NOTE

Testosterone undecanoate improves lipid profile in patients with type 1 diabetes and hypogonadotropic hypogonadism

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Abstract. Testosterone deficiency (Td) has been associated with the metabolic syndrome. Few studies have evaluated this condition in type 1 diabetes (T1D). The primary aim of this study was to evaluate the effectiveness of testosterone undecanoate (TU) on insulin sensitivity, glycemic control, anthropometric parameters, blood pressure and lipid profile in patients with Td and T1D. We performed a randomized placebo-controlled multicenter study. Inclusion criteria: a) age $\geq$ 18 years; b) autoimmune diabetes; c) Td (total testosterone <10 nmol/L or calculated free testosterone <225 pmol/L and low/normal LH; d) ability to sign informed consent; e) comply with the study protocol. Exclusion criteria: a) pituitary tumor, empty sella, hyperprolactinemia, panhypopituitarism or secondary hypogonadism; b) contraindications for treatment with testosterone undecanoate (TU); c) patients who did not agree to sign their informed consent. Six patients were randomly assigned to testosterone undecanoate (TU) treatment and 7 to placebo with the following dosing schedule: baseline, 6 weeks and 16 weeks. Blood test, anthropometric parameters, blood pressure and insulin sensitivity were determined at baseline, 6, 16 and 22 weeks. No differences were observed regarding insulin sensitivity, HbA_{1c} or basal glucose, anthropometric parameters or blood pressure. At 22 weeks, the decrease in total cholesterol was 37.4 ± 27.5 mg/dL in the TU group compared with an increase of 13.2 ± 17.8 mg/dL in the placebo group ($P < 0.005$), and LDL cholesterol concentration decreased 30.2 ± 22.1 mg/dL, compared with an increase of 10.5 ± 13.4 mg/dL in the placebo group ($P = 0.004$). We conclude that treatment with TU in patients with T1D and Td improves lipid profile, with no effects on metabolic control or anthropometric parameters.

Key words: Type 1 diabetes, Metabolic syndrome, Lipid profile, Testosterone deficiency

TESTOSTERONE deficiency has been associated in adults with several components of the metabolic syndrome [1, 2]. In this respect, patients with type 2 diabetes or obesity had a 3-fold higher probability of having hypogonadism than the general population [3]. The few studies conducted in patients with type 1 diabetes (T1D) revealed testosterone deficiency in 8.3% to 9.5% of these patients [4, 5], and its prevalence bears

a direct relationship with age, waist circumference, triglyceride levels and insulin requirements [4].

Testosterone replacement therapy in type 2 diabetes patients with hypogonadism produced a significant reduction in insulin resistance and glycosylated hemoglobin [6-8] as well as an improvement in anthropometric parameters and a drop in blood pressure [9, 10], being controversial the impact on lipid profile [6, 7, 9, 11-14].

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Abbreviations : CUN-BAE, Clínica Universitaria de Navarra-Body Adiposity Estimator; eGDR, estimated glucose disposal rate; HDL-c, high-density lipoprotein cholesterol; IIEF-5, International Index of Erectile Function; LDL-c, low-density lipoprotein cholesterol; LH, luteinizing hormone; MRI, magnetic resonance imaging; T1D, type 1 diabetes; T2D, type 2 diabetes; Td, testosterone deficiency; TU, testosterone undecanoate

In patients with T1D, the initial cause of abnormal carbohydrate metabolism is autoimmune and not due to excess adipose tissue, as occurs in T2D. However, in recent years the rising prevalence of overweight and obesity in patients with T1D has been highlighted, reaching over 50% in some studies [15], and has been particularly associated with a higher percentage of metabolic syndrome [16] and microvascular complications [16, 17].

Given the relationship among testosterone deficiency, metabolic syndrome and type 2 diabetes, the increased frequency of “double diabetes” and the lack of studies in patients with T1D, we conducted a randomized clinical trial in male T1D patients with hypogonadotropic hypogonadism, the primary aim of which was to evaluate the effectiveness of testosterone replacement therapy on insulin sensitivity, glycaemic control, anthropometric parameters, blood pressure and lipid profile. The secondary objective was to analyze changes in the International Index of Erectile Function (IIEF-5) after testosterone undecanoate (TU) therapy in these patients.

Materials and Methods

A randomized placebo-controlled multicenter study, which enrolled T1D patients with hypogonadotropic hypogonadism treated at diabetes units of 3 urban hospitals in Barcelona between July 2013 and December 2014, was conducted. A single 1:1 randomization list was generated for the three centers and patients were centrally assigned to one of the two arms, consecutively. Both, researchers and patients, were blinded. Inclusion criteria were: a) age ≥ 18 years; b) diagnosis of autoimmune diabetes; c) hypogonadotropic hypogonadism (total testosterone levels <10 nmol/L (< 2.99 ng/mL) or calculated free testosterone levels < 225 pmol/L (< 65 pg/mL), all associated with low or normal gonadotropin levels (luteinizing hormone [LH] < 8.6 mIU/mL) on two separate early-morning days at least 1 week apart; d) ability to sign their informed consent; and e) comply with the study protocol. The study protocol was approved by the local Ethics Committee and the Spanish Agency for Medicines and Health Products (AEMPS), and it was registered in the European Clinical Trials database (EUDRA-CTe number: 2012-000291-42).

Magnetic resonance imaging (MRI) focused on the pituitary was performed in all candidate patients.

Exclusion criteria were: a) presence of pituitary tumor, empty sella, hyperprolactinemia, panhypopituitarism or secondary hypogonadism; b) patients with contraindications for treatment with TU; and c) failure to agree to sign the informed consent form.

Measurements

Patients who met the inclusion criteria were randomized to receive TU 1,000 mg or placebo at baseline, 6 weeks and 16 weeks. At each visit and 6 weeks after the last TU administration, extractions were made for analysis and anthropometric parameters, blood pressure and insulin sensitivity were determined. Prior to randomization and at week 22, the International Index of Erectile Function (IIEF-5), a self-administered questionnaire consisting of 5 items with five response options each and a score of 5-25, was completed [18].

Weight, height, waist-hip circumference and blood pressure were measured by standard methods. Diabetes complications were assessed by a specialist in diabetology. Fasting glucose, HbA_{1c}, lipid profile, albumin, microalbumin/creatinine ratio, total testosterone, LH, follicle-stimulating hormone and sex hormone-binding globulin concentrations were measured. Free serum testosterone level was calculated using the Vermeulen formula.

Insulin resistance was calculated using the estimated glucose disposal rate (eGDR) according to the following equation: $24.31 - (12.22 \times \text{waist to hip ratio}) - (3.29 \times \text{hypertension}) - (0.57 \times \text{HbA}_{1c})$; units are expressed in milligrams per kilogram⁻¹ per minute⁻¹. Hypertension was = 1 if blood pressure was $\geq 140/90$ mm Hg (or on medications) and HbA_{1c} the percentage of HbA_{1c} [19]. The metabolic syndrome was diagnosed in accordance with the modified criteria of the National Cholesterol Education Program-Adult Treatment Panel III, and the percentage of body fat was calculated using the CUN-BAE formula (body fat (%) = $-44.988 + (0.503 \times \text{age}) + (10.689 \times \text{gender}) + (3.172 \times \text{BMI}) - (0.026 \times \text{BMI}^2) + (0.181 \times \text{BMI} \times \text{gender}) - (0.02 \times \text{BMI} \times \text{age}) - (0.005 \times \text{BMI}^2 \times \text{gender}) + (0.00021 \times \text{BMI}^2 \times \text{age})$, where male = 0; BMI was expressed as kg/m² and age in years), validated in the Spanish population [20].

Statistical analysis

Sample size calculation: Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 6 sub-

jects are necessary in each group to recognize as statistically significant a difference in eGDR greater than or equal to $1.5 \text{ mg} \cdot \text{Kg}^{-1} \cdot \text{min}^{-1}$. The common standard deviation was assumed to be $1.5 \text{ mg} \cdot \text{Kg}^{-1} \cdot \text{min}^{-1}$ and the correlation coefficient between the baseline and final measurement as 0.85. A drop-out rate of 10% was anticipated.

Continuous variables are expressed as mean $\pm$ standard deviation and categorical variables as percentages and frequencies. Student's *t*-test was used to evaluate differences between two means. When data were not normally distributed, the Mann-Whitney U test was applied. The chi-square test was performed to assess the degree of association between categorical variables. A *p* value <0.05 was considered statistically significant. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS for Windows, v. 20.0, SPSS Inc., Chicago, IL, USA).

Results

Screening was performed in 202 T1D patients of whom 21 had hypogonadotropic hypogonadism, constituting a prevalence of 10.4% (95% CI: 6.2-14.6%). Six patients were excluded owing to contraindications for TU treatment (5 benign prostatic hyperplasia, 1 polyglobulia), one had an empty sella on MRI and one refused to give his consent. Of the total number of patients, one in each group left the study due to causes unrelated to the treatment. The data analysis was made on an intention-to-treat basis.

Mean patient age was 46.3 ± 9.8 years and mean duration of T1D 21.2 ± 12.4 years. Eighty-four per cent of patients with hypogonadism had the metabolic syndrome and 92.3% were overweight or obese. No differences were found in baseline characteristics between groups (Table 1).

As expected, at 22 weeks, total and free testosterone were higher in TU group than in the placebo group ($15.5 \pm 5.7 \text{ nmol/L}$ vs. $9.3 \pm 5.1 \text{ nmol/L}$ and $450.3 \pm 157.7 \text{ pmol/L}$ vs. $182.8 \pm 87.2 \text{ pmol/L}$, respectively). No differences were found in SHBG, insulin sensitivity, HbA_{1c} or basal glucose, anthropometric parameters, blood pressure or daily insulin requirements (Table 2). Regarding lipid profile, the TU group showed a reduction in total and LDL cholesterol concentrations from the second treatment dose. At 22 weeks, the drop in total cholesterol was $37.4 \pm 27.5 \text{ mg/dL}$ in the TU group compared with an

increase of $13.2 \pm 17.8 \text{ mg/dL}$ in the placebo group ($P < 0.005$). In the same week, LDL cholesterol concentration decreased $30.2 \pm 22.1 \text{ mg/dL}$, compared with an increase of $10.5 \pm 13.4 \text{ mg/dL}$ in the placebo group ($P = 0.004$). A greater reduction in total cholesterol/HDL cholesterol ratio, and triglycerides was observed in the TU group *versus* the placebo group (Table 2). Interestingly, a greater reduction in triglycerides/HDL cholesterol ratio, a known surrogate marker of insulin resistance [21], was also observed in the TU group (Table 2). All patients except one in each group received statin therapy, without dose modifications during the study.

With respect to the secondary endpoint, a trend towards an IIEF-5 score improvement was observed in the TU group ($+5.0 \pm 7.5$) compared to the placebo group ($+0.5 \pm 2.1$), without statistical significance. No differences in prostate-specific-antigen (PSA) were observed during the treatment period (Table 2). One patient in the placebo group reported pain at the injection site, which resolved with conventional analgesia in less than 48 hours. The group treated with TU showed an increase in hematocrit and hemoglobin levels (Table 2); however, withdrawal of the medication was not necessary in any case, and no complications occurred.

Discussion

The main findings of the present study were the neutral effect on insulin sensitivity and anthropometric parameters with TU therapy, although an improvement in lipid profile was observed.

In patients with type 2 diabetes, reductions in total cholesterol of 15-17 mg/dL with 3-6 months of testosterone administration, associated with a decrease in weight and waist circumference have been observed [6, 11]. In the present study, differences from placebo at 22 weeks were 50.6 mg/dL in total cholesterol and 40.7 mg/dL in LDL cholesterol. This important fall in LDL cholesterol levels without changes in metabolic and anthropometric parameters suggest that testosterone has an important role in regulating serum cholesterol metabolism, although, to date, the potential molecular mechanisms whereby testosterone deficiency affects cholesterol metabolism are unclear. Experimental studies have shown that testosterone deficiency induces PCSK9 expression and reduces LDLR expression in the livers of castrated male pigs

Table 1 Baseline characteristics and chronic complications in TEST-T1D patients

Characteristic	Overall (n=13)	Testosterone undecanoate (n=6)	Placebo (n=7)	<i>P</i>
Age (years $\pm$ SD)	46.3 $\pm$ 9.8	47.9 $\pm$ 7.3	45.2 $\pm$ 11.7	0.653
T1DM duration (years $\pm$ SD)	21.2 $\pm$ 12.4	21.7 $\pm$ 13.0	20.9 $\pm$ 12.9	0.922
BMI (kg/m ² $\pm$ SD)	32.7 $\pm$ 7.0	30.2 $\pm$ 3.3	34.5 $\pm$ 8.5	0.312
20-24 kg/m ² (n (%))	1 (7.7)	0 (0)	1 (14.3)	0.462
25-30 kg/m ² (n (%))	3 (23.1)	3 (50)	1 (14.3)	
> 30 kg/m ² (n (%))	9 (69.2)	3 (50)	5 (74.4)	
Metabolic syndrome, n (%)	11 (84)	5 (83.3)	6 (85.7)	0.217
HbA _{1c} (% $\pm$ SD)	8.18 $\pm$ 1.4	7.60 $\pm$ 0.5	8.6 $\pm$ 1.7	0.246
HbA _{1c} (mmol/mol)	65.8 $\pm$ 15.3	55.2 $\pm$ 4.8	74.0 $\pm$ 21.7	
eGDR (mg/kg ⁻¹ ·min ⁻¹ $\pm$ SD)	5.42 $\pm$ 1.7	6.12 $\pm$ 2.2	4.9 $\pm$ 1.3	0.959
Insulin requirements (IU/kg/d $\pm$ SD)	0.86 $\pm$ 0.1	0.91 $\pm$ 0.1	0.82 $\pm$ 0.2	0.386
Hip circumference (cm $\pm$ SD)	112.7 $\pm$ 16.0	105.8 $\pm$ 4.9	117.7 $\pm$ 19.5	0.216
Waist circumference (cm $\pm$ SD)	108.4 $\pm$ 15.8	103.0 $\pm$ 10.7	112.3 $\pm$ 18.4	0.340
Waist-to-hip ratio (ratio $\pm$ SD)	0.96 $\pm$ 0.1	0.97 $\pm$ 0.1	0.95 $\pm$ 0.1	0.643
Fat mass (% $\pm$ SD)	33.6 $\pm$ 8.5	31.2 $\pm$ 4.2	35.3 $\pm$ 10.6	0.443
Systolic BP (mm Hg $\pm$ SD)	141.9 $\pm$ 14.1	144.8 $\pm$ 12.9	139.9 $\pm$ 15.6	0.550
Diastolic BP (mm Hg $\pm$ SD)	82.6 $\pm$ 9.9	81.4 $\pm$ 1.1	83.4 $\pm$ 13.3	0.979
Total cholesterol (mg/dL $\pm$ SD)	188.1 $\pm$ 88.5	178.2 $\pm$ 18.5	195.1 $\pm$ 118.3	0.455
LDL cholesterol (mg/dL $\pm$ SD)	116.9 $\pm$ 64.6	114.2 $\pm$ 16.1	118.9 $\pm$ 86.5	0.569
HDL cholesterol (mg/dL $\pm$ SD)	41.1 $\pm$ 7.2	39.8 $\pm$ 9.1	42.0 $\pm$ 6.1	0.956
Total cholesterol/HDL cholesterol ratio (mean $\pm$ SD)	4.72 $\pm$ 2.3	4.75 $\pm$ 1.6	4.71 $\pm$ 2.8	0.976
Triglycerides (mg/dL; median (range))	105 (61-700)	105 (71-150)	105 (61-700)	1.0
Triglycerides/HDL cholesterol ratio (median (range))	2.58 (1.42-16.7)	2.39 (1.51-5.98)	2.77 (1.42-16.7)	1.0
Total testosterone (nmol/L $\pm$ SD)	10.9 $\pm$ 4.1	12.4 $\pm$ 3.5	9.9 $\pm$ 4.5	0.350
Free testosterone (pmol/L $\pm$ SD)	191.6 $\pm$ 35.2	200 $\pm$ 17.6	185.6 $\pm$ 44.3	0.510
SHBG (nmol/L $\pm$ SD)	23.6 $\pm$ 12.1	26.2 $\pm$ 3.4	22.4 $\pm$ 15.2	0.755
Neuropathy, n (%)	3 (23.0)	0 (0)	3 (42.8)	0.091
Nephropathy				0.345
No, n (%)	10 (76.9)	5 (83.3)	6 (85.7)	
Microalbuminuria, n (%)	2 (15.4)	1 (17.7)	0 (0)	
Macroalbuminuria, n (%)	1 (7.7)	0 (0)	1 (14.3)	
Retinopathy, n (%)	5 (38.5)	2 (33.3)	3 (42.3)	0.921
Stroke, n (%)	1 (7.7)	0 (0)	1 (14.3)	0.377

BP, blood pressure; eGDR, estimated glucose disposal rate; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoproteins; LDL, low-density lipoproteins; T1DM, type 1 diabetes mellitus.

Table 2 Observed changes compared with baseline in TEST-T1D patients

Outcome	Testosterone undecanoate (n=6)	Placebo (n=7)	P
eGDR (mg·Kg ⁻¹ ·min ⁻¹ ± SD)			
6 weeks	+0.24 ± 0.6	+0.29 ± 1.1	0.921
16 weeks	+0.46 ± 0.8	+0.46 ± 0.8	0.573
22 weeks	+0.30 ± 0.7	-1.15 ± 0.6	0.276
HbA _{1c} (% ± SD)			
6 weeks	-0.5 ± 0.4	-0.4 ± 0.6	0.638
16 weeks	-0.4 ± 0.6	-0.7 ± 0.7	0.506
22 weeks	-0.4 ± 1.0	-0.4 ± 0.9	0.977
FPG (mg/dL ± SD)			
6 weeks	-26.2 ± 48.6	+48.8 ± 75.7	0.089
16 weeks	-37.4 ± 85.1	+32.7 ± 70.3	0.161
22 weeks	-0.6 ± 93.1	-11.7 ± 87.9	0.844
BMI (Kg·m ⁻² ± SD)			
6 weeks	+0.02 ± 1.0	-0.00 ± 0.6	0.959
16 weeks	+1.46 ± 3.2	+0.16 ± 0.4	0.352
22 weeks	+0.13 ± 1.1	+0.28 ± 0.3	0.753
Waist circumference (cm ± SD)			
6 weeks	-2.8 ± 6.8	-1.0 ± 7.4	0.686
16 weeks	-5.4 ± 5.8	-2.1 ± 6.0	0.065
22 weeks	-5.4 ± 5.1	+1.5 ± 6.3	0.081
Hip circumference (cm ± SD)			
6 weeks	-3.2 ± 3.4	-0.2 ± 5.5	0.311
16 weeks	-3.6 ± 4.6	-0.7 ± 7.9	0.483
22 weeks	-4.6 ± 4.2	-2.3 ± 4.3	0.401
Fat mass (% ± SD)			
6 weeks	+0.03 ± 1.3	+0.2 ± 0.5	0.987
16 weeks	+1.6 ± 3.5	+0.2 ± 0.4	0.347
22 weeks	+0.2 ± 1.4	+0.3 ± 0.3	0.862
Systolic BP (mm Hg ± SD)			
6 weeks	-10.6 ± 6.2	-5.0 ± 19.1	0.548
16 weeks	-5.0 ± 4.4	-1.3 ± 16.9	0.651
22 weeks	-9.6 ± 11.9	+8.8 ± 22.8	0.138
Diastolic BP (mm Hg ± SD)			
6 weeks	-5.0 ± 6.4	+2.8 ± 14.4	0.291
16 weeks	+0.0 ± 6.6	-0.2 ± 10.3	0.976
22 weeks	+1.0 ± 4.5	-1.2 ± 19.9	0.819
Total cholesterol (mg/dL ± SD)			
6 weeks	-20.0 ± 27.3	+8.0 ± 30.1	0.144
16 weeks	-33.4 ± 19.4	+0.5 ± 12.7	0.007
22 weeks	-37.4 ± 27.5	+13.2 ± 17.8	0.005

Table 2 Cont.

Outcome	Testosterone undecanoate (n=6)	Placebo (n=7)	P
LDL cholesterol (mg/dL ± SD)			
6 weeks	-17.2 ± 21.3	-0.5 ± 15.7	0.169
16 weeks	-29.6 ± 13.2	-0.0 ± 8.0	0.001
22 weeks	-30.2 ± 22.1	+10.5 ± 13.4	0.004
HDL cholesterol (mg/dL ± SD)			
6 weeks	+6.6 ± 6.5	+0.5 ± 6.7	0.165
16 weeks	+2.4 ± 7.6	-1.0 ± 2.1	0.321
22 weeks	+2.2 ± 4.3	+0.9 ± 3.1	0.567
Total cholesterol/HDL cholesterol ratio			
6 weeks	-1.2 ± 1.5	+0.1 ± 0.5	0.073
16 weeks	-1.2 ± 1.4	+0.1 ± 0.4	0.066
22 weeks	-1.3 ± 1.2	+0.2 ± 0.3	0.016
Triglycerides (mg/dL ± SD)			
6 weeks	-29.7 ± 40.6	+46.8 ± 85.3	0.101
16 weeks	-16.9 ± 58.1	+22.2 ± 58.4	0.297
22 weeks	-39.7 ± 34.6	+20.2 ± 33.0	0.017
Triglycerides/HDL cholesterol ratio			
6 weeks	-1.06 ± 1.6	+1.00 ± 1.8	0.079
16 weeks	-0.52 ± 2.5	+0.49 ± 1.3	0.409
22 weeks	-1.38 ± 1.7	+0.49 ± 0.92	0.042
IIEF-5 (points ± SD)			
22 weeks	+5.0 ± 7.5	+0.5 ± 2.1	0.800
IIEF-5			0.558
No changes n (%)	3 (60.0)	4 (66.7)	
Improvement n (%)	2 (40.0)	1 (16.7)	
Worsening n (%)	0 (0)	1 (16.7)	
PSA (ng/mL)			
6 weeks	+0.20 ± 0.2	+0.10 ± 0.1	0.435
16 weeks	+0.24 ± 0.3	+0.10 ± 0.0	0.228
22 weeks	+0.33 ± 0.3	+0.10 ± 0.0	0.128
Hemoglobin (g/dL)			
6 weeks	+0.50 ± 0.5	-1.30 ± 1.0	0.025
16 weeks	+1.50 ± 0.5	-0.50 ± 0.7	0.014
22 weeks	+1.63 ± 0.9	-0.30 ± 0.9	0.019
Hematocrit (%)			
6 weeks	+1.40 ± 1.5	-3.00 ± 2.6	0.082
16 weeks	+3.43 ± 1.7	-1.67 ± 2.3	0.036
22 weeks	+4.10 ± 2.7	-0.56 ± 2.6	0.039

BMI, body mass index; BP, blood pressure; eGDR, estimated glucose disposal rate; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoproteins; IIEF, international index of erectile function; LDL, low-density lipoproteins.

following a high fat and cholesterol diet [22]. These findings suggest that increased serum cholesterol levels associated with testosterone deficiency may be attributed to impaired LDL cholesterol clearance. Furthermore, a study in testosterone deficient-LDLr-/- mice suggests a functional modulator role of LDLR in processes associated with hypogonadism-induced metabolic alterations [23].

With respect to triglycerides, in type 2 diabetic patients with hypogonadism, TU therapy produced a decrease of 62 mg/dL at 12 months [7], and up to 138 mg/dL at 8 years [9]. In the present study, the drop observed at 22 weeks *versus* placebo was 59.9 mg/dL, a figure similar to that found in type 2 diabetes.

However, we were unable to confirm the improvement in insulin resistance, glycemic control or anthropometric changes observed in T2D patients. A trend towards an improvement in IIEF-5 was observed, without reaching statistical significance.

With respect to the adverse effects of treatment, no differences were found in PSA, although there was a rise in hematocrit in the TU treatment group. Hemoglobin levels did not exceed 17.0 g/dL in any case, or were associated with any serious adverse event.

The small sample size in the present study could have limited its power to detect significant differences in anthropometric and metabolic parameters. Furthermore, insulin sensitivity and body fat percentage were calculated based on validated formulas, with a good correlation with the hyperinsulinemic euglycemic clamp and bioimpedanciometry, respectively, but were not measured directly, which signifies that the results may not be completely accurate.

In conclusion, treatment with TU in patients with T1D and hypogonadotropic hypogonadism seems to produce a greater improvement in lipid profile than that observed in patients with type 2 diabetes or the metabolic syndrome, with no significant effects on metabolic control or anthropometric parameters. Further studies with a larger sample size and follow-up are needed to confirm these data and to clarify the pathophysiologic mechanisms.

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