ABSTRACT

Background: Depot medroxyprogesterone acetate (DMPA) is a progestogen derivative synthesized in the laboratory. This substance has the ability to suppress ovulation, induce endometrial shrinkage, and even affect the hypothalamic-pituitary-gonadal axis in the reproductive system. Objective: The purpose of this study was to investigate the effects of administration of green tea extract on reducing visceral fat, increasing leptin levels, and improving the lipid profile in female rats injected with depot medroxyprogesterone acetate (DMPA). Results: This study was to look into the effects of green tea extract administration on visceral fat reduction, leptin levels, and lipid profile improvement as a result of DMPA administration. Analysis of HDL and LDL levels was performed by spectrophotometry. DMPA induced a significant increase in HDL levels when compared to the control group (p < 0.05). The first dose of green tea extract can achieve HDL levels comparable to the control group (p > 0.05). All doses of green tea extract can reduce this increase, with the highest doses reaching levels comparable to the control group (p > 0.05). DMPA significantly increased LDL levels compared to the control group (p < 0.05), and the highest green tea extract dose restored levels similar to the control group. DMPA triggered a decrease in HDL levels that was significantly different from the control group (p < 0.05). The first dose of green tea extract can achieve LDL levels comparable to the control group (p > 0.05). Conclusion: It was concluded that green tea extract can protect the metabolic status through decreased leptin and an improvement of the lipid profile induced by DMPA.

Keywords: contraception, tea, lipid metabolism, catechin, weight.

1. BACKGROUND

Depot medroxyprogesterone acetate (DMPA) is a progestogen derivative synthesized in the laboratory. This substance has the ability to suppress ovulation, induce endometrial shrinkage, and even affect the hypothalamic-pituitary-gonadal axis in the reproductive system. Other consequences include suppression of the reproductive cycle, binding to androgenic receptors and glucocorticoids, insulin resistance, and deterioration of cardiometabolic indices (1-5). Weight gain is the most common reason for DMPA users to stop using contraception (6).

Body fat is classified into two types: adipose visceral tissue and subcutaneous adipose tissue. As a risk factor for cardiovascular disease, adipose visceral tissue has a tight association with metabolic disorders (7, 8). Previous research has shown that DMPA users gained weight and gained body fat [9, 10]. However, the mechanism of weight gain is unknown; it is thought to be owing to an appetite effect, glucocorticoid-like action (11, 12), or an increase in resting metabolic rate (13).

Leptin is a 16kDa protein that is mostly generated by white adipose tissue. Breast epithelial tissue and the placenta also produce leptin (14, 15). Leptin has pleiotrophic activities in energy balance, endocrinology, metabolism, reproduction, immunology, and fat oxidation (14, 16). Leptin’s physiological activities include decreased hunger, higher energy storage, glucose utilization control, and better insulin sensitivity (17). Under typical eating cycle conditions, leptin concentration indicates the quality of adipose tissue; increased leptin concentration corresponds to greater adiposity. Women have
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higher leptin levels than men. Women have an increased leptin level during birth (18, 19). Previous study found that DMPA did not increase leptin levels in rats (20). The basal leptin level did not correspond with weight increase in women who received DMPA for 6 months (21). Interestingly, one DMPA-injected woman was found to have lipodystrophy, which is a sign of leptin deficit and should be treated with leptin (22).

Green tea is a popular beverage in Asian countries and is extensively enjoyed around the world. The scientific community is interested in this drink because of its health benefits. Green tea, unlike black and Oolong tea, is not fermented to ensure the presence of polyphenols as active chemicals that are helpful to health. Catechins are polyphenols found in green tea that include epigallocatechin gallate, epicatechin gallate, and gallo catechin gallate. Many research have shown that green tea works as an antiobesity agent, lowering body weight and fat. Fat oxidation stimulation, adipogenesis regulation, decreased fat production, and inhibition of digestive enzymes and nutrition absorption are examples of such mechanisms (23-33). Until far, no study has been conducted to assess the effects of green tea in lowering visceral fat, increasing leptin levels, and improving lipid profiles as a result of DMPA treatment.

2. OBJECTIVE
The purpose of this study was to look into the effects of green tea extract administration on visceral fat reduction, leptin levels, and lipid profile improvement as a result of DMPA administration.

3. MATERIAL AND METHODS

Animals
Thirty female rats (Rattus norvegicus), aged 1-2 months, 130-200 gram weight, were divided into five research groups (n = 6 per group), consisting of control group (without treatment), the group receiving a DMPA injection, and a group receiving DMPA injections and administration of various green tea extract doses (10.8 mg/day, 21.6 mg/day, and 43.2 mg/day).

Before the experiment began, rats were acclimatized in cages in the laboratory. Acclimatization was done in 7 days. Rats were given food and drink on an ad libitum basis. The food provided is pellets (Comfeed’s pellets, Japfa Comfeed Indonesia Tbk, Jakarta, Indonesia). Rats are kept in plastic cages with rice husks. Chaff is replaced every two days. Maintenance is set in a 12 hour temperature and dark light cycle.

Administration of DMPA
DMPA dose administered was determined by human dose conversion, that is 150 mg. Of this dose, it was obtained the dose for this research of 2.7 mg/week administered in four weeks [34]. DMPA was administered intramuscularly to the quadriceps muscle.

Green tea extract preparation
Dry tea leaf extraction was obtained from Wonosari tea plantation, Lawang, East Java, and processed by maceration method with 96% ethanol solvent in Biochemistry Laboratory of Polinema Malang, East Java, Indonesia.

Measurement of visceral fat weight
Visceral fat weight was known after the animals were executed at the end of treatment. Abdominal part was incised to open the abdominal skin. The intraperitoneal fat in the abdominal cavity around the digestive tract and fats surrounds the kidney were removed. Fats were weighed by using an Ohaus scale with sensitivity up to 0.0001 and the results were recorded.

Analysis of HDL and LDL levels
Analysis of HDL and LDL levels was made in serum using EnzyChrom HDL and LDL/VLDL Assay Kit. The analysis was done according to the detailed instructions available in the kit.

Statistical analysis
Data were presented in mean ± standard deviation and analyzed by ANOVA test. Statistical analysis used
4. RESULTS

The DMPA group had a considerable increase in leptin levels when compared to the control group. This shows that DMPA treatment increased leptin synthesis in a variety of leptin-producing cells, including white adipose (14, 15). This result supports recent findings that leptin levels increased considerably in women who used DMPA for a year (41). We assumed that this rise was attributable to enhanced synthesis, even if the number of cells does not grow as a result of adipose cell hypertrophy (42–44), despite the fact that there was no significant increase in the quantity of visceral fat in this study.

In this study, the administration of the second and third dosages of green tea extract reduced leptin levels to normal levels. This suggests that green tea can prevent leptin increases caused by DMPA treatment. According to the findings of a meta-analysis, green tea cannot reduce leptin levels in the circulation when administered for less than 12 weeks (45). This study sheds fresh light on the lowering of leptin levels caused by pharmacological side effects such as contraception. Another investigation found quercetin to interact with leptin genes, limiting leptin synthesis (46).

SPSS for Windows version 14.0 statistical package. The p value < 0.05 was statistically significant.

5. DISCUSSION

There was no significant difference in visceral fat between the groups in this study. This suggests that administering DMPA with or without green tea extract has no effect on the development of visceral fat. This findings supports earlier rat investigations that found that DMPA administration did not cause significant changes in visceral fat levels when compared to the control group (20). Weight gain was observed in post-partum women who were considered fat prior to the pregnancy in a trial of human subjects using DMPA contraceptive medication (37). The glucocorticoid-like effect was responsible for the weight gain (39). We anticipate that the non-significant visceral fat development in our study is related to progestin and glucocorticoid receptors in female adipose cells. The progestin-glucocorticoid receptor interaction will be antagonistic (40).

| Figure 3. The LDL level in the control group and the experimental groups. Note: DMPA: depo medroxyprogesterone acetate; DMPA + T1: DMPA group treated with green tea extract of the first dose; DMPA + T2: DMPA group treated with green tea extract of the second dose; DMPA + T3: DMPA group treated with green tea extract of the third dose. a: The p value <0.05 is compared with the control group; b: p value <0.05 compared with the DMPA group; c: p value <0.05 compared with the DMPA group treated with green tea extract of the first dose; d: p value <0.05 compared with the DMPA group treated with green tea extract of the second dose; DMPA: depo medroxyprogesterone acetate; DMPA + T1: DMPA group treated with green tea extract of the first dose; DMPA + T2: DMPA group treated with green tea extract of the second dose; DMPA + T3: DMPA group treated with green tea extract of the third dose. |
| Figure 4. The HDL level in the control group and the experimental groups. Note: DMPA: depo medroxyprogesterone acetate; DMPA + T1: DMPA group treated with green tea extract of the first dose; DMPA + T2: DMPA group treated with green tea extract of the second dose; DMPA + T3: DMPA group treated with green tea extract of the third dose. a: The p value <0.05 is compared with the control group; b: p value <0.05 compared with the DMPA group; c: p value <0.05 compared with the DMPA group treated with green tea extract of the first dose; d: p value <0.05 compared with the DMPA group treated with green tea extract of the second dose; DMPA: depo medroxyprogesterone acetate; DMPA + T1: DMPA group treated with green tea extract of the first dose; DMPA + T2: DMPA group treated with green tea extract of the second dose; DMPA + T3: DMPA group treated with green tea extract of the third dose. |
Regarding the lipid profile, this study found that DMPA administration increased LDL levels while dramatically decreasing HDL levels when compared to the control group. These findings are consistent with prior research that reported lower HDL and higher LDL as a result of DMPA use (47, 48), but contradict another study (49). Increased LDL levels were induced by increased leptin levels, which resulted in reduced expression of the LDL receptor and LDL uptake (50). As a result of DMPA administration, green tea extract can considerably lower LDL levels while increasing HDL levels. This implies that green tea extract can mitigate the effects of DMPA treatment on lipid profiles. This work adds to recent findings that catechin and epigallocatechin gallate can lower LDL and raise HDL levels (51, 52). This improvement is at least partially due to decreased fat absorption, antioxidant effects, anti-inflammatory effects, decreased fatty acid production, and increased fatty acid oxidation (53).

6. CONCLUSION

It is concluded that green tea extract can protect metabolic status by decreasing leptin and improving lipid profile as a result of DMPA. Green tea can thus regulate leptin and improve lipid profiles, making it an alternate ingredient capable of inhibiting cardiovascular negative effects in women who use contraceptives.

List of abbreviations

- %: percentage
- ANOVA : analysis of variance
- DMPA : depot medroxyprogesterone acetate
- HDL : high density lipoprotein
- kDa : kilo Dalton
- LDL : low density lipoprotein
- mg : milligram
- mg/day : milligram/day
- SPSS : statistical package for social science
- VLDL : very low density lipoprotein

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