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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Ενδοκρινολογικές καταστάσεις που επηρεάζουν την ανδρική γονιμότητα-νέες εξελίξεις

ΔΗΜΗΤΡΑ ΓΟΥΡΜΑ

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Systematic review and meta-anaylsis

“Various interventions for infertility in men with type II diabetes and hypogonadism”

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Author Contributions

DG, EK, OT and NV performed the literature search, data acquisition, data analysis, statistical analysis and manuscript preparation. TK conceived and designed the analysis and performed the manuscript editing and manuscript review.

Abstract

Background: Low levels of testosterone and sexual desire loss are common characteristics of hypogonadism, which is an endocrine disorder often occurring in men. Sexual dysfunction is an uncomfortable condition that both hypogonadal and diabetic men experience nowadays, however the diagnosis and treatment strategies are limited. Type II diabetes is a lifelong disorder of abnormal glucose metabolism with devastating health effects on patients. Sex-related hormones, that normally regulate the reproductive cycle, are found significantly reduced in conditions where the functional activity of the gonads is decreased. An imbalance in the levels of these hormones is also associated with metabolic abnormalities, such as hyperglycemia and insulin resistance. The effectiveness of the existing therapies for sexual dysfunction treatment and the restoration of reproductive hormones in hypogonadal men with type II diabetes remain unexplored.

Methods: We searched the Cochrane Library, Scopus, Science Direct and the Web Search engine "Google Scholar" from January 2011 to July 2021. Randomized controlled trials (RCTs) were included, comparing the treatment of sexual dysfunction and the restoration of sex-related hormones in hypogonadal men with type II diabetes with testosterone replacement or administration of vardenafil or clomiphene citrate, versus placebo treatment. Fixed effect meta-analysis was performed to estimate pooled proportions with 95% confidence intervals (CI).

Results: The review includes nine RCTs regarding: a) Testosterone replacement therapy (five RCTs) and administration of b) Vardenafil (one RCT) or c) Clomiphene citrate (three RCTs) for the treatment of sexual dysfunction in diabetic men with hypogonadism. The aspects of sexual function were evaluated by estimating the: a) Aging male's symptoms' (AMS) rating scale, b) Erectile Function, c) Intercourse Satisfaction, d) Orgasmic Function, e) Sexual Desire, f) Overall Sexual Satisfaction, g) levels of E2 (pg/mL), h) levels of FHS (mU/mL), i) levels of LH (mU/mL), j) levels of SHBG (nmol/L) and k) levels of free testosterone (nmol/L). Our findings suggest that a) testosterone replacement therapy or administration of vardenafil resulted in improved erectile function (95% Cl -0.485 to -0.165; 6 RCTs; I^2=94,8%, p=6.5e-05), b) testosterone supplementation ameliorated intercourse satisfaction (95% Cl -0.4 to -0.064; 4 RCTs; I^2=54,5%, p=0.006783), orgasmic function (95% Cl -0.674 to -0.325; 4 RCTs; I^2=94,6%, p=0) and sexual desire (95% Cl -0.446 to -0.124; 5 RCTs; I^2=94,3%, p=0.00509), but had no impact on AMS rating scale (95% Cl -0.286 to 0.057; 4 RCTs; I^2=93,1%, p = 0.191643) and overall satisfaction (95% Cl 0.03 to 0.402; 3 RCTs; I^2=95%, p=0.023112) and c) administration of clomiphene citrate led in elevated levels of E2 (95% Cl -1.531 to -0.756; 3 RCTs; I^2=0%, p=0), LH (95% Cl -0.674 to -0.325; 3 RCTs;

I^2=0%, p=0), FSH (95% Cl -1.372 to -0.612; 3 RCTs; I^2=0%, p=0), SHBG (95% Cl -0.938 to -0.207; 3 RCTs; I^2=0%, p=0.002151) and free testosterone (95% Cl -1.864 to -1.204; 3 RCTs; I^2=83.1%, p=0), compared to placebo treatment in hypogonadal men with type II diabetes.

Conclusions: Hypogonadal males with type II diabetes receiving either testosterone supplementation, or the compounds vardenafil and clomiphene citrate, displayed improved sexual function and elevated levels of sex-related hormones, versus placebo treatment.

Keywords

hypogonadism, testosterone, sexual dysfunction, diabetes, hormones

INTRODUCTION

Background

This review addresses the use of vardenafil, clomiphene citrate or testosterone replacement as a sexual dysfunction treatment in men with hypogonadism and type II diabetes. In this research we focused on the study of erectile and orgasmic function, as well as of sexual desire and intercourse satisfaction, the main areas of the normal sexual response cycle. Erection, which is associated with heightened sexual arousal, is the ultimate response to multiple stimuli that affect several neurological and vascular events, finally leading to physical changes in male body for a successful intercourse (Martinez-Salamanca, Martinez-Ballesteros et al. 2010). These genital responses are indicators of sexual desire, which is commonly defined as the physical and mental readiness to initiate and maintain a sexual behavior (Mark, Herbenick et al. 2014).

Description of the intervention

Since testosterone is critical for male sexual behavior, replacement therapy is a promising approach against androgen decline and erectile dysfunction in men with hypogonadism (Seidman, Spatz et al. 2001; Byrne and Nieschlag 2003; Miner, Canty et al. 2008; Ide, Vanderschueren et al. 2020; Lee, Shah et al. 2021). In fact, combination therapy of testosterone and vardenafil has been proved effective in treating hypogonadal men who had insufficient response to testosterone monotherapy (S., K. et al. 2013; Yassin, Yassin et al. 2014). Vardenafil is a highly selective phosphodiesterase type 5 (PDE5) inhibitor, with vasodilatory activity, widely utilized for the recovery of erectile function in men with mild to severe erectile dysfunction (Keating and Scott 2003). Administration of testosterone as a replacement therapy has also been shown to improve glycemic control and insulin sensitivity in hypogonadal men with type II diabetes, thus providing additional beneficial metabolic effects (Kapoor, Goodwin et al. 2006; Li, Zhao et al. 2020). On the other hand, treatment of diabetic hypogonadal men with vardenafil resulted in improved erectile function with no effects on glucose regulation (Goldstein, Young et al. 2003; Carson and Lue 2005; Vardi and Nini 2007; Zamorano-Leon, Olivier et al. 2013; Santi, Granata et al. 2017). Similarly, clomiphene citrate, a selective estrogen receptor modulator, has been used for the treatment of male androgen deficiency by raising the endogenous serum FSH, LH and testosterone levels to augment spermatogenesis (Roth, Ryan et al. 2013; Wheeler, Sharma et al. 2019; Delu, Kiltz et al. 2020; Pelusi, Fanelli et al. 2021).

Why it is important to do this review

Administration of pharmacological compounds or the testosterone replacement therapy are widely known strategies to combat sexual dysfunction in hypogonadal men. However, the increasing prevalence rate of both androgen deficiency and type

II diabetes in men raises the question of how effective is the administration of the above therapies for the treatment of sexual dysfunction in diabetic men. In this meta-analysis, we collected research data regarding the improvement of sexual dysfunction and/or the levels of reproduction-related hormones, following treatment with testosterone supplementation, vardenafil or clomiphene citrate in hypogonadal diabetic men.

Objectives

To determine the effectiveness of testosterone replacement or administration of vardenafil or clomiphene citrate in the improvement of sexual function and the levels of reproductive hormones in men with hypogonadism and type II diabetes.

METHODS

Criteria for considering studies for this review:

Types of studies

Only randomized, placebo-controlled trials (RCTs), published since January 2011 were included. Quasi-randomized controlled or randomized controlled animal trials were not included.

Types of participants

Inclusion criteria

Men with hypogonadism and type II diabetes, undergoing treatment with testosterone replacement, vardenafil or clomiphene citrate for at least 12 weeks (see **Table 1**).

Types of interventions

Studies had to compare administration of testosterone, vardenafil or clomiphene citrate versus placebo.

Outcome measures

1. Erectile function: The evaluation is based on the results from the International Index of Erectile Function (IIEF), an internationally used tool for assessing male sexual function.
2. Orgasmic function
3. Sexual desire

4. Intercourse satisfaction
5. Overall sexual satisfaction: An IIEF questionnaire scoring method to assess erectile dysfunction in male participants.
6. Aging male's symptoms' (AMS) rating scale: A tool based on a questionnaire scoring for measuring the severity of symptoms related to aging, including andropause
7. E2 levels:
8. FSH levels:
9. SHBG levels:
10. Testosterone levels: Sex- and fertility-related hormones measured in cases of infertility and hypogonadism.

Search methods for identification of studies

The search incorporated all relevant published RCTs, with language (published in English) and date restriction (from January 2011 to July 2021). We searched the electronic databases "PubMed", "Scopus", "Science Direct" and "Cochrane library" and the Web Search engine "Google Scholar".

Search strategy

From January 2011 to July 2021, keywords contain: "type II diabetes", "male infertility", "male hypogonadism", "glucose metabolism". "testosterone deficiency", "androgen deficiency"

Data collection and analysis

Selection of studies

After an initial screen of titles and abstracts retrieved by the search, conducted by meta-analysis and review author DG, we retrieved the full text of all potentially eligible studies. DG examined these full-text articles for compliance with the inclusion criteria and selected studies eligible for inclusion in the review. We documented the selection process with a "PRISMA" flow chart (see Figure 1).

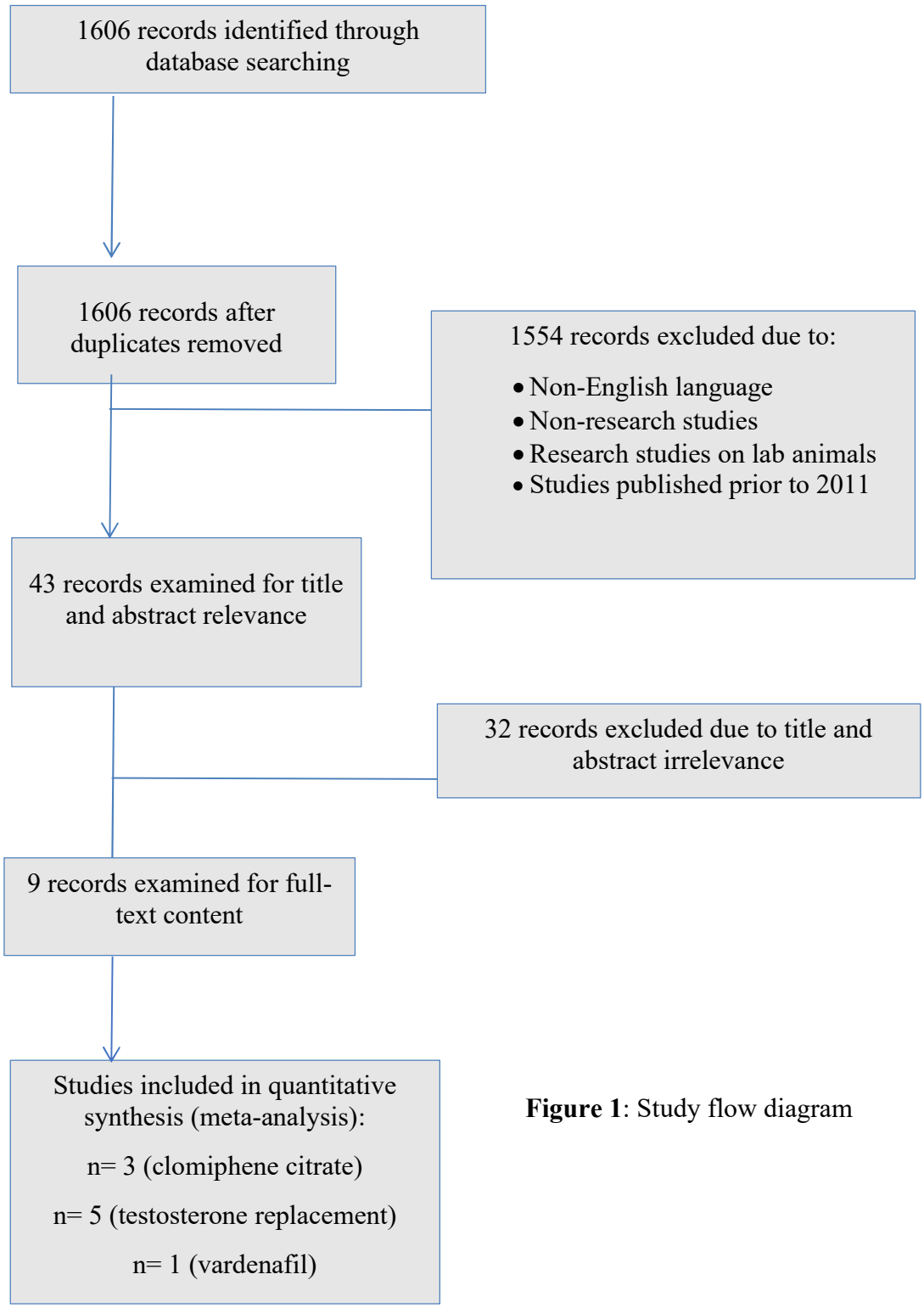

Figure 1: Study flow diagram

Statistical analysis

The data was analyzed using the SPSS software package. The META-MAR V2.7.0 application was used to perform mathematical analysis. The effect sizes were calculated using the fixed-effect model, and the forest plot was generated; confidence interval, p value, weight effect, and the heterogeneity of the studies were also calculated.

RESULTS

Results of the search

In our search 1606 eligible reports were identified, after having removed duplicates. We excluded 1554 as irrelevant and screened 43 in full text. After discarding 32, nine seemed to meet the inclusion criteria (see PRISMA flow chart: **Figure 1**).

Included studies

Study design and setting

We included nine RCTs. In five of them men received testosterone replacement therapy (Jones, Arver et al. 2011; Hackett, Cole et al. 2013; Gianatti, Dupuis et al. 2014; Hackett, Cole et al. 2014; Hackett, Cole et al. 2016), three RCTs included men daily receiving clomiphene citrate (Pelusi, Giagulli et al. 2017; Soares, Horie et al. 2018; Pelusi, Fanelli et al. 2020) and one study involved male patients treated with vardenafil in a daily basis (Santi, Granata et al. 2016). A summary of the treatment received by patients in each study is presented in **Table 1**.

Briefly, in three out of five RCT studies regarding testosterone supplementation therapy, patients received 3 doses (1000 mg) of testosterone (in 0, 6 and 18 weeks) in a total of 30-week randomized placebo-controlled studies (Hackett, Cole et al. 2013; Hackett, Cole et al. 2014; Hackett, Cole et al. 2016). The other two studies referred to a 12-week study of testosterone treatment (60 mg/day) (Jones, Arver et al. 2011) and to a 40-week study of four-doses testosterone administration (1000 mg in 0, 6, 18 and 30 weeks) (Gianatti, Dupuis et al. 2014). In the study of Santi et al. in 2016, vardenafil was administrated in hypogonadal diabetic men for 24 weeks (20 mg/day), whereas two RCTs included treatment of hypogonadal men with clomiphene citrate (25 mg/day) for 12 weeks (Pelusi, Giagulli et al. 2017; Pelusi, Fanelli et al. 2020) and one more study referred to a higher-dose administration of clomiphene citrate (50 mg/day) for 12 weeks (Soares, Horie et al. 2018).

Study	Treatment	Duration of study	Dose(s)	Number of participants	
				Placebo	Treatment
Hackett et al., 2016	Testosterone replacement	30 weeks	1000 mg in 0, 6 and 18 weeks	103	86
Jones et al., 2011	Testosterone replacement	12 weeks	60 mg/day	112	108
Gianatti et al., 2014	Testosterone replacement	40 weeks	1000 mg in 0, 6, 18 and 30 weeks	41	44
Hackett et al., 2013	Testosterone replacement	30 weeks	1000 mg in 0, 6 and 18 weeks	102	97
Hackett et al., 2014	Testosterone replacement	30 weeks	1000 mg in 0, 6 and 18 weeks	102	97
Santi et al., 2016	Vardenafil	24 weeks	20 mg/day	28	26
Pelusi et al., 2017	Clomiphene citrate	12 weeks	25 mg/day	12	12
Pelusi et al., 2019	Clomiphene citrate	12 weeks	25 mg/day	10	10
Soares et al., 2018	Clomiphene citrate	12 weeks	50 mg/day	39	39

Table 1: Summary of findings for the comparison of various treatments versus placebo in hypogonadal men with type II diabetes.

Outcomes

1.1 Aging male's symptoms' (AMS) rating scale

Evidence was insufficient in order to determine whether there was any difference between the groups in AMS rating scale [Hedge's g=-0.11; 95% confidence interval (CI) -0.286 to 0.057; 4 RCTs; n= 538, I^2= 93.1%]. The results were not statistically significant (p= 0.191643> 0.1) and the studies displayed high heterogeneity. No significant effect of testosterone supplementation on AMS was obvious by the forest plot graph (data not shown).

1.2 Erectile function

Testosterone replacement therapy or administration of vardenafil seems to ameliorate erectile dysfunction in men with hypogonadism and type II diabetes, as evident from the forest plot graph [Hedge's g= -0.33; 95% confidence interval (CI) -0.485 to 0.165; 6 RCTs; n= 658; I^2= 94.8%] (Figure 2A). The results were statistically significant (p= 0.000065< 0.05) although the studies displayed high heterogeneity. The studies that contributed most to the analysis were Jones et al., 2011 (weight %= 30.54 %) and Hackett et al., 2013 (weight %= 31.31 %).

1.3 Intercourse satisfaction

Forest plot analysis reveals that testosterone supplementation has a positive impact on intercourse satisfaction in male patients with androgen deficiency and diabetes [Hedge's g= -0.23; 95% confidence interval (CI) -0.4 to 0.064; 4 RCTs; n= 553; I^2= 54.5%] (Figure 2B). The results displayed statistical significance (p= 0.006783< 0.05) and moderate heterogeneity. The studies that contributed most to the analysis were Jones et al., 2011 (weight %= 33,12 %) και Hackett et al., 2013 (weight %= 34,89 %).

1.4 Orgasmic function

Administration of testosterone seems to have a positive effect on orgasmic function of the participants versus placebo, as verified by forest plot analysis [Hedge's g= -0.5; 95% confidence interval (CI) -0.674 to 0.325; 4 RCTs; n= 553; I^2= 94.6%] (Figure 2C). The results were statistically significant (p= 0) although the studies displayed high heterogeneity. The studies of Jones et al., 2011 (weight %= 35,42 %) και Hackett et al., 2013 (weight %= 36,96 %) contributed most to the analysis.

1.5 Overall satisfaction

Testosterone replacement therapy had no effect on the overall satisfaction of hypogonadal and diabetic men that participated in the studies [Hedge's g= 0.22; 95% confidence interval (CI) 0.03 to 0.402; 3 RCTs; n= 461; I^2= 95%]. The results were statistically significant (p= 0.023112<0,05); however, the heterogeneity score was high (data not shown). The studies of Jones et al., 2011 (weight %= 39,6 %) και Hackett et al., 2013 (weight %= 42,37 %) contributed most to the analysis.

1.6 Sexual desire

Administration of testosterone in male participants increased their sexual desire [Hedge's g= -0.29; 95% confidence interval (CI) -0.446 to -0.124; 5 RCTs; n= 634; I^2= 94.3%] (Figure 2D). The results displayed statistical significance (p = 0.000509<0,005) and high heterogeneity. The studies that contributed most to the analysis were Jones et al., 2011 (weight %= 30,3 %) και Hackett et al., 2013 (weight %= 31,19 %).

1.7 E2 levels

Clomiphene citrate administration in male patients dealing with testosterone deficiency and type II diabetes results in elevated levels of E2 (pg/mL), as evident from the forest plot [Hedge's g= -1.6; 95% confidence interval (Cl) -2.202 to -1.185; 3 RCTs; n= 113; I^2= 0%] (Figure 2E). The results displayed statistical significance (p= 0) and high homogeneity. The study of Soares et al., 2018 (weight %= 61,91 %) contributed most to the analysis.

1.8 LH levels

Treatment of patients with clomiphene citrate resulted in elevated levels of LH (mU/mL) [Hedge's g= -1.14; 95% confidence interval (Cl) -1.531 to -0.756; 3 RCTs; n= 115; I^2 = 0%] (Figure 2F). The results were statistically significant (p= 0) and the studies displayed high homogeneity. The study that contributed most to the analysis was Soares et al., 2018 (weight %= 59,59 %).

1.9 FSH levels

Administration of clomiphene citrate in diabetic men with androgen deficiency versus placebo, increased the levels of FSH in their blood (mU/mL) [Hedge's g= -0.99; 95% confidence interval (Cl) -1.372 to -0.612; 3 RCTs; n= 115; I^2 = 0%] (Figure 2G). The results displayed statistical significance (p= 0) and high homogeneity. The study that contributed most to the analysis was Soares et al., 2018 (weight %= 59,61 %).

1.10 SHBG levels

Treatment of patients with clomiphene citrate versus placebo lead to elevated levels of the sex-related hormone SHBG (nmol/L), as presented in the forest plot [Hedge's g= -0.57; 95% confidence interval (Cl) -0.938 to -0.207; 3 RCTs; n= 115; I^2= 0%] (Figure 2H). The results were statistically significant (p= 0.002151<0.05) with no variability displayed in the data. The study of Soares et al., 2018 (weight %= 59.88 %) contributed most to the analysis.

1.11 Free testosterone levels

Infertility treatment (testosterone replacement or vardenafil or clomiphene citrate administration) of male participants with hypogonadism and type II diabetes, resulted in increased levels of free testosterone (nmol/L) [Hedge's g= -1.53; 95% confidence interval (Cl) -1.864 to -1.204; 3 RCTs; n= 185; I^2= 83.1%] (Figure 2I). The results were statistically significant (p= 0); however, the heterogeneity score was high. The study that contributed most to the analysis was Hackett et al., 2014 (weigh %= 63,01%).

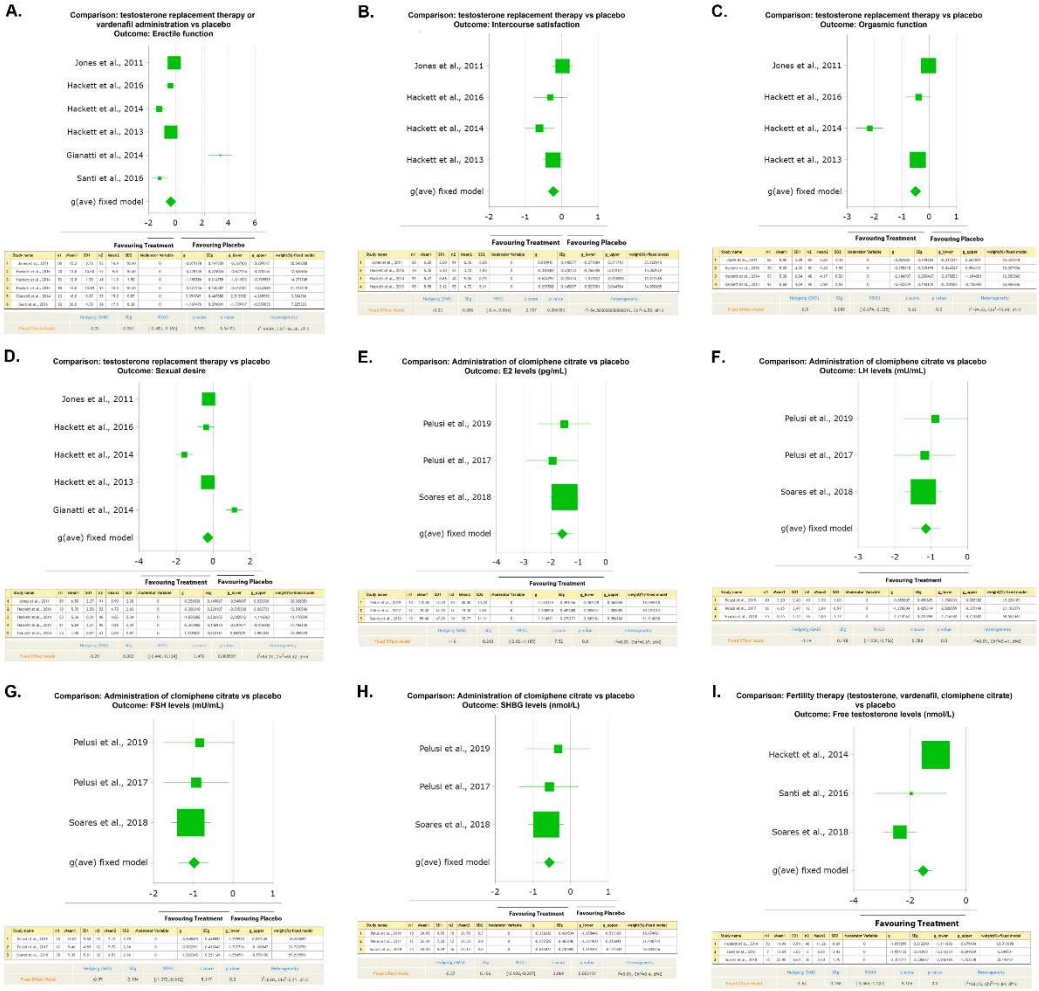

Figure 2. The main outcomes from the meta-analysis regarding the effect of infertility interventions on various areas of the normal sexual response cycle of men with hypogonadism and type II diabetes (**A**) Comparison: Testosterone replacement therapy or administration of vardenafil vs placebo, Outcome: Erectile function. (**B**) Comparison: Testosterone replacement therapy vs placebo, Outcome: Intercourse satisfaction. (**C**) Comparison: Testosterone replacement therapy vs placebo, Outcome: Orgasmic function. (**D**) Comparison: Testosterone replacement therapy vs placebo, Outcome: Sexual desire. (**E**) Comparison: Administration of clomiphene citrate vs placebo, Outcome: E2 levels (pg/mL). (**F**) Comparison: Administration of clomiphene citrate vs placebo, Outcome: LH levels (mU/mL). (**G**) Comparison: Administration of clomiphene citrate vs placebo, Outcome: FSH levels (mU/mL). (**H**) Comparison: Administration of clomiphene citrate vs placebo, Outcome: SHBG levels (nmol/L). (**I**) Comparison: Fertility therapy (administration of testosterone, vardenafil or clomiphene citrate) vs placebo, Outcome: Free testosterone levels (nmol/L).

DISCUSSION

Summary of main results

Our meta-analysis shows that overall, the interventions for infertility studied had a positive effect on sexual dysfunction and on the levels of reproduction- and sex-related hormones, in men dealing with hypogonadism and type II diabetes. Specifically, treatment with testosterone versus placebo ameliorated the erectile and orgasmic function, intercourse satisfaction, and sexual desire of the participants. Vardenafil administration displayed similar effects on erectile function of patients. Finally, treatment with clomiphene citrate led to elevated levels of all fertility- and sex-related hormones tested (E2, LH, FSH, SHBG and free testosterone).

AUTHORS' CONCLUSIONS

It is well-known that men with type II diabetes often suffer from androgen deficiency and sexual dysfunction, thus facing difficulties in their everyday life. In this meta-analysis we studied the effectiveness of various interventions for infertility against the biochemical and clinical symptoms of hypogonadism in diabetic men. According to our findings, treatment of patients with the appropriate infertility therapy versus placebo, resulted in ameliorated erectile and orgasmic function, intercourse satisfaction and sexual desire and in increased levels of various reproductive hormones. These results suggest that testosterone replacement or administration of vardenafil or clomiphene citrate are effective treatments for the improvement of sexual function and the levels of reproduction-related hormones in men with hypogonadism and type II diabetes.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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