

CORRELATION BETWEEN SERUM LEPTIN LEVELS WITH ONSET OF MENARCHE

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ABSTRACT

Background: One of important factor that influences the earlier onset of menarche in children is higher leptin levels. The higher the level of leptin, the earlier onset of menarche. Early onset of menarche has a negative effect in the form of a faster cessation of height due to closure of the epiphyse plate causing a low height and is believed to be a future risk for ovarian and breast cancer. Obesity that occurs during childhood is associated with the risk of long-term health problems including hypertension, diabetes mellitus, infertility, dyslipidemia and psychosocial problems.

Objective: Analyze the correlation between serum leptin levels with onset at menarche.

Methods: This research is an observational descriptive study with a case series design where the *case* is a student aged 10-14 years who has experienced menarche at the Gusti Wijaya School in Medan, North Sumatra, Indonesia. Data is collected from December 2019 until the sample is fulfilled. This study uses a sample of 30 people by simple random sampling. Subjects were measured in body mass index (BMI) and pelvic waist circumference ratio (WHR). Serum leptin levels were examined by conducting laboratory tests on venous blood using the ELISA (Enzyme Linked Immunosorbent Assay) method. Then data is collected and analyzed using statistical analysis.

Results: In this study a negative correlation was obtained between serum leptin levels and age of menarche ($p = 0.0001$; $r = -0.962$). There is a correlation between serum leptin levels with BMI ($p = 0.0001$; $r = 0.876$). There is a correlation between serum leptin levels with WHR ($p = 0.002$; $r = 0.542$).

Conclusion: The higher the level of serum leptin, the lower the onset of menarche, with a very strong correlation. There is a correlation between serum leptin levels with BMI and WHR.

Keywords: Serum Leptin, Menarche, BMI, WHR.

Introduction

Adolescence is a period where there will be considerable changes in physical and psychological aspects in a woman's life. The most obvious change experienced by a young woman is getting her period. Menstrual cycle is a process that involves complex interactions on the hypothalamus-pituitary-ovarian axis and will be affected by physiological and pathological changes that occur in every lifetime. Menarche is the first menstrual period in a woman. The age of a woman's menarche can be influenced by health, genetic, socioeconomic and nutritional status.¹⁻⁷ Generally, menarche will occur at the age of 12-13 years.^{1,6-9} The age range of menarche will vary between countries and is generally found at an older age in developing countries. From a study conducted in Jakarta in 2002, the average age of menarche was 12.3 years which was not much different from that obtained by the *National Health and Nutrition Survey* (NHANES) at the age of 12.2 years.^{10,11}

Nutrition, weight and body fat composition have an important role in the occurrence of the menarche process. Therefore, the acceleration of growth and maturity of reproductive function will be influenced by metabolic factors that play a role in regulating the size and composition of body fat. Two large studies indicate that the magnitude of the Body Mass Index (BMI) is associated with earlier menarche.^{1,6,9,12} The exact mechanism for this relationship is not yet fully known. Most researchers agree that the average age of menarche in modern society tends to decrease.^{1,13,14}

The current condition of obesity is associated with leptin levels. Leptin is a hormone secreted by adipose and works on specific receptors in the central nervous system (CNS), especially the hypothalamus and multiple neuropeptide pathways that will provide information to the brain about the availability of body energy reserves in the form of fat. Leptin will regulate body fat content by controlling food intake and temperature regulation (thermogenesis). Several studies in humans have shown that there is a strong positive relationship between serum leptin levels and body fat percentage.¹⁵

One important factor that influences the earlier age of menarche in obese children is higher leptin levels. The higher the level of leptin, the earlier the age of menarche. Early onset of menarche has a negative effect in the form of faster cessation of height due to closure of the epiphyse plate causing a low height and is believed to be a future risk for ovarian and breast cancer. Obesity that occurs during childhood is associated with the risk of long-term health problems including hypertension, diabetes mellitus, infertility, dyslipidemia and psychosocial problems.^{11,15,16}

Method

This study has measured serum leptin levels with the *Quantikine Human Leptin Immunoassay* (ELISA) technique of 30 research subjects conducted in December 2019. The study sample was part of the study population that met the inclusion and exclusion criteria taken by *simple random sampling*.

Results

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Table 1. Characteristics of the sample in the study

Characteristic	N	(%)	Mean ± SD
Age of menarche (months)			142.9 ± 13.1
120 – 131	7	23.3	
132 – 143	8	26.7	
144 – 155	11	36.7	
156 – 167	3	10.0	
168 – 179	1	3.3	
BMI (CDC 2000)			78.7 ± 24.2
Underweight(< percentile 5)	1	3.3	
Normal(percentile 5- < 85)	12	40.0	
Overweight(percentile ≥85-<95)	8	26.7	
Obesity(≥ percentile 95)	9	30.0	
WHR			0.76 ± 0.06
Normal(<0,8)	27	90.0	
Obesity(≥0,8)	3	10.0	
Leptin Serum levels (ng/mL)			13.1 ± 3.9
Total	30	100.0	

Table 1 shows the characteristics of the research subjects. Menarche were found in the study subjects at the age group of 144-155 months, with the mean age of menarche being 142.9 ± 13.1 months (11 years 9 months). Based on BMI according to the CDC 2000 the majority of subjects in this study were normal in 12 people (40%), with a mean BMI of 78.7 ± 24.2. Based on WHR, it was found that the majority of research subjects had normal WHR of 27 people (90%) with the mean WHR of 0.76 ± 0.06. And in this study, the mean serum leptin levels in the study subjects were 13.1 ± 3.9 ng / mL.

Table 2. Mean serum leptin levels by age of menarche

Age menarche (month)	Serum leptin levels (ng / mL)				
	n	The mean	SD	Min	Max
120 – 131	7	17.7	0.9	16.5	19.4
132 – 143	8	14.3	0.9	12.9	15.4
144-155	11	11.4	0.5	10.3	12.2
156 - 167	3	8.6	0.7	7.8	9.1
168 - 179	1	5.2			

In Table 2, were found in serum leptin levels was highest in the age group of menarche 120-131 months, namely 17.7 ± 0.9 ng / mL. Then followed by the age group 132 - 143 months which is 14.3 ± 0.9 ng / mL, the age group 144 - 155 months is 11.4 ± 0.5 ng / mL, and the age group 156 - 167 months is 8.6 ± 0.7 ng / mL. In these results can be seen leptin levels decrease with increasing age of menarche.

Table 3. Serum leptin levels based on body mass index

BMI	Serum leptin levels (ng / mL)				
	n	The mean	SD	Min	Max
Underweight	1	5.2			
Normal	12	10.8	1.7	7.8	13.6
Overweight	8	14.0	2,4	11.2	17.7
Obesity	9	16.3	2.2	12.0	19.4

Based on the table above, the highest serum leptin levels were found in research subjects with obesity that is 16.3 ± 2.2 ng / mL and it appears that serum leptin levels increased with increasing BMI.

Table 4. Serum leptin levels based on hip waist circumference ratio

WHR	Serum leptin levels (ng / mL)				
	N	The mean	SD	Min	Max
Normal	27	12.8	3.4	5.2	19.4
Obesity	3	16.0	1.3	15.2	17.5

The results in Table 4 shows the levels of serum leptin highest average found in study subjects with obesity waist hip ratio is 16.0 ± 1.3 ng / mL. And the average low leptin level in normal WHR is 12.8 ± 3.4 ng / mL.

Table 5. Correlation of serum leptin levels with age of menarche

Characteristics	r	P
Serum leptin levels	-0.962	<0.001
Age of menarche		

Based on data analysis using Pearson correlation, the correlation coefficient (r) is -0.962 with a significance value ($p = 0.001$). From these results it can be concluded that there is a negative correlation between serum leptin levels with age menarche. The direction of the negative correlation indicates that the higher the level of serum leptin, the lower the age of menarche. The correlation strength obtained in this study shows a very strong correlation.

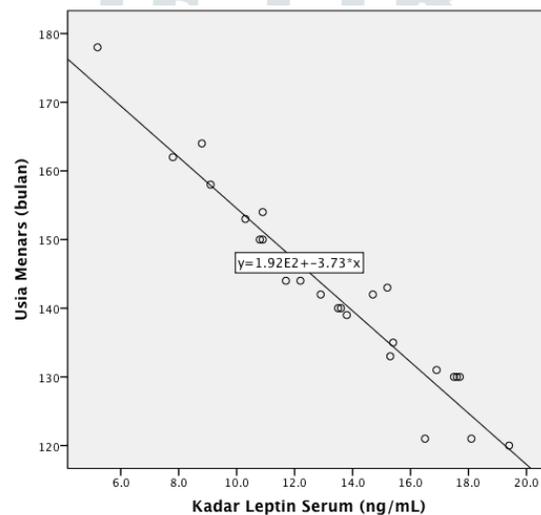


Table 6 Correlation of serum leptin levels with BMI

Characteristics	r	P
Leptin serum levels	0.876	<0,001
BMI		

In table 6 based on data analysis with the Spearman correlation, it can be concluded that there is a correlation between serum leptin levels with BMI, with a very strong correlation ($r = 0.876$) and positive patterning which means the higher the level of serum leptin, the higher the BMI. The statistical results obtained a significant relationship between serum leptin levels with BMI ($p = 0.001$).

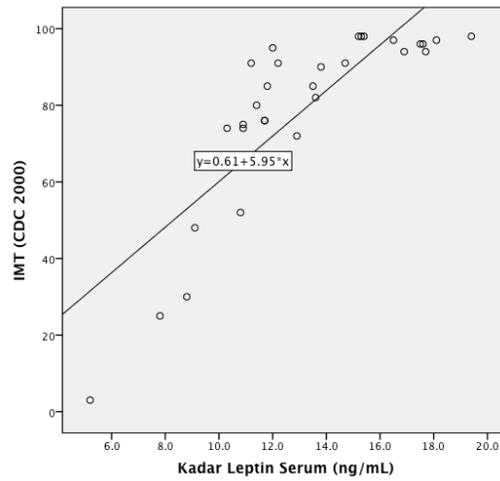
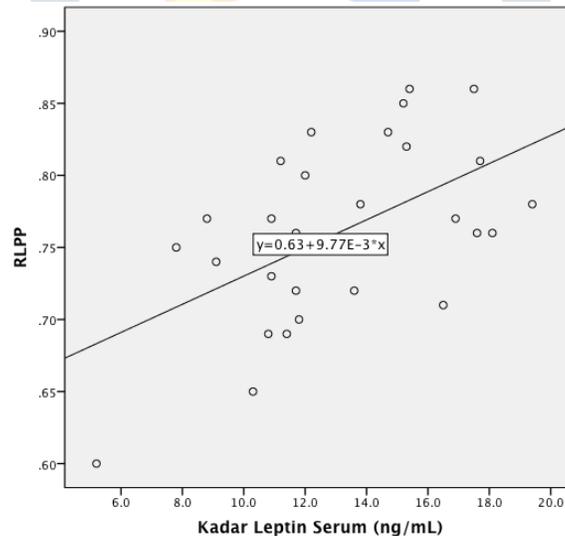


Table 7. Correlation of serum leptin levels with WHR

Characteristics	r	P
Leptin serum levels	0.542	0.002
WHR		

In the results of research with data analysis using Pearson correlation obtained $r = 0.542$ and $p = 0.002$. So it can be concluded that there is a correlation between serum leptin levels with WHR. The correlation strength was moderate ($r = 0.542$) and positive patterned which means that the higher the level of serum leptin, the greater the WHR.



Discussion

This study was conducted on 30 respondents, from the analysis obtained characteristics of research subjects. Menarche were found in the study subjects at the age group of 144-155 months, with the mean age of menarche being 142.9 ± 13.1 months (11 years 9 months). Based on BMI according to the CDC 2000 the majority of subjects in this study were normal in 12 people (40%), with a mean BMI of 78.7 ± 24.2 . Based on WHR, it was found that the majority of research subjects had normal WHR of 27 people (90%) with the mean WHR of 0.76 ± 0.06 . And in this study, the mean serum leptin levels in the study subjects were 13.1 ± 3.9 ng / mL.

This is consistent with Hendry's study, where the mean age of menarche in their study was 11.72 ± 0.82 years; with WHR 0.82 ± 0.04 . They also reported a strong negative correlation between serum leptin levels and age of menarche ($r: 0.98$; $P < 0.05$).²⁰ The results of the 2010 Basic Health Research (Riskesdas) also show that nationally the average age of menarche is 13-14 years.²³ Meanwhile, based on research conducted in Jakarta in 2002, the average age of menarche was 12.3 years, which is not much different from that obtained by the *National Health and Nutrition Survey* (NHANES) at the age of 12.2 years.^{10,11} Based on research by Hillard et al, it is said that the age of menarche usually occurs in the age range of 13-15 years.²² Likewise in the Matkovic study, where their research subjects had an average age of 12.8 ± 0.9 .¹⁹ Based on McDowell et al's report, the age of menarche has decreased, where menarche occurred at the age of 14 years in 1900 and became 12.8 in 1940.¹¹ Based on Matkovic et al's study, the mean BMI in their study was 18.9 ± 3.1 at the age of early premenarche, 20.4 ± 3.6 at the age before menarche and 21 ± 3.7 at the age of menarche.¹⁹ Based on the research of Lassek et al, they reported that the mean WHR ratio in the menarche age group was 0.788 ± 0.022 while the WHR in the non-menarch age was 0.813 ± 0.049 .²⁴

In this study, the highest serum leptin levels were found in the menarche age group of 120-131 months, namely 17.7 ± 0.9 ng / mL (table 4.2). Then followed by the age group 132 - 143 months which is 14.3 ± 0.9 ng / mL, the age group 144 - 155 months is 11.4 ± 0.5 ng / mL, and the age group 156 - 167 months is 8.6 ± 0.7 ng / mL. In these results can be seen leptin levels decrease with increasing age menarche. This is in line with the study of Lassek et al, in which they reported that the mean age of the menarche age group was 12 ± 1 while the group that had not received menarche was 12.4 ± 0.63 .²⁴ Increased leptin levels show a negative correlation, this suggests that increased levels of leptin in the blood will cause women to experience menarche faster. Based on Matkovic et al, menarche are associated with increased levels of leptin. Matkovic reported that, at the age of early premenarche, leptin levels ranged from 8.6 ± 6.4 ; 9.2 ± 7.2 at the age of menarche and 9.9 ± 7.8 at the age of menarche. This shows a negative relationship between age of menarche and leptin levels. He also reported that changes in menarche time and changes in body fat composition showed a negative correlation with $r = -0.814$. Based on data on food intake and leptin levels, it was reported that the group with low food intake and low leptin levels would experience more late menarche compared to the group that had higher levels of leptin and food intake.¹⁹

The highest serum leptin levels were found in research subjects with obesity that is 16.3 ± 2.2 ng / mL and it appears that serum leptin levels increased with increasing BMI. This is in accordance with Shalitin et al, where they report that leptin is a protein product produced by the obese gene (*ob*). So the increase in BMI is associated with an increase in leptin in the blood. Increased fat mass in the obese group can trigger neuroendocrine which causes the onset of menarche. Shalitin also reported that children with BMI are obese more quickly experiencing menarche compared to a group of children who are thinner with a body mass that is less.¹⁵

In this study it was found that WHR was associated with increased levels of leptin. Correlation analysis obtained value $r = 0.542$ and p value = 0.002. This is in accordance with Sumadewi's research, found a correlation coefficient of 0.485 indicates that there is a positive correlation between WHR and leptin levels.²¹

Lassek et al found that there is a relationship between body fat distribution and menarche. Lassek also reported that the incidence of menarche depends on body fat stores. The leptin hormone produced by fat cells, provides a way for fat stores to communicate with neurons that secrete GnRH through the hypothalamus through the leptin receptor in the KiSS-1 neuron.⁵⁸

Based on the research of Kim JY et al, they found that patients who got menarche earlier had a greater waist-to-hip circumference ratio compared to groups who had not received menarche of the same age. While in the group that got the age of menarche slower, did not have a significant difference in waist-hip circumference ratio ($p = 0.954$).²⁵ This is in line with the study of Pursuhottam et al who stated that the value of the waist-hip circumference ratio was higher in the *early menarche* group compared with the *mid menarche* and *late menarche* groups ($p > 0.05$). Pursuhottam also found a correlation between the waist-hip circumference ratio ($r = 0.116$; $p < 0.05$) but the value $r = 0.116$ showed a very weak relationship. Research that connects the waist-

hip circumference ratio with leptin itself does not exist until now. In our study, we found a correlation of waist-hip circumference ratio with leptin levels ($r = 0.542$; $p = 0.002$) this indicates that leptin levels may have a relationship with waist-hip circumference ratio.²⁶

Waist circumference is an indicator of abdominal fat tissue. Some studies in children and adolescents also show a strong correlation between intra-abdominal fat and waist circumference. *Hip circumference* is a measurement that describes the size of the external pelvic fat tissue in the area. The fat tissue in this area is mostly subcutaneous fat and is related to the lower body so it is used as an indicator of the distribution of lower body fat. The waist hip ratio (WHR) is very closely related to total body fat mass. WHR is influenced by race / ethnicity, age, gender and degree of obesity. The ratio will increase with increasing age and excessive body weight. WHO provides waist hip ratio values ≥ 0.80 in women with an increased risk of cardiovascular disease and other metabolic diseases.^{17,18}

References

- [1.] Gordon CM, Laufer MR. Physiology of Puberty. in : Emans SJ (ed) Pediatric and Gynecology. 6th edition. Philadelphia. Lippincott Williams & Wilkins. 2010 : 120 – 55
- [2.] Speroff L, Fritz MA. Clinical Gynecologic Endocrinology and Infertility 9th ed. Philadelphia Lippincott Williams & Wilkins. 2020 : 187 – 231, 401– 63, 490 – 546, 547 - 571
- [3.] Behrman RE, Kliegman RM, Jenson HB (ed), Nelson Textbook of Pediatrics. 16th edition. Philadelphia. WB Saunders Company. 2010 : 52 – 61 , 573 – 577, 1687 – 1688
- [4.] Mc Millan JA et. all (ed) Oski' Pediatrics. 3rd ed. Philadelphia. Lippincott Williams & Wilkins. 2012 : 525 – 42
- [5.] Porterfield SP, White BA . Endocrine Physiology 3rd ed. Philadelphia. Morsby Elsevier. 2007 : 214, 49
- [6.] American Academy of Pediatrics, Comitee on Adolescence, American College of Obstetricians and Gynecologists and Comitee on Adolescent Health Care. Menstruation in Girls and Adolescents : Using the Menstrual Cycle as a Vital Sign. Pediatrics 2011 ; 118 (5) : 2245 – 50
- [7.] Hillard A. Menstruation in Young Girls : A Clinical Perspective. Obstet Gynecol 2010 ; 99 (4) : 655 – 62
- [8.] Hickey M, Balen A. Menstrual disorder in adolescence : investigation and management. Hum Reprod Up date 2013 ; 9 (5) : 493 – 504
- [9.] World Health Organization Task Force on Adolescent Reproductive Health . World Health Organization Multicenter Study on Menstrual and Ovulatory pattern in Adolescent Girls : A. Multicenter Cross- Sectional Study of Menarche. J. Adolesc Health 1986 ; 7 : 229 - 35
- [10.] Dillon D, et.al. Supplementation with vitamin A or riboflavin additional to iron has no or only marginal effect on hemoglobin concentration or iron stores in Indonesian adolescent schoolgirls: a randomized controlled trial. In: Nutritional Health of Indonesian Adolescent Girls. PhD thesis Wageningen University, April 2012 : 77 – 96
- [11.] Mc.Dowell M.A, Brody D.J, Hughes JP, Has age at menarche changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2004, J. Adolesc Health. 2011 ; 40 : 227 – 31
- [12.] Van Hoff MHA et al . Relationship of menstrual cycle pattern in 14 – 17 year old adolescent with gynaecological age, body mass index and historical parameters. Hum Reprod 1998 ; 8 (13) : 2252 – 60
- [13.] Dunger DB, Ahmed ML. Effects of obesity on growth and puberty. Best pract & Res Clin Endokrinol Metab. 2010 ; 19 : 375 – 90
- [14.] Dalemarré-van de Wall HA. Regulation of puberty. Best pract & Res Clin Endokrinol Metab. 2012 ; 16 : 1 – 12
- [15.] Shalitin S. Philip M. Role of obesity and leptin in the pubertal process and pubertal growth – a riview. Int. J. Obes 2010 ; 27 : 869 – 74

- [16.] Kaplowitz PB, et al. Earlier onset of puberty in girls : relation in increased body mass index and race . Pediatrics. 2001 ; 108 : 347 – 53
- [17.] Gibson RS. Principles of nutritional assessment. 2nd edition. Oxford University Press. 2005
- [18.] Heyward VH, Stolarzyk LM. Applied Body Composition Assesment. Champaign. Human kinetic. 1991
- [19.] Matkovic V, et al. Leptin is inversely related to age at menarche in human females. J, Clin Endocrinol Metab. 1997 ; 82 :3239 – 45
- [20.] Hendry D, Lasmini PS, Yusrawati, Bahtiar H. Hubungan Kadar Leptin Serum, Indeks Massa Tubuh, Persentase Lemak Tubuh dan Rasio Lingkar Pinggang Panggul dengan Usia Menarche. Tesis. Bagian Obstetri dan Ginekologi FK UNAND. Padang. 2009
- [21.] Sumadewi K T, Karmaya N M, Adiatmika IP. Korelasi Antara Kadar Leptin dengan IMT, Lingkar Pinggang dan RLPP pada Orang Dewasa Obesitas Usia 19-25 Tahun di Universitas Warmadewa. WMJ (Warmadewa Medical Journal), Vol. 1 No. 2 November 2016, Hal. 71-8
- [22.] Hillard, P. J. A. (2002). Menstruation in young girls: a clinical perspective. *Obstetrics & Gynecology*, 99(4), 655-662
- [23.] Kementrian Kesehatan RI. Riset Kesehatan Dasar 2010. 2010;78
- [24.] Lassek WD, Gaullin, SJ. (2007). Brief Communication: Menarche is related to fat distribution. *American Journal of Physical Anthropology*. 33: 1147-1151.
- [25.] Kim J-Y, Oh I-H, Lee E-Y, et al. the relation of Menarcheal Age to Anthropometric Profiles in Korean Girls. *J Korean Med Sci* 2010; 25: 1405-1410
- [26.] Pursuhottam P, Rakshit S, Saha, P. Physical Determinants of Early Menarche: Study of Age at Menarche and Anthropometric Measure in Bengali Girls. *Sch. J. App. Med. Sci.*, 2015; 3(2C): 723-729

