

Application of Male Hormone in Men with Obesity

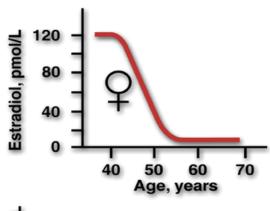
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Low testosterone; Normal or Pathologic Process?

- Andropause: Testosterone ↓ (1.6%/Y from mid 30s), Estrogen ↓
- Adrenopause: DHEA ↓, Cortisol ↑
- Somatopause: GH/IGF-1 ↓







Distribution of Testosterone

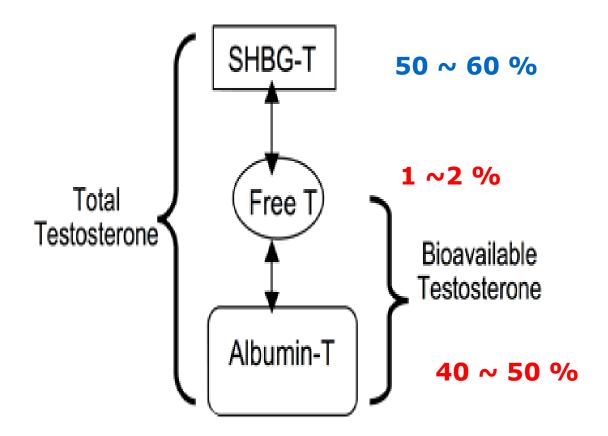
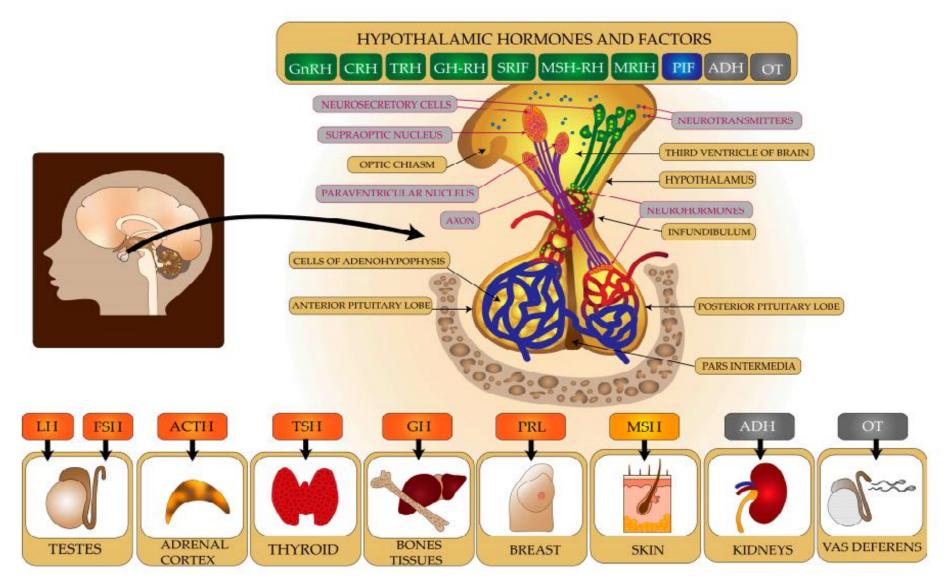
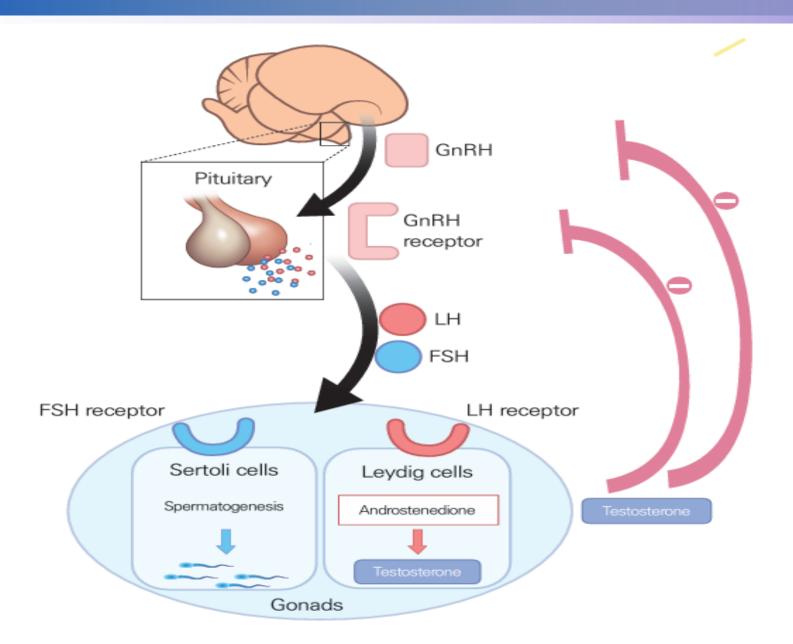


FIGURE 1.FORMS OF TESTOSTERONE IN THE BODY. SHBG-BOUND TESTOSTERONE IS HORMONALLY INACTIVE. T=TESTOSTERONE.

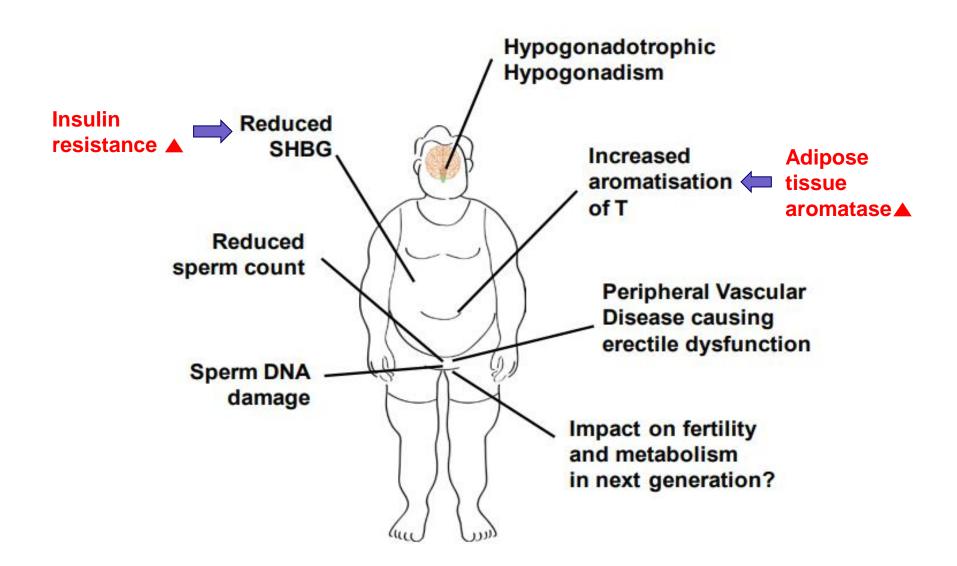
CNC & Endocrine organs



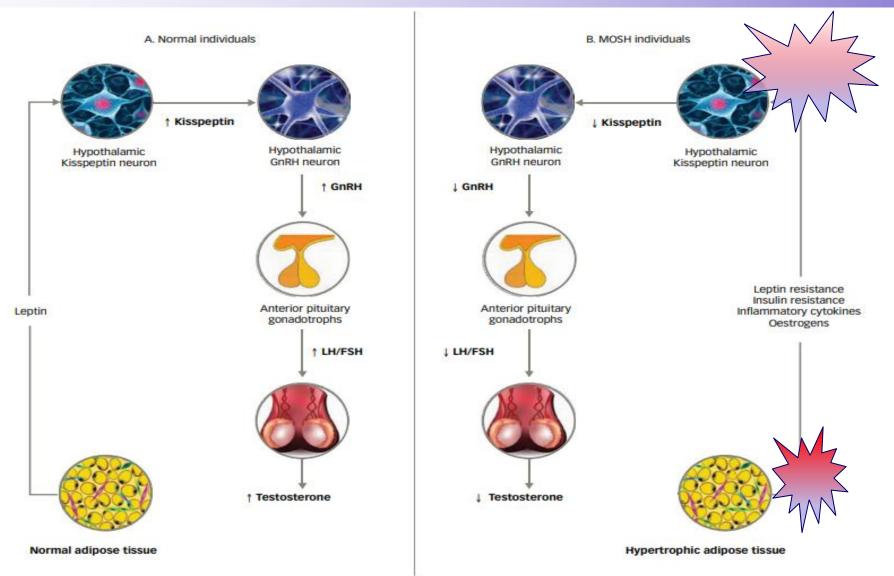
HPG Axis



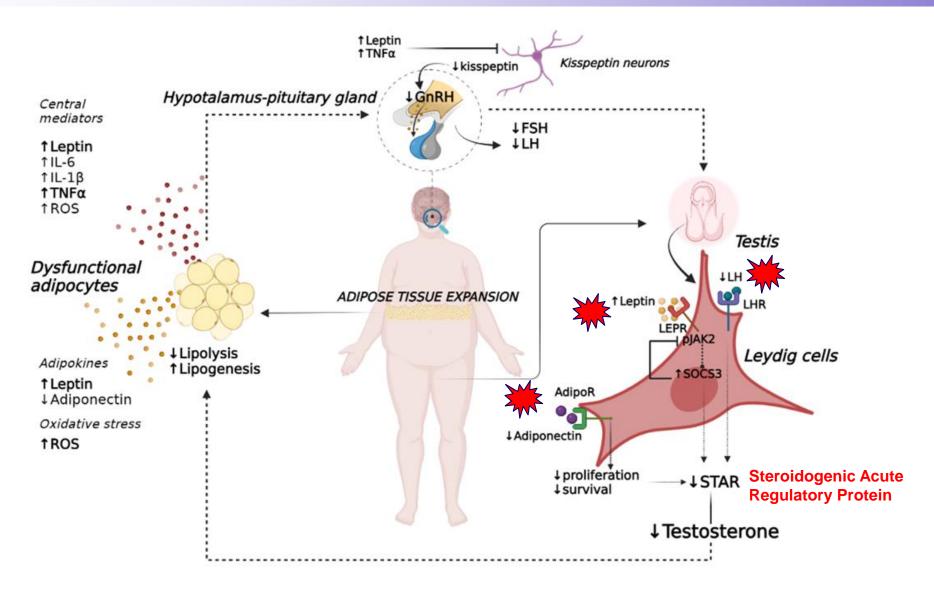
Obesity on reduced fertility



Testosterone regulation in Male Obesity-related Secondary Hypogonadism



The vicious cycle of Obesity-hypogonadism



Obesity-induced HPG Axis Dysfunction

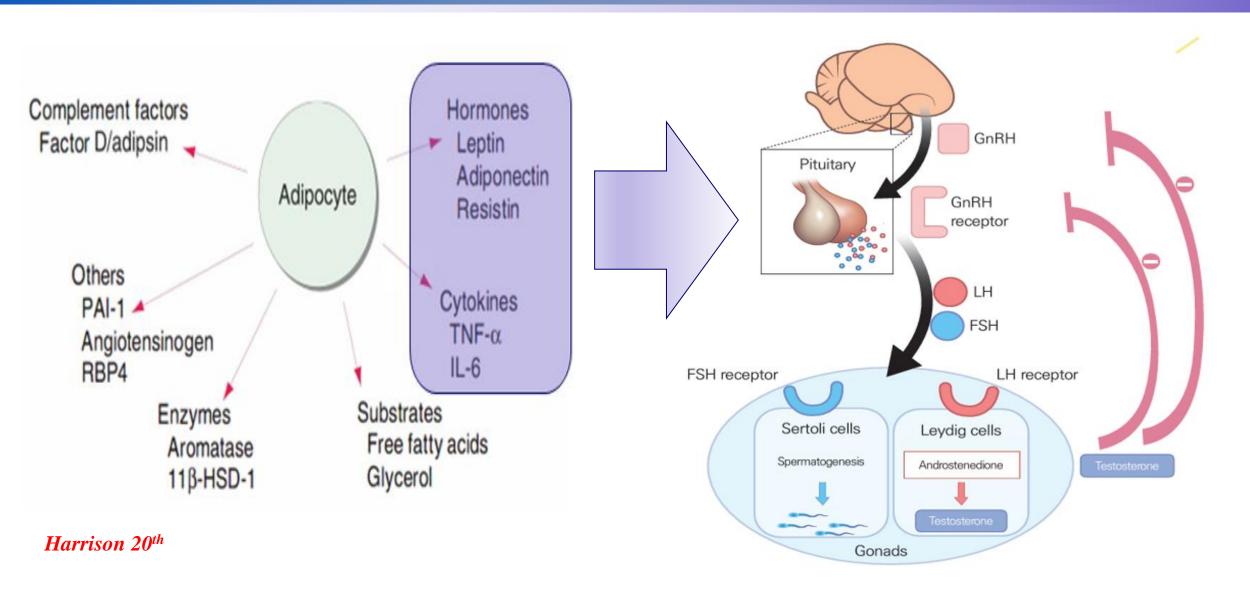
Central mechanisms

- Leptin
- Inflammatory cytokines; IL-1, IL-6, TNF-a
- Hypothalamic gliosis
- Estrogen

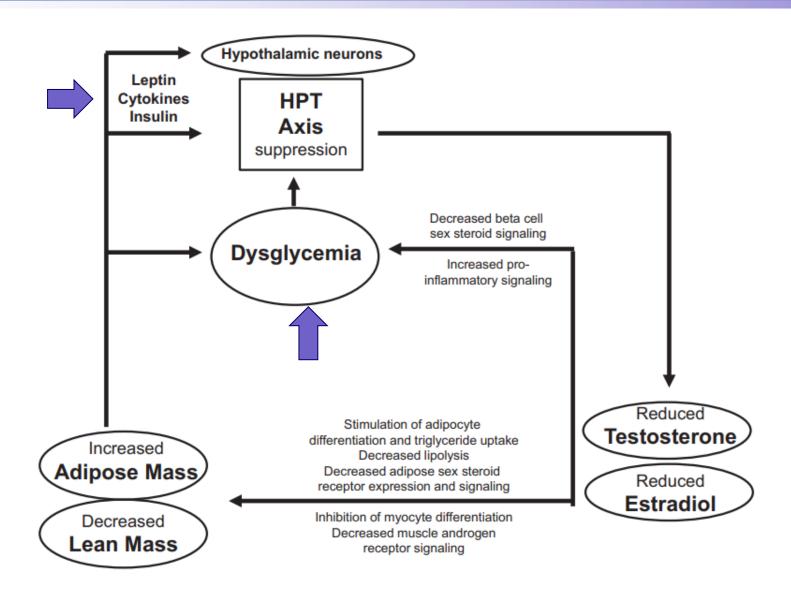
Peripheral mechanisms

- Testis dysfunction
- Adenosine
- Iron retention
- High fat diet
- Adipose tissue resistance by testosterone
- SHBG variation

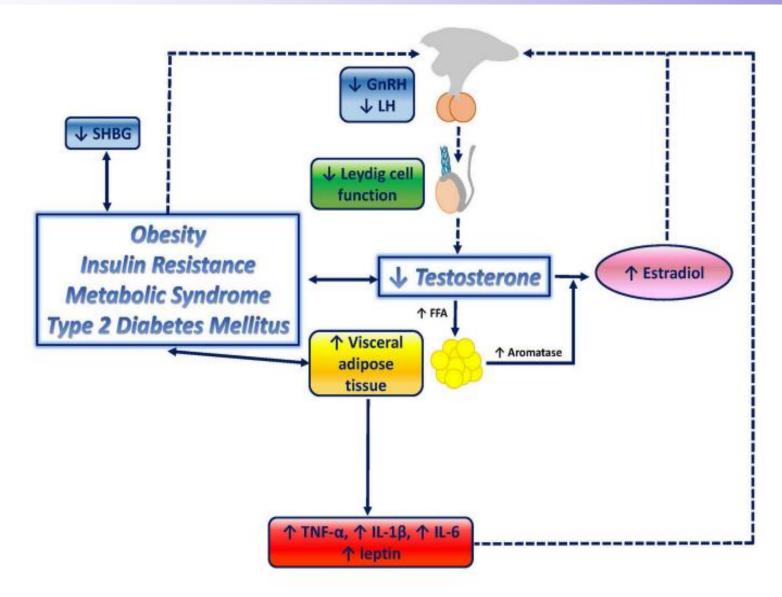
Adipokines on HPG Axis



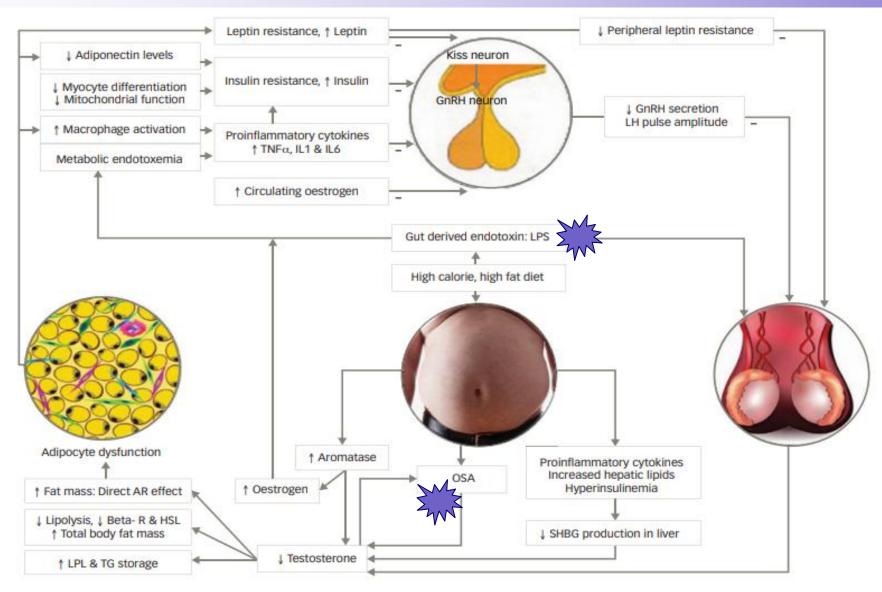
Lowered sex hormones & Diabesity



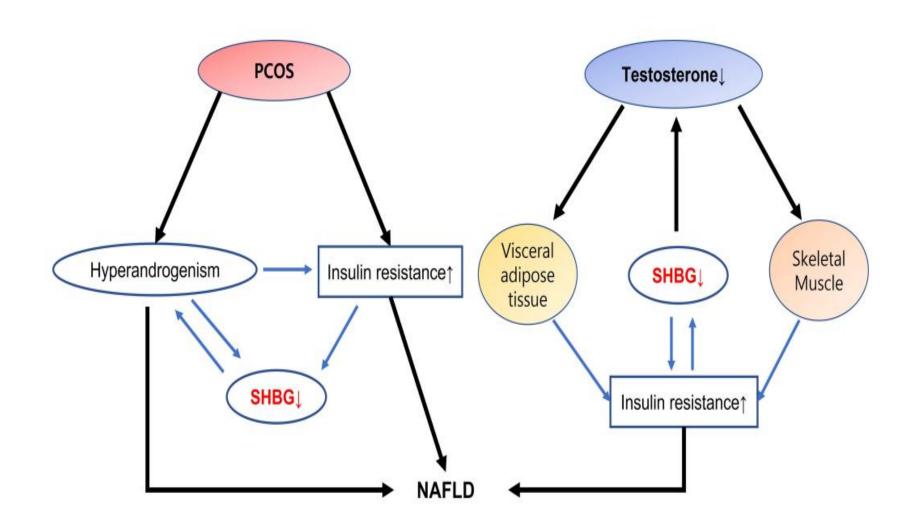
Testosterone deficiency & metabolic disorder



Obesity-related secondary Hypogonadism

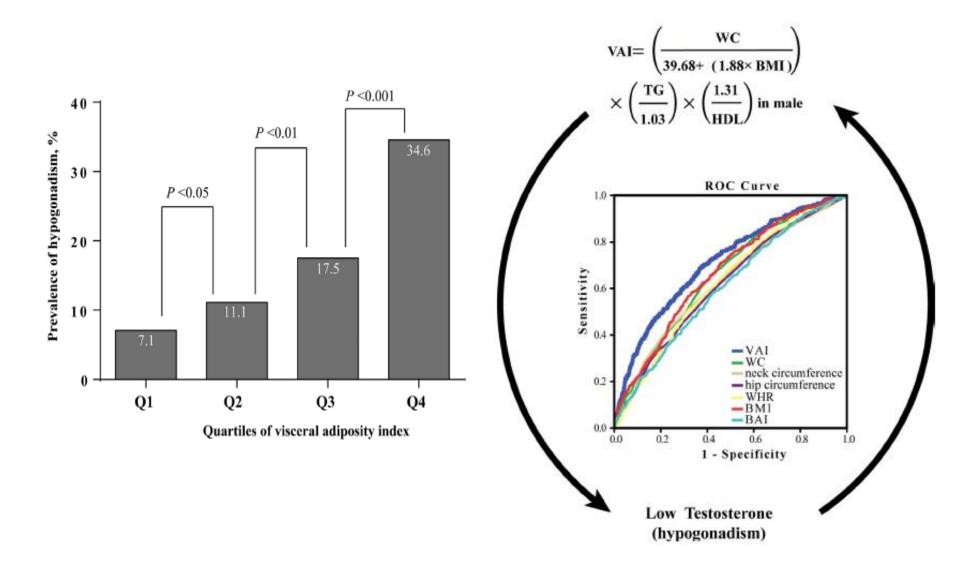


Low T, Low SHBG ► NAFLD

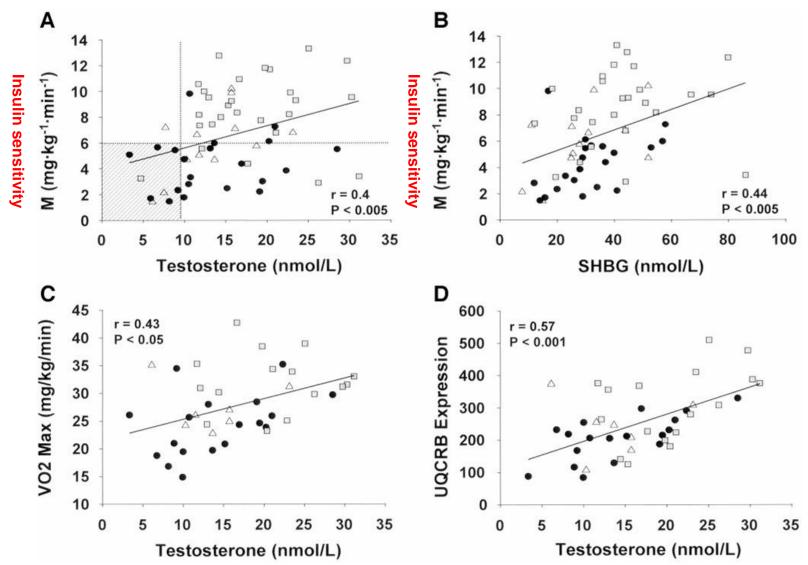


Front. Endocrinol. 13:1053709. doi: 10.3389/fendo.2022.1053709

Visceral fat vs. Hypogonadism (2,759 Chinese men)



Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men





Contents available at ScienceDirect

Diabetes Research and Clinical Practice





Low testosterone and clinical outcomes in Chinese men with type 2 diabetes mellitus – Hong Kong Diabetes Registry



-1.239 Men with T2D -Median duration; 9Y -4.8 Y f/u

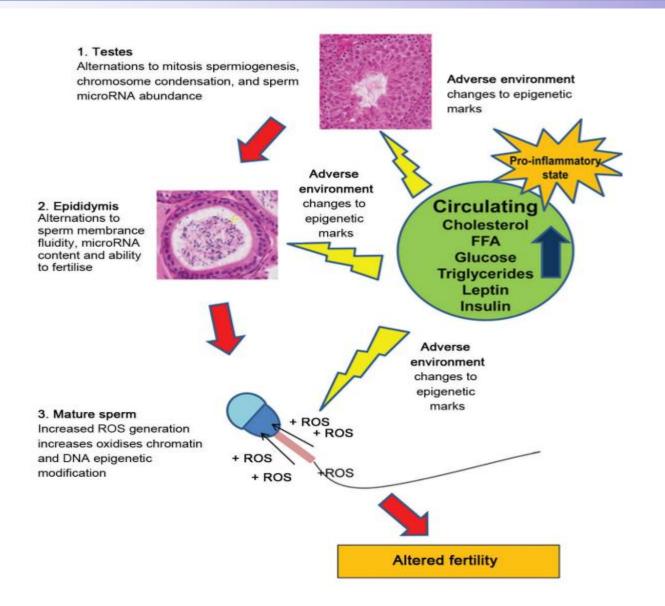
Table 2 – Multivariate logistic regression showing the association of the metabolic syndrome with low testosterone using serum total testosterone < 9 nmol/L as cutoff value after adjustment for covariables in Chinese men with type 2 diabetes mellitus.

	Odds ratio	95% confidence intervals	P
Testosterone < 9 (nmol/L) <3.0ng/ml	2.63	1.56–4.61	<0.001
Covariables			
Age	1.01	1.00-1.02	0.167
Body mass index	1.43	1.36-1.51	< 0.001
HbA1c	1.07	0.97-1.18	0.169
Log urinary albumin to creatinine ratioa ^a	1.28	1.17-1.39	< 0.001
Coronary heart disease at baseline	1.41	0.87-2.31	0.166

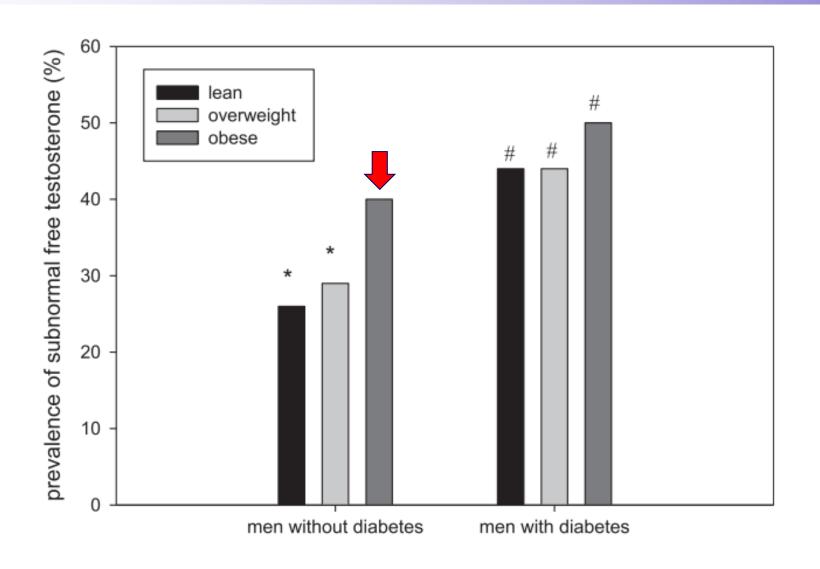
Other covariables not selected by the model included disease duration, current or ex-smoker, family history of diabetes, total cholesterol, LDL-C, eGFR, chronic kidney disease, history of retinopathy, sensory neuropathy, microalbuminuria, macroalbuminuria, congestive heart disease, cerebrovascular disease, and peripheral vascular disease

^a Urinary albumin to creatinine ratio was logarithmically transformed due to skewed distribution.

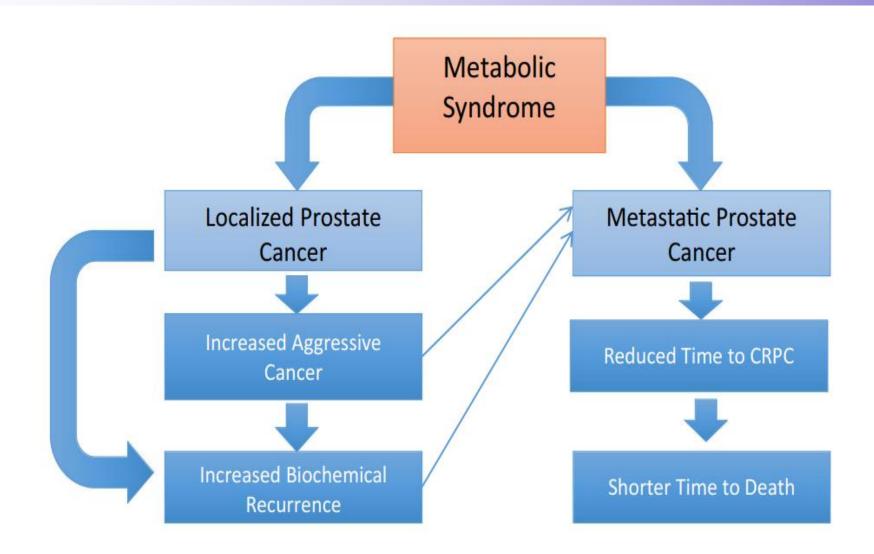
Metabolic derangements on subfertility



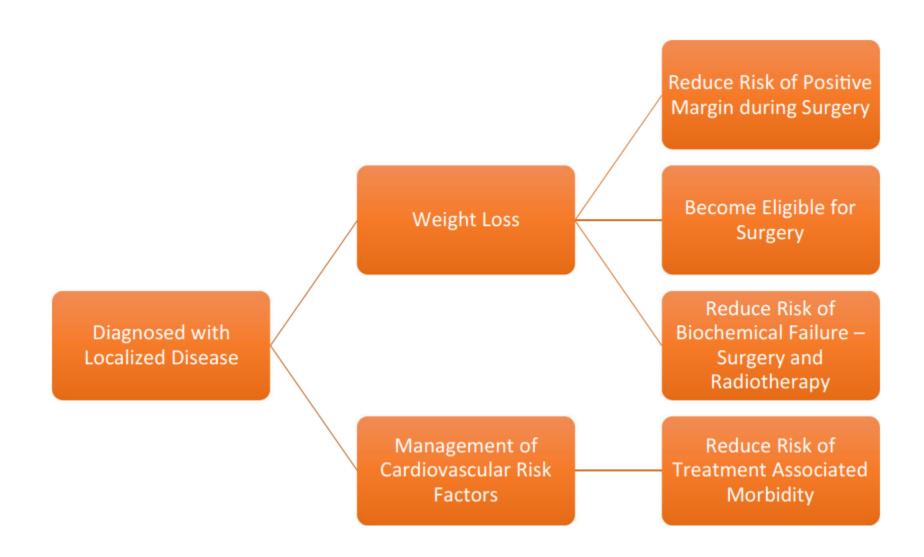
Subnormal Free Testosterone



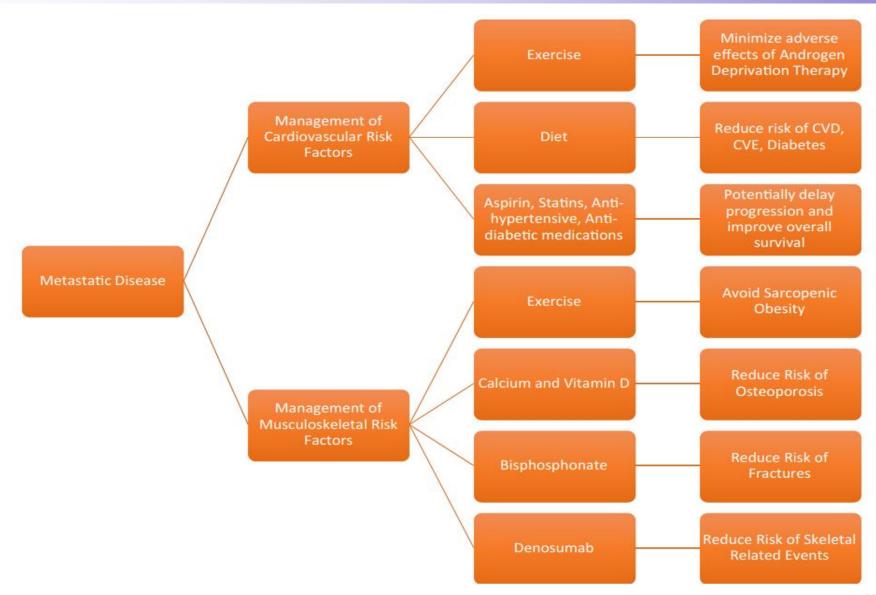
MS on Prostate cancer



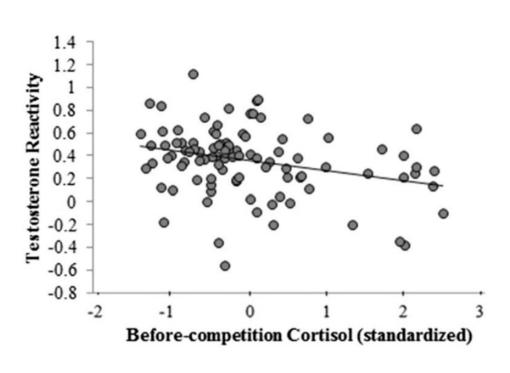
Recommendation in localized disease

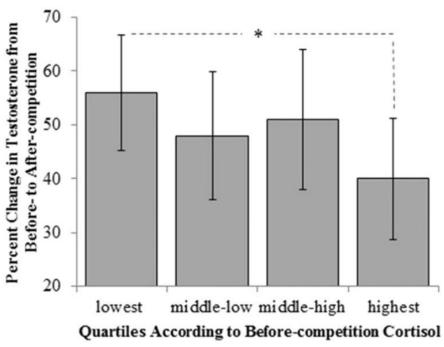


In case of metastatic disease

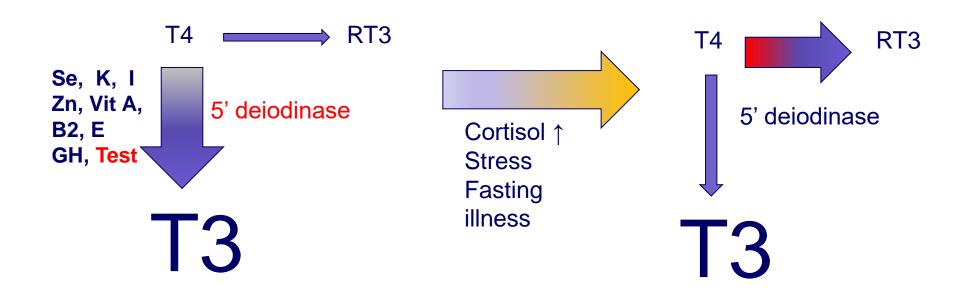


Stress and low Testosterone



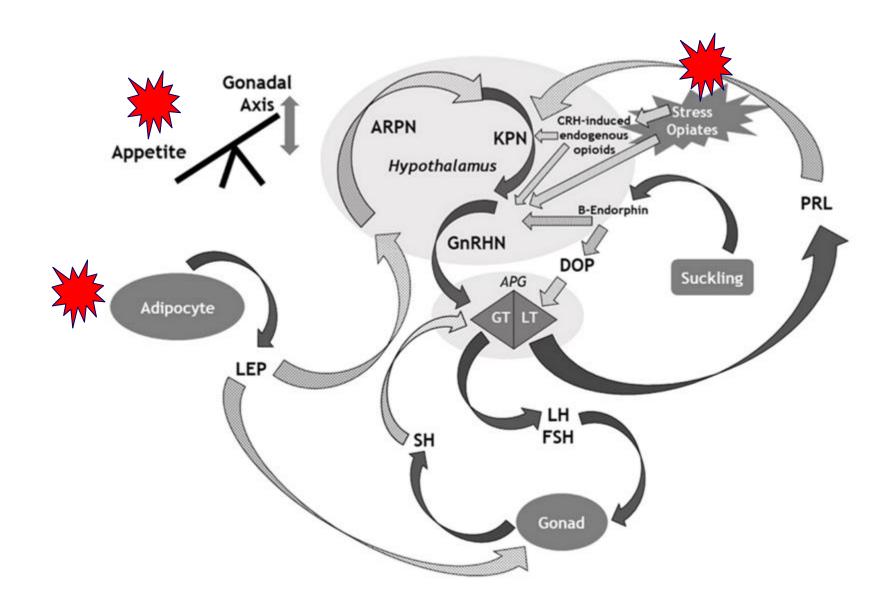


Thyroid Hormone

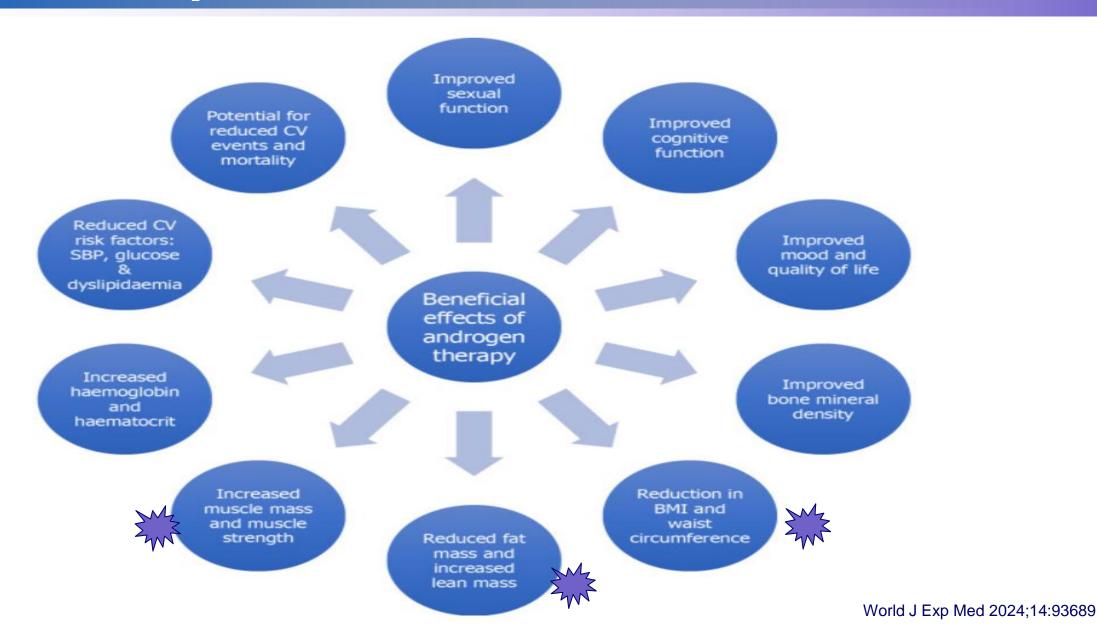


- ✓ Decreased production of T4
- deficiency of Zn, Cu, vit A, B2, B6, C
- ✓ Interference of 5' deiodinase
- Se def, stress, Cd, Hg, Pb, starvation,
- cortisol ↑, DM, inflammation, aging

Main mechanism that influence the gonadal axis



Therapeutic benefits of ART in MOSH



Weight loss on Male Hormones

Table 3. Mediation of effect of intensive lifestyle intervention by mean waist circumference at year 1 on hormones at year 4 of the Look AHEAD study

	Females	Males			
	Percent change in hormone level				
E2	-2.6 (-4.3,-1.1)	-1.2 (-2.4,-0.1)			
Total T	-0.6 (-2.0, 0.7)	0.7 (-0.4, 1.9)			
BioT	-0.1 (-1.4, 1.4)	0.5 (-1.0, 1.9)			
SHBG	-1.2 (-2.4, -0.1)	$-0.8 \; (-2.1, 0.5)$			

Abbreviations: bioT, bioavailable testosterone; E2, estradiol; T, testosterone.
^aMean change in waist circumference at year 1 due to intensive lifestyle intervention in females was -6.4 cm (95% confidence interval: -10.7 to -2.5) and in males was -8.0 cm (95% confidence interval: -12.6, -3.8).

Testosterone response to long-term weight loss

Table 2. Median (IQR) values for sex hormones at each time point. after Op

Parameter IQR (Q1, Q3)	Baseline	6 months	12 months	24 months	36 months
Females					
Testosterone, nmol/L, (0.0-1.8)	0.9 (0.6, 1.4)	0.6 (0.2, 0.9)	0.6 (0.5, 0.9)	0.6 (0.2, 0.85)	0.7 (0.2, 0.95)
SHBG, nmol/L (20-110)	29.1 (21.3, 49)	47.8 (29.5, 70.1)	47.0 (33.6, 64.6)	56 (31.6, 75.5)	46.5 (39.5, 75.2)
LH (IU/L), Postmenopausal Females: (7.7–60)	17.3 (5.7, 30.0)	15.8 (4.75, 34.6)	22.5 (6.6, 37.6)	28.4 (7, 41.9)	25.6 (13.6, 36.0)
FSH (IU/L), Postmenopausal Females: (25–140)	27.4 (5.7, 53.6)	33.1 (4.4, 65.4)	48.0 (9.85, 66.1)	52.1 (12.9, 71.4)	55.2 (37.0, 68.0)
Oestradiol pmol/L, Postmenopausal Females: <100	87 (54.2, 218)	67 (49, 244)	53 (49, 172)	54.5 (49, 109)	49 (49, 56.8)
Males					
Testosterone, nmol/L, (12-36)	11.8 (10.1, 16.4)	15.7 (12.5, 20.0)	17 (13.7, 19.8)	17.7 (14.3, 22.5)	17.8 (14.4, 19.4)
SHBG nmol/L, Males (20–90)	20.1 (17, 31.6)	36.8 (32.1, 41.0)	35.2 (28.3, 43)	41 (30, 50)	37.5 (30.5, 43.5)
LH (IU/L), (1.7-8.6)	4.0 (2.7, 5.3)	4.9 (4.15, 5.65)	4.25 (3.08, 4.25)	5.15 (4.3, 6.1)	4.85(3.97, 5.6)
FSH (IU/L), Males (1.5–13)	4.2 (3.7, 6.3)	4.9 (4.0, 6.8)	4.45 (3.4, 5.2)	4.65 (3.8, 5.6)	5.1 (4.2, 9.3)
Oestradiol pmol/L, (0–160)	113 (80.5, 131)	103 (87.8, 112)	104 (72.2, 130)	106 (88, 120)	102 (69.8, 130)

Bolded values indicate statistical significance for changes in parameters at each timepoint in comparison with the baseline values. FSH Follicle-stimulating hormone, LH Luteinizing hormone, SHBG sex hormone-binding globulin.

Weight Loss as Therapeutic Option to Restore Fertility in Obese Men: A Meta-Analytic Study

Daniele Santi ¹ ², Carla Greco ¹ ³, Arcangelo Barbonetti ⁴, Manuela Simoni ¹ ³, Mario Maggi ⁵, Giovanni Corona ⁶

Affiliations + expand

PMID: 39344112 DOI: 10.5534/wjmh.240091

Abstract

Purpose: Weight loss has been shown to significantly elevate testosterone serum levels, though the impact on semen analysis parameters and fertility remains incompletely understood. The objective of this study was to examine the influence of body weight loss on semen parameters in obese men.

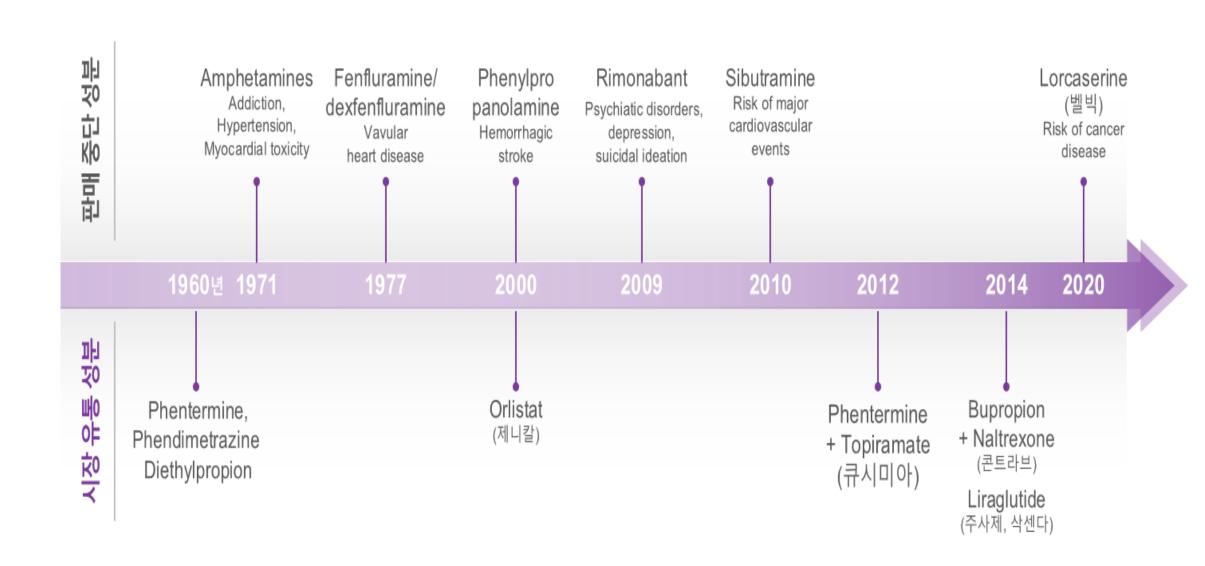
Materials and methods: A meta-analysis was performed that included clinical trials in which a semen analysis before and after weight loss was evaluated. All strategies potentially available for weight loss were considered eligible. The primary outcome was the comparison of conventional semen analysis parameters before and after weight loss.

Results: Twelve studies were considered including 345 subjects (mean age 37.6±7.9 years; mean baseline body mass index 45.4±6.0 kg/m²). Weight loss resulted in a significant increase of sperm concentration (effect size 0.495, standard error 0.251 [0.003, 0.986], p=0.049) and progressive motility (effect size 0.567, standard error 0.372 [0.370, 0.764], p<0.001). Moreover, a significant decrease of sperm DNA fragmentation index after weight loss (effect size -0.689, standard error 0.278 [-1.123, -0.255], p=0.002) was observed.

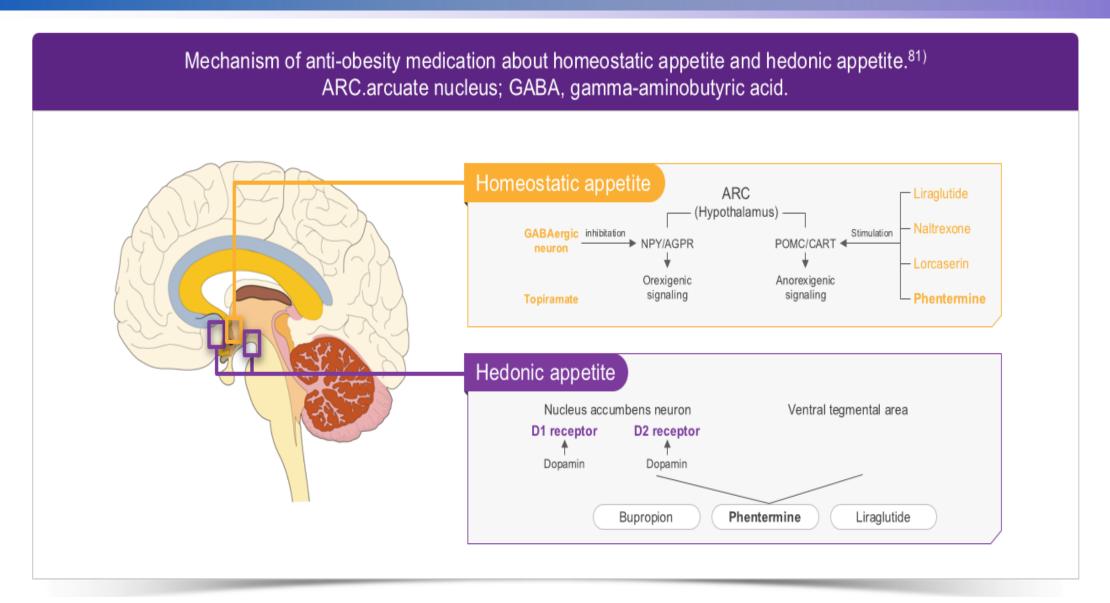
Conclusions: This meta-analytic analysis confirmed that body weight loss may improve qualitative and quantitative sperm characteristics providing evidence for suggesting weight loss to male partners with obesity and semen analysis alteration in couples attempting conception.

World J Mens Health. 2024 Aug 21. doi: 10.5534/wjmh.240091. Online ahead of print.

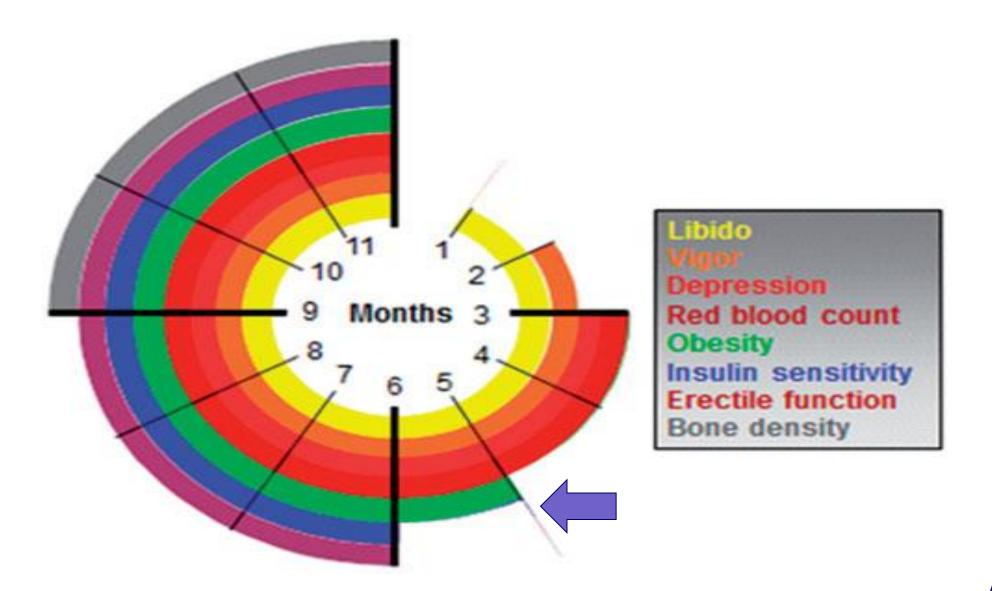
비만 치료 약제들



식욕 조절의 기전



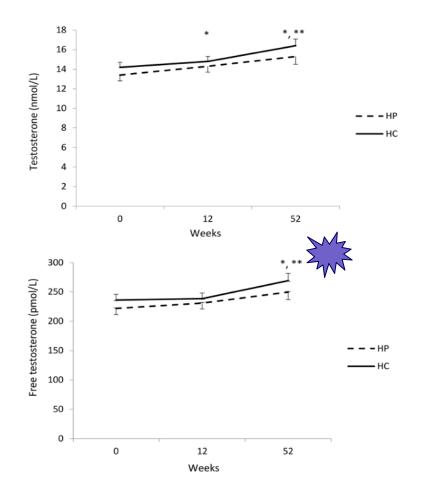
Time-dependent onset of effects after TRT



Diet on testosterone

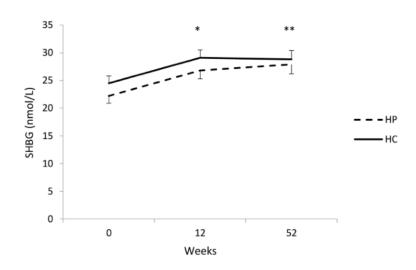
Table 2. Change in outcomes with weight loss intervention for all participants combined.

Outcome measures	0-12 weeks	12-52 weeks	0-52 weeks
Weight (kg)	-8.9±0.4, P<0.001	-1.6±0.6, P = 0.034	-10.5±0.8, P<0.001
BMI (kg/m²)	-2.8±0.1, P<0.001	-0.6±0.2, P = 0.018	-3.4±0.3, P<0.001
Waist circumference (cm)	-10.4±0.4, P<0.001	-0.7±0.5, P = 0.700	-11.0±0.7, P<0.001



HP; **35%** P, 40% C, 25% F (n=57)

HC; 17% P, 58% C, 25% F (n=61)



고탄 ▶ 인슐린 분비 ▶ T합성 자극

Low Carbohydrate?

Table 4 End points before and after the intervention

	Control gourp $(n=6)$			Low Carbohydrate group $(n=12)$		
	Before	After	<i>P</i> -value	Before	After	<i>P</i> -value
Weight (Kg)	98.3	97.3	0.04	96.5	91.9	0.002
Body Mass Index	30.2	29.7	0.07	31.7	30.0	0.01
Abdominal circumference (cm) *	113.3	110.5	0.06	112.2	106.3	0.002
Hip circumference (cm)	105.7	105.2	0.41	104.3	102.3	0.21
Waist circumference (cm) **	108	107.3	0.39	106.4	102.8	0.10
Total testosterone (ng/dL)	217.7	227.2	0.76	229.1	310.7	0.002
Calculated free testosterone (ng/dL)	4.3	4.8	0.58	4.7	6.7	0.001

^{*} Tape measure around person's umbilical scar

Table 3 Hypogonadism and symptoms of hypogonadism prevalence using serum total testosterone level and ADAM score before and after the intervention

	Control gourp (n=6)		Low Carbohydrate group (n = 12)		
	Before	After	Before	After	<i>P</i> -value
Total testosterone < 300 ng/ dL (%)	100	83.3	100	50	0.05
Symptoms of hypogonadism by ADAM score (%)	100	85.7	78.6	21.4	< 0.01

The control group was instructed to continue eating normally but received guidance about healthy eating patterns. The low-carbohydrate group was instructed by a nutritionist, member of the study team, to reduce carbohydrate intake and increase protein and fat intake [18]. Their diet could not contain more than 25–30% carbohydrates per day, aiming for 20–30 g carbohydrate per day. The two diets have the same amount of calories.

^{**} Tape measure around person's middle (between the bottom of the ribs and the top of the hipbones)





Review

Impact of GLP-1 Agonists on Male Reproductive Health—A **Narrative Review**

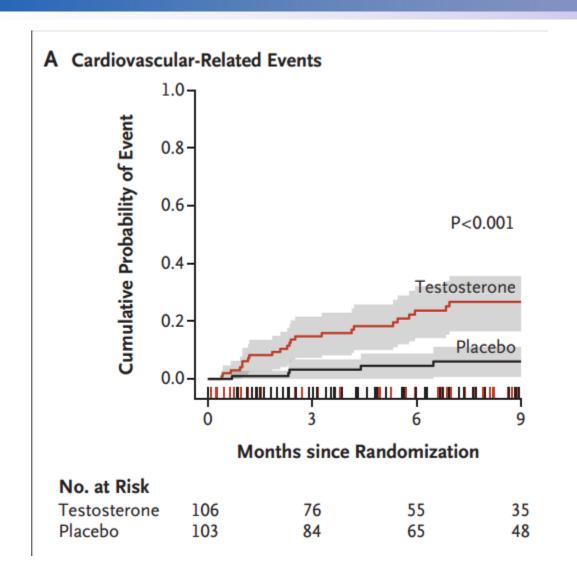
Alexandra Aponte Varnum¹, Edoardo Pozzi^{1,2,3}, Nicholas Allen Deebel⁴, Aymara Evans¹, Nathalie Eid⁵, Hossein Sadeghi-Nejad 5 and Ranjith Ramasamy 1,* [D]

and sperm parameters. Results—GLP-1 receptors have been identified within the male reproductive system according to the existing literature. While the exact mechanisms are not well understood,

in obese men.

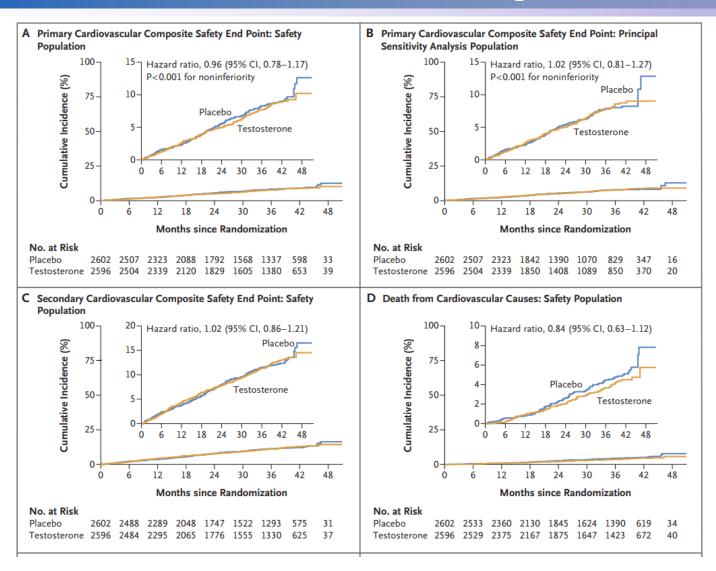
they appear to be involved in glucose homeostasis and energy metabolism, both vital processes in spermatogenesis. Multiple clinical trials have demonstrated the efficacy of GLP-1 RAs for promoting weight loss. Recent studies show that the use of GLP-1 RAs in obese males may enhance sperm metabolism, motility, and insulin secretion in vitro, along with positive effects on the human Sertoli cells. Recent clinical trials discussed in this review demonstrate weight loss associated with GLP-1 RAs is correlated with improvements in sperm count, concentration, and motility. However, the direct impact of GLP-1 RAs on male reproductive hormones remains unclear, necessitating further research to confirm their potential role in treating male infertility. *Conclusions*—This narrative review summarizes the existing literature discussing the potential impact of GLP-1 RA on the male reproductive system, emphasizing their potential therapeutic role in addressing idiopathic infertility in obese men. Despite numerous studies exploring the influence of GLP-1 and GLP-1 RAs on reproductive hormones, testicular function, and spermatogenesis, further clinical trials are crucial to validate initial evidence. Longer follow-up periods are essential to address uncertainties regarding the long-term repercussions and outcomes of GLP-1 RA use. While this holds true, the current literature suggests that GLP-1RAs show promise as a potential therapeutic approach for improving sperm parameters

Testosterone Treatment (TRT) Adverse effect?



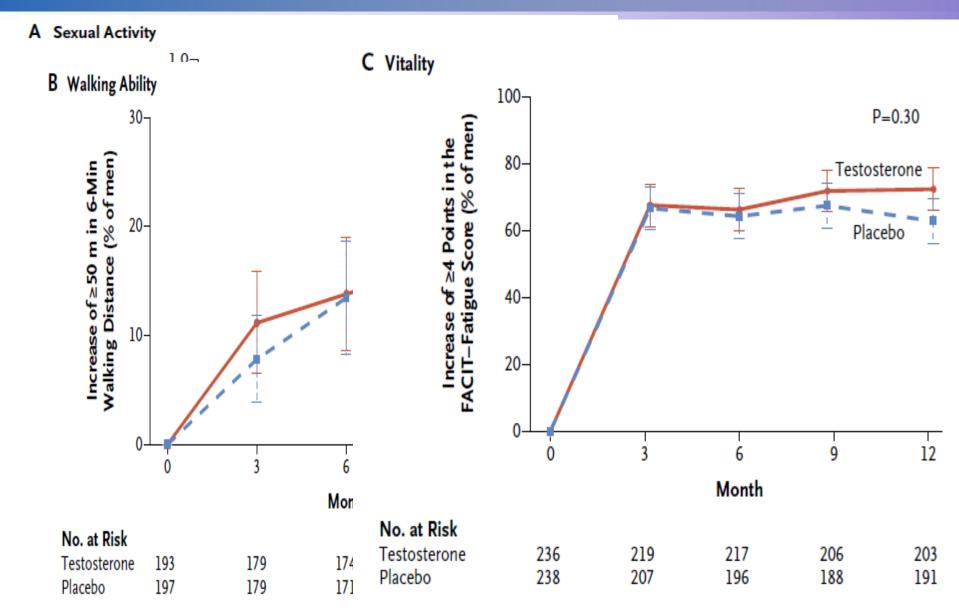
- -RCT, 209 men of mean 74 YO(>65YO)
- -High prevalence of HTN, DM, hyperlipidemia, obesity.
- 100mg Testosterone gel(Testim1%) for 6 m
- dose adjusted, if less than5.0ng/ml
- Stopped prematurely at 6 m

CVD Safety of TRT



-5,246 men, 45~80 YO -High risk of CVD -<3.0ng/dl 등록 -1.62% T gel -3.5~7.5ng/ml로 dose adjust

Effects of TRT



TRT on Weight loss

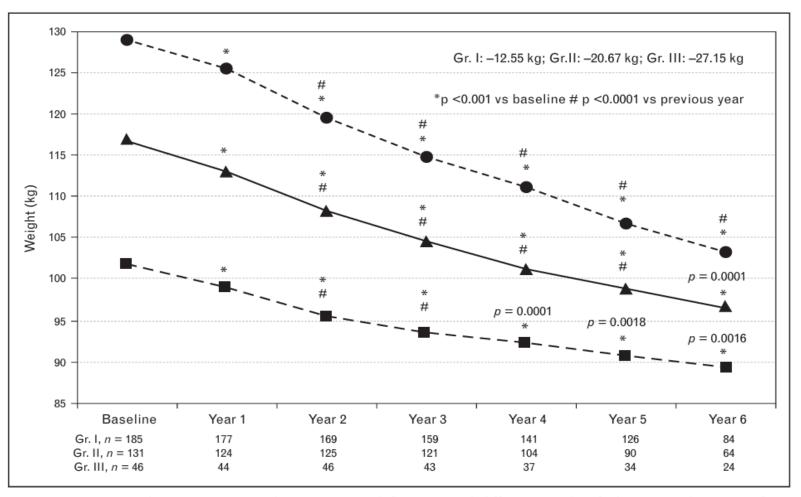
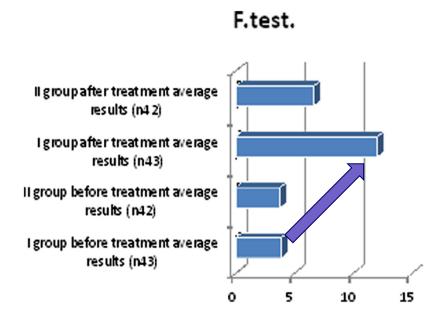
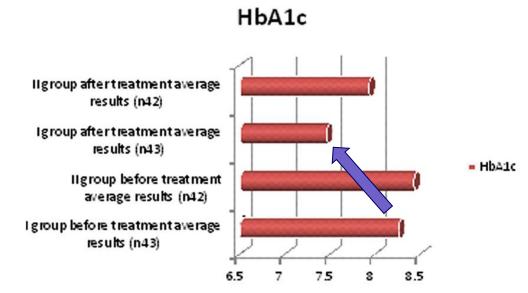


FIGURE 1. Testosterone therapy in men with testosterone deficiency and differing grade of obesity produces significant and sustained weight loss. Hypogonadal men (n=362) with obesity grade I (Gr. I, n=185, mean age: 58.39 ± 8.04 years), grade II (Gr. II, n=131, mean age: 60.62 ± 5.56 years) and grade III (Gr. III, n=46, mean age: 60.28 ± 5.39 years) treated with testosterone undecanoate injections for up to 6 years. Weight expressed in kilogram. Adapted with permission from $[60^{\bullet\bullet\bullet}]$.

TRT on DM with obesity



Eighty-five subjects, with age range 41 to 65 years and BMI from 27.0 to 48.0 kg/m², were randomized in a placebo-controlled study. According to the laboratory and clinical conditions, we divided patients into two groups: 1) a treatment group; 2) a placebo group. In the first group we used diet, physical activity (lifestyle intervention implies reduced calorie diet - the reduction of daily calorie intake to 1800 to 2000 calories – and this was selected individually), patient's antidiabetic therapy and TRT (testosterone undecanoate 250 mg/ml intramuscularly once every 3 months). In the second group we used diet, physical activity (lifestyle intervention



TRT on metabolic parameters

Table 1-Effect of TRT on nonsexual parameters in men with diabesity					
Parameter	Change	References			
Fat mass	↓	(44,49–51,53,54,56,61)			
Lean mass	↑	(44,53,56)			
BMI	\leftrightarrow	(44,45,55,56)			
Insulin sensitivity	↑	(44,49,50,54)			
Glycemic control	\leftrightarrow	(44-46,55,56,61)			
Hemoglobin	↑	(44,62)			
Bone density	Not studied				
Lipids	 ↓ in total cholesterol, LDL, and lipoprotein(a), minor decrease in HDL, ↔ in triglycerides 	(44,45,56)			
Cardiovascular disease	Not studied				
PSA	\leftrightarrow	(44,45,51,54)			

We focused on randomized controlled trials in men with obesity, type 2 diabetes, or metabolic syndrome. If there was disagreement among studies on a parameter, we chose to depict it as increased (\uparrow) , decreased (\downarrow) , or no change/variable results (\leftrightarrow) based on the totality of evidence.

TRT on metabolic parameters

Table 1 Metabolic effects of testosterone treatment in clinical trials

Parameter	Effect
Body weight	No change ^a
Fat mass	Decrease
Lean mass	Increase
Hepatic fat	No change
Visceral fat	Decrease or no change
Insulin resistance (HOMA-IR)	Decrease or no change
Insulin resistance (hyperglycemic-euglycemic clamps)	Decrease or no change
HbA1c	No change ^a
Total cholesterol	Decrease
LDL cholesterol	Decrease
HDL cholesterol	Decrease
Triglycerides	Decrease or no change

^aA decrease has been reported in non-randomized, non-blinded studies.

T4DM Study

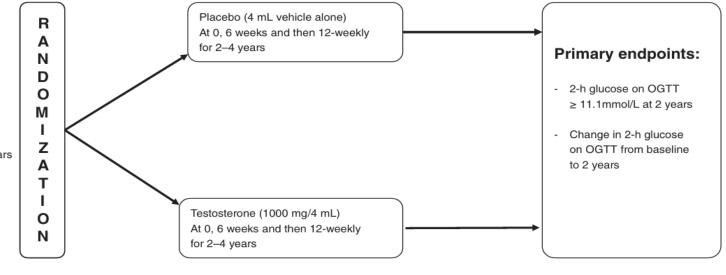
Eligible participants

- Men aged 50-74 years
- Prediabetic or newly diagnosed diabetic
- Serum T ≤ 14 nmol/L
- Waist circumference ≥ 95 cm.

Stratification:

- Centre
- Age group 50–59 years, 60–74 years
- Waist circumference (cm) 95–100; 101–115; > 115.
- 2-h glucose on OGTT (mmol/L) 7.8–9.5; 9.6–11.0;
 - 11.1–15.0.
- Currently smoking-yes, no.
- First-degree family history of T2D-yes, no.

FIGURE 1 T4DM study design



당뇨가 진단된 사람들이었고, 3개월 간격으로 1 g의 testosterone undecanoate 혹은 위약을 주사하였다. 위약 대비 테스토스테론 치료를 받은 군에서 2년째 제2형당뇨의 유병률이 40% 감소함을 보였다. 그렇지만, 당화혈색소에 미치는 영향은 없었다. 정확한 이유는 모르지만, 남성호르몬의 혈구세포 합성능력이 아마도 혼란 변수로 작용했을 가능성이 있다는 것이다. 또한, 중재 전의 테스토스테론의 농도와 연구 결과와도 유의한 상관성이 없었다. 그렇지만, 테스토스테론 치료를 받은 군에서는 체성분의 변화(총지방량 및 내장지방량의 감소, 근육량 증가)에는 좋은 결과를 미쳤으며, 근력 증가, 성기능 개선 등을 보였으나, 위약군에서는 지방량 감소와 더불어 제지방량 및 근력도 함께 감소하였다. 2년간의 치료 동안에 부작용은 두 군에서 차이가 없었고, 전립선 암 발생도 차이가 없었고 치료군에서 고등급의 암 발생이 적었다. 또, 다른 연구에서는 테스토스테론 저하가 있

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Obesity, Male Reproductive Function and Bariatric Surgery

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CONCLUSION

Bariatric surgery seems to be effective to improve free and total testosterone plasma levels in obese men, even if more evidence is needed about changes of other hormones such as gonadotropins and adrenal sex steroids. In addition, while testosterone plasma levels improvement is maintained for a long-term, restored erectile function seems not to be a durable effect, even if increased semen quality is not guaranteed after metabolic surgery. These conditions may be explained by the complex pathophysiology of reproductive function abnormalities occurring in men with obesity. In particular, adipose tissue expansion and consequent biochemical activity impairment (cytokines and adipokines production, increase peripheral androgens aromatization) may be responsible for reduced levels of testosterone while different and even more complex mechanisms, involving not only sex hormones levels but also neuro-vascular abnormalities and gonadal specific alterations, could be responsible for erectile dysfunction and infertility. To this regard, metabolic surgery may present some limitations; however, with respect to nonsurgical weight loss, bariatric surgery remains the most effective treatment for a rapid improvement of global sexual activity and hypogonadism, so it could be considered as a relevant option for severely obese hypogonadal males.

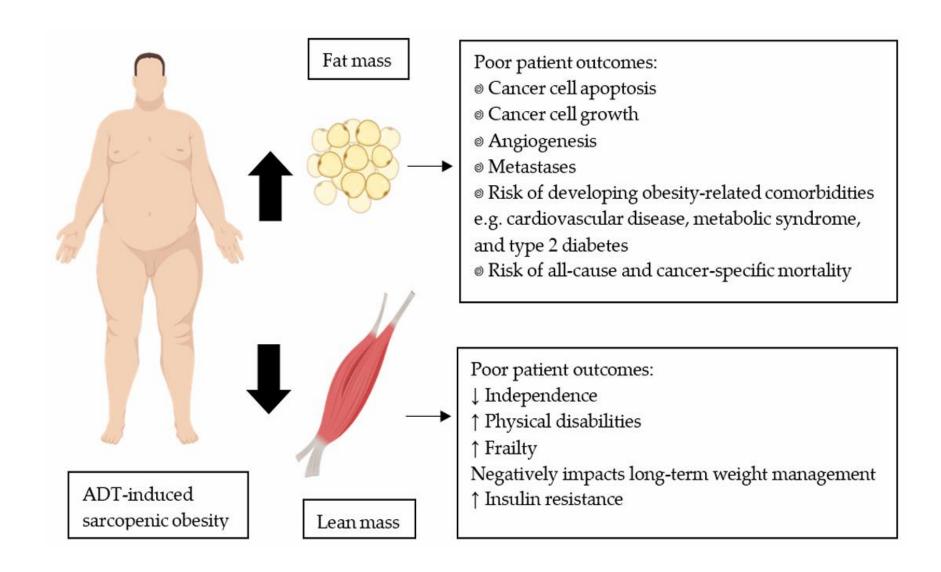
Bariatric surgery

TABLE 1 | Effects of bariatric surgery on hormonal and metabolic profile, erectile dysfunction, semen and sperm parameters.

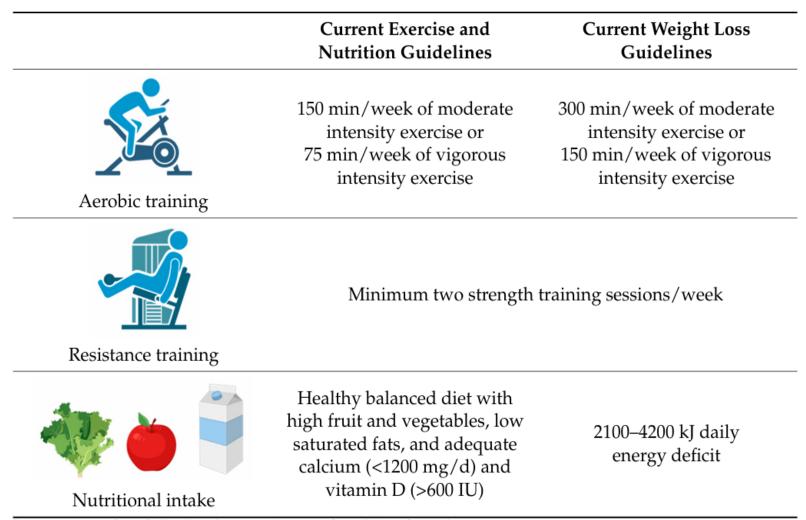
Level of evidence	References	Sample Size	Intervention	Outcome
Level lb	Samavat et al. (58)	103	Gastric bypass	Post operative time point review: 9 months Weight loss achieved: Mean -36.2 ± 20.24 kg Outcome: significant increase in free and total testosterone, OCN and SHBG; decrease in Oestradiol
Level lb	Arolfo et al. (59)	44	Roux-en-y gastric bypass; Sleeve gastrectomy	Post operative time point review: 9 months Weight loss achieved: Mean-39.75 ± 24 kg Outcome: Significant increase in total testosterone, SHBG and IIEF score; decrease in HbA1c, insulin, triglycerides, HDL cholesterol, and CRP
Level lb	Legro et al. (60)	6	Roux-en-y gastric bypass	Post operative time point review: 1, 3, 6 months Weight loss achieved: Mean $-55\pm30~{\rm kg}$ Outcome: improvement in testosterone level
Level lb	Reis et al. (61)	20	Lifestyle modifications, Gastric bypass	Post operative time point review: 4 and 24 months Weight loss achieved: inaccessible Outcome: improvement in total and free testosterone and FSH and reduced prolactin levels

and metabolic hormonal profile. Significant weight loss also alleviates the pro-inflammatory state that is associated with obesity and other co-morbid conditions and helps restore endothelial integrity thereby reducing erectile dysfunction and other cardiovascular risk burden. Bariatric surgery produces successful and encouraging outcomes in terms of the patient's overall health and well-being but more specifically seems to ameliorate hypogonadism and sexual dysfunction.

Androgen Deprivation Treatments

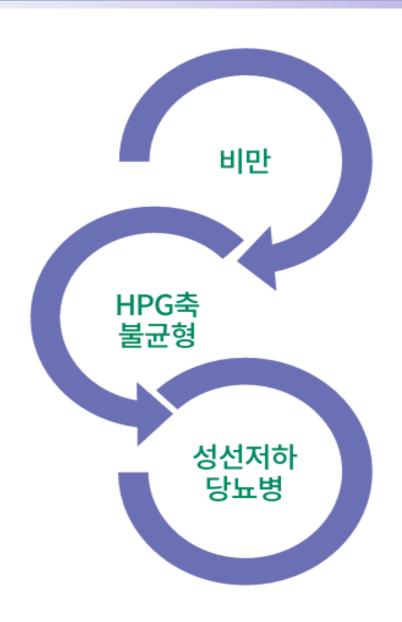


Prostate cancer-specific guidelines



Images created with BioRender.com (accessed on 5 April 2021).

Obesity ► HPG Axis ► Hypogonadism/DM



Treating Obese Male with Hormonal Dysfunction



Thank You!

