Effect of Niacin on Erectile Function in Men Suffering Erectile Dysfunction and Dyslipidemia

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ABSTRACT

Introduction. Dyslipidemia is closely related to erectile dysfunction (ED). Evidence has shown that the lipid-lowering agent, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statins), can improve erectile function. However, information about the potential role of another class of lipid-lowering agent, niacin, is unknown.

Aim. To assess the effect of niacin alone on erectile function in patients suffering from both ED and dyslipidemia.

Methods. A single center prospective randomized placebo-controlled parallel-group trial was conducted. One hundred sixty male patients with ED and dyslipidemia were randomized in a one-to-one ratio to receive up to 1,500 mg oral niacin daily or placebo for 12 weeks.

Main Outcome Measures. The primary outcome measure was the improvement in erectile function as assessed by question 3 and question 4 of the International Index of Erectile Function (IIEF Q3 and Q4). Secondary outcome measurements included the total IIEF score, IIEF-erectile function domain, and Sexual Health Inventory for Men (SHIM) score.

Results. From the overall analysis, the niacin group showed a significant increase in both IIEF-Q3 scores (0.53 ± 1.18, $P < 0.001$) and IIEF-Q4 scores (0.35 ± 1.17, $P = 0.013$) compared with baseline values. The placebo group also showed a significant increase in IIEF-Q3 scores (0.30 ± 1.16, $P = 0.040$) but not IIEF-Q4 scores (0.24 ± 1.13, $P = 0.084$). However, when patients were stratified according to the baseline severity of ED, the patients with moderate and severe ED who received niacin showed a significant improvement in IIEF-Q3 scores (0.56 ± 0.96 [$P = 0.037$] and 1.03 ± 1.20 [$P < 0.001$], respectively) and IIEF-Q4 scores (0.56 ± 1.03 [$P = 0.048$] and 0.84 ± 1.05 [$P < 0.001$], respectively] compared with baseline values, but not for the placebo group. The improvement in IIEF-EF domain score for severe and moderate ED patients in the niacin group were 5.28 ± 5.94 ($P < 0.001$) and 3.31 ± 4.54 ($P = 0.014$) and in the placebo group were 2.65 ± 5.63 ($P < 0.041$) and 2.74 ± 5.59 ($P = 0.027$), respectively. There was no significant improvement in erectile function for patients with mild and mild-to-moderate ED for both groups. For patients not receiving statins treatment, there was a significant improvement in IIEF-Q3 scores (0.47 ± 1.16 [$P = 0.004$]) for the niacin group, but not for the placebo group.

Conclusions. Niacin alone can improve the erectile function in patients suffering from moderate to severe ED and dyslipidemia. **Ng C-F, Lee C-P, Ho AL, and Lee VWY. Effect of niacin on erectile function in men suffering erectile dysfunction and dyslipidemia. J Sex Med 2011;8:2883–2893.**

Key Words. Erectile Dysfunction; Dyslipidemia; Niacin; Lipid-Lowering Agents; Endothelial Dysfunction

Introduction

Erectile dysfunction (ED) is a common condition affecting more than 50% of men aged between 40 and 70 [1]. Currently, phosphodiesterase type-5 inhibitor (PDE5i) is the first-line treatment for ED, with satisfactory results. Nevertheless, a significant proportion of ED patients are either contraindicated for PDE5i or have an inadequate response to PDE5i [2]. Therefore, development of alternative treatments is necessary.

ED is closely related to coronary artery disease and other cardiovascular diseases [3,4]. Endothelial dysfunction and atherosclerosis are believed to

be the common underlying pathophysiology for these conditions. There is evidence suggesting that the improvement of vascular condition and endothelial function by 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors ("statins") may lead to an improvement in ED [5–9]. Niacin is another class of lipid-lowering agent, with characteristics of increasing serum high-density lipoprotein (HDL) cholesterol level and subsequent improvement in lipid profile. Studies have suggested that niacin could also improve endothelial function and atherosclerosis [10,11]. We postulated that niacin may have a similar effect to statins in improving erectile function in patients with ED. Therefore, we aimed to assess the effect of niacin on erectile function in male patients suffering from both ED and dyslipidemia.

Aim

Our aim is to study the effect of niacin on erectile function in patients suffering from both ED and dyslipidemia.

Methods

This was a single center prospective randomized (1:1) placebo-controlled, parallel-group study. The study was approved by the institutional ethical review board and was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. All subjects gave written informed consent prior to enrollment in the study. The trial was registered: ChiCTR-TRC-09000722.

Subjects

The study was performed in a urological center managing ED. Male subjects ≥18 years old with ED and documented dyslipidemia were recruited. ED was defined as a consistent change in the quality of erection that adversely affects the subject's satisfaction with sexual intercourse for at least 6 months. Dyslipidemia was defined as either having a documented history of dyslipidemia and receiving statins treatment or having a documented elevated baseline fasting lipid profile (abnormality in any one of the following four serum lipid parameters—total cholesterol ≥ 5.2 mmol/L, HDL-cholesterol ≤ 1.0 mmol/L, low density lipoprotein (LDL)-cholesterol ≥ 4.1 mmol/L, and triglyceride ≥ 1.7 mmol/L according to local laboratory reference).

The subjects were required to have been in a stable relationship with one single female partner for more than 6 months. Subjects with a history of PDE5i use were included in the study as long as they were willing to undergo a 2-week washout period.

Subjects with untreated endocrine disease (e.g., hypogonadism), a history of previous pelvic surgery that may lead to damage to the cavernosal nerves, significant penile deformity, or history of penile implant insertion for ED, were excluded from the study. Moreover, subjects with significant renal impairment (serum creatinine level > 150 μmol/L), hepatic dysfunction (serum aspartate transaminase and alanine transaminase level >3 times upper limit of normal), or serum hemoglobin A_{1C} (HbA_{1C}) level >13% were also excluded from the study. Because of the potential effects of aspirin or any nonsteroidal anti-inflammatory drugs on the prostaglandin production of niacin, subjects taking these drugs on a regular basis were also excluded.

Study Procedures

The study procedure and follow-up was conducted on an outpatient basis at our center. After informed consent was obtained, subjects were assessed for baseline demographic and medical data. Fasting blood specimens were obtained for the assessment of lipid profile, glucose level, HbA_{1C} level, liver, and renal function. Erectile function was assessed by the International Index of Erectile Function (IIEF). Subjects with a history of PDE5i use underwent a 2-week washout period before the randomization process.

In this study, Niaspan (Abbott Laboratories, Abbott Park, IL, USA) prolonged-release 500 mg tablets were used as the active drug, which contained niacin in a prolonged release form. The advantage of this preparation is the lower incidence and intensity of flushing, which is the main side effect of niacin [12]. The recommended dosage is around 1,000–2,000 mg once daily taken before bed, which helps to reduce flushing during the daytime. The planned maximum dosage was 1,500 mg daily, if patients could tolerate it.

After confirmation of eligibility, subjects were randomly assigned to receive 12 weeks of Niaspan (niacin prolonged-release tablets) or a matched placebo in a 1:1 ratio. They were also instructed not to use other medications for ED during the study period. General sexual counseling, including on adequate sexual activity for the evaluation of sexual performance, was also provided for each

subject. The subjects were initially started on one study tablet (Niaspan 500 mg or placebo) per night for 2 weeks in addition to their stable medical regimen.

The subjects were reviewed at week 2 for assessment of any adverse reaction, IIEF assessment, and blood tests for fasting sugar and liver function. If they tolerated the drug well, they were instructed to increase the medication dosage to two study tablets (Niaspan 1,000 mg) or two placebo tablets per night. The subjects were reviewed again at week 6 for any adverse events and IIEF. Drug dosing was further increased to three study tablets (Niaspan 1,500 mg) or placebo per night if the patient tolerated the previous dosage well. Finally, the subjects were reviewed at week 12 for final assessment of their erectile function and fasting serum lipid profile and liver function.

Each follow-up included an assessment of the subject's tolerance to the drug and any adverse events. However, if the subjects could not tolerate the drug at any point during the study, they were advised to reduce the dose to one that they could tolerate. The patient would then be reassessed after 2 weeks to reconsider a further increase in dosage.

Main Outcome Measures

The primary outcome measurement was the improvement in erectile function as measured by question 3 (frequency of penetration) (IIEF-Q3) and question 4 (frequency of maintained erections after penetration) (IIEF-Q4) of the IIEF [13]. Secondary outcome measures included the total IIEF score, IIEF-EF domain score [14], Sexual Health Inventory for Men (SHIM) score [15], change in fasting serum lipid profile (including total cholesterol level, HDL-cholesterol level, LDL-cholesterol level, and triglyceride level), and adverse events after study medication. All outcome measurements were administered at baseline and at week 12 for comparison.

Sample Size

Based on a mean score difference of 1.33 and assuming a common standard deviation of 2.0 for niacin and placebo, a sample size of 50 patients per treatment arm was sufficient to achieve 90% power to detect the specified difference between the two treatment groups, using an approximation (two sided, $\alpha = 0.05$) of the test comparing two means for normally distributed responses. After accounting for a dropout rate of 10%, a total of 160 patients were needed for the study.

Randomization and Allocation Concealment

All eligible patients were randomly assigned in a 1:1 ratio to receive 12 weeks of niacin or matched placebo. Identical-appearing vials of niacin and placebo were prepared and sealed in packages by a research assistant who was not directly involved in the study. The vials were numbered according to the randomization scheme generated by the website http://www.randomization.com), in a block size of four, without stratification. The sequentially numbered, sealed packages were delivered to the study nurse for administration to subjects. All investigators were unaware of the group assignments.

Statistical Analysis

The intent to treat principle was adopted, and all randomized subjects who had completed at least one outcome measure were included in the statistical analysis. The last-observation-carried-forward method was used to account for patient dropouts at each time point. Between-groups analyses were performed using the Student *t*-test for normal data, and otherwise by Mann–Whitney U-test. Within-group and subgroup analyses were performed using a paired *t*-test or Wilcoxon signed-rank test, as appropriate. All categorical variables were analyzed with the chi-square test or Fisher exact test. A two-tailed *P* value of <0.05 was considered statistically significant. The data were analyzed using the SPSS, version 15.0 (SPSS Inc, Chicago, IL, USA).

Results

Patients were recruited to the study between August 2008 and December 2009. During this period, 183 patients were screened, and 160 fulfilled the recruitment criteria and were randomized into the trial (Figure 1). Of the 23 patients excluded from the study, 19 did not fulfill the recruitment criteria (nine had a normal lipid profile, seven were on aspirin, one had a low serum testosterone level, one had an elevated serum creatinine level, and one had multiple sexual partners), and four others withdrew consent before randomization. Eighty of the 160 patients were randomized into the niacin group, and 80 patients were randomized into the placebo group. All patients received their assigned treatment. The dropout rates for the niacin group and for the placebo group were 19 (23.8%) and 15 (18.8%), respectively. In the niacin group, 12 subjects dropped out

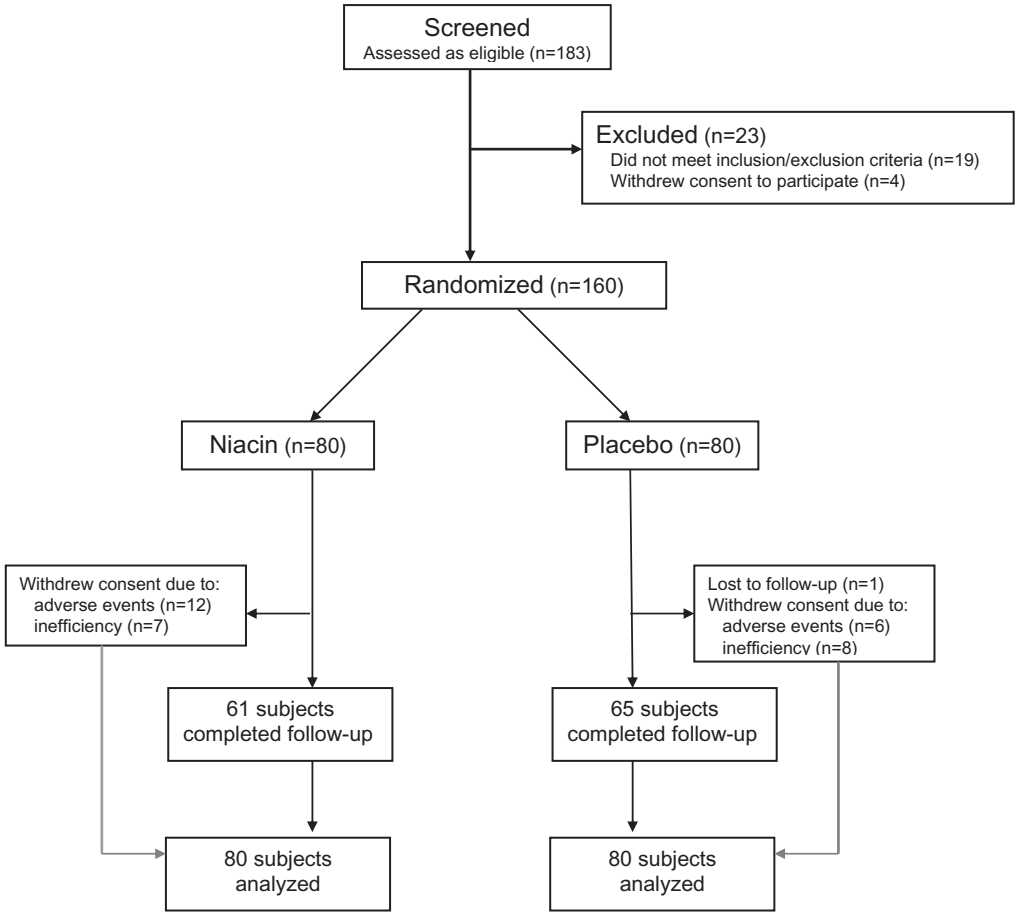

Figure 1 Flow chart for the trial.

because of adverse events and seven because of ineffective treatment. In the placebo group, six dropped out because of adverse events, eight because of ineffective treatment, and one was lost at follow-up and could not be contacted.

The baseline characteristics of the patients are listed in Table 1. The mean age, duration of ED, baseline erectile function (as assessed by IIEF-Q3, IIEF-Q4, total IIEF, IIEF-EF domain, and SHIM scores), and history of PDE5i use were similar for the two groups. The baseline lipid profile and use of statins were also similar for the two groups.

In the overall analysis, the niacin group showed a significant increase in both IIEF-Q3 (0.53 ± 1.18, $P < 0.001$) and IIEF-Q4 (0.35 ± 1.17, $P = 0.013$), compared with baseline values (Table 2). The placebo group also showed a significant increase in IIEF-Q3 (0.30 ± 1.16, $P = 0.040$) but not in IIEF-Q4 (0.24 ± 1.13, $P = 0.084$), compared with baseline values. Both groups also showed a significant improvement in their total IIEF, IIEF-EF domain, and SHIM scores, compared with the baseline level. For the niacin group, the improvement in the total IIEF, IIEF-EF domain, and SHIM scores were 4.76 ± 9.99 ($P < 0.001$), 2.80 ± 5.54 ($P < 0.001$), and 2.25 ± 4.48 ($P < 0.001$), respectively. For the placebo group, the improvement in the total IIEF, IIEF-EF domain, and SHIM scores were 2.68 ± 11.17 ($P < 0.035$), 1.68 ± 5.19 ($P = 0.005$), and 1.25 ± 4.31 ($P = 0.011$), respectively. Although there was no significant difference between the two groups for the four erectile function parameters, in the niacin group, a trend toward a better improvement on all the five erectile function parameters was observed.

However, when the data were analyzed according to the baseline severity of ED, patients with moderate and severe ED receiving niacin showed a significant improvement in IIEF-Q3 and in IIEF-Q4 compared with baseline values (Table 3). The improvements in IIEF-Q3 for the moderate and severe subjects in the niacin group were 0.56 ± 0.96 ($P = 0.037$) and 1.03 ± 1.20

Table 1 Demographic information of study subjects

—	Overall N = 160	Niacin N = 80	Placebo N = 80	*P* value
Age (mean year ± standard deviation)	58.09 ± 7.82	58.34 ± 7.12	57.84 ± 8.48	0.687
ED duration (mean month ± standard deviation)	54.88 ± 39.87	56.16 ± 42.09	53.60 ± 37.75	0.686
Erectile function parameters (mean ± standard deviation [range])				
IIEF-3	2.08 ± 1.13 (0–5)	1.96 ± 1.11 (0–4)	2.20 ± 1.14 (0–5)	0.186
IIEF-4	2.05 ± 1.08 (0–5)	2.03 ± 1.20 (0–5)	2.08 ± 0.95 (0–5)	0.472
Total IIEF score	34.34 ± 11.52 (5–62)	33.0 ± 11.9 (5–57)	35.7 ± 11.0 (5–62)	0.137
IIEF-EF domain score	13.15 ± 5.69 (1–26)	12.56 ± 5.95 (1–25)	13.74 ± 5.40 (1–26)	0.193
SHIM score	10.75 ± 4.64 (1–21)	10.21 ± 4.88 (1–19)	11.34 ± 4.34 (1–21)	0.125
ED severity (number of patient [%])				
Mild	19 (11.88)	11 (13.8)	8 (10.0)	
Mild to moderate	53 (33.13)	21 (26.3)	32 (40.0)	
Moderate	39 (24.37)	16 (20.0)	23 (28.8)	
Severe	49 (30.62)	32 (40.0)	17 (21.3)	
Serum lipid profile (mmol/L) (mean ± standard deviation)				
Triglycerides	2.07 ± 1.27	1.97 ± 1.13	2.17 ± 1.40	0.330
Total cholesterol	5.27 ± 0.93	5.24 ± 1.02	5.29 ± 0.83	0.805
HDL	1.25 ± 0.34	1.24 ± 0.30	1.26 ± 0.37	0.761
LDL	3.19 ± 0.86	3.17 ± 0.92	3.20 ± 0.79	0.831
Concurrent use of statins (number of patient [%])				0.429
Yes	32 (20)	18 (22.5)	14 (17.5)	
No	128 (80)	62 (77.5)	66 (82.5)	
History of PDE5i use (number of patient [%])				0.746
Yes	98 (61.3)	48 (60.0)	50 (62.5)	
No	62 (38.8)	32 (40.0)	30 (37.5)	

ED = erectile dysfunction; HDL = high-density lipoprotein; IIEF-EF = International Index of Erectile Function-erectile function domain; LDL = low density lipoprotein; SHIM = Sexual Health Inventory for Men.

($P < 0.001$), respectively. The improvements in IIEF-Q4 for the moderate and severe subjects in the niacin group were 0.56 ± 1.03 ($P = 0.048$) and 0.84 ± 1.05 ($P < 0.001$), respectively. There were also significant improvements in the total IIEF score (9.13 ± 11.01 [$P < 0.001$]), IIEF-EF domain score (5.28 ± 5.94 [$P < 0.001$]), and SHIM score (4.31 ± 4.66 [$P < 0.001$]) for severe ED patients in the niacin group. For those moderate ED patients in the niacin group, the IIEF-EF domain score (3.31 ± 4.54 [$P = 0.014$]) and SHIM score (3.06 ± 3.51 [$P = 0.003$]) were both significantly improved, while the total IIEF score was marginally significantly improved (4.31 ± 8.27 [$P = 0.054$]). For the placebo group, there was no improvement in IIEF-Q3, IIEF-Q4, and total IIEF and SHIM scores for patients with moderate and severe ED as compared to baseline values. However, there were significant improvements in the IIEF-EF domain scores for both the moderate ED (2.74 ± 5.59 [$P = 0.027$]) and the severe ED (2.65 ± 5.63 [$P < 0.041$]) patients in the placebo group when compared with the baseline value. Among these four groups of patients, only the severe ED patients in the niacin group had a mean improvement of IIEF-EF domain score of more than 4 points. Nevertheless, the absolute improvements and *P* values for IIEF-EF domain score for moderate and severe ED patients in the placebo group were less than the corresponding values in the niacin group. For the mild and mild-to-moderate ED subjects, there was no significant improvement in erectile function, as assessed by all the parameters, in either the niacin or the placebo group.

For those subjects who were not receiving statins treatment, there was a significant improvement in the IIEF-Q3 score (0.47 ± 1.16 [$P = 0.004$]), total IIEF score (4.40 ± 10.18 [$P = 0.001$]), IIEF-EF domain score (2.50 ± 5.41 [$P = 0.001$], and SHIM scores 2.05 ± 4.46 [$P = 0.001$]) for the niacin group when compared with the baseline values. However, for the placebo group, except for the IIEF-EF domain score (1.44 ± 5.38 [$P = 0.033$]) was significantly improved, there was no improvement in other erectile function parameters (Table 4).

As expected, the subjects in the niacin group had a significant improvement in serum fasting lipid profile at the end of the study (Table 5). The changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride levels were –0.44 ± 0.81 mmol/L ($P < 0.001$), 0.21 ± 0.31 mmol/L ($P < 0.001$), –0.44 ± 0.70 mmol/L ($P < 0.001$), and –0.46 ± 1.77 mmol/L ($P < 0.001$), respectively. There was no improvement in the serum lipid parameters in the placebo group. There was no relationship between the absolute changes,

Table 2 Overall results after taking niacin and placebo, with within-group and between-group comparisons

	Niacin N = 80				Placebo N = 80				Comparison between the two groups at week 12 *P* value
	Pretreatment	Posttreatment	Difference (post–pre)	*P* value	Pretreatment	Posttreatment	Difference (post–pre)	*P* value	
IIEF-3	1.96 ± 1.11 (0–4) 2 [1, 3]	2.49 ± 1.21 (1–5) 2 [1, 4]	0.53 ± 1.18 (–2–4)	<0.001	2.20 ± 1.14 (0–5) 2 [1, 3]	2.50 ± 1.30 (0–5) 2 [1, 4]	0.30 ± 1.16 (–2–3)	0.040	0.950
IIEF-4	2.03 ± 1.20 (0–5) 2 [1, 3]	2.38 ± 1.14 (1–5) 2 [1, 3]	0.35 ± 1.17 (–2–4)	0.013	2.08 ± 0.95 (0–5) 2 [1, 3]	2.31 ± 1.23 (0–5) 2 [1, 3]	0.24 ± 1.13 (–2–3)	0.084	0.739
Total IIEF score	32.99 ± 11.93 (5–57)	37.75 ± 11.76 (16–63)	4.76 ± 9.99 (–14–32)	<0.001	35.70 ± 10.99 (5–62)	38.38 ± 13.64 (10–64)	2.68 ± 11.17 (–26–41)	0.035	0.757
IIEF-EF domain score	12.56 ± 5.95 (1–25)	15.36 ± 5.98 (6–29)	2.80 ± 5.54 (–9–19)	<0.001	13.74 ± 5.40 (1–26)	15.41 ± 6.64 (2–29)	1.68 ± 5.19 (–12–18)	0.005	0.960
SHIM score	10.21 ± 4.88 (1–19)	12.46 ± 4.76 (5–24)	2.25 ± 4.48 (–7–15)	<0.001	11.34 ± 4.34 (1–21)	12.59 ± 5.46 (2–24)	1.25 ± 4.31 (–10–15)	0.011	0.878

Results of pre- and posttreatment are reported as mean ± standard deviation (range), median (first quartile and third quartile).
IIEF-EF = International Index of Erectile Function-erectile function domain; SHIM = Sexual Health Inventory for Men.

percentage changes, and normalization of any of the lipid parameters with the erectile function observed in this study. There was no significant difference in other blood parameters (fasting serum glucose level, HbA_{1C} level, liver, and renal function) for both groups at the end of the study.

The incidences of adverse events are listed in Table 6 (clinically significant events or events with an incidence of >2% are included). The overall incidence of adverse events was 73 in the niacin group and 31 in the placebo group. The most common adverse events for the niacin group were flushing (36.3%) and skin itchiness (32.5%), both of which occurred significantly more often than in the placebo group. For other adverse events, there was no statistically significant difference between the two groups. However, despite the relatively high incidence of adverse events, only 12 subjects from the niacin group and six from the placebo group dropped out of the study. Of the 61 patients in the niacin group who completed the study, only two subjects could not tolerate a 1,500 mg daily dose (three tablets) and stayed on a 1,000 mg dose (two tablets).

Discussion

Our results suggest that niacin could significantly improve erectile function in patients suffering from moderate to severe ED with dyslipidemia. In addition, for patients not taking statins treatment, there was a significant improvement in erectile function, as assessed by IIEF-Q3, total IIEF, and IIEF-5 scores. Despite the higher incidence of adverse events after taking niacin, most patients could tolerate it at the preplanned maximum dosage (1,500 mg daily). Therefore, niacin could be an alternative choice of treatment for patients with ED.

Despite the success of PDE5i, only around 60–70% of patients have a satisfactory response to the drug [2]. Hence, there is a need to develop other therapeutic agents for those patients who do not respond satisfactorily to PDE5i or are contraindicated for PDE5i. ED is now considered part of the cardiovascular disease complex related to metabolic syndrome (MS). While endothelial dysfunction and atherosclerosis are believed to be part of the main mechanisms for ED in patients with MS. Other mechanisms account for ED in MS include androgen deficiency, drugs, veno-occlusive mechanism, etc. [16]. Because dyslipidemia is one of the key risk factors for the development of endothelial dysfunction and atherosclerosis in MS

Table 3 Subgroup analysis according to the severity of baseline erectile function

	Niacin				Placebo			
—	Pretreatment	Posttreatment	Difference (post–pre)	*P* value	Pretreatment	Posttreatment	Difference (post–pre)	*P* value
Mild	N = 11				N = 8			
IIEF-3	3.55 ± 0.69 (2–4) 4 [3, 4]	3.55 ± 0.69 (3–5) 3 [3, 4]	0.00 ± 0.77 (–1–1)	1.000	4.13 ± 0.84 (3–5) 4 [3.25, 5]	3.88 ± 0.99 (2–5) 4 [3.25, 4.75]	–0.25 ± 1.28 (–2–1)	0.516
IIEF-4	4.00 ± 0.45 (3–5) 4 [4, 4]	3.45 ± 0.82 (2–5) 3 [3, 4]	–0.55 ± 0.82 (–2–1)	0.058	3.25 ± 1.17 (1–5) 3 [3, 4]	3.63 ± 1.41 (1–5) 4 [2.5, 4.75]	0.38 ± 1.06 (–1–2)	0.317
Total IIEF score	49.55 ± 4.13 (43–57) 50 [47, 53]	47.91 ± 5.05 (41–59) 48 [44, 50]	–1.64 ± 5.64 (–13–6)	0.513	53.38 ± 4.17 (48–62) 53.0 [50.5, 54.75]	54.75 ± 9.00 (37–64) 56.5 [48.75, 62.25]	1.38 ± 8.81 (–11–11)	0.674
IIEF-EF domain score	21.73 ± 2.15 (18–25) 22 [20, 23]	20.82 ± 3.49 (17–29) 19 [19, 23]	–0.91 ± 2.66 (–4–4)	0.280	22.25 ± 2.12 (19–26) 22 [21, 23.75]	22.86 ± 5.00 (14–29) 24 [19.25, 27.25]	0.63 ± 4.27 (–8–4)	0.443
SHIM Score	17.82 ± 0.87 (17–19) 18 [17, 19]	16.64 ± 3.01 (13–24) 16 [14, 18]	–1.18 ± 3.09 (–4–7)	0.100	18.38 ± 1.41 (17–21) 18.5 [17, 19]	19.75 ± 3.85 (12–24) 20 [18.25, 23.25]	1.38 ± 3.50 (–5–5)	0.290
Mild to moderate	N = 21				N = 32			
IIEF-3	2.86 ± 0.57 (2–4) 3 [2.5, 3]	2.86 ± 1.06 (1–4) 3 [2, 4]	0.00 ± 1.18 (–2–2)	0.935	2.66 ± 0.87 (1–5) 3 [2, 3]	2.91 ± 1.17 (0–5) 3 [2, 4]	0.25 ± 1.22 (–2–3)	0.335
IIEF-4	2.86 ± 0.57 (2–4) 3 [2.5, 3]	2.76 ± 1.09 (1–4) 3 [2, 4]	–0.10 ± 1.22 (–2–2)	0.701	2.56 ± 0.67 (1–4) 3 [2, 3]	2.66 ± 1.07 (0–4) 2.5 [2, 4]	0.09 ± 1.28 (–2–3)	0.749
Total IIEF score	41.81 ± 4.59 (33–49) 42 [38.5, 45]	43.62 ± 9.25 (23–56) 43 [37, 52.5]	1.81 ± 8.76 (–14–17)	0.355	41.28 ± 5.08 (33–52) 41 [37.25, 45.5]	42.91 ± 9.74 (18–59) 43 [39.25, 48.5]	1.63 ± 10.05 (–26–18)	0.368
IIEF-EF domain score	17.14 ± 2.08 (14–20) 17 [15, 19]	17.71 ± 4.87 (9–24) 20 [13.5, 22.5]	0.57 ± 5.00 (–9–10)	0.521	17.03 ± 2.07 (14–22) 17 [15, 18]	17.69 ± 5.34 (3–27) 17 [16, 21.75	0.66 ± 4.82 (–12–10)	0.200
SHIM Score	14.19 ± 1.60 (12–16) 15 [12, 15.5]	14.76 ± 3.95 (8–20) 16 [11.5, 18.5]	0.57 ± 4.02 (–7–7)	0.522	13.97 ± 1.43 (12–16) 14 [13, 15.75]	14.19 ± 4.19 (3–21) 14 [13, 16]	0.22 ± 4.03 (–10–7)	0.761
Moderate	N = 16				N = 23			
IIEF-3	1.75 ± 0.45 (1–2) 2 [1.25, 2]	2.31 ± 1.01 (1–4) 2 [2, 3]	0.56 ± 0.96 (–1–2)	0.037	1.83 ± 0.49 (1–3) 2 [2, 2]	2.3 ± 1.19 (0–4) 2 [1, 3]	0.48 ± 1.20 (–2–2)	0.062
IIEF-4	1.75 ± 0.58 (1–3) 2 [1, 2]	2.31 ± 0.87 (1–4) 2 [2, 3]	0.56 ± 1.03 (–1–2)	0.048	1.78 ± 0.42 (1–2) 2 [2, 2]	2.13 ± 1.06 (0–4) 2 [1, 3]	0.35 ± 1.03 (–2–2)	0.123
Total IIEF score	33.75 ± 5.22 (24–41) 34 [28.5, 38.5]	38.06 ± 10.82 (21–63) 34 [31.25, 44.75]	4.31 ± 8.27 (–9–22)	0.054	32.43 ± 4.49 (25–42) 31 [29, 36]	35.57 ± 13.22 (10–60) 33 [25, 45]	3.13 ± 11.95 (–21–25)	0.222
IIEF-EF domain score	12.25 ± 1.29 (10–14) 12.5 [11, 13]	15.56 ± 4.65 (10–24) 13 [12, 19.5]	3.31 ± 4.54 (–3–12)	0.014	11.78 ± 1.72 (9–15) 12 [10, 13]	14.52 ± 5.85 (2–24) 13 [11, 19]	2.74 ± 5.59 (–10–12)	0.027
SHIM Score	9.44 ± 1.15 (8–11) 10 [8, 10]	12.50 ± 3.52 (9–20) 11 [10, 15.5]	3.06 ± 3.51 (–1–11)	0.003	9.83 ± 1.27 (8–11) 10 [8, 11]	11.70 ± 4.85 (2–20) 11 [8, 16]	1.87 ± 4.62 (–9–10)	0.065
Severe	N = 32				N = 17			
IIEF-3	0.94 ± 0.35 (0–2) 1 [1, 1]	1.97 ± 1.26 (1–5) 1.5 [1, 2.75]	1.03 ± 1.20 (0–4)	<0.001	0.94 ± 0.43 (0–2) 1 [1, 1]	1.35 ± 0.79 (0–3) 1 [1, 2]	0.41 ± 0.94 (–1–3)	0.084
IIEF-4	0.94 ± 0.35 (0–2) 1 [1, 1]	1.78 ± 1.04 (1–5) 1.5 [1, 2]	0.84 ± 1.05 (0–4)	<0.001	1.00 ± 0.50 (0–2) 1 [1, 1]	1.29 ± 0.77 (0–3) 1 [1, 1.5]	0.29 ± 1.05 (–2–3)	0.276
Total IIEF score	21.13 ± 5.93 (5–31) 22.5 [18, 25.75]	30.25 ± 10.69 (16–52) 27.5 [21, 35]	9.13 ± 11.01 (–6–32)	<0.001	21.29 ± 7.55 (5–32) 24 [16.5, 26]	25.94 ± 10.43 (10–50) 23 [19.5, 29.5]	4.65 ± 13.49 (–22–41)	0.175
IIEF-EF domain score	6.56 ± 1.97 (1–9) 7 [6, 8]	11.84 ± 5.87 (6–25) 9 [7, 15.5]	5.28 ± 5.94 (–2–19)	<0.001	6.18 ± 2.27 (1–10) 6 [6, 7]	8.82 ± 4.35 (2–19) 8 [6, 10.5]	2.65 ± 5.63 (–7–18)	0.041
SHIM Score	5.38 ± 1.54 (1–7) 5.5 [5, 6]	9.5 ± 4.46 (5–20) 7.5 [6, 12]	4.13 ± 4.66 (–2–15)	<0.001	5.12 ± 1.73 (1–7) 5 [5, 6]	7.41 ± 3.76 (2–16) 6 [5, 9]	2.29 ± 4.67 (–5–15)	0.060

Results of erectile function parameters presented as mean ± standard deviation (range) median (first quartile and third quartile).
IIEF-EF = International Index of Erectile Function-erectile function domain; SHIM = Sexual Health Inventory for Men.

Table 4 Overall results for patients with no concurrent use of statins

	Niacin				Placebo			
	Pretreatment	Posttreatment	Difference (post–pre)		Pretreatment	Posttreatment	Difference (post–pre)	
—	N = 62			*P* value	N = 66			*P* value
IIEF-3	2.05 ± 1.08 (1–4)	2.52 ± 1.20 (1–5)	0.47 ± 1.16 (–2–4)	0.004	2.20 ± 1.14 (0–5)	2.5 ± 1.26 (0–5)	0.30 ± 1.19 (–2–3)	0.065
IIEF-4	2.13 ± 1.21 (1–3)	2.40 ± 1.14 (1–5)	0.27 ± 1.20 (–2–4)	0.101	2.14 ± 0.99 (0–5)	2.27 ± 1.20 (0–5)	0.14 ± 1.12 (–2–3)	0.429
Total IIEF score	33.65 ± 11.34 (22–54)	38.05 ± 11.32 (19–60)	4.40 ± 10.18 (–14–32)	0.001	35.82 ± 11.20 (5–62)	38.29 ± 13.75 (10–64)	2.47 ± 12.09 (–26–41)	0.102
IIEF-EF domain Score	13.18 ± 5.77 (1–25)	15.68 ± 5.75 (6–29)	2.50 ± 5.41 (–9–19)	0.001	13.88 ± 5.32 (1–26)	15.32 ± 6.44 (2–29)	1.44 ± 5.38 (–12–18)	0.033
SHIM Score	10.68 ± 4.76 (1–19)	12.73 ± 4.63 (5–24)	2.05 ± 4.46 (–7–15)	0.001	11.45 ± 4.31 (1–21)	12.47 ± 5.33 (2–24)	1.02 ± 4.54 (–10–15)	0.074

Parameters of erectile function presented in the format: mean ± standard deviation (range).
IIEF-EF = International Index of Erectile Function-erectile function domain; SHIM = Sexual Health Inventory for Men.

Table 5 Comparison of the pre- and post-changes in the serum lipid profiles of the two groups

	Niacin				Placebo				
Mean ± standard deviation	Pretreatment	Posttreatment	Difference (post–pre)	*P* value	Pretreatment	Posttreatment	Difference (post–pre)	*P* value	Between both groups *P* value
Triglycerides	1.98 ± 1.18	1.52 ± 1.52	–0.46 ± 1.77	<0.001	2.29 ± 1.47	2.36 ± 1.88	0.07 ± 1.66	0.981	<0.001
Total cholesterol	5.27 ± 1.05	4.84 ± 0.93	–0.44 ± 0.81	<0.001	5.31 ± 0.84	6.16 ± 7.48	0.86 ± 7.38	0.639	0.005
HDL-cholesterol	1.23 ± 0.27	1.45 ± 0.41	0.21 ± 0.31	<0.001	1.24 ± 0.36	1.23 ± 0.33	–0.01 ± 0.18	0.689	0.001
LDL-cholesterol	3.21 ± 0.96	2.76 ± 0.89	–0.44 ± 0.70	<0.001	3.22 ± 0.80	3.16 ± 0.86	–0.06 ± 0.61	0.475	0.010

LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Table 6 Adverse events in both groups

Adverse events	Niacin N = 80	Placebo N = 80	*P* value
Flushing	29 (36.3%)	2 (2.5%)	<0.001
Itchiness	26 (32.5%)	7 (8.8%)	<0.001
Headache	4 (5.0%)	4 (5.0%)	1.000
Gastric discomfort	1 (1.3%)	4 (5.0%)	0.367
Palpitation	3 (3.8%)	—	0.245
Raised BP	—	2 (2.5%)	0.497
Ankle edema	—	2 (2.5%)	0.497
Dizziness	2 (2.5%)	1 (1.3%)	1.000
Chest pain	1 (1.3%)	1 (1.3%)	1.000
Others	8	10	—
Total	73	31	—

BP = blood pressure.

patients, there is a close relationship between ED and dyslipidemia. In fact, it is common to diagnose dyslipidemia in ED patients [17]. Studies have also shown that the use of statins can help to improve the response of PDE5i in patients suffering from ED because of the improvement in endothelial function/atherosclerosis [5–9]. Hence, statins can be used as an additional treatment to PDE5i for patients with an unsatisfactory response to PDE5i.

Niacin is another class of lipid-lowering agent, with characteristic effects of increasing serum HDL-cholesterol levels by inhibition of lipolysis in adipose tissue, which eventually leads to improvement in all lipid parameters [18]. Studies have also suggested that niacin could improve the clinical outcome of patients suffering from cardiovascular disease [19] and may also lead to regression of atherosclerotic plague [10,11]. Hence, we postulated that it may also have the same beneficial effect as statins on erectile function. Moreover, in addition to the possible effect of niacin on the anti-atherosclerotic process, it may have other potential effects on erectile function. Niacin is well-known for its adverse facial flushing effect, which is related to the release of prostaglandin D2 (PGD2) in the skin by Langerhans cells, leading to vasodilation and hence facial flushing [20]. The production of PGD2 by niacin can also occur in macrophages [21]. Therefore, niacin-induced PGD2 production may affect all body tissue, including cavernosal tissue. PGD2 is one of the potential agents causing the vasodilation of cavernosal tissue, thereby leading to erection [22,23]. Hence, niacin may also improve erectile function by stimulating the production of PGD2. Based on these potential mechanisms, this study aimed to assess the role of niacin in patients with ED. The main difference between our study and other studies is that we use niacin alone rather than in combination with PDE5i [5–9]. As a result, this may provide a better assessment of the efficacy and adverse effects of niacin in patients with ED.

Our results indicate that niacin could improve erectile function in patients with moderate to severe ED but not in those with mild and mild-to-moderate ED. A similar observation was noted for statins, which are also more effective in improving erectile function in patients with more severe ED [9]. We agree with the suggestion of Dadkhah et al. that in patients with more severe ED, the degree of endothelial dysfunction and atherosclerosis are more severe, and hence the effects of these lipid-lowering agents is also more apparent. In another study assessing the effect of vardenafil in patients using statin, patients with higher baseline serum LDL-cholesterol had better improvement in erectile function after vardenafil [24]. This may indirectly support our hypothesis that patients with potentially more serious endothelial dysfunction, as reflected by higher LDL-cholesterol level, may have better response to the combination usage of vardenafil and statin. Certainly, further studies will be beneficial to verify this hypothesis.

Moreover, the beneficial effect of niacin became more evident when we excluded those patients who were already on statins therapy. This might be related to the potential overlapping effect of these two groups of lipid-lowering agents on endothelial function. The chronic use of statins may attenuate the effect of niacin on endothelial function and hence the improvement in erectile function.

There are some limitations to our study. First, we only included patients with dyslipidemia, and the results may not be applicable to those patients with ED but with a normal serum lipid profile. Second, we also excluded patients using aspirin or NSAID during the initial study design to avoid the effect of these drugs in inhibiting prostaglandin D production, which we believe may be one of the potential mechanisms for the effects of niacin on ED patients. However, in daily clinical practice, it is quite common for ED patients to have coexisting cardiovascular disease that required the use of aspirin. Therefore, further study on the interaction of aspirin and niacin in ED patients may be needed to establish the role of niacin in clinical usage. Moreover, patients were not using PDE5i during the study period, and so whether the combined use of niacin can enhance the response of PDE5i, as shown in other studies on statins, is not known. Because we had not recorded the effect of prior PDE5i usage in our patients (before washout

period) during the baseline assessment, we could not compare the efficacy of niacin and other PDE5i. Hence, further studies may be needed to assess the effect of niacin in different groups of ED patients, its efficacy as compared with current PDE5i, and also the effect of its combined usage with PDE5i. The inclusion of the partner's assessment in future studies will also help to provide a more comprehensive assessment of the efficacy of niacin. Finally, although the current 12-week regime of niacin treatment already shown beneficial effects in ED patients, the potential benefit of long-term use of niacin is not addressed, as shown in some cardiovascular studies of niacin [10]. Therefore, further studies are needed to determine the optimal treatment period for niacin usage in ED patients.

Conclusion

The data from this study suggest for the first time in the literature that niacin alone could improve the erectile function of patients with dyslipidemia suffering from ED. The effect is clinically significant in patients with moderate to severe ED. Because of the close relationship between ED and dyslipidemia, niacin might be an important therapy for managing both conditions. Further studies would be beneficial to refine further the indications and benefits of niacin in patients with ED.

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