

## **Bibliography of Important Issues on Testosterone and Prostate Cancer. 3/26/2012**

### **Charles Huggins wins the Nobel Prize for hormones relationship to prostate and breast cancers**

**Huggins C, Hodges CV**, Cancer Res. 1, 293-297, 1941

**Huggins C, Stevens RE, Hodges CV**, Arch Surg 1941 43:209-223

### **Racial and dietary differences and prostate cancers**

**Ross R**. Lancet 1992; 339: 887-889  
Comparison of Japanese, US Caucasian and African males

**Giovannucci E**. 1995 Cancer 75 Suppl:1766-1777  
Asian men both Chinese and Japanese have lower prevalence of prostate cancer but migration to new western countries increases incidence of prostate cancers.

**Whitmore AS** J Natl Cancer Inst 87: 652-661

**Mills PK** Cancer 64:598-604  
Lower incidence in men who do not eat animal products

**Le Marchand L** Epidemiology 5:276-282

**Giovannucci E** 1993, J Natl Cancer Inst 85:1571-1579  
Dietary fat and risk of prostate cancer

### **Hox Genes Genetic Influence on Androgens and Prostate Cancer Risks**

**Daftary GS** Endocrine Reviews 27: 331-355, 2006

**Ewing CM** NEJM 2012; 366: 141-149

**Manning JT** Human Reproduction Vol 13, No11, 3000-3004, 1993

**Manning JT** Developmental Medicine and Child Neurology 2001, 43,160-164

## **Low Testosterone in general population and association with higher mortality**

**Mulligan T.** Int. J. Clin. Pract. 2006; 60:762-769

13 million men effected by hypogonadism. 39% of men between age 45 to 85 have hypogondism

**Morley J.E.** Metabolism 1997; 46:410-413

Longitudinal study of hormones in healthy older men

**Laughlin GA Barret Connor E.** JCEM 2008; 993: 68-75

794 men in a 11.8 years longitudinal study showed that low testosterone was associated with higher mortality in older men

**Neaves W.B.,** J. Clin Edino Metabolism 1984;59: 756-

Testicular Leydig cell atrophy in aging

**Shores M.** Arch Intern Med 2006; 166:1660-5

858 veterans studied for 5 years showed low testosterone had higher risk for death with Hazard Ratio 1.88

**Carrero JJ J** Amer Soc Nephrology 2009; 20: 613-620

Low testosterone and higher mortality in renal dialysis patients

**Maggio M.** Arch Intern Med 2007; 167: 2249-2254

**Khaw K** Circulation 2007; 116: 2694- 2701

**Travison T. McKinlay J.** JCEM 92: 196-202, 2007

Longitudinal study showing transgenerational decline in testosterone levels at the same age. Grandfather had more testosterone than father and father had more testosterone than son. You might say that there is a decline of testosterone within generations of men.

**Feldman H., .McKinlay J.** JCEM 87: 589- 598, 2002

Poor health accelerates age related decline in testosterone levels in longitudinal and cross-sectional study

**Mitchell S.,Blackman M.** JCEM 86: 724-731, 2001

Baltimore Longitudinal Studying on Aging followed 890 men and showed decline of testosterone and free testosterone with age.

## **Testosterone in high doses do not seem to increase PSA**

**Bhasin S.** NEJM 335, 1-7, 1996

High doses used in men do not seem to increase PSA:

**Behre HM, Nieschalag E.** Clin Endocrinology (Oxford Press) 1994, 40: 341-349  
Age matched study with controls looks at volume and PSA

**Jin B, Handelsman D.** JCEM vol81 #12, Dec 1996 , 1-10  
Prevalence study of men who used anabolic steroids in high doses age 20- 40, transsexual men using estrogens and progestins and control comparisons showed central and total volume changes with minimal PSA changes. SHBG was 500% higher in transsexuals compared to controls.

**Cooper C., Williams R.** J Urology Vol. 156, 438-442, August 1996

**Cooper CS Perry PJ** J Urology 1998, 159: 441-443  
The investigators looked at normal healthy young men average age 26 and gave supraphysiological doses of 100 mg, 250 mg, and 500mg every week and followed with blood studies for 28 weeks. There were no significant PSA elevation in this group

**Sveteć .D.** J Urology Vol 158 1775-1777, 1997

**Douglas TH Murphy G J** Surgical Oncology 59: 246-250 1995  
Men without prostate cancer , administration of exogenous testosterone does not correlate with PSA or PSMA. Other factors may influence production of PSA

**Serum testosterone levels in serum are not related prostate cancer.  
Testosterone is not “food for the hungry tumor.”**

**Anderssen S.** Br. J. Cancer 1993;68(1): 97-102  
b 1982 Sloan Kettering looked at 24 hour sex hormone levels of men who had prostate cancer and a control group. Estrone estrogen correlated with cancer not testosterone.

**Nomura A.** Cancer Research 48, 3515-3517 , June 15, 1988  
Japanese Hawaii Cancer Study studied 6860 men no significant association of testosterone and cancer

**Carter B.** Prostate 27:25-31, 1995  
Data from the Baltimore Longitudinal Study of Aging looking at 3 groups of men with BPH, prostate cancer and no disease from 7 to 29 years. There was no measurable differences in serum testosterone levels among men who were destined to develop cancer.

**Heikkilä R.** Cancer 1999; 86:312-315  
Longitudinal population based nested case control study from Finland showing no association with testosterone and prostate cancer

**Roddam A.W.** J. Nat. Cancer Inst. 2008; 100:17 The University of Oxford study of 3886 men with prostate cancer matched to 6438 men same age group as control showed no relationship between risks for cancer and testosterone levels, not high or low. This is the most comprehensive study which included other hormones such as dihydrotestosterone, estradiol and free estradiol, androstenedione, DHEA-s, Adiol-G and SHBG, serum hormone binding globulin.

**Shabsigh R** Int. Impotence Research 2009, 21: 9-23 A large meta-analysis on incidence of prostate cancer with testosterone replacement. No increase incidence

**Slater S.** Drugs and Aging 2000 Dec. 17 (6) 431-439  
Observations support the view that the prostate cancer risks from use of testosterone replacement may not be as great as first feared

**Liverman C.T.** Communications of assessing the need for clinical trial of testosterone replacement therapy: testosterone and aging, clinical research directions 2004

**Coward R.M.** Br.J.Urol. 2009May; 103(9): 1179-1183  
81 hypogonadal men average age 56.8 treated with testosterone and followed for 36 months. 4/ 81 or 4.9% developed prostate cancer and treated. Those who developed cancer increased PSA of 1.8 ng/Dl in 18 months and to 3.6 ng/Dl in 36 months or 3 years therefore there may be clues by rising PSA to select out those who have cancer. The rate of cancer development was no higher than the normal general population.

## **Testosterone promotes rise in PSA and prostate cancer**

**Gaylis FD.** J Urology Vol 174, 534-538, August 2005

**Gann P.** J Natl Cancer Inst 1996; 88: 1118-26

## **Basic science of sex hormones Androgens and Estrogens in animal and human prostate tissues studies**

**Umekita Y.** Proc. Natl Acad Sci 1996; 93: 11802- 7  
Inhibition of human prostate cancer in nude mice studies by androgen

**Hatzoglou A.** JCEM 2005 90: 693-903  
On cellular level most clinicians talk about conversion of testosterone to DHT and alpha reductase inhibitors, but a new paradigm has come with the discovery of both Intracellular and nuclear androgen receptors , slow acting ( iAR), and a more rapid acting membraneous androgen receptor (mAR). iAR promotes cancer growth while mAR receptor leads to apoptosis. The balance of testosterone bonded to each may determine the onset or the retardation of cancer growth. This may also lead to new treatment approaches to prostate cancer.

**Bonkhoff H.** Euro Urology 55 (2009) 533-542  
 Estrogen Receptor Alpha promotes growth and Estrogen Receptor Beta promotes apoptosis.  
 Hormone resistant metastatic prostatic cancers have lost Estrogen Receptor Beta

**Ellem SJ.** J Steroid Biochem Molec Bio 2010 Feb 28;118(4-5): 246-51  
 Concept of Estrogen receptor alpha ERA and beta ERB and epigenetic introduction with methylation of DNA

**Ricke W.** FASEB 2008; 22:1512-20

**Konstantinidis, G.** Mol. Cancer 2008, 7: 88  
 Looking at DU145 non intranuclear androgen receptor human prostatic cancer cell lines, studies looking at this unique TestBSA, Testosterone Bovine Albumin covalently bonded molecule which is not permeable to the cytoplasm, the investors compare cortisol BSA, Estradiol BSA, DHT and antiandrogen Flutamide and look at effect on mAR, membranous androgen receptor. It is the effect the cellular actin reorganization via the cellular cytoskeleton which leads to apoptosis.

**Friedman AE,** Bio Med Central March 18, 2005: 1-4  
 Dr. Friedman has been following the research on prostate cancer. His background is in theoretical biology and presents a comprehensive theory that incorporates all the clinical and basic science on prostate cancer. It may be the we clinicians need a nonbiased referee to put the puzzle together for us to understand the deeper themes of hormonal dependent cancers such as breast and prostate neoplasia.

### **Testosterone treatment exacerbates prostate cancer**

**Fowler J. Whitmore W.,** J Urology 1981; 126(3): 372-5  
 Active prostate cancer patients progressed with testosterone treatment

**Zagars G. Eschenbach A.,** Urology 1997; 49:327-34

**Loughlin K R** J Urology 157: 1845, 1997

**Curran MJ** J Urology 53:423, 1999

**Jackson JA** Arch Intern Med 149: 2365, 1989

### **Testosterone treatment in men who had prostate cancer treated and cured**

**Morgentaler A.** J. Urology 2009; 181:972  
 Scientific considerations of testosterone treatment in men with prostate cancer

**Kaufman J. J.** Urology Vol. 172, 920-922, Sept. 2004

**Agarwal P. J.** Urology Vol. 173, 533-536, Feb. 2005

**Morgentaler A.** European Urology 2009; 55:310

**Khera M.J** Urol. Clin. North America 34, 2007, 549-553

**Khera M.J.** Sex Med. 2009; 6: 1165-1170

**Morales A.** BJU Int. 2008; 103: 62

**Sarosdy M. F.** Cancer 2007; 109: 536-41

5 year follow-up testosterone treatment after brachytherapy radiation with no progression in 31 men

**Ferreira U.** Prostate Cancer Prostate Dis 2006; 9: 39-41

Intermittent androgen replacement for intense hypogonadism in castrated patients

**Brawer M** Rev Urology 2004; 6 (suppl 6) s35-s37

**Sathyamoorthy K** (Abstract1498) J Urology 2010, 183 (suppl) : e577

### **Testosterone Treatment in men with prostate cancer**

**Morgentaler A., Lipschultz L, Khera M** AUA presentation publication, J Urology 2011, Feb 18 in electronic data

13 men with prostate cancer with hypogonadism treated with testosterone replacement for 2.5 years with no progression. These selected men refused to have definitive treatment for the cancer.

**Morgentaler A** Poster Presentation at Sexual Medicine Society of North America Oct 16 2008 Toronto, Poster 49

**Leibowitz R.** B J U international 105; : 1397- 1401 2009,

96 patients who were treated for prostate cancer but not necessarily cured and recieved supraphysiological doses of testosterone achieving mean testosterone levels of 1391 and alpha reductase inhibitors were followed for 3 years. 60% had PSA increases and 40 % did not and able to continue treatment.

### **Intermittent Androgen Suppression, IAS**

**Oefelein M. G.** J. Urology Vol. 160, 1685-1688 Nov. 1998

**Bruchovsky N.** , Goldenberg Cancer 2006; 107: 389-95

**Abrahamsson P.** European Urology 57, 2010, 40-59

**Lane T. M.** Urologia Internationalis 2004; 73: 117-122

**Prapotnich D.** European Urology 43, 2003, 233-240

**Hall M.C.** Urology 53: 898-903,1999

**Buchan N., Goldenberg S.L.** Nat. Rev Urol. 7,552-560, 2010

**Akakura K,** Cancer 71, 2782-2790 (1993)

**Egger SE** The Prostate 66: 495-502, 2006

**Locke JA Bruchovsky N** Canad J Urol 2010; 17 (3): 5162-5169

The combination cycling of IAS with Finasteride in the off periods can prolong off periods

### **Rationale for delayed androgen suppression**

**Blackard C.E., Byar W.,** Urology 1: 553-560 1972

VACUR Veterans Administration Cooperative Urologic Research Study studied 954 men with prostate cancer showing that immediate and delayed androgen suppression did not change survival.

### **Rationale for immediate androgen suppression even for localized disease and with surgical resection**

**Messing ED** NEJM 1999; Vol 341: 1781-81

Immediate hormonal therapy in patients with radical prostatectomy with

**Labrie F** Mol Urology 1999; 3: 217-226

Even for localized prostate cancer androgen suppression indefinitely will control disease with good survival

**Lu YG, Albertson P** JAMA 2009 Jan7; 301 (1) 38

Study looking at elderly men with localized prostate cancer receiving androgen suppression showed no survival advantage except for the higher grade cancers.

### **Low Testosterone and prostate cancer and worse prognosis**

**Wilson DW** Prostate 1985; 7:131-141

**Meikle A. W, Middleton J.** The Prostate, 6 :121-128 1985

Familial factors affecting prostate cancer seems to be related to families with males having lower testosterone plasma levels of normal limits.

**Mulders P.** Cancer 65: 2758-2761 1990

Dutch study observing 175 patients advanced prostate cancer with bone spread to look for prognostic factors. Low baseline testosterone level, hemoglobin, performance status and alkaline phosphatase were variable most important to determine the poor prognosis.

**Iversen P** Scand J Urol Nephrol, suppl, 157:41, 1994

**Ribeiro M.** Am. J. Clin Oncology 20 (6): 605-608 1997

144 patients with advanced prostate cancer D2 with bone spread received androgen suppression therapy. The younger and the lower testosterone level at baseline had the worst prognosis.

**Daniell H** Cancer 1998; 83:1170-1173

Testicular atrophy noted at time of therapeutic surgical orchiectomy for prostate cancer is associated with a poorer prognosis.

**Prehn R.** Cancer Research 59, 4161-4164, 1999

The concept of Biphasic effect of testosterone on prostate cancer. The decline of testosterone contribute to human prostate carcinogenesis.

**Morgentaler A.** J.A.M.A. 1996: 276: 1904-1906

Retrospective consecutive analysis studying 77 men ( mean age 58) with low total and free testosterone and normal sonogram and PSA levels (<4) 11/77 or prevalence rate of 14% of that group had prostate cancer. In general population with normal prostate examination and PSA <4 the incidence is about 1.8% to 4.5%. The higher 14% prevalence seems more like the groups of men with either abnormal prostates or PSA elevations.

**Schatz G., Marberger M.** The Prostate 47:52-58, 2001

Patients with high Gleason score prostate cancer have lower testosterone and estradiol serum levels.

**Morgentaler A.** Urology 2006; 68: 1263

345 hypogonadal men with PSA< 4 ng/ml. had 15% cancer rate: The low testosterone may mean higher risk for prostate cancer

**Morgentaler A** Cancer Jan 18,2011Editorial

**Garcia J.** Cancer 2006; 106: 2583-91



**Colen J.S.** J. Urology Supp.,2009; 181:368 abstract 1027

**Yamamoto S** European Urology52 (2007) 696-710  
Low testosterone an independent predictor of PSA failure

**Massengill JC** J Urology 169:169: 1670,2003  
Low testosterone an independent predictor of extraprostatic disease in men with localized prostate cancer.

**Epstein JI** JAMA 271:368. 1994  
Low testosterone and extracapsular prostate cancer.

**Hoffman M J** Urology Vol 163; 824-827, March 2000

**Teloken C J** Urology Vol 174, 2178-80, 2005  
More positive cancer margins in radical prostatectomy operations for cancer in men with low testosterone levels. 39% to 14.6% of those with normal testosterone level

**Isom-Batz G J** Urology 2005June; 173(6); 1935-1937  
Low testosterone associated with more advanced disease but not PSA

**Ishikawa S., Soloway M., J.** Urology Vol. 141: 1139-1142 May 1989  
110 men after androgen deprivation therapy revealed 2 factors which determined poor prognosis and progression of disease. The baseline low testosterone level  $< 300\text{ng/Dl}$  and  $\geq 6$  bone lesions are the primary and secondary factors which were most important.

### **Ratio of testosterone decline to estradiol increase in aging leading to disease**

**Hill P** Cancer Research 42, 3864-3869 September 1982  
South African study noted decreasing plasma androgen to increasing estrogen as a lead to hyperplasia of prostate and cancer among whites and black population

**Prehn R.** Cancer Research 59, 4161-4164, 1999  
There is concept of Biphasic effect of testosterone on prostate cancer. The decline of testosterone production contributes to human prostate carcinogenesis.

**Lin D.** J Urology Vol 183, No 4, Supple, May 30 , 2010  
Toremifene Selective Estrogen Receptor Modulator used shows less PSA Progression compared to controls

**Daniels NA** Urology 76, 1034-1041, 2010  
Evidence of increasing Estrone Sulfate associated with incidental prostate cancer.

## **One time triple androgen suppression and subsequent adjunctive alpha reductase inhibitor, Proscar (Finasteride) Avodart ( Dutasteride)**

**Clark R.** JCEM 89, 2179-2184, 2004

The blood level of DHT can be decreased from 94% with .5mg to 98% at 5 mg.

**Leibowitz R.**, The Oncologist Vol. 6, No. 2, 177-182 April 2001

**Strum SB** Oncologist 2000;5: 45-52

**Strum SB** Proc AmSocClinOncol 1999; 353a

## **Intracrinology of prostate tissue compared to blood levels with testosterone supplementation. The hormone level within the cell do not reflect what is in blood serum**

**Marks L.** JAMA Nov 15, 2006, Vol 296, #19, 2351

The testosterone replacements did not effect the intracrine levels of DHT or Testosterone. Blood serum levels did change as expected. There were no more prostate cancer cases in the testosterone treated group

**Marks L** Uology 57: 999-1005, 2001

Proscar reversed the ratio of DHT to Testosterone 5/1 to 1/4 Proscar reduced DHT by 70% and Saw Palmetto decreased DHT by 32%

Proscar and Saw Palmetto decreases DHT by 70% and 32% respectively

**NishiyamaT.** Clin Cancer Research Vol 10, 7121- 7126 Nov 1, 2004

With LHRH agonist and flutamide antiandrogen there is still 25% of total DHT left in prostate cancer cells.

**Heracek J.** Steroids 72, 2007, 375-380

Intracrine prostate DHT is 4x higher than blood serum levels.

**Ross RK** Lancet 1992;3 39: 887-889

Racial difference in intracrine DHT with black race having highest intraprostatic DHT but blood serum levels were similar in Caucassian, Blacks and Asians.

## **Doubling Time and Stem Cell Resistance to Hormones – How Should We Use Additional Chemotherapy Before Cancer Are Hormone Resistant**

**Berges RR** Clinical Cancer Res Vol 1, 473-480, May 1995

**Carter HB**, Cancer Research 52, 3323-3328, June 15, 1992

**Schmid HP, Stamey T**, Cancer 1993 Mar 1993 71, (6) 2031-2040

**Shackney SE**, Ann Intern Med 1978 July 89 (1): 107-21

**Tunn S Krieg M**, Prostate 1989 15 (3) 263-271

**Kelloff GJ**, Clinical Cancer Res Vol 10, 3927-3933, June 1, 2004

**Wang Xi Shen M**, Nature 2009 461 (7263): 495-500

**Liu W Bova S** Nat Med 2009 May 15 (5): 559-565

The above references note that prostate cancer both localized and metastatic grow slowly and we are always searching for stem cells which are resistant to hormones. Chemotherapy must address the slow cell kinetics of advancing prostate cancer. It may be that the way we give, the timing, and the dosage of chemotherapy may be more important than the specific agent to match the biology of this solid tumor growth pattern

### **Concept of Membranous Receptors**

**Papadopoulou N**, iubmb Life 61 (1); 56-61, 2009

**Hatzoglou A**, JCEM Vol 90, No 2, 893-903, 2005

**Papadopoulou N**, Molecular Cancer 2008, 7:88

**Sun YH** J Andrology 2006; 27: 671-678

We have always focused on intracellular and intranuclear effects of androgens and its receptor but more evidence suggests other sites including cell membrane and organelle sites.

### **REDUCE Study, Avodart Dutasteride Therapy Prevention Study of Prostate Cancer and Chemoprevention by Selenium and Vitamin E**

**Andriole G**. NEJM 2020; 362:1192-1202

PCPT study, Proscar prevention study of 7 years decreases incidence of prostate cancer but had a sub group of high Gleason score prostate cancer patients . Contrary to proscar study looking at men with PSA of 3 or less, the reduce study looked at 6729 high risk patients

with PSA 2.5 to 10 with negative biopsy to see if we could reduce the incidence of a higher risk group in a 4 year study. 10 core biopsy at 2 and 4 years were mandatory with PSA measurement every 6 months

**Andriole G.** Urology 73, #5a, supplement to May 2009

Avodart Dutasteride is 3x more potent than Proscar Finasteride and has a longer half life of 5 weeks compared to 6 hours. A subgroup looked at men with prostate cancer given 5mg of Avodart and not .5mg for 6 weeks before surgery and found more apoptosis, smaller cancer volume, REDEEM study using .5 mg of Dutasteride is looking at men with diagnosis of prostate cancer to see if it could delay progression

**Tindall D., Rittmaster RS.,** J Urology 2008 April 179 (4) 1235 2005,

Rationale for using alpha reductase inhibitors in prevention and treatment of prostatic cancer

**Thomas LN.** Prostate 2005; 63:231

The investigators show the alterations of 5 alpha reductase type 1 and type 2 during development and progression of prostate cancer. There is more and more intense reductase of both types in recurrent and metastatic human cancers. This data is in direct opposition to the groups opposing use of alpha reductase for cancer treatment and prevention such as the Johns Hopkins group which claim that there is little reductase enzymes in prostate cancer cells (Prostate Cancer Discovery Vol 8, 2011 Page4)

**Bonhoff H** Prostate 1996; 29 (4): 261-267

**Nishiyama T.** Clin Cancer Research Vol 10, 7121- 7126 Nov 1, 2004

With LHRH agonist and flutamide antiandrogen there is still 25% of total DHT left in prostate cancer cells.

**Titus MA., Mohler JL.,** Clin Cancer Research 2005; 11: 4365

Both reductase expression in recurrent prostate cancer

**Stanbrough** 2006 Cancer Research 2006; 66: 2815

Metastatic cancer show a 2x greater reductase expression than primary prostate cancer

**Clark LC.** JAMA 1996; 276: 1957-1963

37% lower incidence of prostate cancer in men using Selenium supplement

## **Other Alpha Reductase Inhibitors**

**Marks L** Urology 57: 999-1005, 2001

Saw palmetto decreases intracellular DHT by 35% compared to Finasteride by 80%

**Anderson M,** J Herbal Pharmacotherapy Vol 5, (1) 2005

2 mg of Astaxanthin antioxidant carotenoid inhibits Reductase by 98%

**Lourdes Arruzabala M**, J Pharmacy Pharmacology 2007, 59, 995-999

Coconut oil's Lauric and Myristic medium chain fatty acids may work the same way as saw palmetto to inhibit prostate gland weight by 82% rats given testosterone to increase prostate enlargement

## **Incidence, Prevalence of Incidental Prostate cancer and Patterns of Metastasis**

**Sakr W**. Pathology Res Pract 1995;191: 834-841

Age related increases in incidental prostate cancers found on autopsy from accidents in young men. At age 40 there was a 35% finding of prostate cancer yet clinically we do not see as many as would be expected from this information. Does small areas of prostate cancer resolve on its own? Similar comparison are being tested in small breast cancer findings from mammography ( Zahle)

**Bubendorf L** Human Pathology Vol 31, 5, 578-583 May 2000

1589 patients with prostate cancer and patterns of metastasis

**Rubin M** Cancer Research 2000 Vol 6, 1038 March 2000

Rapid "Warm" Autopsy Study shows that metastatic prostate cancer has high PSA expression

**Abrahamsson P.A.** clinicaloptions.com Prostate 2007

Incidence is 14.8% but mortality is 2.26% in prostate cancer highlighting the problem of overdiagnosis in ERSPC European study.

## **Screening for Prostate Cancer on Mortality. Are we over diagnosing and over treating?**

**Zahl PH** Arch Intern Med 2008; 168 (21): 2311-2316

Natural course of some screen- detected invasive breast cancers is to spontaneously regress

**Andriole G** NEJM 360;13, 1310-9 March 26, 2009

76,693 annual screening and control of 38,350 after 7 years rate of death from prostate cancer was very low and did not differ significantly in both groups

**Schroder F**. NEJM 2009; 360: 1320

162,243 men age 55-69 of 9 years screened group cumulative incidence was 8.2% and control group 4.8%. 1410 would have to be screened and 48 additional cases of prostate

cancer needs to be treated to prevent 1 death from prostate cancer. Screening reduced death rate from prostate cancer by 20% but associated with high risk of over diagnosis.

### **Testosterone treatment in androgen resistant patients**

**Morris MJ.** J.Clin.Oncology 2004;22 (suppl July 15)Abstract 4559

**Szmulewitz R.** European Urology 56(2009) 97-104

Of 13 patients with androgen resistant cancer, 3 patients PSA actually declined and one up to 43% suggesting that there might an inhibitory effect on cancers.

### **Low testosterone and glucose intolerance, insulin resistance, metabolic syndrome and diabetes**

**Phillips G** Proc. Natl Academy Sci. Vol. 74,#4 P 1729-1733, 1977

**Phillips G** Diabetes Care 27:P 22 85-2286, 2004

This is one of the pioneers who first observed the relationship of sex hormones effecting cardiovascular disease and glucose metabolism

**Mckinlay** Diabetes Care 2000; 23: 490-4

Population based study.Low testosterone is an independent risk for Diabetes 2

**Laaksonen** Diabetes Care 2004;27: 1036-41

Lowest testosterone group has 2.3 fold risk for Diabetes and metabolic syndrome

**Marin** Int J Obes Relat Metab Disorder 1992; 16: 991-997

**Kapoor D** European J. Of Endocrinology 154, 899-906, 2006

Testosterone replacement improves insulin resistance and hypercholesterolaemia in hypogonadal men with type 2 Diabetes.

**Kapoor D. and Jones H.** Current Opinion Drug and Aging 2008; 25(5) 357

Androgen deficiency as a predictor of Metabolic Syndrome in aging men

**Ding E** JAMA March 15, 2006 Vol 295 #11, 1288- 1299

Women have higher risk for diabetes when testosterone is high which the reverse for men

**Muller** JCEM 2005: 90: 2618-2623

Each unit of increase in total testosterone (5.3nmol/L) reduced risk of metabolic syndrome by 57%

**Kupelian** JCEM 2006; 98:843-850

Low testosterone is a clue to risk of future metabolic syndrome in thin men with BMI less than 25

**Niskanen** JCEM 2006; 91:843-850

Weight loss improves testosterone levels

**Kaukua P** Obesity Res 2003; 11:689-694

Weight loss improves testosterone levels

**Guy A. J.** Sex Med. 2007;4:1046-1055

Testosterone, metabolic syndrome, insulin resistance, organic erectile dysfunction

**Pitteloud N.** J.Clin.Endo.Met. 2005;90:2636-

Increasing insulin resistance associated with decrease in Leydig cell testosterone secretion in men

**Pitteloud N** Diabetes Care 28:1636-1642, 2005\

Low testosterone levels and impaired mitochondrial function promote insulin resistance in men

**Pitteloud N** JCEM 2005, 90:2636

Blood glucose levels effect testosterone secretions

**Wang C.,** J. Clin.Endo.Met.2000; 85:2839-2853

Therapeutic trial on hypogonadal men increases lean muscle, decreases fat

**Mauras N Veldhuis JD** JCEM 83: 1886-1892, 1998

Induced hypogonadism in young healthy men with increase in adiposity and decrease in lean muscle, decreased protein anabolism, decreased fat oxidation not related to Growth Hormone and IGF-1. Testosterone has an effect on whole body lipid and protein metabolism

**Smith JC** JCEM 86:4261-4267, 2001

Induced hypogonadism is associated with changes in body composition and reduced insulin sensitivity

**Smith M** JCEM 91: 1305-1308, 2006

Decreased insulin sensitivity and increased fat mass during androgen deprivation

**Smith M.** J. Natl Cancer Inst 2010; 102: 39-46

Androgen deprivation therapy is associated with cardiovascular disease and diabetes

**Michaelson M.D.** Ca. CancerJ.Clin. 2008: 58:196

Complications of Prostate Cancer Treatments

**Keating N.L.,** J. Clin. Oncology 2006;24: 4448

73,196 men with localized prostate cancer

**Yu G, Triash A** 2 Parts Horm Mol Biol Clin Invest 2011; 8 (1) 425- 430 and 431-444

## **Testosterone and erectile dysfunction**

**Khera M. J.** Sex Med. 2009 March Suppl. 3:234-238

**Guay A. J.** Andrology 2001; 22: 793-797

Those who used testosterone and Viagra did better than those who used Viagra alone

**Rosenthal BD** Urology 2006; 67: 571

Testosterone plus Viagra combination leads to erection after initial Viagra failure

**Shabsigh R. J.** Urol. 2004; 172: 658-663

Randomized study of Testosterone adjunctive treatment in men who do not respond to Viagra alone

**Yildiz O.** Urology 74:229-232, 2009

Testosterone effects smooth muscle relaxation of the corporal cavernosum beside the nitric oxide synthase regulation on the endothelial cells

**Baba K.** BJU Int. 2000; 85: 953- 958

Testosterone restores nitric oxide synthase nerve and erection in rats

**Marin R.** Biol Reprod 1999;61: 1012-1016

Androgen dependant nitric oxide release correlates with nitric oxide synthase enzymes

**Triash A.** Endocrinology 1999; 140: 1861-1868

Castration and androgen replacement on erectile function in rabbit model. Fat infiltration with corporal smooth muscle atrophy and reversal with testosterone replacement.

**Schirar A.** J Neruoendocrinol 1997; 9: 141-150

Androgen receptor in nitric oxide synthase nerves of rat penis

**Shabsigh R. J.** Sex Med 2005; 2: 785-292

Testosterone treatment in erectile dysfunction

## **Complications of androgen deprivation therapy**

**Basaria S J.** of Andrology Vol. 29, No 5 September 2008: 534- 539

**Guise T** Reviews in Urology 2007:9 (4): 163-180

Bone osteoporosis increase with bone mineral density decrease from 4% to 13% per year, Fracture rates increased from 5% to \*% per year, gynecomastia, hot flashes

**Smith J.C.,** J CEM 86:4261-4267, 2001



22 patients with prostate cancer stage T2 and T3 had induced hypogonadism studied for 6 months showed increased arterial stiffness and increase in serum insulin from 11.8 to 15.1 (3 months) and 19.3 mU/L (6 months)

**D'Amico A.** J Clin. Oncology 25:2420-22425, 2007

3 randomized prospective study of 1372 men of age 65 with localized prostate cancer treated with radiation therapy with and without Androgen Suppression therapy for 6 months showed increase in fatal myocardial infarctions in the ADT group

**Yu G, Triash A** 2 Parts Horm Mol Biol Clin Invest 2011; 8 (1) 425- 430 and 431-444