Oral supplementation of the Extract of Fish oil to reduce fasting blood Glucose and Endothel damage but not Malondialdehyde level in diabetic male Wistar Rat (Rattus norvegicus)

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Oral supplementation of the Extract of Fish oil to reduce fasting blood Glucose and Endothel damage but not Malondialdehyde level in diabetic male Wistar Rat (Rattus norvegicus)

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Abstract. The main target of hyperglycaemia is endothelial dysfunction involving pathways; protein kinase activation, hexosamine activation, polyol activation, and Advanced Glycation End Products (AGEs) formation, trigger reactive radical superoxide (O2•-) to stress oxidative. Malondialdehyde (MDA) is an end product of lipid peroxidation in body and is an indicator of oxidant-antioxidant level in diabetic patients. Fish oil composing mostly omega 3 as an antioxidant can reduce oxidative stress and hyperglycaemic condition. This study aimed to investigated the effects of omega-3-rich fish oil in lowering blood sugar levels, inhibiting oxidative stress and aortic endothelial cell damage in diabetic rat models. This study was an experimental study using post-test only control group design. Thirty-two rats divided into two study groups (n = 16 individuals per group), including the diabetic rat's group (as control) and the diabetic rats group given fish oil doses of 300 mg/kilogram body weight/day. Provision of fish oil was performed for 28 days used Blackmores® fish oil. Blood sugar and malondialdehyde levels were analyzed by spectrophotometric method. The number of aortic endothelial cells was analyzed by haematoxylin-eosin staining. Comparability test showed that the average number of fasting blood glucose level after treatment in both groups showed highly significant differences (p=0.00). Although MDA level was reduced in treatment group than control group, but statistically not significantly difference, p=0.43. Comparability test showed that average of endothelial cell between control and treatment group significantly different (p=0.00). It was concluded that fish oil supplementation containing omega-3 in diabetic rats can lower blood glucose level and can inhibit endothelial cell damage.

1. Introduction

Hyperglycemia can trigger inflammation process that cause aging and many complications such as microvascular and macrovascular. As a result, this complication and mortality cause socio-economic burden and public financing system [1]. The main target of hyperglycemia is endothelial cell, trigger endothelial dysfunction and atherosclerosis. Endothelial dysfunction is inability to control vascular homeostasis [2,3]. Many evidences declare that endothelial dysfunction happen on type 1 and 2 diabetics. The main target of hyperglycemia is endothelial dysfunction involving pathways; protein kinase activation, hexosamine activation, polyol activation, and Advanced Glycation End Products (AGEs) formation, trigger reactive radical superoxide (O2•-) to stress oxidative. Besides that, path,

reactive oxygen was produced from mitochondria chain respiration [4], eNOS uncoupled [5], NADPH oxidase [6], and xanthine oxidase. Thus, reactive oxygen trigger oxidative stress.

Malondialdehyde (MDA) is an end product of lipid peroxidation in body and is an indicator of oxidant-antioxidant level in diabetic patients [7]. Previous studies proof increased of lipid peroxidation in diabetic compared to control [8-10]. There is positive correlation between MDA and blood glucose in diabetic patients [11]. Lipid peroxidation in diabetic accompanied with increase of endothelial circulating cells as a marker of endothel that released from vascular to circulation [12]. Endothel cell yang mature juga known as Circulating endothelial cells (CECs), as a mature endothel, approximately 15-50 μm in diameter, which are found in the blood. Believed to be endothelial cells released from the intima after vascular damage. Plasma level of CECs increased in vascular disease and are believed to reflect the degree of endothelial damage/stress [13]. Endothelial cells and CECs analyzed with histopathological Hematoxylin-Eosin (HE) staining, light-microscopy, fluorescent microscopy, and immunoassay (flow cytometry) [2,14-17].

Antioxidant needed to reduce oxidative stress and hyperglycemic condition. Fish oil composing mostly omega-3 as an antioxidant. Omega 3 contain of docohexanoic acid (DHA) and eicosapentanoic acid (EPA), have been proof as an antioxidant to many cells. DHA suppress transcription activation of oxidant. DHA supplementation also suppress MDA production MDA and increase catalase in pancreas acinus cell through PPAR γ enzyme thus decrease ROS production. DHA-EPA supplementation inhibit membrane lipid peroxidation. Many studies have been proof DHA-EPA combination repair of endothelial dysfunction to people and animals [18-20]. Omega-3 supplementation 2 gr/day 12 weeks on metabolic syndrome shows decrease of IL-6, triglyceride level, total cholesterol, fasting blood glucose and endothelial dysfunction which measured with FMD (Flow mediated Dilatation) [21,22]. Omega-3 supplementation decrease MDA production as a marker of oxidative stress through endogen antioxidant upregulation [23]. Omega-3 1000 mg/day 12 weeks significantly decrease AGEs serum level in nephropathy diabetic patients compared with control [24].

2. Method

This study is in vivo experimental posttest only control group design to analyze fish oil effect for fasting blood glucose, aorta endothelial cells damage, and peroxidation lipid in diabetic rats. 36 rats divided 2 groups (n=18 each groups). Diabetic rats with placebo as control groups, and diabetic rats with omega-3 300mg/kg/bb/day as an experimental group. Fish oil was given for 28 days [25]. Fasting blood glucose, MDA level, and endothel cell was measured.

2.1. Statistical analysis

Saphiro wilk were used to analyze normality test and Lavene's for homogeneity test. Independent T test was used to compare the differences among groups. Values of P<0,05 were considered significant.

3. Result

Normality test of FBG, MDA level, and average of endothelial cells were test with saphiro wilk. The result showed normal distribution in all groups (p>0,05) which shown in table 1.

Table 1. Normality test result.

Variable	Subjects	N	P	
Fasting blood glucose (mg/dl)	P0	16	0,610	Normal
	P1	16	0,088	Normal
MDA (μM)	P0	16	0,106	Normal
	P1	16	0,718	Normal
Endothelial cells average (cells/4 field of view)	P0	16	0,417	Normal
	P1	16	0,825	Normal

n = samples, p = significance

Homogeneity test of FBG, MDA level, and endothelial cell average between groups were analyze with Lavene's test. The result showed that data variance was homogeny (p>0,05) which shown in table 2.

Table 2. Homogeneity variables result between groups.

Variable	N	P
Fasting blood glucose (mg/dl)	32	0,226
MDA (μM)	32	0,092
Endothelial cells average (cells/4 field of view)	32	0,992

n = samples, p = significance

Comparability test of FBG, MDA, and endothelial cells average between groups shown in table 3 (p<0,05).

Table 3. Comparability test between groups.

Variable	Groups	average	SD	*T*	P
FBG (mg/dl)	P0	261,56	37,284	7,910	0,000
	P1	163,94	31,976		
MDA (μM)	P0	80,68	2,183	0,787	0,437
	P1	75,68	1,482		
Endothelial cells average (cells/4 field of view)	P0	14,54	2,72	-4,096	0,000
	P1	18,54	2,79		

SD = Deviation standard; t = t distribution p = significance

3.1. Discussion

This study showed that fish oil contains omega-3 significantly decrease FBG (p<0,000) compared to control group. It showed omega-3 as hypoglycemic agent. Hypoglycemic mechanism of omega-3 through increase of insulin sensitivity. Omega-3 can modify incorporation phospholipid membrane that inhibit proinflammation cytokine and NF-Kβ from B protein cell and regulate insulin sensitivity and insulin receptor. NF-Kβ inhibition could inhibit the death of β cell pancreas, thus increase insulin production. EPA/DHA inhibit release of NF-Kβ from IK-β in cytoplasm. EPA/DHA also inhibit inflammation pathway through TGF-β inhibition, NLRP3 and Smad 2/3 to nucleus. EPA/DHA activated PPARɤ, thus increase insulin sensitivity through increases of GLUT (protein transporter). Omega 3 increase GLUT4, glucose periphery transporter in muscles and adipose [26-27]. High level of GLUT4 trigger glycogen synthesis and prevent glucose oxidation.

The role of omega 3 in preventing the decrease of GLUT4 prevent polyol pathway, which prevent buildup fructose in the body. Polyol pathway involved aldo-keto reductase enzyme and NADPH that changed glucose to sorbitol. Sorbitol will be oxidized become fructose by sorbitol dehydrogenases enzyme with NAD+ as a co-factor. Hyperglycemia trigger stress oxidative because of due to high usage NADPH to polyol pathway, which NADPH was needed for GSH regeneration [28].

This study showed MDA average in experimental groups (P1) lower than control groups (P0), but comparability test Independent T Test not significantly different between groups (p>0,437). Omega-3 supplementation as an antioxidant cannot reduce MDA level significantly in diabetic rats [29].

This meaningless of MDA level between groups, could be due to several things. Dose, and duration could be one of this cause. Omega 3 inhibit RAGE and activated signaling ROS post-receptor [30]. AGEs have an activity as transcription intracellular factor of NF-Kβ which initiate intracellular signaling cascade. NF-Kβ activate protein kinase C, sorbitol, vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1). This activation produced ROS to DM and caused oxidative

stress. Other mechanism due to omega-3 incorporation to cell membrane and regulate NADPH oxidase expression and activation, thus prevent release of NF-Kβ to nucleus [31,32].

The other factor of this meaningless of MDA level due to endogen antioxidant compensation. Thus need further more research of doses and duration to know the effect of fish oil to MDA level. MDA evaluation should be check serially to know exactly oxidative stress development in diabetic.

Omega-3 supplementation increase endothelial cells amounts in diabetic rats vascular. This indicated omega-3 repair endothelial damage in diabetic rats. This mechanism due to endothelial progenitor cells modulation besides hypoglycemic effects that happened in this study. This result expands previous findings that omega-3 supplementation increases endothelial progenitor cells to cardiovascular disease [36]. Increase of endothelial cells due to raft lipid modification through cell migration [33]. Other mechanism through omega-3 incorporation cell membrane that regulate expression and activation of NADPH oxidase that caused increase of survival rates endothelial progenitor cells [31]. EPA and DHA (EPA: DHA = 0.9:1.5; 9 μM EPA plus 15 μM DHA) increase function and bioavailability endothelial progenitor cells and trigger 23 ovasculogenic [34,35]. EPA decrease cells death of endhotel through reactive oxygen inhibition, activation of NADPH oxidase, and upregulation of inducible nitric oxide synthase [36]. DHA protect endothelial cells from oxidative stress and apoptosis [37]. EPA protect endothelial cells in rat's aorta in vitro, and protect endothelial cells against anoikic through cFLIP repair expression [38]. Endothelial cell average of experimental groups higher than control groups. Thus, couldn't confirm that higher average of endothelial cells was because of repair endothelial dysfunction mechanism from fish oil or because of endothelial damage did not occur. Thus, need further research to know about it.

4. Conclusion

Based on this study, it was concluded that fish oil supplementation containing omega-3 in diabetic rats can lower blood glucose level and can inhibit endothelial cell damage.

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