UNIVERSITI PUTRA MALAYSIA

EFFECTS OF EXERCISE AND DIETARY POLYUNSATURATED FATTY ACID ON STREPTOZOTOCIN-INDUCED DIABETES IN RATS

HASLIZA ABU HASSIM

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By

HASLIZA ABU HASSIM

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

December 2009

To my inspired late father, Abu Hassim b. Haron,

My success is for you and my pray is always with you…

To my beloved husband and families

My deepest gratitude for their love and support…

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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HASLIZA ABU HASSIM

December 2009

Chairman : Noordin Bin Mohamed Mustapha, PhD

Faculty : Veterinary Medicine

Diabetes mellitus is now becoming a major health problem with an increasing prevalence rate. The risk for diabetes mellitus results from lifestyle changes which is related to diet and physical activities. Diabetic patients would have the clinical characteristics of diabetes mellitus such as hyperglycaemia and lipid abnormalities which significantly contribute to produce complications of diabetes mellitus. Attention to diet and weight management, combine with exercise may help to improve the glycaemic control and lipid profiles. A prompt and adequate treatment to prevent or delay the complications of diabetes mellitus by alleviating these deleterious characteristics of diabetes mellitus is needed. Thus, the present study was undertaken to assess the potential of

exercise and dietary polyunsaturated fatty acid (PUFA) intervention in alleviating the detrimental effects of diabetes mellitus.

The efficacy of exercise and dietary PUFA intervention in streptozotocin (STZ)-induced diabetes in rats was investigated on the basis of body weight, blood glucose levels and blood lipid profiles. A total of 32 Sprague-Dawley male rats weighing between 250-300 grams were divided equally into eight groups. Diabetes mellitus was induced by giving a single intraperitoneal injection of STZ at the dosage of 40 mg/kg.

Four groups were exercised daily by swimming for 8 weeks while the other four groups were not subjected to any exercise. Menhaden oil, soybean oil and butter were incorporated into the treatment diets for both exercise and non-exercise groups. The treatment diets were defined as follows: rat chow diet only (Control diet), rat chow added with 6.66% (w/w) menhaden oil and 3.34% (w/w) soybean oil (Diet 1), rat chow added with 3.34% (w/w) menhaden oil and 6.66% (w/w) soybean oil (Diet 2) and rat chow containing 10% (w/w) butter (Diet 3). Experiment I was conducted to determine the body weight and blood glucose levels of rats at week 0, 2, 4, 6 and 8. In Experiment II, blood was collected at the end of 8 weeks for the determination of blood lipid profiles that encompassed:

Triglycerides, Total cholesterol, High-density lipoprotein (HDL)-cholesterol and Low-density lipoprotein (LDL)-cholesterol.

The results obtained from this study showed that exercise and dietary PUFA intervention can be considered as the integral components of treatment and prevention strategy in diabetes mellitus by improving the body weight control and blood glucose levels. The exercise and dietary PUFA intervention groups significantly reduced the body weight gain and showed the hypoglycaemic effects over a period of eight weeks in STZ-induced diabetic rats when compared to the non-exercise group and the normal control group, which is non-diabetic rat. This study also has documented a significance of exercise and dietary PUFA intervention to improve the lipid abnormalities by lowering the triglycerides, total cholesterol and LDL-cholesterol levels.

The values indicated in the treatment and control diet are highly difference as compared to the normal control, which are non-diabetic. Therefore, the impacts of exercise and dietary PUFA intervention to improve body weight gain, blood glucose levels, and blood lipid profiles could be used as an indicator in assessing the health status of patient at high risk of diabetes mellitus or in the diabetic patient itself.

Thus, results obtained in the present study suggested that exercise and dietary PUFA intervention may have an impact on alleviating the detrimental effects of diabetes mellitus by regulating body weight changes, blood glucose levels, and blood lipid profiles. Indeed, the supplementation of dietary PUFA, in combination with exercise did have some effects in improving and delaying those risk factors of complication in diabetes mellitus.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN SENAMAN DAN DIET ASID LEMAK POLITAKTEPU BERANTAI PANJANG KE ATAS DIABETES-RANGSANGAN STREPTOZOTOCIN PADA TIKUS

Oleh

HASLIZA ABU HASSIM

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Diabetes mellitus kini menjadi masalah kesihatan yang utama dengan kadar penularannya yang meningkat. Perubahan gaya hidup seperti diet dan aktiviti fizikal boleh menyebabkan risiko diabetes mellitus. Pesakit diabetes akan menunjukkan tanda-tanda klinikal diabetes mellitus seperti ketinggian kandungan glukosa dalam darah (hyperglyceamia) dan ketidaknormalan lipid yang nyata sekali menyumbang kepada komplikasi diabetes mellitus. Rawatan pantas dan mencukupi yang diperlukan untuk menghalang atau melambatkan komplikasi diabetes mellitus adalah melalui pembaikan ke atas tanda-tanda penyebab penyakit tersebut. Diet dan pengurangan berat badan, digabungkan

dengan senaman boleh membantu untuk membaiki pengawalan glukosa dalam darah dan profil lipid. Oleh sebab itu, kajian ini dijalankan untuk menilai potensi gabungan senaman dan diet asid lemak politaktepu berantai panjang dalam mengurangkan kesan bahaya diabetes mellitus

Keberkesanan gabungan senaman dan diet asid lemak politaktepu berantai panjang ke atas diabetes-rangsangan streptozotocin pada tikus diuji terhadap berat badan, aras glukosa dan profil lipid dalam darah. Sejumlah 32 ekor tikus jantan jenis Sprague-Dawley yang beratnya antara 250-300 gram dibahagikan sama rata kepada 8 kumpulan. Diabetes mellitus dirangsang dengan memberikan satu suntikan streptozotocin melalui intraperitoneal pada dos 40 mg/kg.

Empat kumpulan menjalankan senaman secara berenang setiap hari selama lapan minggu sementara empat kumpulan yang lain tidak menjalankan senaman. Minyak menhaden, minyak kacang soya dan mentega dimasukkan ke dalam rawatan diet untuk kedua-dua kumpulan senaman dan tidak senaman. Rawatan diet ditakrifkan seperti berikut: tikus diberi makan pelet tikus sahaja (Kumpulan kawalan), pelet tikus ditambah dengan 6.66% (w/w) minyak menhaden dan 3.34% (w/w) minyak kacang soya (Diet 1), pelet tikus ditambah

dengan 3.34% (w/w) minyak menhaden dan 6.66% (w/w) minyak kacang soya (Diet 2) dan pelet tikus ditambah dengan 10% (w/w) mentega (Diet 3). Eksperimen I dijalankan untuk menentukan berat badan dan kadar glukosa darah tikus pada minggu 0, 2, 4, 6 dan 8. Dalam eksperimen II, darah dikumpulkan pada akhir minggu ke-8 untuk menentukan profil lipid darah yang merangkumi: Triglycerides, Kolesterol, High-density lipoprotein (HDL)-kolesterol dan Low-density lipoprotein (LDL)-kolesterol.

Hasil ujian menunjukkan bahawa gabungan senaman dan diet asid lemak politaktepu berantai panjang boleh diambil kira sebagai komponen penting dalam rawatan dan pencegahan diabetes mellitus melalui pembaikan dalam pengawalan berat badan dan kadar glukosa dalam darah. Kumpulan yang menjalankan gabungan senaman dan diet asid lemak politaktepu berantai panjang menunjukkan penurunan berat badan dan kesan hypoglyceamia yang signifikan pada tikus diabetes-rangsangan streptozotocin dalam masa lapan minggu apabila dibandingkan dengan kumpulan kawalan yang tidak menjalankan senaman dan kumpulan kawalan normal, iaitu kumpulan yang tidak menghidap diabetes. Kajian ini juga membuktikan gabungan senaman dan diet asid lemak politaktepu berantai panjang mempunyai kesan signifikan

dalam membaiki ketidaknormalan lipid melalui penurunan kadar triglycerides, kolesterol, dan low-density lipoprotein (LDL)-kolesterol.

Nilai bacaan yang ditunjukkan dalam kumpulan rawatan dan kawalan adalah sangat berbeza jika dibandingkan dengan kumpulan yang normal, iaitu yang tidak menghidap diabetes. Oleh itu, impak senaman dan diet asid lemak politaktepu berantai panjang dalam pembaikan berat badan, aras glukosa dan profil lipid dalam darah boleh menjadi pengukur dalam mengukur tahap kesihatan individu yang terdedah kepada penyakit diabetes mellitus dan juga kepada pesakit diabetes mellitus itu sendiri.

Oleh itu, hasil kajian ini menyarankan bahawa gabungan senaman dan diet asid lemak politaktepu berantai panjang memberi kesan dengan mengurangkan bahaya penyakit diabetes mellitus melalui pembaikan berat badan, dan menormalkan aras glukosa dan profil lipid dalam darah. Sesungguhnya, pemberian supplemen diet asid lemak politaktepu berantai panjang, dengan gabungan senaman dapat memberi kesan dalam membaikpulih dan melambatkan faktor-faktor yang boleh menyebabkan komplikasi diabetes mellitus.

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APPROVAL

I certify that a Thesis Examination Committee has met on **22 December 2009** to conduct the final examination of Hasliza Binti Abu Hassim on her thesis entitled **"Effects of Exercise and Dietary Polyunsaturated Fatty Acid on Streptozotocin-induced Diabetes in Rats"** in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

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APPROVAL

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Date: 8 April 2010

DECLARATION

I hereby declare that the thesis is based on my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously or currently submitted for any other degree at UPM or other institutions.

_____

HASLIZA ABU HASSIM

Date : 4 March 2010

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LIST OF ABBREVIATIONS

HDL	High density lipoprotein
LDL	Low density lipoprotein
PUFA	Polyunsaturated fatty acid
IDDM	Insulin dependent diabetes mellitus
NIDDM	Non-insulin dependent diabetes mellitus
WHO	World Health Organization
COOH	Carboxyl
e.g.	*Exemplium gratia* (Example)
mmol/L	milimoles per litre
mg/dL	milligrams per decilitre
g	grams
β	beta
NADH/NAD^+	Nicotinamide adenine dinucleotide
AGEs	Advanced glycated end products
VEGF	Vascular endothelial growth factor
ADA	American Diabetes Association
VLDL	Very low density lipoprotein
SFA	Saturated fatty acid

UFA	Unsaturated fatty acid
MUFA	Monounsaturated fatty acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
GLUT	Glucose transporters
MDA	Malondialdehyde
PEG	Polyethylene glycol
HSDA	N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline
S.I.	Système International d'unités
O_2	Oxygen
LCAT	Lecithin-cholesterol acyltransferase

CHAPTER I

GENERAL INTRODUCTION

Diabetes mellitus is a serious chronic metabolic disorder which is now becoming a major global health problem. It has a significant impact on the health, quality of life and life expectancy of patients, as well as on the health care system (Dey *et al*., 2002). The incidence and prevalence of diabetes is escalating especially in developing countries. In Malaysia, diabetes is a growing concern since the prevalence rate among adults is about 8.2% in 1996 compared to a rate of 6.2% in 1986 (Sidik and Ahmad, 2003).

The World Health Organization (WHO) recognizes two major clinical forms of diabetes mellitus, namely Type I or insulin dependent diabetes mellitus (IDDM) and Type II which also known as non-insulin dependent diabetes mellitus (NIDDM). The risk for diabetes mellitus results from a combination of genetic predisposition and lifestyle changes. The most important lifestyle changes are related to changes in dietary habits and physical activities (Cockram, 2000). Recent data estimate that physical inactivity and poor diet caused 400,000 deaths in 2000 in Unites States, ranking second only to tobacco, and that is likely

that inactivity and diet will soon rank as the leading cause of death in the world (Mokdad *et al.,* 2001).

Diabetic patients would have the clinical characteristics such as hyperglycaemia, elevated low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol and high triglyceride levels. These hyperglycaemia and lipid abnormalities significantly contribute to produce complications of diabetes mellitus, as well as increase the cardiovascular risk (O'Keefe and Bell, 2007). Therefore, they need a prompt and adequate treatment to prevent or delay the complication of diabetes mellitus. Chronic complications of diabetes mellitus may involve the kidneys, eyes, nervous system and cardiovascular system and it can be classified into macrovascular and microvascular complication. There are four major components in the management of diabetes mellitus which might help in preventing and delaying the complication in diabetes mellitus such as diet, exercise, medication and education (Koda-Kimble and Carlisle, 1995).

Fatty acids are organic acids with an aliphatic chain and a carboxyl (COOH-terminal) group. They are essential components of the diet and sources of food energy (Whalley *et al*, 2004). The omega-3 and omega-6 polyunsaturated fatty

acid (PUFA) belong to the essential fatty acid because the body cannot synthesize them and they must be obtained from the diet. Previous studies have shown that diets contain omega-3 and omega-6 may play a role to prevent or delay the complication of diabetes mellitus. Beneficial effects of PUFA supplementation are probably mediated by their lowering blood lipid and preserves pancreas from some later complications of diabetes mellitus (Gvozdjáková *et al*., 2008).

Exercise is a major therapeutic modality in the treatment of diabetes mellitus (Laaksonen and Sen, 2000). Several studies indicate that low fitness increases the risk of diabetes and increased physical activity is effective in preventing diabetes (Helmrich *et al*., 1994). The benefits of exercise performed by the diabetic patients include increased insulin sensitivity, improved glycaemic control, weight loss, lower blood pressure and improved blood lipid profile (Wheeler, 1999).

For diabetic patients, attention to diet and weight management, combined with physical activity such as exercise may help to improve glycaemic control and lipid profiles (Wolever *et al*., 1999). This non-pharmacological management plays an important role in improving and limiting complications of diabetes

mellitus. Booth *et al* (2002) have coined that effective intervention of exercise and dietary management as "the war on chronic disease".

It was hypothesized that exercise either alone or in combination with dietary PUFA alleviated the detrimental effects of diabetes mellitus with respect to body weight gain, glucose levels and blood lipid profiles. Therefore, the aim of the study to be carried out is to determine the efficacy of exercise and dietary PUFA intervention in alleviating the detrimental effects on STZ-induced diabetes in rats, in conjunction with the following objectives ; i.e, to investigate the efficacy of exercise and dietary PUFA intervention on :-

i) body weight gain

ii) blood glucose levels

iii) selected blood lipid profiles

- Triglycerides
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol

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