesterone levels with leukocyte counts, especially with the neutrophil section. This cell-based aspect of inflammation is linked to the chemokine pathways. Several studies demonstrate a clear and positive correlation between leukocyte/neutrophil count and risk of atherosclerosis (for review, see Refs.2 and 36).

There is evidence for a relationship between obesity and inflammation (37, 38) because fat tissue plays a role as the source of atherogenically relevant cytokines (6, 7). These processes are linked to sex steroids, and respective receptors exist in adipose tissue (39). We have previously demonstrated that testosterone influences adipokine secretion (40) and that an androgen-receptor polymorphism affects leptin and insulin concentrations (20). This study corroborates previous findings of progestins elevating leptin levels in women (35). Thus, our results can be explained by three coexisting, interrelated pathways of progesterone on inflammation: monocyte function, neutrophil recruitment, and adipocyte activity.

There are few reports on the metabolic effects of exogenous gestagens in men. In this placebo-controlled setting, we demonstrate an up-regulation of IL-6 in those men receiving NETE, whereas concentrations of the antiinflammatory IL-10 are decreased. If changes in IL-6 concentrations were attributable to the external progestin, associations of parameters further down the inflammatory signal chain can also be explained. Within the same setting, we have previously shown that NETE has unfavorable effects on lipid constellations and hemostasis in men (17, 21).

In comparison with progesterone, synthetic progestins have various affinities to the progesterone receptor and to the other sex steroid receptors, which may be, for example in the case of the androgen receptor, agonistic (*e.g.* levonorgestrel) or antagonistic (*e.g.* cyproterone acetate). Thus, the effects on inflammation may vary between different synthetic progestins. NETE has low androgenic and almost no estrogenic activity combined with a marked gestagenic potential and was thus ideal for the purposes of this investigation focusing on progesterone effects (24, 25). It is possible, however, that different amounts of NETE given at various intervals may result in differential effects on inflammation.

Although clinical effects of progestins used as oral contraceptives by nonsmoking women have not been demonstrated, there are indications that progestins antagonize the protective effects of estrogens on cytokine production in postmenopausal women (14). In addition, the male is probably not comparable to the female in regard to progesterone action (see above) (32).

The progestin megestrol is sometimes used in elderly men to overcome cachexia. Although these desired effects are observed, they are largely a result of an increase of body fat and a decrease of muscle mass relating to the induced hypogonadism. A respective trial demonstrated a decrease of IL-6 in those men receiving additional androgens (41). In principle, this trial demonstrates androgen effects in progestin-induced hypogonadism rather than gestagen action.

External administration of sex steroids will suppress gonadotropin secretion and testicular, but not adrenal, steroidogenesis. Testosterone administration, which has favorable effects on inflammatory processes in hypogonadal patients (10), should suppress the testicular proportion of progesterone production also in eugonadal men. In this case, eugonadal men at cardiovascular risk as mediated by a proinflammatory profile could benefit from testosterone substitution. The men reported in this trial receiving testosterone plus placebo exhibited a decrease in concentrations of IL-6.

In conclusion, we describe a positive relation of progesterone concentrations with an inflammatory profile in healthy men. External progestins elicit a corresponding effect. Men receiving regimens for hormonal male contraception involving progestins have to be monitored in this regard. Speculatively, testosterone treatment decreasing endogenous progesterone production by suppressing the testicular part of steroidogenesis (the adrenal production would remain intact) may facilitate beneficial effects on inflammation profiles even in eugonadal men.

Acknowledgments

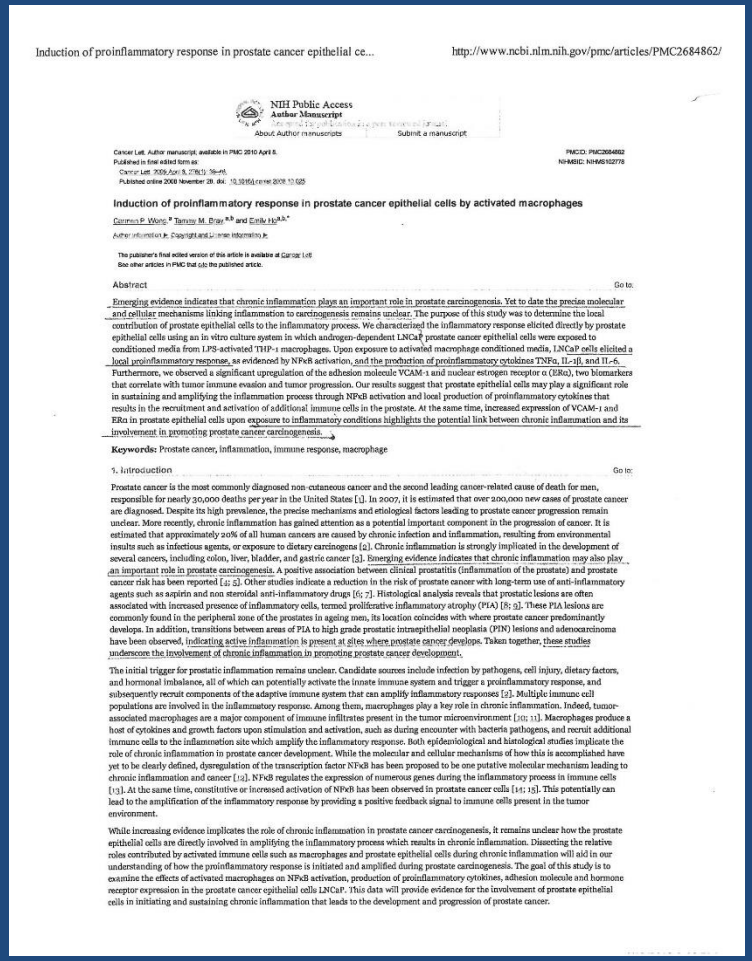
- ILs initiate several inflammatory pathways related to atherosclerosis…and shedding of pro-inflammatory cytokines is increased by progesterone.
- There are three coexisting, interrelated pathways of progesterone on inflammation monocyte function, neutrophil recruitment, and adipocyte activity.

Zitzmann M, Erren M, Kamischke A, et al. Endogenous progesterone and the exogenous progestin norethisterone enanthate are associated with a proinflammatory profile in healthy men. *J Clin Endocrinol Metab*. 2005 Dec;90(12):6603-8.

- The male is probably not comparable to the female in regard to progesterone action.
- The progestin megestrol is sometimes used in elderly men to overcome cachexia.
- Megestrol results in an increase of body fat and a decrease of muscle mass relating to the induced hypogonadism.
- Testosterone administration, which has favorable effects on inflammatory processes in hypogonadal patients, should suppress the testicular proportion of progesterone production also in eugonadal normal men.

- Men at cardiovascular risk as mediated by a pro-inflammatory profile could benefit from testosterone substitution as exhibited by a decrease in concentrations of IL-6.
- We describe a positive relation of progesterone concentrations with an inflammatory profile in healthy men.
- Testosterone treatment decreasing endogenous progesterone production by suppressing the testicular part of steroidogenesis may facilitate beneficial effects on inflammation profiles.

Induction of Proinflammatory Response In Prostate Cancer Epithelial Cells By Activated Macrophages



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Published in final edited form as:
Cancer Lett. 2009 April 8; 274(1): 58–67.
Published online 2008 November 28. doi: 10.1016/j.canlet.2008.10.025
PMCID: PMC2684862
NIHMSID: NIHMS102778

Induction of proinflammatory response in prostate cancer epithelial cells by activated macrophages

Carmen P. Wong,[a] Tammy M. Bray,[a,b] and Emily Ho[a,b,*]

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Abstract Go to:

Emerging evidence indicates that chronic inflammation plays an important role in prostate carcinogenesis. Yet to date the precise molecular and cellular mechanisms linking inflammation to carcinogenesis remains unclear. The purpose of this study was to determine the local contribution of prostate epithelial cells to the inflammatory process. We characterized the inflammatory response elicited directly by prostate epithelial cells using an in vitro culture system in which androgen-dependent LNCaP prostate cancer epithelial cells were exposed to conditioned media from LPS-activated THP-1 macrophages. Upon exposure to activated macrophage conditioned media, LNCaP cells elicited a local proinflammatory response, as evidenced by NFκB activation, and the production of proinflammatory cytokines TNFα, IL-1β, and IL-6. Furthermore, we observed a significant upregulation of the adhesion molecule VCAM-1 and nuclear estrogen receptor α (ERα), two biomarkers that correlate with tumor immune evasion and tumor progression. Our results suggest that prostate epithelial cells may play a significant role in sustaining and amplifying the inflammation process through NFκB activation and local production of proinflammatory cytokines that results in the recruitment and activation of additional immune cells in the prostate. At the same time, increased expression of VCAM-1 and ERα in prostate epithelial cells upon exposure to inflammatory conditions highlights the potential link between chronic inflammation and its involvement in promoting prostate cancer carcinogenesis.

Keywords: Prostate cancer, Inflammation, Immune response, macrophage

1. Introduction Go to:

Prostate cancer is the most commonly diagnosed non-cutaneous cancer and the second leading cancer-related cause of death for men, responsible for nearly 30,000 deaths per year in the United States [1]. In 2007, it is estimated that over 200,000 new cases of prostate cancer are diagnosed. Despite its high prevalence, the precise mechanisms and etiological factors leading to prostate cancer progression remain unclear. More recently, chronic inflammation has gained attention as a potential important component in the progression of cancer. It is estimated that approximately 20% of all human cancers are caused by chronic infection and inflammation, resulting from environmental insults such as infectious agents, or exposure to dietary carcinogens [2]. Chronic inflammation is strongly implicated in the development of several cancers, including colon, liver, bladder, and gastric cancer [3]. Emerging evidence indicates that chronic inflammation may also play an important role in prostate carcinogenesis. A positive association between clinical prostatitis (inflammation of the prostate) and prostate cancer risk has been reported [4; 5]. Other studies indicate a reduction in the risk of prostate cancer with long-term use of anti-inflammatory agents such as aspirin and non steroidal anti-inflammatory drugs [6; 7]. Histological analysis reveals that prostatic lesions are often associated with increased presence of inflammatory cells, termed proliferative inflammatory atrophy (PIA) [8; 9]. These PIA lesions are commonly found in the peripheral zone of the prostates in ageing men, its location coincides with where prostate cancer predominantly develops. In addition, transitions between areas of PIA to high grade prostatic intraepithelial neoplasia (PIN) lesions and adenocarcinoma have been observed, indicating active inflammation is present at sites where prostate cancer develops. Taken together, these studies underscore the involvement of chronic inflammation in promoting prostate cancer development.

The initial trigger for prostatic inflammation remains unclear. Candidate sources include infection by pathogens, cell injury, dietary factors, and hormonal imbalance, all of which can potentially activate the innate immune system and trigger a proinflammatory response, and subsequently recruit components of the adaptive immune system that can amplify inflammatory responses [2]. Multiple immune cell populations are involved in the inflammatory response. Among them, macrophages play a key role in chronic inflammation. Indeed, tumor-associated macrophages are a major component of immune infiltrates present in the tumor microenvironment [10; 11]. Macrophages produce a host of cytokines and growth factors upon stimulation and activation, such as during encounter with bacteria pathogens, and recruit additional immune cells to the inflammation site which amplify the inflammatory response. Both epidemiological and histological studies implicate the role of chronic inflammation in prostate cancer development. While the molecular and cellular mechanisms of how this is accomplished have yet to be clearly defined, dysregulation of the transcription factor NFκB has been proposed to be one putative molecular mechanism leading to chronic inflammation and cancer [12]. NFκB regulates the expression of numerous genes during the inflammatory process in immune cells [13]. At the same time, constitutive or increased activation of NFκB has been observed in prostate cancer cells [14; 15]. This potentially can lead to the amplification of the inflammatory response by providing a positive feedback signal to immune cells present in the tumor environment.

While increasing evidence implicates the role of chronic inflammation in prostate cancer carcinogenesis, it remains unclear how the prostate epithelial cells are directly involved in amplifying the inflammatory process which results in chronic inflammation. Dissecting the relative roles contributed by activated immune cells such as macrophages and prostate epithelial cells during chronic inflammation will aid in our understanding of how the proinflammatory response is initiated and amplified during prostate carcinogenesis. The goal of this study is to examine the effects of activated macrophages on NFκB activation, production of proinflammatory cytokines, adhesion molecule and hormone receptor expression in the prostate cancer epithelial cells LNCaP. This data will provide evidence for the involvement of prostate epithelial cells in initiating and sustaining chronic inflammation that leads to the development and progression of prostate cancer.

- Emerging evidence indicates that chronic inflammation plays an important role in prostate carcinogenesis. Yet to date the precise molecular and cellular mechanisms linking inflammation to carcinogenesis remains unclear.
- Cancer cells elicited a local pro-inflammatory response to inflammatory cytokines TNF-α, Il-1B,and Il-6.

- Exposure to inflammatory conditions highlights the potential link between chronic inflammation and its involvement in promoting prostate cancer carcinogenesis.
- Emerging evidence indicates that chronic inflammation may also play an important role in prostate carcinogenesis.
- Active inflammation is present at sites where prostate cancer develops.
- These studies underscore the involvement of chronic inflammation in promoting prostate cancer development.
- Q: Why would anyone ever give progesterone (that increases inflammation) to a man?

- Men at cardiovascular risk as mediated by a pro-inflammatory profile could benefit from testosterone substitution as exhibited by a decrease in concentrations of IL-6.
- We describe a positive relation of progesterone concentrations with an inflammatory profile in healthy men.
- Testosterone treatment decreasing endogenous progesterone production by suppressing the testicular part of steroidogenesis may facilitate beneficial effects on inflammation profiles.



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from untreated THP-1 macrophages (THP untx), conditioned media from LPS-activated (more ...)

3.4. Upregulation of adhesion molecule VCAM-1 in LNCaP cells treated with LPS-activated THP-1 cells conditioned media

VCAM-1 is an adhesion molecule that plays a direct role in tumor progression by promoting tumor escape from anti-tumor immunity [19]. Furthermore, increased expression of the adhesion molecule VCAM-1 is a biomarker that predicts prostate cancer relapse [20]. Since VCAM-1 expression in endothelial cells can be induced by proinflammatory cytokines such as IL-1β and TNFα, we sought to determine whether VCAM-1 expression will be similarly upregulated in prostate cancer epithelial cells exposed to THP-1 conditioned media. Untreated LNCaP cells, and LNCaP cells treated with LPS or conditioned media from unstimulated THP-1 macrophages did not express detectable levels of VCAM-1 by Western analysis or flow cytometry analysis (Figure 4). In contrast, LNCaP cells exposed to conditioned media from LPS-treated THP-1 macrophages had significantly elevated VCAM-1 expression (Figure 4). Single cell analysis by flow cytometry indicated that the induction of VCAM-1 expression was limited to a subset of treated LNCaP cell (Figure 4b). On average, 11.4 +/- 2.2% of LNCaP cells exposed to conditioned media from LPS-treated THP-1 macrophages had elevated VCAM-1 expression, as compared to less than 1% VCAM-1 expression in control groups (Figure 4c).

Figure 4

Induction of VCAM-1 expression in LNCaP cells treated with LPS-activated THP-1 cells conditioned media. LNCaP cells were treated with 10 ng/ml LPS, conditioned media from untreated THP-1 macrophages (THP untx), conditioned media from LPS-activated THP-1 (more ...)

3.5. Upregulation of the nuclear estrogen receptor α (ERα) in LNCaP cells treated with LPS-activated THP-1 cells conditioned media

Estrogens have been implicated to be involved in prostate carcinogenesis [21; 22]. In particular, ERα is associated with aberrant proliferation, inflammation, and the development of malignancy. Increased expression of ERα has been detected in prostate cancer and premalignant prostatic lesions [23]. To determine if THP-1 macrophage conditioned media affects the expression of ERα in prostate cancer epithelial cells, we quantified nuclear ERα expression in LNCaP cells exposed to THP-1 conditioned media by western analysis (Figure 5). Minimal expression of nuclear ERα was detected in control cells. In contrast, a significantly elevated expression of nuclear ERα was detected in LNCaP cells treated with conditioned media from LPS-stimulated THP-1 cells.

Figure 5

Induction of nuclear ERα in LNCaP cells treated with LPS-activated THP-1 cells conditioned media. LNCaP cells were treated with 10 ng/ml LPS, conditioned media from untreated THP-1 macrophages (THP untx), conditioned media from LPS-activated THP-1 (more ...)

Discussion Go to

Increasing evidence suggests that chronic inflammation plays an important role in prostate carcinogenesis. However to date, it is unclear how chronic inflammation is established in the prostate. Specifically, the relative contribution of activated immune cells such as macrophages, and prostate epithelial cells in perpetuating the inflammatory response that ultimately results in prostate carcinogenesis remains unresolved. Our study focuses on the relationship between macrophages and prostate cancer epithelial cells in sustaining a chronic inflammatory response. In order to distinguish direct inflammatory response elicited by prostate epithelial cells versus inflammatory macrophages, we used an in vitro culture system in which androgen-dependent LNCaP prostate cancer epithelial cells were exposed to conditioned media harvested from LPS-activated THP-1 macrophages. This allows us to evaluate the response of LNCaP cells to the entire collection of soluble mediators produced by activated macrophages. In our study, exposure of LNCaP prostate epithelial cells to conditioned media from LPS-activated THP-1 macrophages triggered significant activation of NFκB as shown by increased nuclear translocation of NFκB p65 protein with concomitant degradation of cytosolic IκBα (Figure 2). Although the short duration of our experiment cannot mimic the sustained exposure of prostate epithelial cells in a chronically inflamed tissue microenvironment, nevertheless, our finding indicated that exposure of prostate epithelial cells to proinflammatory soluble mediators directly activated NFκB and induced local production of proinflammatory cytokines TNFα, IL-1β, and IL-6 in the prostate epithelial cells. Secretion of proinflammatory cytokines by prostate cells likely results in further recruitment and activation of additional immune cells, thus amplifying the proinflammatory response via a positive feedback mechanism. Furthermore, activated macrophages induced prostate epithelial cells to upregulate VCAM-1 and ERα expression, two molecules that are implicated in cancer progression. This study highlights the interactions between inflammatory response and prostate cells during the carcinogenic process and suggests that prostate epithelial cells can play a direct and critical role in propagating a local inflammatory response. Our results also indicate a close interplay between immune cell and prostate epithelial cell responses in both amplifying inflammatory responses and influencing key pathways involved in the carcinogenic process.

Inflammation is a physiologic process mediated by the innate immune system to protect against pathogen infections, environmental insults, and wounding. Chronically inflamed tissues undergo continuous tissue damage and repair, which can eventually lead to sustained and dysregulated cellular proliferation and potentially results in an accumulation of genetic mutations that provides the initiation events in cancer development. Once cancerous lesions develop, a chronically inflamed tumor microenvironment stimulates aberrant angiogenesis, and promotes invasion and migration of tumor cells. The tumor inflammatory microenvironment are infiltrated with multiple subsets of immune cells, including macrophages, neutrophils, eosinophils, dendritic cells, mast cells, and lymphocytes [3]. In particular, we focus on macrophages in this study because

- Estrogens have been implicated to be involved in prostate carcinogenesis.
- ER-α is associated with aberrant proliferation, inflammation, and the development of malignancy.
- Exposure of prostate epithelial cells to pro-inflammatory soluble mediators (like progesterone?) directly induced local production of pro-inflammatory cytokines TNFα, IL-1β, and IL-6 in the prostate epithelial cells.

macrophages are a major component of immune infiltrates present in the tumor microenvironment and play one of the key roles in chronic inflammation [10; 11]. Furthermore, tumor-associated macrophages are involved in promoting tumor progression and metastasis by inhibiting anti-tumor immunity [12].

Recent studies have identified the transcription factor family NFκB as a key modulator in driving inflammation-induced cancers [12]. NFκB is activated by inflammatory stimuli. Targets of NFκB include genes regulating immune response, inflammation, cell proliferation, cell migration, and apoptosis. While normal NFκB activation is tightly regulated, constitutive activation of NFκB has been reported in several types of cancer, suggesting aberrant NFκB activation may play an important role in linking chronic inflammation to the promotion of cancer development [25; 26; 27]. However, in a chronically inflamed tumor environment, it is difficult to distinguish the whether aberrant NFκB activation originates from tumor cells or from immune infiltrates. Our results demonstrated that NFκB can be locally activated in prostate cancer epithelial cells upon stimulation, and induce a significant production of proinflammatory cytokines TNFα, IL-1β, and IL-6 directly by the prostate epithelial cells. This underscores the direct contribution of prostate epithelial cells during the inflammatory process and their involvement in a positive feedback loop that results in chronic inflammation and tumor proliferation.

We have also identified potential links between prostate inflammation and events culminating in prostate cancer progression. The transition from premalignant prostate lesions to adenocarcinoma and eventually metastatic tumors is a multistep process. Among them, immune evasion is one mechanism through which tumor escapes T cell-mediated immune attacks. Expression of the adhesion molecule VCAM-1 in tumor has been shown to result in decreased trafficking of tumor-specific T cells in the tumor microenvironment, leading to tumor escape from anti-tumor immunity [19]. Furthermore, circulating soluble VCAM-1 in blood is a biomarker that predicts prostate cancer relapse after radical prostatectomy in patients [20]. Since VCAM-1 expression in endothelial cells can be induced by proinflammatory cytokines such as IL-1β and TNFα, we sought to determine if VCAM-1 expression was similarly upregulated in prostate epithelial cells upon exposure to activated macrophages. Significant increase in VCAM-1 expression was detected in LNCaP cells treated with LPS-activated THP-1 conditioned media (Figure 4). Flow cytometry analysis indicated that VCAM-1 expression was induced in ~12% of treated LNCaP cells. Our result suggests this subset of VCAM-1 positive prostate cancer cells may have a selective advantage and are more likely to evade anti-tumor immunity. Other mechanisms implicated in prostate cancer progression include estrogen regulation [21]. Estrogen plays a role in regulating the growth, development, and function of the prostate along with androgens. Estrogen regulation has been implicated as one of the risk factors in association with the development of prostate cancer [28; 29]. The action of estrogen is mediated by nuclear estrogen receptors. In particular, expression of ERα is associated with aberrant proliferation, inflammation, and the development of malignancy. Moreover, the extent of detectable ERα expression correlates with the different stages of prostate cancer, from premalignant lesions to adenocarcinoma [23]. In our study, we observed an increased expression of nuclear ERα in LNCaP cells upon stimulation with activated macrophage conditioned media (Figure 5). Our results indicate that exposure of prostate epithelial cells to proinflammatory soluble mediators is one potential mechanism that upregulate ERα expression in prostate epithelial cells, and may in part contribute to prostate cancer progression.

Taken together, we showed that prostate cancer epithelial cells can directly contribute to the propagation of the proinflammatory response upon encountering activated macrophages. This likely establishes a positive feedback mechanism that can further recruit and activate immune cells, and sustain a proinflammatory response in the prostate microenvironment. Furthermore, exposure of prostate cancer epithelial cells to soluble inflammatory mediators may promote tumor progression by increasing their potential for immune evasion and tumor metastasis.

Acknowledgments Go to:

This work is supported by funding from NIH NCI R01 CA107693, and by the National Institute of Environmental Health Sciences Center grant P30 ES00210.

Footnotes Go to:

Conflicts of Interests: None.

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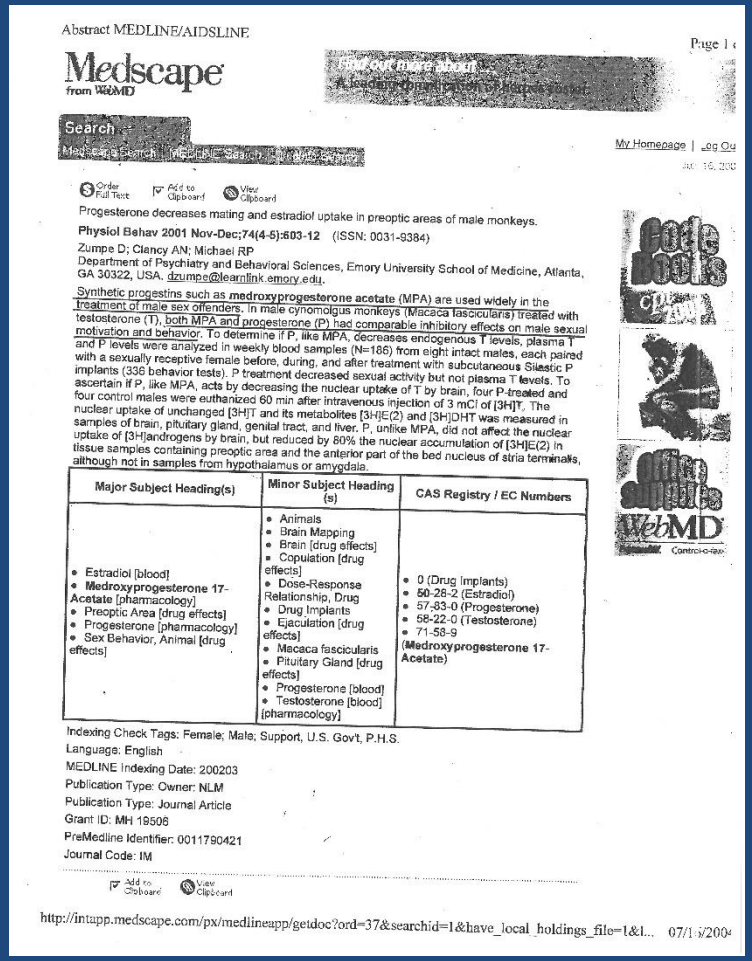
Progesterone Decreases Mating and Estradiol Uptake in Preoptic Areas of Male Monkeys



Abstract MEDLINE/AIDSLINE

Medscape from WebMD

Progesterone decreases mating and estradiol uptake in preoptic areas of male monkeys.

Physiol Behav 2001 Nov-Dec;74(4-5):603-12 (ISSN: 0031-9384)

Zumpe D; Clancy AN; Michael RP

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA. dzumpe@learnlink.emory.edu.

Synthetic progestins such as **medroxyprogesterone acetate** (MPA) are used widely in the treatment of male sex offenders. In male cynomolgus monkeys (Macaca fascicularis) treated with testosterone (T), both MPA and progesterone (P) had comparable inhibitory effects on male sexual motivation and behavior. To determine if P, like MPA, decreases endogenous T levels, plasma T and P levels were analyzed in weekly blood samples (N=186) from eight intact males, each paired with a sexually receptive female before, during, and after treatment with subcutaneous Silastic P implants (336 behavior tests). P treatment decreased sexual activity but not plasma T levels. To ascertain if P, like MPA, acts by decreasing the nuclear uptake of T by brain, four P-treated and four control males were euthanized 60 min after intravenous injection of 3 mCi of [3H]T. The nuclear uptake of unchanged [3H]T and its metabolites [3H]E(2) and [3H]DHT was measured in samples of brain, pituitary gland, genital tract, and liver. P, unlike MPA, did not affect the nuclear uptake of [3H]androgens by brain, but reduced by 60% the nuclear accumulation of [3H]E(2) in tissue samples containing preoptic area and the anterior part of the bed nucleus of stria terminalis, although not in samples from hypothalamus or amygdala.

Major Subject Heading(s)	Minor Subject Heading (s)	CAS Registry / EC Numbers
• Estradiol [blood] • **Medroxyprogesterone 17-Acetate** [pharmacology] • Preoptic Area [drug effects] • Progesterone [pharmacology] • Sex Behavior, Animal [drug effects]	• Animals • Brain Mapping • Brain [drug effects] • Copulation [drug effects] • Dose-Response Relationship, Drug • Drug Implants • Ejaculation [drug effects] • Macaca fascicularis • Pituitary Gland [drug effects] • Progesterone [blood] • Testosterone [blood] [pharmacology]	• 0 (Drug Implants) • **50**-28-2 (Estradiol) • 57-83-0 (Progesterone) • 58-22-0 (Testosterone) • 71-58-9 (**Medroxyprogesterone 17-Acetate**)

Indexing Check Tags: Female; Male; Support, U.S. Gov't, P.H.S.
Language: English
MEDLINE Indexing Date: 200203
Publication Type: Owner: NLM
Publication Type: Journal Article
Grant ID: MH 19506
PreMedline Identifier: 0011790421
Journal Code: IM

http://intapp.medscape.com/px/medlineapp/getdoc?ord=37&searchid=1&have_local_holdings_file=1&l... 07/16/2004

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Zumpe D, Clancy AN, Michael RP. Progesterone decreases mating and estradiol uptake in preoptic areas of male monkeys. *Physiol Behav*. 2001 Nov-Dec;74(4-5):603-12.

Q & A

Even if a patients PSA test is below 4.0, then patients should not be treated with testosterone if their free PSA > 25%. T or F

Men with very low testosterone levels should be first evaluated by:

- Pituitary imaging
- FSH & LH levels
- Prolactin levels
- Estradiol levels

The American Institute of Medicine (IOM) feels strongly that men with hypogonadal symptoms should not be treated until testosterone levels reach <200 ng/ml. T or F

True: MNS

AACE recommendations state that the criteria for treating men requires a testosterone level of < 300 ng/ml. T or F True: MNS

Therefore if men have symptoms of hypogonadism but levels > 300 ng/ml, then they just have to suffer. T or F True: MNS

Testosterone levels according to JCEM do not correlate with symptoms. T or F

According to JCEM, testosterone therapy should be guided by symptom improvement, well-being, & health and not by numbers which do not correlate with symptoms. T or F

Testosterone is FDA approved to improve levels of a deficiency. T or F

If supplemental testosterone therapy is given to men with normal testosterone levels, which might be expected:

a. increased sexual motivation

True

b. increased sexual performance

True: Normal levels of any hormone do not mean the patient won't have symptoms as receptor site resistance can cause symptoms in spite of normal (not optimal) serum levels.

Arimidex is a banned medicine in the Olympics.
T or F

True: It raises testosterone by preventing conversion to estrogen.

If carefully monitored, men with chemically cured prostate CA (PSA <0.1) may be given testosterone for hypogonadism.

T or F

80 y/o male with metastatic prostate CA on Casodex & Lupron. He c/o hot flashes and night sweats. He is otherwise healthy.

TX?

Estradiol patch

Effexor

Clonidine patch

Estrace

All will work but estrace and Vivelle Dot are best for health, longevity, quality of life, and apoptotic effect on cancer cells.

- 68 Y/O male on Casodex and Lupron. Feels like crap, healthy and active, ran daily and played tennis but not now. Feels terrible. C/O HF, NS, and depression, wants to die.

Treatment?

- 68 Y/O male on Casodex and Lupron, s/p proton gun and brachytherapy. Now feels like crap and therefore he stopped/refuses LHRH agonists. Now very fatigued but otherwise has been healthy and active in past. No other meds. PSA recently was 5.1. Treatment?

Estrogen in Men

- Oral DES at a 5mg dose has been shown to be harmful to men in that it increases the risk of heart disease. T or F

- Oral DES at a 1mg dose demonstrated the same harm. T or F

- Oral estradiol has been shown to be harmful to men also. T or F

65 y/o male develops a DVT while on testosterone. His PMD states that he must stop testosterone and never take it again as it caused the blood clot because his blood is too thick. Tx?
NEJM?
FDA warning?

65 Y/O healthy male with prostate cancer with extension outside the capsule, S/P proton gun radiation. PSA is now 10 and climbing in spite of LHRH agonists.

- Tumor is no longer androgen sensitive. T or F

Treatment?

- Another patient with the same problem except for a history of DVT secondary to Factor V Leiden?

Treatment?

DIAGNOSIS & TREATMENT of PROSTATE CANCER

- 65 Y/O male with PSA of 8.4 and Free PSA of 9%. Diagnostic tests?
- First try Bactrim and repeat PSA. If elevated, then work up with:
- MRI with Tesla 3.
- Biopsy under MRI guidance.
- Laser ablation under MRI guidance.
- Avoids usual side effects and complications of conventional therapy but expensive.

65 Y/O MALE WITH PSA OF 6.5. TRUS BIOPSY (-). PMD REFUSES TESTOSTERONE?

- What test will eliminate any fear of possible prostate CA?
- What if the risk that patient still has CA?
- If patient/insurance refuse this test, is testosterone still indicated in light of still having prostate cancer?
- What is the risk of causing further CA progression with testosterone Rx?

Oral vs. Transdermal E2?

- The WHI demonstrated an increase in MI with the use of oral estrogen in women over 60 years of age with risk factors for CAD. T or F
- Studies demonstrate the same effect in men that were prescribed oral high dose DES. T or F
- Studies also demonstrate a significant increase in morbidity and mortality from CAD and CVA in men treated with LHRH agonists. T or F
- Knowing this…

Estrogen in Men: EBM?

- Transdermal estradiol has been shown to be not only safe in men but also protects against heart disease. T or F
- Estrogen has long been a standard therapy for treating prostate cancer in men. T or F
- The higher the serum estradiol level in men, the greater the risk of prostate cancer. T or F

Evidenced Based Medicine

- Since the medical literature demonstrates protection against cardiovascular disease, bone loss, diabetes, prostate cancer, Alzheimer's disease, and dementia with estrogen administration in men, it makes perfect sense to routinely lower estrogen levels in men with aromatase inhibitors. T or F
- There is EBM showing that lowering E2 levels in men is beneficial. T or F
- Understanding the above, it also makes sense to raise progesterone levels in men based on EBM. T or F