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Identification Inflammatory Biomarkers Associated with Metabolically Unhealthy Obesity in Adolescents: A Systematic Literature Review

Cicilia Karlina Lariwu*, R Susanti, Widya Hary Cahyati and RR Sri Ratna Rahayu

Department of Endocrinology, Semarang State University, Semarang, Indonesia

Abstract

Prevalence obesity in children and adolescents keep going increase in a manner significant a number of this decades. Lots of research state that there is connection obesity with incidents disease like hypertension, abnormal blood sugar levels, dyslipidaemia, cancer even death. Children and youth with Metabolically Unhealthy Obesity (MUO) will experience 2 or more symptoms consist of blood pressure 130/85 mm Hg or more, rate triglycerides above 150 mg/dL, HDL levels <40 mg/dL and Blood Fasting Glucose (BFG) >126 mg/dL. In other words that children and youth with the MOU has very high risk for experience disease metabolic. With identify biomarker inflammation, got estimate abnormality related metabolites with obesity in adolescents. The aim of this study is to identify and analyze associated inflammatory biomarkers with metabolically unhealthy obesity in adolescent. This study using method of literature systematic review with PRISMA guidelines for give explanation about associated inflammatory biomarkers with metabolically unhealthy obesity in adolescents. Search relevant article based on four step selection that is identification, screening, eligibility and data extraction. Using 10 relevant articles from 358 articles based on the PubMed data base. As a result, Body Mass Index (BMI) often used for diagnose circumstances obesity but BMI is not can explain circumstances abnormality metabolism of the obesity person. Inflammatory Biomarkers as a cellular mediator characteristic inflammation have a response system immunity body experience when BMI, circumference waist, circumference belly and circumference arm somebody exceed normal size. CRP or hs-CRP, TNF-α, IL-6, IL-8 and adiponectin is marker inflammation secreted by the body during adolescence experience obesity with MUO category. This study conclusion is teenager with MUO have a risk experience infection and inflammation, it has proven exists enhancement hs-CRP, TNF-α, IL-6, IL-8 and adiponectin than teenager with MHO.

Keywords: Inflammatory biomarkers; Metabolically unhealthy obesity; Adolescents; Prevalence

Introduction

Obesity in adolescents keep going increase every year at various parts of the world, with no looking at social, economic, educational and cultural status. Obesity is combined from various mutual determination that integrated in cause accumulation excess body fat. Bad diet, lack activity physique, style life sedentary is contributor important in incident obesity in children and adolescents [1]. There are several mutual factors that contribute to obesity incident, among others factor biological (genetic, immune system, using medicine, transportation system hormones, disorders of the brain and nerves, psychology disease and microbiota) as well factor environment social among them covers culture, advertising food and drink sweetened, work, social media, smoking, use drugs and high screen time and in the end all factor are influence intake food, production energy, metabolism and activity physique [2]

Obesity even said as the pandemic to be factor risk happening death around the world with estimation about 2 million people die related obesity every year [3]. Obesity is also challenge in field increasing health that together with enhancement prevalence diseases catastrophic [4]. Experienced adolescents and children with obesity have an impact bad period long to health they among others will experience trend for experience obesity in adult [5]. Known teenager with experiencing obesity have a disease cardiometabolic as 67%-86%, which consists of type 2 diabetes mellitus, hypertension, fatty liver disease and dyslipidemia, while adults experience consist of heart coronary disease, stroke, kidney failure and cancer [6]. Obesity confiscated the same financing big with incident war. Besides that, obesity cause academic decline ability children and adolescents, limits movement, both at school, at home and on the spot playing that is impact on desire injure self alone even kill self [7].

Globally in 2016 it was recorded there is more of 340 million experienced children and adolescents have an obesity ages 5-19 years [8]. World Obesity Federation forecast in 2025 figures that obesity in children and adolescents in the world increase 206 million and in 2030 it will be 254 million with some countries have level obesity children and youth highest namely China, India, the United States, Indonesia and Brazil with other developed countries [9]. Prevalence obesity children and youth in Korea in 2021 is 30.8% increase from year before and it is indication for serious problem health in Korea [10]. Temporary in the United States amount teenager aged 12-19 years who experienced obesity by 17% [11]. One of the countries with medium income like Mexico has number obesity in children (5-11 years) by 35.6% and adolescents (12-19 years) by 40% [12].

*Corresponding author: Cicilia Karlina Lariwu, Department of Endocrinology, Semarang State University, Semarang, Indonesia; E-mail: cycilialariwu@students.unnes.ac.id

Obesity consists from two criteria that is Metabolically Healthy Obesity (MHO) and Metabolically Unhealthy Obesity (MUO). Children and youth with Metabolically Unhealthy Obesity (MUO) will experience 2 or more symptoms consist of blood pressure 130/85 mm Hg or more, rate triglycerides above 150 mg/dL, HDL levels <40 mg/dL and Blood Fasting Glucose (BFG) >126 mg/dL [13]. Experienced obesity since children or teenager will tend endure until mature, so matter this cause enhancement blood glucose and lipid profile being a trigger hypertension and hyperlipidemia, causing number pain and death tall [14]. Obesity cause cardiometabolic disease proved with exists reaction marked inflammation, with identified marker inflammation in blood [15]. This Systematic literature review's aim is for identify connection inflammatory biomarkers with metabolically unhealthy obesity in adolescent.

Literature Review

This systematic literature review is written based on guidelines Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for helps describe what was done, what was found, in case the review protocol and what is planned [16]. In matter this give explanation about linkages between metabolically unhealthy obesity with biomarkers inflammation consist of Adiponectin, TNF-α, CRP and hs -CRP, IL-6 and IL-8 in obese adolescent. The guide based on four step that is identification, screening, eligibility and data extraction to be explained in the sub-chapter below.

Identification

Relevant articles with tree problem were collected. Searching for article conducted in May 2023, *via* PubMed. Range time publication selected article that is between 2018 to 2023. Searching use related keywords with metabolically unhealthy obesity, biomarkers inflammation and obese adolescents.

Filtering article

Article about acquired obesity were selected based on it is relevance using range time (five years), in the form of article full text. From the PubMed data base, obtained article 358 articles. On filtering, deleted article with obesity in adults up to 204 articles. Filtering done with only choose article with title according to keywords that is metabolically unhealthy obesity so that 166 articles were found. Then filtering third with only choose article selected based on keywords inflammatory biomarkers so that obtained as many as 10 articles that will analyzing.

Criteria eligibility

Stage eligibility involve step selection article other, where still publication found form book, book chapter, proceedings as well as report deleted. This systematic literature review only using related articles with biomarkers inflammatory, metabolically unhealthy obesity and adolescents. Country of place or location study no become consider in this study.

Data extraction

Stage data extraction is performed with read text complete from articles that have collected. Articles that have through a number of stage selection then analyzed, relevant information with problem will extracting. Relevant information are covers title study, year, methods, and results. With thus, at this stage articles that go through a screening and selection process eligibility fully read and selected return if they in accordance with goals and problems in this study. Results obtained will reviewed by the relationship with inflammatory biomarkers, metabolically unhealthy obesity and adolescents. The groove PRISMA research can show in Figure 1.

Figure 1: Flow chart systematic reviews with PRISMA method.
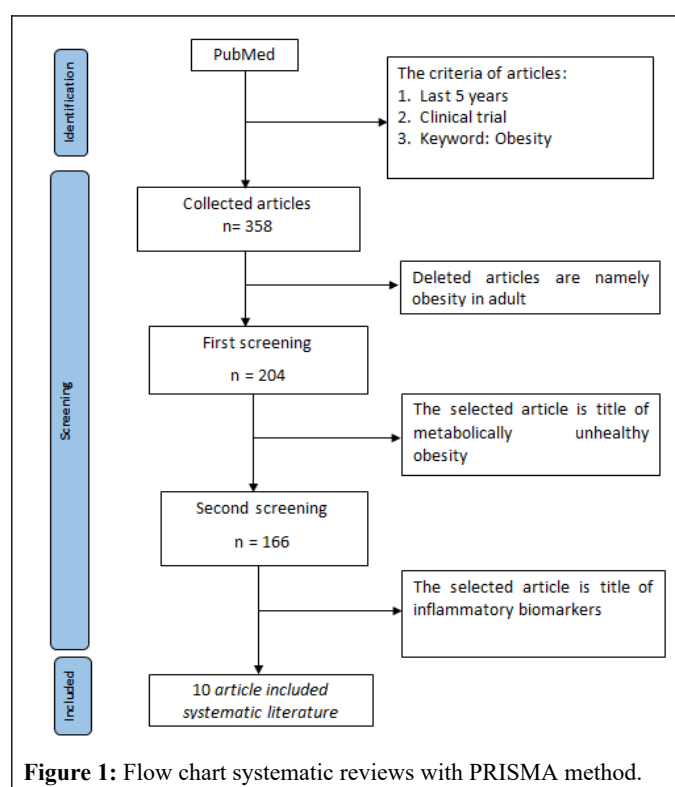
Results and Discussion

Connection inflammatory biomarkers with metabolically unhealthy obesity in adolescents obesity

The results show in Table 1.

Table 1: Article relation between inflammatory biomarkers with metabolically unhealthy obesity in adolescents obesity.

No	Author and year	Title	Method (place, population/ sample, design research, treatment)	Results

1	Ruperez et al. 2020	Antioxidants and oxidative stress in children: Influence of puberty and metabolically unhealthy status	**Place:** Spain **Population/sample:** 1444 children (706 boys and 738 girls), aged 3-17 years **Method:** Case control **Treatment:** The control group consisted from children and youth with normal BMI and group case consists from children and youth with obesity BMI. Both of them become rated MUO. Then measuring anthropometry, examination blood and questionnaire dietary assessment. Inspection blood consists from triglycerides, LDL, HDL, HOMA-IR, GDP, Ox-LDL, Retinol, Carotin, Tocopherol, aPAI-1, IL-6, IL-8, MCP-1 HGF, TNF-a, MPO, MMP-G, PAI -1, hs -CRP.	Children and adolescents who experience MUO are as many as 510. Biomarkers associated inflammation is TNF-a (p=0.045) and IL-8 (p=0.043), which means there is correlation between MUO and enhancement TNF-a and IL-8 levels in affected children and adolescent obesity. Questionnaire dietary assessment also show more control group lots consumption of fruit and vegetables compared to case group.
2	Ruperez et al. 2018	Cardiovascular risk biomarkers and metabolically unhealthy status in prepubertal children: Comparison of definitions	**Place:** Spanish **Population/sample:** 930 children aged 5-11 years, 462 boys and 468 girls, 308 normal BMI and 622 overweight and obese. **Method:** Case control **Treatment:** The control group consisted of child with normal BMI and case group consists of child with BMI overweight and obesity. Both of them become assessed MHO and MUO and then be measured anthropometry and examination composed blood consist of IR, hs-CRP, TNF-a, IL-6, IL-8, MPO, GDP, HOMA-IR, SE-Selectin, PAI-1, SiCAM1, SvCAM1, MMP-G, Triglycerides, HDL, APO-A, APO-B, adiponectin, recistin, leptin.	Boys more lots experience obesity (69.9%) than girl. Biomarkers associated inflammation in MUO is adiponectin (p=0.008), which means there is significant relationship between MUO and decline rate adiponectin in affected children and adolescent obesity. Adiponectin in the MHO group was seen higher than MUO group.
3	Stenzel et al. 2018	Serum antioxidant associations with metabolic characteristics in metabolically healthy and unhealthy adolescents with severe obesity: An observational study	**Place:** Rio de Janeiro **Population/sample:** Teenager age 10-19 years, BMI 99% (severe obesity), 60 respondents. **Method:** Observational study **Treatment:** 60 teenagers be measured anthropometry. An inspection was also carried out clinical for measure fat liver (USG) and frequency of SAH. Inspection laboratory consists of BFG, Trig, HDL and CRP.	**Examination results anthropometry:** Average BMI 46.28% and 63.3% is girl. Teenager with MUO 76.7%. There is enhancement results inspection chemistry blood for CRP (marker inflammation of the vessels blood, related to CVD). The average CRP at MHO was 2.4 mg/L and at MUO was 3.4 mg/L. p value is 0.02, which means there is significant relationship between MUO and enhancement CRP levels in obese children and adolescent.
4	Wan Mohd Zin et al. 2022	Prevalence and clinical characteristics of metabolically healthy obese versus metabolically unhealthy obese school children	**Place:** Malaysia **Population/sample:** 193 children and adolescents aged 8-16 years who experienced obesity, divided in 2 groups (MHO and MUO).	**Results:** Identification of MUO as many as 135 children and adolescent (69.9%) and 60% were boys. Adiponectin higher in the MHO group than MUO (p=0.01), which means there is connection between MUO and decline rate adiponectin in

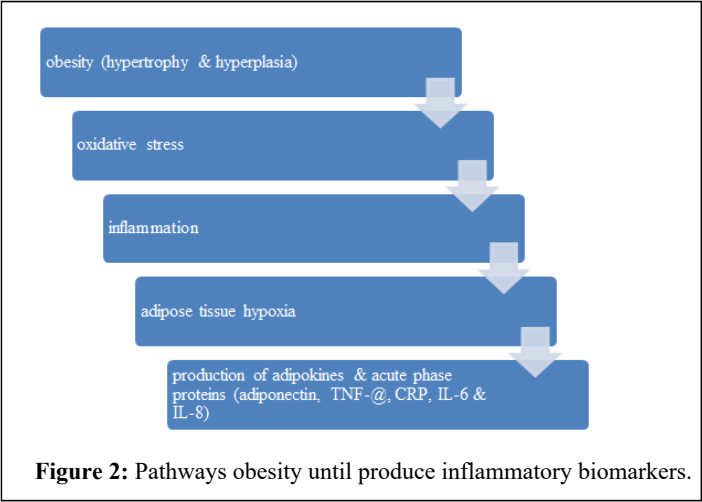|			**Method:** observational study, independent t test and alternative test (Mann Whitney) **Treatment:** Inspection anthropometry as well as clinical trials for assess MHO and MUO. After that inspection consisting of a laboratory from triglycerides, BFG, HDL, LDL, acids urate, APO-A1, APO-B, hs-CRP, adiponectin, ALT, AST, GGT, creatinine, HbA1C, insulin, IL-6 and leptin.	obese children and adolescents.
5	Rocha et al. 2018	Serum uric acid levels as an indicator for metabolically unhealthy obesity in children and adolescents	**Place:** Leipzig, Germany **Population/sample:** 458 children and adolescents aged 6-18 years (239 boys and 219 girls). Shared in 3 groups in accordance BMI criteria, normally as a control group, overweight and obese as a case group. **Method:** Case control, independent t test or alternative for compare results inspection clinical and laboratory studies in the MHO and MUO groups. **Treatment:** Measurement anthropometry and stages of puberty using Tanner Stage. After that, inspection consisting of a laboratory from examination of BFG, triglycerides, LDL, HDL, asparate aminitransferases, ALT, GGT, acids urates, alkaline phosphatase, hs-CRP albumin, C-Peptide.	**Result:** Identification obesity 207 people, overweight 39 people and normal BMI 212 people. MHO as many as 173 people and MUO as many as 73 people. In the MUO group, the mean scores hs-CRP is 0.55 (0.27-1.28) with p value is 0.007, which means there is connection between MUO and enhancement rate hs-CRP in affected children and adolescents obesity.
6	Plaza-Florida et al. 2021	Distinct whole-blood transcriptome profile of children with metabolic healthy overweight/obesity compared to metabolic unhealthy overweight/obesity	**Place:** Spanish **Population/sample:** 27 children obesity ages 9-11 divided into 2 groups that is the MHO group is 13 and the MUO group is 14. **Method:** Case control, independent t test or alternative for compare results inspection clinical and laboratory studies in the MHO and MUO groups. **Treatment:** Measurement anthropometry. After that inspection consisting of a laboratory from BFG examination, insulin, HOMA-IR, Triglycerides, HDL, IL-1 b, IL-6, TNF-a, EGF, VEGF-A. Inspection of DXA (Dual Energy X-Ray Absorptiometry) radiology to see body fat percentage.	**Results:** At MUO an average of BMI is 27.4 kg/m^2, value IL-6 2.6 pg/ml and value TNF-a 4.4 pg/ml. From the results of statistical tests between IL-6 and MUO was obtained p=0.02 and for TNF-a p=0.02. It means there is connection between MUO and enhancement IL-6 and TNF-a levels in obese children.
7	Lischka et al. 2022	Tryptophan metabolism is associated with BMI and adipose tissue mass and linked to metabolic disease in pediatric obesity	**Place:** Spanish **Population/sample:** 125 children and adolescents obesity ages 9-19 years with a BMI percentile of 97%. **Method:** Cohort prospective.	**Results:** Age mean 13 years, 13 patients classified as pre-diabetic and MUO 80 patients. The average value of TNF-a 1.2 pg/ml, CRP 0.7 mg/ml and adiponectin 6.5 mg/ml. The relationship between TNF-a

			Treatment: Measurement anthropometry and stages puberty according to Tanner Stage. After that inspection consisting of a laboratory from examination of BFG, HOMA-IR, Triglycerides, HDL, TNF-a, CRP, Kynurenine, Tryptophan, Serotonin, Adiponectin and C-Peptide.	and MUO is proven with P-value=0.01, CRP with MUO p=0.04 and adiponectin p=0.05. It is can concluded that there is connection between MUO and TNF-a, CRP and adiponectin levels in affected children and adolescents obesity.
8	Gebara et al. 2022	Metabolic inflexibility in youth with obesity: Is it a feature of obesity or distinctive of youth who are metabolically unhealthy?	**Location**: Pittsburgh, United States of America **Population/sample**: 188 children and adolescent obesity 10-20 years old by BMI percentile from 85 to 95. **Method:** Used paired sample t test for compare teenager with MHOs and MUOs. **Treatment:** Measurement anthropometry and stages puberty according to Tanner Stage. It also DEXA check for measure body fat percentage, MRI for measure belly fat, CT-Scan for distance between L5-L5 (lumbal). After that inspection consisting of a laboratory from examination of BFG, Adiponectin, lipid profile and HbA1C.	**Result:** Teenager with MUO as many as 30 people with average age 14 years, average BMI 31.6 kg/m^2, average body fat 40%, average belly fat 56.7% and adiponectin 6.7% (p=0.05). It is can concluded there is connection between MUO and decline rate adiponectin in obese adolescents.
9	Lischka et al. 2021	Circulating microRNAs 34a, 122, and 192 are linked to obesity-associated inflammation and metabolic disease in pediatric patients	**Place:** Vienna, Austria **Population/sample:** 109 children and adolescents obesity (97th percentile BMI) ages 9-19 years. **Method:** Used Pearson correlation test and sample t test and ANOVA to see mean difference of the variables assessed and the relationship characteristics patient with inflammatory parameters. **Treatment:** Measurement anthropometry and stages puberty according to Tanner Stage. It also inspection NAFLD for measure heart fat level. After that done inspection consisting of a laboratory from examination of BFG, insulin, HOMA-IR, AST, ALT, GGT, triglycerides, LDL, HDL, CK-18, CRP, IL-6, Procalcitonin, TNF-a, IL-1Ra.	**Results:** Children and adolescents with MUO as many as 81 people with the average age is 13 years. Emerging inflammatory biomarkers is TNF-a with mean 1.1 pg/ml, CRP 0.6 mg/dl, IL-6 3.6 pg/ml.
10	Fu et al. 2018	Circulating osteonectin and adipokine profiles in relation to metabolically healthy obesity in Chinese children: Findings from BCAMS	**Place:** Beijing **Population/sample:** 1137 children and adolescent obesity (97th percentile BMI) as case group and 982 children and adolescents with normal BMI as control group. Age 6-18 years. **Method:** Cohort, ANOVA test and logistic regression for test connection adiponectin with the	**Results:** Children and adolescents with MUO as many as 905 people with mean age 12 years and boys as much as 65.1%. The average BMI is 26.8 kg/m2. Emerging inflammatory biomarkers is adiponectin with pvalue=0.001.

			metabolic status of the case group. **Treatment:** Measurement anthropometry and stages puberty according to Tanner Stage. It is also given questionnaire for evaluate physical activity and information dietary pattern. After that inspection consisting of a laboratory from examination of BFG, HDL, LDL, triglycerides, insulin, adiponectin, leptin, HOMA-IR, Recystin, FGF21, RBP-4, osteonectin.	

Obesity in children and adolescents who do not quick handled can trigger various disease, causes decline quality alive and even can cause early death. Obesity with high risk more tends to be category Metabolically Unhealthy Obesity (MUO) than Metabolically Healthy Obesity (MHO). This is proven with discoveries biomarkers inflammatory in the MUO group higher than MHO and have significant relationship. Obesity is inflammation chronic degrees low. There are several biomarker inflammation found in the study literature this consists of 10 articles like a adiponectin, TNF-α, CRP and hs-CRP, IL-6 and IL-8 (Figure 2).

Figure 2: Pathways obesity until produce inflammatory biomarkers.

Adiponectin function in guard balance metabolic with method increase function network adipose (muscle and fat), increases insulin sensitivity so rate glucose blood awake, set internal fat metabolism body as well as function in response immunity and trade. Anti-inflammatory properties adiponectin given vessel protection, heart, lungs and large intestine. Higher serum adiponectin levels had reported own effect protection to risk cardiovascular and associated with maintained insulin sensitivity in children with obesity. On this study found has happen decline rate adiponectin in blood in adolescents experiencing metabolic unhealthy obesity. There are five articles that prove that the MUO has significant relationship with decline rate adiponectin. Started with healthy eat pattern, then influential to abnormality metabolism resulting from the reduction rate adiponectin. Study Randomized Controlled Trial (RCT) proves people with vegetarian meals pattern have rate higher adiponectin than omnivore. Consumption saturated fatty acids can influence body fat metabolism, it is caused deposition of fat on the endothelium blood vessels in the end create plaque as beginning from inflammation blood vessels. Increasingly production of adiponectin through intake healthy food can avoid inflammation and healthy blood vessels. Adiponectin is also believed guard gut health with guard function intestinal absorption and transport, as well lower risk intestinal obstruction [17].

The cytokine detected in MOU children and adolescents is TNF-α (Tumor Necrosis Factor-Alpha) which is a results secretion macrophages, T cells, B cells and NK (Natural Killer) cells happen dysfunction muscle heart, infection lungs, syndrome metabolism, disorders rate glomerular filtration, rate sour tendon in high blood, low HDL levels and with IL-6 to be factor trigger left heart fail. Enlarged adipocytes is trigger filtration macrophages to location fat accumulation and cause TNF-α The cytokine detected in MOU children and adolescents is TNF-α (Tumor Necrosis Factor-Alpha) which is a results secretion macrophages, T cells, B cells and NK (Natural Killer) cells happen dysfunction muscle heart, infection lungs, syndrome metabolism, disorders rate glomerular filtration, rate sour tendon in high blood, low HDL levels and with IL-6 to be factor trigger fail heart left. Enlarged adipocytes is trigger filtration macrophages to location fat accumulation and cause secretion of TNF-α. High levels of TNF-α can cause shock septic. TNF-α is one cytokines that occur in inflammation obesity consequence. TNF-α plays a role in defense against such bacteria agents, viruses and fungi. Diet using technical deficit calorie and high intake fiber as well as vitamins have proven significant decrease in TNF-α. Guard intake and metabolism body still healthy will avoid somebody from risk disease cardiovascular like coronary heart disease, hypertension, fail kidney disease, insulin resistance, arthritis and others disease. TNF-α at most increases in adolescents with abdominal obesity. Mechanism of molecular TNF-α secretion in adolescent obesity is that TNF-α inhibits activity insulin receptors on organs target so that insulin does not reach it, temporarily it's the pancreas produce insulin and then happen insulin resistance. Following effect biological from TNF-α, like exert neutrophils and monocytes to location inflammation to get rid of Microbe, stimulate macrophages secrete chemokine as well as exertion leukocytes, stimulate hypothalamus to induce hot. TNF-α levels in high amount lower contractility muscle heart, decrease smooth muscle tone, decrease pressure blood until shock [18].

Obesity and aging being potentially cause enhancement biomarker inflammation, like increased CRP (C Reactive Protein) and hs-CRP (high sensitive-CRP). Study prove exists connection between MUO and height rate hs-CRP in obese patients. CRP is closely related with enhancement risk diabetes, hypertension and cardiovascular disease. CRP is protein molecules produced in inflammation acute phase,

produced by an increased liver after 6-8 hours since the occurrence of a stimulus, which is its concentration reach peak on the day second until day third. Normal CRP level is <5 mg/L, in inflammation light can increased by 10-40 mg/L and in inflammation weight 40-200 mg/L (Figure 3).
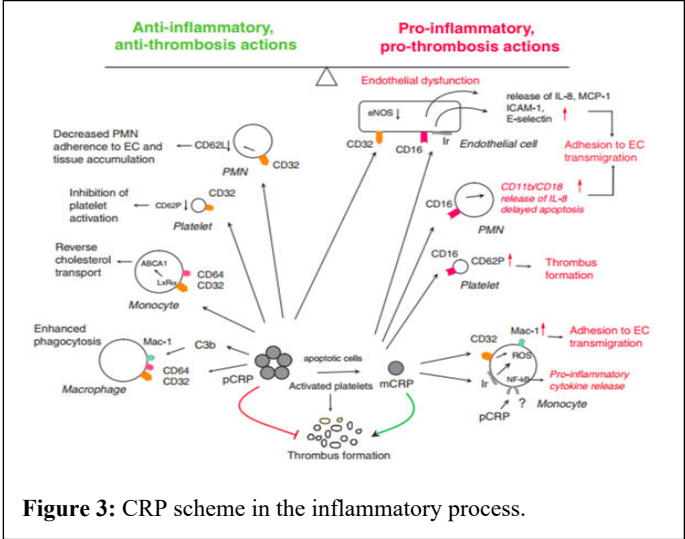

Figure 3: CRP scheme in the inflammatory process.

Based on Figure 3, CRP is divided become mCRP (monomeric CRP) and pCRP (pentameric CRP), each of which works as anti-inflammatory (pCRP) and pro-inflammatory (mCRP). CRP can stimulate secretion monocytes at the time happen inflammation causes change form thrombocyte so that cause thrombus, can activate IL-8 secretion which is also a causative cytokine disturbance function cell endothelium. Change CRP levels by day third is a predictor of mortality some disease. IL-6 is biomarkers that become level of indicator inflammation and damage to the endothelium blood vessels so that happen enhancement atherosclerotic. High levels of IL -6 will influence formation thrombus and cause high risk of cardiovascular disease like hypertension. IL-6 is produced by monocytes in tissues visceral adipose. IL-6 is cast main in inflammation, hematopoiesis and response immune. Circulation healthy individual has 1/3 the level of IL-6. IL-6 is produced will stimulate production of CD4, CD8, T cells and T lymphocytes in the inflammatory process. IL-8 is Cytokines are produced by macrophages (monocytes) and after neutrophils cells and tissues exposed to antigens. IL-8 also induces neutrophils and granulocytes so that migrate to location of infection. IL-8 also affects release histamine and respond to invading viruses breathing channel. Location of infection first of all will release histamine which causes vasodilation of blood vessels and encourage neutrophil migration to that area (Table 2) [19,20].

Table 2: Role of adipokines.

Adipokines	Role	Secretions in adolescents obesity
Adiponectin	Anti-atherogenic, reducing risk of diabetes mellitus	⇓
CRP/hs-CRP	Increase inflammatory, pro-atherogenic	⇑
TNF-a	Pro-atherogenic, pro-diabetic	⇑
IL-6	Increase inflammatory, pro-atherogenetic, pro-diabetic	⇑
IL-8	Pro-atherogenic	⇑

Conclusion

Obesity with Metabolically Unhealthy Obesity (MUO) status in children and adolescents is high risk for experience metabolic disease. This is be marked with enhancement adipokines, namely TNF-α, CRP, IL-6 and IL-8 as well decline adiponectin. Based on results from systematic this literature review obtained conclusion that there is connection between inflammatory biomarkers with MUO in adolescent obesity.

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