Original article:

Insulin sensitivity in normoglycemic offspring of patient with T2dm on graded exercise

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ABSTRACT

Objectives: The primary causes of Type 2 Diabetes Mellitus (T2DM) are largely unknown but insulin sensitivity has been reported to be a risk factor for the T2DM through the alteration of insulin sensitivity pattern. However, it is uncertain if exercise could influence the occurrence of T2DM in offspring of diabetic parents. Therefore this study was designed to assess the effect of exercise on insulin sensitivity (IS) on offspring of T2DM parents compared with offspring of non-diabetic parents.

Design: This study involved purposive selection of 42offspring of T2DM parents attending University College Hospital, Ibadan and 53 offspring of non-diabetic parents who are undergraduate students of the University of Ibadan, Nigeria.. Participants were randomly assigned into four groups; 27 Normal-weight Offspring of Non-Diabetic Parents (NONDP), 21 Normal-weight Offspring of Diabetic Parents (NODP), 26 Overweight Offspring of Non-Diabetic Parents (OONDP) and 21 Overweight Offspring of Diabetic Parents (OODP). Each participant followed a protocol of graded exercise using ''tummy trimmer'' everyday spending 30-45 minutes daily for 24 weeks. Blood samples were obtained after an overnight fasting for determination of insulin sensitivity using standard methods at baseline, six week, 12 week, 18 week and 24 week, respectively. The IS determined by calculations on HOMA's method of measuring fasting insulin level got from immunoassay technique. Data were analyzed using descriptive statistic and repeated ANOVA with significant at $p<0.05$.

Results: After exercise, there were increased insulin sensitivity (ng/L) in all groups. In NONDP, it increased from61.99+4.68to69.68+4.91($p<0.05$),NODPfrom49.19+3.74to57.20+4.91($p<0.05$).OONDP:49.74+3.73to58.28+4.15($p<0.05$), OODP:48.85+3.15to53.18+3.42($p<0.05$).Thereweresignificant changes in insulin sensitivity between baseline and at 24 weeks.

Conclusion : Graded exercise improved insulin sensitivity in all the groups. The clinical importance of graded exercise in prevention of diabetes mellitus among offspring of diabetic parents looks promising.

Keywords: Graded exercise, Diabetic parents' offspring, Insulin sensitivity.

INTRODUCTION

Diabetes mellitus, commonly known as diabetes, is a disorder of intermediary carbohydrate, protein and lipid metabolism. It is characterized by hyperglycemia, glucosuria, polydipsia, polyuria, polyphagia and weight loss. It is usually associated by secondary alterations in glucose, fat and protein metabolism, leading to many biochemical disorders. It is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production with declining β-cell function and eventually leading to β-cell failure [1].Type 2 Diabetes Mellitus (Type 2DM) is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells.

Insulin resistance has been attributed to elevated levels of free fatty acids and pro-inflammatory cytokines in plasma, leads to reduced glucose

transport into muscle cells, elevated hepatic glucose production, and pronounced break down of fat.

Researchers have found that obesity and diabetes are inter-connected. Individuals who are obese are at high risk of developing T2DM, particular if a close family member is affected with T2DM. Researchers have not yet discovered a specific gene that causes obesity although, several genes are considered to play a role. There seems to be a connection between abdominal fat and diabetes, hence anything that will reduce abdominal fat will likely reduce diabetes (2).

Exercise has been known to ameliorate the effect of diabetes by improving insulin sensitivity .It is the aim of this to work to study the effect of exercise on insulin sensitivity of normoglycemic offspring of patients with type 2 DM.

METHODOLOGY

Experimental interventional study was carried out in which blood sample was collected from offspring of patients with type 2 diabetes mellitus and normoglycemic offspring of non-diabetic parents. The parents of the test group were attending the medical out-patient clinic (MOP) of the University College Hospital (UCH), Ibadan and Catholic Hospital Oluyoro, Oke-Ofa, Ibadan, South Western, Nigeria. The normoglycemic offspring of non-diabetic parents aged 25 years and above were randomly selected from general population of Ibadan Community, Ibadan, and South-Western, Nigeria and undergraduate students of University of Ibadan. These are normoglycemic offspring of non-diabetic parents with normal weight that served as control subjects.

The participants were divided into four groups, N=42 as follows:

A – Overweight / Obese offspring of DM parents (OODP).

B – Normal weight / Normal Body Mass Index (BMI) offspring of DM parents (NODP).

C – Overweight / Obese offspring of non-diabetic parents (OONDP).

D – Normal BMI / weight offspring of non-diabetic parents (NONDP)

The study was approved by the University of Ibadan Teaching Hospital Ethical Committee (UI/UCH joint IRB) and Catholic Hospital Ethical Committee prior to its implementation.

The parameters measured include: Insulin sensitivity and Insulin resistance.

10ml of venous blood specimen was obtained from each subject into plain bottles. Separation of serum at centrifugal force of 3,000rpm was carried out at IMRAT (Institute of Medical Research and Training) of the College of Medicine, University of Ibadan. The serum so obtained was stored at temperature not exceeding – 40^{o}c for lipid profile estimation, each in a refrigerator at UCH Pharmacology Department until used for the determination of insulin sensitivity.

Data was got from venous blood sampling and by measurement of anthropometric variables. This is repeated as follows: Baseline measurement and after 6, 12, 18 and 24 weeks.

INSULIN SENSITIVITY BY THE HOMEOSTATIC MODEL ASSESSMENT (HOMA)

(HOMA'S method =IR = Glucose x Insulin level mg/dlxng/ml (Jerry Radziuk, 2014 and Matthew et al, 1985) 405

Insulin was determined using a chemilluminescent microparticle immunoassay (Abbort Japan co., ltd). The IR and later IS was calculated using the homeostasis model assessment method according to Matthew formula (Matthew et al, 1985)$_3$.

IR is Insulin Resistance and **IS** is Insulin Sensitivity. (Since, **IS = 1/IR).** The glucose value (in mg/dl) multiplied by insulin level divided by 405 will give us insulin resistance value. The reciprocal of value got will now give us insulin sensitivity value.

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SAMPLE COLLECTION

10ml of venous blood specimen was obtained from each subject into plain bottles. Separation of serum at centrifugal force of (2,500 - 3,000rpm) was carried out at IMRAT (Institute of Medical Research and Training) of the College of Medicine, University of Ibadan. The serum so obtained was stored at temperature not exceeding- 80^0c for insulin sensitivity test in a refrigerator at IMRAT until used for the determination of insulin sensitivity.

DATA COLLECTION PROCEDURE

This is by venous blood sampling and by measurement of anthropometric variables. This is repeated as follows: Baseline measurement and after 6, 12, 18 and 24 weeks.

Heights of participants were taken using standard hospital adult vertical rule with sliding arms which had been recalibrated and certified by a Biomedical Engineering technician prior to use. The study subject stood erect, upright and bare-footed. Those who had extra clothes such as coats and sweater removed them while Omron equipment measurements of BMI were being taken.

Body mass index (BMI) reading values for the subject were read off as displayed on the screen of Omron equipment (reliability and reproducibility index + 0.01%). The BMI values were used to group subject into four categories. Underweight – BMI<18.5kg/m^2 Normal weight – BMI = 18.5 to 24.9kg/m^2 Overweight – BMI = 25-29.9kg/m^2 Obese – BMI = >30.0kg.m^2 (NIH calculator,2011)$_4$

Omron fat estimator (Yunmai smart scale) (5) was used to measure the BMI. The subject stood uprightly bare-footed put on light clothing. The subject held his stretched hands forward as if he was riding a motor-bike.

BMI readings were read off as displayed on the screen. The readings were then recorded.

Tummy trimmer, a portable, aerobic exercise, lightweight equipment (European Home Choice Company, Lagos, Nigeria) was selected for the study. It is in-door aerobic equipment. It is compact and can fit right in the subject's brief case.

During each phase of exercise the Tummy trimmer, a portable lightweight equipment, is held at the two handles and the sole of the two feet are put inside the pedal rest while the subject assume different positions. The subject will then pull the tummy trimmer's spring towards himself or herself either while lying flat or sitting up on the floor or carpeted hard surface.

Subject sits up with leg straight, leans his or her body backwards until completely lying back with head on floor. He/she returns to sitting position in harmonic fashion. The subject was advised to start slowly and work up to repetition as she/he feels comfortable with harmoniously.

The subject was advised to lie flat on floor, extend his/her legs straight up in the air. He will be keeping his/her back on the floor and raise lower legs without bending them. The subject was later advised to sit erect with legs straight horizontally, he/she raises handle to tummy height using arms only.

Then finally, subject was advised to lie flat on the floor while he/she bends knees up to his/her chest. He/she makes a circular motion push feet up and then round towards the floor again. The different positions were observed for exercise period of 30 to 40 minutes (a video clip of the exercise procedure was shown to the subject before the commencement of the exercise).

Each subject was advised as follows:

(1) He/she to undergo the 4 phases of exercise between 30 and 40 minutes daily (either in the mornings or evenings).

(2) He/she to contact the researcher on cell phone anytime when he/she has any problems with the unit.

(3) There were regular cell phone calls made to each of the subjects by the research assistant to ensure compliance with exercise schedule.

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(4) The research assistant called them on cell phone and sent s.m.s (Short Message Service) to them to keep return appointments every six weeks. This was done one or two days before appointment schedule.

Statistical analysis of the data was carried out by using the ANOVA. The data obtained was analyzed using computer statistical programme package SPSS version 15.0 Probability value of **P** less than 0.05 was considered statistically significant.

RESULTS

INSULIN SENSITIVITY

This is shown in Table 1 and figure 1.There was an increase in insulin sensitivity in all the groups after 24 weeks of exercise. The p-values are shown in the last column of the table.

In OODP, the insulin sensitivity increased significantly (p<0.05)from 48.85± 3.15 to 53.18±3.42 ng/ml. Between OODP and NONDP is significant (P< 0.05). In NODP, the insulin sensitivity increased significantly from 49.19± 3.74 to 57.20±4.91 ng/ml. In OONDP, the insulin sensitivity increased significantly from 49.74± 3.73 to 58.28±4.15 ng/ml. In NONDP, the insulin sensitivity significantly increased from 61.99± 4.68 to 69.68±4.91 ng/ml(P< 0.05) (P< 0.05).

Figure 1 shows all the groups expressed in a graphical form. It was observed that mean insulin sensitivity was least in OODP group with level of 48.85± 3.15 ng/ml at onset to 53.18± 3.42ng/ml after six months of exercise. It was highest in group NONDP with 61.99± 4.68ng/ml at onset 69.68± 4.91ng/ml after six months of exercise.

Table1: Insulin sensitivity measurements in offspring of diabetic and non-diabetic parents before and after 6months exercise (ng/ml).

	Before exercise	**After exercise**	
	Mean±SE	**Mean±SE**	**p**
Overweight/Obese offspring of diabetic parents (OODP) n=21	48.85±3.15	53.18±3.42	0.001*
Normal weight offspring of diabetic parents (NODP) n=21	49.19±3.74	57.20±4.91	0.001*
Overweight/Obese offspring of Non-diabetic parents (OONDP) n=26	49.74±3.73	58.28±4.15	0.000*
Normal weight offspring of Non-diabetic parents (NONDP) n=27	61.99±4.68	69.68±4.91	0.003*

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F	2.720	1.830	
P	0.049*	0.147	

All values are mean±SE

*Significant at p<0.05 after 24 weeks of exercise.

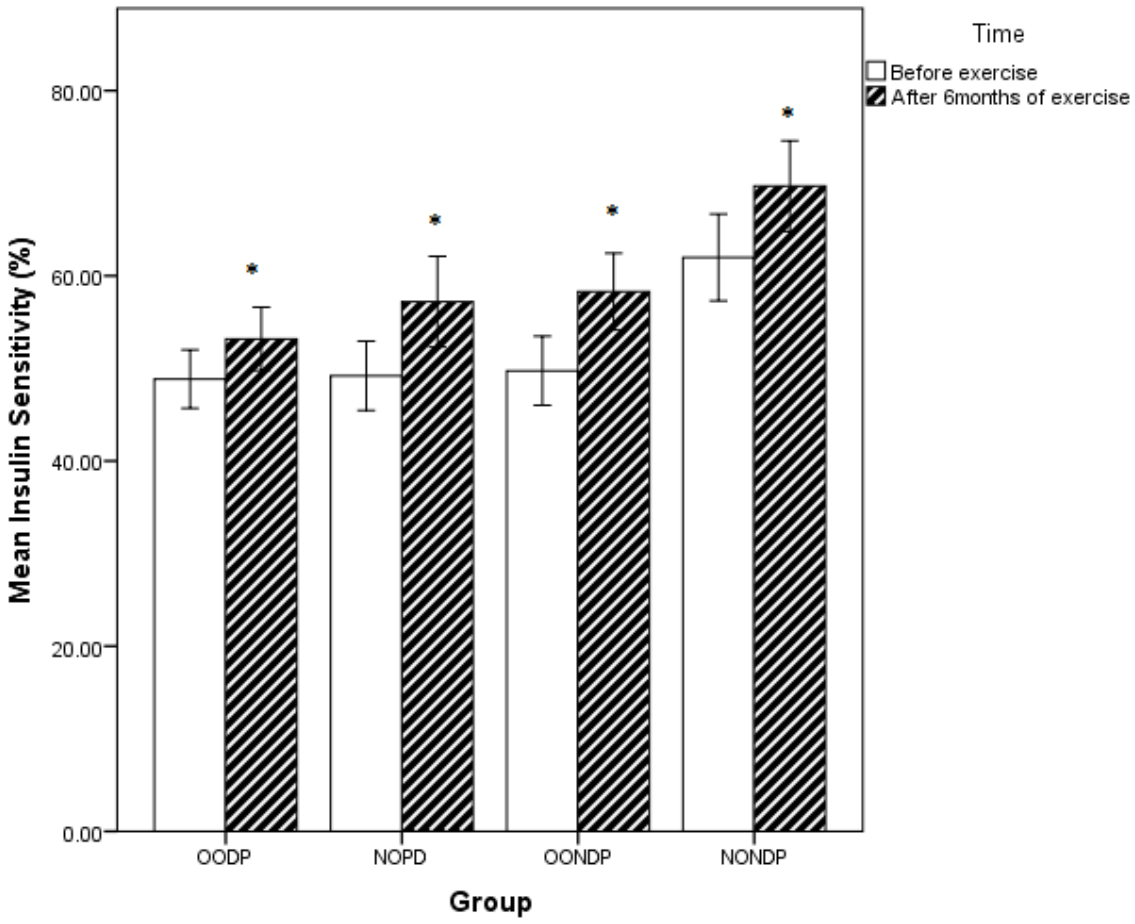

Figure 1: Showing mean insulin sensitivity (%) and different groups at onset and 6 months after

***Significant at p<0.05 for all groups after 24 weeks of exercise.**

DISCUSSION

In this study, insulin sensitivity is a major parameter which was tested in the offspring of type 2 diabetes mellitus patients. Insulin sensitivity is a very important index, in glucose metabolism by the cell. Inability of the insulin to enter into the cells adequately will lead to insulin resistance which will eventually result in the development of diabetes mellitus. This is a disorder of intermediary carbohydrate, protein and lipid metabolism characterized by high blood glucose level (hyperglycemia) and presence of glucose in the urine (glucosuria). It is accompanied in many cases by secondary alteration in fat and protein metabolism resulting in an array of biochemical disorders. An impairment of the first phase of insulin secretion may serve as a marker of the risk for type 2 diabetes

mellitus in family members of individuals with type 2 diabetes mellitus (6).

Many studies have demonstrated the presence of either insulin deficiency or insulin resistance before the onset of type 2 diabetes (2).

In addition, first degree relatives of patients with type 2 diabetes have been found to have impaired insulin action upon skeletal muscle glycogen synthesis due to both decrease stimulation of tyrosine kinase activity of the insulin receptor and reduced glycogen synthase activity.

Based upon these divergent studies, it is impossible to dissociate insulin resistance from insulin deficiency in the pathogenesis of type 2 diabetes. However, both entities unequivocally contribute to the fully established disease (2).

At this point, it is pertinent to highlight the fact that the present study is the first, as far as we are aware, in which the insulin sensitivity was determined in overweight offspring of T2DM using tummy trimmer as exercise apparatus.

The results obtained here will therefore serve as a baseline of comparison in similar studies that may be undertaken in future. However, it will be instructive to compare these results with the one done by Borghout et. al., $(1999)_7$ using bicycle ergometer as instrument apparatus to measure insulin sensitivity. All searches on the internet and books could not get previous studies using Tummy Trimmers as an apparatus for exercise.

Furthermore, regular exercise has been shown to reduce fasting triglyceride concentration in some patients (3). Hannele et al, $(1989)_8$ studied the effect of body composition and maximal aerobic power on insulin sensitivity. They found that body sensitivity to insulin is directly related to the muscle mass and inversely proportional to adiposity. They also reported that one factor contributing to decrease in insulin sensitivity is obesity which occurred during physical inactivity. Therefore in this present study, increase in insulin sensitivity after six months of exercise confirm the importance of physical activity in improving insulin sensitivity in offspring of T2 diabetes patients.

Insulin resistance may play a pivotal role in the development of diabetic dyslipedemia by influencing several factors such as insulin resistance and type 2 diabetes, increased efflux of free fatty acids into the liver (9,10).

Hepatic lipase activity is responsible for hydrolysis of phospholipids in LDL and HDL particles and lead to smaller and denser LDL particles and decrease in HDL (11, 12) and so leading to increase in serum lipids which is seen in obesity.

Lifestyle interventions such as diet, physical activity, weight loss, and smoking cessation are integral part of any diabetes management plan.

Epidemiologic and intervention studies have shown significant improvements in the features of diabetic dyslipaedemia such as medical nutrition therapy and physical activity (13, 14).

Exercise is a major therapeutic modality in the treatment of diabetes mellitus [15]. Exercise training has been known to be effective in type 2 diabetes mellitus by increasing insulin sensitivity [16], and regular exercise can strengthen antioxidant defenses and may reduce oxidative stress [17]. Exercises including yoga postures have been shown to play a role in preventing type 2 diabetes [18]. The yoga postures are slow rhythmic movements which emphasize the stimulation of the organs and glands by easy bending and extensions which do not over-stimulates muscles but concentrate on glandular stimulation [19].

A major benefit of non-exhaustive exercise such as yoga is to induce a mild oxidative stress that stimulates the expression of certain antioxidant enzymes. This is mediated by the activation of redox-sensitive signaling pathways [20].

Over the past three decades, the etiology of insulin resistance and beta-cell dysfunction has been subject to intense study [21, 22]. Obesity, as a result of

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inactivity in combination with overeating, plays a key role in the development of pancreatic beta-cell dysfunction as well as insulin resistance. Several mechanisms mediating this interaction have been identified. It is now well established that a number of circulating hormones, cytokines, and metabolic fuels, such as non-esterified fatty acids (NEFAs), are being released by adipose tissue and can modulate insulin action.

An increased mass of stored triglyceride, especially in visceral or deep subcutaneous adipose depots, leads to large adipocytes that are themselves resistant to the ability of insulin to suppress lipolysis. This results in increased release and circulating NEFA and glycerol levels both of which aggravate insulin resistance in skeletal muscle [9] and the liver [23, 24].

Ectopic fat storage in hepatocytes, so-called intrahepatic lipids (IHL), has also been related to the development of hepatic insulin resistance [25] and hepatic inflammation, initiating non-alcoholic fatty liver disease [26]. In rodents, 3 days of a high-fat diet induces hepatic insulin resistance, while no significant changes in fat content in muscle or visceral tissue could be detected [27]. Experimental research now suggests that hepatic insulin resistance arises from DAG-induced activation of protein kinase C, which directly binds to and inhibits insulin receptor tyrosine kinase activity [28]. As such, fat-induced hepatic insulin resistance and hepatic inflammation are considered important etiological factors in the development of systemic insulin resistance.

Our study, however, examine the insulin sensitivity of offspring of diabetes on graded exercise using tummy trimmer as exercise apparatus.

CONCLUSION

In conclusion, graded exercise using tummy trimmer is an important tool which improves insulin sensitivity. It should be recommended for offspring of diabetes patients to delay or prevent the onset of diabetes mellitus.

ACKNOWLEGMENTS

We thank everybody who has one way or the other in contributing to the success of this article.

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