

# Μεταβολικό Σύνδρομο ως Αιτιολογία Παθήσεων του Γεννητικού Συστήματος

➤ Επιπτώσεις στον Όρχη




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**Διευθυντής Ουρολογικής Κλινικής**  
**Πανεπιστημίου Ιωαννίνων.**

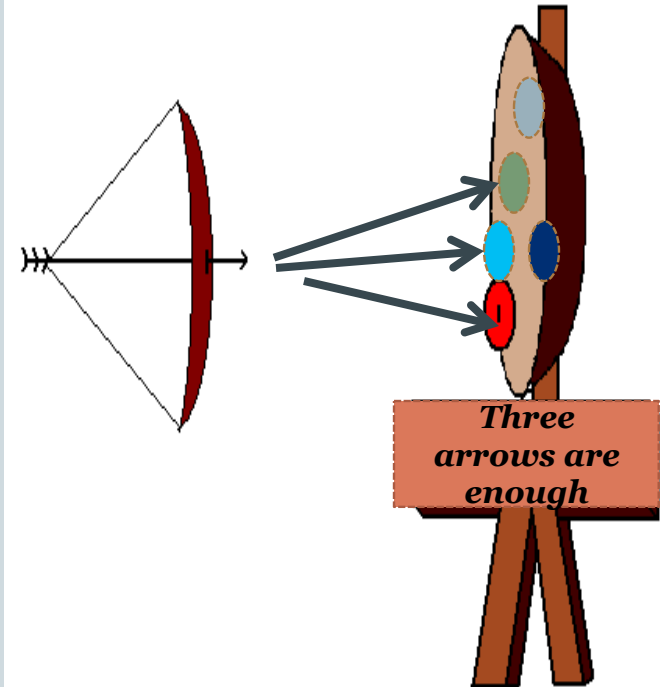
# Δήλωση συμφερόντων



Δεν υπάρχει καμία σύγκρουση συμφερόντων σχετικά με αυτήν την παρουσίαση

# Criteria for Diagnosis of Metabolic Syndrome

- Visceral obesity defined by waist circumference (population and country specific definitions)
- Triglycerides  $\geq 150$  mg/dL
-  high density lipoprotein cholesterol levels men  $\leq 40$  mg/dL
- blood pressure  $\geq 130$  and/or 85 mmHg
- fasting glucose  $\geq 100$  mg/dL

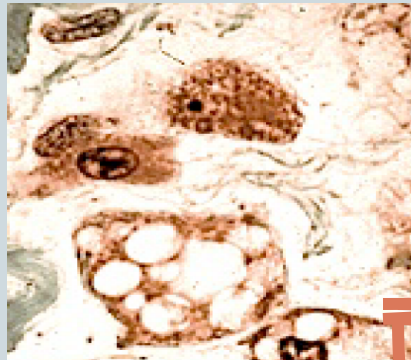


*Review Article*

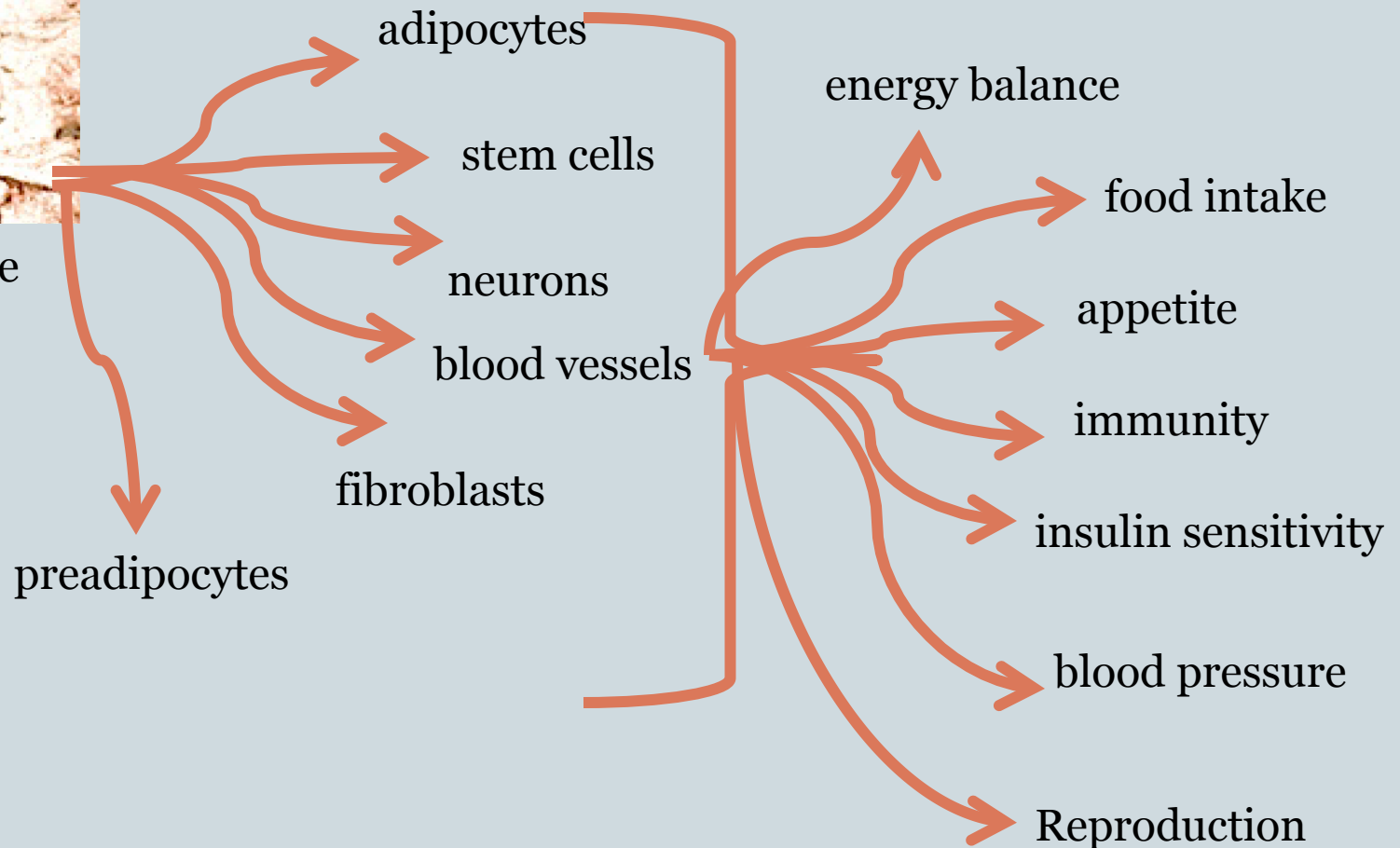
# **Androgens and Adipose Tissue in Males: A Complex and Reciprocal Interplay**

**Caterina Mammi,<sup>1</sup> Matilde Calanchini,<sup>2</sup> Antonella Antelmi,<sup>1</sup> Francesca Cinti,<sup>1</sup>  
Giuseppe M. C. Rosano,<sup>1</sup> Andrea Lenzi,<sup>3</sup> Massimiliano Caprio,<sup>1</sup> and Andrea Fabbri<sup>2</sup>**

# Adipose tissue as an endocrine tissue



Adipose tissue



# White Adipose Tissue and Brown Adipose Tissue



White Adipose Tissue



Providing fuel for energy generation

Brown Adipose Tissue



adaptive thermogenesis

# Subcutaneous vs Visceral Fat



**THE GOOD**  
(Subcutaneous Fat)



Protecting Health

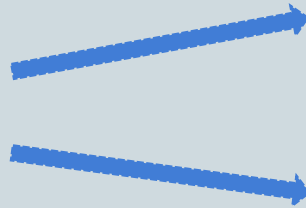
**THE BAD**  
(Visceral Fat)



cardiovascular and metabolic  
complications

# Metabolic Syndrome (MS) & Hypothalamo – Pituitary Axis (HPA)

**MS**



Testosterone



SHBG



Men with MS have a greater decline of free testosterone and total testosterone and SHBG compared to men who were never classified as obese.

- Derby, CA., et.al: Clin.Endocrinol.65:125-131, 2006.
- Gray A., et.al: J.Clin.Endocrinol.Metab.73:1016-1025, 1991.



# Effect of distribution of adipose tissue on plasma androgen levels



<u>Relationship between</u>	<u>Type of Relationship</u>
Plasma Testosterone <u>with</u> Visceral Fat	Inverse
Free Testosterone <u>with</u> Visceral Fat	Inverse
SHBG <u>with</u> Visceral Fat	Inverse
Plasma Total Testosterone <u>with</u> Subcutaneous Adipose Tissue	Inverse

- Nielsen T.L.,et.al: J.Clin.Endocrinol.Metab.92:2696-2705, 2007.
- Haffner S.M.:Int J.Obes.Relat.Metab.Disord.24(Suppl.2): S56-S58,2000.

# Central Effects of Metabolic Syndrome and LH Pulsatility

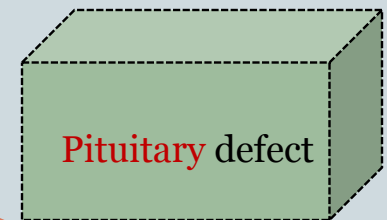
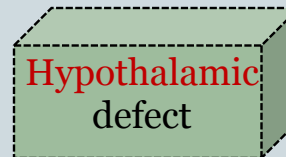
Total and Free Testosterone levels in Obese men were lower compared to non-obese men independent of the decrease in SHBG



Failure at the **Hypothalamic – Pituitary** level

Unchanged or decreased LH

LH Pulsatility remains undisturbed in MS-men



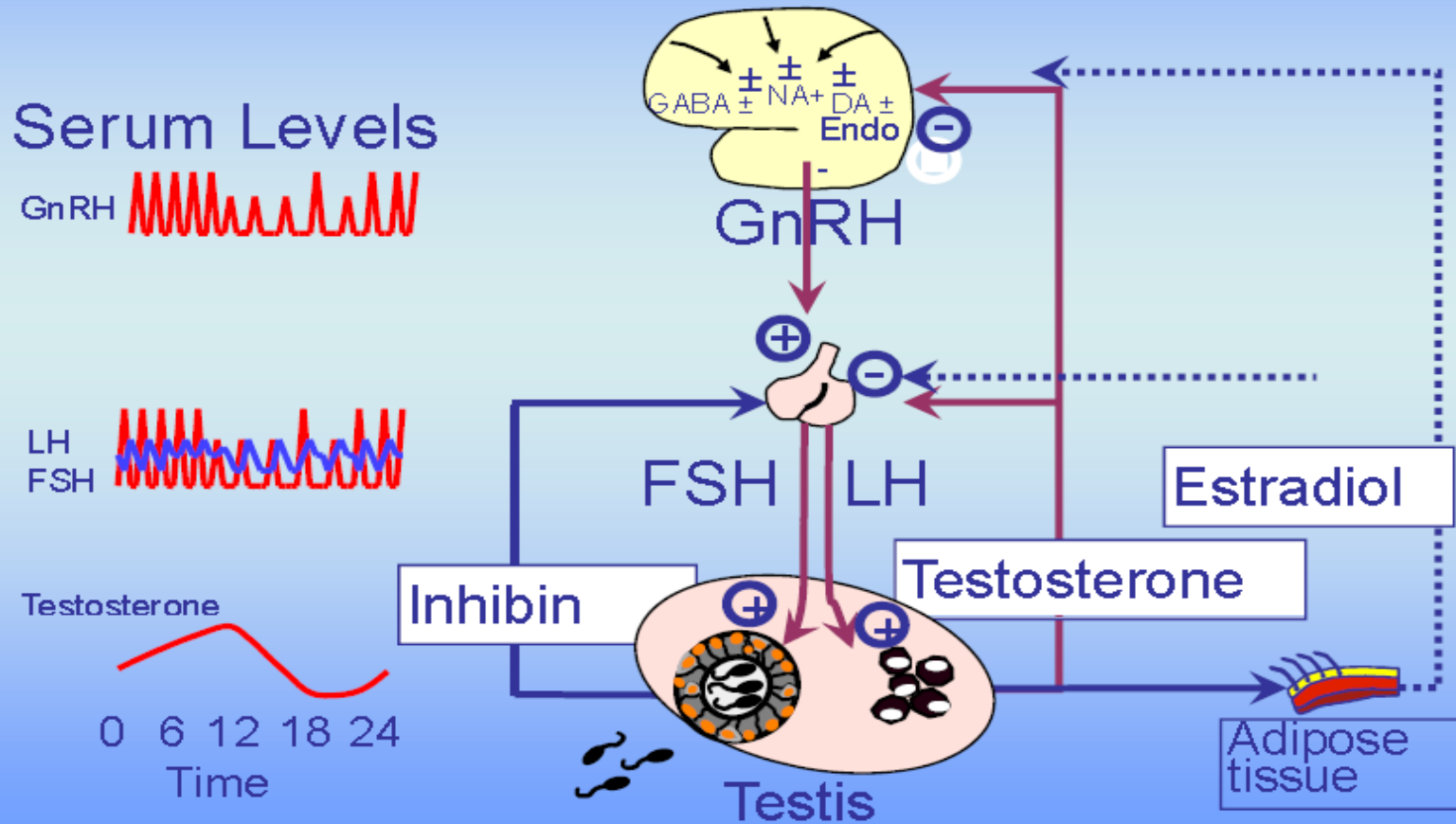
LH Amplitude is significantly attenuated

LH  
FSH



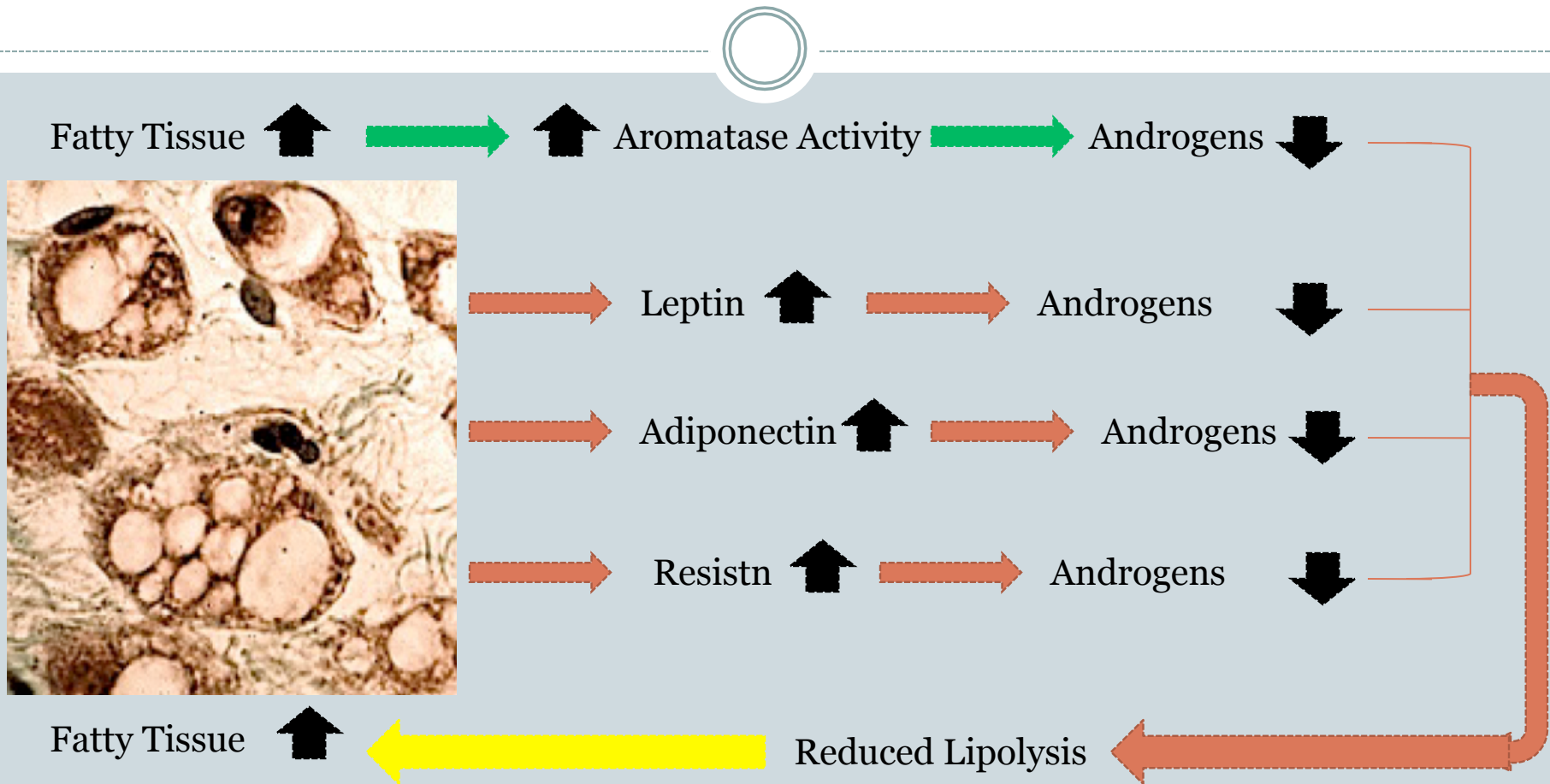
- Wu E.C: J.Clin.Endocrinol.Metab:93,2737-2745,2008
- Giagulli et.al:J.Clin.Endocrinol.Metab:73,1016-1025,1994

# Regulation of Testicular Function





# The Role of Adipose Tissue Derived Hormones (A VICIOUS CYCLE)

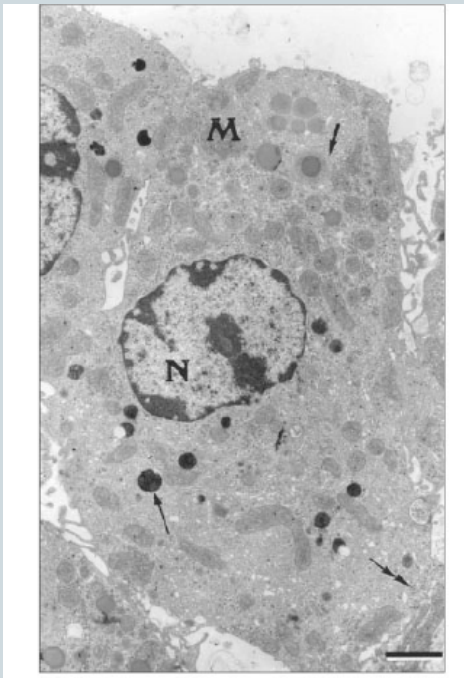


- Isidori A.M.,et.al: J.Clin.Endocrinol.Metab.84:3673-3680,1999
- Luc J.Martin: Endocrine (2014), 46:16-28

# Metabolic Syndrome and Leydig Cell?



LH



Leydig Cell

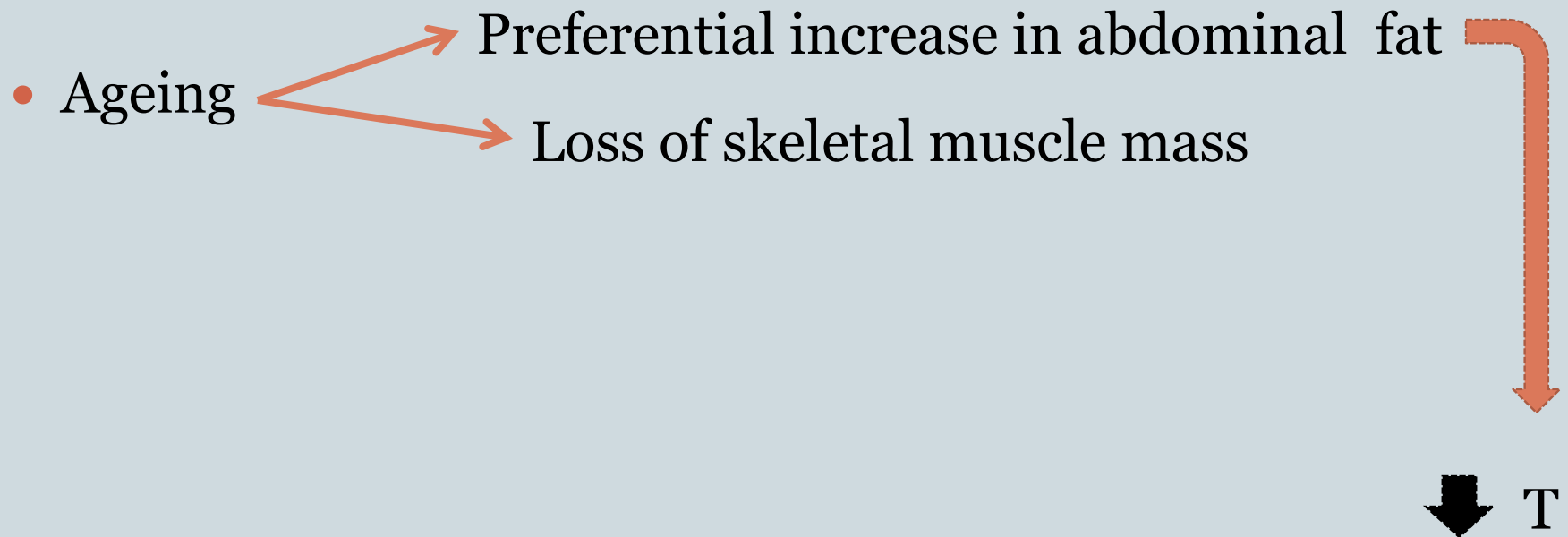


T (↓ in MS)

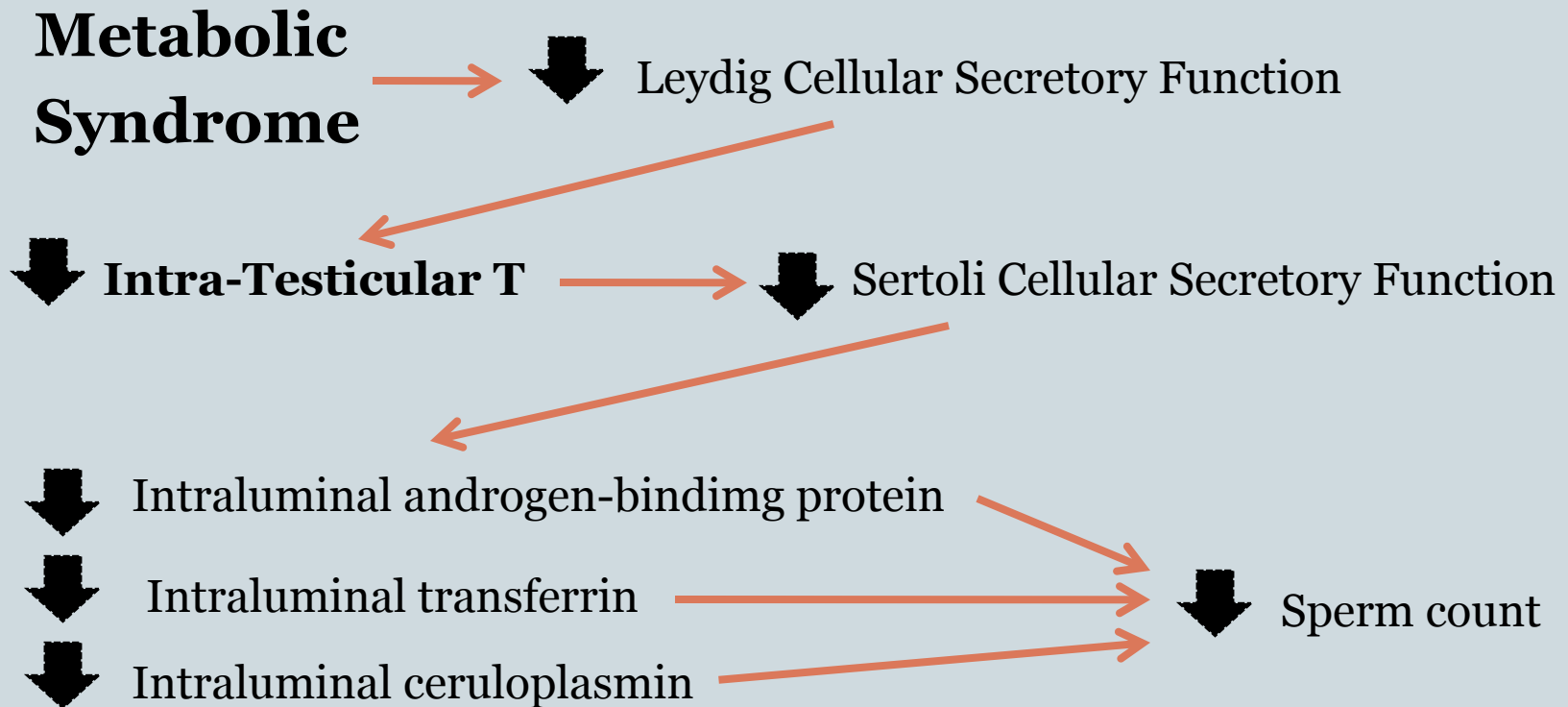


InsL3 (No Change in MS)

# Ageing and Plasma Testosterone



# Metabolic Syndrome and Spermatogenesis



➤ In addition, the decreased concentrations of testosterone, inhibin B and AMH in patients with MS confirm an impaired Leydig and Sertoli cell function.

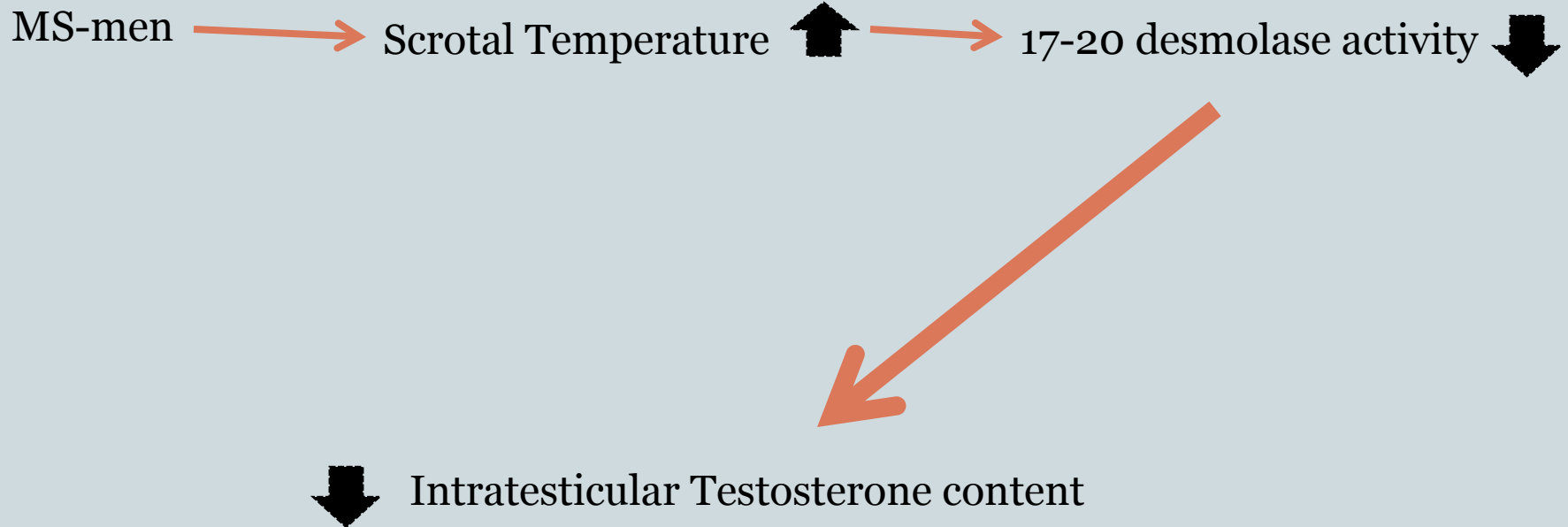
- Jenssen et al Fertile Sterile, 82:863-870,2004
- Robeva R,et.al: Andrologia,(2012),44: 329-334



# **Twenty-four-hour monitoring of scrotal temperature in obese men and men with a varicocele as a mirror of spermatogenic function**

**Andrea Garolla, Mario Torino, Paride Miola, Nicola Caretta, Damiano Pizzol, Massimo Menegazzo, Alessandro Bertoldo, and Carlo Foresta\***

# Metabolic Syndrome and Spermatogenesis



# The Metabolic Syndrome has an easy target: The sensitive and weak human spermatogenesis



There are fundamental differences between spermatogenesis in the human and other species that result in production of lower quality sperm overall. This may make spermatogenesis in humans inherently more vulnerable to disruption by the metabolic syndrome, as there is little room for manoeuvre in terms of maintaining the production of adequate numbers of normal sperm, and thus fertility. Such concerns are reinforced by the evidence that sperm counts in humans may have declined substantially over the past 50 years or so.

# Metabolic Syndrome and Epididymal Sperm Maturation Process

**Metabolic Syndrome**

→ High binding capacity of type-1 cannabinoid receptor

↓  
Fast saturation of the receptor

↓  
Sperm Potential for Progressive Motility

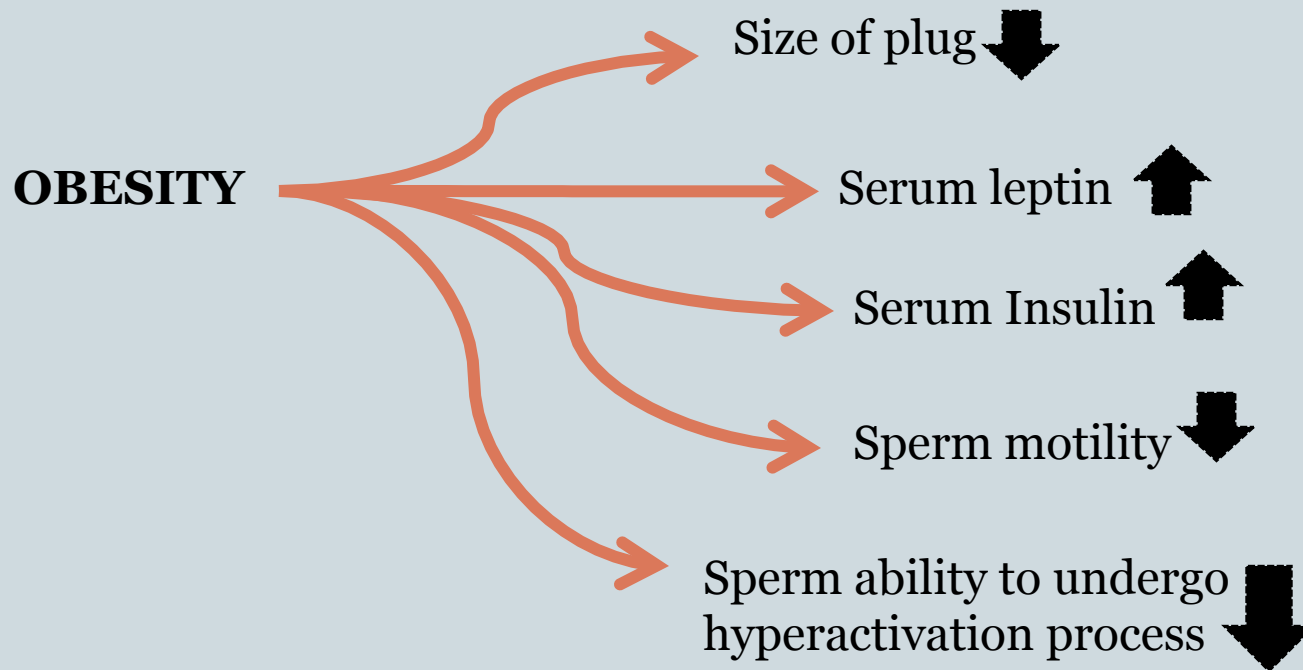


BIOLOGY OF REPRODUCTION 82, 96–104 (2010)

## **Diet-Induced Obesity in Male Mice Is Associated with Reduced Fertility and Potentiation of Acrylamide-Induced Reproductive Toxicity<sup>1</sup>**

**Burhan I. Ghanayem,<sup>2,3</sup> Re Bai,<sup>3</sup> Grace E. Kissling,<sup>4</sup> Greg Travlos,<sup>5</sup> and Undi Hoffler<sup>3</sup>**

# Metabolic Syndrome and Epididymal Sperm Maturation Process





RESEARCH

Open Access

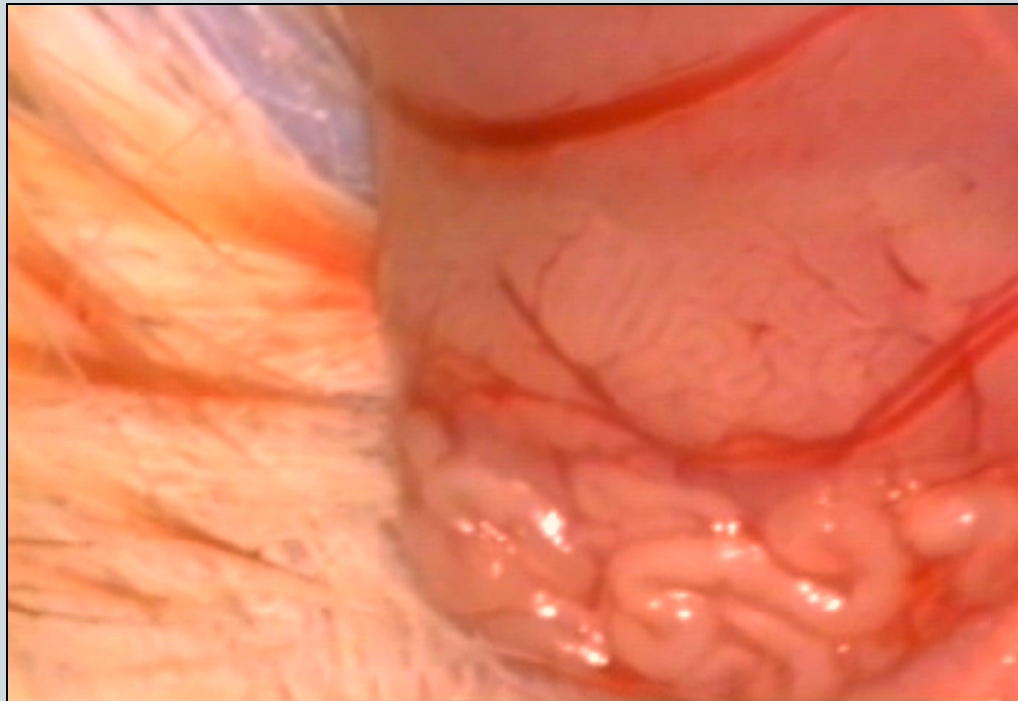
# Glutamate-induced obesity leads to decreased sperm reserves and acceleration of transit time in the epididymis of adult male rats

Glaura SA Fernandes<sup>1</sup>, Arielle C Arena<sup>2\*</sup>, Kleber E Campos<sup>3</sup>, Gustavo T Volpato<sup>3</sup>, Janete A Anselmo-Franci<sup>4</sup>, Débora C Damasceno<sup>5</sup> and Wilma G Kempinas<sup>2</sup>

# Obesity and Epididymal Sperm Maturation Process



The sperm transit time was accelerated in obese rats.







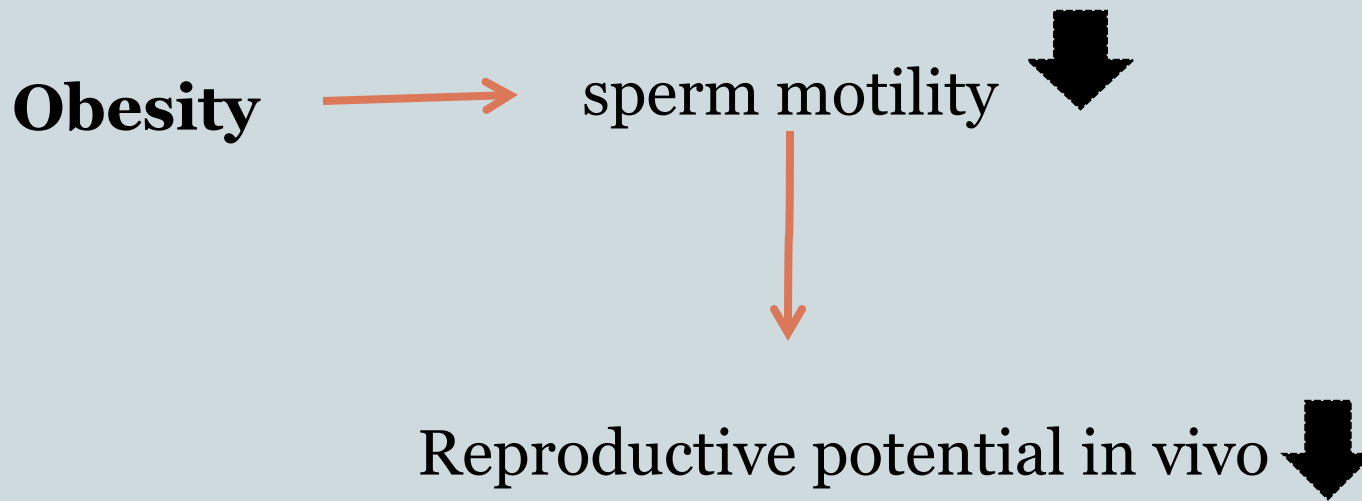
RESEARCH

Open Access

# Diet-induced obesity in rats leads to a decrease in sperm motility

Carla DB Fernandez<sup>1,2\*</sup>, Fernanda F Bellentani<sup>2</sup>, Glaucia SA Fernandes<sup>1,2</sup>, Juliana E Perobelli<sup>1,2</sup>, Ana Paula A Favareto<sup>1,2</sup>, André F Nascimento<sup>3</sup>, Antonio C Cicogna<sup>3</sup>, Wilma DG Kempinas<sup>2</sup>

# Obesity and sperm motility



# Metabolic Syndrome and Epididymal Sperm Maturation Process

Metabolic Syndrome

↓ Leydig Cellular Secretory Function

↓ Sertoli Cellular Secretory Function

↓ Intraepididymal T

↓ Intraepididymal ABP

Defect in Epididymal Sperm Maturation Process

➤ There is a clear evidence of an effect of metabolic syndrome on epididymal function.

• Rosa Mari 'a Viguera-Villasenor, et.al: *acta histochemica* 113 (2011) 214–220

## ORIGINAL ARTICLE

### Correspondence:

Birgitte Lindman, Division of Environmental Medicine, Norwegian Institute of Public Health, PO Box 4404 Nydalen, N-0403 Oslo, Norway.  
E-mail: birgitte.lindeman@fhi.no

### Keywords:

gene expression, infertility, obesity, sperm chromatin structure assay

Received: 1-Nov-2013

Revised: 29-Nov-2013

Accepted: 2-Dec-2013

# Impaired sperm chromatin integrity in obese mice

<sup>1</sup>N. Duale, <sup>1</sup>I.-L. Steffensen, <sup>1</sup>J. Andersen, <sup>2</sup>A. Brevik, <sup>1</sup>G. Brunborg and <sup>1</sup>B. Lindeman

<sup>1</sup>Division of Environmental Medicine, Norwegian Institute of Public Health, and <sup>2</sup>Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, Oslo, Norway

# Metabolic Syndrome and Male Reproductive Potential



Sperm Count



Sperm Motility



DNA Fragmentation



**Male  
Reproductive  
Potential**



Hindawi Publishing Corporation

Advances in Urology

Volume 2013, Article ID 836121, 6 pages

<http://dx.doi.org/10.1155/2013/836121>

## *Research Article*

# **Weight Loss and Melatonin Reduce Obesity-Induced Oxidative Damage in Rat Testis**

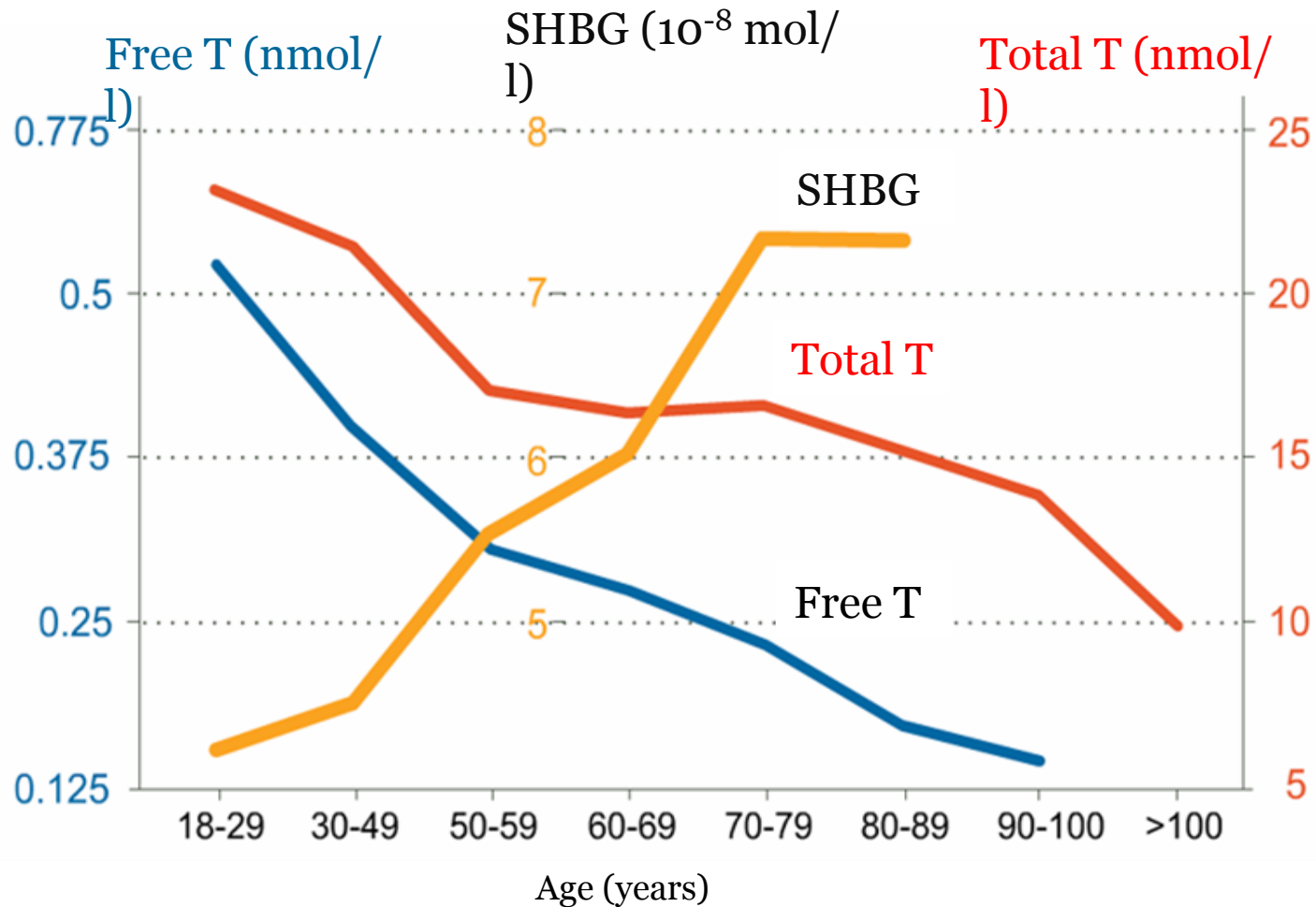
**Dogan Atilgan,<sup>1</sup> Bekir S. Parlaktas,<sup>1</sup> Nihat Uluocak,<sup>1</sup> Fikret Erdemir,<sup>1</sup> Sahin Kilic,<sup>1</sup> Unal Erkorkmaz,<sup>2</sup> Huseyin Ozyurt,<sup>3</sup> and Fatma Markoc<sup>4</sup>**

# Protective effects of melatonin on oxidative stress induced by Metabolic syndrome



- Experimentally created obesity caused oxidative stress and both melatonin and weight loss reduced oxidative stress parameters in rat testes.
- These results may arise a thought that melatonin has beneficial effects on inflammation that reduces neuromediators migration due to oxidative stress

# Endocrine changes with age





# Obesity and hypogonadism: cause or effect?



T predict the development of



SHBG



MS (when BMI < 25kg/m<sup>2</sup>)



# In contrast

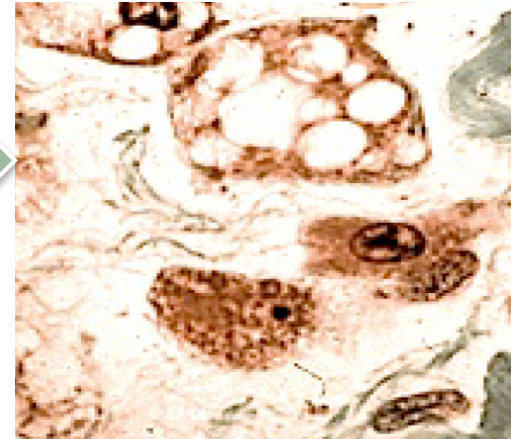
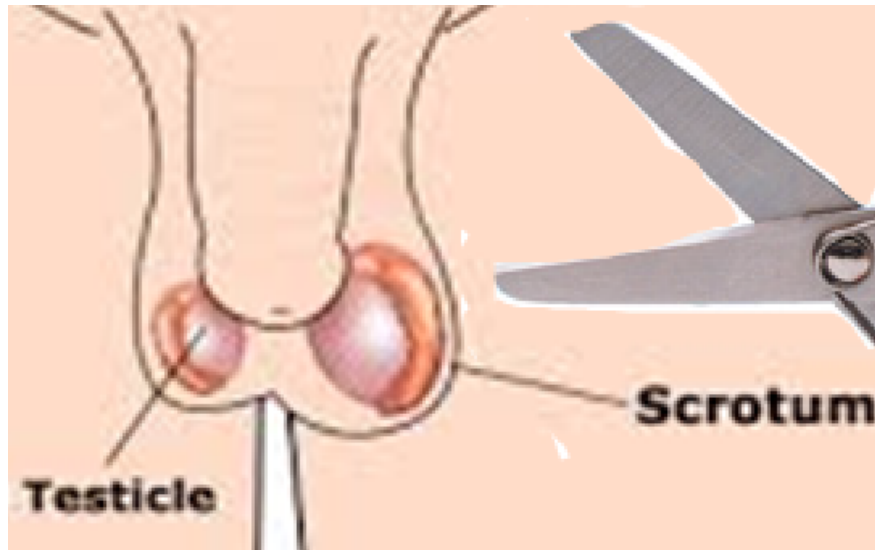


MS Independent risk factor for →

Hypogonadism



# Effects of androgen ablation on body composition and metabolism



Fat mass

Androgen ablation therapy  
to treat advanced prostate  
cancer



Increase in Total body Fat  
mass

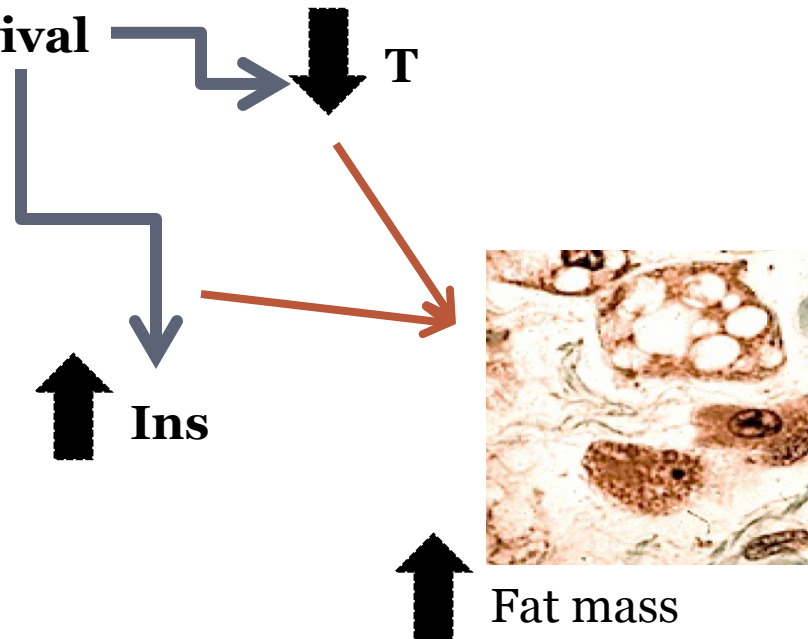
# Effects of androgen reduction on body composition and metabolism



## CHEMOTHERAPY



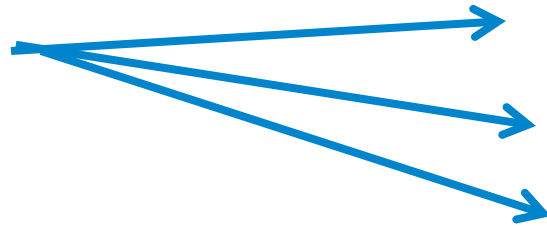
Cancer survival



# Effects of weight loss on plasma androgen levels



Substantial weight loss



SHBG

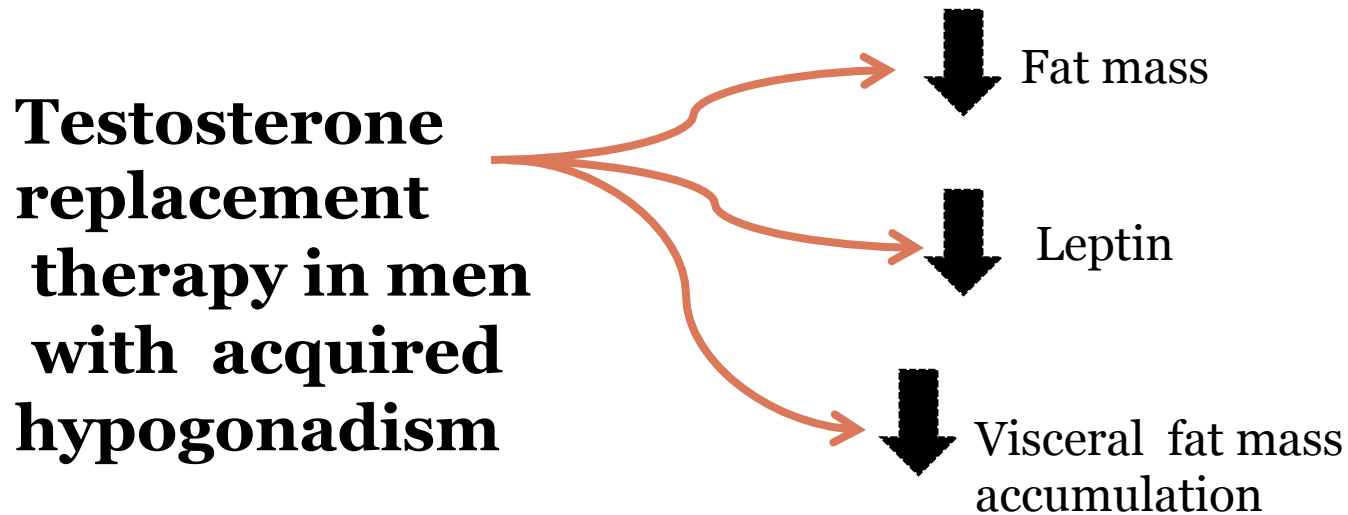


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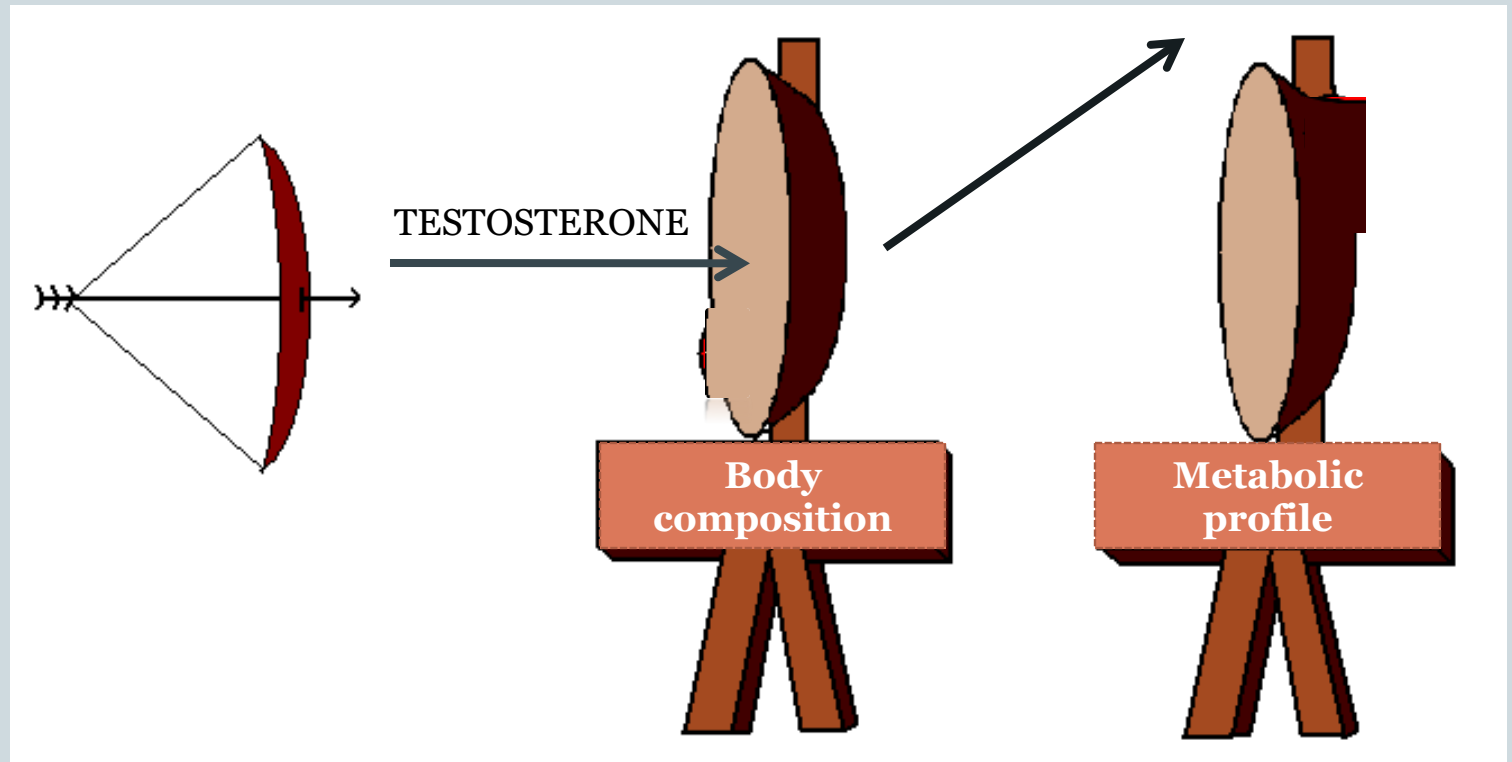


FT

# Effects of testosterone replacement therapy

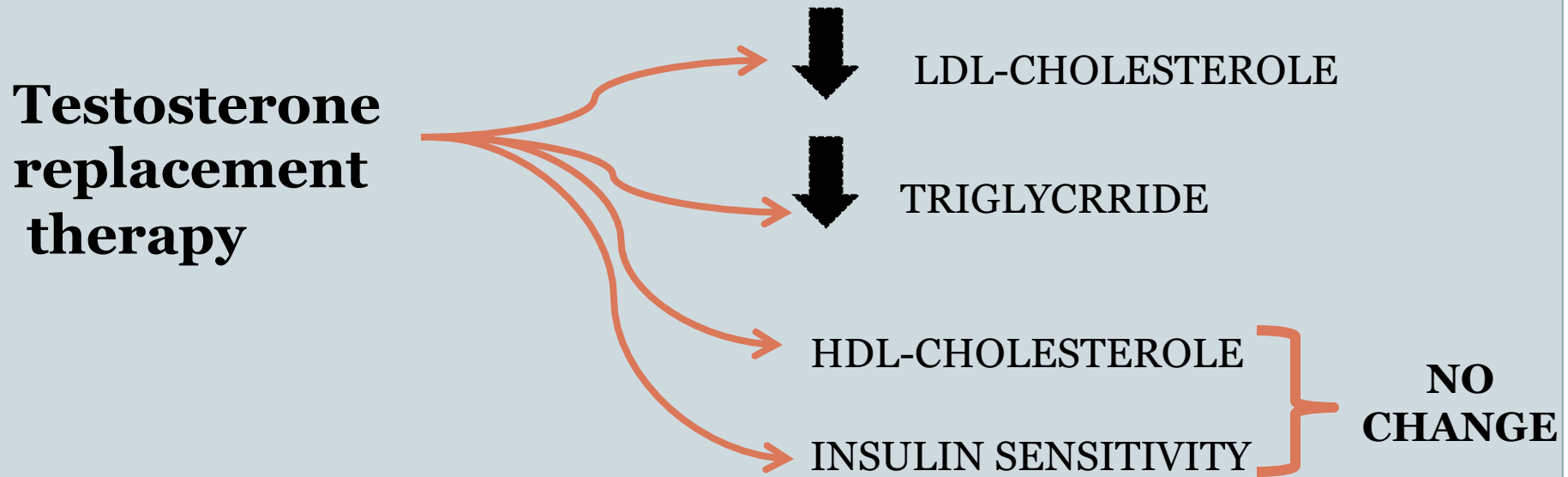


# Effects of testosterone replacement therapy in body composition and metabolic profile



**Which is the target of testosterone replacement therapy?**

# Effects of testosterone replacement therapy on metabolic profile







First International Journal of Andrology

# ANDROLOGIA

ORIGINAL ARTICLE

## **Resveratrol appears to protect against oxidative stress and steroidogenesis collapse in mice fed high-calorie and high-cholesterol diet**

H.-J. Wang<sup>1\*</sup>, Q. Wang<sup>1\*</sup>, Z.-M. Lv<sup>1</sup>, C.-L. Wang<sup>2</sup>, C.-P. Li<sup>2</sup> & Y.-L. Rong<sup>2</sup>



- Resveratrol attenuates mitochondrial oxidative stress and serves as a potent antioxidant as well
- Resveratrol attenuates detrimental effects on Leydig cells steroidogenesis in HCD-fed mice, and its upregulations of antioxidant defence mechanisms and LH level may play a role in its protection.
- It may be suggested resveratrol appears to have the potential for therapeutic approaches targeting male obesity-associated secondary hypogonadism.



# ANDROLOGY



ISSN: 2047-2919

ANDROLOGY

ORIGINAL ARTICLE

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50139, Italy.  
E-mail: m.maggi@dfc.unifi.it

Received: 23-Jul-2012

Revised: 21-Sep-2012

Accepted: 25-Sep-2012

## **Seminal, ultrasound and psychobiological parameters correlate with metabolic syndrome in male members of infertile couples**

F. Lotti,\* G. Corona,\*<sup>†</sup> S. Degli Innocenti,\* E. Filimberti,\* V. Scognamiglio,\*  
L. Vignozzi,\* G. Forti\* and M. Maggi\*



- Among ultrasound features, in an age-adjusted logistic model, only testis inhomogeneity was significantly associated with increasing MetS factors ( $p < 0.01$ ).
- Does Metabolic Syndrome Represents a Risk for Testicular Cancer?

Human Reproduction vol.14 no.6 pp.1516–1521, 1999

# **Effects of hypercholesterolaemia on Leydig and Sertoli cell secretory function and the overall sperm fertilizing capacity in the rabbit**

**Yasuhisa Yamamoto, Kenji Shimamoto,  
Nikolaos Sofikitis<sup>1</sup> and Ikuo Miyagawa**

Department of Urology, Tottori University School of Medicine,  
36 Nishimachi, Yonago 683, Japan



**Table II.** Testosterone and androgen-binding protein (ABP) profiles in hypercholesterolaemic rabbits (group A) compared to controls (group B)

Group	Testosterone (ng/ml)		ABP (pmol/mg protein)
	Basal	Response to HCG	
A	2.4 ± 0.9 <sup>a</sup>	6.0 ± 1.1 <sup>a</sup>	0.29 ± 0.09 <sup>a</sup>
B	2.5 ± 0.8 <sup>b</sup>	8.9 ± 2.0 <sup>c</sup>	0.46 ± 0.10 <sup>c</sup>

Within each column, a versus b:  $P > 0.05$  (non-significant); a versus c:  $P < 0.05$  (statistically significant).

HCG = human chorionic gonadotrophin.



**Table IV.** Effects of seminal plasma components on the motility of spermatozoa isolated from hypercholesterolaemic (group A) and control (group B) rabbits

Sample	% motile spermatozoa		Motility grade	
	0 h	3 h	0 h	3 h
Group A spermatozoa and group B seminal plasma	44 ± 12 <sup>a</sup>	36 ± 14 <sup>b</sup>	2.1 ± 0.5 <sup>c</sup>	1.5 ± 0.6 <sup>d</sup>
Group B spermatozoa and group A seminal plasma	68 ± 10 <sup>a</sup>	61 ± 1 <sup>b</sup>	2.7 ± 0.6 <sup>c</sup>	2.2 ± 0.6 <sup>d</sup>

a,b,c,d Within each line: a versus b or c versus d:  $P > 0.05$  (non-significant).



- control spermatozoa do not demonstrate lower motility parameters when placed in seminal plasma from hypercholesterolaemic rabbits
- motility of spermatozoa from hypercholesterolaemic rabbits do not improve significantly when placed in control seminal plasma





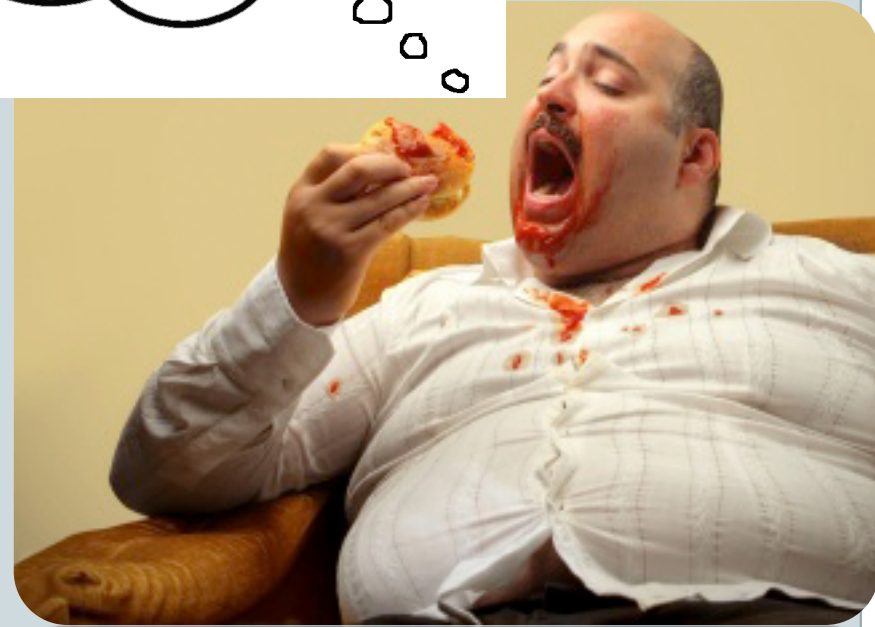
- The absence of a significant difference in seminal plasma cholesterol concentration between control rabbits and hypercholesterolaemic rabbits indicates that cholesterol does not increase in the seminal plasma of animals on a cholesterol-enriched diet.
- It has also been suggested that there is no increase in testicular tissue cholesterol of hypercholesterolaemic animals. This may imply the existence of either a blood–seminiferous tubule (since the testicular volume mainly comprises seminiferous tubules) and/or a blood–reproductive tract selective barrier against high concentrations of cholesterol.



- There is an adverse effect of cholesterol-enriched diets on Leydig and Sertoli cell secretory function, spermatogenesis and sperm cytoskeleton, epididymal sperm maturation process, and the overall sperm fertilizing capacity and ability to initiate further embryonic development.

NO!!! There is a blood-testis cholesterol barrier!!!

Am I going to increase my semen cholesterol???



Hindawi Publishing Corporation  
Oxidative Medicine and Cellular Longevity  
Volume 2014, Article ID 190945, 14 pages  
<http://dx.doi.org/10.1155/2014/190945>

*Research Article*

# **Leptin Level and Oxidative Stress Contribute to Obesity-Induced Low Testosterone in Murine Testicular Tissue**

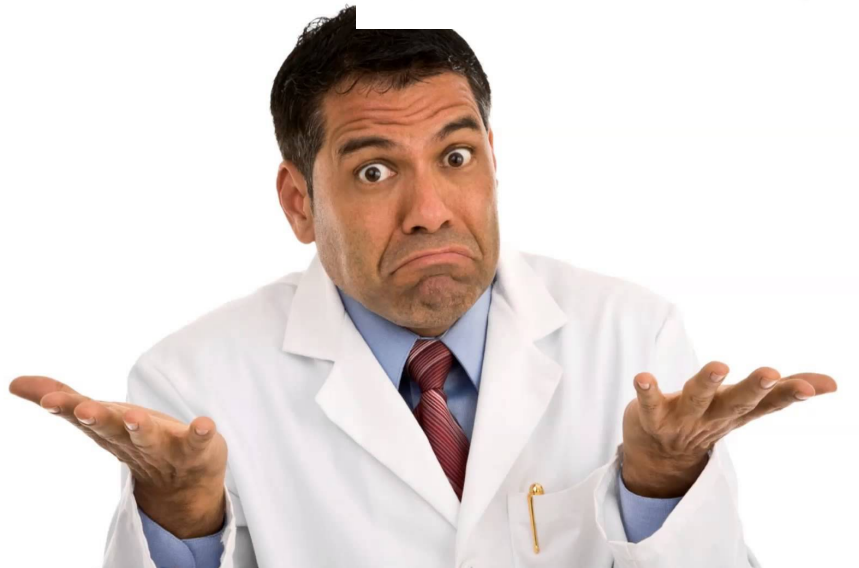
**Jian Zhao,<sup>1</sup> Lingling Zhai,<sup>2</sup> Zheng Liu,<sup>1</sup> Shuang Wu,<sup>1</sup> and Liping Xu<sup>1</sup>**



- Pathological damage of Leydig cells, oxidative stress in testis tissue, and high level of leptin may provide some evidence to clarify the mechanisms of male hypogonadism in obesity.
- Adipose cytokines such as leptin are secreted in adipose cells. The level of adipose cytokines is high and may suppress secretion of testosterone.

**Eating in the absence  
of hunger correlates  
with body weight and  
semen quality**

I eat everything in  
the absence of hunger.  
Is it a mistake?





Zhonghua Nan Ke Xue. 2014 Sep;20(9):792-7.

**[Expression of the kisspeptin/kiss1r system in the hypothalamic arcuate nucleus of rats with diet-induced obesity and its influence on the hypothalamic-pituitary-testis axis].**

[Article in Chinese]

Liu RR, Zhang HQ.



- Kisspeptin is encoded by the KISS1 gene and is a peptide ligand of the G protein-coupled receptor KISS1R (GPR54). Defective onset of puberty was observed to be associated with mutation of KISS1R in humans. Moreover, central or peripheral Kisspeptin administration to several mammalian species, including humans, induced robust release of GnRH and gonadotropin.
- Lateral ventricular injection of kisspeptin can upregulate obesity induced low expression of GnRH, correct the dysfunction of the hypothalamo-pituitary axis, and thus improve reproductive function in rats.





J Endocrinol Invest. 2011 Nov;34(10):e336-42. doi: 10.3275/7855. Epub 2011 Jul 7.

## **Elevated body mass index correlates with higher seminal plasma interleukin 8 levels and ultrasonographic abnormalities of the prostate in men attending an andrology clinic for infertility.**

Lotti F<sup>1</sup>, Corona G, Colpi GM, Filimberti E, Degli Innocenti S, Mancini M, Baldi E, Noci I, Forti G, Adorini L, Maggi M.



- Higher BMI was significantly related to higher prostate volume and several ultrasonographycal features of the prostate, including macrocalcifications, inhomogeneity, higher arterial peak systolic velocity, but not with abnormalities of testis, epididymis, seminal vesicles. Furthermore, higher BMI and BMI class were significantly related to higher serum IL8, a reliable surrogate marker of prostate inflammatory diseases.
- both IL-8 and IL-6 levels in the prostatic fluid are correlated with serum PSA level.

# Metabolic Syndrome and Prostatitis

Additional studies  
are necessary ...

Does eating many  
hamburgers every  
day contribute to the  
development of  
prostatitis?

