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ORIGINAL ARTICLE

Postprandial effects of long-term niacin/laropiprant use on glucose and lipid metabolism and on cardiovascular risk in patients with polycystic ovary syndrome

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Aim: This study investigated the effect of long-term niacin/laropiprant therapy on CV risk and IR in obese women with PCOS.
Methods: In this double-blind randomized placebo-controlled trial, 13 and 12 PCOS women completed a 12 week course of niacin/laropiprant or placebo, respectively. Fasted subjects had an endothelial function test (EndoPat2000) and then consumed a mixed meal with blood sampled postprandially for 6 h before and after intervention.
Results: By 12 weeks, niacin/laropiprant lowered low-density lipoprotein cholesterol (LDL-c) (13%) and increased HDL-c (17%). Despite a reduction in fasting triglycerides (21%), the drug had no effect on their postprandial rise (2.69 ± 1.44 vs. 2.49 ± 1.14 mmol/l, $p = 0.72$). However, following the mixed meal, plasma glucose area under the response curve increased from 13.1 ± 2.9 to 14.0 ± 2.8 mmol/l, $p = 0.05$, as a consequence of both increased insulin resistance [HOMA-IR: 2.2 (1.2, 4.2) vs. 3.8(1.3, 5.5), $p = 0.02$] and a reduced acute insulin response to glucose [424 (211, 975) vs. 257(122, 418) pmol/mmol, $p = 0.04$]. Niacin/laropiprant did not improve RHI (1.97 ± 0.40 vs. 2.05 ± 0.58, $p = 0.33$) or hsCRP.
Conclusions: In PCOS, niacin/laropiprant had a significant negative impact on postprandial glucose and no improvement in postprandial hypertriglyceridaemia, with at least the former mediated through increased IR and reduced β-cell function. This data may help explain why the improvement in fasting lipids has not translated into improved CV risk markers in PCOS.
Keywords: endothelial dysfunction, insulin resistance, niacin/laropiprant, polycystic ovary syndrome, triglycerides

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Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder of reproductive women and its prevalence ranges from 6 to 12% [1]. PCOS is associated with multifaceted metabolic abnormalities such as obesity [2], metabolic syndrome [3], dyslipidaemia [4] and insulin resistance [5]. Women with PCOS are therefore at risk of impaired glucose regulation [6] and subsequent cardiovascular (CV) disease [7]. Typical dyslipidaemia found in PCOS are a decrease in high-density lipoprotein cholesterol (HDL-c), preponderance of atherogenic small dense low-density lipoprotein cholesterol (LDL-c) [4], a rise in fasting and postprandial triglyceridaemia [8]. Postprandial hypertriglyceridaemia is reported to cause endothelial dysfunction in both diabetic and normal subjects [9] and is strongly and independently correlated with carotid intima-media thickness in type2 diabetes mellitus (T2DM) [10]. Similarly, evidence of early arthrosclerosis such as impaired endothelial dysfunction [11], increased carotid intima-media thickness [12] and coronary artery calcium [13] seems to be prevalent in PCOS.

Niacin raises HDL-c and reduces both LDL-c and triglycerides (TG), and on this basis it has been used to treat patients with hyperlipidaemia and CV disease for over 50 years [14]. Extended release niacin improves carotid intima-media thickness, endothelial function and vascular inflammation in patients with metabolic syndrome [15]. Sathyapalan et al. reported that reduction of TG by atorvastatin in PCOS is positively correlated with improvement in insulin resistance and free androgen index (FAI) in addition to lowering high-sensitivity C-reactive protein (hsCRP) [16]. Effect of niacin on CV risk markers and postprandial TG in PCOS has not been studied.

Niacin, however, has clinically insignificant negative impact on glycaemia: it can cause a modest, transient and reversible increase in fasting glucose of 4–5% and haemoglobin A1c (HbA1c) of <0.3% [17]. The effect of niacin on glucose

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metabolism might be significant as women with PCOS are at risk of diabetes. Postprandial glucose (PPG) is recognized as a CV risk as it has a linear relationship with CV death, and treatment targeted at PPG has been shown to reduce the progression of atherosclerosis and CV events according to the Report of the International Prandial Glucose Regulation Study Group [18]. In a prospective cohort study, a total of 57% of patients who presented with acute coronary event had abnormal glucose metabolism [19].

The therapeutic effect of niacin on CV risk including postprandial TG and insulin resistance in obese women with PCOS using a mixed meal model has not been investigated, so we examined the long-term effect of modified release niacin/laropiprant on lipid and glucose homeostasis in both the fasting and postprandial state together with an assessment of its influence on CV risk markers.

Materials and Methods

Subjects and Randomization

This was a double-blind, randomized placebo-controlled trial conducted at Hull and East Yorkshire Hospital NHS trust after receiving an ethical approval from Leeds Research Ethics Committee. This study was registered in the ClinicalTrials.gov registry and the clinical trial registration number is NCT01118598. PCOS patients were recruited from the endocrine clinics with the permission of their clinicians and their practitioners. Written informed consent was obtained from all participants. PCOS was diagnosed according to the Rotterdam criteria [20] based on the presence of two of three criteria, oligomenorrhoea, clinical or biochemical hyperandrogenism and polycystic ovaries on ultrasound after exclusion of other endocrine causes of hyperandrogenism [21]. Participants who had impaired glucose regulation on oral glucose tolerance test at screening were excluded. Participants had no concurrent illness and were not on any prescription or over-the-counter medication that was likely to affect insulin sensitivity or lipids including hormonal contraceptives for the preceding 3 months. None were breast feeding or were planning to conceive and all were using barrier contraception. They were advised not to change their lifestyle, including physical activity or dietary habits, during the study period. All were non-smokers. Participants who fulfilled the inclusion and exclusion criteria were randomly assigned to either Tredaptive® (niacin 1000 mg/laropiprant 20 mg) (Merck Sharp & Dohme Ltd, Hoddesdon, UK) or placebo. Randomization was performed by hospital pharmacy with 1 : 1 allocation in random blocks of 12. Tredaptive® and placebo tablets were provided by MSD (Merck Sharp & Dohme, Hoddesdon, UK) Ltd (unrestricted gift).

Procedures and Protocols

The EndoPAT 2000 (Itamar Medical, Caesarea, Israel) was used to non-invasively quantify functional endothelium-mediated changes in vascular tone as per manufacturer protocol. The postocclusion to preocclusion ratio calculated gives the reactive hyperaemic index (RHI) [22].

On the study day, participants attended the research centre at 08:00 hours following an overnight 12 h fast. Weight, height, waist, hip and resting blood pressure were measured and followed by endothelial function assessment with the EndoPAT 2000. A mixed meal test was undertaken following fasting venous blood sampling. The participants consumed a standard 900 kcal mixed meal (45 g fat, 32 g protein, 92 g carbohydrates; 9 g of those was refined sugar) made of breakfast cereal and milk, a cheese sandwich and a milkshake. Serial blood samples from 30 min after the meal were collected at half-hourly intervals for the first 3 h and then hourly for 3 h. Blood samples were centrifuged within 30 min of sampling at 1500 g for 15 min at 4 °C to isolate plasma or serum. The aliquots of serum and plasma were stored at −80 °C until analyses. This protocol was repeated at the end of the study.

According to randomization, participants were prescribed with one tablet of either Tredaptive® or identical placebo per day for the first 4 weeks, and then two tablets per day for the remaining 8 weeks. One tablet of Tredaptive® used in this study contained 1000 mg of niacin and 20 mg of laropiprant. Participants were advised to take tablets whole, with food, at bedtime. Participants were seen once in every 4 weeks to ensure their tolerability, safety and compliance with treatment. Compliance was checked by counting the tablets returned.

Biochemical Analysis

Total cholesterol (TC), TG and HDL-c were measured enzymatically using a Synchron LX20 analyser (Beckman-Coulter, High Wycombe, UK). LDL-c was calculated using the Friedewald Equation. Non-esterified fatty acids (NEFA) were analysed using enzymatic colorimetric methods (Wako NEFA-HR2) on Konelab20 autoanalyzer (Thermo Fisher Scientific Inc., UK) with an interassay coefficient of variation was 1.4%. Plasma glucose was measured using a Synchron LX 20 analyser (Beckman-Coulter Ltd, High Wycombe, UK). Serum insulin was assayed using a competitive chemiluminescent immunoassay, performed on the manufacturer's DPC Immulite 2000 analyser (Euro/DPC, Llanberis, UK). Serum testosterone was measured by high-pressure liquid chromatography linked to tandem mass spectrometry (Waters Corporation, Manchester, UK) and sex hormone-binding globulin (SHBG) was measured by immunometric assay with fluorescence detection on the DPC Immulite 2000 analyser. The FAI was obtained as the quotient 100* Testosterone/SHBG. A turbidimetric method using a Beckman SYNCHRON® System was used to measure hsCRP.

Calculations

The total and incremental TG area under the response curve (AUC), and insulin, glucose and NEFA AUC were calculated using a trapezoidal rule [23] Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by the formula: HOMA-IR = fasting plasma insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 [24]. On the basis of the hyperbolic relationship between insulin response and insulin sensitivity, the oral disposition index (ODI) was calculated from acute insulin response to glucose (AIRg) multiplied by insulin

sensitivity [25]. The AIRg was determined as the ratio of mean increment in insulin and glucose from time 0 to 30 min following the mixed meal test ($\Delta I0-30/\Delta G0-30$). Insulin sensitivity was calculated from one divided by fasting insulin level. The ODI was used as a measure of compensatory β-cell function in response to insulin resistance [26]. A sample size of 36 with 1 : 1 randomization was calculated to show a one standard deviation difference in the primary outcome measure, fasting HDL-c, between the two groups (80% power, 5% significance, two-tailed) with an assumption of 10% loss to follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows NT, version 19.0 (SPSS, Chicago, IL, USA). Comparison before and after treatment within the group was made using the Wilcoxon signed-rank test for the variables that violated the assumptions of normality when tested using the Kolmogorov–Smirnov test, and the *t*-tests for normally distributed variables. Relative changes (percentage) of variables from baseline were compared between the groups using unpaired *t*-test for normally distributed variables and Kruskal–Wallis test for skewed variables. Results are expressed as means ± standard deviation for normally distributed data and medians (25th, 75th centiles) for skewed variables. For all analyses, a two-tailed $p \leq 0.05$ was considered to indicate statistical significance.

Results

A total of 37 patients were screened for the study and 3 patients failed to meet the eligibility criteria. Thirteen of 17 (76%) participants in the niacin/laropiprant group and 12 of 17 (70%) patients in the placebo group completed the study. Two patients (12%) dropped out due to intolerance of hot flushes in the niacin/laropiprant group. Two patients from the niacin/laropiprant group and four patients from the placebo group were withdrawn because of loss of follow-up. One patient from the placebo group was withdrawn as she became pregnant while using barrier contraception (Figure 1). Nobody required a new antidiabetic medication during the study period.

Baseline characteristics of the participants are shown in (Table 1). The age and body mass index of the PCOS subjects between the groups were comparable. PCOS subjects in niacin/laropiprant-treated group had non-significantly higher HOMA-IR and ODI than those in the placebo-treated group by chance. The clinical and biochemical parameters before and after intervention within the groups (niacin/laropiprant or placebo) and between the groups (niacin/laropiprant vs. placebo) are summarized in Table 2. Changes in PPG, and relationship between insulin sensitivity and AIRg following the meal tests, before and after interventions, are illustrated in Figures 2 and 3, respectively.

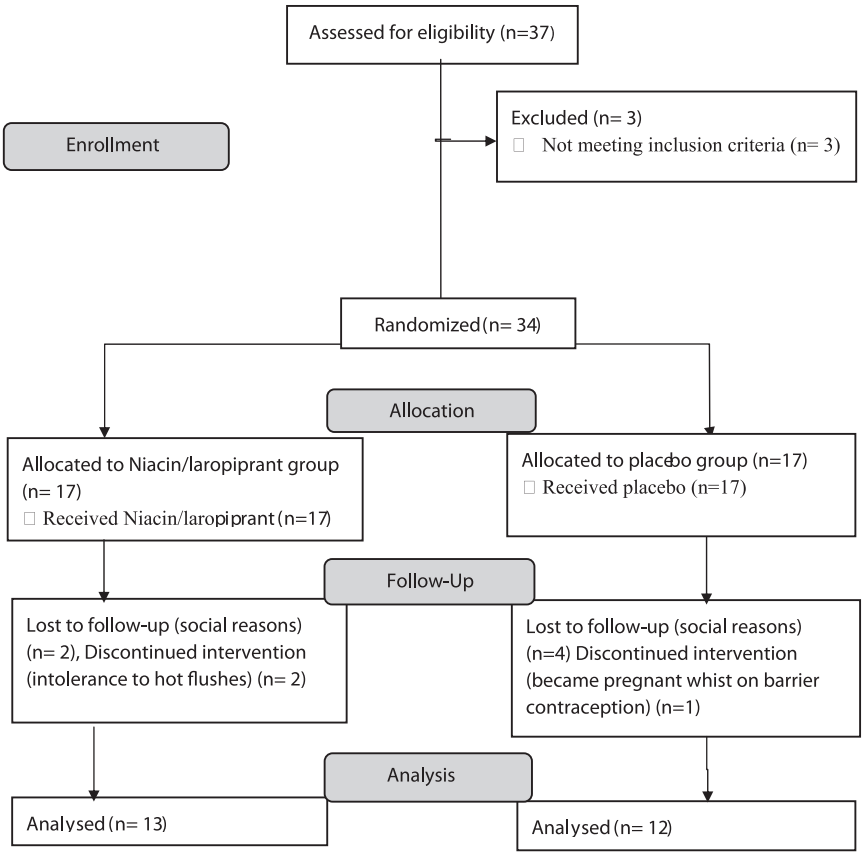

Figure 1. Clinical trial flow diagram.

Table 1. Baseline clinical characteristics of the participants.

	Niacin/ laropiprant (N = 13)	Placebo (N = 12)
Age (years)	31.0 ± 6.33	31.7 ± 6.51
Body mass index (kg/m^2)	35.8 ± 5.55	34.8 ± 5.03
Waist (cm)	108 ± 13.5	104 ± 13.5
Systolic blood pressure (mmHg)	125 ± 13.8	121 ± 12.5
Diastolic blood pressure (mmHg)	80.2 ± 15.4	71.2 ± 6.55
Testosterone (nmol/l)	1.44 ± 0.58	1.41 ± 0.54
Free androgen index	5.63 ± 2.40	5.93 ± 3.09
Sex hormone-binding globulin, SHBG (nmol/l)	29.2 ± 12.5	27.6 ± 12.6
Alanine aminotransferase (IU/l)	31.8 ± 11.3	31.5 ± 18.9
Thyroid-stimulating hormone (IU/l)	1.97 ± 1.38	1.25 ± 0.42

Results are expressed as means ± SD. To convert values for testosterone to ng/dl, divide by 0.03467. To convert values for SHBG to µg/dl, divide by 34.7.

Effect of Niacin/Laropiprant on Cardiovascular Risk

By 12 weeks, no significant improvement in RHI was observed in either the niacin/laropiprant (1.97 ± 0.40 vs. 2.05 ± 0.58, p = 0.33) or placebo (1.95 ± 0.50 vs. 1.96 ± 0.47, p = 0.92) groups. There was a reduction in hsCRP within the niacin/laropiprant group but that reduction was not significant when compared with that of the placebo group (Table 2). Blood pressure, SHBG, total testosterone and FAI were not changed within the groups at the end of the study (data not shown).

Effect of Niacin/Laropiprant on Fasting and Postprandial Lipids

At the end of the study, there was a significant difference (% change) in fasting TC (−8 vs. 1%), TG (−21 vs. 4%), LDL-c (−13 vs. 3%) and HDL-c (17 vs. 1%) between the niacin/laropiprant and placebo-treated groups. Although niacin decreased absolute postprandial TG AUC at the end of 6 h following a mixed meal (9.44 ± 2.9 vs. 7.74 ± 3.2 mmol/l, p = 0.03), it had no effect on increment of postprandial TG AUC (2.69 ± 1.44 vs. 2.49 ± 1.14 mmol/l, p = 0.64) above the fasting value. No change in postprandial TG was seen in the placebo group. By 12 weeks, there was a trend of rise in fasting NEFA (relative increase in fasting NEFA after intervention – niacin/laropiprant group: 23% vs. placebo group: −2%) and NEFA AUC per 6 h (relative increase in postprandial

Table 2. Effect of niacin/laropiprant on lipid and glucose metabolism and on CV risk.

	Niacin/laropiprant (n = 13)			Placebo (n = 12)			Pecentage change from baseline		
	Baseline	12 week	p*	Baseline	12 week	p*	Niacin/ laro	Placebo	p†
BMI (kg/m^2)	35.8 ± 5.55	35.9 ± 5.7	0.55	34.8 ± 5.0	34.6 ± 4.6	0.7	0.03	−0.01	0.70
Waist (cm)	108 ± 13.5	106 ± 12.0	0.36	104 ± 13.5	103 ± 14	0.43	−0.02	−0.01	0.64
FAI	6.02 ± 2.2	5.0 ± 2.5	0.35	6.48 ± 3.5	6.02 ± 3.0	0.32	−0.04	−0.05	0.96
HbA1c (mmol/mol)	36.5 ± 3.6	37.2 ± 4.1	0.21	34.1 ± 2.5	35.1 ± 2.7	0.24	0.02	0.03	0.65
hsCRP (mg/ml)	6.14 ± 3.9	5.11 ± 3.5	0.06	3.44 ± 2.2	3.58 ± 2.4	0.81	−0.09	0.11	0.3
RHI	1.97 ± 0.4	2.05 ± 0.58	0.33	1.95 ± 0.50	1.96 ± 0.5	0.92	0.12	−0.01	0.11
TC (mmol/l)	4.6 ± 1.2	4.18 ± 1.01	0.01	4.65 ± 0.87	4.72 ± 0.8	0.55	−0.08	0.01	0.05
LDL-c (mmol/l)	2.8 ± 0.93	2.36 ± 0.74	0.01	2.84 ± 0.54	2.89 ± 0.6	0.62	−0.13	0.03	0.05
HDL-c (mmol/l)	1.2 ± 0.3	1.35 ± 0.37	0.04	1.14 ± 0.25	1.13 ± 0.2	0.86	0.17	0.01	0.03
TG (mmol/l)	1.22 ± 0.6	0.9 ± 0.41	0.03	1.29 ± 0.59	1.37 ± 0.7	0.26	−0.21	0.04	0.05
Fasting PG (mmol/l)	5.54 ± 0.6	5.56 ± 0.6	0.81	5.31 ± 0.38	5.2 ± 0.5	0.23	0.01	0.03	0.45
Fasting insulin (pmol/l)	51 (37, 95)	113 (39, 150)	0.01	96 (59, 115)	95 (73, 153)	0.33	0.6	0.02	0.04
HOMA-IR	2.2 (1.2,4.2)	3.8 (1.3, 5.5)	0.02	3.3 (2.2,4,1)	3.2(1.8, 4.4)	0.48	0.54	−0.12	0.05
Fasting NEFA (µmol/l)	414 (353, 583)	506 (410, 656)	0.35	561 (376, 653)	499 (387, 604)	0.58	0.23	0.00	0.58
TG AUC per 6 h (mmol/l)	9.44 ± 2.9	7.74 ± 3.2	0.03	11.0 ± 5.0	11.4 ± 4.7	0.77	−0.17	0.14	0.06
NEFA AUC per 6 h (µmol/l)	1567 (1273, 1781)	1811 (1304, 2021)	0.06	1547 (1142, 2134)	1639 (1406, 1813)	0.58	0.11	−0.01	0.35
2 h PG (mmol/l)	6.08 ± 1.1	6.72 ± 1.4	0.02	6.24 ± 0.9	6.56 ± 1.6	0.3	0.14	0.02	0.04
PG AUC per 2 h (mmol/l)	13.1 ±2.9	14.0 ±2.8	0.05	12.9 ±2.0	13.0 ±2.8	0.89	0.08	0.01	0.05
Insulin AUC per 2 h(pmol/l)	814 (717, 1645)	1140 (587, 1946)	0.51	1102 (844, 1908)	1042 (785, 1282)	0.8	−0.14	−0.05	0.59
AIRg (pmol/mol)	424 (211, 975)	257 (122, 418)	0.04	320 (244, 879)	564 (334, 664)	0.96	−0.31	0.29	0.04
ODI (mM^{-1})	10.2 (3.1, 13.9)	2.12 (0.96, 4.7)	0.01	4.08 (2.41, 17.3)	5.0 (3.95, 8.73)	0.33	−0.61	0.06	0.04

Skewed variables are provided as the median (25th, 75th centile). Normally distributed variables are shown as the mean ± standard deviation. To convert values for glucose to mg/dl, divide by 0.056. To convert values for insulin to µU/ml, divide by 6. To convert values for cholesterol and HDL-c to mg/dl, divide by 0.0259. To convert values for triglycerides to mg/dl, divide by 0.0113. To convert values for testosterone to ng/dl, divide by 0.03467. To convert values for SHBG to µg/dl, divide by 34.7. AIRg, acute insulin response to glucose; AUC, area under the response curve; BMI, body mass index; CV, cardiovascular; FAI, free androgen index; HbA1c, haemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; ODI, oral disposition index; PG, plasma glucose; RHI, reactive hyperaemic index; TC, total cholesterol; TG, triglycerides.

*Significance from baseline within the groups.

†Significant differences for the comparison between the groups.

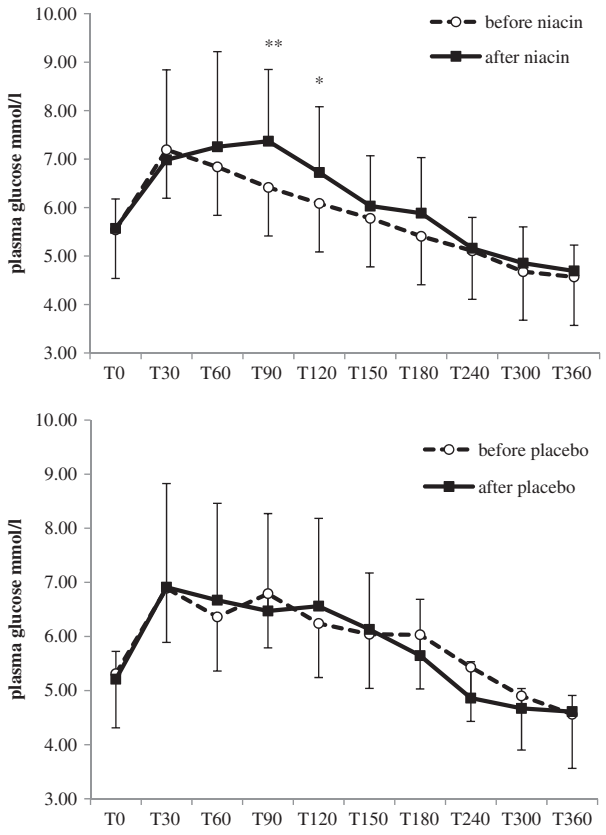

Figure 2. Postprandial glucose following a mixed meal test in polycystic ovary syndrome (PCOS) women before and after intervention with niacin or with placebo. Values were mean ± standard deviation. *p ≤ 0.05; **p ≤ 0.01; T, time (min).

NEFA AUC after intervention – niacin/laropiprant group: 11% vs. placebo group: −1%) from baseline with niacin therapy when compared with placebo.

Effect of Niacin/Laropiprant on Fasting and PPG

At the end of 12 week, HOMA-IR rose from baseline [2.2 (1.2, 4.2) to 3.8 (1.3, 5.5), p = 0.02] and it was accompanied by a rise in fasting insulin levels [51 (37, 95) vs. 113 (39, 150) pmol/l, p = 0.01] which maintained fasting plasma glucose unchanged (5.54 ± 0.57 vs. 5.56 ± 0.61 mmol/l, p = 0.81). By comparison, when stimulated with a mixed meal, plasma glucose at 2 h rose from 6.08 ± 1.1 to 6.72 ± 1.4 mmol/l (p = 0.02) and postprandial plasma glucose AUC 2 h from 13.1 ± 2.9 to 14.0 ± 2.8 mmol/l (p = 0.05) following niacin treatment. This was at least partly due to a decrease in AIRg [424 (211, 975) vs. 257 (122, 418) pmol/mmol, p = 0.04]. Consequently, the ODI was reduced [10.2 (3.1, 13.9) vs. 2.12 (0.96, 4.71) p = 0.01] in the niacin/laropiprant group. The differences were statistically significant when compared between the niacin/laropiprant and placebo groups.

Discussion

In this study, niacin lowered fasting LDL-c, TG, TC and increased HDL-c in PCOS. However, following a mixed meal,

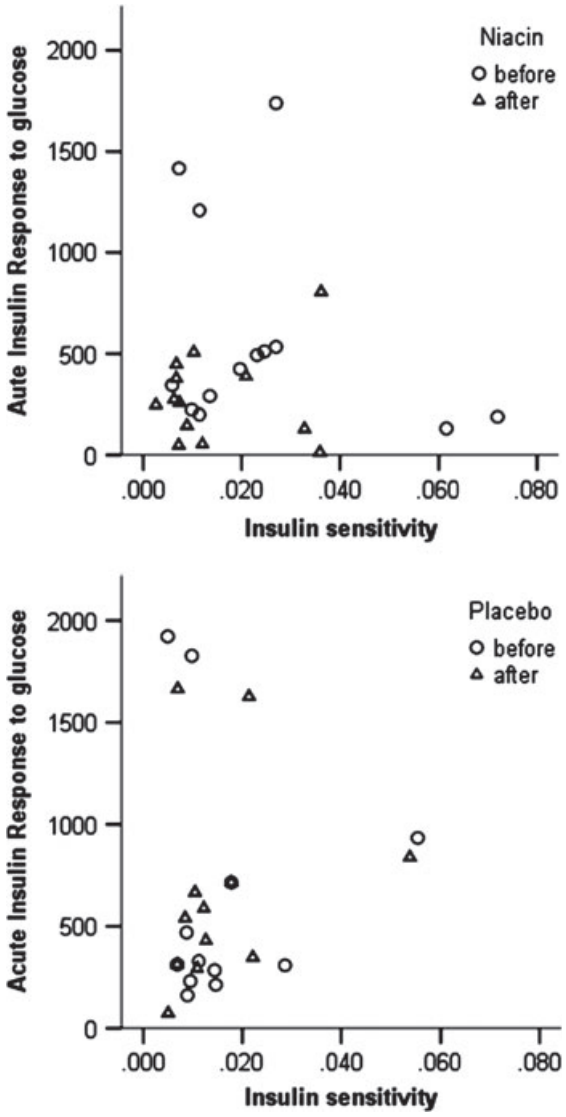

Figure 3. Relationship between insulin sensitivity (pmol/l) and acute insulin response to glucose (AIRg) (pmol/mmol) in polycystic ovary syndrome (PCOS) women before and after intervention with niacin or with placebo.

niacin did not influence the postprandial excursion of TG. Therefore, the improvement seen in total postprandial TG with niacin was mainly due to a decrease in fasting TG rather than an effect on any postprandial rise to a meal. This lack of change in postprandial hypertriglyceridaemia with niacin is likely to be related to the 23% increase in NEFA at the beginning of the meal and the overall 11% rise in the NEFA AUC, which compares with no change in the placebo group. This finding is consistent with similar rebound rises in NEFA found with niacin including the extended release form in previous studies [27].

Niacin, by acting on nicotinic receptors in adipose tissue, inhibits the hydrolysis of TG and reduces the release of NEFA into the liver and subsequently reduces the hepatic synthesis and release of very low density lipoproteins (VLDL)-TG [28]. Thus, the effect of niacin on adipose tissue alone cannot explain the paradoxical reduction in TG despite a rebound

rise in NEFA. Kashyap et al. reported that niacin enhances Apo B degradation and subsequently decreases TG synthesis in hepatoblastoma G2 cells [29]. In addition, niacin directly inhibits diacylglycerol acyltransferase 2 (DGAT2) resulting in decreased triglyceride synthesis [30]. Niacin also reduces the hepatic expression of apolipoprotein CIII and the peroxisome proliferator-activated receptor (PPAR) gamma co-activator-1β (PGC-1β), a transcriptional co-activator and subsequently lowered TG [31]. Therefore, the reduction of fasting TG with no apparent decrease in NEFA is possibly due to direct effect of niacin on hepatic TG synthesis [30].

Two prospective population cohorts, Women's Health Study [32] and Copenhagen City Heart Study [33], reported that elevated non-fasting TG rather than fasting TG is associated with CV events independent of conventional CV risk factors. Furthermore, the incremental area under the response curve rather than fasting TG or total TG AUC accurately described the TG response to an oral fat load in both healthy and T2DM subjects [34]. In the recent Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study, niacin/laropiprant plus statin therapy did not improve CV outcome compared to statin therapy after a median of 3.9-year follow-up in patients who were at high risk of CV events. The low RHI detected by EndoPAT was consistent with endothelial dysfunction and was associated with late CV adverse outcome [35]. In this study, niacin had no effect on either RHI or on hsCRP, both measures of CV risk. Therefore, the failure of niacin to decrease the postprandial rise in TG AUC may have direct relevance to the clinical observation of its lack of CV protection in PCOS.

In respect of the effect of niacin on glucose homeostasis, this study showed that the drug therapy increased fasting insulin resistance which was associated with a significant rise of fasting insulin level. The fasting plasma glucose level did not change after drug therapy and therefore it suggested that increased fasting insulin secretion from β cell was able to compensate for a rise in insulin resistance in the fasting state. The rise in HOMA-IR was associated with a trend of rise in fasting NEFA. This suggested that this rebound rise in NEFA during niacin therapy would contribute to worsening IR, especially as acute and chronic elevation of circulating NEFA are known to be associated with increased insulin resistance [36]. In this study, HOMA-IR was increased by 54% from baseline after 12 week of niacin therapy. Therefore, this rate of rise of insulin resistance in women with PCOS, who has underlying insulin resistance, could accelerate the progression to diabetes in the settings of long-term use of niacin or chronic elevation of NEFA related to obesity.

The information derived solely from the HOMA-IR [24] is limited because it does not determine the ability of β cells to respond to rising glucose concentrations in the postprandial period. Although β cell function and insulin sensitivity can be measured following an intravenous glucose infusion or an oral glucose load, we used a mixed meal in preference as the presence of other nutrients such as proteins and fat make it a much more physiological challenge [37]. Using this, we found that at the end of niacin therapy there was a significant rise in postprandial plasma glucose AUC despite an increase in postprandial insulin AUC levels towards the end of 2 h. This resulted in a significant fall in AIRg suggesting a relative reduction in insulin secretion in response to postprandial rise in glucose levels. Looked at in more detail, we assessed the ODI as it is able to give an indication as to whether β cells were responding appropriately to any change in insulin resistance. The significant fall in ODI following niacin suggests that β cells did indeed fail to meet the larger insulin requirement demanded during the postprandial period.

It means that the increased PPG and HbA1c found in a meta-analysis of niacin clinical trials could be as much due to the effect of the drug on β cell function as it is on insulin resistance [17]. In the Whitehall Study, the Paris Prospective Study and the Helsinki Policemen Study, a 20-year follow-up of healthy middle aged working non-diabetic men showed that high postprandial, as well as fasting glucose were risk factors for CV and all-cause mortality [38]. Postprandial hyperglycaemia impairs vascular endothelial dysfunction seen by a reported reduction in flow-mediated vasodilatation (FMD), and an increase in lipid peroxidation and asymmetric dimethylarginine (ADMA) level in healthy [39] as well as in diabetes subjects [40]. This niacin-induced postprandial rise in glucose, therefore, may be contributory to understanding why niacin therapy did not produce CV benefit despite improvements in HDL-c and LDL-c in the previous studies [41] and in this study.

Atorvastatin lowered the TG and insulin resistance accompanied by a reduction in FAI in PCOS [16]. However, niacin/laropiprant therapy did not improve the androgen profile in PCOS despite a reduction in TG. It might possibly relate to a rise in insulin resistance by niacin/laropiprant.

This study is not without its limitations, the main one being the dropout rate of 23%. This was the same in both the placebo and active treatment groups. Although the actual loss of follow-up was more than expected at the end of this study, the primary outcome difference in HDL-c was reached between the groups. If there was insufficient power then in all likelihood it would have been reflected in a false negative rather than false positive result. We have used niacin/laropiprant instead of niacin alone to improve the tolerability of participants. Therefore, the effect of laropiprant on the results cannot be excluded although there is no known effect of laropiprant on glucose and lipid metabolism.

In summary, this study has found that niacin/laropiprant did not improve postprandial triglyceride excursions in response to a mixed meal in PCOS. The drug did, however, significantly increase PPG through an increase in insulin resistance and a detrimental effect on β cell function. Together, these findings are likely to offset many of the potentially beneficial effects of niacin/laropiprant on fasting lipids and so may help explain the observed clinical ineffectiveness of niacin on CV outcomes in other studies and lack of improvement in CV risk markers in PCOS in this study.

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Conflict of Interest

There are no conflicts of interest to declare.

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