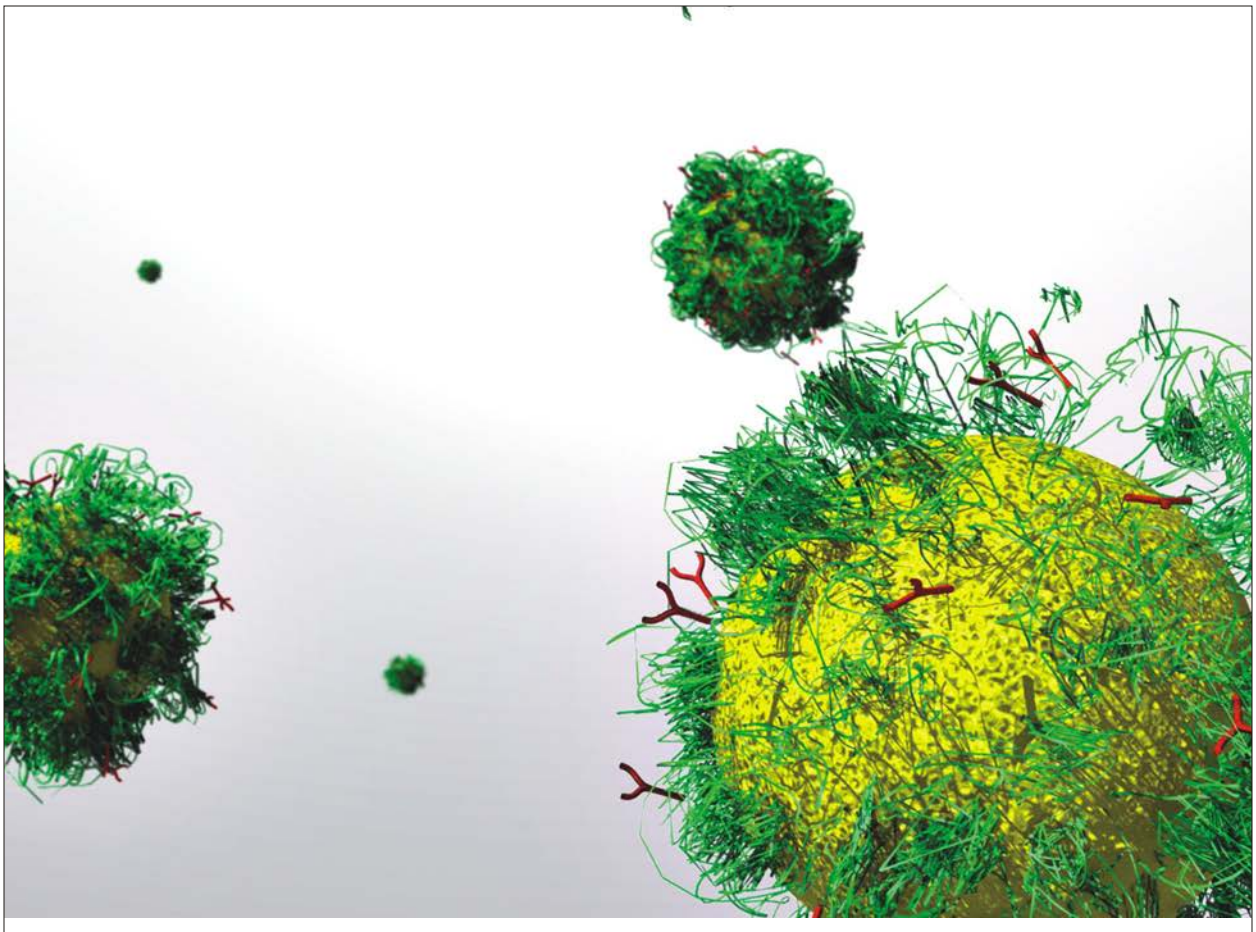

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Effect of Exercise on Lipid Profile and Oxidative Stress in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Regular physical exercise has been reported to be effective in the prevention or delay of onset of type 2 diabetes, increases insulin sensitivity and ameliorates glucose metabolism and therefore considered beneficial for type 2 diabetes mellitus management. This study investigated the effect of physical exercise on glycaemic control in patients with type 2 diabetes. Overnight fasted blood samples were drawn from the median cubital vein on the anterior forearm of diabetics and the control subjects into plain and fluoride oxalate tubes. The serum from the plain tubes was used to estimate the lipid profile: Blood glucose, serum total cholesterol, triglycerides, low-density lipoproteins, very low-density lipoproteins and high-density lipoproteins were determined using an autoanalyser. The plasma from the fluoridated anticoagulated blood was used to estimate the fasting blood glucose. Malonyldialdehyde level in serum was estimated spectrophotometrically. Anthropometric parameters; height, bodyweight and blood pressures were also measured. Fasting blood glucose was significantly ($p<0.05$) reduced in the subjects who had longer duration of exercise, triglycerides were significantly ($p<0.05$) reduced even in mild exercise, whilst HDL was increased ($p<0.05$) in subjects who did 3 h and over exercise per week. Malonyldialdehyde was significantly ($p<0.05$) decreased even in moderate exercise. The study demonstrates that exercise modulates fasting blood glucose, lipid profile, oxidative stress in patients with type 2 diabetes and suggest that exercise may have therapeutic, preventative and protective effects on diabetes mellitus and should therefore be used to complement drug therapy.

Key words: Oxidative stress, lipid profile, malonyldialdehyde

INTRODUCTION

Physical exercise alone can have a therapeutic effect in the management of diabetes mellitus (Laaksonen and Sen, 2000). Moderate exercise is associated with about tenfold increase in fat oxidation due to increased energy expenditure coupled with greater fatty acid availability. The increased in fatty acid is the result of both increases in lipolysis and decrease re-esterification of Non-esterified Fatty Acid (NEFA) to triglycerides (Wolfe *et al*., 1990). NEFA levels are reduced during exercise by β-blockade, primarily due to a suppression of lipolytic activity.

The release of NEFA through lypolysis from adipose tissue can be modulated through the action of insulin and other catecholamiones (Van Raaij *et al*., 1995). Not only are catecholamines increased by exercise, adipocytes, following exercise has increased lipolytic responsiveness to

β-adrenergic actions of the catecholamines (Harant *et al*., 2002). There is sufficient evidence to show that fuel for working muscle is derived not only from adipocytes, but also from intramuscular triglycerides stores (Horowitz and Klein, 2000). Triglycerides are used as source of energy, even mild to moderate exercise can lower plasma triglycerides levels (Decombaz *et al*., 1983). Most clinical trials have evaluated that exercise interventions in people with type 2 diabetes mellitus should be at least thirty minutes of moderate intensity activity, three times in a week and not exceeding seventy two hour in all the three consecutive days combined. This is clinically adequate to improve insulin sensitivity and prevent the various complications associated with the disease (Boule *et al*., 2001). Indeed physical exercise has been reported to increase insulin sensitivity and ameliorates glucose metabolism (Derouich and Boutayeb, 2002). Diabetes mellitus patients who exercise frequently have changes in their lipid profile and reactive oxygen species (oxidative stress) levels. Improvement in biochemical parameters after continuous exercise can alleviate diabetic complications including neuropathy, retinopathy and nephropathy (Adubofour *et al*., 1993).

Oxidative stress is a summed expression between free radical-generation and free radical scavenging systems (Mullarkey *et al*., 1990). Implication of oxidative stress in the pathogenesis of diabetes is suggested not only by the oxygen free-radical generation but also the non-enzymatic glycation of proteins, auto-oxidation of glucose, impaired glutathione metabolism (which is mainly due to utilization of NADH during auto-oxidation of glucose, also needed in the synthesis of glutathione), alteration in antioxidant enzymes, lipid peroxide formation and decrease ascorbic acid levels (Mullarkey *et al*., 1990).

Excessive generation of free radicals (oxidative stress) results in oxidation of cell membranes polyunsaturated fatty acids and therefore generating malondialdehyde, which is a Thiobabituric Acid Reacting Substance (TBARS) (Gupta and Chari, 2006). Oxidative stress has been studied quantitatively by the determination of plasma concentration of some metabolic products including lipid hydroperoxides, TBARS, isoprostanes, protein carbonyls etc. and even DNA-strand breaks (Kadiiska *et al*., 2005). Physical exercise has been shown to be effective in type 2 diabetes mellitus management not only by increasing insulin sensitivity (Ibanez *et al*., 2005), but also by improving the levels of antioxidant molecules and thereby ameliorating oxidative stress (Kim *et al*., 1996). Repeated exercise has been shown to upregulate the expression of endogenous antioxidant enzymes such as catalase and Superoxide Dismutase (SOD) (Jill, 2002). This is mediated by the activation of redox-sensitive signaling pathways. For example, gene expression of muscle mitochondrial super oxide dismutase is enhanced after an acute exercise which is followed by an elevated level of Nuclear Factor kB (NF-kB) and activator protein 1 (AP-1) binding (Jill, 2002). However, it has been proven in the past two decades that heavy exercise increases free radical generation and the risk of oxidative damage to skeletal muscle (Jill, 2002). This study investigated the beneficial effect of exercise in diabetes management as a supplement to drug therapy.

MATERIALS AND METHODS

This study was conducted on diabetes mellitus patients who patronize the Komfo Anokye Teaching Hospital (KATH) in the Kumasi metropolis (Ghana) and were on some form of drug medication. Healthy volunteers marching age to sex of the diabetic patients were selected for the negative controls. All procedures were approved by the Committee on Human Research Publication and Ethics of School of Medical Sciences, KNUST (CHRPE/Student/113/09). A written informed consent form was completed by all the participants who were recruited into the study after the study was explained in a language they understand.

The subjects were selected on the bases of being on regular medication and have being undergoing routine physical exercise for at least three months (Subjects group) or no exercise (Control Group) for within the same period and matched age and sex. An exercise intervention was defined as a predetermined program of physical activity described in terms of type (walking, jogging), frequency, intensity and duration. Subjects in whom the intervention consisted only of recommending increased physical activity were not included within the analyses since it would be impossible to quantify the exercise intervention and compliance. To be included, compliance with exercise interventions was verified by direct interviews. Also excluded were patients on medications having direct lipid metabolic effect e.g., statins.

Body weights were measured (to the nearest 0.5 kg), with the subject standing on a weighing scale after it was adjusted to zero kg and calibrated using known weights. Heights were measured (to the nearest 1.0 centimeter), with the subject standing in an erect position against a vertical scale of portable standiometer and an L-square placed on the head and the head positioned to level with the inferior margin of the bony orbit. Body Mass Index (BMI) was then calculated. Systolic and diastolic blood pressures were measured with a mercury sphygmomanometer. Two readings were made after the subject was made to rest for about five minutes and the mean taken as the reading.

Overnight fasted blood samples were drawn from the vein on the anterior forearm into plain and fluoride oxalate tubes (to prevent glycolysis), BD vacutainer®, (BD, Plymouth, PL6 7BP. UK). The fluoridated anticoagulated blood was centrifuged (Zentrifugen, D-78532, Tuttlingen, Germany) at 3000 rpm for 5 min to separate the plasma from the deposit. The plasma was used to estimate the fasting blood glucose. The clotted blood was centrifuged (Zentrifugen, D-78532, Tuttlingen, Germany) at 2000 rpm for 5 minutes to separate out the serum. The serum was used to estimate the lipid profile: Total cholesterol, high density lipoprotein cholesterol, low density lipoprotein and triglycerides were estimated as well as oxidative stress levels using the malondialdehyde (MDA) test. Serum Total Cholesterol, (TC), High Density Lipoprotein (HDL,), low density lipoprotein LDL, VLVDL cholesterol and triglycerides were measured by enzymatic assay procedure on COBAS Intergra 400 Plus auto analyser: Roche. Interassay coefficient of variation (2.3 and 2.1% for low and high total cholesterol controls respectively comply with National Cholesterol Education Programme recommendation (National Heart Lung and Blood Institute, 1988).

Malondialdehyde (MDA): The malonyldialdehyde level in serum was estimated spectrophotometrically according to Buege and Aust (1978). About 0.2 mL aliquot of serum was added to 1.0 mL of 0.375% thiobarbituric acid solution in 0.25 M HCl and mixed with 4.0 mL of 15% trichloroacetic acid. After incubation at 10°C for 15 min, the samples were cooled, centrifuged and the supernatants were evaluated spectrophotometrically at 535 nm against a reference blank. The MDA was determined by using a molar extinction coefficient of 1.56×10^5 M^{-1} cm^{-1} and results were expressed in μmol L^{-1}.

Data analysis and statistics: Results were expressed as Means±SEM. Data were analysed by one-way ANOVA followed by the Bonferroni test for multiple comparison using Graph Pad Prism version 4 (Graph Pad Software, San Diego California). Unpaired Student t-tests were used to assess for significance. Statistical significance was set at p-values = 0.05 for the various parameters in the study.

RESULTS AND DISCUSSION

The main objective of this work was to study the effect of exercise interventions on the management of diabetes mellitus and to further establish the fact that physical exercise is a non pharmacological therapeutic remedy for diabetes. The mechanisms underlying the improved glucose tolerance in type 2 diabetes mellitus from the resulting physical exercise include an increase in the glucose clearance rate associated with increased muscular blood flow and an increased ability to utilize glucose (LeBlanc *et al*., 1981; Dela *et al*., 1995; Goodyear and Kahn, 1998; Mayer-Davis *et al*., 1998).

Lipoprotein abnormalities play an important role in the development of diabetic atherosclerosis (Lewis and Steiner, 1996). Dyslipidaemia causes morbidity and mortality in patients with type 2 diabetes mellitus and the most common features in type 2 diabetic patients are elevated triglycerides and LDL and decreased HDL cholesterol concentrations (Loh *et al*., 1996). This atherogenic pattern is likely to increase the risk of cardiovascular complications including myocardial infarction and premature atherosclerosis (Mehta and Reilly, 2005; Carr, 2003). Also, the modification of LDL lipoprotein (ox-LDL) increase the atherogenicity and available data suggest that LDL is more atherogenic in individuals with type 2 diabetes mellitus (Steiner *et al*., 1999).

Table 1 describes the physical activities of diabetic patients in attempt of glycaemic control. Seventy five percent of the subjects were engaged in walking as an exercise, whilst only 2% jogged and 23.5% did not engage in any form of exercise. Of the subjects engaged in exercise, 13.3% exercised over 6 h a week and 24.5% exercised between 3-5 h a week, 21.4% between 1-2 h a week whilst 17.3% did less than 1 h a week.

The majority of the patients in this study did very mild exercise involving waking (76.5%) (Table 1) and even those who did moderate to intensive exercise to take advantage of its therapeutic effect did it for a relatively short time and a low frequency. Only 38% who exercised for 3 h and over really significantly benefit from the exercise.

Fasting blood glucose was significantly ($p<0.05$, $p<0.001$) reduced in the subjects who had a longer duration of exercise for between 3-5 h and over 6 h a week, respectively (Table 2). It is difficult to evaluate the intensity of the exercise but the effect on blood glucose is time dependent.

Table 1: Type, frequency and duration of exercises done within a week

Variables	n	Percent
Type of exercise		
Walking	73	74.5
Jogging	2	2.0
None	23	23.5
Frequency of exercise		
0	23	23.5
Once	24	24.5
Twice	24	24.5
Thrice	24	24.5
Four to seven times	3	3.1
Duration (h) in a week		
None	23	23.5
<1	17	17.3
1-2	21	21.4
3-5	24	24.5
6-10	13	13.3

Table 2: The effects of exercise on the biochemical parameters in the diabetics (n = 98)

	Duration of exercise in a week (hours)				
Variables	None	<1	1-2	3-5	6-10
FBG (mmol L^{-1})	8.98±4.51	6.99±3.04	7.72±2.05	6.36±1.72*	5.65±0.76**
Trig. (mmol L^{-1})	1.83±0.78	2.07±1.33	1.30±0.64*	1.37±0.54*	1.24±0.44*
Total chol. (mmol L^{-1})	4.96±1.40	5.93±1.79	4.97±1.29	4.54±1.14	4.40±1.85
VLDL (mmol L^{-1})	0.84±0.39	0.95±0.61	0.60±0.29	0.62±0.25	0.57±0.21*
HDL (mmol L^{-1})	0.93±0.04	0.94±.05	0.94±.04	0.96±.04*	1.01±.04*
LDL (mmol L^{-1})	4.02±0.06	4.89±0.04	4.03±0.02	3.76±0.06	3.42±0.05
Malondialdehyde (nmol L^{-1})	1.53±0.35	1.74±0.53	1.45±0.33	1.32±0.31*	1.37±0.52*

Total Chol: Total cholesterol, Trig: Triglycerides, HDL-CHOL: High density lipoprotein cholesterol. LDL-CHOL: Low density lipoprotein cholesterol, MDA: Malondialdehyde, Values represent Mean±SE **p<0.001, *p<0.05, significantly different from control (non exercising subjects)

Similarly triglycerides were significantly reduced in subjects who exercised for between 1-10 h a week. There was also significant ($p<0.05$) reduction in the plasma levels of very low density lipoproteins and malondialdehyde. There were no significant changes in the plasma levels of total cholesterol and low density lipoproteins. However plasma levels of high density lipoproteins were significantly increased for subjects who exercised over three h a week (Table 2).

The study confirmed the positive effects of exercises on lipid profile on type 2 diabetics engaged in routine exercise for at least 3-5 h per week (Table 2) over at least a three month period as a supplement to conventional antidiabetic drug therapy. Type 2 diabetic patients engaged in physical exercise demonstrated a significantly reduced fasting blood glucose, serum triglycerides and VLDL concentrations, whilst HDL was significantly ($p<0.05$) increased. There were no significant changes in total cholesterol and LDL cholesterol. Though, the results are similar in trend to the effect of yoga exercise, which however significantly decreased Fasting Blood Glucose (FBG), serum TC, LDL, VLDL, triglycerides and TC/HDL ratio in individuals attending a lifestyle education based program for 9 days (Bijlani *et al*., 2005). In our study TC and LDL were not significantly changed even over a longer period of exercise as compared to the effect of yoga over a shorter period reported by Bijlani *et al*. (2005), because yoga is a more intensive form of physical and mental exercise, associated with higher energy expenditure compared to the mild walking exercise engaged by most of our subjects. The significantly ($p<0.05$) reduced serum triglycerides, VLDL ($p<0.05$) concentrations and increased ($p<0.05$) HDL concentrations, improves insulin sensitivity, ameliorates diabetes and cardiovascular diseases (Bruce *et al*., 2004).

Oxidative stress is associated with many chronic diseases. Increased production of Reactive Oxygen Species (ROS) has been implicated in the initiation and progression of both diabetes and cardiovascular diseases and it may be that oxidative stress accounts for the unexplained increase in cardiovascular risk observed in diabetes (Stephens *et al*., 2009).

Malondialdehyde concentration, a lipid peroxidation product and marker of oxidative stress levels are higher in patients with newly diagnosed type 2 diabetes mellitus (Armstrong *et al*., 1996) and in poorly controlled type 2 diabetic patients (Peuchant *et al*., 1997). In this study the decreased lipoperoxidation was marked by decreased concentration of MDA in the exercise groups. The control of glycaemia and the decreased lipid profile parameters in exercises are important influences on the decreased oxidative stress parameter and provide more support for the evidence of a possible protective effect of exercise against oxidative stress in diabetes.

Table 3: The effects of exercise on the biochemical parameters in the non-diabetics (n = 42)

	Duration of exercise in a week (hours)				
Variables	None	<1	1-2	3-5	6-10
FBG (mmol L^{-1})	5.63±0.48	5.83±0.79	6.63±2.65	5.63±0.78	5.59±0.78
Trig (mmol L^{-1})	1.62±0.42	1.16±0.49	1.56±0.81	1.26±0.53	1.19±0.54*
Total chol. mmol L^{-1})	5.20±1.19	5.56±1.40	5.15±1.68	4.43±1.41	4.40±1.41
VLDL (mmol L^{-1})	0.73±0.22	0.53±0.23	0.71±0.38	0.59±0.23	0.54±0.22
HDL (mmol L^{-1})	0.93±0.04	0.94±.05	0.95±.06	0.97±07*	1.03±04*
LDL (mmol L^{-1})	4.27±0.16	4.69±0.24	4.23±0.22	3.56±0.06	3.08±0.15
Malondialdehyde (nmol L)	1.51±0.36	1.60±0.42	1.52±0.50	1.28±0.41*	1.18±0.41*

Total Chol: Total cholesterol, Trig: Triglycerides, HDL-CHOL: High density lipoprotein cholesterol. LDL-CHOL, Low density lipoprotein cholesterol, MDA, Malondialdehyde, Values represent Mean±SE *p<0.05; significantly different from control

Table 4: The effect of greater than 3 h of exercise per week on Obese subjects (BMI = 30 kg m^{-2})

Parameter	Control (n =17)	Exercise = 3 h/week (n =15)
Age	62.80±7.43	60.66±14.09
SBP (mmHg)	160.67±18.31	135.00±15.70*
DBP (mmHg)	99.33±13.87	86.81±10.98*
Duration of Diabetes (yrs)	6.60±4.93	6.37±4.98
Weight (kgs)	93.07±8.97	87.35±14.09*
BMI (kg m^{-2})	34.71±2.37	30.89±3.74*
FBS (mmol L^{-1})	9.28±0.73	8.48±0.64*
Total Chol (mmol L^{-1})	5.23±0.80	5.76±1.50
Trig (mg dL^{-1})	3.23±1.48	2.60±1.25*
HDL-CHOL (mmol L^{-1})	1.14-±0.17	1.32±0.41*
LDL-CHOL (mmol L^{-1})	3.92±0.53	4.31±0.81
MDA (nmmol L^{-1})	1.71±0.36	1.28±0.41*

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, DD: Duration of diabetes, FBS: Fasting blood glucose, Total Chol: Total cholesterol, Trig: Triglycerides, HDL-CHOL: High density lipoprotein cholesterol, LDL-CHOL: Low density lipoprotein cholesterol, MDA: Malondialdehyde, Values represent Mean±SE *p<0.05, Significantly different from control

The results of this study and others indicate the positive effect of exercise on glycaemic control and oxidative stress and suggest that such would be beneficial for the treatment of diabetes mellitus Plasma concentration of triglycerides and malodiadehyde in the non diabetics (Table 3) were significantly ($p<0.05$) reduced after six hour of exercise per week. HDL was significantly ($p<0.05$) increased after more than 3 hour of exercise per week. In non diabetics only severe exercise of at least greater than six h a week significantly reduced plasma triglycerides and MDA. Plasma glucose and the other lipid profiles VLDL and LDL were not significantly changed even in sever exercise. This is because there was no physiological defect to address and therefore the body's homeostasis mechanisms simply reestablish the blood parameters in their physiological ranges. Exercise seems to be beneficial even in people with no physiological defect in their lipid profile. The upregulated HDL and a complementary reduction in MDA suggest a potential to further improve the lipid profile.

Both systolic and diastolic blood pressures were significantly reduced ($p<0.05$) in the obese subjects doing more than 3 h of exercise per week. There were also significant reductions ($p<0.05$) in body weight, BMI, fasting blood sugar, triglycerides and malondialdehyde. There was however a significant increase in HDL but no change in the total cholesterol and LDL cholesterol (Table 4).

Apart from glycaemic control and improved lipid profile, obese diabetics who were engaged in exercise for at least three h a week enjoyed a significantly ($p<0.05$) reduced body weight, BMI and reduced blood pressures. Such physiological changes reduce the rate of atherosclerosis and slow down the onset of cardiovascular diseases and diabetes. Similar results have also been observed by Wing *et al.* (1988).

CONCLUSION

The study demonstrates that exercise modulates fasting blood glucose, lipid profile, oxidative stress in patients with type 2 diabetes and suggest that exercise may have therapeutic preventative and protective effects on diabetes mellitus independent of drug therapy.

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