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Mechanism of Pufas (Polyunsaturated Fatty Acids) in Soy Milk Against Insulin Resistance Improvement

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ABSTRACT

Diabetes mellitus (DM) still becomes a health problem in many countries around the world. Among DM cases, almost 90-95% are diabetes mellitus type 2 (DMT-2). Diabetes mellitus is closely associated with the condition of insulin resistance. Improvement of insulin resistance in DMT-2 can be conducted in pharmacologic and non-pharmacologic. One of non-pharmacological improvement efforts is the administration of soy milk. Soy milk contains PUFAs (polyunsaturated fatty acids) consisting of linoleic acid (n-6) or omega-6 and alpha-linolenic acid (n-3) or omega 3. Epidemiological studies have shown that administration of a diet which contains PUFAs particularly alpha-linolenic acid (n-3) can reduce insulin resistance and impaired glucose tolerance in DMT-2. PUFAs can reduce insulin resistance through the mechanism of activation of PPAR (α and γ) and the increased secretion of adiponectin.
KEYWORDS: PUFAs, insulin resistance

INTRODUCTION

Diabetes mellitus (DM) still becomes a health problem in many countries around the world. According to the International Diabetes Federation (IDF), the world's population experiencing DM in 2012 has reached 371 million and is estimated to reach 592 million in 2035 or increase of 55%. IDF data in 2012 shows that Indonesia ranks 7th world's largest number of diabetic patients, namely about 7.6 million, with the number of death amounted to 155 thousand people per year. Among DM cases, almost 90-95% are diabetes mellitus type 2 (DMT-2). DMT-2 is a metabolic disease characterized by chronic hyperglycemia and hyperinsulinemia. Diabetes mellitus is closely associated with the condition of insulin resistance.

The insulin resistance improvement or management aims to prevent further complication namely the occurrence of DMT-2. The improvement of insulin resistance in DMT-2 can be conducted in pharmacologic and non-pharmacologic. Pharmacological improvement is done by administering drugs to improve insulin sensitivity. While non-pharmacological improvement is in the form of lifestyle changes, physical exercises and nutritional therapies such as soy milk administration [1].

Soy milk is one of processing products from the extraction of soybean. Soy milk protein has an amino acid sequence that is almost similar to cow milk so that soy milk is often used as a substitute for cow milk, especially for those who are allergic to animal proteins [2]. Soy milk is available in liquid or powder form. Soy milk is a high nutritious drink, especially its protein content. Besides soy milk also contains fat, carbohydrates, calcium, phosphorus, iron, pro-vitamin A, vitamin B complex (except B12), water, PUFAs (polyunsaturated fatty acids), and is flavones.

The administration of soy milk is more effective than the administration of soy milk extract. Administration of soy milk has the inhibitory effect of the production of pro-inflammatory cytokines, including more significant TNF-α, IL-6, IL-βand prostaglandin than that of soy milk extract [3]. Many studies have been done associated with the use of soy in cases of obesity and diabetes mellitus. One of soy contents which are currently developed in the research is isoflavone genistein content. In addition, soy milk also contains PUFAs.

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PUFAs (polyunsaturated fatty acids), usually called plural unsaturated fatty acidsare a fatty acid containing two or more double bonds, are liquid at a room temperature and remain liquid even at cold temperature due to its melting point. PUFAs natural sources which are essential for the health are nuts and seeds such as soybean. PUFAs are classified in the long chain fatty acids as found in Figure 1 below.

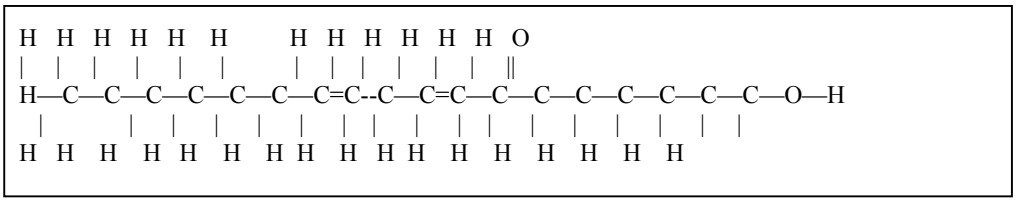

Figure 1. Long Chain PUFAs

Fat in soybean mostly consists of unsaturated fatty acids and the rest is saturated fatty acids. Unsaturated fatty acids contained in soybean are in the form of linoleic acid, oleic acid and arachidonic. Soybean contains about 18-20% fat and of that number consists of unsaturated fatty acids that are free of cholesterol. In addition, the soybean fat contains several important phospholipids namely lecithin, sepalin and lipositol [4].

PUFAs consist of linoleic acid (n-6) or omega-6 and alpha-linolenic acid (n-3) or omega 3. Epidemiological studies have shown that the administration of a diet containing a lot of PUFAs, particularly alpha-linolenic acid (n-3), can decrease insulin resistance and impaired glucose tolerance in diabetes mellitus type 2. Soybean has a high fat content namely between 14-24% and the average 18% are unsaturated fatty acids and 15% are saturated fatty acids. The composition of fatty acids contained in soybean can be seen in Table 1 below.

Table 1. Fatty Acid Sequence of Soybean

Type of fatty acid	Total (%)
Saturated fatty acids	
Palmitic acid	7 – 10
Stearic acids	2 – 5
Arachidonic acids	0.2 – 1
Lauric acids	0 – 0.2
Unsaturated fatty acids	
Linoleic acids	25 – 64
Oleic acids	11 – 60
Linoleic acids	1 – 12
Hexadecanoic acids	1 – 5

One of the factors underlying the development of insulin resistance is the increased level of free fatty acids in the plasma. The increased level of free fatty acids in the plasma will cause insulin resistance, among others (1) the excessive production of TNF-α cytokines can decrease insulin sensitivity so that it stimulates the development of insulin resistance (2) hyperlipidemia can increase the activity of tyrosine phosphatase enzyme which may cause decreased activity of Insulin Signaling through protein dephosphorylation of insulin receptor substrate 1 (IRS-1)[5,6,7]. With insulin resistance, signal transduction through the insulin receptor is interrupted with a marked decrease in downstream activation of protein molecules such as IRS-1, Akt, and PKC (protein kinase C) involved in the stimulation of protein translocation of Glucose transport 4 (GLUT-4) to the cell surface [8].

The mechanism of soy milk to improve the activity of IRS-1 and GLUT-4 in the condition of insulin resistance occurs indirectly, some of the soy milk contents works by affecting the activity of several proteins which are up-regulation of IRS-1 and GLUT-4. One of soy milk contents which is very instrumental to the improvement of the activity of IRS-1 and GLUT-4 is PUFAs.

Based on the description above, further discussion about the content of PUFAs (polyunsaturated fatty acid) in soy milk to the improvement of insulin resistance is needed. PUFAs can improve insulin resistance through several mechanisms, among others, (1) the activation of PPAR (α and γ) and (2) an increase in the secretion of adiponectin. The explanation of the two mechanisms is as follows.

Mechanism of PUFAs to the Activation of PPAR (α and γ)

PPAR (Peroxisome proliferator activated receptor) has three isoforms, namelyα, β/δ, andγ. PPAR-α plays a role in beta-oxidation of fatty acids and is highly expressed in the liver, kidney, heart, and muscle [9]. PPAR-β/δ contributes to the stimulation of fatty acid oxidation. While PPAR-γ is the main regulator of adipogenesis which plays an important role in fat and glucose storage as well as cholesterol metabolism. PPAR-γ is highly expressed in adipose tissue [10].

Epidemiological studies have shown that the administration of a diet containing a lot of PUFAs, particularly alpha-linolenic acid (n-3) or omega 3 can reduce insulin resistance and impaired glucose tolerance in DMT-2. The mechanism of omega 3 in lowering insulin resistance is to change membrane fluidity and receptor function on the cell membrane. Besides omega 3 is also a ligand for PPAR-γ that regulates the expression of genes involved in homeostasis [11]. Activation of PPAR-γ will lead to increased adipogenesis, thus causing a decrease in the concentration of fat in the blood [12]. The mechanism of regulation of fat metabolism by PPAR can be seen in Figure 2 below.

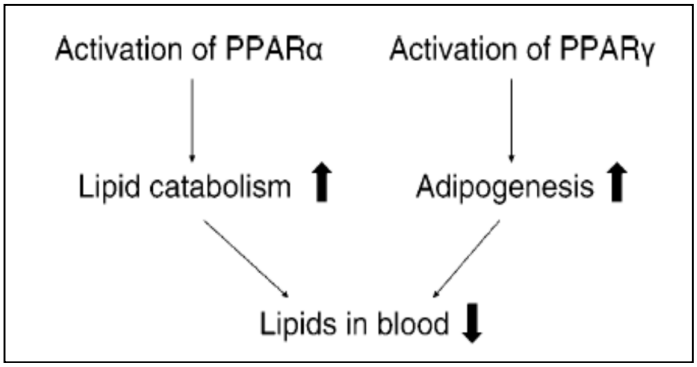

Figure 2. The Mechanism of Regulation of Fat Metabolism by PPAR [13]

Activation of PPAR-γ leads to the increased of gene expression encoding the GLUT-4 resulting in GLUT-4 up-regulation. GLUT-4 is required to transport the glucose into the muscle cells. Glucose transportation on insulin resistance can be explained by a defect in GLUT-4regulation including at the level of expression, translocation, and enters the cell surface membrane or intrinsic activity. Research by Carvalhoin subjects with insulin resistance showed that there is a decline of about 60% of the glucose transportation stimulated by insulin [14]. Activation of PPAR-γ on insulin resistance leads to increased insulin sensitivity in the liver resulting in suppression of hepatic glucose production and insulin sensitivity skeletal which leads to an increased uptake of glucose [11]

In the experimental individuals and animals that are DMT-2, specific ligands of PPAR-γ are anti-diabetic components that can reduce hyperglycemia and hyperinsulinemia particularly in fat tissue [15]. The mechanism of activation of PPAR-γwill increase the inflow (channeling) of free fatty acids to adipose tissue so as to decrease the concentration of fatty acids in the plasma. This causes the response of TNF-α decreases resulting in an increase of insulin signal transmission through the increased activity of tyrosine kinase in the insulin receptor and IRS-1 activation. Reduced availability of free fatty acids may reduce insulin resistance.

Mechanism of PUFAs to the Increased Adiponectin Secretion

Another very important factor contributing to insulin resistance is adiponectin. Adiponectin is adipokine which has insulinomimetic properties. This hormone is characterized in 1995 and 1996 by four groups of scientists using different methods. Low level of adiponectin is found in obesity and the administration of adiponectin improves the state of insulin resistance in animal models. Adiponectin functions in increasing the sensitivity of the body organs to insulin, thus contributing to regulate glucose balance in the body. In normal condition, adiponectin will maintain blood glucose balance through the reduction of glucose produced by the liver and maximize the use of glucose by the body organs that need sugar as an energy source [16].

With insulin resistance, there is a decreased level of adiponectin. Adiponectin is a new adipokine class which has an important role in various biological effects of adipose tissue. A research conducted by Ajuwon showed that adiponectin actively participates in the improvement of

insulin sensitivity in lipid and glucose metabolism [17]. The mechanism of adiponectin improving insulin sensitivity is very complex. The data show that in the animals, there is a decreased insulin resistance by adiponectin due to changes in the content of free fatty acids and triglycerides. Mice that received the injection of adiponectin result in decreased level of free fatty acids through the increased free fatty acid oxidation in muscle cells. Adiponectin also lowers triglyceride levels through an increase in PPAR-α and γ gene expression.

The increased level of triglycerides affects insulin stimulated activation against phosphatidylinositol 3 kinase and protein translocation of glucose transporter 4 (GLUT-4) and glucose uptake, which cause insulin resistance resulting in decreased level of free fatty acids and tissue triglycerides. In this case, adiponectin will improve insulin sensitivity. Adiponectin also increases the molecule stimulation of tyrosine phosphorylation of signaling, insulin receptor, insulin receptor substrate 1 (IRS-1) and skeletal muscle actin.

Some studies show that adiponectin plays an important role in obese subjects who have insulin resistance. Adiponectin increases the phosphorylation of AMP-activated kinase, an enzyme that plays a role against the insulin-sensitizing and decreased level of glucose. Adiponectin can increase the activity of peroxisome proliferator activated receptor α (PPAR-α), which can decrease liver glucose production, increase the glucose uptake and free fatty acid oxidation in muscle [16, 17]. The role of adiponectin to the increased insulin sensitivity can be seen in Figure 3 below.

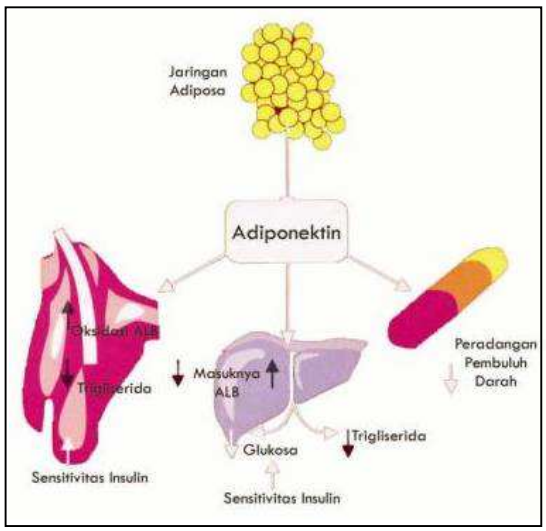

Figure 3. The Role of Adiponectin to the Increased Insulin Sensitivity

The concentration of adiponectin in the body will decrease on the state of obesity and insulin resistance. The administration of adiponectin improves insulin resistance in animal models. Mice lacking adiponectin will suffer premature glucose intolerance induced by diet and insulin resistance as well as experience the increased serum fatty acids [18]. In contrast, transgenic overexpression of adiponectin in mice leads to improvement in insulin sensitivity, glucose tolerance, and decreased level of serum fatty acids. In the liver, adiponectin increases insulin sensitivity, lowers the influx of fatty acids, increases fatty acid oxidation, and reduces hepatic glucose output. In muscle, adiponectin stimulates the use of glucose and fatty acid oxidation probably due to the activation of cellular fuel sensor, AMPK.

High level of adiponectin will increase insulin sensitivity in peripheral tissues. Its level is lower in DMT-2 and prediabetic patients. Hipoadiponectinemia can predict the occurrence of DMT-2 in normal people. The results of animal studies and several studies on the metabolic showed that adiponectin may decrease their risk of diabetes through the process of gluconeogenesis suppression in the liver, stimulation of free fatty acid oxidation in the liver, the increased glucose uptake in skeletal muscle and can also stimulate the secretion of insulin in the pancreas.

Hipoadiponectinemia has now been reported as a new risk factor for developing diabetes [3]. Research on the people of Korea showed that adiponectin level is lower in the non-diabetic populations who have a family history of diabetes when compared with populations that do not have

a family history of diabetes [23]. The research also showed that lower adiponectin level in populations with a family history of diabetes is not affected by the presence of obesity and insulin resistance.

Omega 3 in PUFAs affects the secretion of adiponectin. Adiponectin increases the phosphorylation of AMP-activated kinase, an enzyme that plays a role against the insulin-sensitizing and decreased glucose level. Adiponectin can increase the activity of peroxisome proliferator activated receptor α (PPAR-α) so as to decrease liver glucose production, increase the glucose uptake and free fatty acid oxidation in muscle. From the research conducted by M. Kolapo Ajuwon, it is found that adiponectin directly suppresses the expression of TNF-α mRNA in adipocytes, other adipocytes, macrophages, and inflammatory mediators that are associated with obesity in adipose tissue. Furthermore, the direct induction of PPAR-Ɣ by adiponectin indicates that the transcription factor of PPAR-Ɣ suppresses the activity of NK-kB and the production of IL-6 and IFN-α [17].

Omega 3 can increase adiponectin levels due to the suppression of inflammatory mediators through decreased activation of NF-kB (through a reduction in IKB phosphorylation) and the activation of peroxisome proliferator activated receptor Ɣ, thus lowering the liver glucose production, increasing the glucose uptake and oxidation of free fatty acids in muscle [19,20,21]. Omega-3 fatty acids also regulate the secretion of adiponectin and activate other elements of genetic transcription, namely PPAR-α and γ, which are an important control of lipid metabolism and insulin sensitivity [20,21,22].

Conclusion

PUFAs (polyunsaturated fatty acids) can improve insulin resistance through several mechanisms, (1) the activation of PPAR (α and γ) and (2) an increase in the secretion of adiponectin. PUFAs contribute to the activation of PPAR-γ. The activation of PPAR-γcauses an increase in expression and translocation of GLUT-4. The mechanism of activation of PPAR-γ will increase the inflow (channeling) of free fatty acids to adipose tissue so as to decrease the concentration of fatty acids in the plasma. This causes the response of TNF-α decreases resulting in an increase of insulin signal transmission through the increased activity of tyrosine kinase in the insulin receptor and IRS-1 activation. PUFAs also affect the secretion of adiponectin. Adiponectin increases the molecule stimulation of tyrosine phosphorylation of signaling, insulin receptor, insulin receptor substrate 1 (IRS-1) and skeletal muscle actin.

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