MECHANISM OF PHYSICAL EXERCISE ON LOWERING LEVELS OF C-REACTIVE PROTEIN (CRP) IN OVERWEIGHT AND OBESE

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ABSTRACT

The cases of overweight and obesity in the world increased continuously. In 2016, obesity increased by 3% in men and 6% in women compared to 1975. Overweight cases also increased by 20% in men and 23% in women compared to 1975. Overweight and obesity have been linked to an increase in adipose tissue in the body. Increased adipose tissue associated with inflammation, where one of its characteristics is an increase levels of C - Reactive Protein (CRP). This study aimed to describe the mechanism of physical exercise to diminish CRP level in overweight and obesity. Adipose tissue produced and released various pro-inflammatory and anti-inflammatory factors, such as leptin, adiponectin, resistin, TNF-?, IL-6, MCP-1 and CRP. One of the prevention and treatment of inflammatory for overweight and obesity cases was to do physical exercise. In cases of overweight and obesity, the physical exercise aims to increase energy expenditure. Physical exercise decreased the volume and amount of adipose and pre-adipose tissue as well as the number of endothelial cells and macrophages in adipose that contained pro-inflammation, such as IL-1, TNF-?, CRP, serum amyloid protein (SAA), and cytokines. Physical exercise risen anti-inflammatory properties, such as IL-10, IL-1ra which played a role in inhibiting the transduction of IL-1? signals and inhibiting TNF-? synthesis. Physical exercise also amplified antioxidant enzymes, such as SOD and GPX. The antioxidants played a role in fighting free radicals to reduce inflammation.

***Keywords**: overweight; obesity; inflammation; CRP; exercise; anti-inflammatory*

ABSTRAK

Kasus overweight dan obesitas di dunia terus mengalami peningkatan. Pada tahun 2016 obesitas mengalami peningkatan 3% pada laki-laki dan 6% pada perempuan dibandingkan tahun 1975. Kasus overweight juga mengalami peningkatan yaitu 20% pada laki-laki dan 23% pada perempuan dibandingkan tahun 1975. Overweight dan obesitas telah banyak dikaitkan dengan peningkatan jaringan adiposa di dalam tubuh. Peningkatan jaringan adiposa berhubungan dengan terjadinya inflamasi, yang ditandai antara lain dengan adanya peningkatan kadar C-Reactive Protein (CRP). Artikel ini bertujuan untuk memapaparkan mekanisme latihan fisik terhadap penurunan kadar CRP pada overweight dan obesitas. Jaringan adiposa menghasilkan dan melepaskan berbagai faktor pro-inflamasi dan anti-inflamasi seperti leptin, adiponektin, resistin, TNF-?, IL-6, MCP-1 dan CRP. Salah satu pencegahan dan penanganan inflamasi kasus overweight dan obesitas adalah dengan melakukan latihan fisik. Pada kasus overweight dan obesitas, latihan fisik bertujuan untuk meningkatkan pengeluaran energi. Latihan fisik menurunkan volume dan jumlah jaringan adiposa dan pre-adiposa serta jumlah sel endotel dan makrofag di adiposa yang mengandung pro-inflamasi seperti IL-1, TNF-?, CRP, serum amiloid protein (SAA), dan sitokin. Latihan fisik meningkatkan anti-inflamasi seperti IL-10, IL-1ra yang berperan dalam menghambat transduksi sinyal IL-1? dan menghambat sintesis TNF-?. Latihan fisik juga meningkatkan enzim antioksidan seperti SOD dan GPX. Peningkatan antioksidan berperan dalam melawan radikal bebas sehingga menurunkan terjadinya inflamasi.

***Kata kunci**: overweight; obesitas; inflamasi; CRP; latihan fisik; anti-inflamasi*

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INTRODUCTION

Heart disease, atherosclerosis, hypertension, and type 2 diabetes mellitus are the risk of diseases caused by overweight and obesity. The cases of obesity in the world in 2016 has increased by 3% in men and 6% in women compared to 1975 (World Health Organization 2016). Whereas overweight cases have increased by

20% in men and 23% in women compared to 1975 (World Health Organization 2016). In Indonesia, cases of obesity in 2018 amounted to 21.8% of Indonesia's population and 13.6% including overweight (Basic Health Research, 2018). This indicates that there is a need for prevention and treatment of overweight and obesity for reducing the prevalence.

The increase of overweight and obesity is partly due to the high-calorie intake (high-calorie diet) and the lack of physical activity. Kurdanti et al (2015) found that obese adolescents had a higher average energy intake than non-obese adolescents. The adolescent who had more active physical activity, had a lower risk of obesity compared to inactive one. This can occur, because calories excess in the body is stored in the form of glycogen and fat. The lack of physical activity also supports an increase of fat (triglycerides) as a result of lower energy expenditure than energy intake. This also leads to an increase of C-reactive protein (CRP).

C-reactive protein (CRP) is an indicator used to determine risk factors for various diseases, such as hypertension, heart disease, and atherosclerosis and the level of systemic inflammation. Overweight and obesity have a significant correlation with CRP, because 75% of overweight and 93.5% of obesity have high CRP levels (Lavanya et al 2017). The CRP level more than 3 mg/L have an increased risk of coronary heart disease and diabetes (Soinio et al 2006). Lavanya et al (2017) found average CRP levels in normal people about 2.37 mg/L, in overweight people about 6.63 mg/L, and obese people about 10.22 mg/L.

Physical exercise can prevent and treat overweight and obesity through one the several the mechanisms including the reduction of CRP levels. Continuous physical exercise significantly reduces CRP levels in obese and breast cancer women (Tizdast et al 2016). Continuous aerobic exercise also significantly reduces CRP levels in cases of type 2 DM (Alizadeh et al., 2012). Continuous physical exercise with moderate-intensity (55-59% HRR) can also reduce CRP levels in cases of obesity (Vella et al 2017). Based on previous evidence, this study aimed to describe the mechanism of physical exercise to diminish CRP level in overweight and obesity.

OVERVIEW

C-Reactive Protein

C-Reactive Protein (CRP) is a protein secreted mainly by hepatocyte cells in response to inflammation, injury, and infection. Tillet and Francis in 1930 firstly identified CRP in the blood of patients infected with Pneumoccocal pneumonia by identifying substances that can precipitate and interact with phosphorylcholine residues from C polysaccharides, and their ability to precipitate calcium ions (Tillet & Francis 1930). The CRP belongs to the amino acid family of short pentraxin with high phylogenetic conservation (Mantovani et al 2008). CRP is one of an important regulators of the body's immune system and mediators of acute responses which link to various chronic or systemic inflammatory diseases.

CRP plays a role in inflammation of the body's immune system. CRP binds to phospholipids especially lysophospholipids and recognizes bacterial lipids as well as parts of the innate immune system (Strang & Schunkert 2014). CRP binds to bacteria or cells and interacts with NK cells and monocytes, activates endothelial cells to increase the adhesion of molecules, chemokines, and cytokines and mediates LDL uptake into macrophages (Chandrashekara 2014). CRP also strengthens the inflammatory response in both acute and chronic.

CRP is mainly synthesized by liver cells (hepatocytes). In healthy individuals, the CRP serum levels are around 1 mg/dl (Zhou et al 2016). When receiving a stimulus, such as a bacterial infection and tissue injury, hepatocytes will synthesize and secrete CRP to the blood circulation 1000 times higher than the basal condition (Zhou et al 2016). Hepatocytes are stimulated by IL-6 and gradually rise by IL-1? and TNF-? (Salazar et al 2014). STAT3, C/EBPs, and NF?B play a role in increasing CRP transcription (Zhou et al 2016). Obesity or an increase in fatty tissue (hypertrophy or hyperplasia) causes an increase in chronic inflammation. Increased inflammation triggers an increase in the synthesis of cytokines and cell pro-inflammatory proteins, such as neutrophils, monocytes, IL-6, and TNF-? (Teixeira et al 2014). An increment of IL-6 causes a raise of CRP production in hepatocytes. If the increment of IL-6 continues, the serum CRP levels will be higher due to chronic inflammation.

On the other hand, CRP is not only synthesized in the liver, but in other cells where mRNA is located and can respond to inflammation. The mRNAs that have been found in extra-hepatic sites include adipose tissue, lungs, atherosclerotic lesions, renal tubular epithelial cells, lymphocytes, macrophages, and smooth muscle cells (Salazar et al 2014). CRP is synthesized as a monomer and then converted to a pentamer in the endoplasmic reticulum. In hepatocyte cells, pentameric protein is retained in the endoplasmic reticulum and CRP is released slowly at rest (non-inflammatory) (Sproston & Ashworth 2018). When it gets an inflammatory stimulus, CRP is secreted in the blood

vessels quickly. Then serum CRP levels tend to increase significantly 6-8 hours after the initial stimulus and reach a peak at 24-48 hours, with a half-life of about 19 hours and the concentration is determined by the rate of synthesis (Salazar et al 2014).

Other effect of CRP is that the CRP influences an apoptosis. Devaraj et al. (2005) found that CRP stimulates the production of pro-apoptotic cytokines and pro-inflammatory mediators such as IL-1?, TNF-?, and reactive oxygen compounds. CRP also regulates p35 in monocytes and affects CD32 thereby inducing apoptosis (Kim et al 2014). CD32 has been shown to trigger apoptotic signals and is expressed on monocytes that are polarized into pro-inflammatory macrophages (Tugal et al 2013). This presents that CRP could cause apoptosis in monocytes.

CRP has a role in cardiovascular disorders. CRP is involved in monocyte adhesion and recruitment of intracellular molecules such as E-selectin and monocyte chemoattractant protein-1 (MCP-1) in atherosclerotic plaques (Sproston & Ashworth 2018). CRP also plays a role in increasing LDL uptake in macrophages and activating the complement system that leads to atherogenesis (the process of plaques formation in arteries). The role of CRP in atherosclerosis is what makes CRP as an indicator of cardiovascular risk. CRP also causes apoptosis of smooth muscle cells in the human coronary heart mediated by caspase 3 (Blaschke et al 2004).

CRP has been extensively studied concerning cardiovascular diseases, such as atherosclerosis, heart failure, and myocarditis. High sensitivity CRP reagent is also used to detect basal CRP levels in patients at risk of cardiovascular disease. Individuals who have CRP levels higher than 3 mg/L have an increased risk of coronary heart disease and this risk is increased in cases of diabetes (Soinio et al 2006). The importance of CRP measurement is to detect early risk of cardiovascular disease so that prevention and treatment can be done.

Table 1. CRP levels for the risk of cardiovascular

CRP Levels	The Level of Cardiovascular Risk
<1 mg/L	Low
1-3 mg/L	Medium
>3 mg/L	High

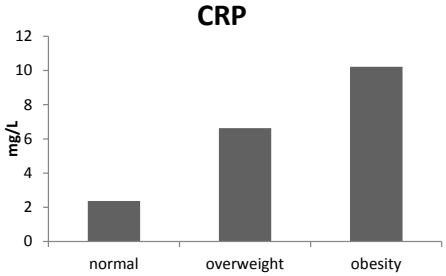
Source: Bonaca and Morrow (2008)

In atherosclerosis, CRP had various influences, such as activating the complement and apoptotic systems, activation of vascular cells, recruitment of monocytes, fat accumulation and thrombosis. CRP also activated NF?? which increases the production of cytokines, chemokines, molecular adhesions, growth factors, and cell immune receptors in atherosclerotic plaques (Salazar et al 2014). CRP also regulated endothelial cell activation and dysfunction, by inducing the expression of intracellular adhesion molecules, E-selectin and monocyte chemoattractant protein-1 (MCP-1) which allowed chemotaxis and binding of monocytes to endothelial cells during the early stages of atherogenesis (Chi et al 2002, Hattori et al 2003). The awareness of the rising level of CRP in atherogenesis should be realized to prevent the risk of plaques formation in in blood vessels.

CRP on Overweight and Obese

Overweight and obesity had more adipose tissue in the body than normal people. There were 2 kind of adipose tissues, namely brown and white adipose tissue. In newborns, brown adipose tissue helped to regulate energy expenditure through thermogenesis mediated by the expression of Uncoupling protein-1 (UCP-1) (Aaron et al., 2009). White adipose tissues had an active role in regulating physiological and pathological processes, such as immunity and inflammation (Karastergiou & Mohamed-Ali 2010). Increased adipose tissue associated with inflammation was characterized by an increase in C-Reactive Protein (CRP). Various studies had proven that CRP levels of overweight and obesity were higher than non-overweight and obese persons (Dayal et al 2014, Ishii et al 2012, Lavanya et al 2017, Mirhoseini et al 2018, Shilpa et al 2014).

The average CRP level in normal people was around 2.37 mg/L in overweight people around 6.63 mg/L and obese people around 10.22 mg/L with aged from 20 to 70 years (Lavanya et al 2017). Dayal et al (2014) found an average CRP level in overweight and obese adolescents around 3.92 mg/L and normal/non-obese adolescents around 2.15 mg/L in India with an average age of 11 years. Normal adults had an average CRP level of around 1.2 mg/dl, overweight and obese adults had an average CRP level of about 3.8 mg /dl withan average age of 32-34 years (Shilpa et al 2014).



Source: Lavanya et al (2017)

Figure 1. CRP serum level in a person with normal, overweight, obesity BMI-70 year-old

Inflammation that occured in overweight and obesity was chronic inflammation. This was marked by lymphocytes, macrophages, the proliferation of blood vessels and connective tissue (Seki et al 2009). Macrophages were a component of adipose tissue and actively participate in the immune system (Ellulu et al 2017). Adipose tissue produced and released various pro-inflammatory and anti-inflammatory factors, such as leptin, adiponectin, resistin, TNF-?, IL-6, MCP-, and CRP. One-third of the total IL-6 concentration came from adipose tissue (Fontana et al 2007). Excessive pro-inflammatory cytokines in overweight and obesity had been considered as links to inflammation.

The exessive nutrients that entered the body were responded by adipose tissue through adipocyte hyperplasia and hypertrophy. An enlargement that occured in adipocytes progressively caused the blood supply to adipocytes to decrease, thereby causing hypoxia (Cinti et al 2005). Hypoxia triggered necrosis and infiltration of macrophages into adipose tissue and causes increased production of pro-inflammatory cytokines. Macrophages produced three pro-inflammatory mediators including TNF-?, IL-6 and adiponectin (Karastergiou & Mohamed-Ali 2010). IL-6 was a stimulus for hepatocytes to produce and secrete CRP and assisted by TNF-? and IL-1? (Salazar et al 2014, Zhang et al 2009). The accumulation of free fatty acids in overweight and obesity activated the pro-inflammatory serine kinase cascade, such as IkB kinase and c-Jun N-terminal kinase which promoted adipose tissue to release IL-6 and triggered hepatocytes to synthesize and secrete CRP (Rocha & Libby 2009).

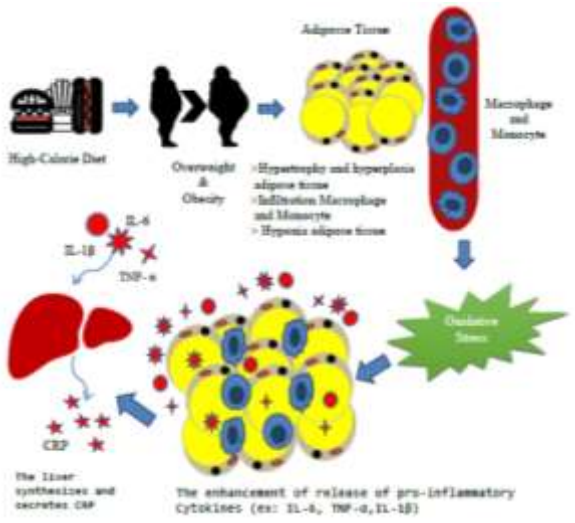


Figure 2. Mechanisms of increasing CRP in overweight and obesity

The relationship between overweight and obesity to CRP has been described as pathophysiological. Klisic et al. (2014) found that CRP and triglyceride (TG) levels were higher in overweight women compared to normal women. Dayal et al (2014) revealed and identified through anthropometric measurements correlate with CRP in children in India, it showed that each increase of 1 unit of BMI could increase the CRP odds ratio by 37%. Increased CRP in overweight and obesity had also been linked to various risks such as atherosclerosis due to decreased endhothelial nitric oxide synthase (eNOS) activity, thereby reducing nitric oxide (NO) levels and increasing concentrations of ET-1 (endhotelin-1) as vasoconstrictors which weaken the endothelium vasodilation process (Teixeira et al 2014). Vasoconstriction caused an increase in shear stress resulting in greater damage to blood vessels and created conditions that led to atherosclerosis and thrombus formation (Teixeira et al 2014).

Physical Exercise on Overweight and Obese Person

Exercise is a physical activity carried out in sequence and repeatedly to improve body fitness. Physical exercise in people with overweight and obesity aims to increase energy expenditure and body physiology and reduce adipose tissue and weight. Physical exercise is also able to increase anti-inflammatory which can suppress pro-inflammation such as CRP. Moderate-intensity aerobic physical exercise for 12 weeks significantly decreases CRP levels in obese children with or without metabolic syndrome in Egypt (Kamal & Ragy 2012). Continuous moderate-intensity exercise reduces CRP levels significantly in women with obesity and breast cancer (Tizdast et al 2016).

Adaptation to physical exercise in overweight and obese people affects the level of inflammation. Physical exercise affects the immune system by reducing the number of mononuclear cells in peripheral blood which are a source of pro-inflammatory cytokines such as (IL-1, IL-6, IL-1?, IL-8, CRP) (Echavez et al 2016). Physical exercise also enhances anti-inflammatories such as IL-10, IL-1ra which have important part in inhibiting the transduction of IL-1? signals and inhibiting TNF-? synthesis (Pedersen 2017). A decrease in IL-6 also affects a decrease in CRP, IL-6 is a stimulator of liver CRP secretion. Continuous moderate exercise can reduce levels of CRP and IL-6 in cases of obesity (Vella et al 2017). These evidences revealed exercise can decrease pro-inflammatory and increase anti-inflammatory thereby reducing the level of systemic inflammation and CRP.

Physical exercise decreased inflammation by reducing fat mass in cases of overweight and obesity. Physical exercise decreased the volume and amount of adipose and pre-adipose tissue and the number of endothelial cells and macrophages in adipose containing pro-inflammatory such as IL-1, TNF-?, CRP, serum amyloid protein (SAA) and cytokines (Nicklas et al 2005, Echavez et al 2016, Sirico et al 2018). Physical exercise decreased fat mass which caused an increase in free radicals and oxidative stress consequently reducing inflammation and CRP levels. Physical exercise also enhanced regulation of the Nrf2 gene where physical exercise increased free radicals which stimulated Nrf2 to increase the transcription of antioxidant enzymes (Done & Traustadóttir 2016). Antioxidants ' function was fighting free radicals as a result the inflammation reduced.

The role of physical exercise in reducing CRP levels and pro-inflammation in overweight and obesity varied depending on the type of exercise as well. Moderate-intensity aerobic exercise using treadmills and elliptical trainers for 6 weeks could reduce CRP levels by 29% in postmenopausal obese women (Ryan et al., 2014). The combination of walking aerobic physical exercise and strength training for 60 minutes with diet also decreased average CRP levels from 7.6 to 5.3 mg/L in overweight and obese adults with knee osteoarthritis with an average age of 65 years (Beavers et al 2015). Continuous moderate-intensity exercise using treadmills, ergometer and elliptical cycles for 8 weeks reduced average CRP levels from 21.9 nmol/L (0.0003942 mg/L) to 14.9 nmol/L (0.0002682 mg/L) in overweight and obese cases with the adult age of 28 years (Vella et al 2017).

Figure 3. Alteration of CRP serum level.

Pre= before training session, Post= after training session. Adopted data from Kamal dan Ragy (2012)*, Vella et al. (2017)** and Beavers et al. (2015)***.

Moderate aerobic exercise with walking and running for 12 weeks decreased the average CRP level from 2.1 mg/L to 1.2 mg/L in obese children with metabolic syndrome in Egypt at the age of 8-12 years (Kamal & Ragy 2012). Endurance training with submaximal intensity running (34 minutes) for 8 weeks reduced average CRP levels from 4620 pg/ml (0.00462 mg/L) to 595 pg/ml (0.000595 mg/L), and resistant exercises, such as pull-down, bench press, leg press, calf exercise, biceps curls, leg curls, lateral raise by dumbbell and overhead press reduced the average CRP level from 4411 pg/ml (0.004411 mg/L) to 666 pg/ml (0.000666 mg/L) in overweight and obese women with a mean age of 22 years (Mogharnasi et al 2019). The selection of the accurate dose of exercise was needed to get maximum results for overweight and obese. However, the principle of physical exercise was that physical exercise should be carried out regularly and progressively (gradually increasing). It would have a positive impact on reducing the level of inflammation including CRP in overweight and obese persons.

CONCLUSION

People with overweight and obesity had risk factors for various diseases, such as heart disease, metabolic syndrome, atherosclerosis, hypertension, and type 2 diabetes mellitus. As risk factors, overweight and obesity were associated with chronic inflammation through increased pro-inflammation such as IL-6, TNF-? and CRP. TNF-? is secreted excessively when overweight and it plays a role in increasing the rate of CRP synthesis. IL-6 is associated with obesity and it stimulated the liver to synthesize and secrete CRP associated with systemic inflammation. Inflammation was also followed by vascular and endothelial dysfunction that is characterized by a decrease in nitric oxide and an increase in reactive oxygen species (ROS) and can cause atherosclerosis, hypertension, changes in

metabolic markers and leads to heart disease. Physical exercise had an important part in increasing the physiology function and energy expenditure of the body. Physical exercise increased antioxidant enzymes, such as superoxide dismutase (SOD) and anti-inflammatories which consisted of IL-10, IL-1ra, and adiponectin that could suppress free radicals and pro-inflammatory. Physical exercise could also reduce fat mass, free fat mass, pro-inflammatory, such as IL-6 TNF-? and CRP.

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