Correlation between body mass index and leptin level on *depo medroxy progesterone acetate* (DMPA) hormonal contraceptive users

T.E. MAYNIAR, D. LUTAN, M.F. GANIS SIREGAR, S.N. LUMBANRAJA, I. HELMI EFFENDI, C. ADEYA ADELLA

**Summary:** Correlation between body mass index and leptin level on *depo medroxy progesterone acetate* (DMPA) hormonal contraceptive users.

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**Background.** Indonesia is the fourth most populated country in the world with a high rate of population growth and maternal mortality. To resolve this matter, Indonesian government implement the “Keluarga Berencana” program. According to BKKBN in 2007, 55.5% women are using injection contraceptive and the majority has an elevated BMI. Elevated BMI is associated with the increased number of adipose cell in the body thus influencing the leptin level.

**Objective.** To determine the correlation between Body Mass Index (BMI) and leptin level on Depo Medroxy Progesterone Acetate hormonal contraceptive users.

**Methods.** This research method applied in this study is cross sectional. The study is conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Sumatera Utara, H. Adam Malik General Hospital and Puskesmas Helvetia on August 2017 by consecutive sampling. After participants agree with the informed consent, BMI was measured and 3 cc of blood was drawn from median cubiti vein at 07.00-08.00 during fasting. Data were analyzed using Spearman correlation test with p value < 0.05.

**Results.** Out of 95 participants, 42 participants (44.2%) have age interval between 30-39 years old and 79 participants (83.2%) have leptin level > 5. Most of DMPA hormonal contraceptive users were overweight at month 0 and 12, in which 42 participants (44.2%) and 33 participants (34.7%) at month 24, 46 participants (48.4%) have obesity grade I.

**Conclusion.** There is a strong and significant correlation between body mass index and leptin level on DMPA hormonal contraceptive users ($r= 0.70, p= 0.0001$).

**Key Words:** Depo Medroxy Progesterone Acetate - Body mass index - Leptin level.

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**Introduction**

Indonesia is the fourth most populous country in the world and the rate of growth is still high. Indonesia’s population growth rate of 2000-2010 is 1.49% per year. Based on Indonesia Demographic and Health Survey 2012, maternal mortality rate in Indonesia is still high at 359 per 100,000 live births. The 3rd Global Target of SDGs (Sustainable Development Goals) is to reduce the Maternal Mortality Rate (MMR) to 70 per 100,000 live births by 2030. The MMR in Indonesia is still relatively higher compared to other ASEAN member countries. The risk of maternal mortality due to childbirth in Indonesia is 1:65 births (1-4).

To overcome this problem, a strategic intervention in the form of a pillar of Safe Motherhood effort is needed, and one of the efforts to enforce the pillar of safe motherhood is to implement Keluarga Berencana (KB) program. One of the contraceptive methods used in Keluarga Berencana (KB) programs is the injectable hormonal contraceptive method. Injectable contraception (combination or progesterone only) is a safe and effective contraceptive and is reversible, does not require daily, simple, cheap, and acceptable use by many people. Injectable contra-
ceptives consist of 2 types of combined hormonal injectable contraceptives (consisting of medroxyprogesterone and estradiol cypionate) and progesterone injections (consisting of Depo Medroxy Progesterone Acetate (DMPA) or Norethisterone Enantate (NET-EN)) (5, 6).

DMPA represents a microcrystalline suspension of synthetic progestin, injected intramuscularly every 3 months for contraception. DMPA is a 17α hydroxyprogesterone derivative. DMPA is a potent inhibitor of gonadotropin by a progestin effect. The function of progestin is to inhibit LH spikes (LH-surge) to prevent ovulation. Progestin levels in the circulation is high enough to inhibit the occurrence of LH spikes that play a role during ovulation so that LH in the circulation will be reduced consequently will inhibit the occurrence of fertilization (6-9).

The injection of DMPA has several side effects. An increase in body mass index is a side effect of hormonal contraceptive use. Many studies have shown a significant increase in body mass index against the use of progestin hormonal contraceptives. DMPA has an increased effect of body fat composition compared to non-hormonal contraception after 6 months of use. Other studies were similar in that there was an increase in body mass index after the use of DMPA in one, two, and three years of use compared to the IUD group (Intra Uterine Device) (10).

DMPA can bind to glucocorticoid receptors. High-dose DMPA is associated with glucocorticoid-like which affects the body’s fat composition (including visceral fat). DMPA alters the neurohormonal regulation of appetite. Based on studies there is an increase in leptin that is directly related to increased appetite. In the study of Batista et al., an increase in body mass index (3.01 kg) and a significant BMI after the use of DMPA for 12 months (11, 12).

Based on the results of the study, there are several mechanisms that allegedly play a role in causing increased body mass index on DMPA acceptor. First, DMPA has a glucocorticoid-like activity, which is associated with increased fat including visceral fat. Second, the hypoestrogenism state induced by DMPA injections leads to increased visceral and subcutaneous fat visible from increased waist circumference. Third, DMPA alters the neurohormonal regulation of appetite (13-20).

Methods

This was an observational analytic study with cross sectional design to find out the correlation between body mass index and leptin level in hormonal contraceptive users of Depo Medroxy Progesterone Acetate (DMPA). This research was conducted at the Department of Obstetrics and Gynecology Faculty of Medicine University of North Sumatra-Haji Adam Malik General Hospital, while the data was taken from Helvetia Community Health Centre in August 2017.

The samples in this study were 95 hormonal contraceptive acceptors of Depo Medroxy Progesterone Acetate (DMPA) that met the inclusion criteria of the study and were selected by non-random selection method by consecutive sampling technique.

Results

The frequency distribution of DMPA users by age can be seen in Table 1.

Of the 95 subjects who used DMPA, age characteristics were divided into 3 age groups. The largest frequency of DMPA users in the age group of 30-39 years (44.2%), age group of 29-30 years (30.5%), and age group of ≥40 years (25.3%).

The frequency distribution of leptin content based on age characteristics can be seen in Table 2.

The mean leptin level in women in the age group of 20-29 years was 10.03, age group 30-39 years was 11.92, and the age group was ≥40 years was 13.35 (Table 3).

At 0 months (before DMPA), body mass index of

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pengguna DMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>20-29 years</td>
<td>29</td>
</tr>
<tr>
<td>30-39 years</td>
<td>42</td>
</tr>
<tr>
<td>≥ 40 years</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
</tr>
</tbody>
</table>
study subjects showed weight category less and obesity II not found, normal category was 39 people (41.1%), obesity risk 42 person (44.2%), and the obese I as many as 14 people (14.7%). At 12 months after DMPA, body mass index of obese research subjects I increased to 31 people (32.6%). while that have normal IMT kateogi as many as 31 people (32.6%) and obesity risk as much as 33 people (34.7%). At 24 months after DMPA, the number of obese subjects increased again to 46 (48.4%), while the normal BMI category was 17 (17.9%) and the risk of obesity was 32 (33.7%).

Table 4 shows that the frequency of subjects with leptin > 5 (increased) was 79 people (83.2%), while the frequency of subjects with leptin ≤5 (normal) was 16 (16.8%).

Table 5 shows that DMPA acceptors with normal BMI have most leptin ≤ 5 counts of 15 people (88.2%), whereas with leptin > 5 levels of 2 people (11.8%). DMPA acceptors with the highest risk of obesity have leptin > 5 levels of 31 people (95.9%), while with ≤ 5 counts of 1 person (3.1%). All DMPA acceptors with obesity I BMI have leptin > 5 levels of 46 (100%).

From this research found a significant relationship with the value p = 0.0001 which the value is smaller than 0.05. Thus, it can be concluded that there is a significant relationship between body mass index with leptin levels.

**Table 2 - Frequency Distribution of Leptin Levels Based on Age Group.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age Group</th>
<th>20-29 years</th>
<th>30-39 years</th>
<th>≥ 40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Leptin Level</td>
<td></td>
<td>10.03</td>
<td>11.92</td>
<td>13.35</td>
</tr>
</tbody>
</table>

**Table 3 - Distribution of Body Mass Index Based on Duration of DMPA Usage.**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Duration of DMPA Usage</th>
<th>0 month</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Underweight</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normoweight</td>
<td>39</td>
<td>41.1</td>
<td>31</td>
<td>32.6</td>
</tr>
<tr>
<td>Overweight</td>
<td>42</td>
<td>44.2</td>
<td>33</td>
<td>34.7</td>
</tr>
<tr>
<td>Obesity grade I</td>
<td>14</td>
<td>14.7</td>
<td>31</td>
<td>32.6</td>
</tr>
<tr>
<td>Obesity grade II</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>100.0</td>
<td>95</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table 4 - The Frequency Distribution of DMPA Users Is Based on Leptin Levels.**

<table>
<thead>
<tr>
<th>Leptin Level</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 (normal)</td>
<td>16</td>
<td>16.8</td>
</tr>
<tr>
<td>&gt; 5 (increased)</td>
<td>79</td>
<td>83.2</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table 5 - Relationship of Body Mass Index to Leptin Level.**

<table>
<thead>
<tr>
<th>IMT</th>
<th>Leptin Level</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 5</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Normoweight</td>
<td>15 (88.2%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1 (3.1%)</td>
<td>31 (95.9%)</td>
</tr>
<tr>
<td>Obesity grade I</td>
<td>0 (0%)</td>
<td>46 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (16.8%)</td>
<td>79 (83.2%)</td>
</tr>
</tbody>
</table>
Discussion

Age is one of the factors that influence a person’s behavior including contraceptive use, the elderly have less chance of using contraception than the young. The statements are in accordance with the results of this study, where obtained DMPA users most often found in the age group 30-39 years as much as 44.2% (Table 1). But increasing age is not a major reason for using contraception, because the number of children is also one of the considerations of permitting for using contraceptives.

Age plays an intrinsic factor in relation to family planning. Age is related to organ structure, physiological function, biochemical composition including female hormonal system. The period of reproduction (fertility) is the basis in the pattern of rational contraceptive usage divided into 3, namely: the period of delaying pregnancy (fertility), the period of regulating fertility (increment), the period of ending fertility (not pregnant again) (21).

Based on the results of the BKKBN (2013) survey, younger women (aged 15-19 years) and older (aged 45-49 years) were fewer using contraceptives than women of middle age (20-44 years of age). In older women (aged 30-44), in addition to FP injections, the use of pills and long-term contraceptive methods such as IUDs, implants and sterilization of women is higher than in younger women (5). This is similar to the results of this study DMPA users in the fertile age group.

Based on the results of research Pratiwi shows that the most widely accepted DMPA injection acceptor is acceptors with age 41 - 45 years, as many as 9 acceptors (22.5%). But these results are not much different than other age groups. Infertile couples use contraceptives to adjust the number of children and the desired birth spacing (19).

The results of Lange et al’s study of mean age of DMPA users in adolescents were 16.2 ± 1.5 years (fertile age) with an increase in BMI of 23.7 ± 5.3 to 25.3 ± 5.7 within 12 month (22).

The results of this study of 95 subjects of DMPA-treated DMPA had leptin > 5 (increased) of 79 people (83.2%), whereas with leptin ≤5 (normal) level of 16 people (16.8%) (Table 2).

Leptin is a hormone produced by adipocyte cells that have the function of inhibiting feeding and enhancing thermogenesis. The function of leptin is regulated by the hypothalamus via a feedback mechanism through: the sensory signal is regulated from the adipose tissue mass, the hypothalamus as the sensory receiving center and integrating the leptin signal via the leptin receptor (LRb), the effector pathway includes the sympathetic system that regulates the energy balance and energy expenditure. Leptin has functions such as fertility through the Hypothalamic-Pituitary-Gonadal-Axis system through the control of gonadotropin releasing hormone (GnRH) and contributes to energy regulation and body mass index via neuroendocrine mechanism (23-26).

The factor that regulates leptin production is adiposity. Leptin levels are higher in women than men because the effects of estrogen are known to promote leptin and androgen synthesis. In DMPA users, the MPA binds to glucocorticoid receptors and has glucocorticoid-like properties that affect the composition of body fat (including visceral fat), altering neuroendocrine regulation of appetite. The effect of glucocorticoids on appetite and high energy intake may contribute to an increase in body mass index. Glucocorticoids primarily stimulate the intake of proteins and carbohydrates in humans. Glucocorticoid is an important hormone that not only gives catabolic peripheral tissue but also plays a role in the synthesis and release of neuropeptides in the hypothalamus, thus affecting food intake and central nervous system. The hormone acts on the hypothalamic neuropeptide aims to regulate food intake and assist peripheral metabolism through the efferent nerves of the autonomic nervous system. A slight increase in glucocorticoid production and excessive cortisol response in obese people results from hyper-responsiveness of HPA-axis or reduced HPA-axis sensitivity to negative feedback. It can also be accompanied by peripheral tissues that become more sensitive to glucocorticoids (14, 15).

In obesity high levels of plasma leptin are associated with the amount of adipose tissue but without the appropriate response (e.g. appetite suppression). There is a defect in the leptin receptor at the central nervous system appetite. In obese patients leads to leptin resistance whereas when energy deficits leptin levels in plasma decreases where fat storage decreases.

Based on research Chow and Phoon leptin content difference in women normoweight and underweight significant (p = 0.001) with value r = 0.44. Similar to research Monti et al. about leptin and ghrelin levels and their association with BMI. Leptin levels were significantly associated with BMI (r = 0.72, p = 0.001) and waist circumference (r = 0.71, p
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hormonal contraceptive users

= 0.0001) while ghrelin had protective factors for increased BMI and waist circumference (23-26).

Based on the results of this study, at 0 months before the DMPA body mass index of research subjects most often found in the category of obesity risk in months 0 and 12 consecutive as many as 42 people (44.2%) and 33 people (34.7%), while in the 24th month after DMPA, the most common body mass index was obesity I of 46 people (48.4%) (Table 3).

The cause of weight gain in DMPA users occurs because the hormone progesterone facilitate the changes of carbohydrates and sugar to fat, so the fat under the skin increases. The hormone progesterone causes increased appetite and decreased physical activity, consequently the use of injections may cause weight to increase (27). Generally the increase in body mass index in DMPA is influenced by several factors, namely: fluid retention, muscle mass and fat deposition. Initially research on the relationship of increased body mass index and DMPA explains the mechanism of occurrence through changes in the amount of compartment fluid (total, intravascular, extravascular), creatinine excretion rate, or nitrogen metabolism. A major factor in increasing body mass index in DMPA use is a significant increase in body fat deposits, contributing to metabolic and vascular disorders. Central fat deposits are a component of the metabolic syndrome and develop directly into insulin resistance. Research on the follow-up of DMPA for 30 months by Clark and Cols showed an increase in body mass index averaging 6.1 kg, followed by increased body fat levels (11, 12, 28).

Based on the results of Veisi and Zangeneh research, states that the main side effect of DMPA is an increase in body mass index by 48% within 6 months (29). According to the results of Lange et al. study, states that the average IMT increased by 23.7 ± 5.3 - 25.3 ± 5.7 in 12 months with a caloric intake of 1781.4 ± 554.1 kilo calories / day.22. Similarly, Bonny et al. results show that there was an initial increase in body mass index of 20 patients with IMT growth was 23.4, 23.3, 24.2 at months 0, 6 and 12, respectively (30).

Based on Tables 4 and 5, most of the DMPA acceptors with normal BMI had leptin ≤ 5 levels of 15 (88.2%), whereas DMPA acceptors with the overweight and obese grade I had the highest leptin > 5 levels in 31 consecutive (95.9%) and 46 people (100%). From this research found a significant relationship with the value p = 0.0001 which means there is a relationship between body mass index with leptin levels.

The results of this study are similar to the results of Mpalaris et al. study which showed a strong correlation between leptin levels with BMI with r = 0.73, p <0.001) (29). In Masoud & Adel’s study comparing leptin levels in obese and non-obese women, that there were significant differences (p = 0.001) serum leptin levels in obese group (34.78 ± 13.96 ng/ml) and non obese group (10.6 ± 4.2 ng/ml). A strong and significant correlation was found between leptin and IMT levels (r = 0.51, p = 0.001) (31). Similarly, the Costance et al. study showed that there was a strong correlation between BMI and leptin with r = 0.68, the higher the sample IMT the higher the leptin level. High levels of leptin indicate the presence of signals from the adipocytes to the brain that there is room to store more fat in the body. Increased levels and expression of leptin occur along with an increase in triglyceride deposits in adipose tissue (32).

Conclusion

1. Most of the research subjects were age group 30-39 years old.
2. The highest mean leptin levels were found in the ≥40 year age group of 13,35.
3. Most of the study subjects had BMI index of obesity risk at months 0 and 12, whereas at month 24, most subjects had obesity BMI index I.
4. Most of the study subjects had obesity I BMI with leptin> 5 levels.
5. There was a significant relationship with p = 0.0001 between body mass index and leptin level. Given the diverse role of leptin in life especially its relationship with reproduction, it is hoped that further research will compare other variables in women with DMPA.

References