

## Relationship between exercise capacity using Bruce protocol and correlates of type 2 diabetes

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### Abstract

**Introduction:** Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from problems in insulin secretion, insulin action or combination of both. For diabetes management, exercise is considered to be a cornerstone, along with diet and medication.

**Materials and Methodology:** 50 subjects were selected by using purposive sampling method. Baseline measures such as age, BMI, waist hip ratio, duration of diabetes, resting heart rate, fasting blood sugar were determined prior to treadmill protocol. The subjects were asked to walk on a treadmill using Bruce Protocol and their recovery heart rates were measured. The time taken and stage covered were observed and estimated VO<sub>2</sub> max was calculated at each session. The data was analyzed using the Mean, Standard deviations and Pearson's correlation coefficient.

**Results:** The result showed that there is relationship of exercise capacity with Age, BMI, waist hip ratio, recovery heart rate but no relationship between fasting blood sugar and duration of diabetes.

**Conclusion:** The study can be concluded that Exercise capacity in Type 2 Diabetes using Bruce protocol was correlated with age, BMI, waist hip ratio and recovery heart rate.

**Keywords:** Body Mass Index (BMI), Bruce protocol, Recovery heart rate, Type 2 diabetes, Maximal oxygen uptake.

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### Introduction

Diabetes mellitus is defined as a group of metabolic disorders with the presentation of hyperglycemia resulting from problems in insulin secretion, insulin action (hepatic and peripheral glucose uptake), or both. A consequence of this is chronic hyperglycemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism [1]. Risk factors include diet, obesity, elevated fasting blood sugar, lack of exercise, hypertension [2]. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy and increased risk of cardiovascular disease [3].

Diabetes has now become a global pandemic and unfortunately, the prevalence of diabetes is increasing most rapidly among developing countries of the world. In India from 1989 to 1995, the prevalence of diabetes in Chennai increased by 39.8% (8.3-11.6%); between 1995 and 2000 by 16.3% (11.6-13.5%) and between 2000 and 2004, by 6% (13.5-14.3%). Thus within a span of 14 years, the prevalence of diabetes increased significantly by 72.3% [4].

For diabetes management, exercise is considered to be a cornerstone, along with diet and medication [5]. The physiotherapists usually advice diabetic patients to engage in either indoor or outdoor exercises and encourage use of fitness equipment such as treadmill as it are same as walking. Treadmill provides convenience and ease of accessing patients with T2D.

Exercise capacity can be evaluated by direct laboratory

measurement [6]. Exercise capacity expressed in terms of (VO<sub>2</sub>) is the common clinical measure of exercise tolerance and is strongly influenced by age [7]. Exercise capacity (in VO<sub>2</sub>) is estimated on the basis of the speed and grade of the treadmill [8]. VO<sub>2</sub> max on the other hand, is defined as the maximal amount of oxygen consumed during exercise. In recent decades, VO<sub>2</sub> max has had a growing importance in clinical settings and has become the gold standard measure of cardiovascular fitness and exercise capacity [9].

The relative risk of developing Type 2 diabetes increases steeply with increasing BMI. Abdominal obesity, as measured by waist-to-hip ratio, may be a stronger predictor of diabetes than BMI alone. As expected, epidemiologic studies have demonstrated that these three obesity indicators (Body mass index, Waist circumference, Waist hip ratio) are strong and consistent predictors of diabetes mellitus, Type 2 [10].

According to Adeniyi et al. (2010), the relationship between 6 minute walk test and correlates of Type 2 Diabetes can be determine through cost effective variables include age, gender, waist hip ratio and body mass index because they are easily measured in the clinic or home setting [11].

Bruce protocol was designed in 1963 by Robert A Bruce The Bruce protocol stress exercise test is a maximal exercise test in which the individual works to complete exhaustion as the treadmill speed and grade of inclination is increased every three minutes [12,13]. The length of time on the treadmill is the test score and can be used to estimate the VO<sub>2</sub> max value. The treadmill is started at 2.74 km/hr (1.7 mph) and at a gradient

(or incline) of 10%. At three minute intervals the incline of the treadmill increases by 2%, and the speed increases [14-18].

This study is aimed to determine the exercise capacity using Bruce protocol in patients with T2D and to identify its relationship with each of the correlates including Age, Glycaemic control, and Waist hip ratio, Duration of diabetes, Hypertension and Body mass index. The Bruce protocol is normally used as a measure of functional exercise capacity of the individual which is considered in this study to evaluate whether exercise capacity is related with the correlates of the Type 2 Diabetes.

## Materials and Methodology

### Study setting

For study purpose the Cardio Respiratory lab, Department of Physiotherapy, Sri Ramakrishna Institute of Paramedical Sciences, Tamil Nadu, India was selected.

### Sampling technique

A convenient sampling was used in the study.

### Sample size

50 subjects were taken in which there were 28 Males and 22 Females with Type 2 Diabetes.

### Sampling criteria

**Inclusion;** Patients with below criteria are taken into consideration

- Type 2 Diabetes
- Hypertension
- Age > 35 years

**Exclusion;** Peripheral vascular disease

- Autonomic neuropathy
- Advanced nephropathy with renal failure
- Arthritis
- Peripheral nerve injury

### Instruments and tools

1. Treadmill (RMS vega 201)
2. ECG Electrodes
3. Ruler
4. Weight apparatus
5. Stadiometer
6. Inch tape
7. B.P apparatus (Mercury Sphygmomanometer)
8. Glucometer

### Parameters

1. Age (years)
2. BMI (kg/m<sup>2</sup>)
3. Fasting blood sugar (mmol/L)

4. Recovery heart rate number
5. Waist hip ratio
6. Duration of diabetes (years)
7. Systolic blood pressure
8. VO<sub>2</sub> Max

## Procedure

Patients were invited to participate in the study through signed informed consent forms. Fifty subjects with Diabetes Type 2 were selected with convenient sampling and procedure was explained to them. Baseline measures such as age, BMI, waist hip ratio, duration of diabetes, resting heart rate, fasting blood sugar were determined prior to treadmill protocol. The data was analyzed using the Mean, Standard deviations and Pearson's correlation coefficient. The eligible subjects underwent exercise testing with incremental loading using Bruce protocol. ECG electrodes were attached to the participant's chest and monitored throughout the exercise testing. The blood pressure was measured after completion of each stage. The participants were instructed to continue treadmill walking till voluntary exhaustion. During the protocol the grade of inclination increased by 2% and the speed increased by 0.8 mph every 3 minutes for the first five stages with 0.5 mph for the next two stages. After the protocol Recovery heart rate was recorded. The time taken and stage covered were observed and estimated VO<sub>2</sub> max was calculated at each session.

The Bruce Protocol formula for estimating VO<sub>2</sub> max

For Men VO<sub>2</sub> max = 14.8 - (1.379 × T) + (0.451 × T<sup>2</sup>) - (0.012 × T<sup>3</sup>)

For Women VO<sub>2</sub> max = 4.38 × T - 3.9

## Result

### VO<sub>2</sub> max

The mean and standard deviation of VO<sub>2</sub> max in males and females are (30.36 ± 6.965) and (26.22 ± 4.811) respectively.

### VO<sub>2</sub> max and age

The result showed significant relationship between age and VO<sub>2</sub> max both in males and females. The mean and standard deviation of age in males and females are (55.85 ± 10.42) and (58.81 ± 8.688) respectively.

In males correlation coefficient of age and VO<sub>2</sub> max r = -0.753 and P value is < 0.0001, considered extremely significant.

In females correlation coefficient of age and VO<sub>2</sub> max r = -0.4834 and P value is 0.0227 considered significant.

### VO<sub>2</sub> max and BMI

The result showed significant relationship between BMI and VO<sub>2</sub> max in both males and females. The mean and standard deviation of BMI in males and females are (27.85 ± 3.263) and (27.72 ± 2.798) respectively.

In males correlation coefficient of BMI and VO<sub>2</sub> max r = -0.5384 and P value is 0.0031 considered very significant.

In females correlation coefficient of BMI and VO<sub>2</sub> max r = 0.7045 and P value is 0.003 considered extremely significant.

**VO2 max and waist hip ratio**

The result showed significant relationship between WHR and VO2 max in both male and females. The mean and standard deviation of waist hip ratio in males and females are  $(0.980 \pm 0.098)$  and  $(0.863 \pm 0.063)$  respectively.

In males correlation coefficient of waist hip ratio and VO2 max  $r=-0.5944$  and P value is 0.0009 considered extremely significant.

In females correlation coefficient of waist hip ratio and VO2 max  $r=-0.6122$  and P value is 0.0025 considered very significant.

**VO2 max and recovery heart rate**

The result showed significant relationship between recovery heart rate and VO2 max in both males and female. The mean and standard deviation of recovery heart rate in males and females are  $(2.575 \pm 0.554)$  and  $(2.736 \pm 0.779)$  respectively.

For males correlation coefficient of recovery heart rate and VO2 max  $r=0.8644$ . The two tailed P value is  $<0.0001$  considered extremely significant.

For females correlation coefficient of recovery heart rate and VO2 max  $r=0.8843$ . The two tailed P value is  $<0.0001$  considered extremely significant.

**VO2 max and fasting blood sugar**

The result showed no significant relationship between fasting blood sugar and VO2 max in both males and female. The mean and standard deviation of fasting blood sugar in males and females is  $(141.1 \pm 13.96)$  and  $(146.31 \pm 15.388)$  respectively.

In males correlation coefficient of fasting blood sugar and VO2 max  $r=0.2587$  and P value is 0.1838 considered not significant.

In females correlation coefficient of fasting blood sugar and VO2 max  $r=0.1729$  and P value is 0.4415 considered not significant.

**VO2 max and duration of diabetes**

The result showed no significant relationship between VO2 max and duration of diabetes in both males and females. The mean and standard deviation of duration of diabetes in males and females are  $(4.642 \pm 2.628)$  and  $(5.090 \pm 4.720)$  respectively.

In males correlation coefficient of duration of diabetes and VO2 max  $r=-0.2155$  and P value is 0.2707 considered not significant.

In females correlation coefficient of duration of diabetes and VO2 max  $r=-0.09462$  and P value is 0.6753 considered not significant.

**VO2 max and systolic blood pressure**

The result showed no significant relationship between VO2 max and systolic blood pressure in males and females. The Mean and Standard deviation of Systolic blood pressure in males and females are  $(165.2 \pm 14.68)$  and  $(164.54 \pm 13.415)$  respectively.

In males correlation coefficient of systolic blood pressure and VO2 max  $r=-0.8749$  and P value is 0.6580 considered not significant.

In females correlation coefficient of systolic blood pressure and VO2 max  $r=-.1150$  and P value is 0.6102 considered not significant.

**Discussion**

The primary finding of this study was that Bruce protocol can be used to evaluate exercise capacity for diabetes type 2 patients and parameters like age, BMI, waist hip ratio, duration of diabetes, fasting blood sugar, recovery heart rate, systolic blood pressure were correlated with VO2 max to determine their interrelationship.

However in this study it was found that parameters like age, BMI, waist hip ratio, recovery heart rate were significantly correlated with VO2 max in both males and females whereas fasting blood pressure, duration of diabetes, systolic blood pressure show no correlation with VO2 max in both males and females. The result showed that there is relationship of exercise capacity with Age, BMI, waist hip ratio, recovery heart rate but no relationship between fasting blood sugar and duration of diabetes.

**Age**

In this study there was significant correlation of Age with VO2 max. According to Paul M and Wei L peak exercise capacity in healthy normal weight population of men and women decline naturally with age. Exercise capacity in women is 20% lower than in men across the age range. In this study exercise capacity was more in males than females. Zhi demonstrated that exercise capacity associations with aging, female sex, and obesity, impaired exercise capacity in TYPE 2 Diabetes was associated with poor diabetes control, LV diastolic dysfunction, and reduced HRR [19-23].

**BMI**

In this study Exercise capacity showed significant correlation of BMI with VO2 max [24-28]. Obesity is present in many individual with cardiovascular disease and decreases exercise capacity to increase in resting metabolic requirements and greater respiratory and cardiac work required by obese individual when exercising. BMI is a highly significant determinant of exercise capacity [29-35]. Obesity determine an increase in fatigue due to high BMI that cause increase in work for any given speed and inclination of treadmill workload on obese patient consume more oxygen have reduce exercise capacity [36-43].

**Fasting blood sugar**

In this study, exercise capacity showed no correlation with fasting blood sugar. Exercise capacity often reduces fasting blood plasma insulin level and lower insulin output indicating improved insulin sensitivity [44]. The exercise increases the blood flow to the working muscle so that the size of the perfused capillary bed increases and it thereby increases the available number of insulin receptors, counter balancing this increased sensitivity to insulin [45].

**Waist hip ratio**

In this study exercise capacity showed significant correlation of waist hip ratio with VO2 max. Waist hip ratio is associated with poor gas exchange at rest and during exercise there is decrease in Exercise capacity in obese patients is due to added energy need to move fat mass during exercise [46].

### **Recovery heart rate**

In this study exercise capacity (VO<sub>2</sub>) showed significant correlation with Recovery heart rate. HR recovery after exercise depends on several factors: the intensity of exercise, the cardio respiratory fitness, cardiac ANS modulation, hormonal changes and baro reflex sensitivity [33,47].

### **Duration of diabetes**

In this study, exercise capacity showed no correlation with duration of diabetes. Several studies considered that poor glycemic control, disease duration, hypertension and dyslipidaemia are to be important risk factors for micro vascular complications [48].

### **Systolic blood pressure**

In this study exercise capacity showed no correlation with Systolic blood pressure. Patricia et al. suggested that in subject with Type 2 Diabetes without cardiovascular disease, an elevated exercise systolic blood pressure is not associated with reduced exercise capacity. The elevated peak exercise SBP observed in our subjects is probably partly associated with the arterial stiffness observed in subjects with diabetes. In theory, a cascade of events will take place following the appearance of arterial stiffness: 1) increased after load, 2) reduced stroke volume, 3) LV remodeling, 4) increased SBP, 5) diastolic dysfunction, 6) reduced exercise performance and, 7) systolic dysfunction results related to elevated peak SBP [49].

## **Limitations and Recommendations**

### **Limitations**

- Sample size is small due to time constrain.
- There may be falsification of individual answers intentionally or unintentionally by the patients for subjective parameters like age and duration of diabetes.
- Smoking history was not taken into consideration during the study.
- This study was one time study and hence result may have varied if it had been carried out at another point in time.
- Relationship between the correlates of T2D was not taken into consideration.

### **Recommendations**

- Further research could be done in exercise capacity taking a number of confounding factors like cardiovascular disease, history of smoking, etc into account.
- Patient of Type-1 Diabetes could be considered.

## **Conclusion**

In summary, as interpretation from the result the exercise capacity using Bruce protocol show significant relationship between age, BMI, recovery heart rate, waist hip ratio but no significant relationship between fasting blood sugar, duration of diabetes, systolic blood pressure. Thus result of the study can be concluded that Exercise capacity in Type 2 Diabetes using Bruce protocol was correlated with age, BMI, waist hip ratio and recovery heart rate.

## **References**

1. Adekunle AE, Akintomide AO. Gender differences in the variables of exercise treadmill test in type 2 diabetes mellitus. *Annals of African medicine.* 2012;11(2):96-102.
2. Albouaini K, Egred M, Alahmar A, et al. Cardiopulmonary exercise testing and its application. *Postgraduate medical journal.* 2007 Nov 1;83(985):675-82.
3. Almeida JA, Campbell CS, Pardono E, et al. Predictive equations validity in estimating the VO<sub>2</sub>max of young Brazilians from performance in a 1600 m run. *Revista Brasileira de Medicina do Esporte.* 2010 Feb;16(1):57-60.
4. Bentley DJ, Newell J, Bishop D. Incremental exercise test design and analysis. *Sports medicine.* 2007 Jul 1;37(7):575-86.
5. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation.* 2011 Mar 8;123(9):1010-20.
6. Bruce R, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *American heart journal.* 1973 Apr 1;85(4):546-62.
7. Bruce RA, Kusumi F, Niederberger M, et al. Cardiovascular mechanisms of functional aerobic impairment in patients with coronary heart disease. *Circulation.* 1974 Apr 1;49(4):696-702.
8. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: Joint position statement. *Diabetes care.* 2010 Dec 1;33(12):e147-67.
9. Smirmaul BP, Bertucci DR, Teixeira IP. Is the VO<sub>2</sub> max that we measure really maximal? *Frontiers in physiology.* 2013 Aug 5;4:203.
10. Strong PC, Lee SH, Chou YC, et al. Relationship between quality of life and aerobic capacity of patients entering phase II cardiac rehabilitation after coronary artery bypass graft surgery. *Journal of the Chinese Medical Association.* 2012 Mar 1;75(3):121-6.
11. Adeniyi AF, Uloko AE, Sani-Suleiman I. Relationship between the 6-minute walk test and correlates of type 2 diabetes: indication for caution in exercise prescription. *African Journal of Physiotherapy and Rehabilitation Sciences.* 2010;2(1):21-4.
12. Warburton DE, Haykowsky MJ, Quinney HA, et al. Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. *Sports medicine.* 1999 Jan 1;27(1):23-41.
13. Midgley AW, Bentley DJ, Luttikholt H, et al. Challenging a dogma of exercise physiology. *Sports Medicine.* 2008 Jun 1;38(6):441-7.
14. Peterson MJ, Pieper CF, Morey MC. Accuracy of VO<sub>2</sub> (max) prediction equations in older adults. *Medicine and science in sports and exercise.* 2003 Jan;35(1):145-9.
15. Regensteiner JG, Sippel J, McFarling ET, et al. Effects of

- non-insulin-dependent diabetes on oxygen consumption during treadmill exercise. *Medicine & Science in Sports & Exercise*. 1995 May.
16. Saunders PU, Pyne DB, Telford RD, et al. Factors affecting running economy in trained distance runners. *Sports Medicine*. 2004 Jun 1;34(7):465-85.
  17. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*. 1998 Sep 12;352(9131):837-53.
  18. Gray A, Raikou M, McGuire A, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). *Bmj*. 2000 May 20;320(7246):1373-8.
  19. Faas A, Schellevis FG, Van Eijk JT. The efficacy of self-monitoring of blood glucose in NIDDM subjects: a criteria-based literature review. *Diabetes Care*. 1997 Sep 1;20(9):1482-6.
  20. Coster S, Gulliford MC, Seed PT, et al. Self-monitoring in Type 2 diabetes mellitus: a meta-analysis. *Diabetic Medicine*. 2000 Nov 1;17(11):755-61.
  21. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes care*. 2006 Aug 1;29(8):1963-72.
  22. Mathers C, Penm R, Carter R, et al. Health system costs of diseases and injury in Australia 1993-94: an analysis of costs, service use and mortality for major disease and injury groups.
  23. Colagiuri S, Colagiuri R, Conway B, et al. DiabCost Australia: assessing the burden of Type 2 diabetes in Australia 2002. Canberra: Diabetes Australia Google Scholar.
  24. Burgers JS, Bailey JV, Klazinga NS, et al. Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. *Diabetes Care*. 2002 Nov 1;25(11):1933-9.
  25. Self-monitoring of blood glucose. *Diabetes Australia*. 2006 Feb 1;1(2):11-20.
  26. American Diabetes Association: Standards of Medical Care in Diabetes—2006 (Position Statement). *Diabetes Care* 29. 2006 (Suppl. 1):S4-S42.
  27. Wing RR, Epstein LH, Nowalk MP, et al. Does self-monitoring of blood glucose levels improve dietary compliance for obese patients with type II diabetes? *The American journal of medicine*. 1986 Nov 1;81(5):830-6.
  28. Fontbonne A, Billault B, Acosta M, et al. Is glucose self-monitoring beneficial in non-insulin-treated diabetic patients? Results of a randomized comparative trial. *Diabetes & metabolism*. 1989;15(5):255-60.
  29. Muchmore DB, Springer J, Miller M. Self-monitoring of blood glucose in overweight type 2 diabetic patients. *Acta diabetologica*. 1994 Dec 1;31(4):215-9.
  30. Guerci B, Drouin P, Grange V, et al. Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. *Diabetes & metabolism*. 2003 Dec 1;29(6):587-94.
  31. Davidson MB, Castellanos M, Kain D, et al. The effect of self-monitoring of blood glucose concentrations on glycosylated hemoglobin levels in diabetic patients not taking insulin: a blinded, randomized trial. *The American journal of medicine*. 2005 Apr 1;118(4):422-5.
  32. Estey AL, Tan MH, Mann K. Follow-up intervention: its effect on compliance behavior to a diabetes regimen. *The Diabetes Educator*. 1990 Aug;16(4):291-5.
  33. Allen BT, DeLong ER, Feussner JR. Impact of Glucose Self-Monitoring on Non-Insulin-Treated Patients With Type II Diabetes Mellitus: Randomized Controlled Trial Comparing Blood and Urine Testing. *Diabetes Care*. 1990 Oct 1;13(10):1044-50.
  34. Rutten GE, Van Eijk J, de Nobel E, et al. Feasibility and effects of a diabetes type II protocol with blood glucose self-monitoring in general practice. *Family practice*. 1990 Dec 1;7(4):273-8.
  35. Gallichan MJ. Self-monitoring by patients receiving oral hypoglycaemic agents: A survey and a comparative trial. *Practical Diabetes*. 1994 Jan 1;11(1):28-30.
  36. Miles P, Everett J, Murphy J, et al. Comparison of blood or urine testing by patients with newly diagnosed non-insulin dependent diabetes: patient survey after randomised crossover trial. *BMJ*. 1997 Aug 9;315(7104):348-9.
  37. McMurray SD, Johnson G, Davis S, et al. Diabetes education and care management significantly improve patient outcomes in the dialysis unit. *American journal of kidney diseases*. 2002 Sep 1;40(3):566-75.
  38. Ozmen B, Boyvada S. Can self-monitoring blood glucose control decrease glycosylated hemoglobin levels in diabetes mellitus. *The Endocrinologist*. 2002 Jul 1;12(4):349-56.
  39. Schwedes U, Siebolds M, Mertes G. Meal-related structured self-monitoring of blood glucose: effect on diabetes control in non-insulin-treated type 2 diabetic patients. *Diabetes care*. 2002 Nov 1;25(11):1928-32.
  40. Jones H, Edwards L, Vallis TM, et al. Changes in diabetes self-care behaviors make a difference in glycemic control: the Diabetes Stages of Change (DiSC) study. *Diabetes care*. 2003 Mar 1;26(3):732-7.
  41. Nyomba BL, Berard L, Murphy LJ. Facilitating access to glucometer reagents increases blood glucose self-monitoring frequency and improves glycaemic control: a prospective study in insulin-treated diabetic patients. *Diabetic Medicine*. 2004 Feb 1;21(2):129-35.
  42. Polonsky WH, Earles J, Smith S, et al. Integrating medical

- management with diabetes self-management training: a randomized control trial of the Diabetes Outpatient Intensive Treatment program. *Diabetes care.* 2003 Nov 1;26(11):3048-53.
43. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *New England Journal of Medicine.* 2000 Jun 22;342(25):1878-86.
44. Davis TM, Zimmet P, Davis WA, et al. Autoantibodies to glutamic acid decarboxylase in diabetic patients from a multi-ethnic Australian community: the Fremantle Diabetes Study. *Diabetic Medicine.* 2000 Sep 1;17(9):667-74.
45. Bruce DG, Davis WA, Davis TM. Glycemic control in older subjects with type 2 diabetes mellitus in the Fremantle Diabetes Study. *Journal of the American Geriatrics Society.* 2000 Nov 1;48(11):1449-53.
46. Bruce DG, Davis WA, Cull CA, et al. Diabetes education and knowledge in patients with type 2 diabetes from the community: the Fremantle Diabetes Study. *Journal of Diabetes and its Complications.* 2003 Mar 1;17(2):82-9.
47. Davis TM, Clifford RM, Davis WA. Effect of insulin therapy on quality of life in Type 2 diabetes mellitus: The Fremantle Diabetes Study<sup>1</sup>. *Diabetes research and clinical practice.* 2001 Apr 1;52(1):63-71.
48. Karter AJ, Ackerson LM, Darbinian JA, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry\*. *The American journal of medicine.* 2001 Jul 1;111(1):1-9.
49. DCCT Research Group. Reliability and validity of a diabetes quality-of-life measure for the diabetes control and complications trial (DCCT). *Diabetes care.* 1988 Oct 1;11(9):725-32.