THE CORRELATION BETWEEN ADIPONECTIN LEVELS WITH C-REACTIVE PROTEIN LEVELS IN ADULT OBESE NON-DIABETIC AMONG STAFF OF DR. M. DJAMIL HOSPITAL PADANG

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ABSTRACT

The adiponectin and C-reactive protein (CRP) are markers of chronic low-grade inflammation related to obesity. This study aims to determine a correlation between adiponectin level and CRP level in adult obese individuals. This study was analyzed with a cross-sectional design of 55 subjects at Dr. M Jamil Central Hospital Padang from January to September 2019. The subjects included were type 1 obese (25≤BMI≤29.9 kg/m2) and type 2 obese (BMI 30.0 kg/m2). Enzyme-linked immunoassay (ELISA) was used to measure adiponectin and High Sensitivity C-Reactive Protein (Hs-CRP) levels. Univariate statistical analysis is processed and presented in distribution, frequency, mean (standard deviation), median (minimum-maximum value). Bivariate data were analyzed using the Pearson correlation test, significant if p<0.05. The study consists of 16 males and 39 females. The mean age was 35 years old (the range 23 to 57 years old), the mean BMI was 30.8 (4.5) kg/m2. This study consists of 28 subjects, type 1 obese and 27 types II obese. The mean adiponectin level in type 2 obese is lower than in type 2 obese groups. The mean CRP levels are high in all populations. Pearson ln-adiponectin and CRP correlation test in the entire population: r =-0.105 (p=0.444).

Keywords: Adiponectin, Chronic low-grade inflammation, C-reactive protein, obesity.

INTRODUCTION

Adipocyte tissue plays a role in actively secreting adipocytokines.[1] Thus, enlarging and increasing the number of adipocyte tissues in obesity are accompanied by immune-associated cells that increase pro-inflammation cytokines.[2] This condition leads to chronic inflammation, marked by lymphocytes, macrophages, new blood vessel formations, and proliferation of connective tissues.[3]

Low-grade inflammation in adipocyte tissue could cause an increased level of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).[4,5] TNF-α relates to insulin resistance, increased adipocyte-free fatty acids, decreased adiponectin synthesis, and disturbance of insulin-signal.[5]

Decreasing level of adiponectin as an anti-inflammation marker and increasing of C-reactive protein (CRP) show a lower grade of chronic inflammation.[3,6,7]

Adiponectin is a collagen-like plasma protein secreted particularly by adipocytes.[8,9] Clinical studies revealed that hypoadiponectinemia is one of the independent risk factors for cardiovascular disease,[10] insulin resistance, and type 2 diabetes.[5]

Adiponectin holds down scavenger receptor class A1 (SRA1) expression, thus inhibiting macrophage derivatives' transformation into foam cells. Adiponectin inhibits the production of inflammatory chemokines and regulates the production of the anti-inflammatory cytokine. It also suppresses classic pro-inflammatory activity by inhibiting myeloid differentiation into macrophages. It initiates alternative anti-inflammatory activation by triggering the proliferation of macrophages into an anti-

inflammatory stage and decreasing Toll-Like Receptor 4 (TLR4) expression on macrophages and progenitor cells.[11]

Adiponectin circulates in plasma at a high enough concentration compared to other adipocytokines. Adiponectin levels reached 0.01%-0.05% of the total serum protein.11 Normal levels of adiponectin in individuals with a BMI <25.0 kg/m^2 are 4-26 µg/mL in male and 5-37 µg/mL in female.[11] Overweight and obese individuals have significantly lower adiponectin levels.[12]

C-reactive protein (CRP) is a major marker of inflammation. CRP is a non-specific acute reactant commonly used to detect acute injury infection and inflammation.[3] It is synthesized in the human liver through stimulation of IL-1 and IL-6.[13,14] The mean CRP level in normal individuals is 0.89 ng/mL. CRP levels increase rapidly after bacterial infection, surgery, acute myocardial infarction, rheumatic disease, burns, trauma, and its level persists in chronic inflammation. High CRP levels have also been observed in patients with depressive disorders. CRP levels will increase rapidly after 4-6 hours of the onset of infection or tissue injury. CRP secretion recurs every 8 hours and peaks and returns to normal after 24-48 hours.[15]

High Sensitive C-reactive Protein (Hs-CRP) is a parameter that could measure low levels of CRP. Hs-CRP is stable, available in clinical laboratories, standardized by WHO standardization, and can detect inflammation to the lowest level.[16] The American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC) proposed a CRP cut-off point in evaluating the risk of CVD to be low (<1.0 ng/mL), moderate (1.0-3.0 ng/mL), and relatively high risk (>3.0 ng/mL).[1,5] There is now growing evidence that CRP plays important roles in inflammatory processes and host responses to infection including the complement pathway, apoptosis, phagocytosis, nitric oxide (NO) release, and the production of cytokines, particularly IL-6 and TNF-α.[17]

Chronic low-grade inflammation is indicated by a decrease in adiponectin levels and an increase in CRP levels.[6,7] Significantly negative correlations between adiponectin and CRP were reported in populations with obesity, type 2 diabetes, and coronary artery disease.[1,18] Adiponectin levels of <3,0 µg/mL and CRP 3,0 ng/mL are stated as abnormal results.[5]

A study by Li et al., in a group of healthy college students (aged 18.8 (1.6) years old) showed an inverse correlation between BMI and fasting adiponectin, a positive correlation between BMI and CRP, and a significant negative correlation between adiponectin and Hs-CRP (r=-0.433; p <0.01).[7] Conroy et al., analyzed a negative correlation in a study with obese female subjects of Asian and Caucasian race (r=-0.02; p<0.01).19 Ahonen et al. assessed the risk of metabolic syndrome (MetS) with inflammatory markers found that there was a partial negative correlation between adiponectin and CRP, the association was stronger in obese women of Asian race than Caucasians.14

Abraham et al., analyzed 111 African American type 2 diabetes subjects (34 males and 77 females) aged 18-60 years, female subjects with BMI subjects 32.3 (0.7) and men 29.2 (1.1). They found those adiponectin levels in male subjects were lower than in females. CRP levels were higher in female subjects than in males. Significant inverse correlation between adiponectin and CRP both females (r = -0.32; p= 0.01); and male (r=-0.34; p≤0.05).[1] The study about the correlation between adiponectin and CRP in Indonesia was conducted by Regina et al. on children aged 9-15 years, consisting of 57 obese and 58 norm weight children. They found that there was no significant correlation between adiponectin and CRP levels (r=0,048; p=0,362).[6]

Amudi et al. examined CRP and adiponectin levels in 30 young adult males with central obesity at Prof. Dr. R. D. Kandou Hospital, Manado. Amudi used different cut off high CRP levels >0.1 mg/dL (10 µg/mL) and low adiponectin levels <5000 ng/mL. They did not analyze the correlation between adiponectin with CRP levels.[20]

This study aims to analyze how the adiponectin and CRP levels of obese non-diabetic adults affect the strength and direction of the correlation between

adiponectin levels and CRP as a marker of low-grade chronic inflammation in obese adults. This was the first study that analyzed adiponectin levels and CRP levels in adults non-diabetic obese and analyzed the correlation between adiponectin levels with CRP in obese adults staffs of Dr. M. Djamil hospital Padang in West Sumatra, Indonesia.

MATERIAL AND METHODS

A cross-sectional analytical study was conducted from June to September 2019. This study is part of a more extensive study that analyzes several parameters in obese and non-obese subjects among Dr. M. Djamil Padang Central Hospital staff.

The inclusion criteria were subjects aged 18-60 years and BMI ≥25.0 kg/m^2. Meanwhile, the exclusion criteria were subjects with bacterial infection, surgery, acute myocardial infarction, rheumatic disease, burns, trauma, type 2 diabetes, autoimmune diseases, infectious diseases, history of heart disease, liver problems, being pregnant, and taking steroids. The research procedure was approved by the ethics and research committee of Dr. M. Djamil Padang Hospital.

Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m2). Subjects were grouped into obese type I (BMI 25.0-29.9 kg/m^2) and obese type II (BMI ≥30.0 kg/m^2). The population was not separated between men and women. the procedure was approved by the ethics and research committee of Dr. M. Djamil Padang Central Hospital.

Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m^2). Subjects were grouped into obese type I (BMI 25.0-29.9 kg/m^2) and obese type II (BMI ≥30.0 kg/m^2).

The population was not separated between men and women. Adiponectin and CRP levels were analyzed by the enzyme-linked immunoassay (ELISA) method.[21,22] Adiponectin levels <3.0 µg/mL and CRP ≥3.0 ng/Ml were defined as cut-offs representing a low-grade risk of chronic inflammation.[5]

The Data were analyzed using SPSS version 22.0 statistical software. Univariate data were presented in distribution, frequency (percent), mean (standard deviation), and median (minimum and maximum values). The Kolmogorov-Smirnov test carried out the normality test. Bivariate data were analyzed

Table 1. Basic Characteristics of Subjects

Characteristics	Total	Group Based on BMI	
		Type 1 Obese	Type 2 Obese
Number (%)	55	28(51)	27(49)
Gender			
Male(%)	16 (29)	7	9
Female(%)	39 (71)	21	18
Age (Year)			
Mean (SD)	34,78 (7,80)	36,93 (8,73)	32,56 (6.08)
Median (min-max)	33 (23-57)	34 (25-57)	33 (23-52)
BMI (kg/m^2)			
Mean (SD)	30,78(4,50)	27,21 (1,40)	34,48 (3,49)
Median (min-max)	29,99 (25,00-42,67)	27,19(25,00-30,00)	33,33(30,00-42,67)
Adiponectin (µg/mL)			
Mean (SD)	3,25 (1,78)	3,69 (1,98)	2,78 (1,44)
Median (min-max)	2,86 (1,06-9,34)	3,26 (1,32-9,34)	2,47 (1,06-5,60)
CRP (ng/mL)			
Mean (SD)	5,09(2,58)	4,86(2,39)	5,33(2,81)
Median (min-max)	4,74 (1,01-9,89)	2,39 (0,17-9,89)	4,74 (1,01-8,72)

using Pearson's correlation test on normally distributed data. Significant value if p<0.05.[23]

RESULTS

The study analysis consisted of 55 people with 16(29%) male subjects and 39(71%) female subjects (range aged was 23-57 years old). The Mean(SD) of BMI was 30.58(4.43) kg/m2. A total of type I obese 28(51%) subjects and type 2 obese 27(49%) subjects. Type I obese group consisted of 7 male subjects and 21 female subjects; type II obese consisted of 9 male subjects and 18 female subjects (Table 1).

The median adiponectin levels was 2,86(1,06-9,34) µg/mL. Meanwhile, the median adiponectin level in obese group II was lower than in the obese group. The mean CRP level of the study population was 5.09(2.58) ng/mL. Meanwhile, the mean CRP levels in the type 2 obese group were higher than the type 1 obese group (Table 1).

Most of the study subjects had abnormal levels of adiponectin and CRP (Table 2); 55% of subjects had adiponectin levels <3.0 µg/mL, and 83% of subjects had a high risk of chronic inflammation (CRP levels >3 ng/mL). Only two subjects had low risk, and eight subjects had a moderate risk of cardiovascular disease and chronic inflammation (Table 2).

Table 2. Adiponectin and CRP Stratification

Variable	N (%)
Adiponektin (µg/mL)	
Normal (≥3,0)	25 (45)
Abnormal (<3,0)	30 (55)
Hs-CRP (ng/mL)	
Low risk (<1,0)	2 (3,4)
Moderate (1,0-3,0)	8 (13,6)
High risk (>3,0)	45 (83,1)

The mean of adiponectin levels in the male group was lower and below the normal value of 2.49 (1.3) µg/ml than the female group of 3.56 (1.87) ng / mL. The mean levels of CRP in the female group were higher (5.57(2.67) ng/mL) than the male group (3.83(2.01) ng/mL) (Table 3).

Table 3. Adiponectin and CRP Levels Based On Gender

	Gender	
	Male	**Female**
Number	16	39
Adiponectin (µg/mL)		
Mean (SD)	2,49 (1,30)	3,56 (1,87)
CRP (ng/mL)		
Mean (SD)	3,83 (2,01)	5,57 (2,67)

Parametric tests were performed between ln-adiponectin and CRP using Pearson's test. The correlation was significant if p <0.05. The Pearson ln-adiponectin and CRP correlation test showed a weak and insignificant negative correlation (r = -0.105 and p = 0.444) shown in Table 4 and Figure 1.

Table 4. Korelasi Ln-Adiponectin with CRP

Variable	n	Mean (SD)	r	*p*
ln-Adiponectir	55	1,04 (0,53)	-0,105	0,444
Hs-CRP		5,09 (2,58)		

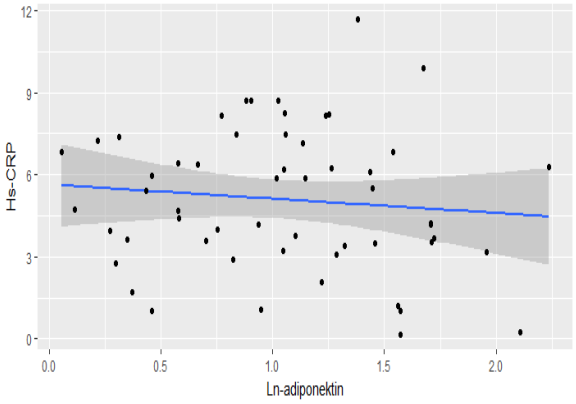

Figure 1. Correlation between Ln-Adiponektin and CRP **(** r=-0,105; p= 0,444)

DISCUSSION

The first study analyzed the correlation between adiponectin with CRP in adults obese in West Sumatera. A total of 55 obese subjects were recruited in this study. 71% of subjects were female, the mean age of subjects was 35 (8) years old with a range of 25-57 years; agrees to the distribution of staff at Dr. M Djamil Hospital Padang.

The Mean BMI was 30.58 (4.43) kg/m^2. There was an extreme BMI value (42.67 kg/m^2). The obese type 1 group consisted of

28 (51%) subjects; meanwhile, the type 2 obese group consisted of 27(49%) subjects. Obese criteria in this study were slightly different from other studies. The subpopulation is divided based on the WHO BMI classification for the Asia Pacific population.

The characteristic study differs from other studies due to differences in the groups studied. Some studies evaluated older obese subjects, while other studies evaluated children and adolescents.

The median adiponectin levels in the population were lower than the cut-off value. All of the subjects were Indonesian. There was no interval range adiponectin for the adult population of Indonesia.[25] A total of 55% of subjects had abnormal level adiponectin.

Adiponectin levels in type 2 obese group were lower than the type 1 obese group. This result consistent with the previous study. Unlike most adipokines, adiponectin is inversely proportionate to the degree of obesity, meaning that its concentration decreases when obesity becomes more severe and is restored by reducing bodyweight.[26]

A total of 83% of the population have a high-risk stratification of inflammation and cardiovascular disease (CRP ≥3.0 ng/mL).[5] The mean CRP levels in type 2 obese group were higher than the type 1 obese. The result was consistent with the previous study that found CRP was increased significantly by the increase of BMI.[25,27]

Enlarging and increasing adipocyte tissues in obesity are mediated by immune-associated cells that increase pro-inflammation cytokines.[28] High CRP levels are related to the increased expression and release of IL-6 by adipose tissue. CRP is synthesized not only primarily in liver hepatocytes but also in smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes.[17]

We set a limit on the abnormal value of adiponectin <3.0 µg/mL.[5] A total of 55% of subjects had adiponectin levels <3.0 µg/ml. IL-6 and TNF-α decreased adiponectin mRNA in vitro. Therefore, hypo-adiponectinemia may be a consequence of chronic inflammation in obesity.[29]

Our study found insignificant inverse correlation (r=-0.105;p=0.444). This study was not consistent with the study by Abraham, and Li.[1,7] Insignificant correlation was also found in the study by Regina et al., but Regina found a positive correlation in obese children (r=0,048; p=0,362).[6] Weak inverse correlation also found in the study by Conroy.[19]

Several possible reasons may explain this discrepancy in the other study. The different results from other studies due to differences in the groups studied. Some studies evaluated children, adolescents, and type 2 diabetes. Most of the subjects are productive adult non-diabetic obese; 71% are women. Subjects with abnormal adiponectin levels (55%) were less than a subject with abnormal CRP levels (83%). There were even subjects with high levels of adiponectin but high levels of CRP.

Women, compared to men, have higher percent body fat and deposit it in a different pattern, with relatively more adipose tissue in the hips and thighs. This 'female' fat distribution, independent of total body fat, confers protection against metabolic diseases. Much more work will be required to integrate all the data arising from studies of global gene and miRNA expression, as well as of epigenetic changes, and to understand why females can accumulate more adipose tissue than men without deleterious metabolic consequences and how gluteal-femoral adipose tissue, in particular, lessens metabolic risk.[30]

A high percentage of subjects with high CRP levels is associated with low-grade local and systemic inflammatory conditions that rapidly stimulate CRP synthesis and secretion. CRP production is not only in the liver, even by the adipocytes themselves. This raises the possibility that adipose tissue contributes directly to the circulating pool of CRP.[17]

The adiponectin resistance mechanism could cause inadequacy of the presentation of subjects with high CRP but normal adiponectin. Adiponectin in early obesity acts as an anti-inflammatory. Adiponectin

resistance occurs due to the downregulation of adiponectin receptors (AdipoRs).[17]

This study did not analyze the degree of adiposity and duration of obesity. Adiponectin in early obesity acts as an anti-inflammatory. The course of obesity is accompanied by a decrease and loss of adiponectin receptor population in the liver and muscles, leading to low adiponectin levels. Low adiponectin levels as an anti-inflammatory will tend to worsen the inflammatory process in obese patients.[17] But this study did not analyze the degree of adiposity and duration of obesity.

CONCLUSION

Most of the subjects had a risk of chronic inflammation based on decreased adiponectin levels and elevated CRP levels. The type II obese group had lower adiponectin levels than the type I obese group. Female adiponectin and CRP levels were higher than male. There is no correlation between Ln-adiponectin and CRP in obese adults.

It is necessary to carry out further research with a more diverse population. The research group should differentiate between males and females. The study also needs to analyze the population; based on more sensitive adiposity measurements.

REFERENCES

1. Abraham PA, Attipoe S, Kazman JB, Zeno SA, Poth M, Deuster PA. Role Of Plasma Adiponectin / C-Reactive Protein Ratio In Obesity And Type 2 Diabetes Among African Americans. Afri Health Sci.2017;17(1):99-107.
2. Asghar A, Sheikh N. Role Of Immune Cells In Obesity Induced Low Grade Inflammation And Insulin Resistance. Cellular Immunology. 2017; 315:18–26.
3. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity And Inflammation: The Linking Mechanism And The Complications. Arch Med Sci. 2017;4:851–863.
4. Susantiningsih T, Mustofa S. Ekspresi IL-6 Dan TNF-α Pada Obesitas. JK Unila. 2018;2(2):1-7.
5. Jain V, Kumar A, Agarwala A, Vikram N, Ramakrishnan L. Adiponectin, Interleukin-6 And High-Sensitivity C-Reactive Protein Levels In Overweight/Obese Indian Children. Indian Pediatrics. 2017:(54), 858-861.
6. Regina F, Tirtamulia K, Warouw SM. Adiponectin And Highly Sensitive C-Reactive Protein, Levels In Obese Children Aged 9 To 15 Years. Paediatr Indones. 2011;51(1):7-11.
7. Li J, Liao C, Su H, Peng Q, Zhang Z, Yan S,Yang Q. The Relationship Among Adiponectin, High Sensitive C Reactive Protein And Triacylglycerol Level In Healthy Young Persons, Lipids In Health And Disease. 2011;10(109): 1-5.
8. Goksen D, Levent E, Kar S, Özen S, D S. Serum Adiponectin And hsCRP Levels And Non-Invasive Radiological Methods In The Early Diagnosis Of Cardiovascular System Complications In Children And Adolescents With Type 1 Diabetes Mellitus. J Clin Res Pediatr Endocrinol 2013;5(3):174-181
9. Al-Hamodi Z, AL-Habori M, Al-Meeri, Saif-Ali R. Association Of Adipokines, Leptin/Adiponectin Ratio And C-Reactive Protein With Obesity And Type 2 Diabetes Mellitus. Diabetol Metab Syndr 2014;6(99):1-8.
10. Balsan GA, Vieira JL, Oliveira AM, Portal VL. Relationship Between Adiponectin, Obesity And Insulin Resistance. Rev Assoc Med Brass. 2015;61(1):72–80.
11. Fang H, Judd RL. Adiponectin Regulation And Function. Comprehensive Physiology, 2018;8: 1031–1063.
12. Yu N, Ruan Y, Gao X, Sun J. Systematic Review And Meta-Analysis Of Randomized, Controlled Trials On The Effect Of Exercise On Serum Leptin And Adiponectin In Overweight And Obese Individuals. Horm Metab Res. 2017;49(03):164–173.
13. Kawamoto R, Kusunoki T, Abe M, Kohara K, & Miki T. An Association Between Body Mass Index And High-Sensitivity C-Reactive Protein Concentrations Is Influenced By Age In Community-Dwelling Persons. An International Journal Of

Biochemistry And Laboratory Medicine. 2013: 50(5), 457–464.
14. Ahonen TM, Saltevo J. T., Kautiainen, H. J., Kumpusalo, E. A., & Vanhala, M. J. The Association Of Adiponectin And Low-Grade Inflammation With The Course Of Metabolic Syndrome. Nutrition, Metabolism And Cardiovascular Diseases. 2012. 22(3), 285–291. Doi:10.1016/J.Numecd.2010.07.001
15. Delongui F, Kallaur AP, Oliveira SR, Bonametti AM, Grion CMC, Morimoto HK, et al., Serum Levels Of High Sensitive C Reactive Protein In Healthy Adults From Southern Brazil. Journal Of Clinical Laboratory Analysis. 2013; 27(3):207–210.
16. Choi J, Joseph L, & Pilote L. Obesity And C-Reactive Protein In Various Populations: A Systematic Review And Meta-Analysis. Obesity Reviews, 2012:14(3):232–244.
17. Sproston NR, & Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Frontiers in Immunology. 2018;*9*(757):1-11.
18. Ding D, Wang M, Su D, Hong C, Li X, Yang Y, Zang Y, Hu G, Ling W. Body Mass Index, High Sensitity C-Reactive Protein And Mortality In Chinese With Coronary Artery Disease. Plose One. 2015;10(8):1-11.
19. Conroy SM, Chai W, Lim U, Franke AA, Cooney RV,& Maskarinec G. Leptin, Adiponectin, and Obesity among Caucasian and Asian Women. Mediators of Inflammation.2011; 1–7.
20. Amudi T, Pandelaki K, & Palar S. Hubungan antara hs-CRP , Adiponektin, Fetuin A terhadap Resistensi Insulin pada Pria Dewasa Muda dengan Obesitas Sentral. e-CliniC. 2021;9(1):231-237
21. Diagnostics Biochem Canada, Adiponectin Elisa, 2018a; Ref: CAN-APN-5000: 1-2.
22. Diagnostics Biochem Canada. High Sensitivity C-Reactive Protein (CRP) Elisa.2018b; Ref: CAN CRP-4360 :1-2.
23. Dahlan MS. Hipotesis Korelatif, Dalam Statistik Untuk Kedokteran Dan Kesehatan. Seri 1.Jakarta: Sagung Seto. 2014; 6: 223-24.
24. Engin, A. Adiponectin-Resistance in Obesity. Advances in Experimental Medicine and Biology. Springer International Publishing. 2017;18.415–441.
25. Pangestu YM, Sarah M, Warouw S, Tatura SN. Hubungan kadar 25-hydroksivitamin D dan high molecular weight adiponectin pada remaja obes. Sari Pediatri; 17(1):64-70.
26. El husseny MWA, Mamdouh M, Shaban S, Ibrahim Abushouk A, Zaki MMM, Ahmed OM, & Abdel-Daim MM. Adipokines: Potential Therapeutic Targets for Vascular Dysfunction in Type II Diabetes Mellitus and Obesity. Journal of Diabetes Research, 2017, 1–11.
27. Ebron K, Andersen C J, Aguilar D, Blesso C N, Barona J, Dugan CE, et al. A Larger Body Mass Index Is Associated With Increased Atherogenic Dyslipidemia, Insulin Resistance, And Low-Grade Inflammation In Individuals With Metabolic Syndrome. Metabolic Syndrome And Related Disorders. 2015;13(10):458–464.
28. Ahmed B, Sultana R, & Greene MW. Adipose Tissue and Insulin Resistance in Obese. Biomedicine & Pharmacotherapy. 20201;137 :1-13.
29. Reinehr T. Inflammatory Markers in Children and Adolescent with Type 2 Diabetes Mellitus. Clinica Chimica Acta .2019;496:100–107
30. Karastergiu K, Smith SR, Greenberg As, & Fried SK. Sex Difference in Human Adipose Tissue- The Biology of Pear Shape. Biology of Sex Differences.2012;3:13.
31. Febriza A, Ridwan, As'ad S, Kasim VN, & Indrus HH. Adiponectin and It's Role in Inflammatory Process of Obesity. Mol Cell Biomed Sci. 2019; 3(2): 60-6.