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TITLE PAGE

ADDITION OF METFORMIN TO SILDENAFIL TREATMENT FOR ERECTILE DYSFUNCTION IN EUGONADAL NON–DIABETIC MEN WITH INSULIN RESISTANCE. A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND PILOT STUDY.

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Running Title: Metformin Treatment in Erectile Dysfunction

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Abstract

Erection depends largely on the release of nitric oxide (NO) by vascular endothelial cells. Insulin resistance (IR) is a metabolic abnormality that produces endothelial dysfunction characterized by decreased synthesis and release of NO. Aim: To evaluate the effect of treatment with metformin on the response to sildenafil in patients with erectile dysfunction (ED) and IR. Methods: Prospective, randomized, controlled, double-blind placebo study. We included 30 male patients with ED, IR and poor response to sildenafil. Exclusion criteria: pharmacologic, anatomic or endocrine ED, diabetes, prostatic surgery or chronic illnesses. Erectile function was rated according to the International Index of Erectile Function 5 (IIEF-5). IR was measured by HOMA (IR=HOMA $\geq$3). Patients were randomized to receive metformin (n=17) or placebo (n=13). Results: After treatment with metformin, patients with ED showed a significant increase in IIEF-5 score and a significant decrease in HOMA both occurring at months 2 (IIEF-5: 17.0±6.0 vs. 14.3±3.9, p=0.01 and HOMA: 3.9±1.6 vs. 5.5±2.4, p=0.01) to 4 of treatment (IIEF-5: 19.8±3.8 vs. 14.3±3.9, p=0.005 and HOMA: 4.5±1.9 vs. 5.5±2.4, p=0.04), with no changes in these parameters in patients with ED receiving placebo. Patients treated with metformin had more adverse events than those who received placebo: 61.5% versus 7.7%, p=0.03, respectively. AEs were mild, mainly gastrointestinal, and did not cause discontinuation of treatment. Conclusion: Treatment with metformin in patients with ED and poor response to sildenafil reduced the IR and improved erectile function.

Key words: Male Sexual Function; Erectile dysfunction; Insulin resistance; Metformin; Sildenafil.

Text

Introduction:

Erection is a neuromyovascular phenomenon, where nitric oxide (NO) released by the vascular endothelium induces smooth muscle relaxation with subsequent flow of blood to the penis.

Insulin resistance (IR), present in most subjects with obesity and metabolic syndrome (MS) and type 2 diabetes mellitus (DM2), is a metabolic disorder that produces endothelial dysfunction characterized by decreased synthesis and release of NO, combined with an excessive consumption of NO in tissues exposed to high concentrations of free radicals (Cersosimo and De Fronzo, 2006; Aljada and Dandona, 2000). The decrease in the levels of NO affects different arteries, impairing vasodilation (McFarlane et al, 2001; Vlachopoulos et al, 2008). Erectile dysfunction (ED) is often associated with endocrine–metabolic diseases, such as MS and DM2, where IR plays a decisive physiopathological role (McCulloch et al, 1980; Hsueh and Quinones, 2003).

Insulin–sensitizing agents have been shown to improve endothelial function in early IR states. In patients with DM2 treated with insulin and metformin, improvement in endothelial function apparently is unrelated to glycemic control (De Jager et al, 2005). All these data suggest that in IR states there is a disorder in endothelial function that can be reversed by treatment with insulin–sensitizing agents such as metformin.

Inhibitors of phosphodiesterase type 5, such as sildenafil, require adequate levels of NO to be effective. As there are decreased levels of NO in IR states, and insulin–sensitizing agents improve IR, we postulate that in patients with ED and IR and poor response to sildenafil, the addition of metformin can optimize the response to sildenafil improving endothelial function.

This study aims to assess the effect of treatment with metformin on the response to sildenafil in patients with ED, IR and poor response to sildenafil.

Methods:

Thirty patients with ED and IR (and a prior history of poor response to sildenafil, defined as: IIEF-5 < 21 after taking sildenafil correctly at maximum dosage and at least on 4 occasions, and still complaining about ED) were included. Patients were chosen from a group of 78 males who had been included in a previous study where the presence of obesity, IR, and testosterone levels in subjects with ED was evaluated (Knoblovits et al, 2010).

The following exclusion criteria were established: pharmacologic (onset of ED within 6 months of beginning treatment with any drugs described as associated with ED) or anatomical ED (Peyronie's Disease), hyperprolactinemia, hypogonadism (defined when bioavailable testosterone levels are below the lower limit: < 0.8 ng/mL in two samples on different days), previous diagnosis of type 1 or type 2 DM, alcohol abuse, history of prostate or pelvic surgery, severe chronic illness and/or patient use of drugs that may interfere with

laboratory results or cause hypogonadism (e.g., opiates, antiandrogens, corticosteroids, metformin).

A detailed questionnaire was prepared, focusing on clinical history with regard to arterial hypertension, dyslipidemia, general diseases, smoking, alcohol consumption, medication, hours and type of physical activity per week (the degree of physical activity was assessed according to a scale proposed in The Da Qing IGT and Diabetes Study) (Pan et al, 1997).

Erectile function was assessed by the International Index of Erectile Function 5 (IIEF-5), a brief, reliable, self–administered questionnaire which is a validated approach to assess the degree of ED and consists of 5 questions with 5 possible answers per question with scores ranging from 0 to 5. An IIEF-5 score <21 is considered as ED; with this cutoff value, the questionnaire has a sensitivity of 98% and a specificity of 88% for the diagnosis of ED (Rosen et al, 1999). The patients answered each item and obtained a total 5-item score.

The physical examination included waist circumference (cm) and body mass index (BMI), according to the formula: weight (kg) / height (m^2); and levels were considered normal when BMI < 25 kg/m^2, overweight between 25 and 29.9 kg/m^2 and obese when BMI > 30 kg/m^2.

Laboratory:

At the onset of the original previous study, blood samples were taken at 8:00 am after 12-hour nocturnal fasting to measure:

- Total testosterone (TT) (DSL RIA; normal: 2.8-8.8 ng/mL or 280-880 ng/dL)
- Bioavailable testosterone (BT) (Vermeulen Calculation; normal: 0.8-6 ng/mL)
- Insulin (In–House RIA Assay)
- Total cholesterol (Enzymatic Endpoint Method)
- HDL (Direct Enzymatic Method)
- LDL (Modified Friedewald Equation)
- Triglycerides (Enzymatic Endpoint Thunder Method)
- Fasting serum glucose (Enzymatic O2 Consumption Method)

IR was assessed with HOMA–IR (Homeostasis Model Assessment) index, according to the formula: glucose (mg%) x insulin / 405. Patients were considered to be IR if HOMA ≥ 3.

A prospective, randomized, double–blind, placebo–controlled, parallel-group study was conducted. Patients were randomized into 2 treatment groups for 4 months as follows (Figure 1):

- Group M (n = 17) used metformin at 1700 mg/day in 2 doses (850 mg at lunch and another 850 mg at dinner) plus sildenafil on demand during 4 months.

- Group P (n = 13) used metformin placebo in 2 doses/day (one at lunch and one at dinner) plus sildenafil on demand during 4 months.

All patients were instructed to take sildenafil between 1 and 2 hours prior to sexual intercourse, and 2 hours after meals. At baseline all patients were taking 100 mg of sildenafil.

Randomization was performed using a computer generated randomization list that our hospital provides for that purpose. Participants were randomly assigned following simple randomization procedures (computarized random numbers) to 1 of 2 treatment groups. The placebo was prepared with the same matrix as metformin and was packaged in the same way, they were prepacked in boxes with number 1 or 2 for placebo or metformin. The packaging was done by personnel not involved in the delivery of medication to patients. Block randomization was by a computer generated random number list performed by an investigator with no clinical involvement in the trial. Investigators and participants remained masked regarding treatment and trial results.

The 4-month follow–up of both groups included three visits: basal (pretreatment), month 2 and month 4, where we performed: physical examination, assessment of adherence to treatment, assessment of adverse events, IIEF-5, measurement of blood glucose and insulin levels and HOMA index calculation. Changes in the IIEF-5 score were taken as efficacy criteria for the proposed treatment.

Of all patients who were randomized, 14 patients of group M and 6 patients of group P completed the study. Two patients in each group were lost of follow-up, 1 patient discontinued treatment in group M and 5 in group P. Patients who discontinued treatment were contacted by telephone and they responded that the cause of treatment discontinuation was the lack of response.

Statistical Analysis: Data was analyzed using Instat Statistical Software (GraphPad Software, Version 3.01). Differences in the characteristics within and between group M and group P were compared with a two-sample *t* test (parametric) or Wilcoxon Signed–Ranks Test (not parametric) for continuous variables; categorical variables were compared using Chi–square. Data are presented as the mean ± SD. All *p* values quoted are two–sided, and values below 0.05 were taken to indicate statistical significance.

Patients signed an informed consent and the study was approved by the Ethics Committee of our hospital.

Results:

A total of 30 subjects with ED, IR and a history of poor response to sildenafil were randomized and received at least 1 dose of metformin or placebo in conjunction with sildenafil.

Treatment groups were well matched with regard to demographic and anthrophometric parameters. There were no differences with regard to glucose, insulin, HOMA, TT, BT and the IIEF-5 score between both groups (Table 1).

BMI decreased in group M in months 2 and 4 of treatment in comparison with the basal values: 27.7 ± 3.3 versus 28.2 ± 3.8 kg/m^2, p=0.01 and 26.9 ± 3.3 versus 28.2 ± 3.8 kg/m^2, p=0.03, respectively. No changes in BMI were observed in group P in months 2 and 4 of treatment in comparison with basal values: 29.4 ± 2.0 versus 28.7 ± 2.1 kg/m^2 and 29.1 ± 1.7 versus 28.7 ± 2.1 kg/m^2, respectively. The HOMA index value decreased significantly with respect to basal values in patients from group M at months 2 and 4 of treatment: 3.9 ± 1.6 versus 5.5 ± 2.4, p=0.01 and 4.5 ± 1.9 versus 5.5 ± 2.4, p=0.04, respectively. The changes in this parameter for group P were not significant at months 2 and 4 of treatment with respect to basal values: 4.0 ± 1.7 versus 6.3 ± 3.5 and 6.7 ± 4.0 versus 6.3 ± 3.5, respectively (Figure 2).

During treatment with metformin, a significant increase in the IIEF-5 score was shown both at months 2 and 4 of treatment, with no changes observed in the IIEF-5 score of patients receiving placebo (Figure 3).

By comparing differences between groups in BMI, HOMA and IIEF-5 at months 2 and 4 of treatment, there was a statistically significant difference between groups with respect to BMI and IIEF-5 both at month 2 and month 4 and a statistically significant difference between groups with respect to HOMA only at month 4 (Table 2).

A higher incidence of adverse events was observed in patients from group M versus group P: 61.5 % versus 7.7 % (p=0.03), respectively. In all cases, the adverse events were gastrointestinal (diarrhea, bloating, nausea, and abdominal distension) that did not require stopping the treatment and disappeared over time.

Discussion:

In this study, the response to combined treatment with sildenafil and metformin in patients with ED, IR and poor response to sildenafil has been evaluated. Treatment groups were well matched with regard to demographic and anthrophometric parameters. There were no differences with regard to HOMA, TT, BT and the IIEF-5 score between groups.

In patients that received treatment with metformin, there was a significant decrease in the HOMA index and marked improvement in erectile function at months 2 and 4 of treatment. No significant changes were observed in the HOMA index nor in the erectile function of patients using sildenafil and the metformin placebo.

Erection is a neuromyovascular phenomenon, where the nitric oxide (NO) released by vascular endothelial cells plays a key role, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. An increase in free radicals caused by various risk factors (such as arterial hypertension, dyslipidemia, obesity, smoking, sedentarism, hyperglycemia) may enable the oxidative stress that reduces the production and availability of NO with the subsequent appearance of ED (Jones et al, 2002; Jeremy et al, 2000).

Inhibitors of phosphodiesterase type 5, such as sildenafil, require adequate levels of NO to be effective. There is a percentage of men with suboptimal response (20-30 %). Although this lack of response is generally due to a severe impairment of the erectile function, it is likely that in some situations it may be the result of endothelial dysfunction in the cavernous bodies.

Different authors have previously documented a higher prevalence of obesity and other cardiovascular risk factors like hypertension and dyslipidemia among patients with ED in comparison with the general population (Virag et al, 1985; Walczak et al, 2002). In addition, there is a high prevalence of ED in patients with MS and DM2 (Bansal et al, 2005; Corona et al, 2007; Costanzo et al, 2008). Insulin resistance, present in most subjects who have obesity and DM2, is the pathophysiological basis of a number of cardiovascular and metabolic disturbances known collectively as the metabolic syndrome (Grundy, 1999).

The IR state brings about a decrease in the synthesis and release of NO due to lower activity and expression of NO synthase, which combined with an accelerated consumption of NO during the neutralization of oxidative stress produces a decrease in its availability (Cersosimo and De Fronzo, 2006; Aljada and Dandona, 2000).

Therefore, the presence of IR and associated disorders of glucose and lipid metabolism, such as obesity and DM2, produces a decrease in the levels of NO, which leads to a change in endothelium–mediated vasodilation. The small diameter (1-2 mm) and the relatively high content of smooth muscle and endothelial cells per unit of tissue volume compared with other organs, determines higher susceptibility of the cavernous arteries to

damage (Sullivan et al, 1999; Kim et al, 2007). The association between ED and IR may be explained as a result of endothelial dysfunction of the cavernous arteries secondary to reduced insulin sensitivity.

In a previous study, a greater incidence of IR was observed among men with ED between the ages of 40 and 70, in comparison with men of the same age range with maintained erectile function. In that study, the male population with ED had a HOMA index significantly higher than the control group and this index had reverse correlation with the erectile funtion rated according to the IIEF-5 score. Within the population of ED patients, those with IR had worse erectile function (less IIEF-5 score) than ED patients without IR. Therefore, it may be inferred that ED is associated to a higher level of IR and that there is greater impairment of erectile funtion as the IIEF-5 score worsens (Knoblovits et al, 2010).

Bansal T., et al. assessed the incidence of IR in 154 men with ED, using QUICKI as an index. They reported 79.2% incidence of IR among ED patients, although there was no comparison with a control group (Bansal et al, 2005).

The euglycemic clamp is the gold standard for assessing IR. It is difficult to perform: it requires special equipment and trained staff and is not feasible for large–scale screening of the population (Bergman et al, 1985). Simple methods have been performed for assessing insulin sensitivity, such as the homeostatic model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI) (Matthews et al, 1985; Katz et al, 2000). HOMA is the most often used method to assess IR because it is simple, cheap, and has very good correlation with the euglycemic clamp ($r = 0.88$) (Garcia–Estevez et al, 2003; Trussell and

Legro, 2007). In our country there are several studies that analyzed the HOMA index for healthy people and the cut-off is 2.6 to 3.6. We take as reference one of these studies that evaluate to 420 healthy men, blood donors, and define IR as HOMA $\geq$ 3 (Litwak et al, 2004).

There are different questionnaires to assess the presence and degree of sexual dysfunction in men, of which one of the most used is the IIEF score made up of 15 questions that evaluate the five domains of sexual function (sexual desire, erectile and orgasmic functions, intercourse satisfaction, and overall sexual satisfaction) (Rosen et al, 1997). The extensive content of the 15 items makes the IIEF somewhat time–consuming, and it is not specific to erectile function (Chang et al, 2000). In this study, an abridged 5-item version of this score (IIEF-5) was used. It consists of five items selected to identify predominantly the presence or absence of ED (Rhoden et al, 2002). IIEF-5 has less content and is more specific for ED. It has already been used for evaluating pharmacological therapy for ED in clinical trials because it is a useful tool, especially to assess changes over time in a patient, with a high degree of internal consistency.

Another factor that may determine the appearance of ED and a lower response to treatment with sildenafil are decreased levels of testosterone. IR states of obesity, MS and DM2 are associated with low testosterone concentrations (Kupelian et al, 2006; Makhsida et al, 2005; Muller et al, 2005; Pitteloud et al, 2005; Ding et al, 2006). Testosterone influences sexual activity through different mechanisms, which include the production of NO through NO synthase stimulation. In a previous study, lower levels of TT and BT were observed in eugonadal patients with ED in comparison with the control group, as well as a negative

correlation between testosterone levels and the degree of obesity and IR (Knoblovits et al, 2010). In this study patients with hypogonadism were excluded. Using the RIA method for TT can be considered a limitation for the evaluation of hypogonadism, given its lower sensitivity than the reference method. But the use of this method is more accepted for the diagnosis of the eugondal state (Rosner et al, 2007).

Insulin sensitivity improves with lifestyle changes such as weight loss or exercise. These interventions, however, may be difficult to implement due to difficulties in adhering to these changes over a prolonged period. Drug therapy may be appropriate when these interventions are ineffective or unfeasible.

Metformin is a biguanide that has been available for over 40 years. Its exact mechanism of action remains unclear but improves insulin sensitivity and is an inexpensive medication. One 12-week trial of metformin showed improvement in endothelial function as measured by forearm plethysmography (Mather et al, 2001). In the UK Prospective Diabetes Study, metformin induced improvement in insulinemia and reduced the incidence of cardiovascular disease (UKPDS, 1998). Research studies have proven that treatment with metformin in rats with ED and IR caused a higher synthesis of NO at the level of the cavernous arteries and an improvement in the dysfunction (Kim et al, 2007).

In our study, patients using metformin had more adverse events than the placebo group. In all cases, the adverse events were mild, transient, gastrointestinal (diarrhea, bloating, nausea, and abdominal distension) and did not require stopping the treatment. This might be the result of starting with a high dose of metformin without titration. Previous

studies from diabetes centers have reported the same adverse gastrointestinal events with the use of metformin, with a significant decrease in frequency when higher dosages begin to be used (Florez et al, 2010; Howlett and Bailey, 1999).

To our knowledge, this is the first randomized trial that has been performed using insulin sensitizer agents in patients with ED. Insulin sensitizers, such as metformin, may someday be a part of combination treatment options for men with IR and ED recalcitrant to oral agent therapies. Only 6 patients in the placebo group complete the study, the high drop out was due to lack of therapeutic effect, understandable in a study where the desirable therapeutic effect is so evident (the erectile reponse for intercourse), these and the low number of subjects included are the major limitations of our study**.** Future trials should include larger populations and a dose escalating design.

In conclusion, IR is likely to be a mechanism involved in ED and its treatment can optimize the response to sildenafil. Likewise, the identification of IR may enable early therapeutic intervention with the aim of preventing progression to DM2 and cardiovascular disease. Diagnosis and treatment of IR should be part of an initial management plan for ED.

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Tables

Table 1: Comparison of demographic and anthrophometric parameters, laboratory and IIEF-5 score between group M and group P.

Table 2: Comparison of differences between groups in BMI, HOMA and IIEF-5 at month 2 and month 4 of treatment.

Figure legends

Figure 1: Schematic of enrollment and retention patterns of patients who participated in the study.

Figure 2: Variations in BMI and HOMA index after treatment in both groups.

Figure 3: Variations in IIEF-5 score after treatment in both groups.

Table 1

	Group M (n=17)	Group P (n=13)	p
Age (years)	65.7 ± 5.2 (57-74)	62.6 ± 6.6 (50-73)	0.18
Hypertension (%)	88.2	76.9	0.74
Dyslipidemia (%)	76.4	69.2	0.97
Smoking (%)	11.8	15.4	0.77
Sedentary Lifestyle (%)	41.2	46.2	0.78
BMI (kg/m^2)	28.2 ± 3.8	28.7 ± 2.1	0.71
Waist Circumference (cm)	103.5 ± 10.4	107.5 ± 7.0	0.26
Glucose (mg/dL)	97.6 ± 12.6	90.3 ± 11.5	0.12
Insulin (IU/mL)	23.2 ± 8.9	27.9 ± 12.5	0.26
HOMA	5.5 ± 2.4	6.3 ± 3.5	0.45
IIEF-5	14.3 ± 3.9	15.2 ± 3.4	0.54
TT (ng/mL)	3.6 ± 1.1	4.1 ± 1.0	0.17
BT (ng/mL)	1.6 ± 0.5	1.7 ± 0.4	0.49

Table 2

		BMI (kg/m^2)	HOMA	IIEF-5
Group M (n=14)	Basal	28.2 ± 3.8	5.5 ± 2.4	14.3 ± 3.9
	Month 2	27.7 ± 3.3	3.9 ± 1.6	17.0 ± 6.0
	Difference at month 2 (95% CI)	-0.5 (-0.76 to -0.23)	-1.6 (-2.02 to -1.17)	2.7 (1.58 to 3.81)
	Month 4	26.9 ± 3.3	4.5 ± 1.9	19.8 ± 3.8
	Difference at month 4 (95% CI)	-1.3 (-1.60 to -0.99)	-1.0 (-1.30 to -1.69)	5.5 (5.44 to 5.56)
Group P (n=6)	Basal	28.7 ± 2.1	6.3 ± 3.5	15.2 ± 3.4
	Month 2	29.4 ± 2.0	4.0 ± 1.7	14.8±5.2
	Difference at month 2 (95% CI)	0.7 (0.60 to 0.79) *	-2.3 (-3.96 to -0.63)	-0.4 (-2.06 to 1.26) **
	Month 4	29.1 ± 1.7	6.7 ± 4.0	15.8 ± 5.6
	Difference at month 4 (95% CI)	0.4 (-0.09 to 0.89) *	0.4 (-0.22 to 1.02) *	0.6 (-2.13 to 3.33) ***

*p<0.0001 with respect to group M.
**p=0.002 with respect to group M.
***p=0.007 with respecto to group M.

Figure 1

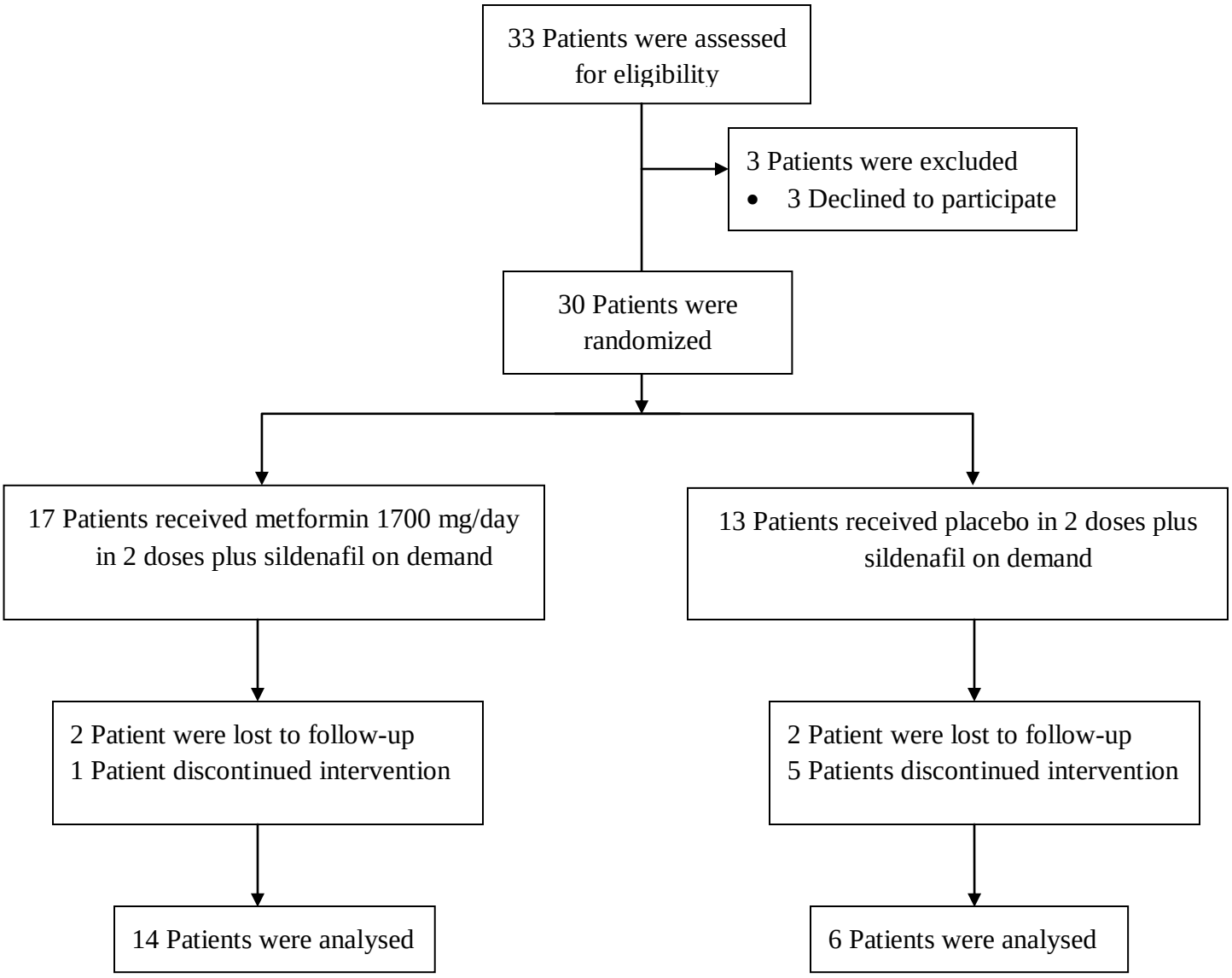
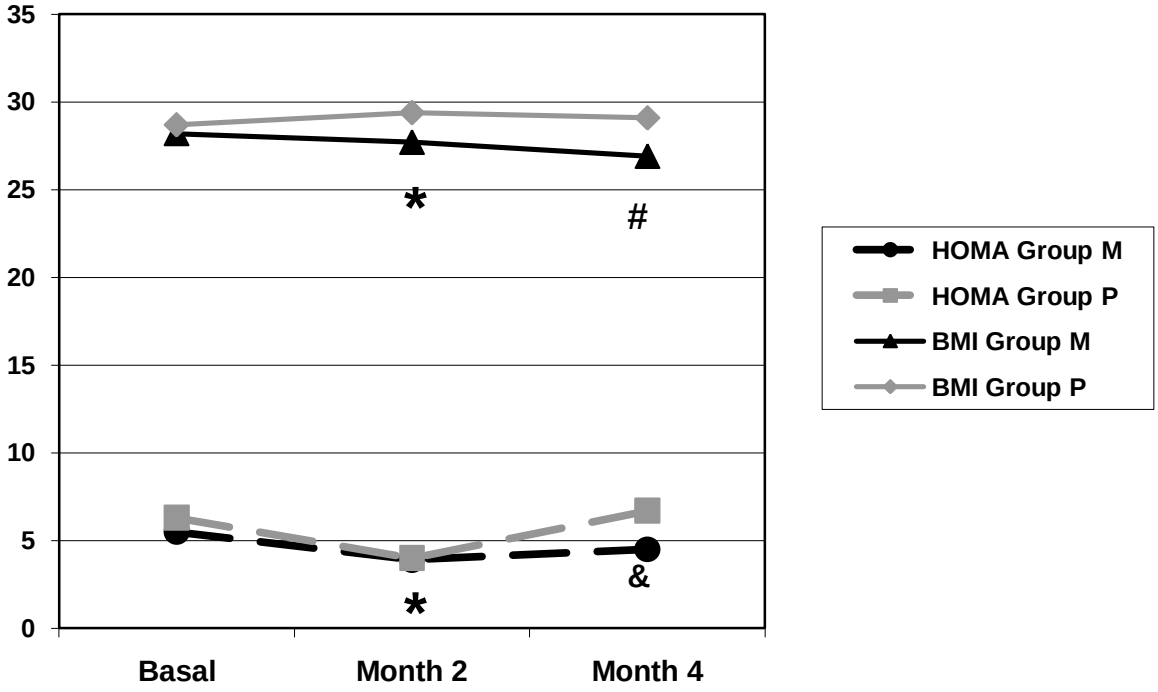
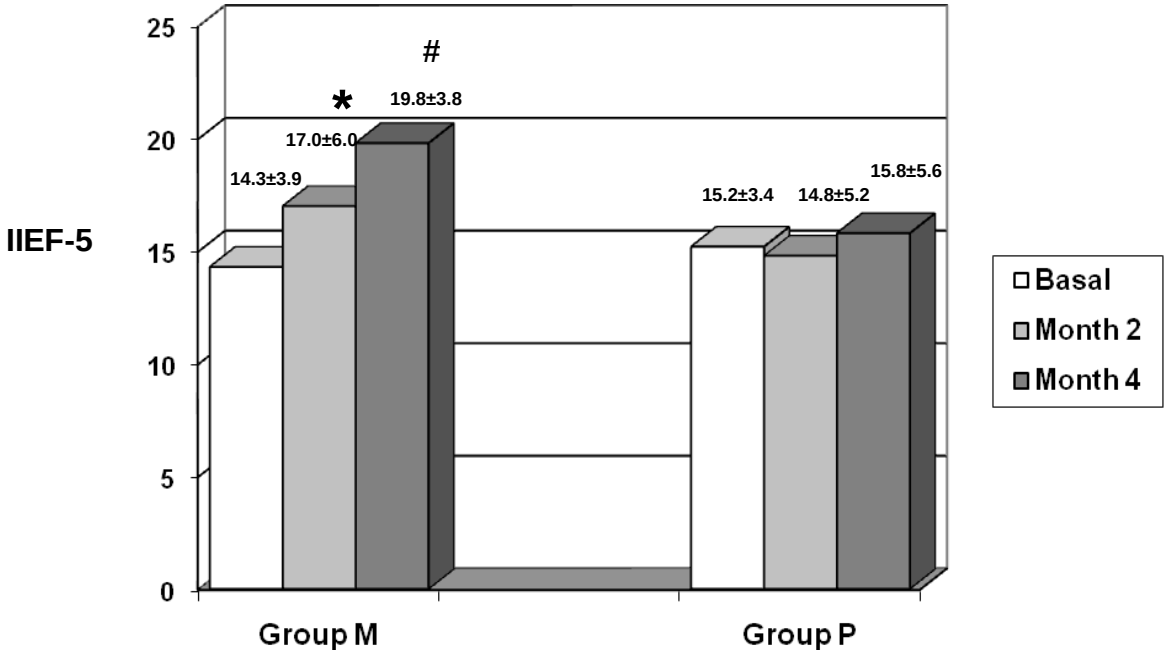

33 Patients were assessed for eligibility
3 Patients were excluded
3 Declined to participate
30 Patients were randomized
17 Patients received metformin 1700 mg/day in 2 doses plus sildenafil on demand
13 Patients received placebo in 2 doses plus sildenafil on demand
2 Patient were lost to follow-up
1 Patient discontinued intervention
2 Patient were lost to follow-up
5 Patients discontinued intervention
14 Patients were analysed
6 Patients were analysed

Figure 2



* p=0.01 with respect to basal.
# p=0.03 with respect to basal.
& p=0.04 with respect to basal.

Figure 3



* p=0.01 with respect to basal.
# p=0.005 with respect to basal.