Instituto de Educação Médica

2009 Course on
Prostate Cancer (PCA)

March 7, 2009

Endocrine Therapy-Induced Metabolic Syndrome

practical implications

by

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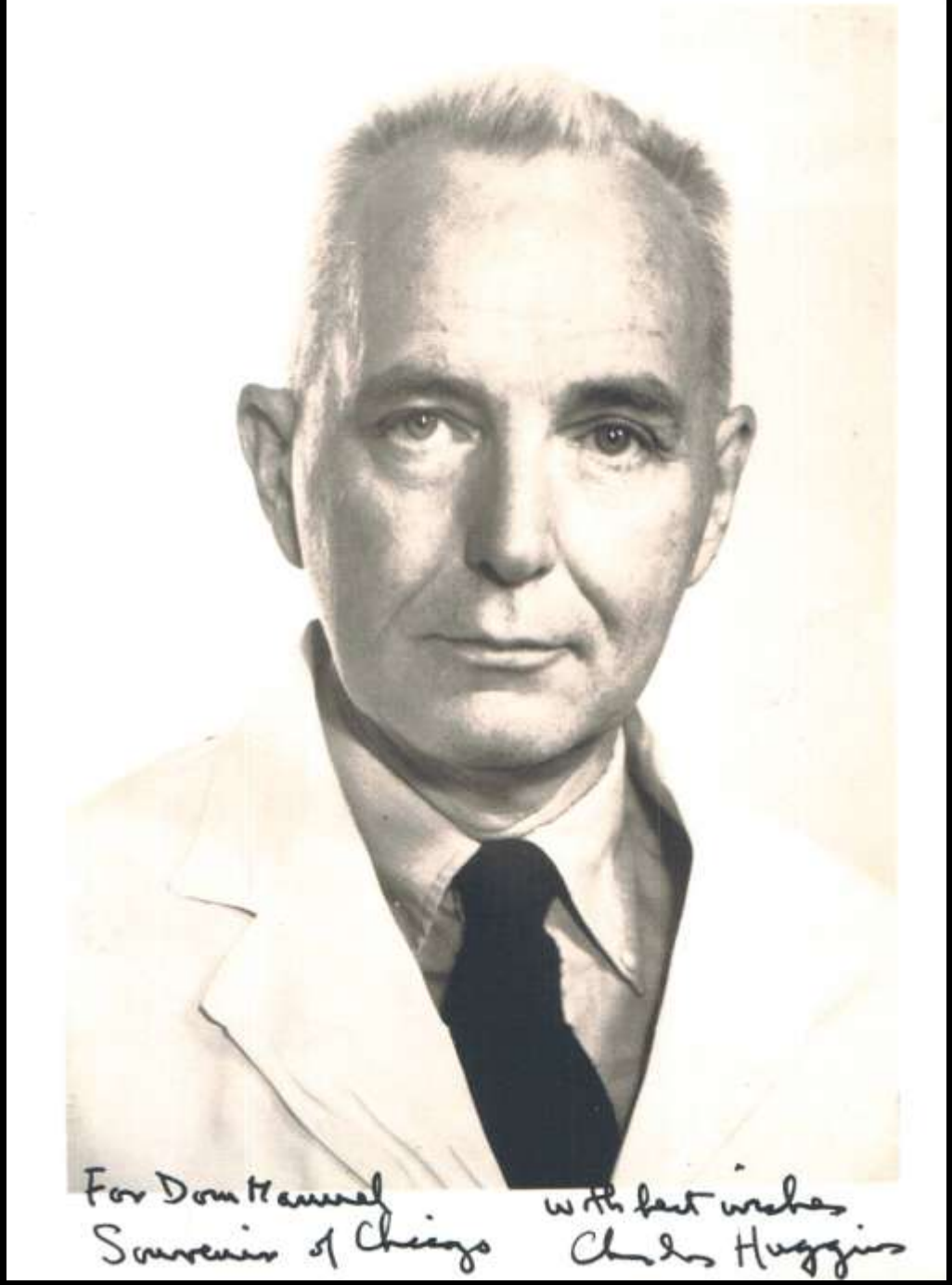

For Dom Mammel
Souvenir of Chicago
With best wishes
Charles Huggins

Outline of this Presentation

1.In Prostate Cancer Patients (PCP) Androgen Deprivation (AD) may lead to a special metabolic syndrome (SMS).

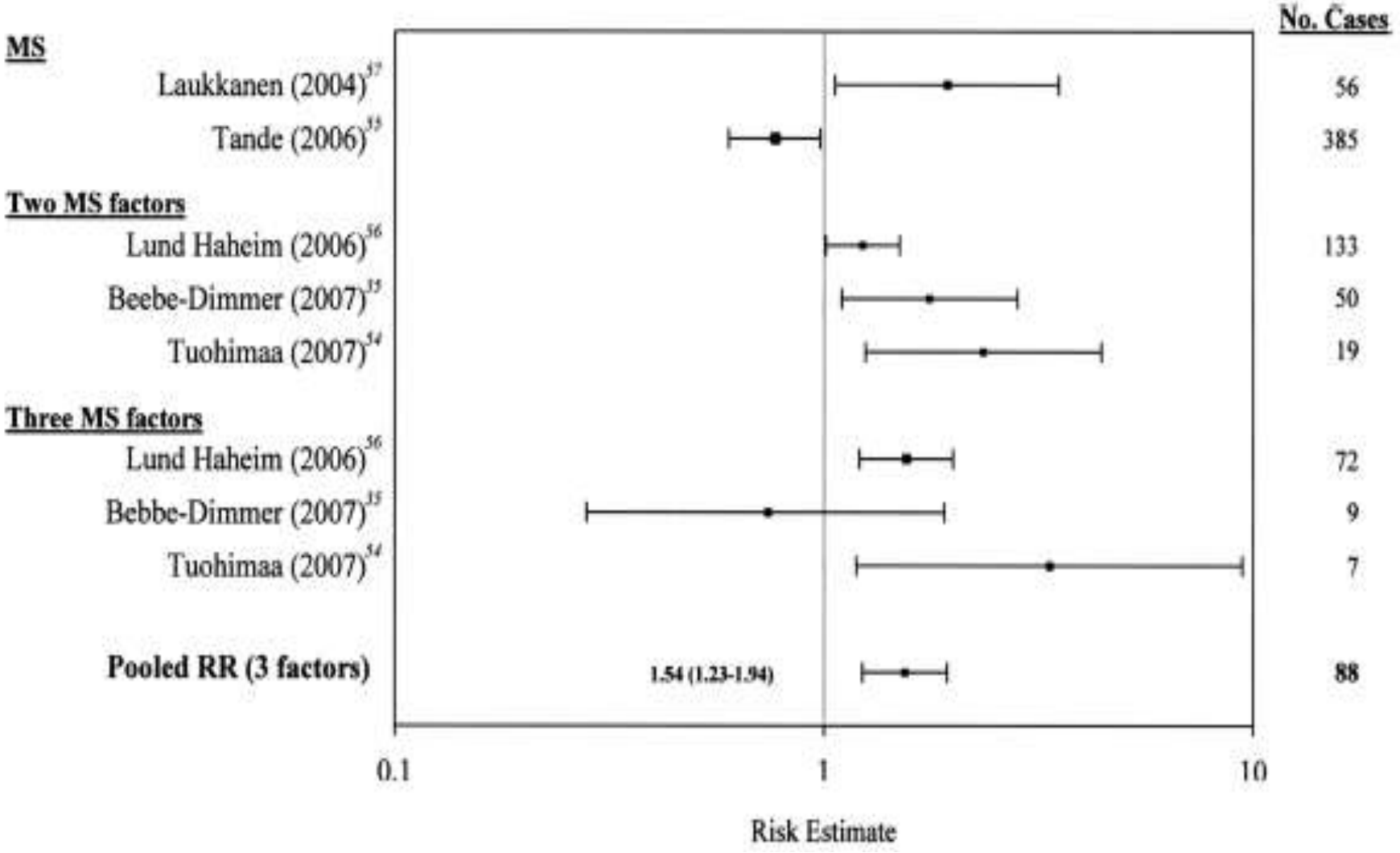
2.This SMS due to AD is an important risk factor for cardiovascular diseases and osteoporosis.

3.Important measures must be taken to properly select and treat the PCP that are candidates for AD.

Metabolic Syndrome in Men With Prostate Cancer undergoing long-term androgen-deprivation therapy

Metabolic syndrome was present in more than 50% of the men undergoing long-term ADT, predisposing them to higher cardiovascular risk.

Basaria MB et al. J Clinical Oncology 2006;24(24):3979-83



. Hsing AW et al. Obesity, metabolic syndrome, and prostate cancer. Am J Clin Nutr 2007;86(3):843S-57S

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

The classic metabolic syndrome is characterized by *visceral obesity, insulin resistance, low HDL cholesterol, high triglycerides, elevated C-reactive protein, and low adiponectin levels.*

Smith MR et al. Cancer 2008;112(10):2188-94

TABLE 1
Definitions of Metabolic Syndrome for Men

ATP III definition (≥3 of the following)

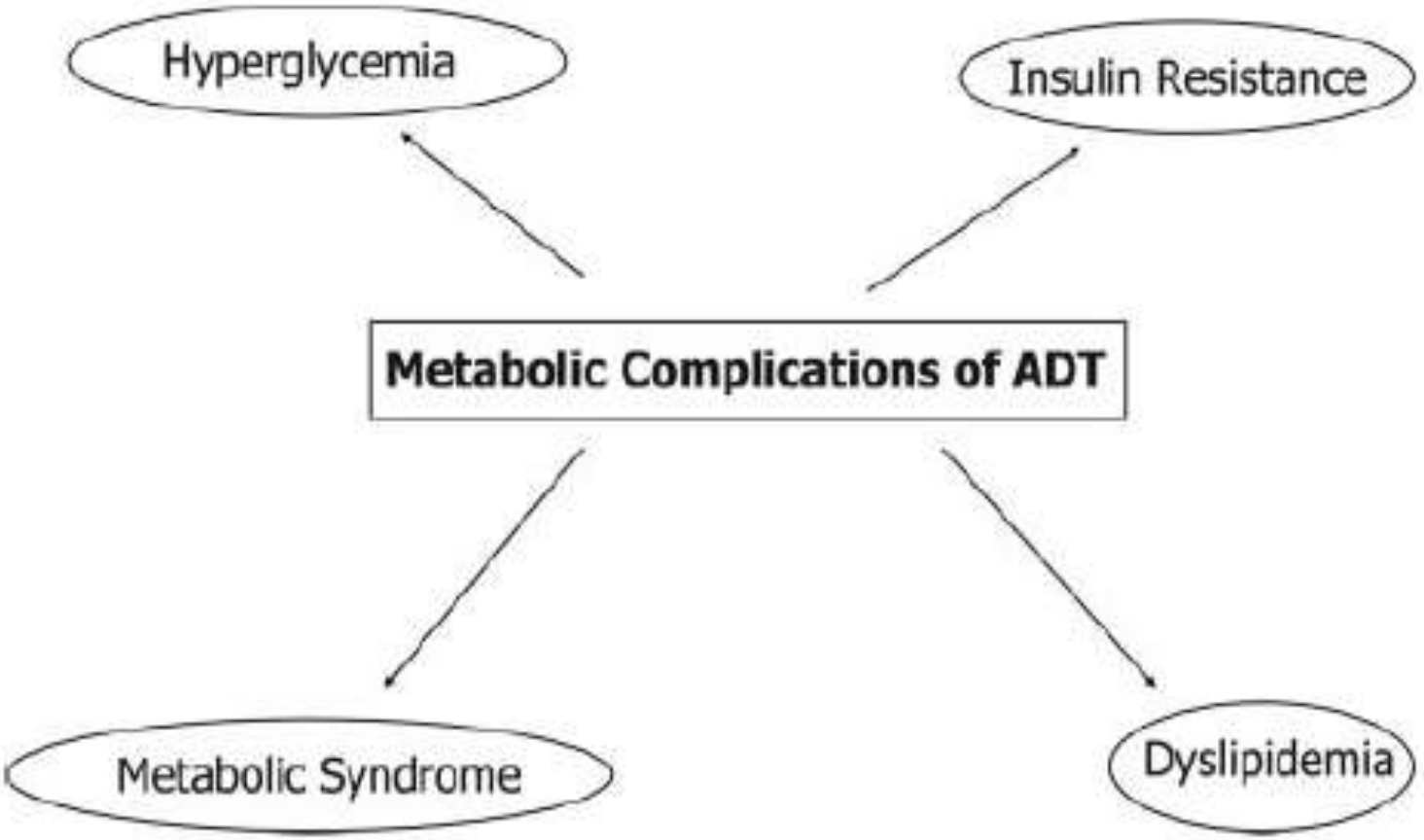
1. Waist circumference > 102 cm
2. Serum triglycerides ≥1.7 mmol/L
3. Blood pressure ≥130/80 mmHg
4. HDL cholesterol < 1.0 mmol/L
5. Serum glucose ≥6.1 mmol/L (≥5.6 mmol/L may be applicable)

WHO definition
Diabetes, IFG, IGT, or insulin resistance (assessed by clamp studies) and at least 2 of the following criteria:

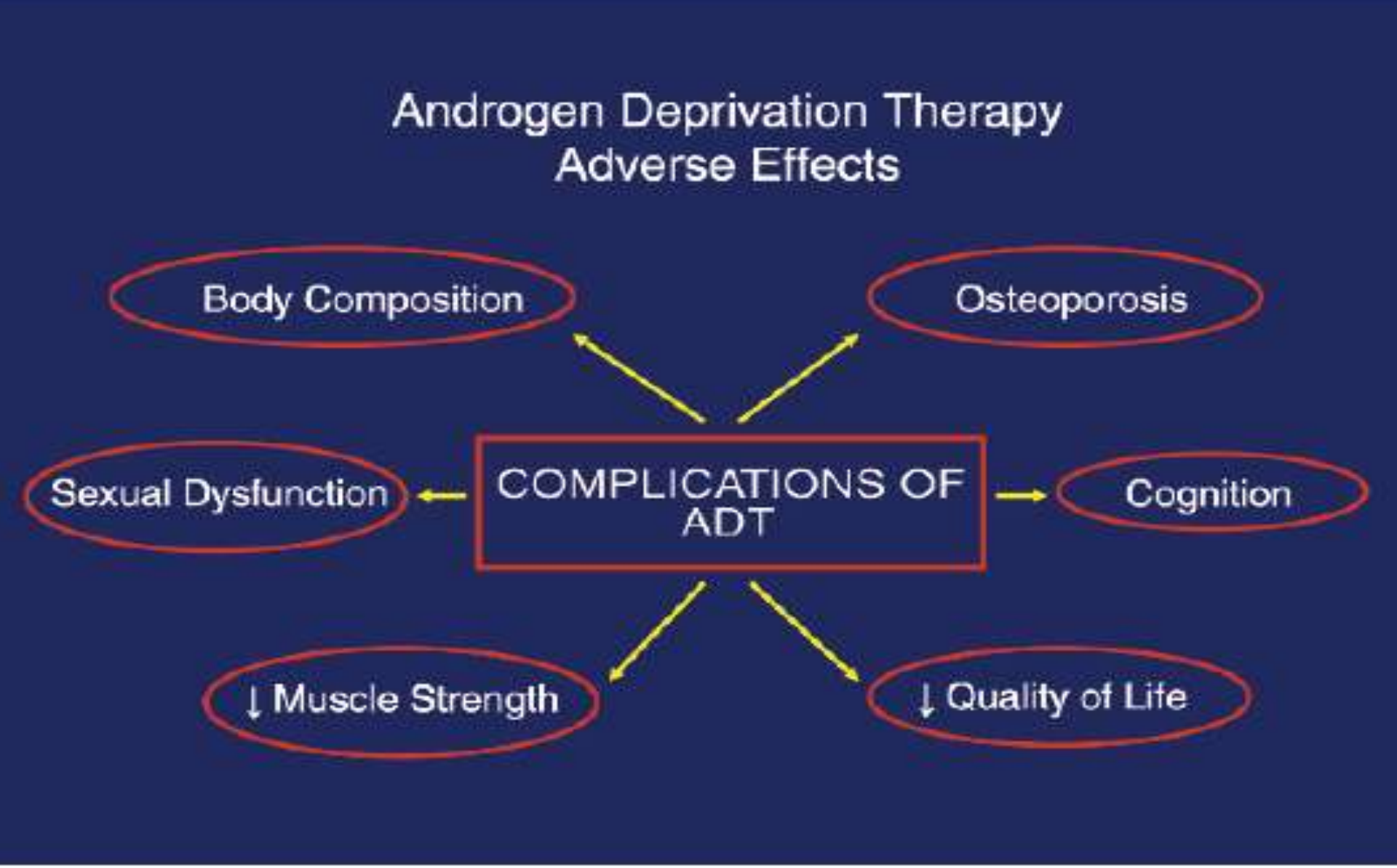
1. Waist-to-hip ratio > 0.90
2. Serum triglycerides ≥1.7 mmol/L
3. Blood pressure ≥140/90 mmHg
4. Urinary albumin excretion rate > 20 lg/minute or albumin-to-creatinine ratio ≥30 mg/g

ATP III indicates the National Cholesterol Education Program's Adult Treatment Panel; HDL, high-density lipoprotein; WHO, World Health Organization; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer. Smith MR et al. Cancer 2008;112(10):2188-2194



Androgen Deprivation Therapy in Prostate Cancer & Metabolic Risk for Atherosclerosis.
Sahani A, Basaria MB and Basaria S.J Clin Endocrinol Metab 2008;93(6):2042-2049



Androgen deprivation therapy, insulin resistance, and cardiovascular mortality: An Incovenient Truth. Basaria S. Journal Andrology 2008;29(5):534-9

Obesity, metabolic syndrome, and prostate cancer

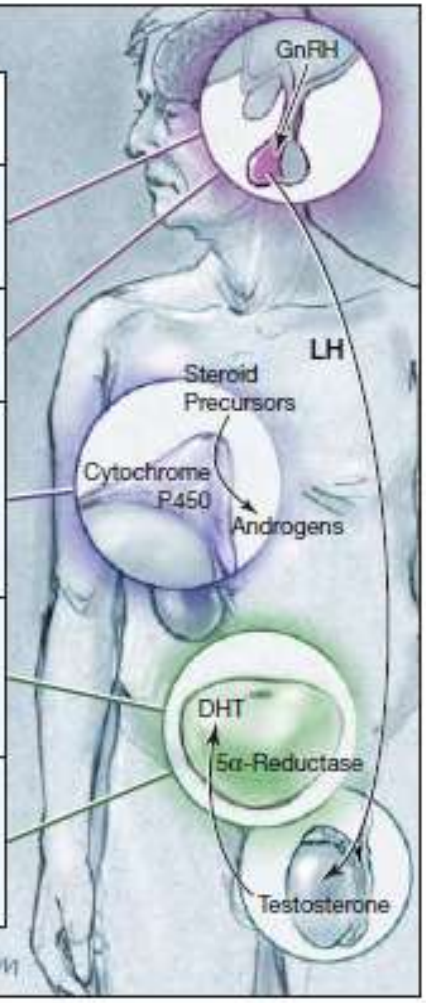
Obese men have an increased risk of high-grade prostate cancer and a lower concentration of serum testosterone,

which has been shown to be associated with increased risk of high-grade tumors

Hsing AW et al. Am J Clin Nutr 2007;86(3):843S-57S

Figure. Hormonal Interventions and Endocrine Axis in Prostate Cancer

Drug Class	Drugs	Site of Action	Mechanism of Action	Comments/Risks
Gondatropin-Releasing Hormone (GnRH) Agonists	Leuprolide Goserelin	Anterior Pituitary Gland	Decreases Release of LH Through Down-regulation of GnRH Receptors	Testosterone Surge
GnRH Antagonists	Abarelix*	Anterior Pituitary Gland	Directly Inhibits GnRH Receptors	Anaphylaxis
Adrenal Ablating Drugs	Ketoconazole	Adrenal Gland	Decreases Androgen Synthesis From Steroid Precursors Through Inhibition of Cytochrome P450 Enzymes	Administration Requires Steroid Supplementation to Prevent Adrenal Insufficiency
Androgen Receptor Antagonists	Flutamide Bicalutamide Nilutamide	Prostate Gland	Inhibits Androgen Receptor Ligand-Binding Domain Through Competitive Binding	Gynecomastia, Increased Liver Transaminases, and Mastodynia
5α-Reductase Inhibitors	Finasteride	Prostate Gland	Decreases Conversion of Testosterone to DHT Through Inhibition of 5α-Reductase	No Defined Role in Standard Care of Prostate Cancer



DHT indicates dihydrotestosterone and LH, luteinizing hormone. Asterisk indicates no longer available for new patients in the United States. Illustration based on original concept by Lydia Kibiuk.

Androgen deprivation therapy for prostate cancer. Sharifi N, Gulley JL, Dahut WL.JAMA 2005;294(2):238-244

TABLE 3. Testosterone levels during ADT in studies evaluating metabolic parameters

Author	Prospective studies		
	Baseline testosterone (ng/dl)	Testerone after 12 wk of ADT (ng/dl)	Testosterone assay
Smith *et al.* (17)	418	34	ICMA
Dockery *et al.* (25)	568	46	RIA
Smith *et al.* (26)	431	24	RIA

	Cross-sectional studies			
		TT (ng/dl)	FT (ng/dl)	Testosterone assay
Basaia *et al.* (27)	ADT	11	0.6	TT=RIA
	Non-ADT	325	12.3	FT=ED
	Controls	506	14.4	
Braga-Basaria *et al.* (37)				
	ADT	7.0	0.37	TT=RIA
	Non-ADT	325	12.5	FT=ED
	Controls	534	13.6	

Androgen Deprivation Therapy in Prostate Cancer & Metabolic Risk for Atherosclerosis.
Sahani A, Basaria MB and Basaria S.J Clin Endocrinol Metab 2008;93(6):2042-2049

Androgen deprivation therapy for prostate cancer

An earlier study comparing daily injections of a GnRH-A vs GnRH-A plus an androgen antagonist found survival benefit for combined androgen deprivation

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

Nonsteroidal antiandrogen monotherapy has a less severe adverseeffects profile than that of ADT, making it a potential alternative. In a metaanalysis comparing bicalutamide and castration, overall survival with bicalutamide monotherapy was statistically not worse than that with castration.

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

The American Society of Clinical Oncology states that monotherapy with a nonsteroidal antiandrogen may be discussed as an alternative to ADT.

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

However, a second large, randomized study found no survival benefit for combined androgen blockade when surgical castration was used. A meta-analysis of 27 randomized trials found a slight but significant 5-year survival benefit for combined androgen blockade.

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

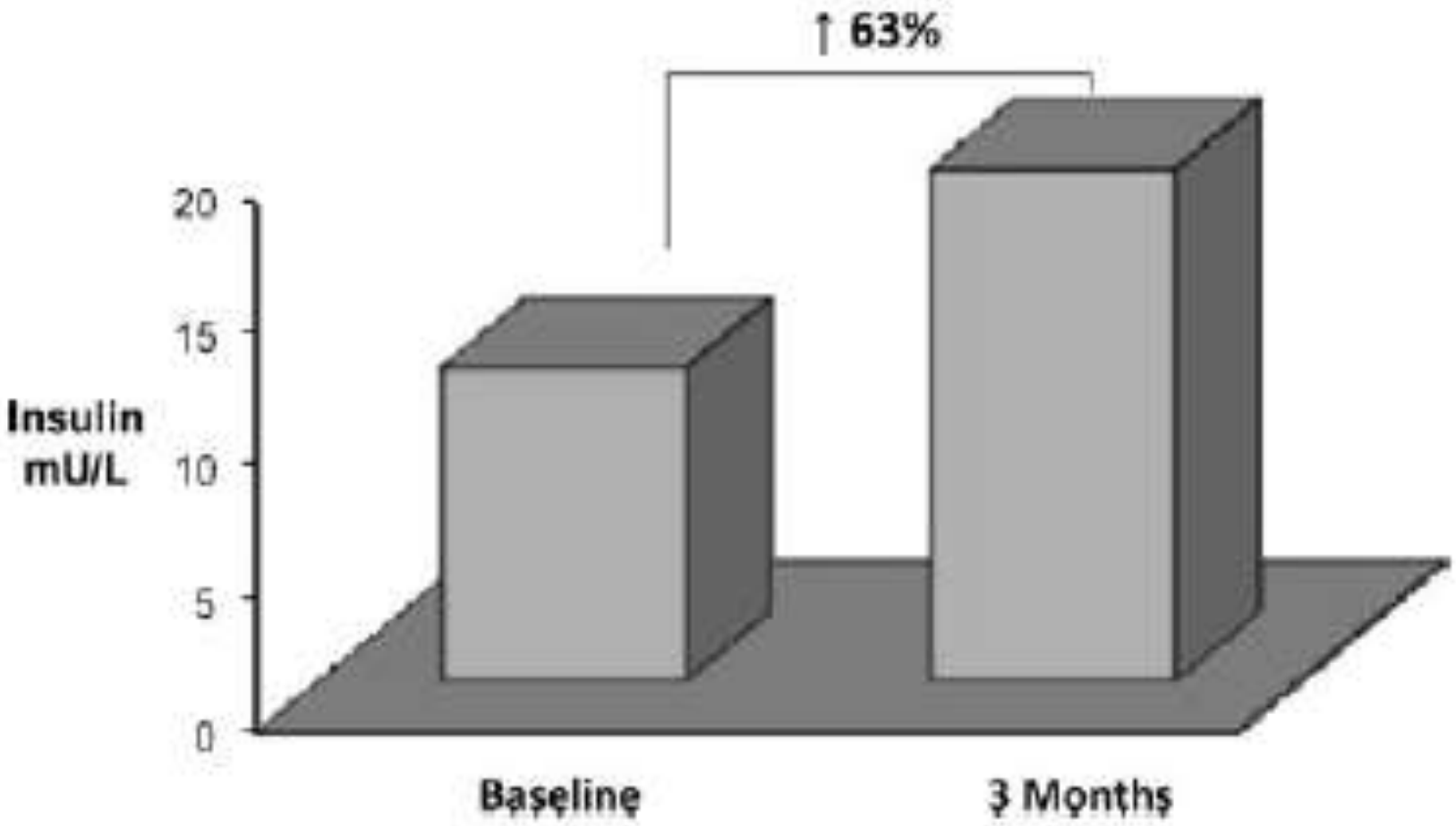
The **number needed to treat** with combined androgen blockade to prevent 1 death is estimated at **20 to 100**.

Sharifi N et al. JAMA 2005;294(2):238-244

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

The term metabolic syndrome does not appear to adequately describe the effects of GnRH agonists in men with prostate cancer. *In contrast to the metabolic syndrome, GnRH agonists increase subcutaneous fat mass, HDL cholesterol, and adiponectin, and do not alter the waist-to-hip ratio, blood pressure, or C-reactive protein level.*

Smith MR et al. Cancer 2008;112(10):2188-94



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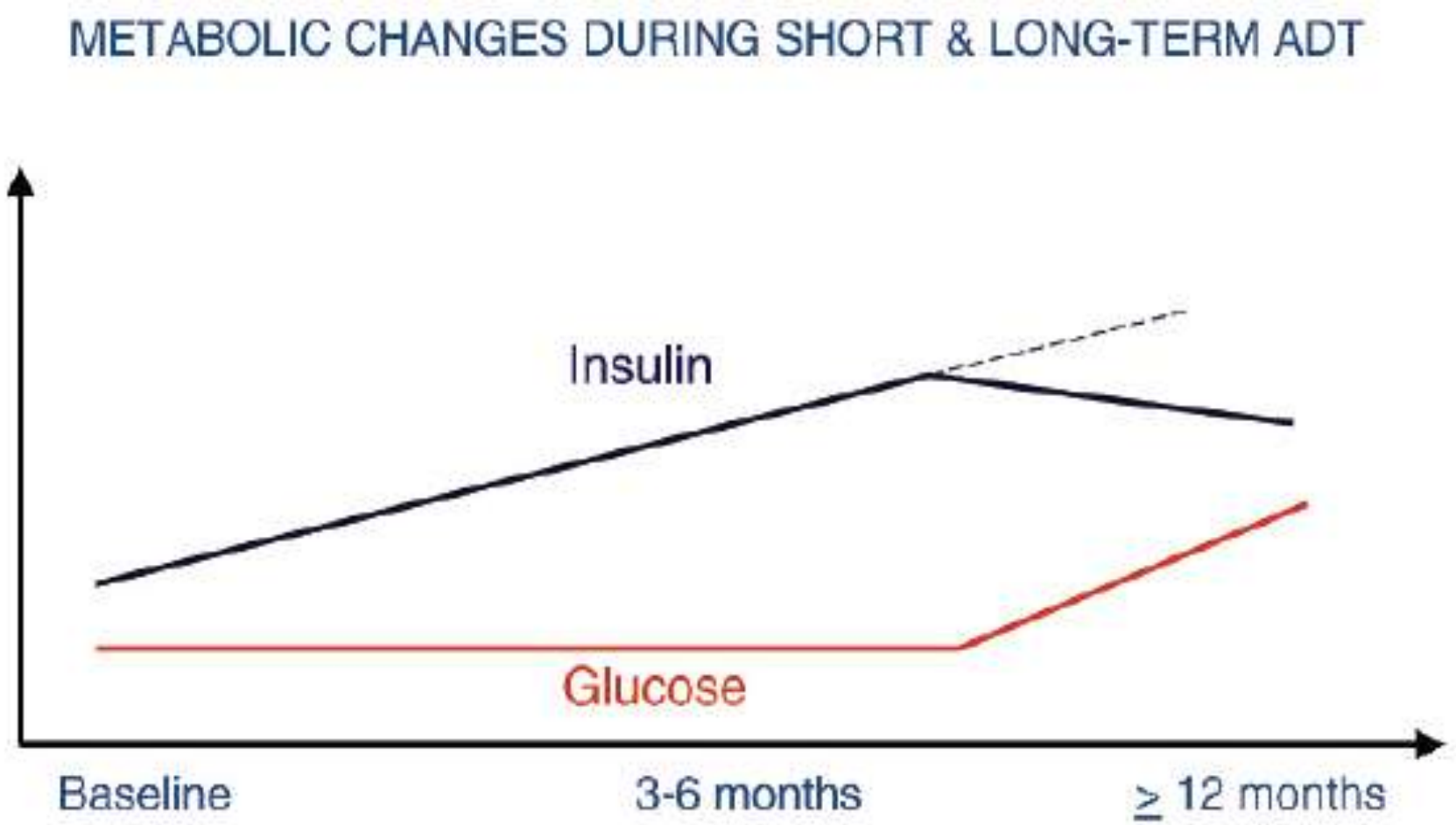

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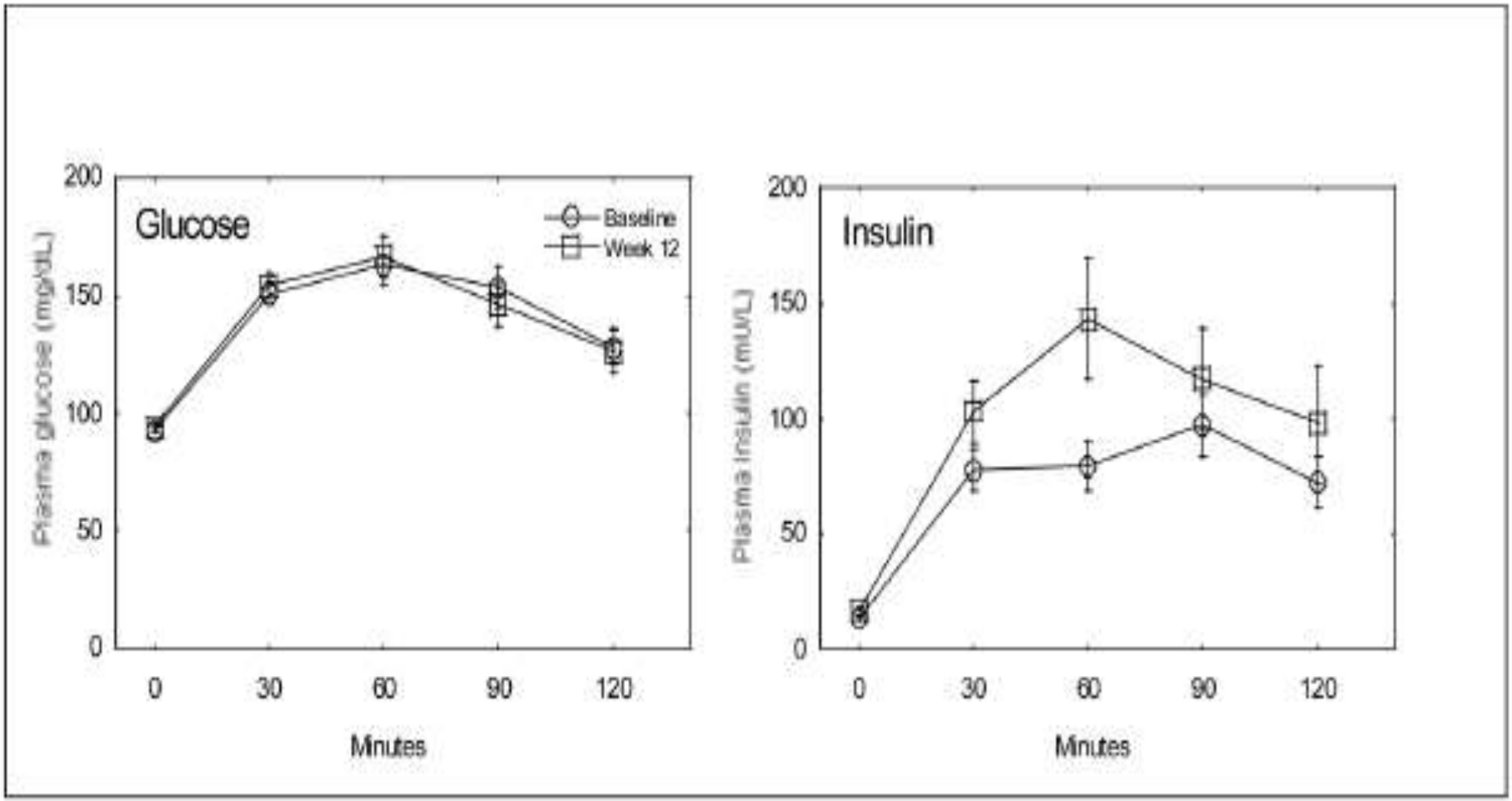
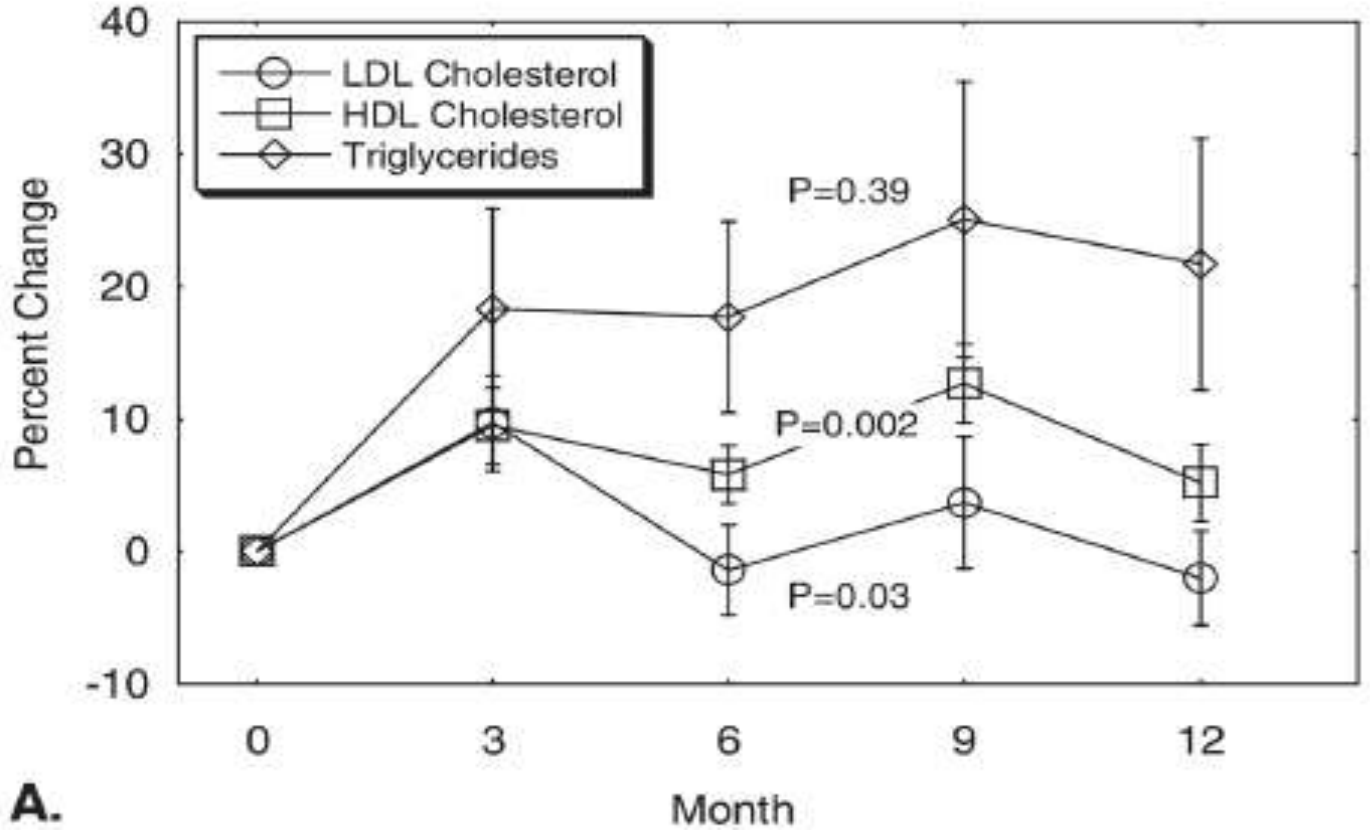


Adipocytokines, Obesity, and Insulin Resistance During Combined Androgen Blockade for Prostate Cancer: Evidence for a Distinct Hypogonadal Metabolic Syndrome?Smith MR et all.Urology 2008;71(2):318-322



Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer. Smith MR et al. Cancer 2008;112(10):2188-2194

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

GnRH agonists result in a pattern of metabolic alterations that are distinct from the metabolic syndrome.

Smith MR et al. Cancer 2008;112(10):2188-94

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

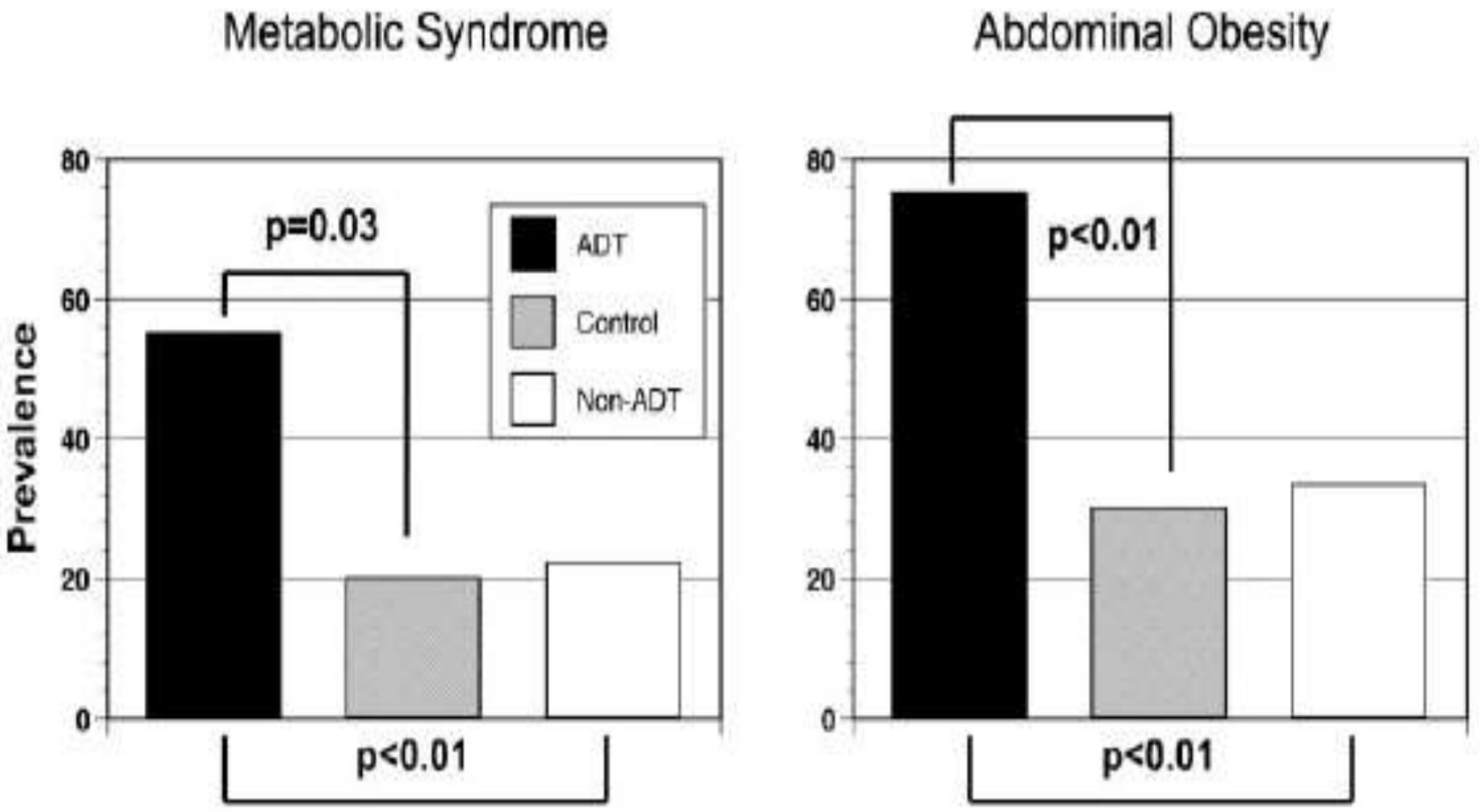
Several other observations from the current study also appear to distinguish the metabolic phenotype of GnRH agonist-treated men from the classic metabolic syndrome.

Smith MR et al. Cancer 2008;112(10):2188-94

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

First, leuprolide preferentially increased subcutaneous fat mass in our subjects, whereas the visceral fat accumulation is more closely associated with the metabolic syndrome

Smith MR et al. Cancer 2008;112(10):2188-94



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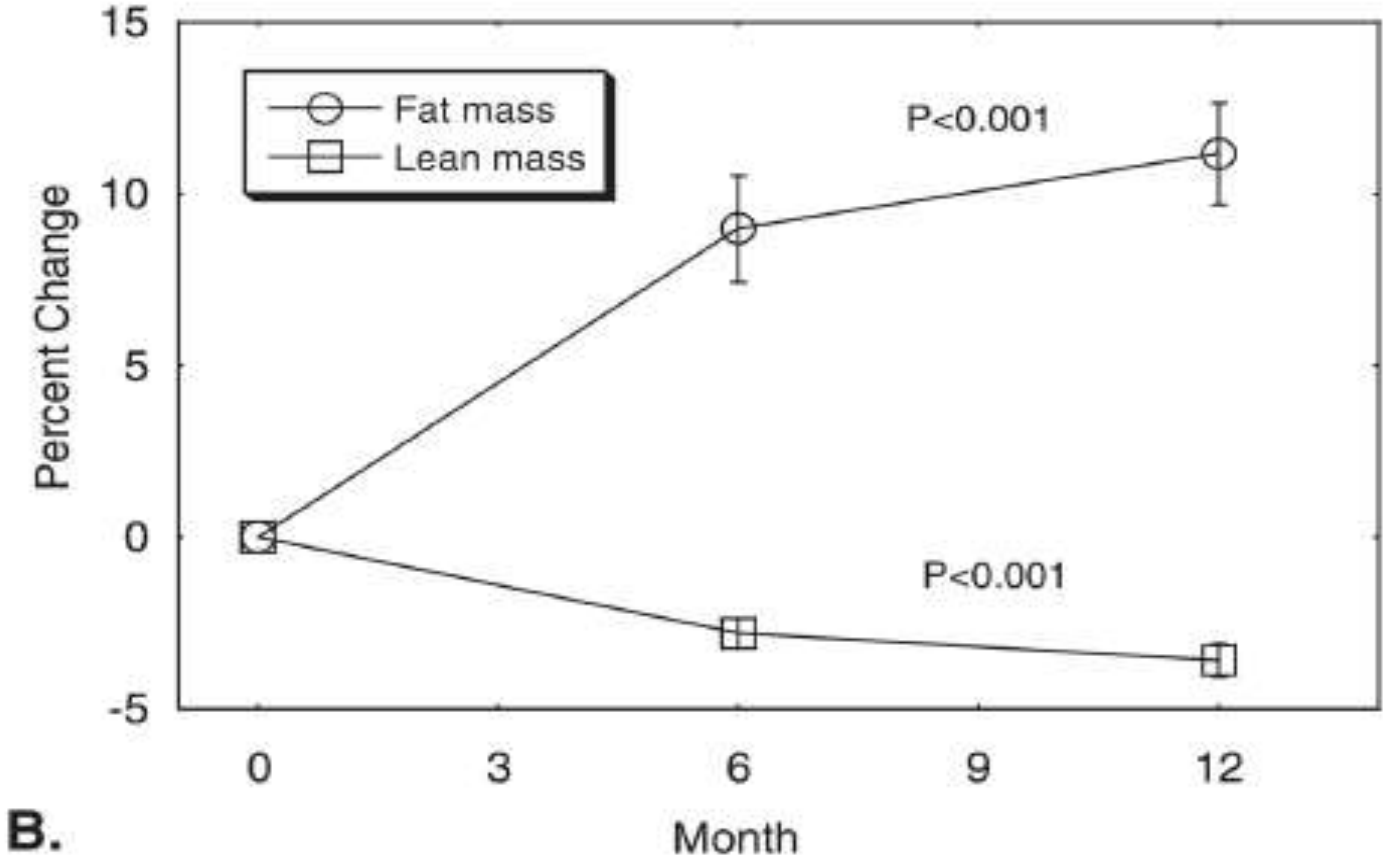

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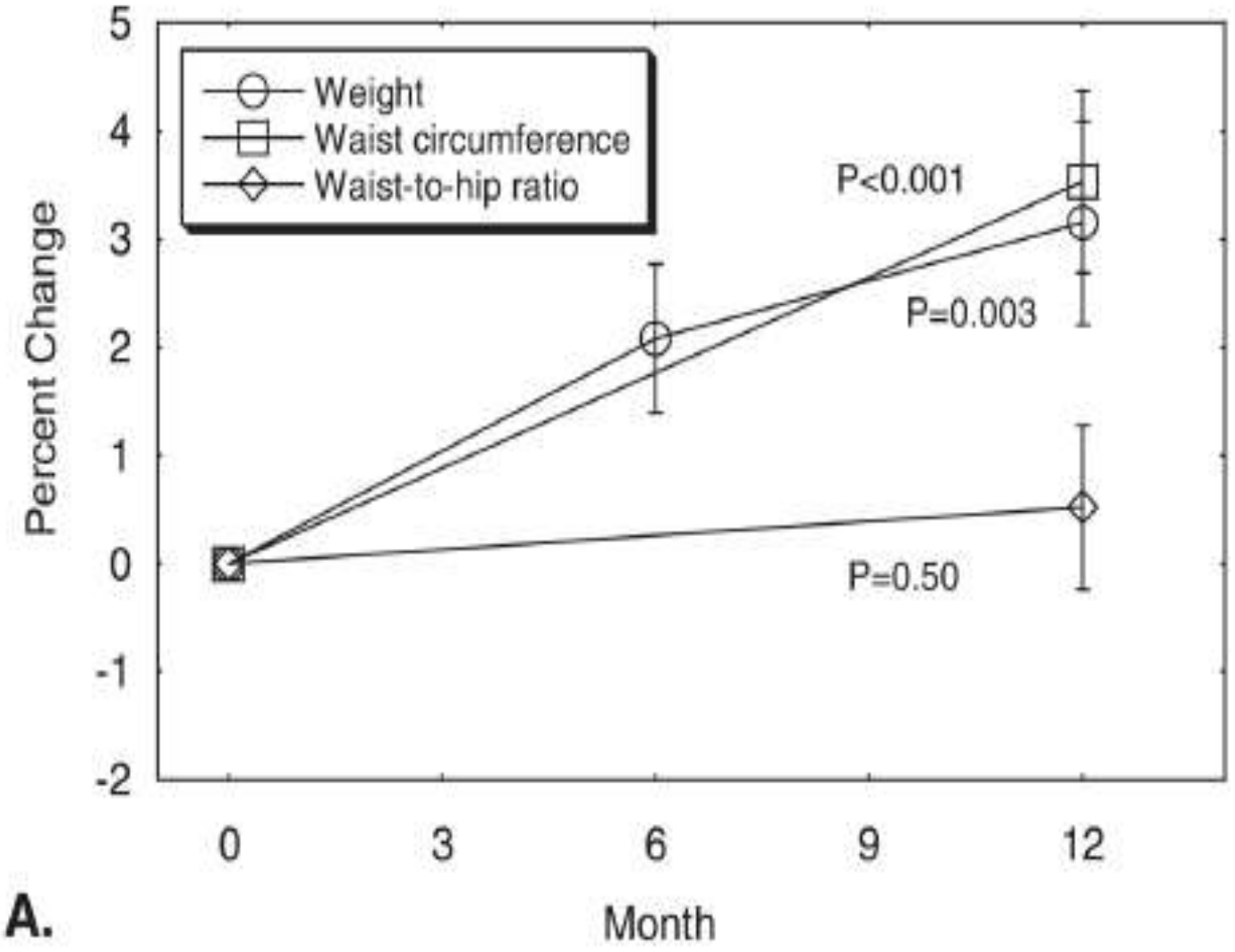
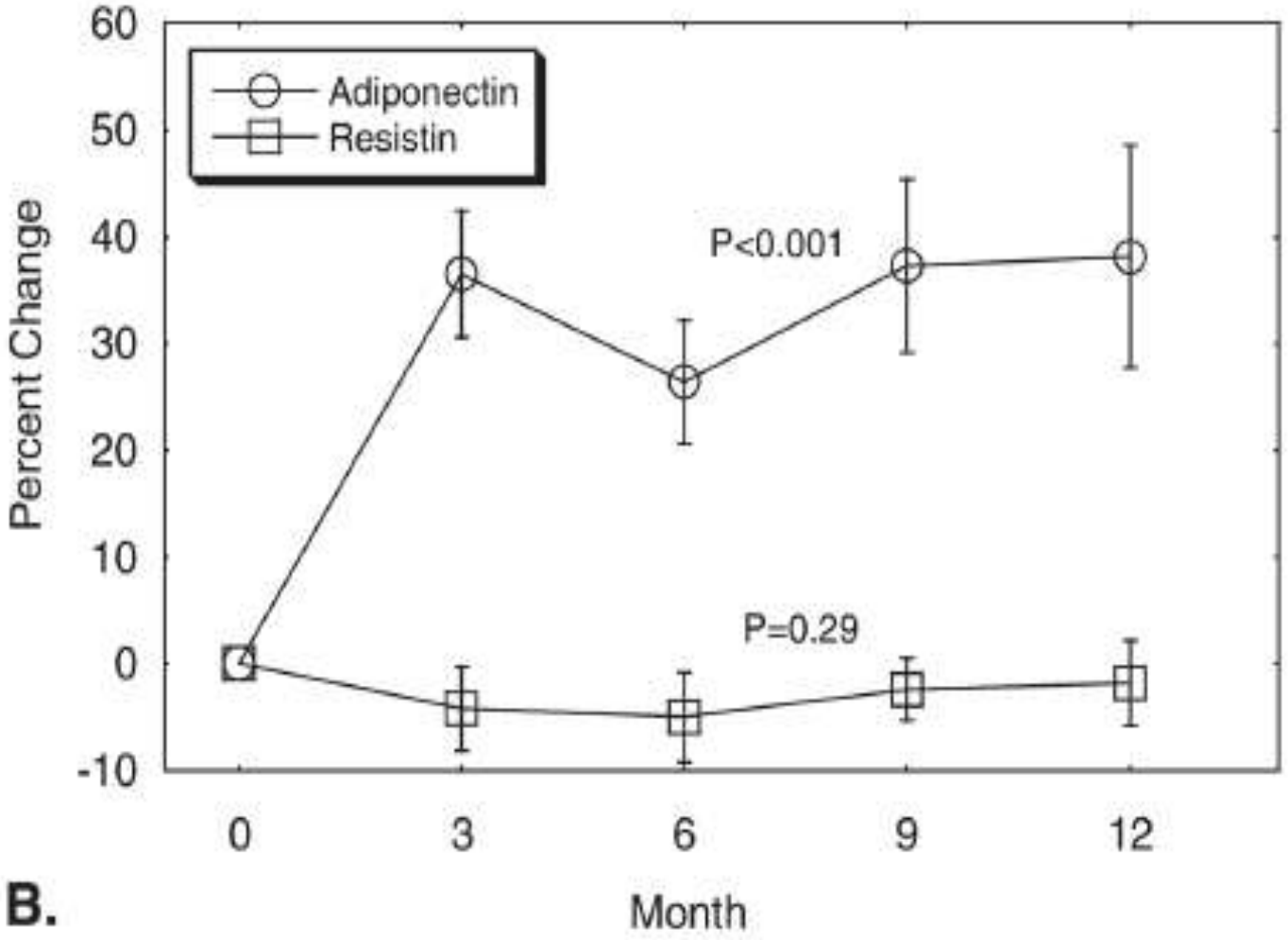


Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer. Smith MR et al. Cancer 2008;112(10):2188-2194

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

Second, leuprolide was found to significantly increase adiponectin levels but cross-sectional studies have reported that low adiponectin levels are associated with features of the metabolic syndrome.

Smith MR et al. Cancer 2008;112(10):2188-94



Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer. Smith MR et al. Cancer 2008;112(10):2188-2194

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

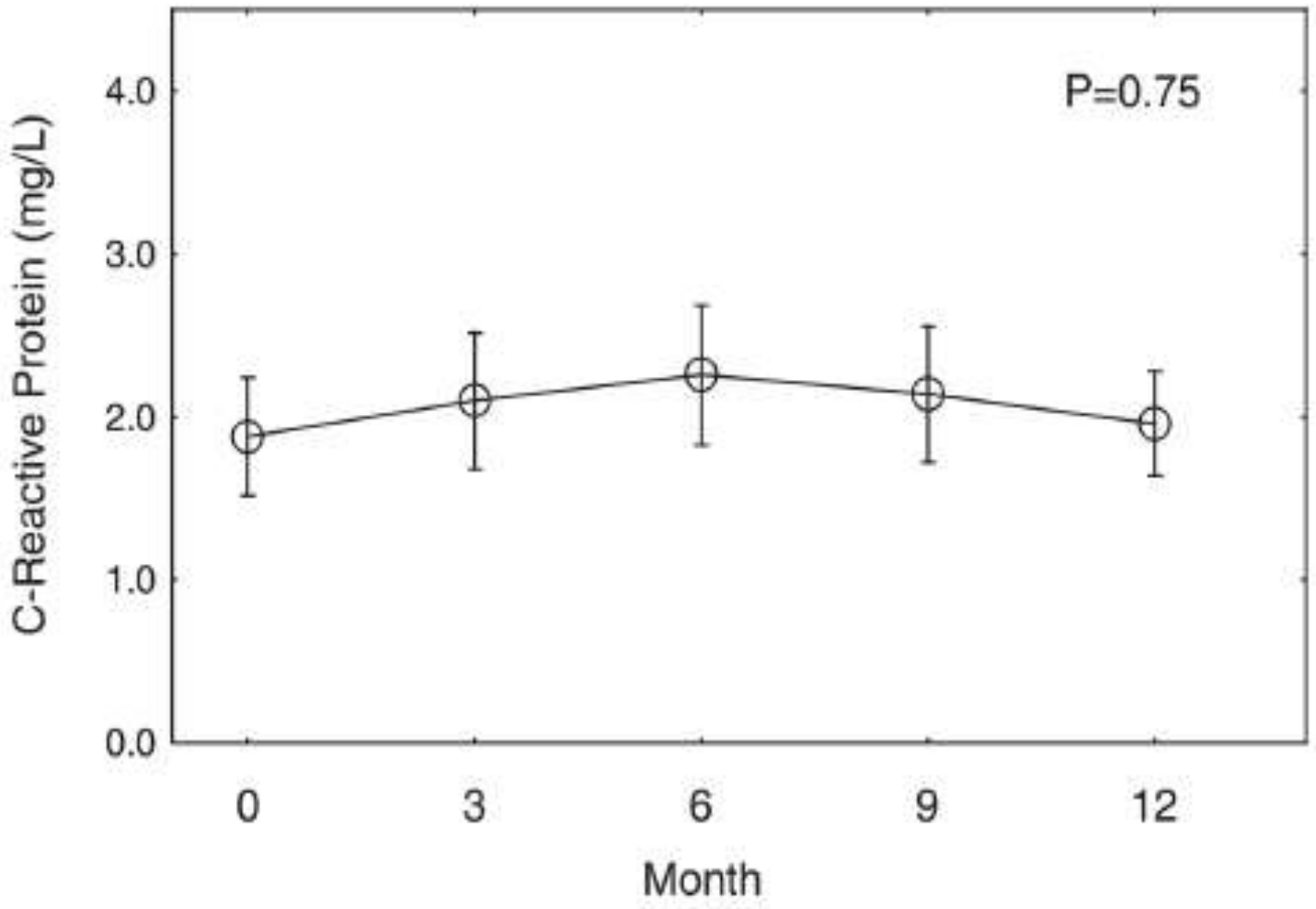
A recent prospective study reported that higher adiponectin levels are associated with greater cardiovascular mortality in men

Smith MR et al. Cancer 2008;112(10):2188-94

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

Third, leuprolide did not significantly alter C-reactive protein levels, whereas the metabolic syndrome is associated with elevation of C-reactive protein and other markers of inflammation

Smith MR et al. Cancer 2008;112(10):2188-94



Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer. Smith MR et al. Cancer 2008;112(10):2188-2194

Adipocytokines, Obesity, and Insulin Resistance During Combined Androgen Blockade for Prostate Cancer: Evidence for Distinct Hypogonadal Metabolic Syndrome?

We propose the term **"hypogonadal metabolic syndrome"** to distinguish the phenotype of GnRH agonist treated men from that of the classical defined metabolic syndrome

Smith MR et al.Urology 2008;71(2):318-322

Androgen deprivation therapy for prostate cancer

Men who were treated with AD had an increased risk of fracture starting 1 year after diagnosis

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

Several prospective trials have established that bone mineral density (BMD) is significantly decreased in men receiving ADT compared with a control group.

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

Men receiving or starting ADTshould be evaluated for risk of osteoporosis.

These risks include *family history of osteoporosis, lowbodyweight, prior fractures, excessive alcohol use, smoking, glucocorticoid use, low vitamin D levels, and other medical comorbidities.*

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

The number needed to harm for an occurrence of fracture 1 to 5 years after diagnosis was

28 for men treated with GnRH-A and

16 for men treated with orchiectomy

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

All men should start calcium and vitamin D supplementation.

Studies that examined total cholesterol and triglycerides found a significant increase in both of these measures.

Sharifi N et al. JAMA 2005;294(2):238-244

Table 2. Selected Adverse Effects of ADT and Evidence for Treatment

Adverse Effect	Source	Treatment for Adverse Effect	Study Results			
			Outcome	Control Arm	Intervention Arm	*P* Value
Hot flashes	Loprinzi et al,[9] 1994	Megestrol acetate*	Reduction in hot flashes	20%	74%	<.001
Osteoporosis and increased risk of fracture	Smith et al,[10] 2001	Pamidronate	BMD change	Decrease of 1.8%-8.5%	No change	≤.02
	Smith et al,[11] 2003	Zoledronic acid	BMD change	Decrease of 2.2%	Increase of 5.6%	<.001

Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density.
*May cause disease progression.

Androgen deprivation therapy for prostate cancer. Sharifi N, Gulley JL, Dahut WL.JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

Hot flashes can significantly affect quality of life for men undergoing ADT. Up to 80% of patients undergoing treatment with GnRH-A report hot flashes and up to 27% report this as the most troublesome adverse effect.

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

A randomized, double-blind, placebo-controlled trial of megestrol acetate for prevention of hot flashes in women with a history of breast cancer and men undergoing ADT for prostate cancer showed a reduction in hot flashes in 74% of the megestrol group and 20% of the placebo group by intention to treat (*P*.001).

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy for prostate cancer

However, PSA levels have been reported to increase in men who commence megestrol while receiving ADT and decline with discontinuation of megestrol

Sharifi N et al. JAMA 2005;294(2):238-244

Hot Flashes

In women we have good results with monthly injections of 150 mg of **medroxyprogesterone acetate** ("*Depo-Provera*")

SSRIs (Venlafaxine,Paroxetine,Fluvoxamine)

Gabapentin *("Neurontin")*

Estrogens

PSA

"Our data demonstrated that the prevalence and sum of MS components were inversely associated with serum PSA levels."

" In particular, serum PSA levels were significantly affected by abdominal obesity and impaired fasting glucose levels "

Kim Y-J . Int.J.Urology 2008;15:905-909

several studies have demonstrated **the inverse correlation between PSA levels and obesity**

our results demonstrated that obesity and insulin resistance significantly influenced PSA levels,

and in addition that **MS was significantly associated with decreased PSA levels.**

Kim Y-J . Int.J.Urology 2008;15:905-909

Androgen deprivation therapy for prostate cancer

Gynecomastia occurs in 1% to 16% of men treated with ADT. Treatment options include breast irradiation, surgery, and tamoxifen. Surgical therapies are also an option. Other adverse effects of ADT include dry eyes, body hair loss, and vertigo

Sharifi N et al. JAMA 2005;294(2):238-244

Androgen deprivation therapy, insulin resistance, and cardiovascular mortality: An incovenient truth

Men with existing coronary artery disease may benefit from cardiology consultation prior to initiation of ADT.

Basaria S. Journal of Andrology 2008;29(5):534-9

Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer

We recommend that clinicians evaluate and treat individual cardiovascular disease risk factors without regard for whether a prostate cancer survivor meets the criteria for diagnosis of metabolic syndrome

Smith MR et al. Cancer 2008;112(10):2188-94

Metabolic Syndrome in Men With Prostate Cancer undergoing long-term androgen-deprivation therapy

Recent studies have shown that approximately half of men with PCa die of causes unrelated to the cancer itself, with CVD being the most common noncancer etiology. An earlier report had shown that, after the deaths directly attributable to PCa and its complications, CVD was the second leading cause of death (responsible for27%of the deaths).

Basaria MB et al. J Clinical Oncology 2006;24(24):3979-83

Androgen deprivation therapy, insulin resistance, and cardiovascular mortality: An incovenient truth

It is recommend that physicians screen all their patients, those already receiving or planning to receive ADT, for diabetes by checking fasting glucose and HbA1c (at baseline and then every 3 months). Counseling for diet and exercise should be given to all subjects.

Basaria S. Journal of Andrology 2008;29(5):534-9

Androgen deprivation therapy in prostate cancer and metabolic risk of atherosclerosis

Furthermore, prevention of these metabolic complications with diet, exercise, and insulin sensitizers needs to be studied. Prospective studies are under way to answer some of these questions.

Shahani S et al. J Clin Endocrinol Metab 2008;93(6):2042-9

Summary

1. **The benefits of AD in PCP are not devoid of life threatning risks.**
2. **Most PCP die from CVD, not from their cancer**
3. **Urologists who treat PCP should always ask the cooperation of cardiologists, endocrinologists and rheumatologists.**
4. **Urologists should always advise their patients to have a proper diet (Calcium suplements, low carbohydrates, low fat) and exercise a lot.**
5. **The prevention of several diseases is as good as the treatment of one single disease.**

Thank you

Have a nice day