

# **Hypogonadism in the Aging Male in Taiwan**

**Thomas I-sheng Hwang**

**Division of Urology, Shin Kong Memorial Hospital**

**School of Medicine, Taipei Medical University**

**School of Medicine, Fu-Jen Catholic University**

# Clinical Picture of Adult Hypogonadism

- Inconsistent
- Not predictable
- Onset, speed and depth of clinical manifestations vary
- Mostly gradual, insidious and subtle, but sometimes rapid, stormy and intolerable

# Commonest Symptoms

Androgen Deficiency	Aging Symptoms
Sexual Dysfunction	Sexual Dysfunction
Fatigue	Generalised weakness
↓ Muscle Strength	Impaired mobility
Feminine distribution of fat	Impaired balance
Anaemia	Declining endurance Osteoporosis
Osteoporosis	Susceptibility to infectious diseases, humurolological dysfunction, depression

# The Saint Louis University Androgen Deficiency in Aging Males (ADAM) questionnaire

---

- 1. Do you have a decrease in libido (sex drive)?**
2. Do you have a lack of energy?
3. Do you have a decrease in strength an/or endurance?
4. Have you lost height?
5. Have you noticed a decreased “enjoyment of life”?
6. Are you sad and/or grumpy?
- 7. Are your erections less strong?**
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

---

Positive answers to questions 1 or 7 or any three other questions suggest testosterone deficiency.

# Hormonal alteration in aging male

Sex hormone

Growth hormone

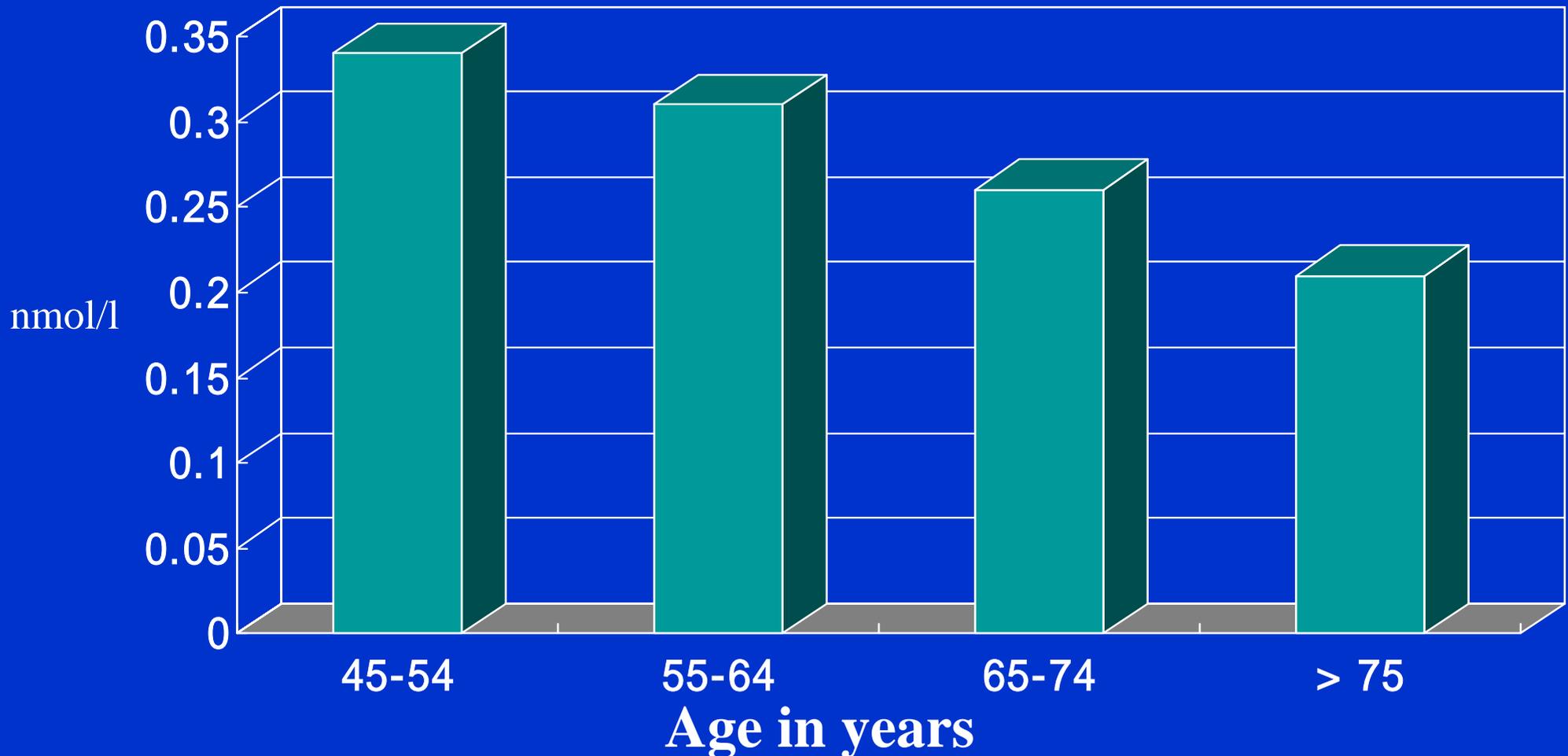
Melatonin

Leptin

Dehydroepiandrosterone (DHEA)

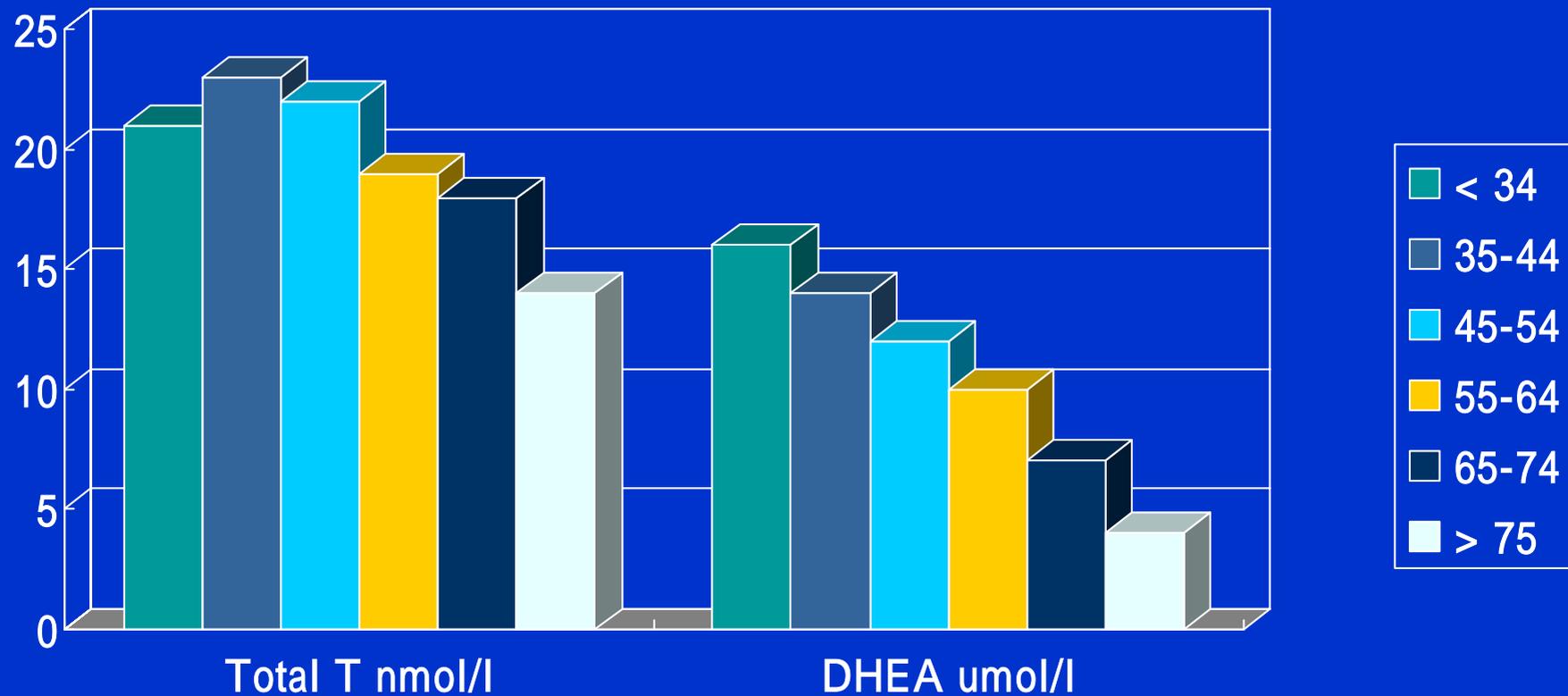
Others

# Decrease in serum free testosterone relative to age



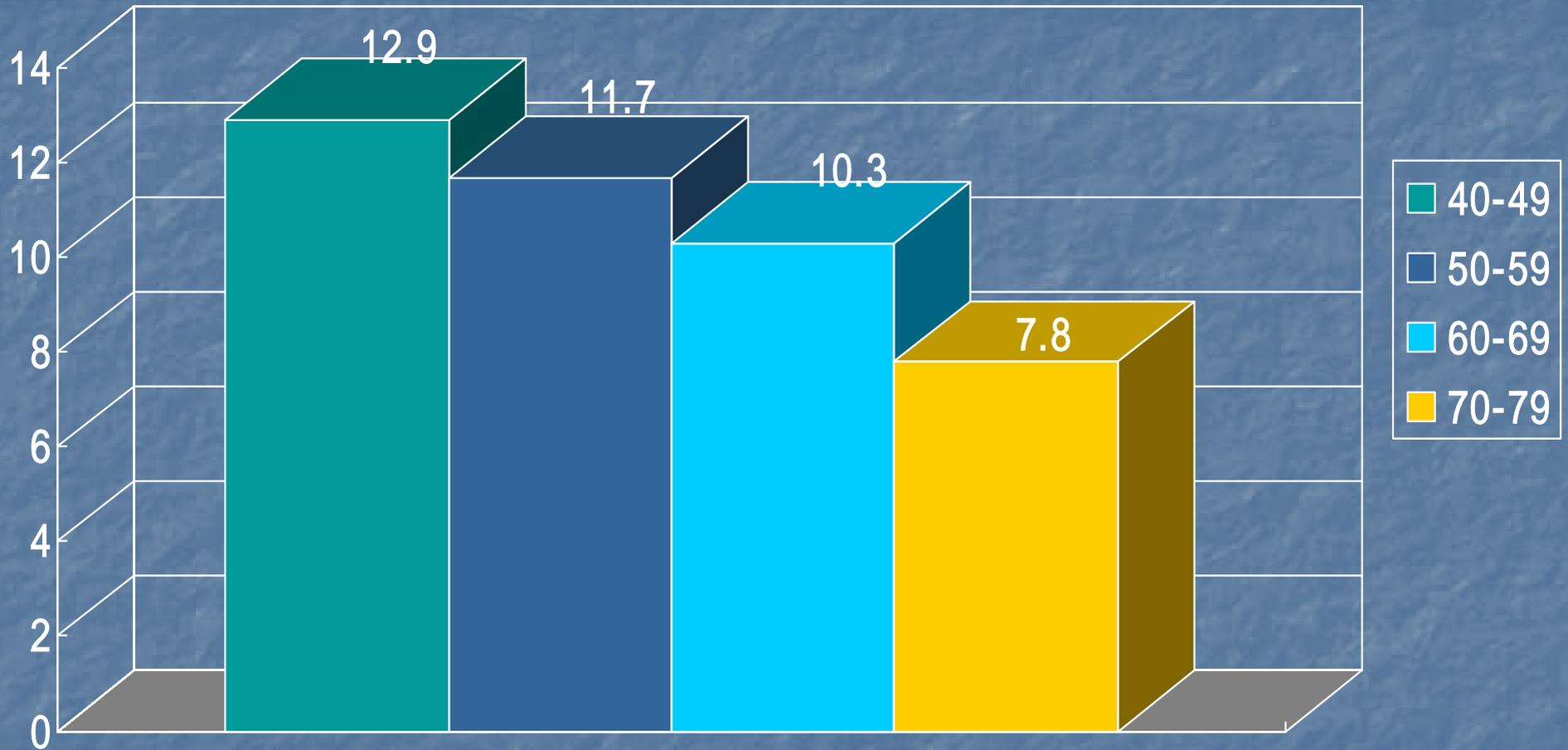
*Vermeulen et al, 1995*

# Mean plasma sex hormone in healthy men



*Vermeulen et al, 1995*

pg/mL

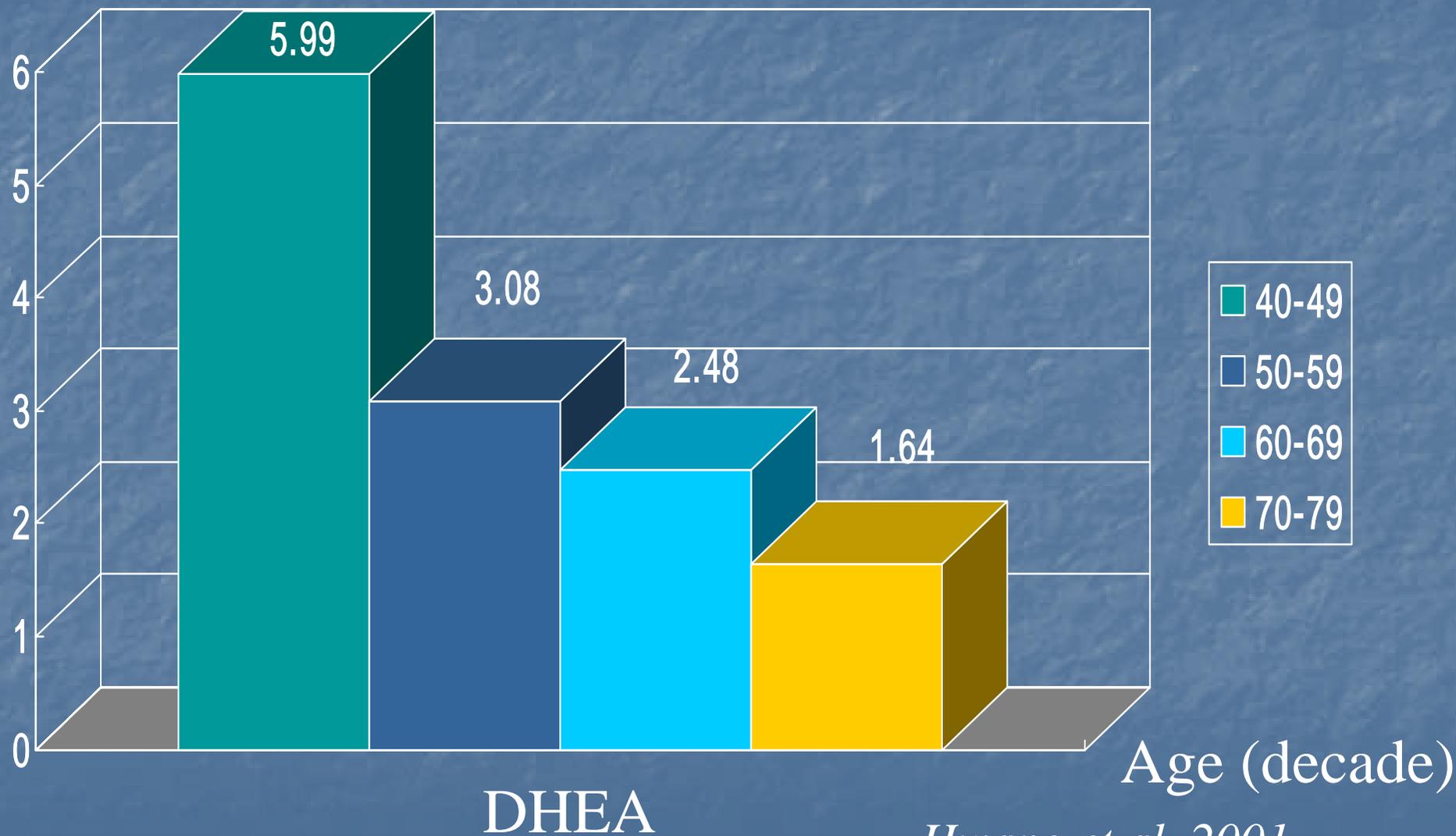


Free testosterone

Age (decade)

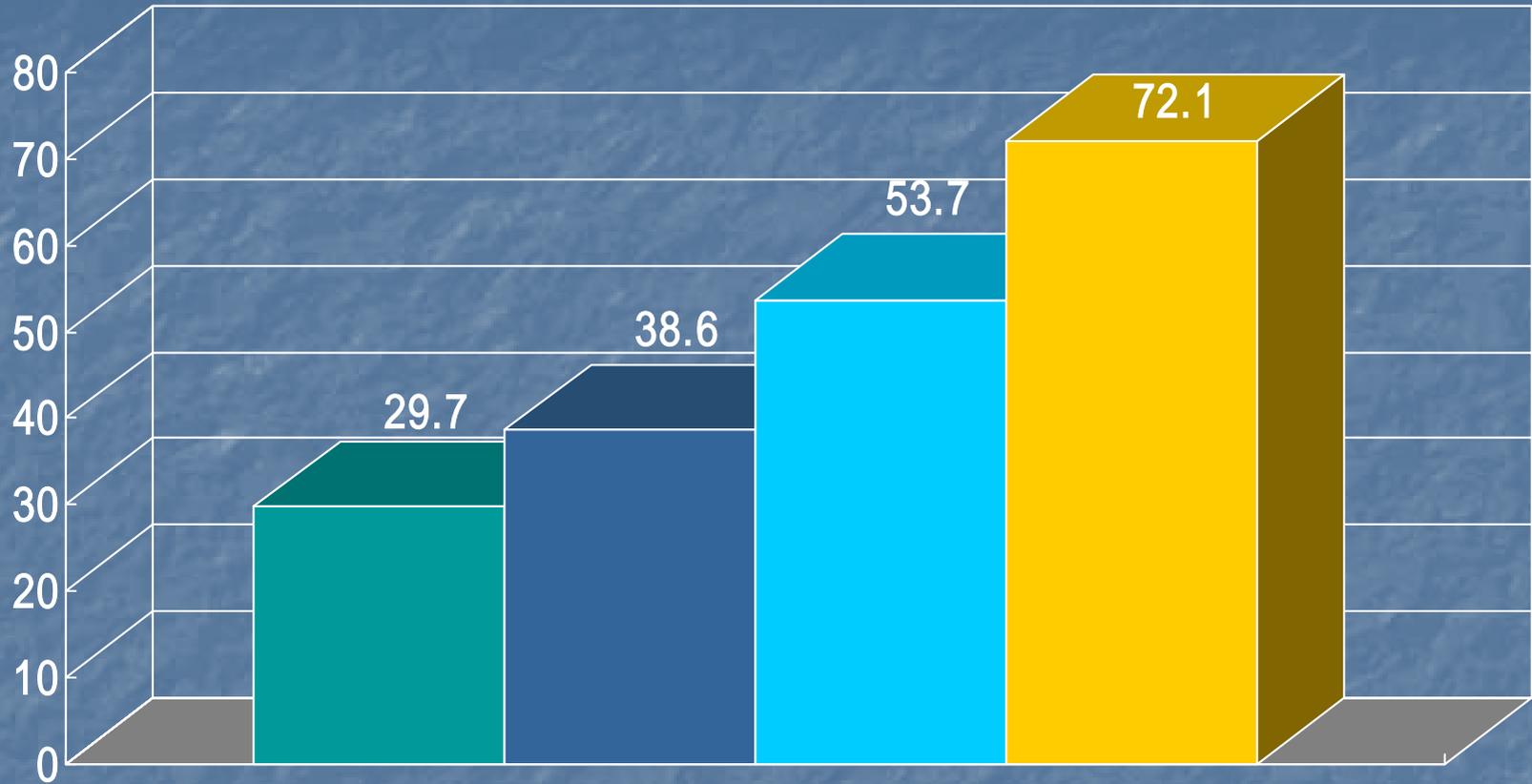
*Hwang et al, 2001*

ng/mL



*Hwang et al, 2001*

nM/L



SHBG

Age (decade)

*Hwang et al, 2001*

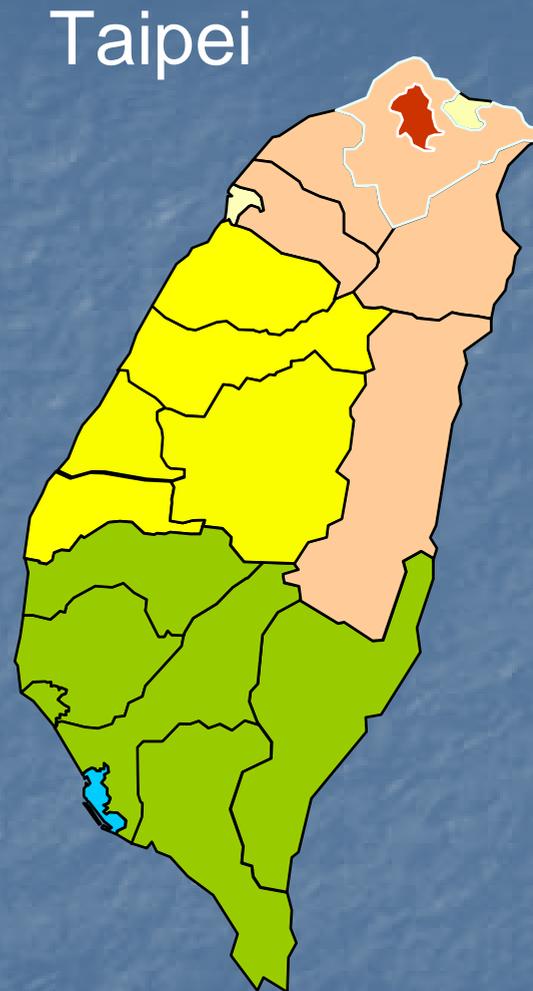
# Second Asian ISSAM Meeting on the Aging Male



Aging on the Male — Hot Topics of the New Century

6<sup>th</sup>– 9<sup>th</sup> March, 2003 Taipei, Taiwan  
*Second Announcement*

<http://www.issam2-asia.org>



Taipei

Taiwan

# Asian Aging Data

Country	Life Expectations		% of Aging Populations	
	2000	2005	2000	2005
Burma	54.9	63.4	7.09	12.56
China	71.4	77.4	10.20	19.69
India	62.5	70.9	7.02	11.76
Indonesia	68.0	74.9	7.17	13.80
<b>Japan</b>	<b>80.7</b>	<b>82.9</b>	<b>17.01</b>	<b>27.57</b>
Malaysia	70.8	76.9	6.52	12.15
Philippines	67.5	74.6	5.65	10.04
Singapore	80.1	82.5	6.84	12.52
South Korea	74.4	79.2	6.90	16.42
<b>Taiwan</b>	<b>76.4</b>	<b>80.4</b>	<b>8.62</b>	<b>17.26</b>
Thailand	68.6	75.3	9.74	19.94
Vietnam	69.3	75.8	5.65	10.04

WHO report, 2001

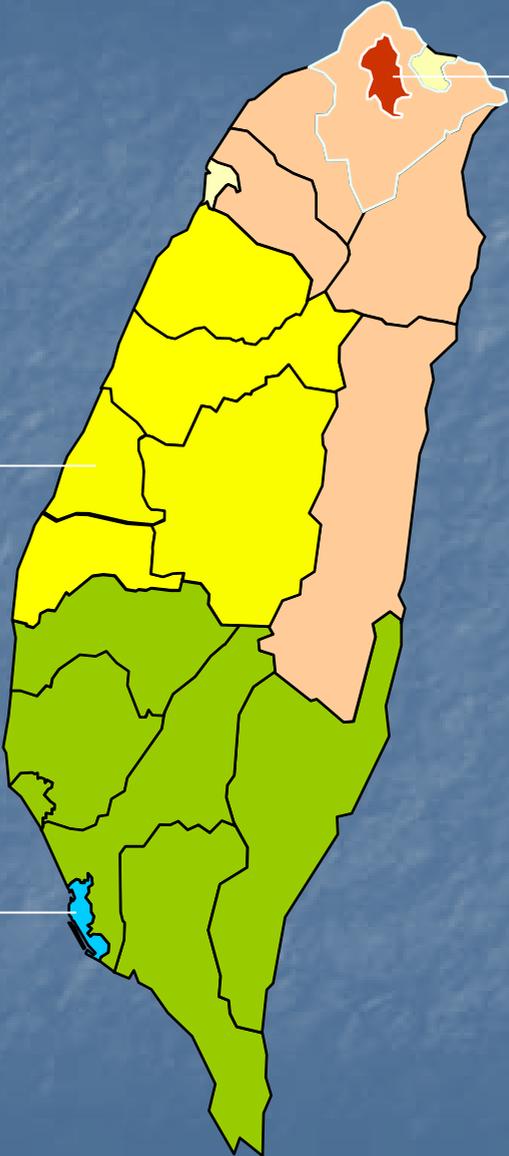
# Prevalence of ADAM

Age Group	Prevalence	Author
< 40	1%	Vermeulen, A. 1999
> 60	20%	
80's	40%	
4-50	2-5%	Morley, JE. 1997
51-60	6-30%	
61-70	20-45%	
> 70	34-70%	

**Taichung**  
VGH-Tc  
CMUH

**Taipei**  
SKMH

**Kaohsiang**  
VGH-Kh  
KMUH



# Materials and Methods (—)

Subjects: Community living men 40-80 years old were recruited from Taiepi (North) Taichung (middle) and Kaoshiang (South) cities. (n=650)

Hosp. / Age	SKH (n=242)	CMPUH (n=156)	VGHT (n=50)	KMUH (n=140)	VGHK (n=62)
40-49	32 (13%)	14 (9%)	13 (26%)	23 (16%)	0
50-59	99 (41%)	61 (39%)	19 (38%)	49 (35%)	8 (13%)
60-69	87 (36%)	40 (26%)	8 (16%)	45 (32%)	33 (53%)
70-80	24 (10%)	41 (26%)	10 (20%)	23 (16%)	21 (34%)

SKH: Shin Kong Memorial Hosp.

CMPUH: Chinese Medical Pharmacological University Hosp.

VGHT: Veterans General Hosp.-Taichung

KMUH: Kaoshiang Medical University Hosp.

VGHK: Veterans General Hosp. -Kaoshiang

**Table 1. Mean biochemical markers of androgen stratified into 10-year ranges (n=650)**

Age	TT (nmol/l)	cFT (nmol/l)	BT (nmol/l)
40-49 (n=82)	16.45	0.32	7.71
50-59 (n=236)	15.50	0.29	6.95
60-69 (n=213)	16.23	0.26	6.19
70-80 (n=119)	15.67	0.22	5.19
Mean	15.89	0.27	6.47

TT: total testosterone

cFT: calculated free testosterone

BT: bioavailable testosterone

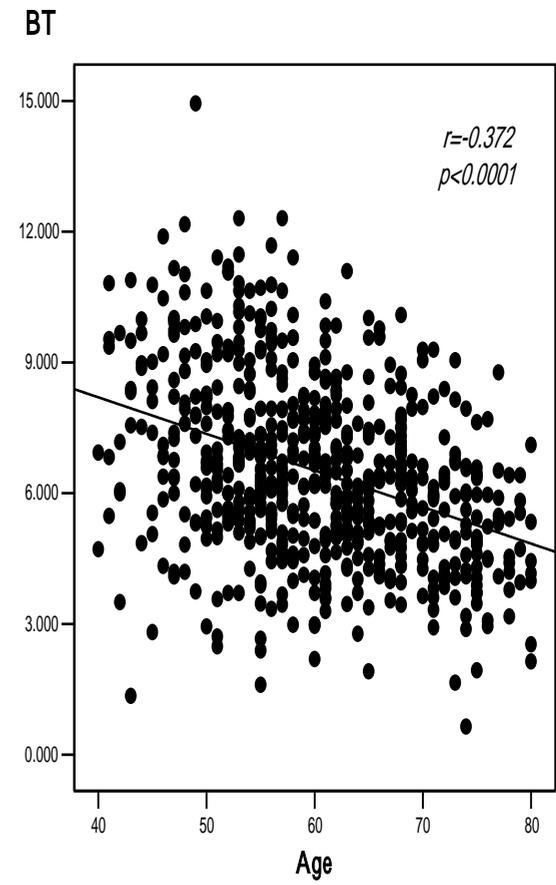
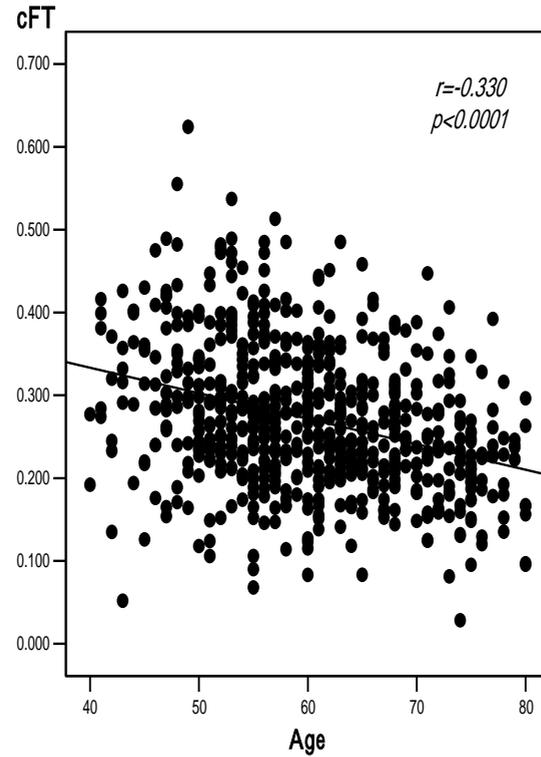
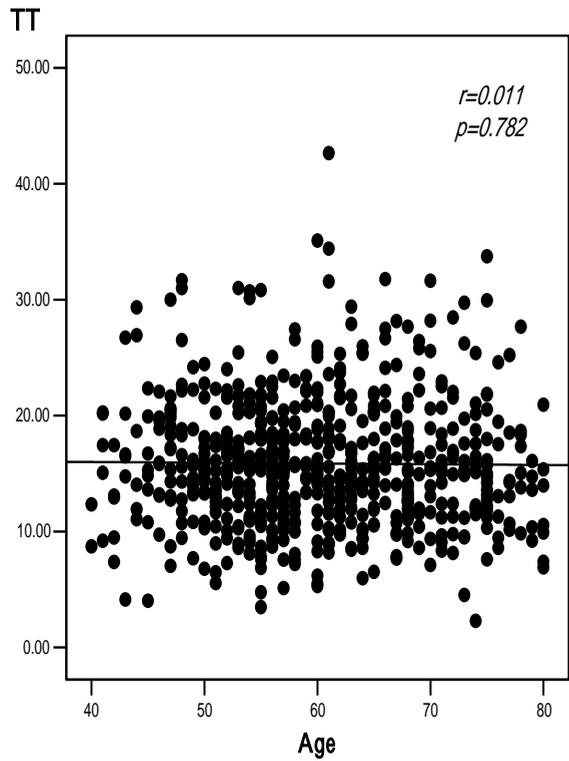


Fig. Correlations between the biochemical markers, total testosterone (TT), calculated free testosterone (cFT), and bioavailable testosterone (BT), with age. cFT and BT are correlated with age.

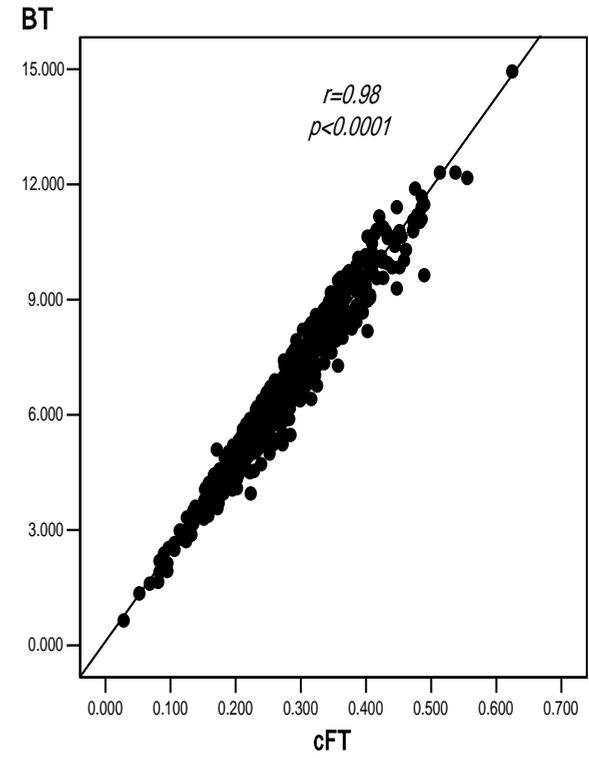
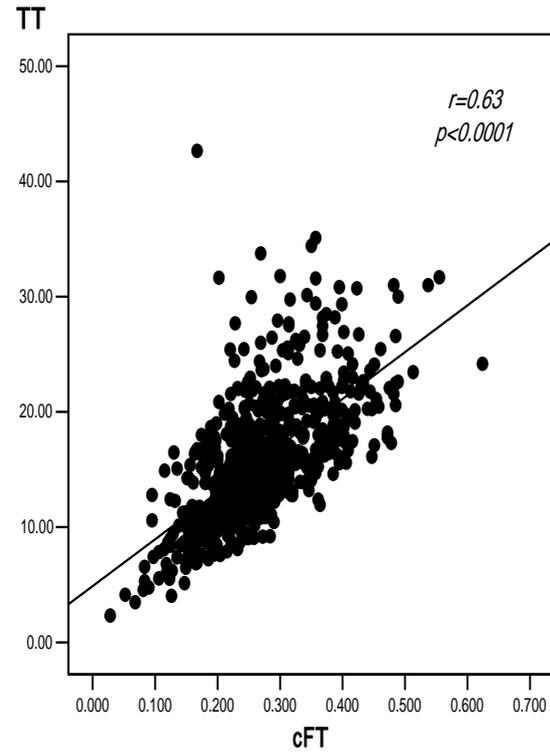
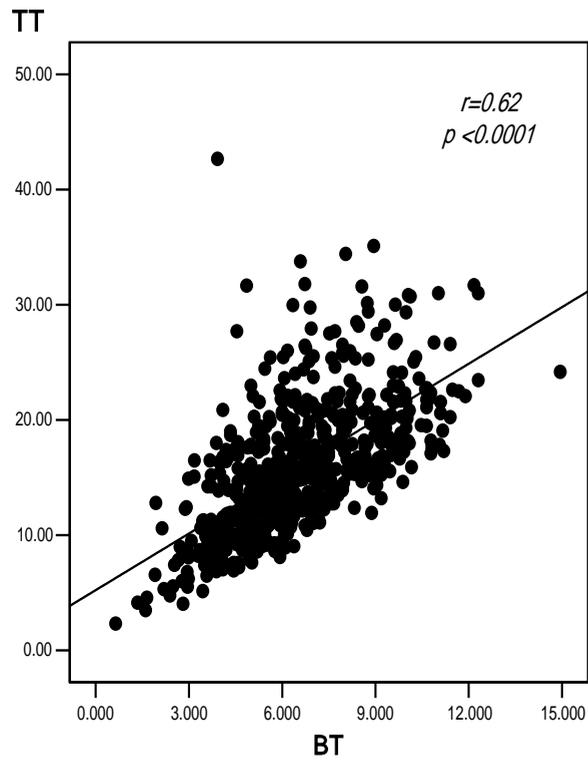
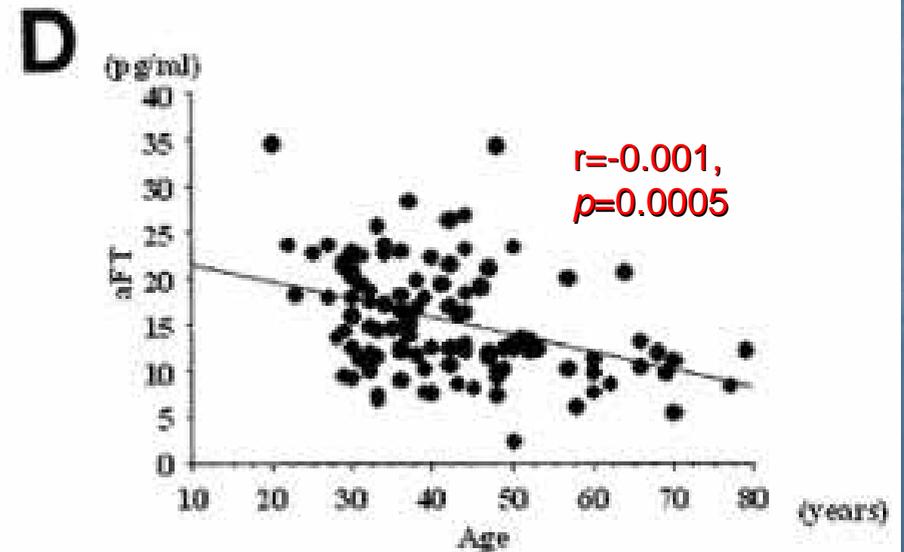
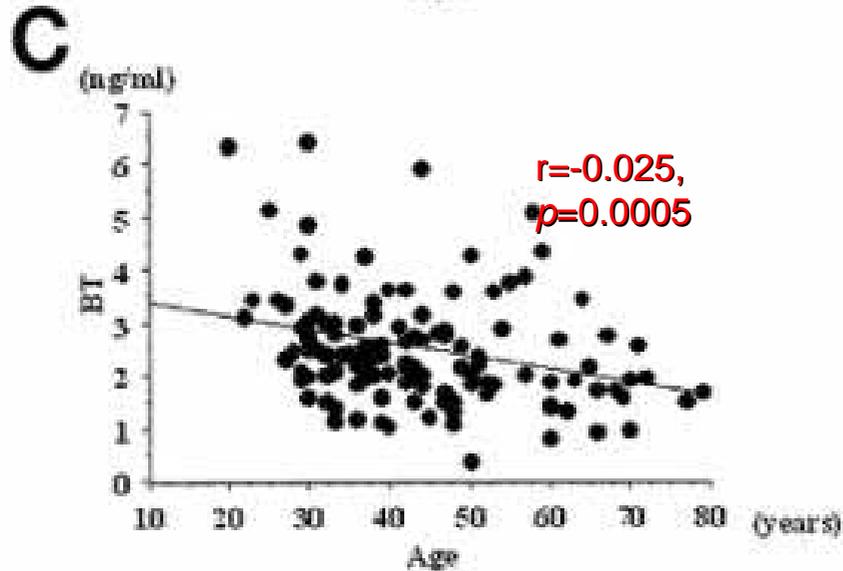
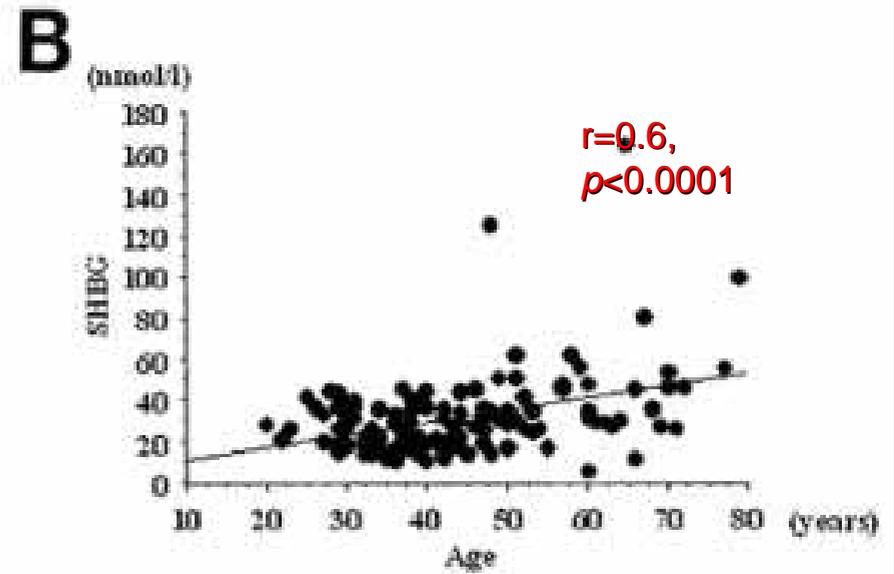
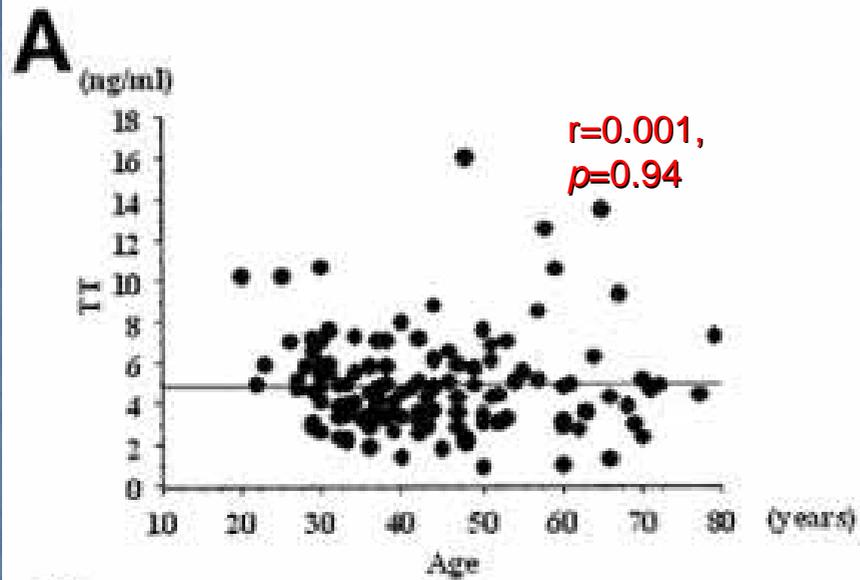


Fig. Correlations between the three biochemical markers, cFT and BT are well correlated with TT.

# (Tsujimura et al., 2003)



**Table 2. Distributions of men with androgen deficiency in different age groups (n=650)**

Age	TT<11 nmol/l		cFT<0.23 nmol/l		BioT<5 nmol/l	
	number	%	number	%	number	%
40-49	14	11	15	7	11	7
50-59	47	39	56	27	36	23
60-69	37	30	75	36	52	33
70-80	24	20	70	33	60	38
<b>Total</b>	<b>122</b>	<b>19</b>	<b>216</b>	<b>33</b>	<b>159</b>	<b>24</b>

**Table 3. The distribution of ADAM questionnaire results stratified by age.**

Age	SLQ Positive		SLQ Negative		
	number	%	number	number	%
40-49	60	73	22	27	82
50-59	178	75	58	25	236
60-69	175	82	38	18	213
70-80	108	91	11	9	119
	521	80	129	20	650

# St. Louis University ADAM questionnaire: (Morley JE, 2000)

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased “enjoyment of life”?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you failing asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A positive questionnaire is defined as “yes” answers to questions 1 or 7 and/or “yes” answers to any three other questions.

**Table 4. Correlations between biochemical markers of androgen level and SLQ in 10-year ranges**

Age		<u>SLQ positive</u> Mean±SD	<u>SLQ negative</u> Mean±SD	<i>p</i> value
<b>40-49</b>		<b>n=60</b>	<b>n=22</b>	
	TT (nmol/l)	16.58±5.76	16.43±5.97	0.962
	cFT(nmol/l)	0.33±0.10	0.30±0.09	0.571
	BT(nmol/l)	7.86±2.41	7.29±2.15	0.430
<b>50-59</b>		<b>n=178</b>	<b>n=58</b>	
	TT (nmol/l)	15.74±4.83	14.58±5.00	0.197
	cFT(nmol/l)	0.29±0.09	0.28±0.08	0.431
	BT(nmol/l)	7.03±2.12	6.71±1.98	0.302
<b>60-69</b>		<b>n=175</b>	<b>n=38</b>	
	TT (nmol/l)	16.43±6.10	15.83±4.74	0.572
	cFT(nmol/l)	0.26±0.07	0.28±0.07	0.146
	BT(nmol/l)	6.10±1.72	6.63±1.54	0.085
<b>70-80</b>		<b>n=108</b>	<b>n=11</b>	
	TT (nmol/l)	15.97±5.53	13.61±8.02	0.207
	cFT(nmol/l)	0.22±0.07	0.18±0.07	0.033
	BT(nmol/l)	5.30±1.60	4.12±1.46	0.023

**SLQ: St. Louis University questionnaire of androgen deficiency in aging male**

# Summary

1. Adult hypogonadism is prevalent in Taiwan.
2. Bioavailable testosterone and calculated free testosterone are better correlated with age and may be the better biochemical markers for androgen deficiency.
3. SLQ (St. Louis University Questionnaire) may not be the single measurement for androgen deficiency and biochemical markers should be used together.



# Benefits of TRT

Cardioprotective effects

Circulation, 99:1666,1999

Improvement in lipid profile

Proc. Natl Acad Sci USA,  
98,3589.2001

Improvement in mood disorder  
and cognition

Am J Psychiatry 159, 56,2002

Increase in striated muscle mass  
and strength

Endocrinol Metab 75, 1092,  
1992

Increase in bone mineral density

J. Clin. Endocrinol Metab,  
1966, 1999

Improvement in response to  
PDE5

J. Urol. 172; 658, 2004

# Commercially available testosterone preparations

---

## Preparation

## Generic Name

---

Injectable

Testosterone cypionate

Testosterone enanthate

Oral

Fluoxymesterone

Methyltestosterone

Testosterone undecanoate

Transdermal

Testosterone patch

Testosterone gel

---

# Monitoring patients on hormonal replacement

1. Liver
2. Lipid profile and cardiovascular disease
3. Prostate
4. Sleep disorders
5. Social behavior and emotional state

# Testosterone replacement and Prostate

BPH : mediated by 5  $\alpha$ -DHT  
PSA } modest increase  
Prostate volume } but insignificant  
LUTS }  
*Tenover J.L. 1998*

Prostate cancer:

Testosterone promote growth of established cancer.

? Promote development of cancer.

*Nomura et al 1998.*

*Cooper et al 1998.*

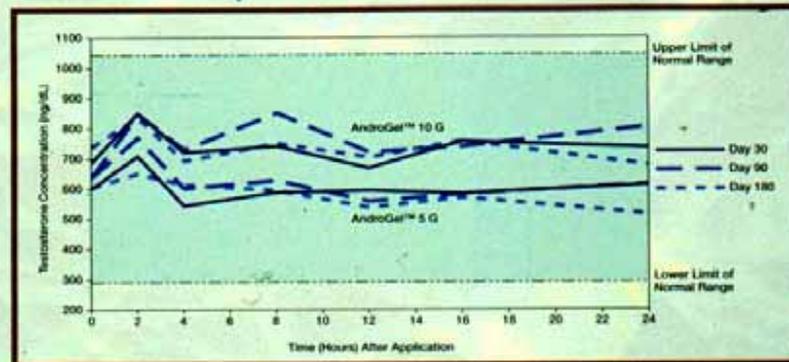
# **Transdermal Testosterone Gel Increased Serum Testosterone Level in Hypogonadal Men With Improvements of Sexual Function in Taiwan**

**Han-Sun Chiang and Thomas I.S. Hwang**

**Submitted to European Urology 2005**

# A novel testosterone delivery system NO PATCHES, NO INJECTIONS

Effectively raises serum testosterone levels<sup>1</sup>



- Maintains consistent 24-hour serum testosterone levels<sup>1</sup>
- Minimizes serum level fluctuations associated with IM therapy<sup>2</sup>
- Significantly improves libido and lean body mass<sup>1</sup>
- Improves quality and duration of erection<sup>1</sup>
- Improves mood and fatigue<sup>1</sup>



### Contraindications

Androgens are contraindicated in men with carcinoma of the breast, or known or suspected carcinoma of the prostate.

AndroGel™ is not indicated for use in women, has not been evaluated in women, and should not be used in women. Pregnant women should avoid skin contact with AndroGel™ application sites in men. Testosterone may cause fetal harm.

### Warning

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

### Precautions

To minimize potential transfer of testosterone to another person, patients should wash the hands immediately with soap and water after application of AndroGel™. They should cover the application site(s) with clothing after the gel has dried.

If unwashed or unclothed AndroGel™-treated skin comes in direct contact with another person, the area of contact should be washed with soap and water as soon as possible.

**Table 2. Treatment group changes (mean  $\pm$  SD) from baseline at 1-month intervals for 3 months in serum TT (ng/dL) levels (ITT population)**

Visit	Transdermal testosterone gel (N =20)	Placebo (N=18)	p value ‡
Baseline (95% CI)	213.1 $\pm$ 158.3 (138.9 ~287.2)	263.4 $\pm$ 198.1 (164.9 ~ 362.0)	0.397
Month 1(95% CI)	392.7 $\pm$ 288.4* (257.7 ~ 527.6)	270.6 $\pm$ 205.8 (164.8~376.4)	0.024*
Month 2 (95% CI)	384.1 $\pm$ 288.9* (248.9~51.93)	264.6 $\pm$ 211.9 (155.7~373.6)	0.025*
Month 3 (95% CI)	330.7 $\pm$ 314.6 (183.4~477.9)	266.9 $\pm$ 187.9 (173.5~360.3)	

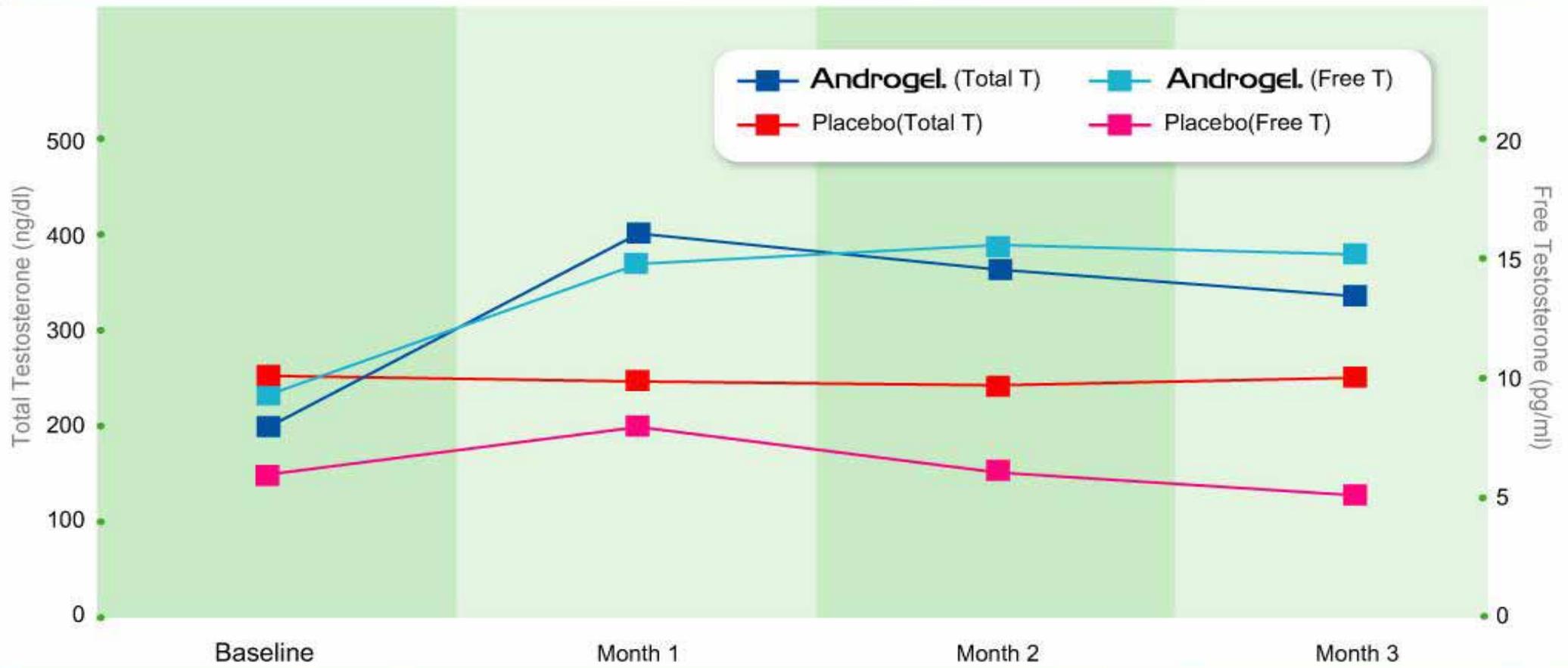
\* Statistically significant difference, paired t-test; † paired t-test; ‡ 2-way ANOVA

**Table 3. Treatment group changes (mean  $\pm$  SD) from baseline at 1-month intervals for 3 months in serum FT (Pg/mL) levels (ITT population)**

Visit	Transdermal testosterone gel (N =20)	Placebo (N=18)	p value†‡
Baseline (95% CI)	9.32 $\pm$ 17.39 (1.18~17.46)	6.11 $\pm$ 4.15 (4.04~8.17)	0.445
Month 1(95% CI)	14.04 $\pm$ 17.20 (5.99~22.09)	8.06 $\pm$ 6.34 (4.81~11.32)	0.020*
Month 2	17.11 $\pm$ 22.19* (6.73~27.49)	6.63 $\pm$ 4.56 (4.29 ~ 8.97)	0.004*
Month 3	15.90 $\pm$ 19.83 (6.62~25.17)	6.07 $\pm$ 3.45 (4.35~7.78)	0.059

\*Statistically significant difference, paired t-test; † paired t-test; ‡ 2-way ANOVA

# ➔ Androgel Increases Taiwanese Male's Serum T Level



**Table 4. Treatment group changes (mean  $\pm$  SD) from baseline to month 3 in DHT, E2, LH, FSH, and SHBG levels (ITT population)**

Visit	Transdermal testosterone gel (N =20)	Placebo (N =17)	p value†‡
<b>DHT (pg/mL)</b>			
Baseline (95% CI)	366.89 $\pm$ 436.21 (162.7~571.04)	393.82 $\pm$ 374.02 (201.51~586.12)	
Month 3 (95% CI)	625.22 $\pm$ 496.73 (392.74~857.69)	361.35 $\pm$ 428.47 (141.05~581.65)	0.031
<b>E2 (pg/mL)</b>			
Baseline (95% CI)	46.14 $\pm$ 23.66 (35.06~57.21)	52.07 $\pm$ 16.02 (43.84~60.31)	
Month 3 (95% CI)	54.53 $\pm$ 24.73 (42.96~66.10)	47.34 $\pm$ 21.81 (36.12~58.55)	0.274
<b>LH (mIU/mL)</b>			
Baseline (95% CI)	5.05 $\pm$ 4.44 (2.97~7.13)	4.98 $\pm$ 5.69 (2.05~7.90)	
Month 3 (95% CI)	3.29 $\pm$ 5.73* (0.61~5.97)	5.34 $\pm$ 6.30 (2.10~8.58)	0.014*
<b>FSH (mIU/mL)</b>			
Baseline (95% CI)	10.32 $\pm$ 10.21 (5.54~15.09)	10.64 $\pm$ 10.22 (5.38~15.89)	
Month 3 (95% CI)	6.37 $\pm$ 7.12* (3.03~9.70)	9.60 $\pm$ 9.29 (4.82~14.38)	0.019*
<b>SHBG (nmol/L)</b>			
Baseline (95% CI)	73.68 $\pm$ 50.25 (50.17~97.20)	91.65 $\pm$ 64.62 (58.42~124.87)	
Month 3 (95% CI)	65.38 $\pm$ 46.44 (43.65~87.11)	88.21 $\pm$ 54.37 (60.25~116.16)	0.211

\*Statistically significant difference, paired t-test

† paired t-test; ‡ 2-way ANOVA

**Table 5. Treatment group changes (mean  $\pm$  SD) from baseline to month 3 in mean total IIEF and IPSS scores (ITT population)**

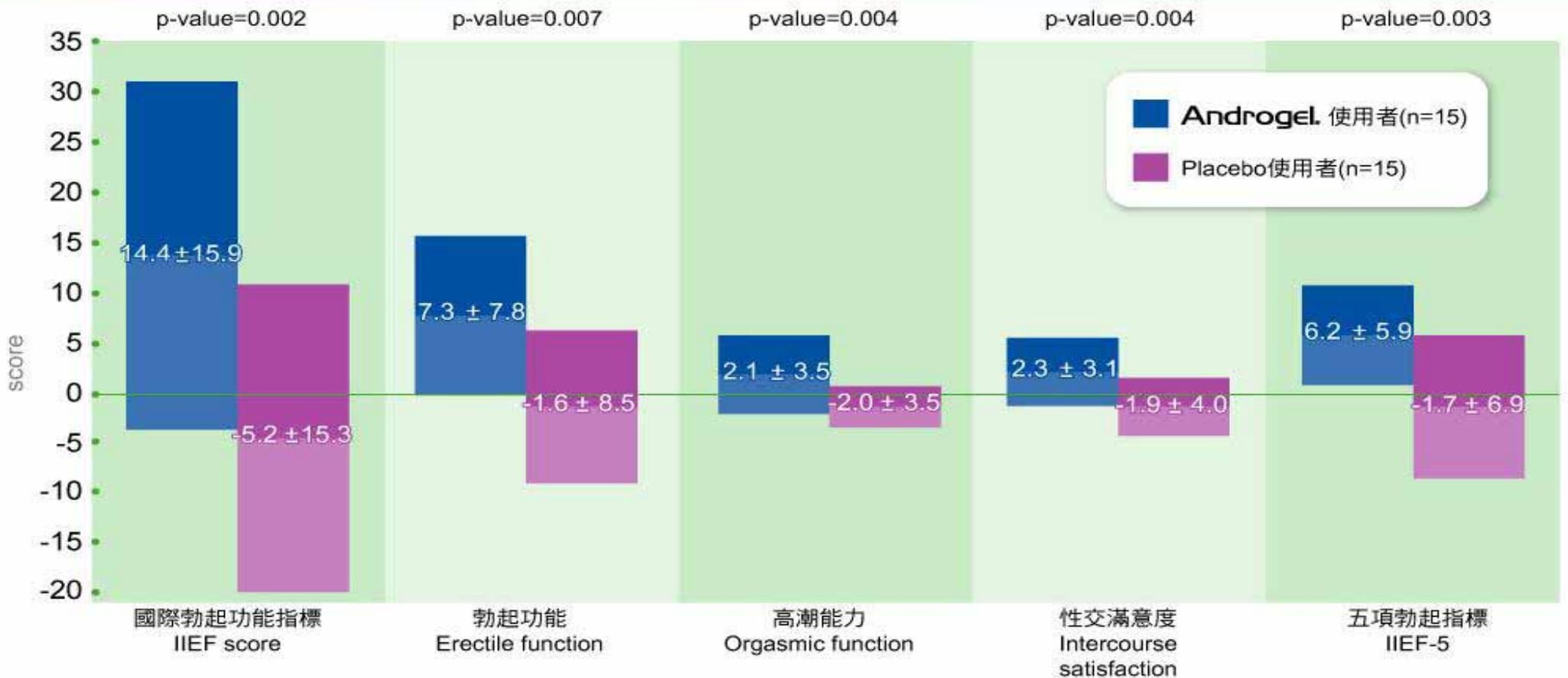
Visit	Transdermal testosterone Gel (N =20)	Placebo (N =15, IIEF; N=17, IPSS)	p value†‡
	<b>IIEF</b>		
Baseline (95% CI)	34.1 $\pm$ 14.0 (26.4~41.9)	42.4 $\pm$ 16.8 (33.1~51.7)	0.159
Month 3 (95% CI)	48.5 $\pm$ 13.9* (40.8~56.3)	37.2 $\pm$ 16.5 (28.0~46.4)	0.003*
	<b>IPSS</b>		
Baseline	8.6 $\pm$ 6.9 (5.2~11.9)	8.8 $\pm$ 5.9 (5.8~11.9)	0.920
Month 3	7.0 $\pm$ 5.0 (4.6~9.4)	6.8 $\pm$ 5.0 (4.2~9.3)	0.091

\*Statistically significant difference, paired t-test

† paired t-test; ‡ 2-way ANOVA

# Androgel Improves Taiwanese Male's Sexual Function

## Result of IIEF

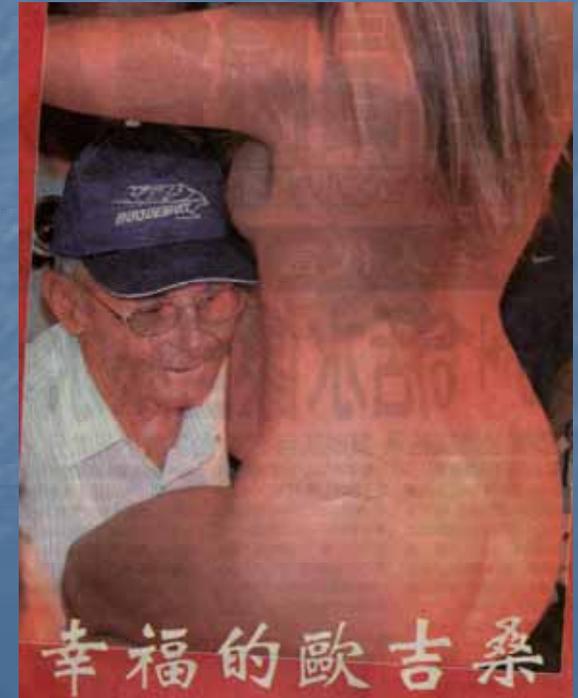


勃起功能(Erection function)為IIEF問卷的第1,2,3,4,5,15題的總合。  
性交滿意度(Intercourse satisfaction)為IIEF問卷的第6,7,8題的總合。

高潮能力(Orgasmic function)為IIEF問卷的第9,10題的總合。  
五項勃起指標(IIEF-5)為IIEF問卷的第2,4,5,7,15題的總合。

# Summary

- Transdermal testosterone gel is an effective and well-tolerated form of TRT for hypogonadal men.
- It can effectively restore serum testosterone level and improve sexual function with few adverse effects.





# Combined Use of Androgen and Sildenafil for Hypogonadal Patients Unresponsive to Sildenafil Alone

Thomas I-sheng Hwang<sup>1,2,3</sup>, Hung-En Chen<sup>1</sup>, Te-Fu Tsai<sup>1</sup>,  
Yi Chia Lin<sup>1</sup>

<sup>1</sup>Division of Urology, Department of Surgery, Shin Kong WHS Memorial Hospital, Taipei, Taiwan

<sup>2</sup>Department of Urology, Taipei Medical University

<sup>3</sup>Department of Urology, College of Medicine,  
Fu-Jen Catholic University.

**Table 1. Demographic of hypogonadal patients (*n*=32)**

	Mean	Range
Age (yr, median)	51.0	(23-73)
BMI (median)	25.6	(23.4-29.8)
ED duration		
3-6 months	2	
6-12 months	5	
> 12 months	25	
Hypogonadism (TT)		
< 290 ng/dL (n=23)	259	(166-290)
< 145 ng/dL (n=9)	67.6	(10-135)
Concurrent conditions		
Alcohol consumption	17	
Smoking	11	
DM	4	
Hypertension	13	
Hyperlipidemia	7	

**Table 2. Total testosterone (TT) and free testosterone (FT) before and after treatment**

	Before (n=32)	Sildenafil (Sil) (n=32)	Testosterone (T) (n=32)	T + Sil (n=21)
TT (ng/dL)	220±101	278±158	415±163*	498±178*
FT (ng/dL)	5.1±1.9	5.6±2.7	10.4±4.0*	11.7±4.6**

\*  $p < 0.01$ ; \*\*  $p < 0.001$

**Table 3. Changes in the International Index of Erectile Function (IIEF) before and after treatment**

	Before (n=32)	Sildenafil (Sil) (n=32)	Testosterone (T) (n=32)	T+Sil (n=21)
IIEF-EF	12.6±7.5	12.0±8.5	14.8±6.8*	17.5±5.2**
Question-3	2.4±0.6	2.3±0.8	3.1±0.7**	3.5±1.0***
Question-4	2.3±0.6	2.3±0.8	2.3±0.6	3.6±0.9***

p < 0.05; \*\* p<0.01; p<0.001

IIEF-EF: erectile function domain of IIEF.

Question-3: patient's ability to achieve an erection sufficient for satisfactory sexual intercourse.

Question-4: patient's ability to maintain an erection sufficient for satisfactory sexual intercourse.

**Table 4. Changes in International Prostate Symptoms Score (IPSS) and uroflow rate (UFR) before and after treatment**

	Before (n=32)	Sildenafil (Sil) (n=32)	Testosterone (T) (n=32)	T+Sil (n=21)
IPSS	12.4±3.4	13.0±3.9	15.9±4.0	19.2±4.0
UFR	18.5±6.5	20.5±6.3	20.2±8.3	21.7±9.2

# Summary

In hypogonadal patients unresponsive to sildenafil, androgen supplementation may improve erectile function and enhance therapeutic effect of PDE-5 inhibitors.

# Conclusion

- Adult hypogonadism is prevalent in Taiwan
- Adult hypogonadism is likely a treatable disorder.
- It is an inspiring challenge for andrologists (urologists) to assess and treat patients with adult hypogonadism.

# Treatment of Andropause- Evidence based ?

Extensive evidence that Testosterone Replacement Therapy (TRT) has a beneficial effect in the short term on many manifestations of andropause.

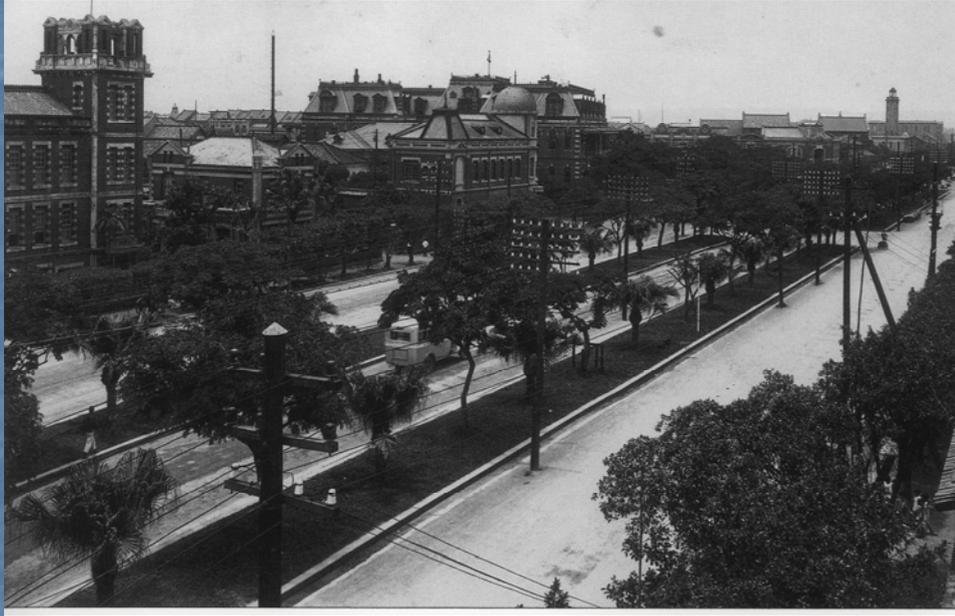
**Circulation, 99: 1666, 1999**

**Am. J. Psychiatry, 159:456, 2002**

**J. Urol. 172: 658, 2004**

# Normal Values of Testosterone

- Criteria for normal testosterone levels are based on data from young men ( $\pm 2.5$  SD)
- Normal total testosterone  $> 11$  nmol/L (or  $> 300$  ng/dL)
- Normal free testosterone  $> 0.225$  nmol/L (or  $6.5$  ng/dL)



Taiwan, 1930



Taiwan, 2005

**Table 1. Mean biochemical markers of androgen stratified into 10 year ranges.**

Age	Number	TT (nmol/l)	cFT (nmol/l)	BT (nmol/l)
40-49	82	16.45	0.32	7.71
50-59	236	15.50	0.29	6.95
60-69	211	16.23	0.26	6.19
70-80	119	15.67	0.22	5.19
Mean		15.89	0.27	6.47

TT: total testosterone

cFT: calculated free testosterone

BT: bioavailable testosterone

# Andropause

Male menopause

Male climacteric

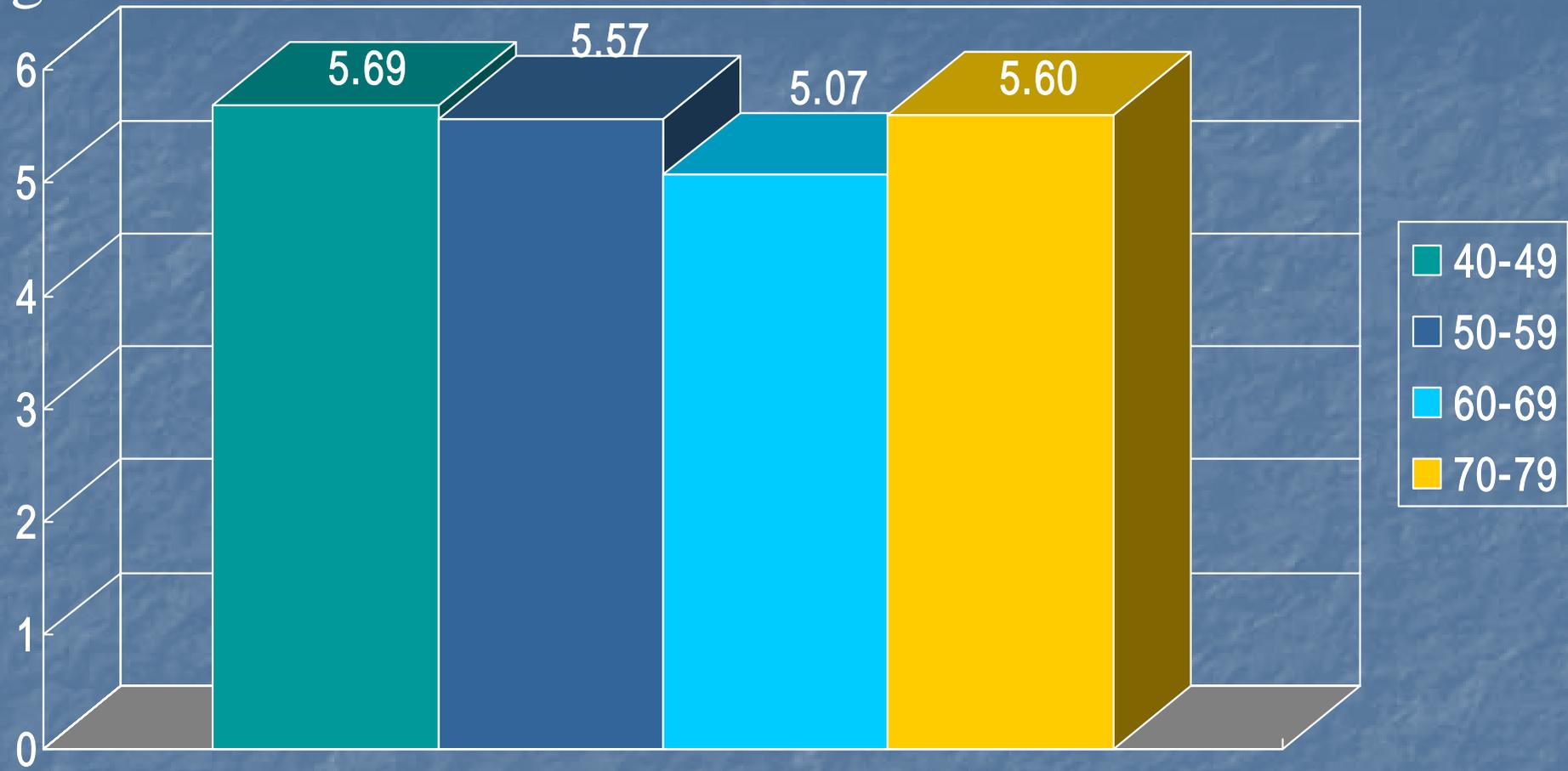
Androgen decline in the aging male  
(ADAM)

Partial androgen decline in the aging  
male (PADAM)

# The characteristics of ADAM:

- The onset is unpredictable
- The manifestations are subtle and variable.

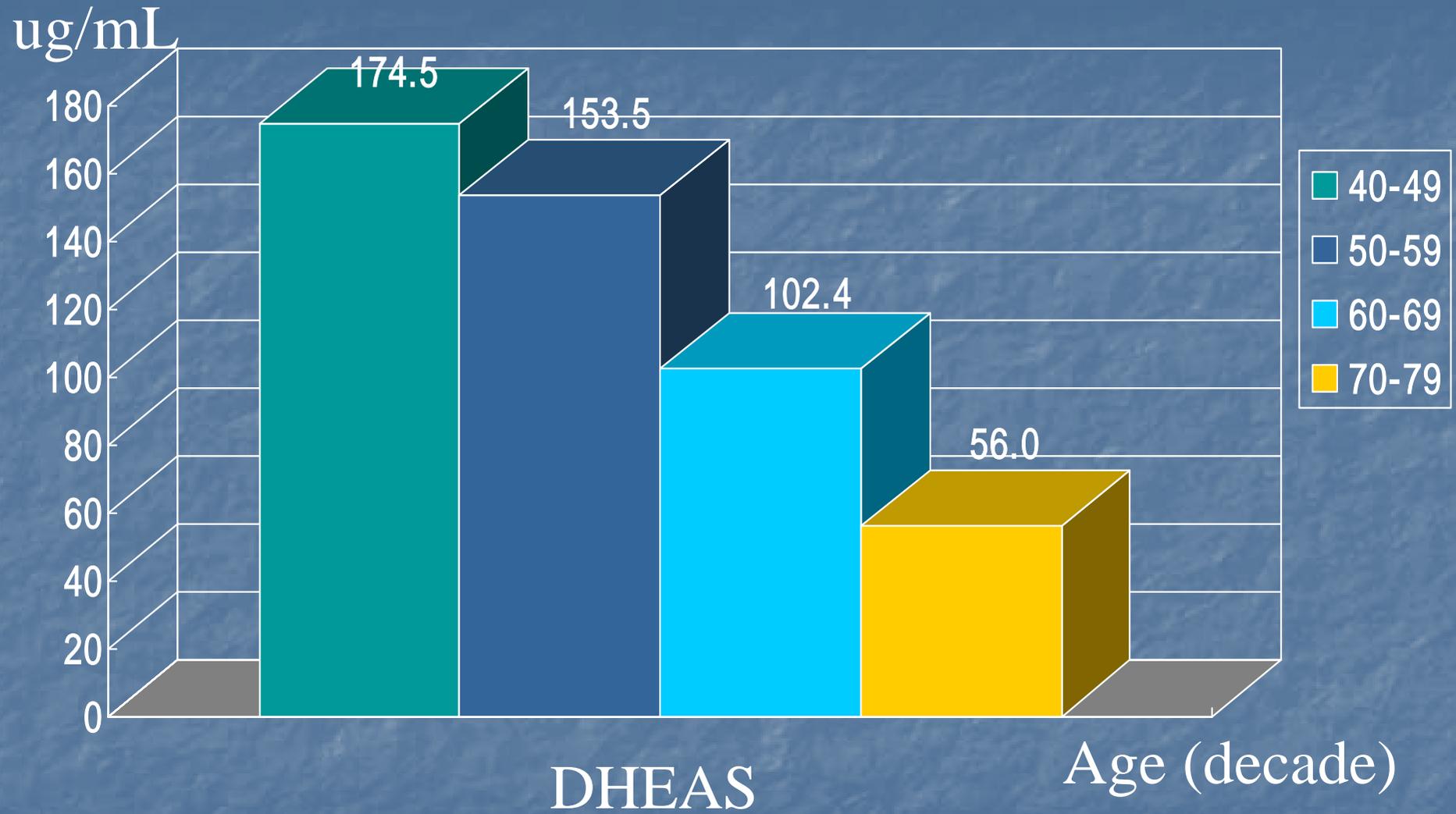
ng/mL



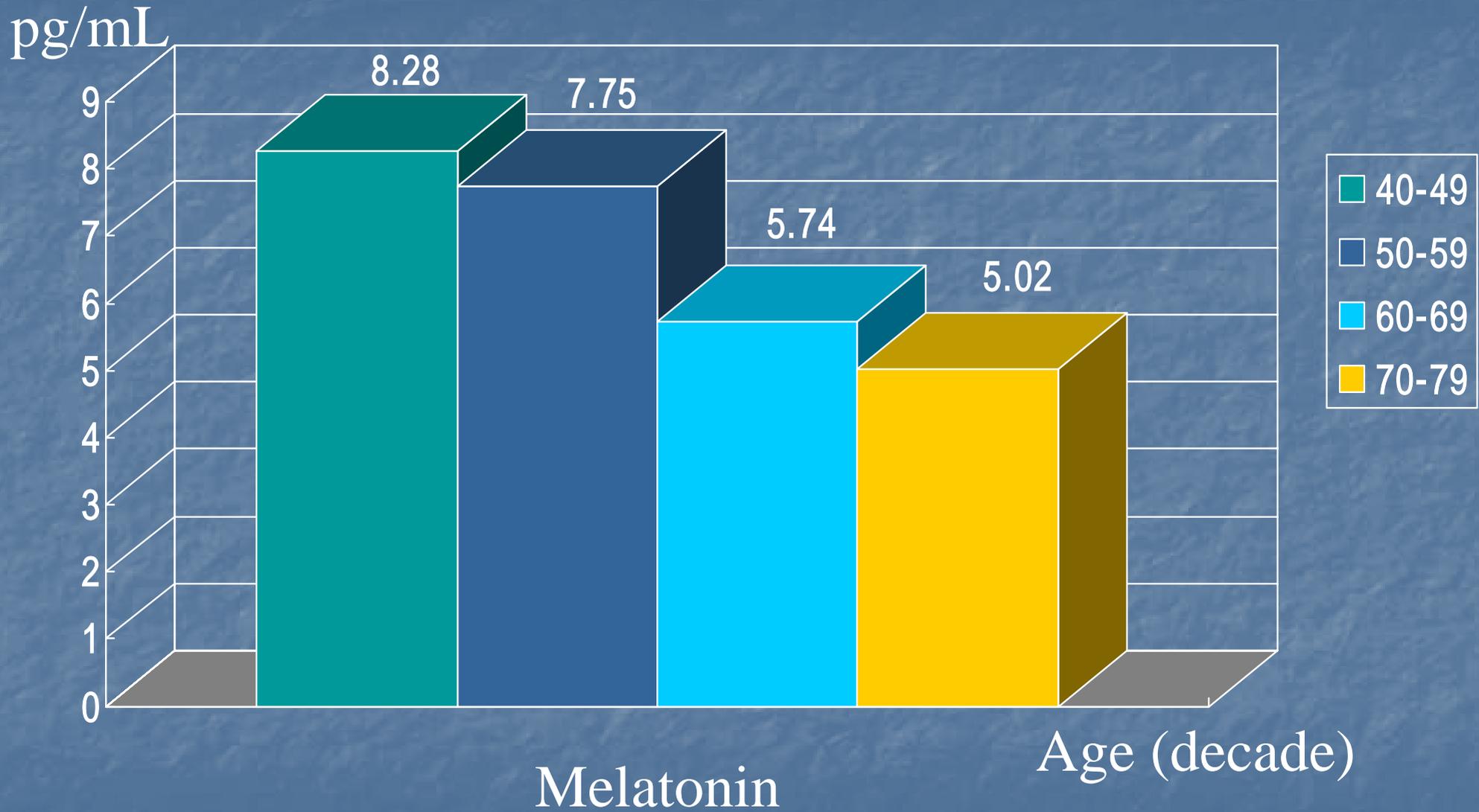
Testosterone

Age (decade)

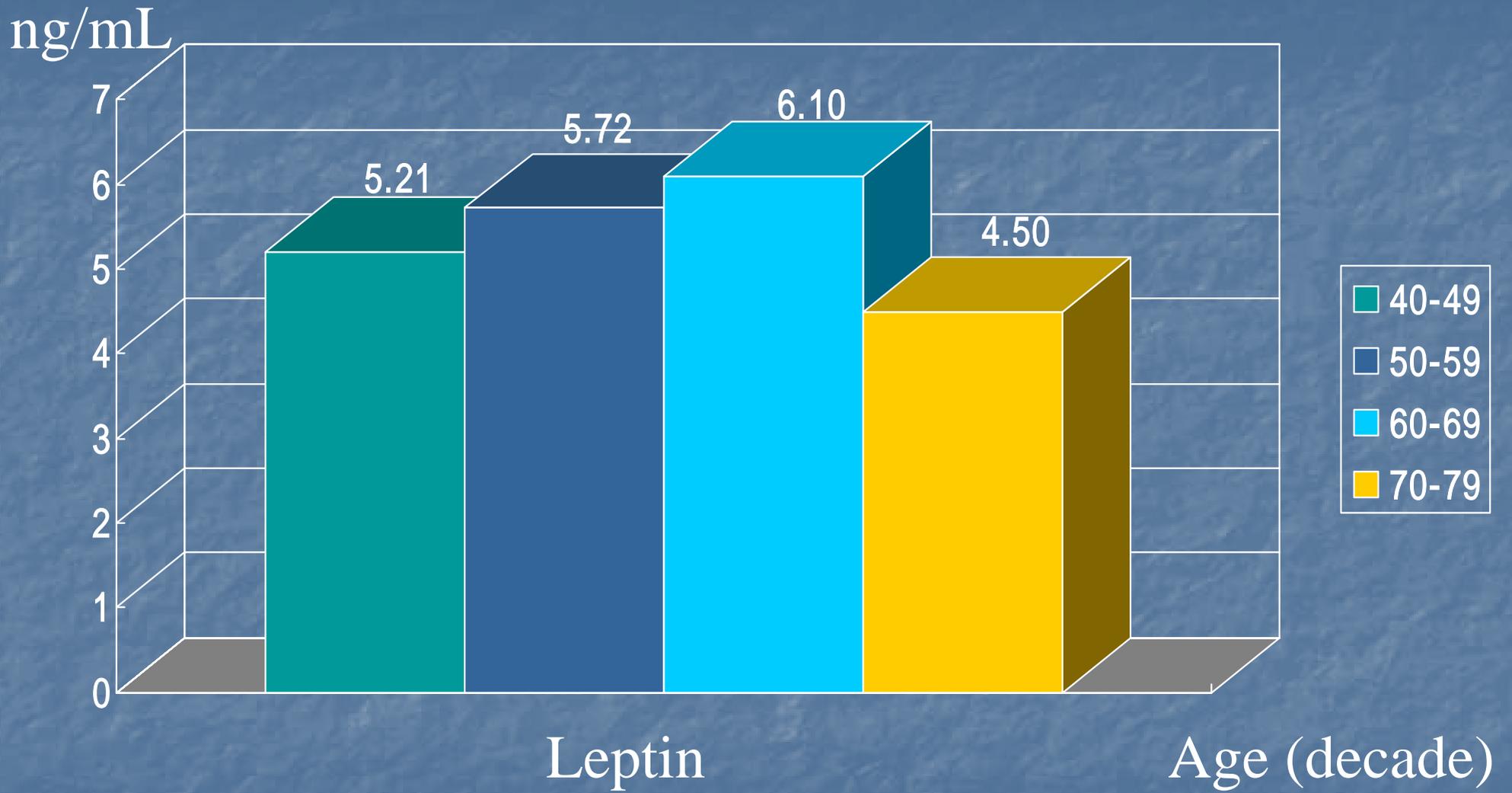
*Hwang et al, 2001*



*Hwang et al, 2001*



*Hwang et al, 2001*



*Hwang et al, 2001*

# Andropause syndrome

- ↓ 1. Libido, erectile dysfunction.
2. Mood change, depression, anger, fatigue.
- ↓ 3. Lean body mass, → muscle strength.
- ↓ 4. Body hair, skin alteration.
- ↓ 5. Bone density
- ↑ 6. Visceral fat.

# ADAM

\* a clinical entity characterized biochemically by a decrease in :

- Androgen
- Growth hormone
- Melatonin
- DHEA(s)
- Others

Suspected Hypogonadism

Check serum testosterone

Low

Normal

Free T, SHBG  
FSH, LH, Prolactin

Seek other causes

Diagnostic algorithm for andropause (I)

Free T, SHBG  
FSH, LH, prolactin

Abnormal

Normal

High gonadotropin

Normal/low  
gonadotropin

Seek other causes

Testosterone  
Supplementation

Investigate  
pituitary

Diagnostic algorithm for andropause (II)

# Putative benefits of testosterone replacement in older men

---

1. Enhanced libido
2. Enhanced erectile capability
3. Increased muscle strength
4. Increased bone density
5. Decreased minimal trauma hip fracture
6. Decreased leptin
7. Increased cognitive function.
8. Enhanced coronary artery blood flow.
9. Improved functional status.