

Effect of Oligopin Supplementation on Polycystic Ovary Syndrome: A Randomized Controlled Trial

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Abstract

Background: A double blind clinical trial was performed to evaluate whether polycystic ovary syndrome (PCOS)-specific serum markers and metabolic parameters would change in women with PCOS during three months administration of oligopin.

Methods: In this double-blind multicenter trial, we randomly assigned 80 PCOS women, in a 1:1 ratio, to receive oligopin (n= 40) or placebo (n = 40) for up to 3 months. As PCOS- specific outcomes, we investigated changes in testosterone, sex hormone binding globulin (SHBG), free androgen index (FAI), dehydroepiandrosterone (DHEA), *follicle-stimulating hormone (FSH)* and increase *luteinizing hormone (LH)*. Secondary end points were metabolic (fasting glycaemia, hemoglobin A1c (HbA1c), lipids, insulin resistance (HOMA-IR)), anthropometrics parameters and blood pressure from baseline to end of treatment. We investigate serum transaminase, alkaline phosphatase (ALP), creatinine (Cr) and blood urea nitrogen (BUN) levels as hepatic and kidney outcomes, respectively.

Results: PCOS-specific serum parameters did not change during three months administration of oligopin ($p > 0.05$) except for small increase in FSH levels ($p=0.03$). Oligopin neither changed the metabolic profile nor the anthropometric parameters or blood pressure. ALP levels significantly increased in placebo group compared with oligopin ($p=0.01$).

Conclusion: Oligopin supplementation does not seem to be exerting a beneficial effect on both hormonal and metabolic parameters in women with PCOS.

The study was registered at www.irct.ir with the identifier number of IRCT20140406017139N3.

Registered 22 December 2018 - Retrospectively registered.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine- metabolic disorder and cause of infertility affecting 5-20% of women in reproductive lifespan (1). PCOS often can be characterized by elevated circulating androgen levels, hirsutism, acne, and oligomenorrhea or amenorrhea, and/or polycystic ovarian morphology (PCOM) determined by ultrasound. Endocrine and metabolic derangements and cardiovascular disorders may also coexist (2). Hyperinsulinemia, a consequence of insulin resistance, can cause hyperandrogenism and leading to inappropriate gonadotropin secretion (reduce *follicle-stimulating hormone (FSH)* and increase *luteinizing hormone (LH)* levels) in *PCOS* (3). There is large evidence on a relationship between oxidative stress and metabolic disease (4), an independent correlation between oxidative stress and PCOS has been reported. In particular, oxidative stress has been implicated in mediating the insulin resistance and excessive ovarian androgen levels seen in these patients (5, 6). Such findings have provoked the development of specific therapeutic strategies intended to increase antioxidants levels.

In recent years, several studies have demonstrated the efficacy of antioxidant such as bioflavonoids in reducing PCOS associated hyperinsulinemia and in correcting common endocrine and metabolic dysfunctions found in women with PCOS (7). Among the available compounds, oligopin (a pine bark extract of French maritime pine), a plant extract containing procyanidins (catechin and epicatechin), where it protect tissues from oxidative stress and inflammation related damage due to its strong antioxidant and anti-inflammatory activity (8, 9).

Therefore, the aim of the present study was to assess the efficacy and safety of 3 months oligopin administration on the hormonal and metabolic features of women affected by PCOS.

Methods

Study design

This trial (IRCT.IR identifier) was a 3 months randomized placebo- controlled double blind trial performed at three university hospitals in Tehran, Iran. Patients were included if they were 18 -40 years of age and provided written informed consent. Further, had documented PCOS according to Rotterdam criteria if 2 out of the 3 following conditions were met: a) oligomenorrhea (menstrual cycle>35 days) or amenorrhea, b) clinical and/or biochemical signs of hyperandrogenism c) polycystic ovaries (≥ 12 follicles of 2-9 mm diameter on at least one ovary and/ or *ovarian volume* ≥ 10 mL) on abdominal ultrasound (10). Key exclusion criteria included pregnancy, history of diseases that cause menstrual disturbances (e.g., elevated prolactin and thyroid disease) or use of drugs known to influence metabolism and ovarian function for at least 30 days or more before screening, evidence of diabetes, significant liver and renal impairment, Cushing's syndrome and acromegaly.

Ethics approval was obtained from the Ethics Committee of Endocrinology Metabolism Research Institute, Tehran University of Medical Sciences (REC.1396.00163).

Randomization

Patients were randomized 1:1 according to the method of block randomization and placebo was provided in identical; the recommended intake was oligopin 50 mg/day or placebo, for duration of the study (3 months).

Procedures

The trial was undertaken in the early follicular phase (cycle days 3-7) in regularly menstruating women or random days in oligo/amenorrhea women. The height was measured with a wall mounted centimeters with an approximation of 0.5 cm. Body weight and composition was measured without footwear and

with light clothing using body impedance analyzer (BIA) (Tanita, Japan). The circumferences of waist were measured as value of between the iliac crest and the lateral costal margin. Body mass index (BMI)= weight (kg)/ height (m²) was calculated. The grade of hirsutism was established using the ferryman – gallwey score (11). Acne was evaluated in four grades as described previously (12).

A trans-abdominal ultrasound was performed by one of two well-trained radiologist

a 3 MHz to 5.5 MHz curvilinear probe (acuson s2000, Siemens Medical Solutions, USA). Ovarian volume was calculated for each ovary using the prolate ellipsoid formula: $\pi/6 \times \text{maximum diameter in transverse} \times \text{anteroposterior} \times \text{longitudinal axes}$ (13). The total number of antral follicles (2 - 10 millimeter in diameter) was counted (14).

The blood samples were collected between 8:00 and 9:00 AM after an overnight fast and frozen and stored at 20 °C until analysis. The serum levels of sex hormone binding globulin (SHBG) were assessed using ELISA kits (Demeditec, Germany). The free androgen index (FAI) was calculated (FAI) = testosterone (ng/ml) $\times$ 3.47/SHBG (nmol/L)(15). All remnant hormonal (dehydroepiandrosterone (DHEA), testosterone, FSH, LH, prolactin, C-peptide, insulin and thyroid stimulating hormone (TSH)) assays were performed with ELISA kits (Monobind Inc. Lake Forest, California, USA). Fasting blood glucose levels was measured using the glucose oxidase method on an auto analyzer (Cobas c 311, Roche Dignostics, Risch-Rotkreuz, Switzerland). Hemoglobin A1c (HbA1c) level was determined on a daily basis using a high performance liquid chromatography analyzer (Tosoh, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula. The estimate of insulin resistance was calculated by the Homeostasis Model Assessment (HOMA): $\text{HOMA-IR} = (\text{fasting glucose (mg/dl)}) \times (\text{fasting insulin (}\mu\text{lu/ml)})/405$ (16). Concentration of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), liver function tests (alanine transaminase (ALT), aspartate transaminase (AST) and Alkaline phosphatase (ALP)), kidney function tests (BUN, creatinine (Cr)) and high sensitive- C reactive protein (hs-CRP) were measured by ELISA kit (Roche, Germany).

Statistical analysis

Statistical analysis was carried out with the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) on an intention-to-treat basis. Continuous variables evaluated for normality by Shapiro-Wilk test. Non-normally distributed variables were transformed using appropriate transformation method. Continuous and categorical variables were reported as mean (standard deviation (SD)) and number (%) respectively. Comparison of continuous variables between the oligopin group and placebo group at baseline were assessed using independent-samples t tests. Two-way repeated-measures of ANOVA were used to assess effect of intervention on continuous outcomes. Chi-squared test was used to assess categorical variables at baseline between groups. All statistical tests were two-tailed, P< 0.05 was considered threshold significant level.

Results

The first participant was enrolled on April 18, 2018, and the last patient visit was on May 14, 2019. Of 239 patients assessed for eligibility, 80 were enrolled and randomly assigned to treatment with once- daily 50 mg oligopin (n=40) or placebo(n=40) (figure 1). The treatment schedule was completed by 31(77.5%) participants in the oligopin group and 30(75%) in the placebo group. Baseline characteristics are shown in Table 1. The mean (SD) age was 27.99 $\pm$ (6.28) years, mean disease duration was 6.17 years and the majority were non- smoker (98.8%), and had irregular menses (80%). Hirsutisim degree was different between two group at baseline (p=0.008) (Table1). Other baseline characteristics were similar for 2 treatment groups, with respect to anthropometrics and laboratory data except for Cr, AST, ALP, HDL-C, and hs-CRP levels (Table 2, 3). As safety, no serious oligopin-related adverse events occurred during the study.

Regarding the primary endpoints, changes in androgen levels such as testosterone, SHBG, FAI, DHEA levels from baseline to 3 months didn't differ significantly between the two study groups (p>0.05), except for increase in FSH levels in oligopin group (mean differences 0.62 mIU/mL[95%CI, 0.04 to 1.19]), compared with placebo(mean differences -0.41 mIU/mL[95%CI, -1.13 to -0.33]), p=0.03. Similarity, none of the indicators of metabolic control (fasting blood glucose, HbA1c, insulin levels, lipid profile), hs-CRP levels and anthropometric parameters (BMI, fat free mass (FFM), fat mass (FM), waist circumference) showed significant changes between the oligopin group and placebo after 3 months (Table 3). Changes in ALP at the end of the trial differed between oligopin group (mean differences 4.66 U/L [95%CI, -1.14 to 10.45]), and placebo group (mean differences 25.15 U/L [95%CI, 11.08 to 39.21]), (p=.001). But changes in other transaminases levels (ALT and AST) and kidney function factors (Cr, BUN) and TSH levels were not significantly different between treatment and placebo groups (P>0.05). Parameters related to blood pressure (systolic and diastolic) were also similar in PCOS patients after oligopin treatment.

Discussion

Scientific literature on commercially available pine bark extract (oligopin or pycnogenol) is scare. To the best of our knowledge, this is the first randomized, double-blind, placebo controlled trial of oligopin supplementation performed in women with PCOS. We hypothesis that including oligopin to our subjects would induce benefits, however, with except of change in FSH level, our intervention fail to change levels of androgens and metabolic profile. These results occurred with no unexpected safety finding.

This trial showed that an antioxidant intervention based on oligopin supplementation has no effect on serum androgen levels except for a small increase in FSH level. The changes in FSH levels observed in this trial over the 3 months are difficult to explain, even though the mean FSH increased following oligopin treatment, there was no significant changes in insulin or androgen levels. On the other hand, although the mean FSH levels were lower for women with PCOS compared to those with normal ovaries (17), this small rise in FSH concentrations is not clinically important in patients with PCOS. Whether the FSH raising effect of oligopin is partly due to catechin reminded unclear. It was reported that a significant dose responses relationship was found between catechin supplementation and FSH levels in PCOS rats (18).

Similarity, no differences could be demonstrated in any of metabolic profiles and anthropometrics parameters, blood pressure and hs-CRP levels except for increase in ALP levels in placebo group compared to oligopin. Our finding that oligopin failed to significantly influence cardiovascular disease risk factors (insulin, fasting glucose, lipid profiles and hs-CRP) is an observation that has been recorded previously in overweight and obese adults (19). The meta-analysis by Malekamadi et al. and collaborators, showing several biological effect of this extract such as decreased glycemia and lipid profile, decreased weight and blood pressure and reduced hs-CRP level, was faulted by pooling low quality and high heterogeneity studies (20). Notably, the Meta-analysis of randomized trials indicated that pycnogenol significantly raised AST levels and decreased GGT concentration by 1.53 U/l (20). In the present study we did not observe any significant changes in ALT and AST levels in oligopin group. However, there was an increase of ALP levels in both treatment groups, which to be greater in placebo group compared to oligopin. Overall, based on our results and previous study oligopin did not show toxic effects on liver function (20). The hypoglycemic effects of pine bark extract may be related to inhibition of alpha glycosidase activity in the small intestinal brush border due to procyanidins (flavonoids), independent of effect on insulin secretion (21, 22). We speculated that efficiency of oligopin on glycemia and HbA1c depends on baseline glycemia. We enrolled patients with normal glycemia (glycated hemoglobin levels less than 6% and FBS less than 126 mg/dl).

Pycnogenol (pine bark extract) has been explored as a potential natural antihypertensive agent. Although not consistent, pycnogenol supplementation has been shown to reduce systolic and diastolic blood pressure (23). The effect is mediated via nitric oxide (NO) production (23) or angiotensin converting enzyme (ACE) inhibition (24) and /or reduction of endothelin-1 (25). In our study, blood pressure was reduced after oligopin treatment for 3 months, although the difference was not significant. As most of our study participants displayed well controlled blood pressure levels (97.5% SBP < 140 mmHg, 85% DBS < 90 mmHg) at the baseline, we postulated that oligopin supplementation could exert favorable effects on blood pressure only among hypertensive patients (20, 24, 26). On the other hand, the subgroup analysis in recent meta-analysis indicated that the effect of this extract on blood pressure is more prominent in trials with longer intervention duration (>12 weeks) (23). As a result, a longer period is required to obtain results.

Supplementation with oligopin has been suggested to decrease the levels of CRP and have anti-inflammatory effect (27). However, our data failed to detect any significant change in hs-CRP levels with oligopin administration. We have not measured circulating other inflammatory factors in this study, as results we cannot conclude that oligopin is ineffective on inflammation.

There are a few possible explanations for the apparent lack of a positive finding in our study. First, the dose of oligopin may be inadequate. One study involving the use of oligopin in type 2 diabetes has shown a daily consumption in an amount of 100 mg/d to 200 mg/d is required to achieve a protective effect (28). It is uncertain whether the dose required to achieve androgen reduction is similar, or the response to oligopin may be different in different subjects, we included PCOS women. Moreover, the recent Meta-analysis suggested that a possible benefit for pine bark extract supplementation when add other treatments and no benefit when consume pine bark extracts as a solitary therapy (23).

Furthermore, the impact of oligopin on hormonal and cardiometabolic may be different between the two sexes and sex may be a modifier of the effect of pine bark extract on the cardiometabolic profile, or the link between oligopin and PCOS may be appreciated only in subpopulation of PCOS patients; insulin resistance vs. noninsulin-resistance and also between lean and obese. This can be partially explained by the fact that substantial portion of population in our trial were not insulin resistance (mean HOMA < 3.8) and were relatively lean (overweight in average).

One of our study limitation was high dropout rate; which is relatively high in infertility trials (29).

Conclusion

This study demonstrated for the first time that a nutraceutical intervention based on 3 months 50 mg oligopin (pine bark extract) administration among PCOS women was safe but did not improve androgen or metabolic/ anthropometric parameters.

Declaration

Ethical Approval and Consent to participate: Ethics approval was obtained from the Ethics Committee of Endocrinology Metabolism Research Institute, Tehran University of Medical Sciences (REC.1396.00163). All patients were provided written informed consent.

Consent for publication: Not applicable

Availability of data and materials: Data are available upon reasonable request.

Competing interests: None of the authors have any conflicts of interest or financial ties to disclose.

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Authors' contributions: A.M. Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical revision, M.S. Acquisition of data, M.R.M.T. Critical revision, A.M.G. Critical revision, S.K. Acquisition of data, H.G. Acquisition of data, N.S.H. Critical revision, M.S. Acquisition of data, F.B. Critical revision, M.Q. Analysis and interpretation of data, S.H. Study conception and design

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Tables

Table 1 Baseline characteristics of patients according to study group

	Placebo (n= 40)	Oligopin (n=40)	P value
Age (year)	27.6±6	28.38±6.57	0.58 [‡]
Smoking (yes) n(%)	0	1(2.5)	0.31 [*]
Height(meters)	160.05±5.91	159.72±5.67	0.8 [‡]
Disease duration	4.83±5.69	7.51±7.28	0.07 [‡]
Menes n(%)	8(20)	8(20)	0.99 [*]
Regular	32(80)	32(80)	
irregular			
Hair losses n(%)	22(64.7)	32(80)	0.14 [*]
Hirsutism	17.28±5.54	21±6.58	0.008 [‡]
Acne score	1.5±1.48	1.55±1.39	0.87 [‡]

[‡]Independent samples t-test

^{*}chi- square

Each value represents mean± SD except for smoking n(%), menes n(%), hair losses n(%).

Table 2 hormonal and metabolic parameters at baseline and after 3 months of treatment with oligopin and placebo in the study population.

	Placebo (n= 40)	Oligopin (n=40)	P value
	means(95%CI)	means(95%CI)	
Testosterone (ng/ml)	0.41(0.34 to 0.48)	0.44(0.38 to 0.51)	0.49 [¥]
Baseline	0.41(0.34 to 0.50)	0.46(0.38 to 0.55)	0.84 [*]
12 weeks			
DHEA (ng/dl)	160.02(138.53 to 183.06)	155.07(133.81 to 177.87)	0.75 [¥]
Baseline	131.14(106.91 to 157.65)	151.16(125.19 to 179.56)	0.13 [*]
12 weeks			
SHBG (nmol/l)	44.77(35.16 to 57.02)	33.11(26 to 42.17)	0.08 [¥]
Baseline	40.83(33.8 to 49.2)	31.77(26.3 to 38.28)	0.74 [*]
12 weeks			
FAI	2.98(2.20 to 4.03)	4.33(3.20 to 5.87)	0.08 [¥]
Baseline	3.19(2.47 to 4.11)	4.84(3.75 to 6.24)	0.84 [*]
12 weeks			
LH (mIU/mL)	10.44(7.57 to 14.42)	8.95(6.48 to 12.33)	0.49 [¥]
Baseline	9.88(7.83 to 12.47)	10.66(8.45 to 13.45)	0.34 [*]
12 weeks			
FSH (mIU/mL)	5.76 (5.13 to 6.4)	5.16(4.52 to 5.8)	0.19 [¥]
Baseline	5.35(4.91 to 5.79)	5.79(5.35 to 6.23)	0.03 [*]
12 weeks			
LH/FSH	1.96(1.51 to 2.54)	1.88(1.45 to 2.43)	0.81 [¥]
Baseline	1.9(1.52 to 2.38)	1.91(1.52 to 2.38)	0.8 [*]
12 weeks			
Prolactin (ng/ml)	14.69(12.79 to 16.86)	13.49(11.75 to 15.50)	0.38 [¥]
Baseline	15.27(13.40 to 17.42)	14.38(12.62 to 16.40)	0.73 [*]
12 weeks			
TSH (mIU/mL)	2.28(1.95 to 2.63)	1.98(1.67 to 2.31)	0.2 [¥]
Baseline	2.69(2.34 to 3.1)	2(1.69 to 2.34)	0.15 [*]
12 weeks			
Insulin (µIU/mL)	12.98(11.41 to 14.55)	13(11.43 to 14.57)	0.98 [¥]
Baseline	13.41(11.95 to 14.86)	12.31 (10.85 to 13.76)	0.41
12 weeks			
C-peptide (ng/ml)	1.17(1 to 1.35)	1.32(1.15 to 1.5)	0.21 [¥]
Baseline	1.25(1.12 to 1.38)	1.32(1.19 to 1.46)	0.44 [*]
12 weeks			
Fasting blood sugar (mg/dl)	88.3(85.29 to 91.31)	89.32(86.32 to 92.33)	0.63 [¥]
Baseline	88.62(86.27 to 90.97)	90.486(88.14 to 92.83)	0.69 [*]
12 weeks			
HOMA-IR	2.58(2.22 to 3)	2.63(2.26 to 3.06)	0.87 [¥]
Baseline	2.73(2.42 to 3.1)	2.58 (2.28 to 2.92)	0.55 [*]
12 weeks			
HbA1C	5.24(5.14 to 5.33)	5.29(5.19 to 5.39)	0.41 [¥]
Baseline	4.82(4.6 to 5.05)	4.93(4.7 to 5.16)	0.76 [*]
12 weeks			

Triglyceride (mg/dl)	98.17(86.09 to 112.20)	109.14(95.5 to 124.45)	0.27 [‡]
Baseline	98.17(85.9 to 111.94)	105.20(92.04 to 119.94)	0.56 [*]
12 weeks			
Cholesterol (mg/dl)	168.72(158.24 to 179.20)	177.45(166.97 to 187.93)	0.24 [‡]
Baseline	165.55(155.73 to 175.37)	174(164.18 to 183.82)	0.94 [*]
12 weeks			
HDL-C (mg/dl)	41.57(38.6 to 44.54)	46.27(43.3 to 49.24)	0.03 [‡]
Baseline	42.03(39.35 to 44.7)	46.09(43.41 to 48.75)	0.65 [*]
12 weeks			
LDL-C (mg/dl)	96.38(89.33 to 103.99)	98.85(91.83 to 106.65)	0.62 [‡]
Baseline	95.49(88.92 to 102.32)	98.85(92.26 to 105.92)	0.76 [*]
12 weeks			
AST (U/L)	19.01(17.74 to 20.41)	18.7(17.39 to 20.23)	0.001 [‡]
Baseline	16.18(15.06 to 17.33)	16.14(14.92 to 17.45)	0.77 [*]
12 weeks			
ALT (U/L)	10.52(9.43 to 10.53)	9.61(8.69 to 10.75)	0.24 [‡]
Baseline	10.64(9.26 to 12.5)	8.47(7.57 to 9.61)	0.21 [*]
12 weeks			
ALP (U/L)	122.37(104.77 to 139.97)	149.52(131.93 to 167.12)	0.03 [‡]
Baseline	147.52(129.32 to 165.74)	154.19(135.98 to 172.39)	0.01 [*]
12 weeks			
hs-CRP (mg/L)	1.03(0.72 to 1.47)	1.61(1.12 to 2.3)	0.08 [‡]
Baseline	1.32(0.92 to 1.89)	1.77(1.24 to 2.54)	0.38 [*]
12 weeks			
Urea (mg/dl)	22.37(20.48 to 24.27)	22.97(21.08 to 24.86)	0.65 [‡]
Baseline	23.35(21.25 to 25.43)	23.57(21.48 to 25.66)	0.75 [*]
12 weeks			
Creatinine (mg/dl)	0.78(0.75 to 0.82)	0.86 (0.82 to 0.89)	0.004 [‡]
Baseline	0.8(0.77 to 0.84)	0.87(0.83 to 0.91)	0.63 [*]
12 weeks			

[‡]Independent samples t-test

^{*} Time to treatment interaction according to two-way repeated measure ANOVA

Comparisons were adjusted for baseline value of outcome being analyzed. Data are not conforming to a normal distribution were log or square root or inverse transformed.

DHEA *Dehydroepiandrosterone*, SHBG *Sex hormone-binding globulin*, AFI *Free androgen index*, LH *Luteinizing hormone*, FSH *Follicle-stimulating hormone*, TSH *Thyroid stimulating hormone*, HOMA-IR *Homeostasis model assessment insulin resistance*, HbA1c *HemoglobinA1c*, HDL-C *High-density lipoprotein cholesterol*, LDL-C *Low-density lipoprotein cholesterol*, AST *aspartate aminotransferase*, ALT *alanine aminotransferase*, ALP *hs-CRP High-SensitivityC-Reactive Protein*.

Table 3 Anthropometrics, blood pressure and physical activity at baseline and after 3 months of treatment with oligopin and placebo in the study population.

	Placebo (n=40)	Oligopin (n=40)	P value
	means(95%CI)	means(95%CI)	
Body mass index (kg/m ²)	26.3(24.55 to 27.54)	27.54(25.7 to 29.51)	0.2 [‡]
Baseline	26.3(24.54 to 28.18)	28.18(26.66 to 30.06)	0.5 [*]
12 weeks			
Fat mass(kg)	22.85(20.09 to 26)	27.41(24.10 to 31.19)	0.05 [‡]
Baseline	23.5(20.84 to 26.48)	28.38(25.18 to 31.99)	0.87 [*]
12 weeks			
Fat free mass (kg)	43.35(41.97 to 44.67)	42.36(41.02 to 43.65)	0.29 [‡]
Baseline	43.35(42.17 to 44.46)	43.05(41.88 to 44.15)	0.14 [*]
12 weeks			
Waist circumference(cm)	91.62(87.7 to 95.94)	93.32(89.12 to 97.5)	0.6 [‡]
Baseline	92.47(88.71 to 96.38)	93.32(89.53 to 97.27)	0.59 [*]
12 weeks			
Systolic blood pressure (mmHg)	111.15(106.34 to 115.96)	104.3(99.54 to 109.05)	0.05 [‡]
Baseline	107.36(102.56 to 112.16)	101.83(97.09 to 106.57)	0.67 [*]
12 weeks			
Diastolic blood pressure (mmHg)	76.28(72.54 to 80.02)	73.25(69 to 76.95)	0.25 [‡]
Baseline	73.99(70.44 to 77.54)	69.46(65.95 to 72.96)	0.49 [*]
12 weeks			
Physical activity (METs/h)	29.62(28.38 to 30.87)	29.03(27.8 to 30.26)	0.5 [‡]
Baseline	30.59(29.38 to 31.8)	29.34(28.15 to 30.54)	0.48 [*]
12 weeks			

[‡]Independent samples t-test

^{*} Time to treatment interaction according to two-way repeated measure ANOVA

Comparisons were adjusted for baseline value of outcome being analyzed. Data are not conforming to a normal distribution were log and square root transformed.

Figures

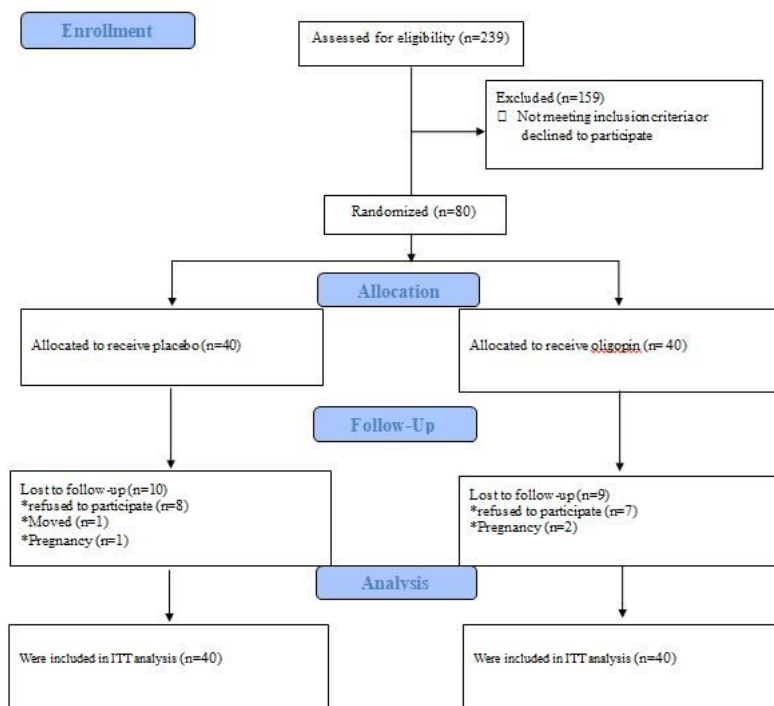


Figure 1

trial profile