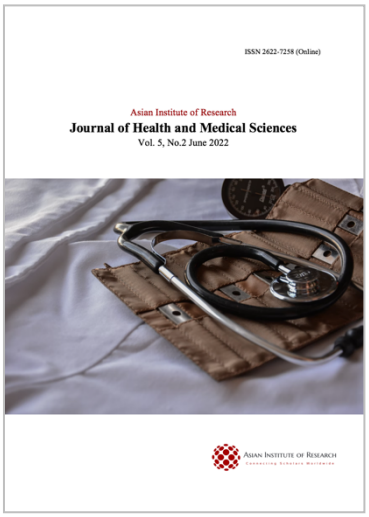

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Comparison of Effect of Exercise on Insulin Sensitivity of Overweight Normoglycemic Offspring of T2DM Parents and Non-Diabetic Parents

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Abstract
Background: The primary causes of Type 2 Diabetes Mellitus (T2DM) are largely unknown but insulin insensitivity has been reported to be a risk factor for the T2DM through the alteration of insulin sensitivity pattern. There is paucity of studies on the effect of exercise on occurrence of T2DM in offspring of diabetic parents in our population. Objectives: 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 60 offspring of T2DM parents attending University College Hospital, Ibadan and 60 offspring of non-diabetic parents who are undergraduate students of the University of Ibadan, Nigeria. Participants were randomly assigned into two groups. Each participant followed a protocol of graded exercise using ''tummy trimmer'' everyday spending 45 minutes daily for 24 weeks. Blood samples were obtained after an overnight fasting for determination of insulin sensitivity using standard methods at baseline and at 24 weeks. Data were analyzed using descriptive statistic and student t test with significance at $p<0.05$). Results: The most populated aged group was 26 to 35 years of which 47.3% (n=26) were OODP and 52.7% (n=29) were OONDP. However, all subjects were overweight with mean BMI of OODP and OONDP (29.30kg/m^2±0.71 versus 26.37kg/m^2±0.88) p=.0.035. Significantly, total insulin sensitivity between the two groups increased after 6 months of exercise p=0.045(3.36µ /l±0.24 versus 3.48µ /l±0.24). Conclusions: Male subjects tend to have higher insulin sensitivity than females.

Keywords: Diabetes Mellitus, Body Mass Index, Insulin Sensitivity, Offspring of Diabetes

1. 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 (Bacha, et al, 2010). 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, leading 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.

Obesity at younger age, significantly increased lifetime risk of type 2 diabetes mellitus (T2DM) (Bacha et al, 2010). Family history of T2DM is associated with higher body mass index (BMI), dyslipidemia, and impaired glucose tolerance (IGT) in offspring (Narayan et, al 2007, Tan et al,, 2008) There seems to be a vicious cycle, where obesity increases risk for T2DM and a family history of T2DM increasing the risk for obesity (Bacha et al,2010, Jouret et al, 2007). Parental history of T2DM is one of the dominant risk factors for development of T2DM (Chathurvedi et al, 2009). The phenotype varies depending on which parent is affected and if the child was exposed to hyperglycemia in utero (Chathurvedi et al, 2009, Meigs et al, 2000) β-cell dysfunction has been observed even in non-diabetic offspring of T2DM, more accentuated among those with maternal T2DM compared to paternal inheritance (Shaw et al,1999). Here we report the effect of exercise on insulin sensitivity in normoglycemic subjects.

Maintenance of normal glucose tolerance depends on a finely tuned balance between insulin sensitivity and β-cell function (Bacha et al 2010). The concept that a feedback loop governs the interaction of the insulin-sensitive tissues and the β-cell, as well as the elucidation of the hyperbolic relationship between insulin secretion and insulin sensitivity, explains the elevated insulin response in insulin-resistant subjects and a lower response in insulin-sensitive subjects (Narayan et al, 2007). Consideration of this hyperbolic relationship has helped to recognize the critical role of β-cell dysfunction, in the development of impaired glucose tolerance and type-2 diabetes, (Tan et al, 2008). Assessment of several ethnic groups has shown a progressive reduction in β-cell function from normal to impaired glucose tolerance and subsequently to type-2 diabetes, accompanied by a decline in insulin sensitivity (Bacha et al, 2010). The progressive nature of β-cell dysfunction in type-2 diabetes mellitus (T2DM) was also established in landmark clinical studies, (Natali et al, 2010). The therapeutic or lifestyle interventions should address the underlying pathology and should be started early along the spectrum of glucose tolerance to prevent declining insulin sensitivity and β-cell failure, (Jouret et al, 2007).

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 (Narayan et al, 2007). Exercise has been known to ameliorate the effect of diabetes by improving insulin sensitivity. It is the aim of this to work to compare the effect of exercise on insulin sensitivity of normoglycemic offspring of patients with type 2 DM and non-diabetic parents.

2. Methods

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 control subjects were normoglycemic offspring of non-diabetic parents who were randomly selected from general population of Ibadan Community, Ibadan, and South-Western, Nigeria and undergraduate students of University of Ibadan.
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 after an overnight fasting.

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- 80^{o} C in a refrigerator at IMRAT until used for the determination of insulin sensitivity.

2.1. Insulin Sensitivity by the Homeostatic Model Assessment

Insulin was determined using a chemi-lluminescent micro particle immunoassay (Abbort Japan co., ltd). The IR and later IS were calculated using the homeostasis model assessment method according to Matthew formula (Matthew et al, 1985)[8]. 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 (Jerry Radziuk, 2014 and Matthew et al, 1985)[8].

The measurement of anthropometric variables was done at baseline and after 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 height of the subject was imputed into the Omron equipment. 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 readings were then recorded.

The following definitions were utilized: Underweight: BMI <18.5 kg/m^2. Normal weight: BMI 18.5-24.9 kg/m^2, Overweight: BMI 25.0-29.9 kg/m^2, Obesity: BMI ≥30 kg/m^2.

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 hand-bag. 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 assumes 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 45 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 for 45minutes daily (in the 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 weekly cell phone calls made to each of the subjects by the research assistant to ensure compliance with exercise schedule.

2.2. Sample size estimation

This was performed using formula $\underline{(Z_{1-\alpha}/2)^2 x SD^2}$ /d^2 where Z= normal variant, d= 5.0%, Type 1 error was used with SD of 25mg/dl of fasting blood glucose from previous study. Attrition was 25%. This is equal to $\underline{1.96^2(25)^2}$ = 96

5.0^2

If we add 25% attrition (24) making a total of 120 subjects. Cochran's formula (1977).

2.3. Statistical Analysis

Statistical analysis was done using SPSS version 15 software (Lead Technologies, Chicago, USA). The data were expressed as mean ± SD for various continuous parameters studied.

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

3. Results:

A total of 60 subjects with family history of T2DM (OODP) and 60 subjects without family history of T2DM (OONDP) underwent the exercise procedure. There were 60 males and 60 females study subjects, aged 16 to 55 years. The most populated aged group was 26 to 35 years of which 47.3% (n=26) were OODP and 52.7% (n=29) were OONDP. However, all subjects were overweight with mean BMI of OODP and OONDP (29.30kg/m^2±0.71 versus 26.37kg/m^2±0.88) p= 0.035. Significantly, total mean insulin sensitivity between the two groups increased at 6 months of exercise p=0.045(3.36(µ /l±0.24 versus 3.48(µ/ /l±0.24) In OODP, the mean insulin sensitivity increased from 3.60(µ/l ±0.41to3.80 (µ/l ±0.42 after six months of exercise p=0.122. In OONDP, the mean insulin sensitivity increased from 3.17(µ/l ±0.27 to 3.23µ/l ±0.27) after six months of exercise p=0.198. The increase is higher in OODP than OONDP (-1.620 versus -1.324). The increase is higher in male OODP than female subjects (-2.020 versus 0.048) and similarly for OONDP group (-0.975 versus-0.857). However, all values were not statistically significant but clinically important.

Table 1: Anthropometric Parameters of the Study Groups

Variable	Category	Total	OODP	OONDP	P
Gender	*Male*	60 (50.0)	30 (50.0)	30 (50.0)	
	Female	60 (50.0)	30 (50.0)	30 (50.0)	
Age (years)	*16-25*	43 (35.8)	22 (36.7)	21 (35.0)	
	26-35	55 (45.8)	26 (47.3)	29 (52.7)	
	36-45	19 (15.8)	9 (15.0)	10 (16.7)	
	46-55	3 (2.5)	3 (5.0)	0 (0.0)	
Mean Weight(Kg)		69.80±1.59	73.28±2.38	67.00±2.01	0.185
Mean BMI(Kg/m2)		27.70±0.61	29.30±0.71	26.37±0.88	0.035*

P value significant at 0.05.

Table 2: Mean insulin sensitivity before and after Exercise in the study groups.

Variable	Category	Before Exercise	After Exercise	T	P
Mean Insulin Sensitivity(µ/l)	*Total*	3.36±0.24	3.48±0.24	-2.014	0.045*
	OODP	3.60±0.41	3.80±0.42	-1.620	0.122
	OONDP	3.17±0.27	3.23±0.27	-1.324	0.198
	OODP-Male	4.14±0.88	4.57±0.86	-2.020	0.078
	OODP-Female	3.16±0.18	3.16±0.18	-0.048	0.963
	OONDP-Male	3.18±0.28	3.26±0.28	-0.975	0.355
	OONDP-Female	3.16±0.42	3.21±0.41	-0.857	0.406

P value significant at 0.05

4. Discussion

The present study assessed the insulin sensitivity among normoglycemic offspring of T2DM subjects and controls without family members with T2DM. We observed higher mean insulin sensitivity in the subjects studied after six months of exercise in normo-glycemic offspring of individuals with T2DM compared to controls. It mean that the total insulin sensitivity were significantly higher in the offspring of subjects with diabetes. Pimenta *et al*., 1995 observed similar insulin sensitivity and loss of first-phase insulin secretion in subjects with family history of DM compared to BMI-matched controls (Matthews et al, 1985). Van Haeften *et al*.,1998 observed similar insulin sensitivity but reduced insulin secretion at 90 and 120 minute during OGTT in offspring of individuals with T2DM (Jensen et al, et al,2002). There were three reports where mean age of subjects was less than 16 years. Two of these reports where cases and controls were matched for BMI have reported lower insulin sensitivity in offspring/ first-degree relative using clamp studies (Weyer et al,1999, Warram et al, 1990). The third which did not match

cases and controls for BMI observed higher BMI, fasting insulin levels, and HOMA-IR for cases and the differences were not significant after adjusting for BMI (Meigs et al, 2000) A longitudinal study in Pima Indians reported a twofold greater increase in weight in subjects who progressed to diabetes compared to the non-progressors (Pimenta *et al*., 1995). Our observation of higher BMI in offspring of subjects with T2DM compared to controls is in accordance with these above-mentioned studies. The San Antonio heart (SAH) study has shown that both mean fasting insulin levels and mean insulin sums increased in a stepwise fashion as the family history of diabetes became stronger. The significance of fasting insulin became marginal when adjusted for BMI (Danadian et al, 1999). Mean age of offspring (20 years) in the present study was lower compared to the SAH study which is 42 years. There was significantly higher plasma insulin, C-peptide, HOMA-IR, and BMI when three or more family members were affected (FHD3 group).

In the present study, the mean age of subjects was in their twenties, reducing the confounding effects due to age. Whole-body insulin sensitivity in the present study was measured as WBISI as described by Matsuda and DeFronzo, which was shown to be having an excellent correlation with euglycemic hyperinsulinemic clamp technique by large scale studies (Danadian et al, 1999). The calculated disposition index by OGTT highlighted the inability of β-cell to compensate for declining insulin sensitivity (Taiwo et al, 2017). In their prospective studies, the disposition index declined well before glucose levels rise into the diabetic range, and was mentioned as an early marker for inadequate β-cell compensation or β-cell dysfunction21 (Srinivasan et al, 1998).

Finally, we observed higher BMI, plasma insulin sensitivity in normoglycemic offspring of T2DM subjects compared to controls. In normal glucose-tolerant subjects, insulin sensitivity and insulin secretion varied over a large range. According to a study in obese youth by Yeckel et al., 2005 insulin secretion as measured by the insulinogenic index has a strong impact on postprandial glucose levels even within the normal range, and in all insulin sensitivity tertiles (Chathurvedi et al, 2009).

5. The limitations of this study

The limitations of this study were that we did not consider 1° relatives or 2° relatives in particular but only in offspring, however, other family relations were not taken into considerations.

6. Conclusion

In conclusion, insulin sensitivity increased after six months of exercise. Male OODP subjects tend to have higher insulin sensitivity than females. Based on the outcome of this research, people with family history of T2DM should reduce their tendency to obesity and engage in exercise

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Contributions of Authors

Conflict of interest

No conflict of interest.

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