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Issue No. 5

Metformin, testosterone, or both in men with obesity and low testosterone:
A double-blind, parallel-group, randomized controlled trial. Fernandez-Garcia, JC et al.
Metabolism 136 (2022) 155290

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Metformin, testosterone, or both in men with obesity and low testosterone:
a double-blind, parallel-group, randomized controlled trial
(TESEO study)

STUDY DESIGN: the **TESEO** (**T**estosterone, m**E**tformin, or both, for low te**S**tosterone in m**E**n with **O**besity) trial – 1-year, single-center, double-blind, parallel-group, randomized, placebo-controlled independent trial

Department of Endocrinology and Nutrition at the Virgen de la Victoria University Hospital (Malaga, Spain)

INCLUSION criteria (+)

- ✓ male gender
- ✓ age 18-50 years
- ✓ DM2 diagnosis
- ✓ obesity (BMI≥30 kg/m2)
- ✓ reduced serum concentrations of testosterone (total <230 ng/dl (8 nmol/l) or free <70 pg/ml (240 pmol/l)

*The study protocol was approved by the institutional review boards and the local ethics committee.

EXCLUSION criteria (-)

- ✓ DM (fasting plasma glucose ≥126 mg /dl [7 mmol/l]
- ✓ glycated hemoglobin ≥6.5 %
- ✓ evidence of intercurrent pituitary disease
- ✓ hyperprolactinemia
- ✓ increased LH levels
- ✓ additional pituitary hormone deficiencies
- ✓ hemochromatosis, malignancy
- ✓ PSA>4 ng/ml
- ✓ hematocrit >50 %
- ✓ severe lower urinary tract symptoms
- ✓ hepatic, renal, or cardiovascular disease and uncontrolled hypertension
- ✓ androgens, phosphodiesterase 5 inhibitors, clomiphene, human chorionic gonadotropin, or alprostadil admission
- ✓ abnormal pubertal development

- ✓ Number of patients: **106** men with obesity and low testosterone
- ✓ Mean age – 37.9 years
- ✓ Mean BMI – 42.5 kg/m²

RANDOMIZATION: 4 groups

Placebo (n=26)	Metformin (n=27)	Testosterone (n=26)	Metformin + Testosterone (n=27)
2xDay placebo tablets & injections in weeks 0, 6, 18, 30, 42	2xDay 850 mg metformin + placebo injections in weeks 0, 6, 18, 30, 42	2xDay placebo tablets + 1000 mg TU injections in weeks 0, 6, 18, 30, 42	2xDay 850 mg metformin + 1000 mg TU injections in weeks 0, 6, 18, 30, 42

1 year follow-up

Study samples measurement: immunoassay, electrochemiluminescence, high-performance liquid chromatography-mass spectrometry

PRIMARY outcome:
- ✓ changes in insulin resistance (HOMA-IR)

SECONDARY outcomes:
- ✓ changes in total and free serum testosterone
- ✓ Changes in body composition and metabolic variables
- Changes in erectile function (measured by the IIEF-5-Q)
- Changes in HRQoL (measured by the AMS scale)

Trial population

No significant between-group differences in baseline characteristics: age, education, smoking status, BP, BMI, waist circumference, total & free testosterone and free testosterone, LH, hematocrit, glucose, glycated hemoglobin, insulin, HOMA-IR, cholesterol, HGL, LDL, triglycerides, PSA, IIEF-5 & AMS total score.

Insuline resistance

↓ **HOMA-IR** in all active groups, compared to placebo (95% CI)

→ | Metformin: **-2.4** (-4.1, -0.8)

→ | Testosterone: **-2.7** (-4.3, -1.1)

→ | Metformin + Testosterone : **-3.4** (-5.0, -1.8)

p-Values <0.05 were considered to indicate statistical significance
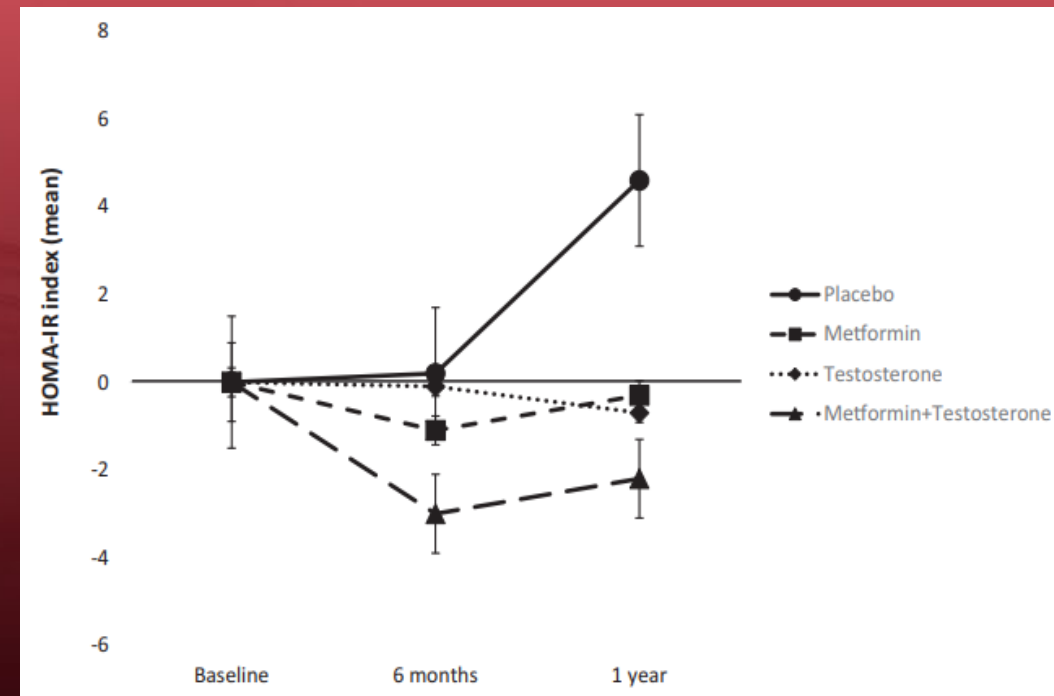
HOMA-IR index **decreased significantly** in all active groups compared to placebo

Testosterone concenrations

	Metformin vs placebo	Testosterone vs placebo	Combination vs placebo	Combination vs testosterone
Total testosterone - ng/dl	−1.6 (−42.5 to 39.2) p = 0.937	13.1 (−27.3 to 53.5) p = 0.524	42.9 (2.1 to 83.7) p = 0.040	−29.7 (−10.7 to 70.1) p = 0.149
	[0.3 (−38.1 to 38.6) p = 0.990]	[17.2 (−20.8 to 55.1) p = 0.375]	[46.9 (8.6 to 85.3) p = 0.016]	[29.8 (−8.2 to 67.7) p = 0.124]
Free testosterone - pg/ml	2.2 (−10.3 to 14.7) p = 0.727	6.7 (−5.7 to 19.1) p = 0.288	14.9 (2.7 to 27.4); p = 0.020	8.2 (−4.2 to 20.5) p = 0.195
	[2.5 (−9.4 to 14.3) p = 0.683]	[7.5 (−4.2 to 19.2) p = 0.211]	[15.5 (3.6 to 27.3) p = 0.011]	[8.0 (−3.8 to 19.7) p = 0.183]

*p-Values <0.05 were considered to indicate statistical significance

The combination of metformin plus testosterone **significantly increased** total and free testosterone concentrations, compared to placebo.

Body weight and composition

	Metformin vs placebo	Testosterone vs placebo	Combination vs placebo	Combination vs testosterone
Fat-free mass - kg	−1.7 (−3.0 to −0.4) $p = 0.011^c$ 0.990]	−1.0 (−2.6 to 0.3) $p = 0.124^c$ 0.375]	−1.8 (−3.1 to −0.5) $p = 0.007^c$ 0.016]	−0.8 (−2.1 to 0.4) $p = 0.206^c$ 0.124]

*p-Values <0.05 were considered to indicate statistical significance

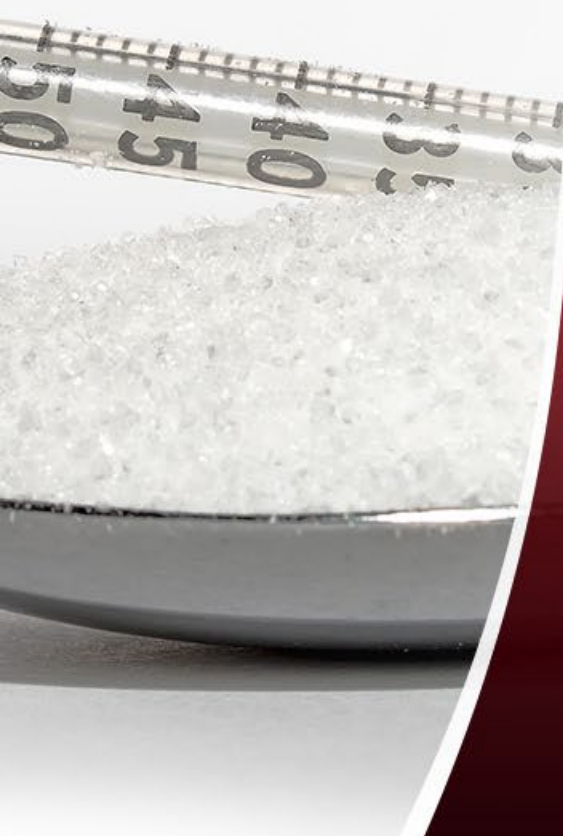The combination of metformin plus testosterone **significantly decreased** fat mass compared to placebo.

Erectile function

None of the treatments **significantly improved** erectile function compared to placebo (p = 0.247).

HRQoL

There were **no significant** between-group **changes** in the AMS severity category at 1 year. The AMS score did not differ between the study groups (p = 0.192).

CONCLUSIONS

- ✓ Total and free testosterone increased in the combination group

- ✓ Decreased fat mass in the metformin and combination group

- ✓ No significant changes in other variables between study group

Among non-diabetic men with obesity and low testosterone concentrations, the combination of

- metformin plus testosterone,
- metformin only,
- testosterone only,

compared to placebo, **reduced insulin resistance** with no evidence of additive benefit.

THE INCIDENCE AND AGGRAVATING FACTORS OF MALE HYPOGONADISM IN TYPE 2 DIABETES, 2022

"The remedy comes too late when the disease has gained strength by long delays".

(Ovid)

OBJECTIVES: To evaluate the prevalence and aggravating factors of male hypogonadism in patients with type 2 diabetes mellitus.

STUDY DESIGN: a full-design, cross-sectional, screening, single-center, non-interventional study of men with T2DM.

STUDY PERIOD: October 2021 – January 2022

INCLUSION criteria (+)	EXCLUSION criteria (-)

INCLUSION criteria (+)

- ✓ male gender
- ✓ age 40–65 years
- ✓ DM2 diagnosis

Men who refused to participate in a clinical trial were also excluded. The clinical trial was approved by the local Ethical Committee.

EXCLUSION criteria (-)

- ✓ disorders of sex development
- ✓ absence of at least one of testicles
- ✓ cryptorchidism
- ✓ genital injuries and/or genital surgery
- ✓ androgens, anabolic steroids, gonadotropins, antiestrogens or antiandrogens current administration or in anamnesis
- ✓ alcoholism and drug addiction

- Number of patients: 505 men with T2DM
- Median age – 58.0 years (range 52.0 – 62.0 years)
- Median duration of T2 DM – 11.0 years (range 6.0 – 16.0 years)
- Total testosterone measurement by isotope dilution liquid chromatography/tandem mass spectrometry (ID LC/MS)

*ID LC-MS provides the most specific and sensitive method for the analysis of testosterone defficiency

3 more centers in Russian Federation

Rozhivanov RV, Chernova MO, Mel'nichenko GA, Shestakova MV, Mokrysheva NG. The incidence and aggravating factors of male hypogonadism in type 2 diabetes. Diabetes Mellitus. 2022;25(4):338-346. doi: hiips://doi.org/10.14341/DM12913

RESULTS: laboratory confirmed hypogonadism was present in **355** out of 505 men with DM T2 **(70.3%)**.

Characteristics	Hypogonadism (n=355)	Eugonadism (n=150)	P-value
Total testosterone nmol/l	8,5 [6,7; 10,2]	15,0 [13,2; 17,7]	<0,001*
BMI kg/m2	33,0 [29,0; 37,4]	30,4 [27,3; 33,3]	<0,001*
HbA1c, %	8,7 [7,5; 10,3]	8,1 [6,7; 9,5]	0,002*
HDL mmol/l	0,97 [0,84; 1,11]	1,03 [0,90; 1,17]	0,006*
Triglycerides mmol/l	2,01 [1,35; 2,94]	1,67 [1,17; 2,33]	<0,001*
Metformin treatment	64,2	51,3	0,009**
Diabetic foot syndrome	33,0	23,3	0,041**

p-Values <0.05 were considered to indicate statistical significance

Patients WITH hypogonadism:

- ✓ statistically significantly more severe degree of obesity
- ✓ worse compensation of carbohydrate metabolism
- ✓ lower HDL levels and high TG
- ✓ higher metformin admission (as hypoglycemic therapy)
- ✓ higher frequency of diabetic foot syndrome (DFS)

Rozhivanov RV, Chernova MO, Mel'nichenko GA, Shestakova MV, Mokrysheva NG. The incidence and aggravating factors of male hypogonadism in type 2 diabetes. Diabetes Mellitus. 2022;25(4):338-346. doi: hiips://doi.org/10.14341/DM12913

Comparison of patients with hypogonadism depending on the presence of obesity

Characteristics	Obesive (n=214)	Non-obesive (n=141)	P-value
Total testosterone nmol/l	8,1 [6,4; 10,0]	9,2 [7,5; 10,6]	0,005*
BMI kg/m2	35,3 [32,9; 39,5]	27,2 [25,8; 29,0]	<0,001*
Triglycerides mmol/l	2,21 [1,57; 3,06]	1,50 [1,16; 2,27]	<0,001*
Metformin treatment	72,0	53,4	0,002**

*p-Values <0.05 were considered to indic
statistical significance

Statistically significant differences between groups:

- ✓ total testosterone levels – lower in obese men
- ✓ Triglycerides – higher in obese men
- ✓ Patients with obesity were more likely to use metformin

Rozhivanov RV, Chernova MO, Mel'nichenko GA, Shestakova MV, Mokrysheva NG. The incidence and aggravating factors of male hypogonadism in type 2 diabetes. Diabetes Mellitus. 2022;25(4):338-346. doi: hiips://doi.org/10.14341/DM12913

Comparison of non-obesive patients depending on the presence of hypogonadism
(additional comparative analysis)

Characteristics	Hypogonadism (n=103)	Eugonadism (n=71)	P-value
Total testosterone nmol/l	9,2 [7,5; 10,6]	16 [13,9; 18,4]	<0,001*
HbA1c, %	9,1 [7,9; 10,5]	8,0 [6,7; 9,5]	0,002*
HDL mmol/l	0,98 [0,85; 1,16]	1,06 [0,90; 1,21]	0,042*

*p-Values <0.05 were considered to indica
statistical significance

Statistically significant differences between groups:

✓ glycated hemoglobin – higher in men with hypogonadism
✓ HDL – lower in men with hypogonadism

Rozhivanov RV, Chernova MO, Mel'nichenko GA, Shestakova MV, Mokrysheva NG. The incidence and aggravating factors of male hypogonadism in type 2 diabetes. Diabetes Mellitus. 2022;25(4):338-346. doi: hiips://doi.org/10.14341/DM12913

CONCLUSIONS: this study demonstrates that the measurement of serum TT by **isotope dilution liquid chromatography/tandem mass spectrometry** improves biochemical hypogonadism diagnosis.

Chemiluminescent microparticle immunoassay, CMIA & Capillary electrophoresis (CE) (2019)	**VS**	Isotope dilution liquid chromatography/tandem mass spectrometry (2022)
33,7%		**70.3%**

- ✓ Hypogonadism in men with DM T2 is associated with obesity and worse compensation of carbohydrate metabolism.
- ✓ Taking into account the high prevalence of hypogonadism, a higher priority should be given to its diagnostics.
- ✓ A wide introduction of isotope dilution LC-MS method in clinical practice could enhance the accuracy of hypogonadism diagnosis.

Rozhivanov RV, Chernova MO, Mel'nichenko GA, Shestakova MV, Mokrysheva NG. The incidence and aggravating factors of male hypogonadism in type 2 diabetes. Diabetes Mellitus. 2022;25(4):338-346. doi: hiips://doi.org/10.14341/DM12913

THANK YOU FOR YOUR ATTENTION!

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