

Terapia dell'obesità: Infertilità maschile

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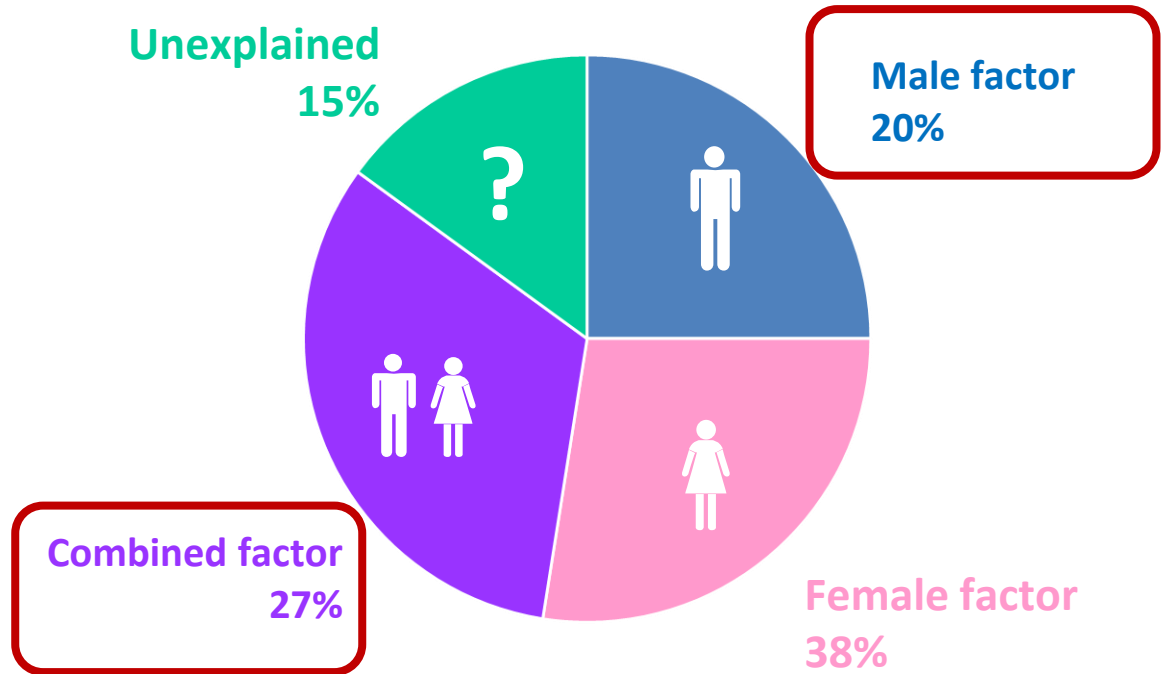
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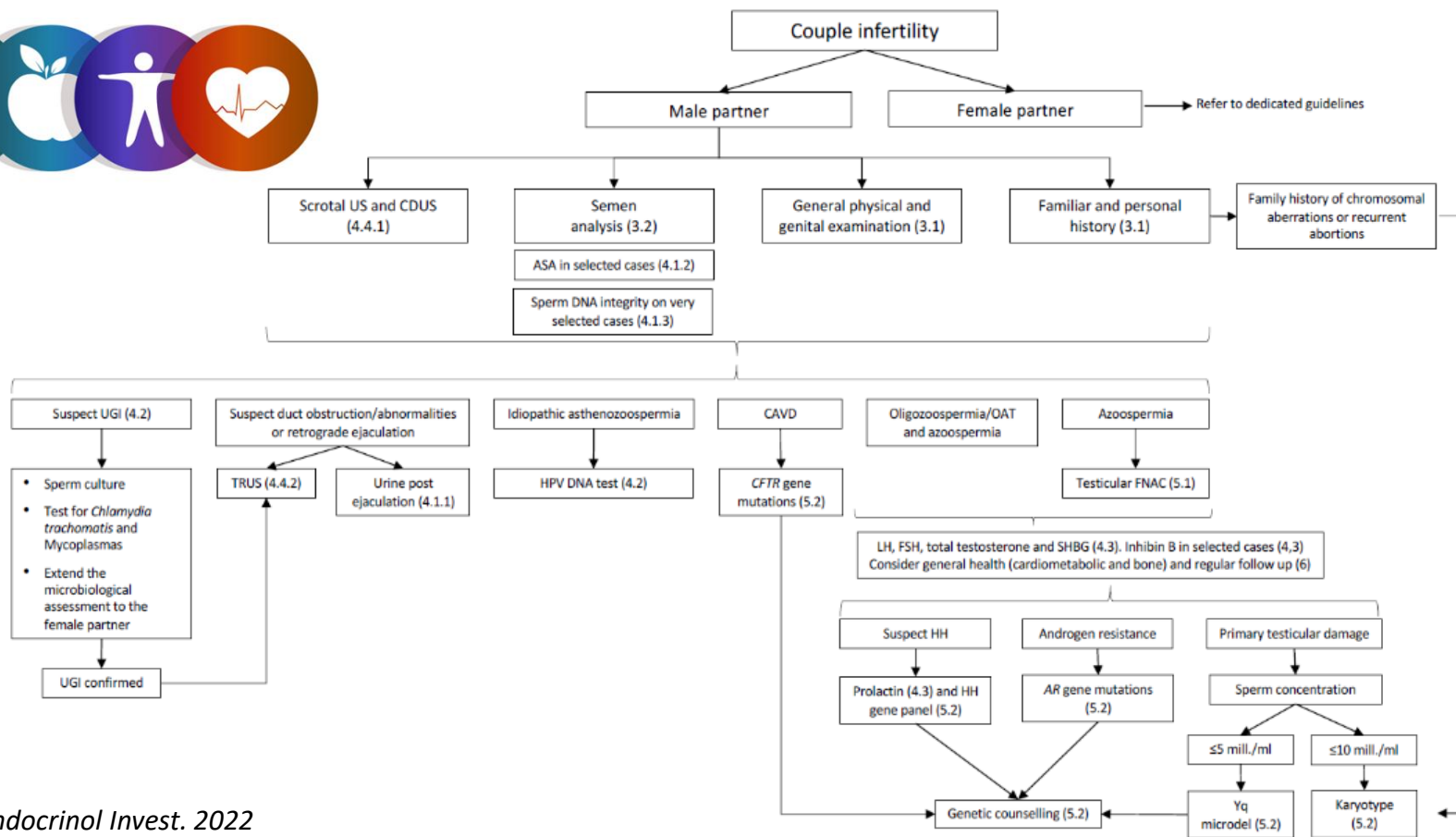
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Male infertility

COUPLE INFERTILITY:
“**Infertility** is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year”



Diagnostic flow-chart



Male infertility: NEW diagnostic categories

Primary testicular damage
(**hypergonadotropic** or **normogonadotropic**)



Secondary testicular dysfunction
(**hypogonadotropic hypogonadism**)



Duct obstruction and retrograde ejaculation

Inflammation and infection of the genital tract

Unexplained Infertility



Idiopathic semen alteration

Unexplained infertility

Treatment strategies for male infertility

Etiologic → Remove the cause

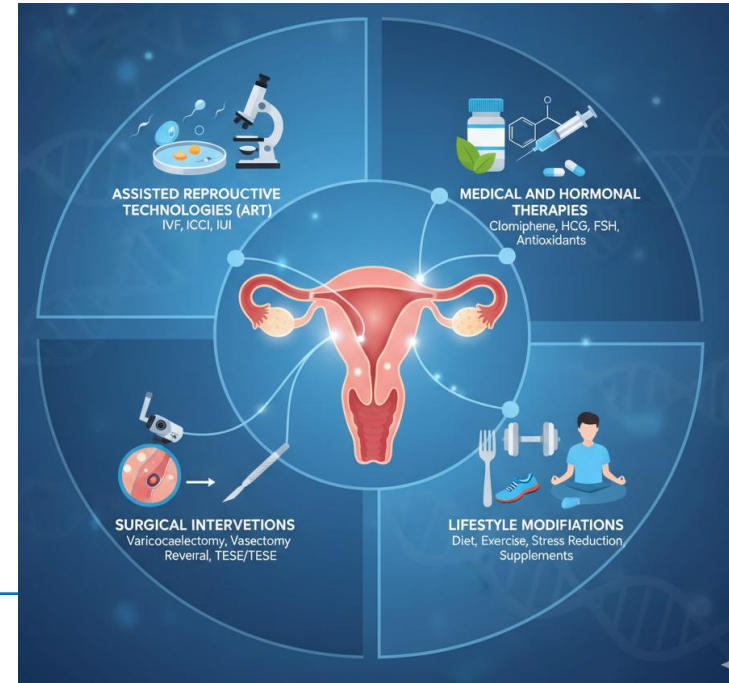
Oriented → Act on risk factor

Goal-oriented → Bypass the problem

Empirical → Acting on testicular function

AIMS of the treatment

- If possible, restore natural fertility
- Allow ART or allow gradual application of ART, improving ART success
- Preserve fertility
- Cure the underlying disorder and preserve reproductive health



Agenda

1. The evaluation of the male component of couple infertility is complex and required multiple steps to reach a diagnosis and selected among potential therapeutic approaches. Among these, **the management of risk factors for male infertility is mandatory.**



Oriented management



Male infertility-**oriented management**, acting on risk factor

Intervention	Recommendation*	Level of evidence	Comments
Cessation of smoking	2	ØOOO	Association between smoking and impairment of semen quality is established but no evidence for improvement of semen quality after quitting smoking. Suggestion is based on other positive health effects
Weight reduction	2	ØOOO	Evidence for association between overweight/obesity and impairment of semen quality is contradicting and evidence for improvement of semen quality after weight reduction is lacking. Suggestion is based on other positive health effects and positive effect on reproductive hormone levels
Reduced alcohol intake	2	ØOOO	Evidence for association between low/moderate alcohol consumption and impairment of semen quality is debatable and evidence for improvement of semen quality after cessation is lacking. Suggestion is based on positive effect in females and for social reasons
Continuing physical activity	1	ØOOO	Continuing physical activity may have a positive impact on body weight (see above)
Scrotal cooling/changes in clothing and/or working conditions	1	ØOOO	The recommendation considers no measures for active scrotal cooling or changes in working place or clothing habits

Hypogonadism & body weight

Symptoms

Sexual dysfunction



Signs

Reduced body hair

**3 | IN THE BIDIRECTIONAL
RELATIONSHIP BETWEEN OBESITY AND
HYPOGONADISM, WHAT IS CAUSE AND
CONSEQUENCE?**

sweating

Infertility



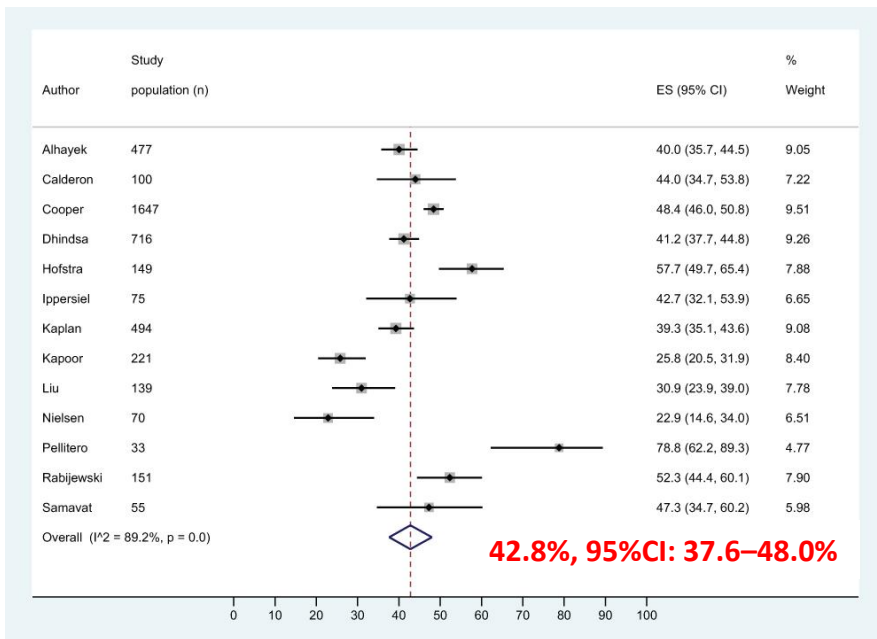
Anemia

Reduced Bone Density

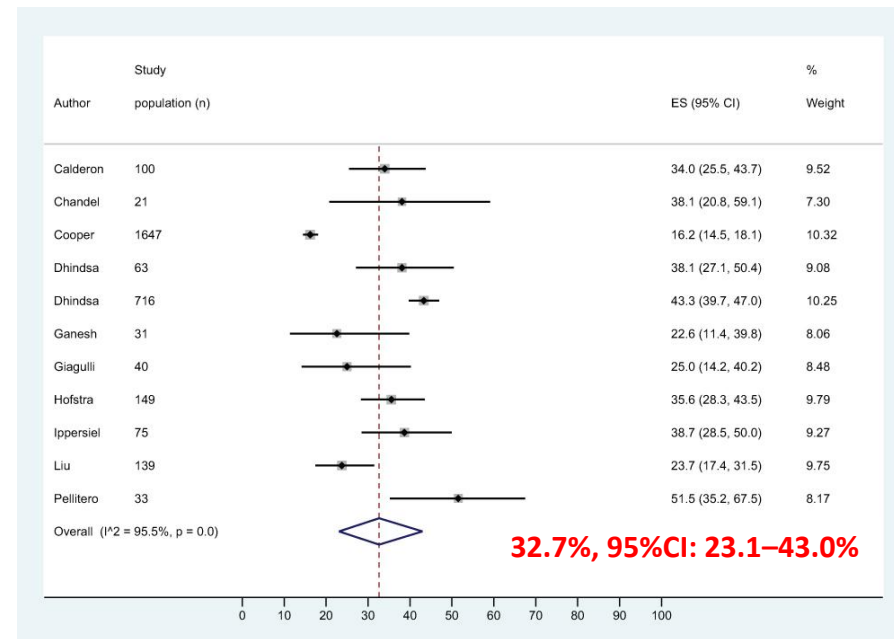
Hypogonadism & body weight

18 included studies, reporting hypogonadism prevalence on 4546 obese male patients

Total testosterone serum levels



Free testosterone serum levels

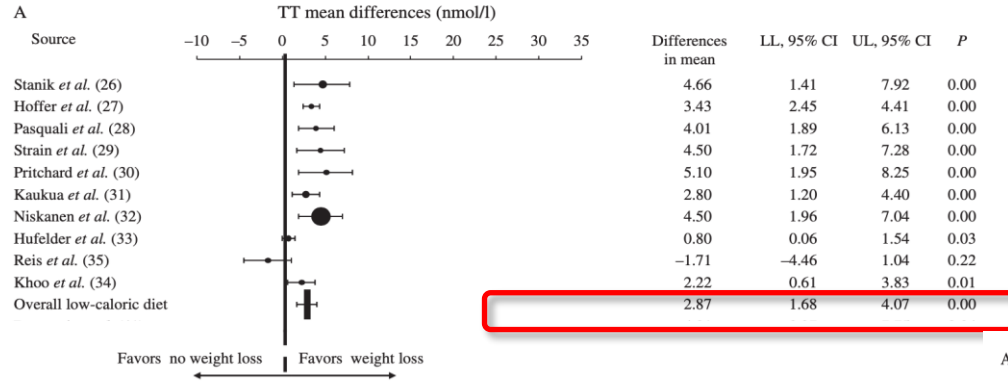


Agenda

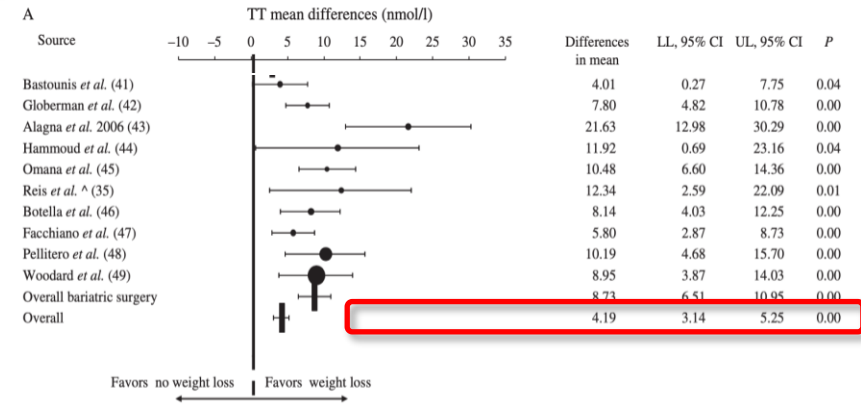
1. The evaluation of the male component of couple infertility is complex and required multiple steps to reach a diagnosis and selected among potential therapeutic approaches. Among these, the management of risk factors for male infertility is mandatory.
2. **Body weight excess is bidirectionally associated to a reduced testicular function, in terms of testosterone production.**

Body weight reduction & Testosterone

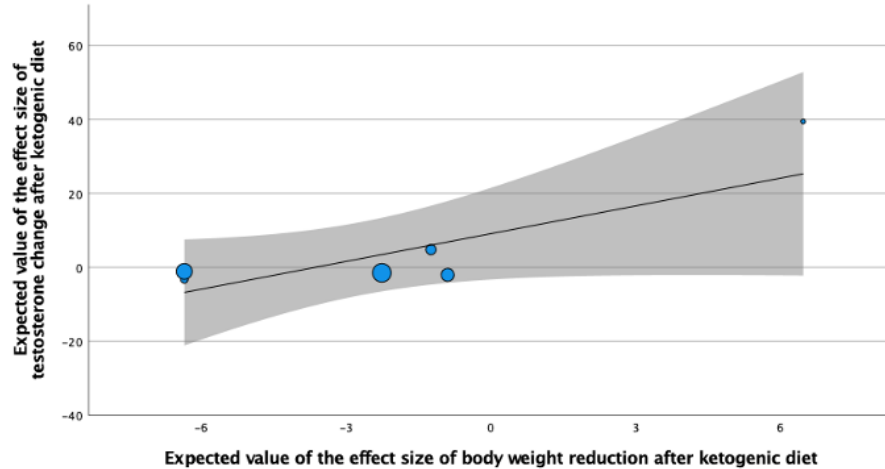
13 studies evaluated the effect of **low-calorie diet**



11 studies investigated the role of **bariatric surgery**
2 gastropasty, 6 biliopancreatic diversion, and 3 mixed interventions



Testosterone & Ketogenic diet



Model: random effect
Weight: random effect

La Vignera 2020	12.88	1.51	20	6.16	1.26	20	16.3%	4.74 [3.48, 5.99]
Mongkol 2020a	16.35	0.11	4	12.38	0.09	4	0.7%	34.35 [10.68, 58.02]
Mongkol 2020b	17.29	0.11	34	13.25	0.73	34	16.1%	7.65 [6.24, 9.06]
Subtotal (95% CI)			58			58	33.1%	6.75 [3.31, 10.20]

Heterogeneity: $\tau^2 = 5.84$; $\chi^2 = 14.66$, $df = 2$ ($P = 0.0007$); $I^2 = 86\%$
Test for overall effect: $Z = 3.84$ ($P = 0.0001$)

Total (95% CI) 101 101 100.0% 2.90 [0.83, 4.97]

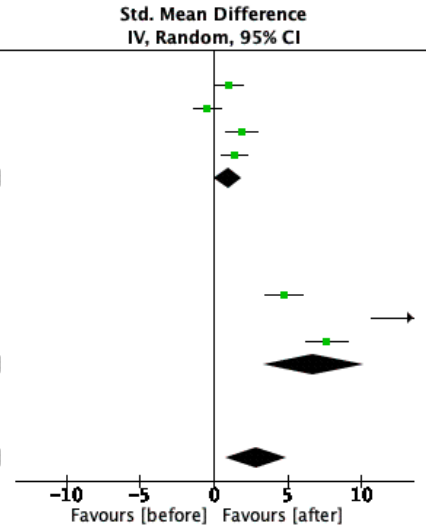
Heterogeneity: $\tau^2 = 6.42$; $\chi^2 = 119.70$, $df = 6$ ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: $Z = 2.75$ ($P = 0.006$)

Test for subgroup differences: $\chi^2 = 10.09$, $df = 1$ ($P = 0.001$), $I^2 = 90.1\%$

	Before diet			Std. Mean Difference	
I	Mean	SD	Total	Weight	IV, Random, 95% CI
1	19.77	3.85	11	16.8%	1.03 [0.13, 1.93]
2	21.76	5.33	9	16.7%	-0.45 [-1.38, 0.49]
3	17.96	3.3	10	16.5%	1.91 [0.81, 3.01]
4	19.77	2.85	13	16.8%	1.40 [0.53, 2.27]
5			43	66.9%	0.96 [-0.01, 1.92]

3 ($P = 0.006$); $I^2 = 76\%$

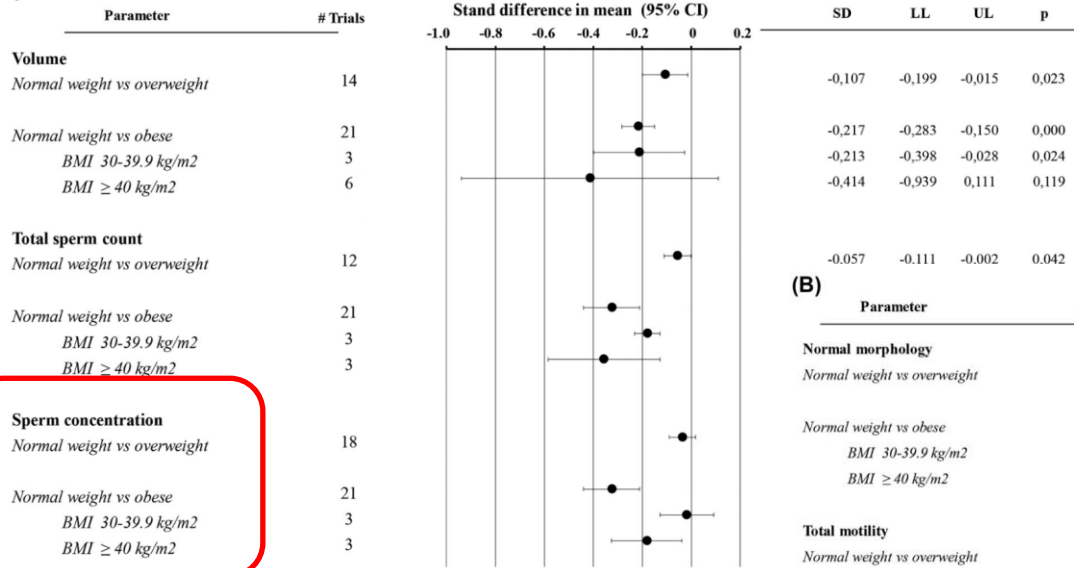


Agenda

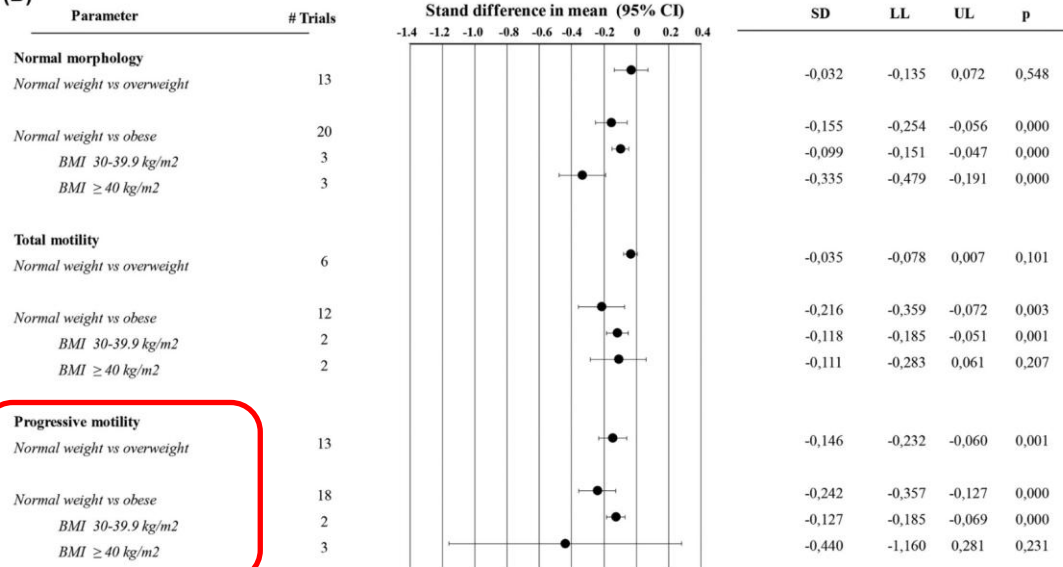
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2. Body weight excess is bidirectionally associated to a reduced testicular function, in terms of testosterone production.
3. **A reduction in body weight leads to an improvement in testosterone production**, regardless of the strategy used to achieve it. **The greater the reduction in body weight, the greater the increase in serum testosterone levels.**

Male infertility & body weight

(A)



(B)



Out of 865 retrieved articles, **29** were included in the study

Overall, 60,383 subjects were included (mean age 34.9 years, BMI 26.9 kg/m²)

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3. A reduction in body weight leads to an improvement in testosterone production, regardless of the strategy used to achieve it. The greater the reduction in body weight, the greater the increase in serum testosterone levels.
4. **Body weight excess is associated to a spermatogenesis impairment, showing reduced sperm concentration in obesity compared to normale weight and reduced sperm motility in overweight and obesity compared to normal weight.**

Male infertility & body weight reduction

12 studies

345 subjects

mean age 37.6 ± 7.9 years

BMI 45.4 ± 6.0 kg/m²

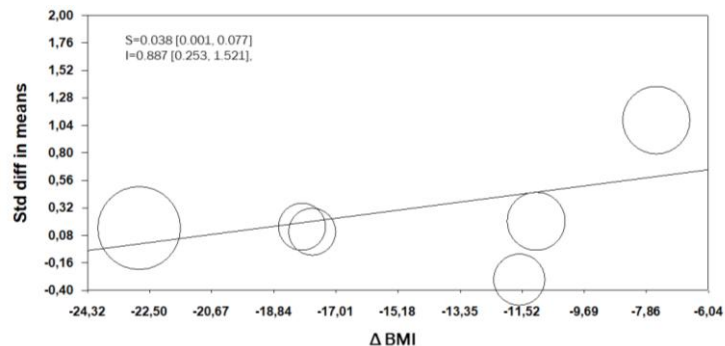
BMI reduction - 6.4 ± 0.1 kg/m²

1. Diet: 2 studies
2. Bariatric-metabolic surgery: 9 studies
3. Drugs (GLP1RA): 1 study

First author	Year	Study type	Intervention	Patients number	Age (y)	Inclusion criteria	Control group	Length of follow up (mo)	WHO edition for semen analysis	BMI change after treatment (kg/m ²)
Reis [25]	2012	Interventional	Bariatric-metabolic	20	39.3 $\pm$ 11.3	NA	Yes, 10 subjects not undergoing surgery	24	WHO 2010	-12.1 $\pm$ 5.0
Faure [26]	2014	Observational	Diet	6	31.8 $\pm$ 6.3	Abdominal fat >4 as measured by bioimpedance	No	4.6	WHO 2010	-1.2 $\pm$ 6.5
Legro [27]	2015	Observational	Bariatric-metabolic	6	35.6 $\pm$ 9.5	BMI $\geq$ 35.0 kg/m ² and presence of comorbidities or BMI $\geq$ 40.0 kg/m ² and aged 20–50 years	No	3, 6, and 12	NR	-5.0 $\pm$ 7.0
El Bardisi [28]	2016	Observational	Bariatric-metabolic	46	37.0 $\pm$ 6.0	National Institute of Health (NIH) criteria indicating weight loss surgery	No	12	WHO 2010	-22.89 (median)
Samavat [29]	2017	Observational	Bariatric-metabolic	23	45.8 $\pm$ 7.4	BMI >40 kg/m ²	Yes, 8 subjects not undergoing surgery	6	WHO 2010	-11.1 $\pm$ 5.1
Calderón [30]	2019	Observational	Bariatric-metabolic	15	40.0 $\pm$ 8.0	BMI >35 kg/m ²	No	24	WHO 2010	-18.0 $\pm$ 8.5
Carette [31]	2019	Interventional	Bariatric-metabolic	46	38.9 $\pm$ 7.9	BMI $\geq$ 40 kg/m ² or 35 kg/m ² and, at least one obesity comorbidity	No	12	WHO 2010	12.7 (min, -11.6; max, -13.8)
Wood [32]	2020	Interventional	Bariatric-metabolic	18	39.0 $\pm$ 12.9	BMI $\geq$ 35.0 kg/m ² and presence of comorbidities or BMI $\geq$ 40.0 kg/m ² , and aged 20–50 years	Yes, 14 subjects not undergoing surgery	6	WHO 2010	11.6 (median)
Fariello [33]	2021	Interventional	Bariatric-metabolic	15	NR	BMI $\geq$ 35.0 kg/m ² and presence of comorbidities or BMI $\geq$ 40.0 kg/m ² , and aged 20–50 years	No	3, 6, 9, and 12	WHO 2010	-7.6 $\pm$ 1.4
Velotti [34]	2021	Observational	Bariatric-metabolic	35	36.4 $\pm$ 5.2	Obesity and idiopathic infertility	No	6	WHO 2010	-17.7 $\pm$ 6.0
Andersen [36]	2022	Interventional	Diet and GLP1RA	37	41.1 $\pm$ 9.7	BMI 32–43 kg/m ²	No	2	WHO 2010	-5.0 $\pm$ 2.8
La Vignera [35]	2023	Interventional	GLP1RA	35	26.0 $\pm$ 6.0	BMI >30 kg/m ²	Yes, 40 subjects treated with testosterone	2	WHO 2010	-6.0 $\pm$ 2.5

Male infertility & body weight reduction

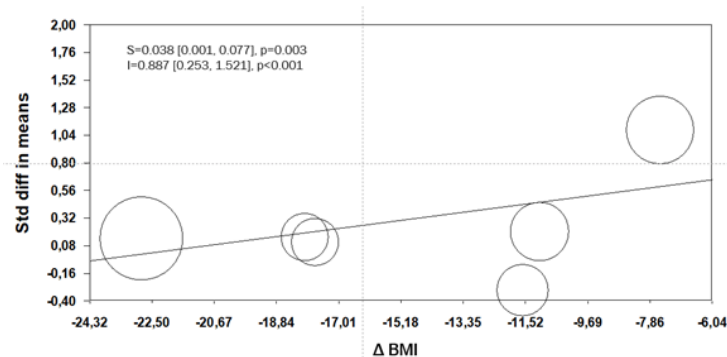
Parameter	#Trials	Stand difference in mean (95% CI)						SD	LL	UL	p
		-1.5	-1.0	-0.5	0	0.5	1.0				
Sperm concentration	15							0.495	0.003	0.986	0.049
Total sperm number	9							0.251	-0.110	0.613	0.172
Progressive motility	11							0.567	0.370	0.764	0.000
Total motility	11							-0.076	-0.242	0.091	0.371
Normal morphology	15							0.411	-0.010	0.831	0.056
Sperm DNA fragmentation	3							-0.689	-1.123	-0.255	0.002



Progressive sperm motility

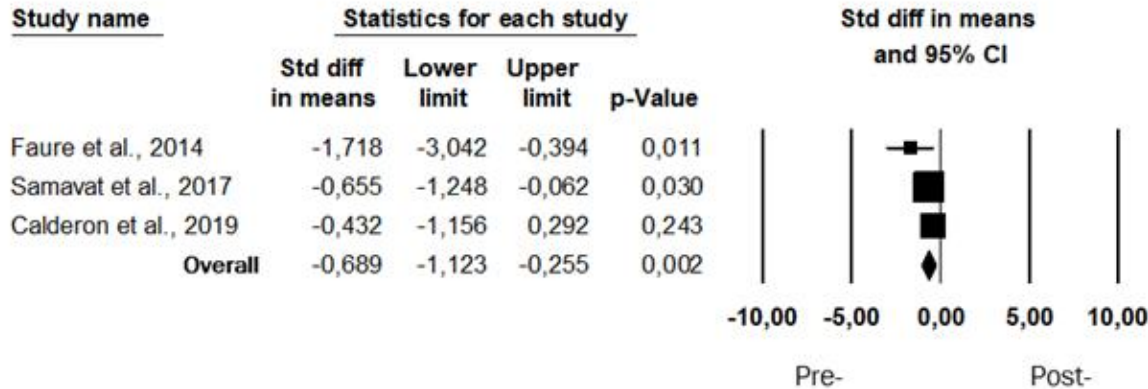
Sperm concentration

overall sperm concentration improvement of about an overall amount of 7.6 million/mL

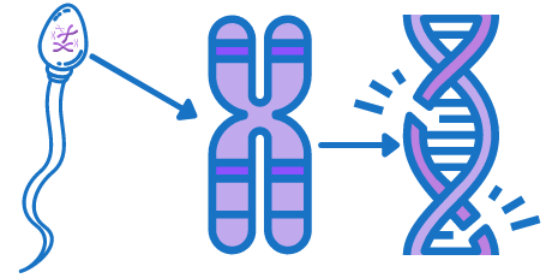


Male infertility & body weight reduction

Sperm DNA fragmentation index



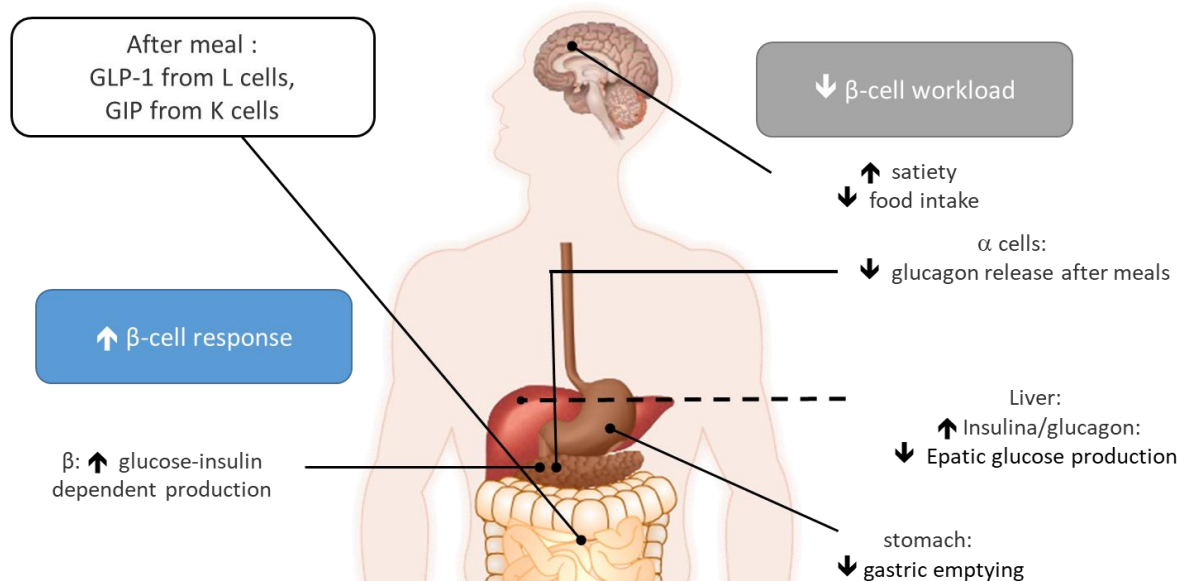
Sperm DNA fragmentation



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 5. **A reduction in body weight leads to an improvement in male fertility related parameters. The greater the reduction in body weight, the greater the increase in sperm parameters.**
-

Drugs used for body weight reduction



GLP1RAs might have implications for fertility throughout different mechanism:

1. INDIRECT:

1. Reducing body weight
2. Improving glycaemic control

2. DIRECT → GLP1 receptors are present in both Sertoli cells and Leydig cells, thus these therapies could directly stimulate testicular function

Testosterone & GLP1RA

Group A (n = 35): Patients with an active desire for fatherhood.

FSH 150 IU + **hCG** 2000 IU

Table 1. Anthropometric and biochemical parameters in the three groups of patients at baseline.

Parameters	Group A	Group B	Group C
Weight (kg)	114 ± 6	116 ± 10	111 ± 5
BMI (kg/m ²)	35 ± 3	36 ± 3	33 ± 2
Waist circumference (cm)	106 ± 5	108 ± 6	108 ± 4
Total testosterone (ng/mL)	1.6 ± 0.2	1.4 ± 0.6	1.8 ± 0.4
Follicle-stimulating hormone (IU/L)	1.8 ± 0.2	1.6 ± 0.3	1.2 ± 0.4
Luteinizing hormone (IU/L)	2.2 ± 0.2	2.0 ± 0.3	1.8 ± 0.4
Sex hormone-binding globulin (nmol/L)	11.5 ± 3.0	14.0 ± 3.0	16 ± 6.0
Prostate-specific antigen (ng/mL)	0.8 ± 0.2	0.6 ± 0.3	0.7 ± 0.1
Hematocrit (%)	40 ± 4	38 ± 6	42 ± 4
HOMA index	6.0 ± 1.2	6.5 ± 1.9	5.6 ± 1.6

Group C (n = 40): Patients who had already fathered a child and were not seeking fertility

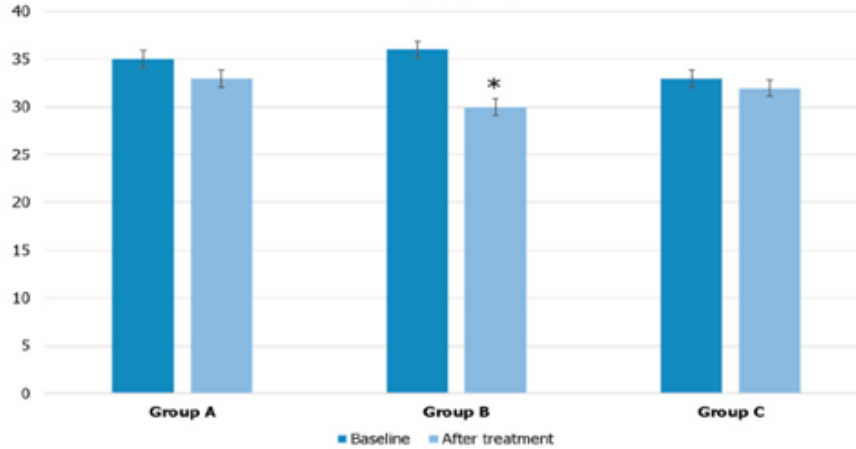
Testosterone gel (2%) 60 mg

Group B (n = 35): Patients with no active desire for fatherhood.

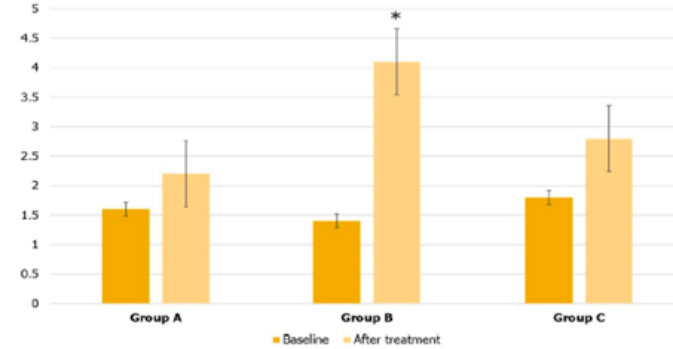
Liraglutide 0.6 mg daily for the first week, then 1.2 mg (second week), 1.8 mg (third week), 2.4 mg (fourth week), and 3.0 mg (from the fifth week for another three months)

Testosterone & GLP1RA

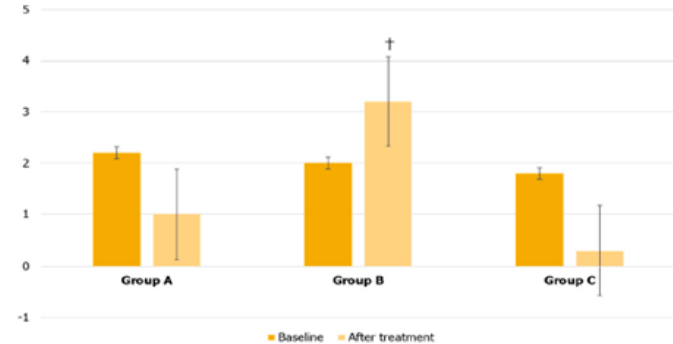
BMI (Kg/mq)



Total testosterone (ng/ml)



LH (IU/L)



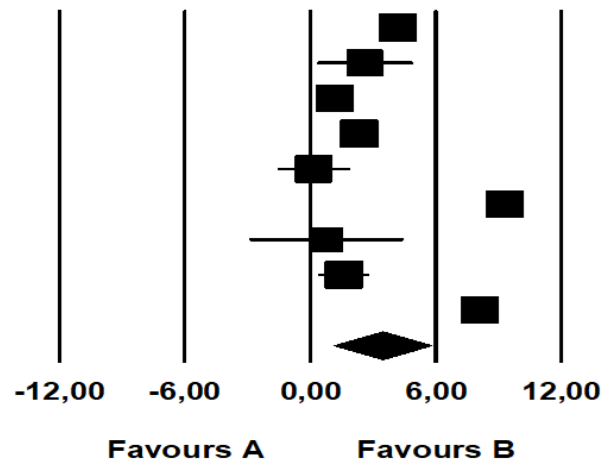
Testosterone & GLP1RA

Study name

Statistics for each study

Difference in means and 95% CI

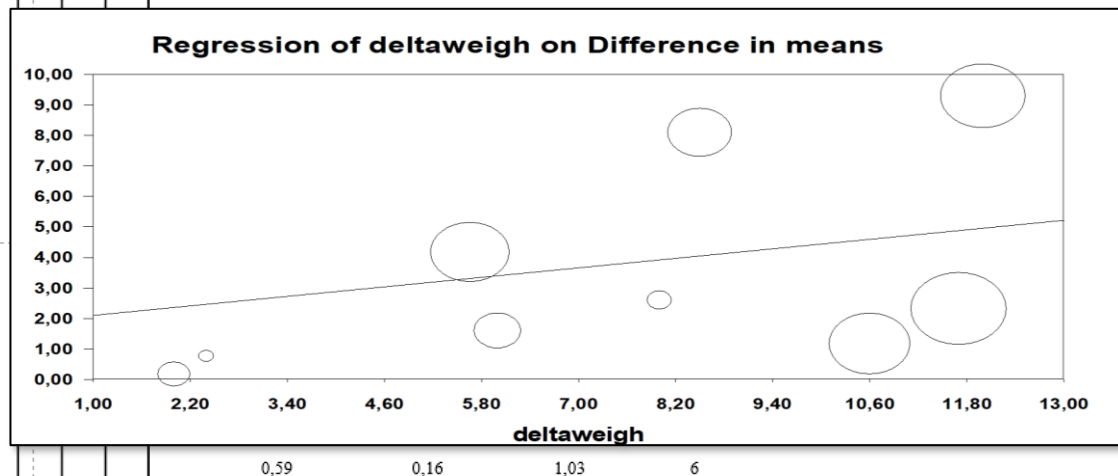
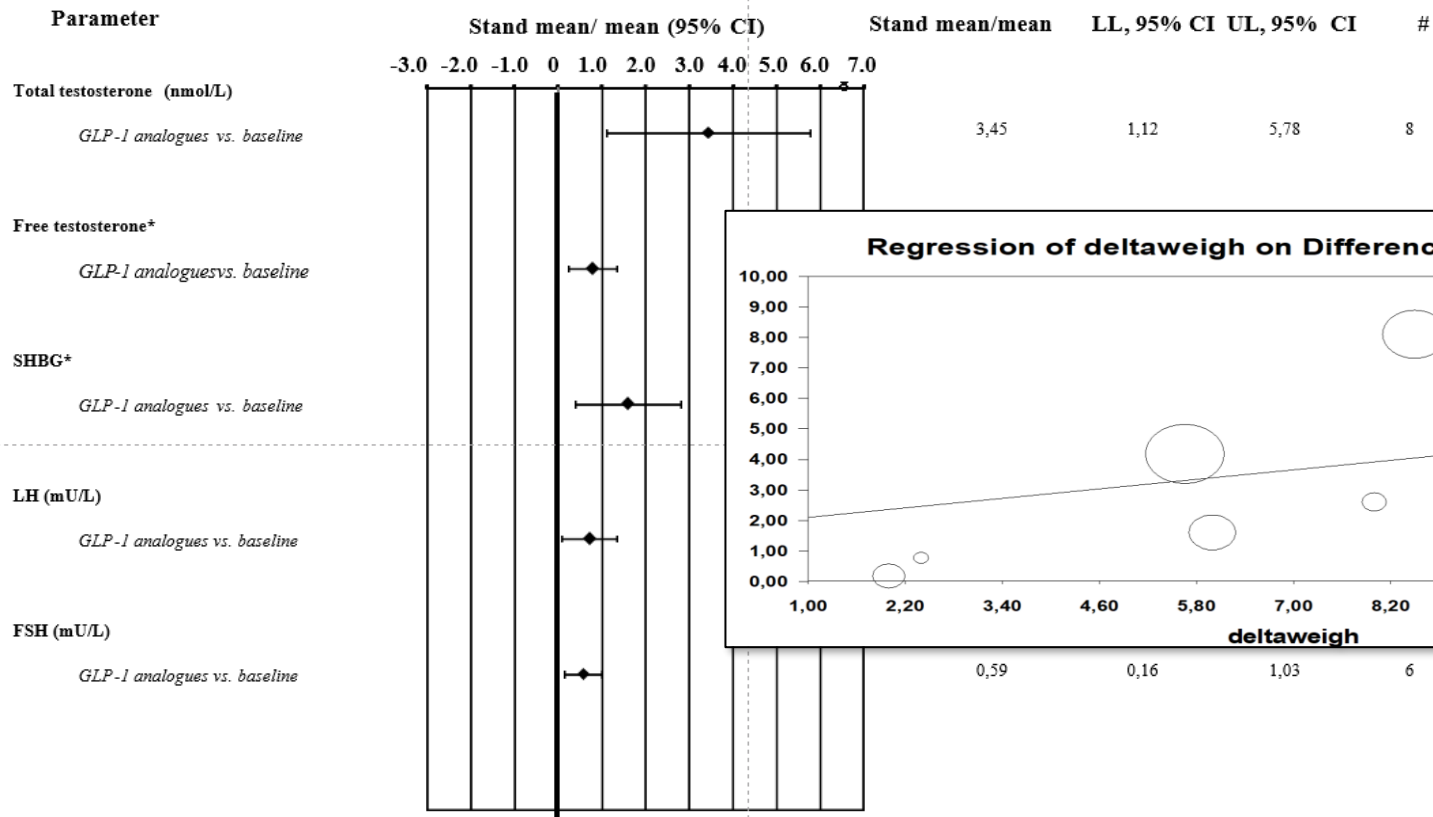
	Difference in means	Lower limit	Upper limit	p-Value
Shao et al., 2018	4,17	3,47	4,88	0,00
Jensterle et al., 2019	2,60	0,34	4,86	0,02
Giagulli et al., 2020	1,17	0,48	1,86	0,00
Giagulli et al., 2020*	2,32	1,74	2,90	0,00
Graybill et al., 2021	0,17	-1,55	1,90	0,85
La Vignera et al., 2023	9,30	8,64	9,96	0,00
Lengsfeld et al, 2024	0,77	-2,88	4,41	0,68
Gregori;c et al., 2025	1,60	0,41	2,79	0,01
La Vignera et al., 2025	8,10	7,23	8,97	0,00
	3,45	1,12	5,78	0,00



Meta Analysis

Random-effects pooled mean difference of total T (nmol/L) before and after GLP1/GIP analogues

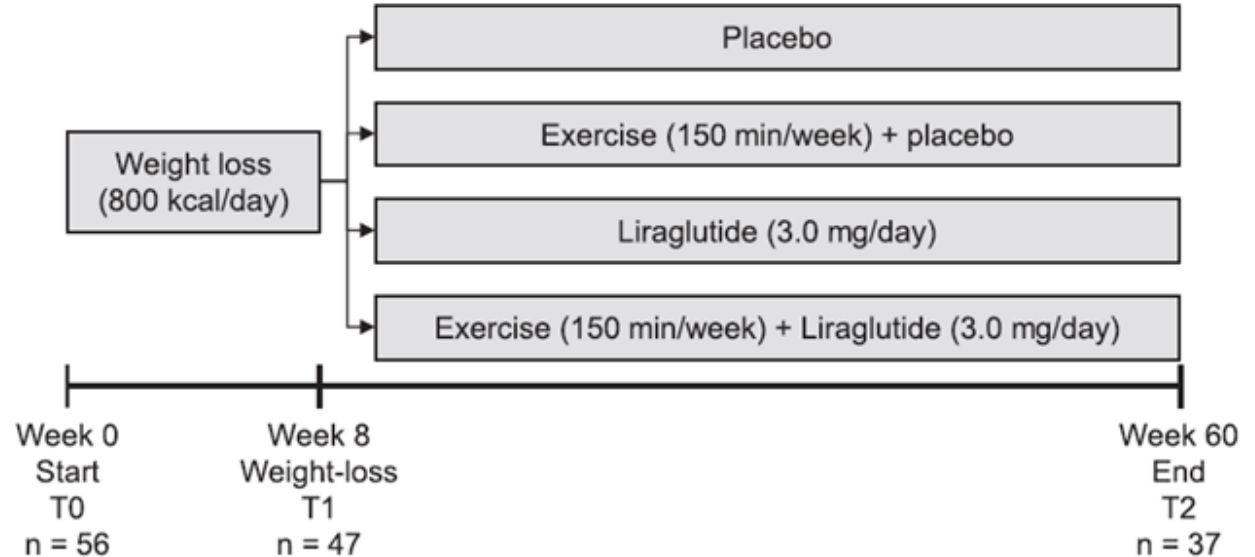
Testosterone & GLP1RA



GLP1RA & Spermatogenesis: Liraglutide

Design: sub-study of men with obesity enrolled in a randomized, controlled, double-blinded trial (the S-LITE trial)

56 men were included in the study and assigned to an initial 8-week low-calorie diet (800 kcal/day) followed by randomization with **Liraglutide** to 52 weeks of either:

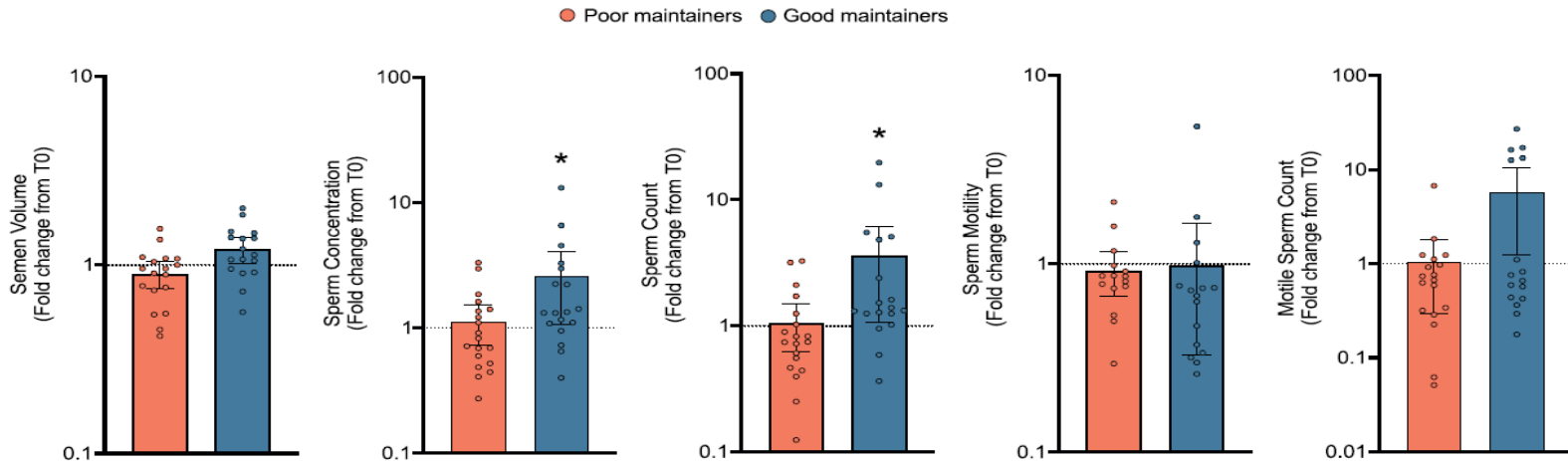


GLP1RA & Spermatogenesis: Liraglutide

Results:

Weight loss obtained during diet leads to sperm parameters improvement

This improvement was maintained at the end of the study, regardless to the groups



However, no subgroup analyses were performed

GLP1RA & Spermatogenesis: Semaglutide

Design: Randomised open-label trial in 25 men with type 2 diabetes mellitus aged 50 [46-60] years, BMI 35.9 [32.8–38.7] kg/m² and functional hypogonadism

- SEMA group: **Semaglutide** 1mg/week for 24 weeks
- TRT group: testosterone undecanoate 1000 mg once 10–12 weeks i.m. for 24 weeks

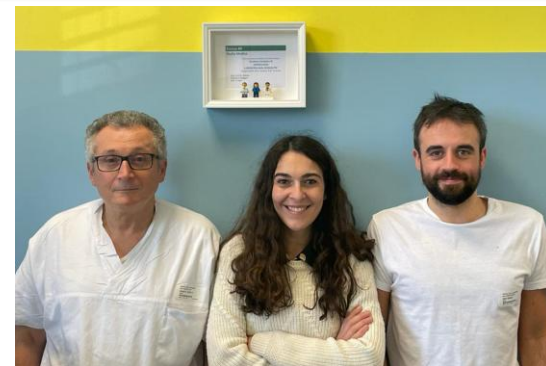
Results: Considering SEMA group, 24 weeks of treatment with semaglutide leads to:

1. reduction of mean weight of 6 kg
2. reduction in HbA1c of 1.2%
3. improvements in sperm parameters, although statistically significant only for sperm morphology

	Semaglutide (n = 13)			
	Baseline	24 weeks	Difference (%)	p value
Volume (mL)	1.3 (0.8; 1.5)	1.3 (0.5; 2.1)	–19 (–45; 57)	0.98
Concentration (10 ⁶ /mL)	25 (15; 125.5)	37 (16.5; 60.5)	17 (–2; 71)	0.58
Total number (10 ⁶ /ejaculate)	34.5 (19.6; 64.8)	41 (15.3; 70)	–5 (–59; 167)	0.79
Total motility (%)	30 (21.3; 43.8)	30 (22.5; 35)	–17 (–41; 15)	0.09
Normal morphology (%)	2 (2; 3.5)	4 (2; 5.5)	37 (21; 88)	0.012

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5. A reduction in body weight leads to an improvement in male fertility related parameters. The greater the reduction in body weight, the greater the increase in sperm parameters.
6. **GLP1RAs could be in the future considered for the management of male infertility in obese/overweight patients.** However, so far, the evidences available in the literature are still poor.



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